Network Meta-analysis of Four Chinese Patent Medicines Combined with Angiotensin Converting Enzyme Inhibitors or Angiotensin Receptor Blockers in Early Diabetic Nephropathy Treatment

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Abstract

The objective of the study is to systematically evaluate the efficacy of four Chinese patent medicines in combination with angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB) in the treatment of early diabetic nephropathy (DN). Retrospectively, previously published randomized controlled trials (RCTs) of four different Chinese patent medicines combined with ACEI or ARB in the treatment of patients with early DN were searched overall from databases. The data were analyzed by R, Generate Mixed Treatment Comparisons and STATA softwares. A total of 78 RCTs were finally included. Network meta-analysis showed that the total effective rate of the Jinshuibao capsule-ACEI/ARB combination group and Huangkui capsule-ACEI/ARB combination groups were better than the others; Jinshuibao capsule-ACEI/ARB combination group reduced the 24-h urinary protein excretion (24-h UTP), urine microalbumin excretion rate (UAER), serum creatinine (Scr), and glycosylated hemoglobin (HbAlc) values. The Huangkui capsule-ACEI/ARB combination demonstrated a better reduction of (blood urea nitrogen [BUN]). Reduced incidences of adverse effects were only observed on treatment with Bailing capsule-ACEI/ARB combination. In early DN, combination of Jinshuibao capsule-ACEI/ARB provided the highest effective rate; moreover, it could reduce the 24-h values of UTP, UAER, Scr, and HbAlc; Huangkuai capsule-ACI/ARB combination group showed a good effect on reducing BUN. Bailing capsule-ACEI/ARB combination group had reduced the incidences of adverse reactions.

Keywords: Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, Chinese patent medicine, drug combination, early diabetic nephropathy, network meta-analysis

INTRODUCTION

Diabetic nephropathy (DN) is among the most common and serious chronic complications of diabetes mellitus. The current therapeutic strategies for DN are based on changing lifestyle and dietary habits, controlling blood glucose and blood pressure, and lipid-lowering therapy.[1] A study found that the use of angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) can reduce serum creatinine and albuminuria, and slow down the development of DN.[2] However, the use of ACEI/ARB has limitations. St Peter Wendy L researches showed that although there have been remarkable achievements in RAAS system blockers, it can only reduce the risk of developing end-stage renal disease in <30% of the patients with DN and slow the development of DN in 10% of the patients. The effect is not ideal. In addition, it is not cost-effective and can cause hyperkalemia, transient renal insufficiency, or other complications.[3] In recent years, the combination of Chinese patent medicine and ACEI/ARB has been reported to have improved the clinical efficacy for treating DN. However, because of

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the lack of randomized controlled trials (RCTs) for direct comparison of Chinese patent medicine, and the inability of traditional meta-analyses to compare between different therapeutic effects, there is a lack of evidence as to which Chinese patent medicine is efficacious in the treatment of DN. Network meta-analysis (NMA) is an extension of traditional meta-analysis. Based on the frequency method or Bayesian theory, combined with direct and indirect comparison studies, the therapeutic effects of three or more interventions, can be compared. [4] The biggest advantage of NMA is that it can quantitatively compare different interventions in the treatment of the same disease and rank the efficacy of a certain outcome index, so as to provide evidence to support clinical drug selections. [5] Therefore, it is important to perform NMA to compare the efficacy between the Chinese patent medicine–ACEI/ARB combination group and ACEI/ARB alone.

**MATERIALS AND METHODS**

**Search strategy**

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses: The PRISMA Statement. In this study, the following databases were searched: CNKI, Wanfang Data, VIP, PubMed, EMBASE, and the Cochrane Library. The search duration ranged from the inception of the individual database to August 2019. We also manually the reference lists of all full-text papers for additional relevant reports. The search terms used included “early DN,” “diabetic renal disease,” “Niaoduqing,” “Jinshuibao,” “Huangkui,” “Bailing,” “ACEI/ARB,” and “randomized control.”

**Inclusion and exclusion criteria**

**Study design**

RCTs or quasi-RCTs were included, regardless of whether the blind methods were blinded, and the assignment was hidden or not. No restrictions on language, population characteristics, and publication types were imposed.

**Participants**

Patients with DN diagnostic standards were eligible for inclusion, and patients were classified as Stage I–III DN according to the Mogensen DN staging system. [6]

**Exclusion criteria**

Exclusion criteria include (1) a control group was not included, or the control group was not designed to meet the principles of randomization or semi-randomization. (2) Animals experiments or cell experiments. (3) Theoretical articles and literature reviews. (4) Interventions included other traditional patent medicine. (5) Data were not available for analysis, or the article was identified as a repetitive publication. (6) Retrospective studies. (7) The target population did not meet the diagnostic criteria for DN Stages I–III diagnosis according to the Mogensen staging system.

**Interventions**

The study compared four different Chinese patent medicines–ACEI/ARB combinations with ACEI/ARB alone, regardless of the dosage, type, and duration of treatment. The basic therapies in the four kinds of Chinese patent medicines – ACEI/ARB combination group and ACEI/ARB group were similar.

**Outcomes**

The primary outcomes were the 24-h UTP, urinary microalbumin excretion (UAER), blood urea nitrogen (BUN), serum creatinine (Scr), and total effective rate. Secondary outcomes were glycosylated hemoglobin (HbA1c) level.

**Efficacy criteria**

Remarkable effect: Decrease in Scr decreased by 15%–30% or more; or increase in Ccr increased by >15% and obvious improvement in the clinical symptoms. Moderate effect: Decrease in Scr by 5%–15%; or increase in Ccr by 5%–15%, with partial improvement in clinical symptom. No effect: Therapy did not provide the standard of efficiency, and moreover, the clinical symptoms exacerbation. Therefore, total effect = remarkable effect + moderate effect.

**Data extraction**

Two investigators (Zhang J and Huang JQ) independently extracted information from the selected publications. The extracted contents included author (year), sample size, disease stage, patient age, interventions, comparators, treatment period, outcome measures, and main results. The difference of opinions was resolved by consultation with the corresponding author (Li J), who made an independent assessment and provided the final judgment.

**Risk of bias assessment**

Two investigators (Zhang J and Huang JQ) independently evaluated the quality of the selected publications using the Cochrane Collaboration’s risk of bias tool. Assessments included random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other possible biases. Using relevant criteria listed in The Cochrane Handbook for Systematic Reviews of Interventions, the publications were categorized as having “low risk of bias,” “high risk of bias,” and “unclear risk of bias.”

**Statistical analyses**

Statistical analyses were performed using in The R Project for Statistical Computing (R version 3.5.1, Vienna, Austria, active worldwide), Generate Mixed Treatment Comparisons (Groningen, The Netherlands), and STATA 14.0 softwares (Texas, USA). Risk ratio and a 95% confidence interval were measured for dichotomous variables. Continuous data are presented as mean difference with 95% CI.

**RESULTS**

**Studies identified**

From among 2442 articles, 78 RCTs [7–84] were finally included.
in the NMA. All the RCTs were conducted in China and published in Chinese. Figure 1 shows the search process and study selection.

**Study characteristics**

All 78 RCTs were published between 2007 and 2019. A total of 5984 participants were included (3010 in the Chinese patent medicine-ACEI/ARB combination group and 2974 in the ACEI/ARB group). The sample sizes of the included studies ranged from 40 to 205. All 78 studies included the corresponding basic treatments in the treatment strategy. The duration of the combination treatment ranged from 4 to 48 weeks. Characteristics of the included trials are listed in Table 1.

**Quality of the included studies**

Randomized was mentioned in all 78 studies. However, only 24 trials claimed that they had used the random number table or random synthesis sequential. Only 2 trials mentioned single blind. In addition, all the trials did not mention allocation concealment. Therefore, the risk of bias of included studies was high. More details of the trials were presented in Figure 2.

**Outcome measures**

**Total effective rate**

All 78 RCTs included herein, all of which were dual-arm studies; therefore, a consistency test was not required. The effective evidence network of five therapeutic measures for early DN is shown in Figure 3.

NMA of 21 trials was conducted to compare the total effective rate of four Chinese patent medicines in the treatment of early DN. The results showed that the total effective rate of the Jinshuibao capsule-ACEI/ARB combination group and Huangkui capsule-ACEI/ARB combination groups was higher than that of the others, as shown in Figure 4.

**Quantitation of 24-h urine protein**

The 24-h UTP was reported in 28 studies. Only the Jinshuibao capsule-ACEI/ARB combination group demonstrated a reduced 24-h UTP level [Figure 5].

**Urine microalbumin excretion rate**

Forty-three studies reported UAER. The Niaoduqing granule-ACEI/ARB, Jinshuibao capsule-ACEI/ARB, and Bailing capsule-ACEI/ARB combination groups could reduce UAER. The Jinshuibao capsule-ACEI/ARB combination group compared to other groups, demonstrated a better effect to reduce UAER [Figures 6 and 7].

**Serum creatine**

Scr was reported in 56 studies. Jinshuibao capsule-ACEI/ARB, Huangkui capsule-ACEI/ARB, and Bailing capsule-ACEI/ARB combination groups could reduce UAER, and among them, the Jinshuibao capsule-ACEI/ARB combination group demonstrated a comparatively better effect [Figures 8 and 9].

**Blood urea nitrogen**

There were 30 studies that reported BUN values in their results. Only the Huangkui capsule-ACEI/ARB combination group reduced BUN values [Figure 10].

**Glycosylated hemoglobin**

Twenty-two studies reported HbA1c values in their results. The results show that only the Jinshuibao capsule-ACEI/ARB combination group reduced HbA1c values [Figure 11].

**Adverse reactions**

Twenty-six studies reported adverse reactions in their results. The results show that only the Bailing capsule-ACEI/ARB combination group reduced the incidence of adverse reactions, whether the other combinations could not [Figure 12].

**Publication bias of effective rate**

We used a funnel plot to visualize the publication bias of the effective rate. The scatter plot was generated using the effect value as the abscissa and sample size as the ordinate. Without any publication bias, the inverted funnel plot is basically appears symmetrical. However, because of publication bias, the inverted funnel plot is incomplete and partially asymmetrical. At present, the funnel plot was partially asymmetrical, which suggested the possibility of publication bias [Figure 13].

**Discussion**

**Significance of network meta-analysis**

DN belongs to consumption and thirst-associate illness in Chinese medicine and considered to be caused by kidney damage. The disease primarily affects the kidneys and often involves the liver, spleen, and other organs. Subsequently, the heart and lung are also affected, resulting in the Five Visceral...
### Table 1: Characteristics of the included studies

| Study ID | Participants (T/C) | Average age (years) | Therapeutic interventions | Course (weeks) | Outcomes | Mogensen stage |
|----------|--------------------|---------------------|---------------------------|---------------|----------|----------------|
| Hao 2015 | 24/24              | T: 42.8±10.2        | B                         | 4             | 1 3 4 5 6 | Phase III      |
|          |                    | C: 45.2±10.8        | A                         |               |          |                |
| Li 2016  | 34/34              | T: 57.6±6.5         | B                         | 12            | 2 4 5 6 7 | Phase III      |
|          |                    | C: 64.3±5.9         | A                         |               |          |                |
| Liu 2012 | 30/30              | T: 56.35±9.82       | B                         | 24            | 4 5 6    | Phase III      |
|          |                    | C: 56.45±9.86       | A                         |               |          |                |
| Shi 2016 | 29/28              | T: 51.3±9.2         | B                         | 12            | 4 5 6    | Phase III      |
|          |                    | C: 50.1±8.7         | A                         |               |          |                |
| Wang 2009| 32/32              | T: 57.45±9.82       | B                         | 24            | 4 5 6    | Phase III      |
|          |                    | C: 58.12±8.28       | A                         |               |          |                |
| Tao 2010 | 39/39              | T: 68.4±5.1         | C                         | 6             | 4        | I-III          |
|          |                    | C: 67.5±4.7         | A                         |               |          |                |
| Zhang 2015| 41/41             | 68.4±5.1            | C                         | 6             | 3 5      | I-III          |
| Ding 2016| 50/50              | 51±9.5             | C                         | 16            | 3 5 6    | I-III          |
| Wang 2007| 35/33              | T: 58.3±3.6         | C                         | 24            | 1        | I-III          |
|          |                    | C: 57.6±3.8         | A                         |               |          |                |
| Wei 2010 | 30/30              | 51                 | C                         | 8             | 3 5 6    | III            |
| Xu 2018  | 30/30              | T: 56.1±7.5         | C                         | 12            | 1 3 5 6 7 | I-III          |
|          |                    | C: 54.6±6.8         | A                         |               |          |                |
| Shen 2018| 30/30              | T: 58.2±4.5         | C                         | 12            | 5 6 7    | III            |
|          |                    | C: 59.1±4.3         | A                         |               |          |                |
| Zhang 2014| 41/41             | 50.4±10.2           | C                         | 8             | 5        | I-III          |
| Yang 2013| 30/30              | T: 50.8±7.3         | C                         | 12            | 5 6 7    | III            |
|          |                    | C: 49.1±7.9         | A                         |               |          |                |
| Huang 2010| 32/32             | T: 71.1±10.7        | C                         | 12            | 3 4 9    | III            |
|          |                    | C: 71.3±11.6        | A                         |               |          |                |
| Zhu 2017 | 53/53              | T: 52.9±10.8        | C                         | 8             | 4        | III            |
|          |                    | C: 54.6±10.4        | A                         |               |          |                |
| Liu 2017 | 41/41              | 63.3±5.7            | C                         | 8             | 1 3 5 6 7 | I-III          |
| Feng 2017| 43/43              | T: 46.92±2.11       | C                         | 4             | 1 3 5 6 7 | I-III          |
|          |                    | C: 47.02±2.06       | A                         |               |          |                |
| Lv 2012  | 28/28              | 36-57               | C                         | 12            | 2 4 5    | III            |
| Yu 2013  | 40/40              | 47.6±3.2            | C                         | 12            | 3        | I-III          |
| Xiang 2014| 60/60             | T: 52               | C                         | 12            | 1 3 4 5 7 | I-III          |
|          |                    | C: 51               | A                         |               |          |                |
| Zhang 2016| 33/34             | T: 56.4±3.3         | C                         | 12            | 5 7      | III            |
|          |                    | C: 55.6±4.1         | A                         |               |          |                |
| Cao 2007 | 30/30              | 60.18±14.25         | C                         | 24            | 4        | I-III          |
| Wang 2014| 22/22              | T: 69.2±7.6         | C                         | 12            | 1 2      | I-III          |
|          |                    | C: 68.6±5.2         | A                         |               |          |                |
| Gao 2013 | 100/105            | T: 57.3±5.7         | C                         | 12            | 3 5 6    | III            |
|          |                    | C: 59.3±5.2         | A                         |               |          |                |
| Shen 2015| 30/30              | T: 52.5±6.9         | C                         | 24            | 4 7      | I-III          |
|          |                    | C: 51.5±6.5         | A                         |               |          |                |
| Xiu 2016 | 55/55              | T: 53.2±6.8         | C                         | 12            | 2 4 7    | I-III          |
|          |                    | C: 52.8±5.7         | A                         |               |          |                |
| Wu 2016  | 34/34              | T: 52.12±3.23       | C                         | 8             | 1 5 6    | I-III          |
|          |                    | C: 50.56±4.12       | A                         |               |          |                |
| Wang 2018| 40/40              | T: 54.8±11          | C                         | 12            | 1        | I-III          |
|          |                    | C: 55.4±10.1        | A                         |               |          |                |
| Zhang 2014| 30/30             | 64±6.3              | C                         | 8             | 5 6      | I-III          |
| Li 2012  | 38/38              | T: 48.6             | C                         | 4             | 1        | I-III          |
|          |                    | C: 49.3             | A                         |               |          |                |

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### Table 1: Contd...

| Study ID     | Participants (T/C) | Average age (years) | Therapeutic interventions | Course (weeks) | Outcomes | Mogensen stage |
|--------------|--------------------|---------------------|---------------------------|----------------|----------|----------------|
| Chen 2010    | 20/20              | T: 60.84±6.4        | C A                        | 8              | 2③④⑤⑥ | I-III          |
|              |                    | C: 61.21±6.1        |                           |                |          |                |
| Gao 2018     | 76/76              | T: 67.20±5.34       | C A                        | 6              | 5⑥⑦     | I-III          |
|              |                    | C: 67.19±5.21       |                           |                |          |                |
| Dai 2016     | 45/45              | T: 52±7.5           | C A                        | 28             | 3④⑤⑦    | I-III          |
|              |                    | C: 51±7.5           |                           |                |          |                |
| Ge 2011      | 45/45              | 57.4                | C A                        | 8              | ①②③④     | I-III          |
| Pan 2016     | 40/40              | T: 64.5±4.7         | C A                        | 12             | ③⑤⑥     | I-III          |
|              |                    | C: 65.7±5.2         |                           |                |          |                |
| Zhou 2016    | 48/48              | T: 65.9±2.4         | D A                        | 8              | ④⑤      | III            |
|              |                    | C: 66.3±2.3         |                           |                |          |                |
| Ou 2015      | 30/30              | T: 54±4.8           | D A                        | 12             | ②③⑥⑦    | I-III          |
| Li 2014      | 3/33               | T: 49.2±18.2        | D A                        | 16             | ③④⑤⑦    | I-III          |
|              |                    | C: 49.3±16.9        |                           |                |          |                |
| Lin 2011     | 30/30              | T: 47.4±5.23        | D A                        | 8              | ②④⑤     | III            |
|              |                    | C: 46.85±4.95       |                           |                |          |                |
| Li 2015      | 36/36              | 48.3±8.6            | D A                        | 12             | ③④⑤     | III            |
| Jia 2015     | 38/32              | T: 50.3±15.50       | D A                        | 4              | ②③⑤⑦    | I-III          |
|              |                    | C: 52.5±14.61       |                           |                |          |                |
| Li 2017      | 60/60              | T: 61.5±5.0         | D A                        | 8              | ①②      | I-III          |
|              |                    | C: 62.0±4.5         |                           |                |          |                |
| Zhou 2007    | 60/37              | Unclear             | D A                        | 8              | ①②      | I-III          |
| Hu 2011      | 40/40              | Unclear             | D A                        | 8              | ①③④⑥    | I-III          |
| Xiao 2010    | 33/32              | T: 57.98±16.07      | D A                        | 16             | ③④⑤⑦    | I-III          |
|              |                    | C: 58.53±16.24      |                           |                |          |                |
| Liang 2013   | 25/25              | 43.2±12.8           | D A                        | 8              | ②④      | I-III          |
| Ding 2019    | 55/55              | T: 56.35±6.34       | D A                        | 12             | ①⑤⑥    | I-III          |
|              |                    | C: 56.75±7.37       |                           |                |          |                |
| Li 2010      | 39/33              | T: 52±8.1           | D A                        | 8              | ①②      | I-III          |
|              |                    | C: 53±7.6           |                           |                |          |                |
| Ma 2016      | 40/40              | 49.1±4.6            | D A                        | 6              | ②④⑤⑦    | III            |
| Cai 2010     | 25/25              | T: 45.66±12.23      | D A                        | 8              | ②④⑤⑦    | III            |
|              |                    | C: 44.89±12.75      |                           |                |          |                |
| Jin 2018     | 54/54              | T: 58.4±5.9         | D A                        | 8              | ①②⑤     | III            |
|              |                    | C: 55.4±5.9         |                           |                |          |                |
| Li 2014      | 48/47              | 48.3±11.41          | D A                        | 6              | ②④⑤⑥    | III            |
| Deng 2014    | 30/30              | T: 42.3±11.8        | D A                        | 16             | ②④⑤     | I-III          |
|              |                    | C: 45.3±12.4        |                           |                |          |                |
| Guo 2015     | 68/68              | T: 42.5±11.5        | D A                        | 8              | ①②④⑤⑥  | I-III          |
|              |                    | C: 43.1±10.9        |                           |                |          |                |
| Dai 2017     | 40/40              | T: 46.21±12.13      | D A                        | 12             | ②③⑤⑥    | I-III          |
|              |                    | C: 47.24±11.18      |                           |                |          |                |
| Tang 2017    | 42/42              | T: 57.0±9.5         | D A                        | 8              | ②③④⑤⑦  | I-III          |
|              |                    | C: 56.1±10.4        |                           |                |          |                |
| Qian 2013    | 36/34              | 47.6±6.5            | D A                        | 24             | ②④⑤⑥⑦  | I-III          |
| Qu 2013      | 25/31              | 45.3±1.2            | D A                        | 24             | ②④⑤⑥⑦  | I-III          |
| Hu 2016      | 20/20              | T: 57.5±5.7         | D A                        | 8              | ①③④⑥⑦  | I-III          |
|              |                    | C: 56.3±5.6         |                           |                |          |                |
| Qi 2016      | 42/42              | T: 61.4±10.7        | D A                        | 12             | ④⑤⑥⑦   | I-III          |
| Song 2009    | 30/30              | T: 51.2±17.2        | E A                        | 16             | ③④⑤⑦   | III            |
|              |                    | C: 50.3±16.7        |                           |                |          |                |

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Table 1: Contd...

| Study ID | Participants (T/C) | Average age (years) | Therapeutic interventions | Course (weeks) | Outcomes | Mogensen stage |
|----------|---------------------|---------------------|---------------------------|----------------|----------|----------------|
| Wang 2009 | 25/25 | Unclear | E: Combination, A: Control | 12 | ④⑤ | III |
| Ma 2011 | 25/25 | T: 48.1±9.3, C: 46.2±7.9 | E: Combination, A: Control | 12 | ④⑤⑦ | I-III |
| Luo 2011 | 40/40 | Unclear | E: Combination, A: Control | 12 | ④⑤ | III |
| Luo 2018 | 31/31 | T: 53.61±12.86, C: 54.75±10.69 | E: Combination, A: Control | 12 | ①3④⑤⑥ | III |
| Wang 2016 | 50/50 | 69.5±7.0 | E: Combination, A: Control | 24 | ①2③④⑥⑦ | I-III |
| Ye 2016 | 26/26 | T: 54±5, C: 55±5 | E: Combination, A: Control | 4 | ④③ | III |
| Zhu 2015 | 45/40 | T: 57.4±6.4, C: 57.5±6.9 | E: Combination, A: Control | 16 | ⑤⑥ | III |
| Wang 2008 | 30/30 | Unclear | E: Combination, A: Control | 12 | ④⑤ | III |
| Jin 2016 | 50/50 | T: 55.3±9.8, C: 54.1±10.1 | E: Combination, A: Control | 12 | ①③⑤⑥ | III |
| Guan 2010 | 31/31 | T: 53.3±5.7, C: 52.2±6.5 | E: Combination, A: Control | 24 | ⑤⑦ | III |
| Liu 2011 | 32/32 | T: 54±17, C: 52±14 | E: Combination, A: Control | 12 | ③⑤ | III |
| Qiao 2013 | 62/62 | T: 55.9±11.8, C: 54.6±12.4 | E: Combination, A: Control | 12 | ②④ | III |
| Wu 2014 | 30/30 | 57.3±9.4 | E: Combination, A: Control | 12 | ④⑤⑦ | III |
| Chen 2010 | 28/26 | 36.73 | E: Combination, A: Control | 8 | ③④ | III |
| Cao 2015 | 45/45 | T: 57.8±6.0, C: 57.4±6.1 | E: Combination, A: Control | 16 | ②⑤⑥ | III |
| Xie 2013 | 34/34 | T: 63.4±8.7, C: 62.2±7.9 | E: Combination, A: Control | 4 | ③⑤ | I-III |

A: ACEI/ARB, B: Niaoduqing granule+A, C: Jinshuibao capsule+A, D: Huangkui capsule+A, E: Bailing capsule+A, ①: Total effective rate, ②: Adverse reaction, ③: 24h UTP, ④: UAER, ⑤: Scr, ⑥: BUN, ⑦: HbAl: Glycosylated hemoglobin, 24-h UTP: 24-h urinary protein excretion, UAER: Urinary microalbumin excretion, BUN: Blood urea nitrogen, Scr: Serum creatinine

Figure 2: Risk of bias graph

Disease. Ancient physicians treated it as kidney deficiency, whereas modern physicians also focus on blood stasis.

Niaoduqing granule is composed of 16 traditional Chinese medicines, the synergistic effect of these components can improve renal function through multiple targets and pathways, and effectively slow the development of DN.[85] Several clinical studies have also reported that Niaoduqing granule improves renal function, and prevents glomerulosclerosis and renal interstitial fibrosis. In addition, it can also protect the endothelial function of patients with DN.[86] Cai HD reported that yellow sunflowers from Sichuan, a traditional Chinese herbal medicine, are widely used in the treatment of renal diseases in China, it reduces diuresis, reduces swelling and aids detoxification. It is found that the Huangkui capsule, extracted from Sichuan yellow sunflowers, confers nephroprotection by reducing the contents of urinary protein, Scr and BUN in

Figure 3: Network meta-analysis of five therapeutic measures
nephrotic rats, however, the underlying mechanism needs further exploration.\(^\text{[87]}\) Ma T found that there were four active ingredients of Huangkui capsule, which confers a protective effect on the kidneys.\(^\text{[88]}\) The Jinshuibao capsule is composed of artificially fermented Cordyceps sinensis hyphae (cs-4 strain), which can strengthen the lungs and kidneys, fills essence, and invigorates the qi.\(^\text{[89]}\) It can relieve cough, reduce blood lipid levels and inflammation, strengthen the heart and lungs, and prevent plaque to accumulation. Relevant studies have shown that Jinshuibao capsule can effectively improve the phenomenon of renal blood perfusion in patients, prevent the impairment of the physiological function of renal tubules from being impaired, and effectively inhibit the fibrosis of renal tubules.\(^\text{[90]}\) Bailing capsule is a commonly marketed artificial preparation made from Cordyceps sinensis hyphae. The pharmacologically active ingredient is present in the artificial extract of Cordyceps mycelia and has become an excellent substitute for natural Cordyceps sinensis. Clinical studies and animal experiments show that Bailing capsule can tonify and benefit the lungs and kidneys and has the ideal clinical effect of renal function improvement in patient with DN.\(^\text{[91]}\) These four kinds of common Chinese patent medicines demonstrate good curative effects in a patient with DN, and therefore, can be used as excellent supplements in routine treatment using western medicine. Therefore, the NMA of four different Chinese patent medicines combined with ACEI/ARB in the treatment of early DN was a pressing necessity.

**Summaries of results**

Seventy-eight RCTs were analyzed in the present study to evaluate the clinical effects of the four Chinese patent medicines-ACEI/ARB combinations in patients with early DN. A total of 5984 participants were included (3010 in the Chinese patent medicine-ACEI/ARB combination group and 2974 in the ACEI/ARB group). NMA showed that the total effective rate of Jinshuibao capsule and Huangkui capsules were better than the others; Jinshuibao capsule demonstrated superior effect to reduce the 24-h UTP, UAER, Scr, and HbAlc levels. Huangkui capsule was comparatively more...
effective to reduce BUN levels. However, only the Bailing capsule-ACEI/ARB combination group had less incidence of adverse reactions.

**Limitations**

1. The literature included in this study was not of superior quality. All the 78 trials included in this study described the use of randomization. However, no study provided the randomization protocol, and only 2 trials used blinded methods. These might have caused measurement bias and may have an impact on the overall quality of the NMA.

2. The risk of bias among the included studies was high and may affect the strength of the results. Most trials with positive findings had a small sample size. All the included RCTs were published in Chinese.

3. The trials included in this study had different treatment courses (range 4–48 weeks), many of which were short, had small sample size, lacked multicenter collaboration, and had differences in the evaluation of clinical efficacy judgment, all of these factors may have affected the reliability of the study results. Studies that reported adverse reactions were few, which might have contributed to limited research evidence.

**Conclusion**

The results in this study suggested that the combined treatment with Jinshuibao and Huangkui capsules with ACEI/ARB had superior effects on the total effective rate than treatment with ACEI/ARB. Jinshuibao capsule can reduce the 24-h UTP, UAER, Scr, and HbA1c levels, whereas, the Huangkui capsule could reduce BUN levels better than other treatment groups. However, compared with the ACEI/ARB group, only Bailing capsule-ACEI/ARB combination group demonstrated reduced the incidence of adverse reactions. The others cannot reduce the occurrence of adverse reactions. Adverse reactions primarily included cough, diarrhea, and fatigue. None of the adverse reactions required intervention. This observation, however, may have been caused by insufficient sample sizes of the included studies. Therefore, a more rigorous randomized, double-blind, multicenter, with a sufficiently large cohort is needed in future to validate the efficacy of Chinese patent medicines in combination with ACEI/ARB in the treatment of early DN. The Chinese patent medicines may have a significantly superior role in the treatment of early DN.

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**Conflicts of interest**

There are no conflicts of interest.

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