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Original Article

Effects of Niaoduqing Particles (尿毒清颗粒) on Delaying Progression of Renal Dysfunction: A Post-trial, Open-Label, Follow-up Study*

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ABSTRACT **Objective:** To follow up the participants of the randomized clinical trial "Efficacy and Safety of Niaoduqing Particles (尿毒清颗粒) for Delaying Moderate-to-Severe Renal Dysfunction", and assess the long-term effects of Niaoduqing Particles on delaying the progression of renal dysfunction. **Methods:** Participants, who had previously been randomly assigned to receive Niaoduqing Particles or placebo for 24 weeks (146 cases in each group), were invited to follow-up and all were administered Niaoduqing Particles 5 g thrice daily and 10 g before bedtime for 24 weeks. The primary endpoints were changes in baseline serum creatinine (Scr) and estimated glomerular filtration rate (eGFR) after completion of the open-label treatment period. **Results:** After the double-blind period, the median (interquartile range) changes in Scr were 1.1 (–13.0–24.1) and 11.7 (–2.6–42.9) μmol/L for the Niaoduqing Particle and placebo groups, respectively (P=0.008), and the median changes in eGFRs were –0.2 (–4.3–2.7) and –2.21 (–5.7–0.8) mL•min^{-1}•1.73 m^{-2}, respectively (P=0.016). There were significant differences in the double-blind period changes in renal function between groups. After the open-label period, the median changes in Scr were 9.0 (–10.0–41.9) and 17.5 (–6.0–50.0) μmol/L for the Niaoduqing Particle and placebo groups according to baseline grouping, respectively (P=0.214), and the median changes in eGFRs were –2.3 (–6.4–1.9) and –3.7 (–7.5–1.1) mL•min^{-1}•1.73 m^{-2}, respectively (P=0.134). There were no statistical differences in the open-label period changes in renal function between groups. The eGFR reduction of participants who accepted Niaoduqing Particle treatment for 48 weeks was projected to 2.5 mL•min^{-1}•1.73 m^{-2} per year. **Conclusions:** Niaoduqing Particles appear to have long-term efficacy for patients with moderate-to-severe renal dysfunction. Although there was no statistical difference, the early use of Niaoduqing Paticles seems to ameliorate the worsening of renal function. (Trial registration No. ChiCTR-TRC-12002448)

KEYWORDS chronic kidney disease, moderate-to-severe renal dysfunction, Niaoduqing Particles, post-trial follow-up, Chinese medicine

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Over the last two decades, the high prevalence and suboptimal prognosis of chronic kidney disease (CKD) have been clearly established through many surveys, cohorts, and clinical trials.[1] The ideal therapeutic goal for CKD is to correct abnormal renal function and maintain the average speed of age-related renal functional decline in long term. Although some animal experiments have achieved regression of CKD, there are few examples in clinical practice.[2,3] After years of effort, blood pressure control and blockade of the renin-angiotensin system (RAS) are still the major methods of retarding CKD progression.[4]

Current potential approaches to delay renal failure include using high-dose RAS inhibitors,[5] selective inhibitors of protein kinase C,[6] endothelin blockers,[7] and anti-inflammatory drugs.[8] However, clinical trials of these drugs were either terminated early for adverse events or required further evaluation.[8,9] To improve the treatment of CKD, we need to introduce novel strategies and multifaceted approaches to interrupt multiple mechanisms of renal disease progression.[10] In recent years, there are a lot of theoretical and experimental research of Chinese medicine (CM) on CKD.[11,12] And researchers have detected the multi-targeted renoprotective mechanisms of CM Niaoduqing Particles (尿毒清颗粒) through experiments both *in vivo* and *in vitro*.[13,14] This evidence from basic research and previous clinical practice prompted us to evaluate Niaoduqing Particles using modern well-established clinical research methods.

The study of the "Efficacy and Safety of Niaoduqing Particles for Delaying Moderate-to-Severe Renal Dysfunction" was a randomized, double-blind, placebo-controlled, multi-center clinical study.[15] In the study, we found that relative to baseline, estimated glomerular filtration rate (eGFR) at 24 weeks in the Niaoduqing group increased by –0.2 (–4.3–2.7) mL•min^{-1}•1.73 m^{-2}, while the placebo group increased by –2.2 (–5.7–0.8) mL•min^{-1}•1.73 m^{-2} (P=0.016). Therefore, Niaoduqing Particles are supported as a promising medication for patients with moderate-to-severe renal dysfunction. We subsequently hypothesized that early use of Niaoduqing Particles could better delay renal dysfunction. To test this hypothesis, participants, who had previously finished the double-blind trial period, were invited to follow up for another 24 weeks with Niaoduqing Particles administration.

METHODS

Subjects

The original study was a prospective, randomized, double-blind, placebo-controlled, multicenter clinical trial (No. ChiCTR-TRC-12002448). In brief, in the double-blind trial, 300 eligible CKD patients were recruited from 22 hospitals in 11 Chinese provinces. A competitive block randomization was used and the randomized block was produced by SAS 9.2 software. Patients were randomized in a 1:1 ratio to either a Niaoduqing group, which was administered Niaoduqing Particles 5 g thrice daily and 10 g before bedtime for 24 weeks, or a control group, which was administered a placebo with the same regimen.

The Ethics Committee of the Chinese People's Liberation Army General Hospital reviewed and approved the study protocol (No. 2012032-02). All participants provided signed informed consent before entering the study. The detailed study design and results had been published.[15]

Open-Label Period Follow-up

Participants, who had previously been assigned to Niaoduqing Particles or placebo for 24 weeks, were invited to follow-up, and all were administered Niaoduqing Particles 5 g thrice daily and 10 g before bedtime for 24 weeks.

Quality Control of Niaoduqing Particles

The composition of the Niaoduqing Particles includes 16 herbs: *Rheum palmatum*, *Atractylodes macrocephala*, *Poria cocos*, *Fallopia multiflora*, *Salvia miltiorrhiza*, *Plantago depressa*, *Astragalus membranaceus*, *Morus alba* L., *Paeonia lactiflora*, *Codonopsis pilosula*, *Ligusticum chuanxiong hort*, *Dendranthema morifolium*, *Sophora flavescens aiton*, *Pinellia ternata*, *Bupleurum chinense* and *Glycyrrhiza uralensis*. Medication preparation and manufacturing included boiling, concentrating, and drying (Consun Pharmaceutical Group, China; 5 g/pack, 15 packs/packet; lot No. 20120507, 20120508). Raw materials were examined according to the current edition of the Chinese Pharmacopoeia, and the production process abided with Good Manufacturing Practices for Drugs and State Food and Drug Administration drug standards: new drug registration standard 26 WS3-229 (Z-033-2000 [Z]) requirements.

Chin J Integr Med 2019 Mar;25(3):168-174

Observation Index

The primary endpoints were changes in baseline serum creatinine (Scr) and eGFR after completion of the open-label period treatment. A central laboratory used an enzymatic method to examine Scr (COBAS Integra 800, Roche Co., Switzerland; Scr, 1 mg/dL=88.4 μmol/L) and the Chinese version of the Modification of Diet in Renal Disease (MDRD) equation to measure eGFR ($eGFR=175\times Scr^{-1.234}\times age^{-0.179}$ [$\times 0.79$ if female]).[16] The secondary endpoints were changes in 24-h urinary protein excretion (24-h UPE) between baseline and completion of the open-label period treatment. Participants were instructed to collect urine over 24 h (from 7:00 AM to 7:00 AM next day). A medical flask was used to measure total urine output. After stirring, 10 mL of urine was preserved at –40 ℃. Protein concentration was measured using the Biuret method (Siemens; ADVIA® 2400 Clinical Chemistry System), and 24-h UPE was calculated based on multiplying protein concentration by 24-h urine volume.

Statistical Analysis

Normally distributed quantitative data were described using means ± standard deviations ($\bar{x}\pm s$), non-normally distributed quantitative data were described using medians (interquartile ranges, IQR), and qualitative data were described using proportions. A *t*-test or Wilcoxon rank sum test was used to compare quantitative data between the groups based on data distribution, and the chi-square or Fisher exact tests were used to compare qualitative data. All statistical tests were two-tailed, and a *P* value of less than 0.05 was considered statistically significant. SAS 9.2 software was used for statistical analyses.

RESULTS

Characteristics of Follow-up Patients

The patient enrollment protocol for the double-blind trial period was published previously.[15] As shown in Figure 1, 146 participants in each group entered the full analysis set (FAS). The characteristics of the entire trial cohort at baseline, post-double-blind period and post-open-label period are shown according to the original study-group assignments, and there were no significant differences at the three periods between Niaoduqing and placebo groups (age: 50.8 ± 11.7 *vs*. 50.7 ± 11.9 years; male proportion: 56.9% *vs*. 56.2%, *P*>0.05, Table 1).

Primary Outcomes

At baseline, and after the double-blind period and open-label period, there were no significant differences in median Scr between the groups (*P*=0.933, 0.157, and 0.158, respectively). However, there was a significant difference between the two treatment groups in the change of Scr after 24-week treatment compared with that of the baseline, with the Niaoduqing and placebo groups increasing by 1.1 (–13.0–24.1) and 11.7 (–2.6–42.9) μmol/L, respectively (*P*=0.008). After 48-week treatment, the changes in Scr compared with the baseline value were 9.0 (–10.0–41.9) and 17.5 (–6.0–50.0) μmol/L in the Niaoduqing and placebo

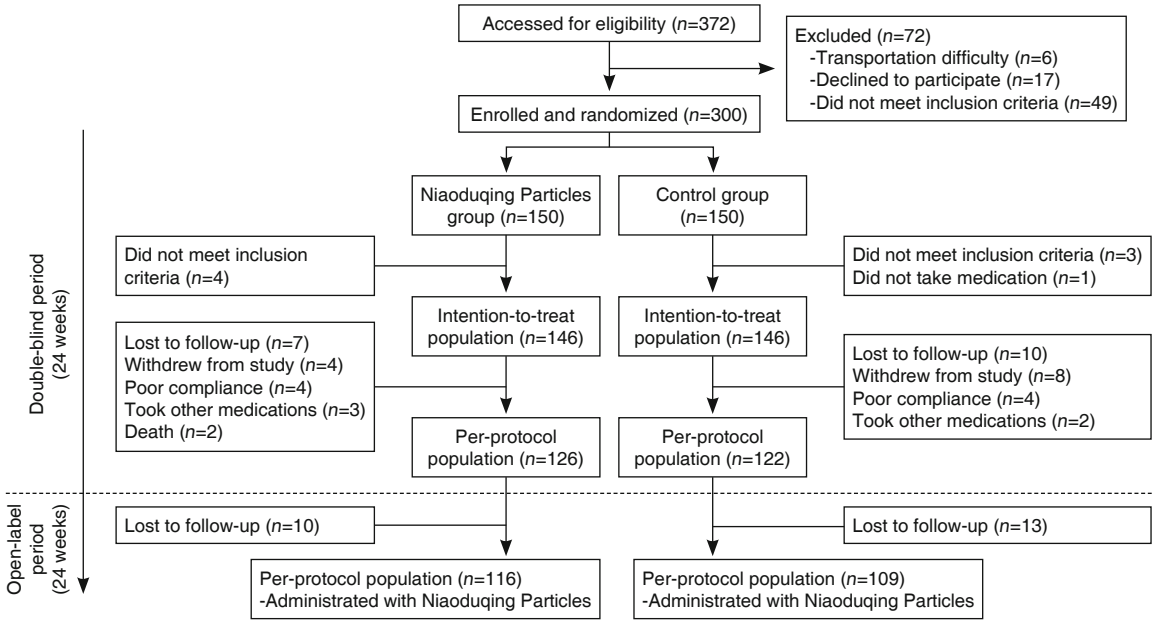

Figure 1. Flow Diagram of Study on Niaoduqing Particles for Treatment of CKD Patients

Table 1. Clinical Characteristics of CKD Participants [Median (IQR)]

Group	Time	Scr (μmol/L)	eGFR (mL•min^{-1}•1.73 m^{-2})	24-h UPE (g)	SBP (mm Hg)	DBP (mm Hg)
Niaoduqing (*n*=146)	Baseline	191.6 (162.0–223.8)	31.0 (24.0–37.1)	1.1 (0.4–2.1)	130.0 (125.0–134.0)	80.0 (75.0–82.0)
	Post-double-blind period	198.6 (164.7–239.6)	29.4 (23.5–35.9)	1.3 (0.4–2.6)	130.0 (125.0–135.0)	80.0 (77.0–85.0)
	Post-open-label period	196.1 (164.6–236.9)	29.0 (23.5–34.9)	1.0 (0.5–1.9)	130.0 (124.0–136.0)	80.0 (75.0–85.0)
Placebo (*n*=146)	Baseline	185.0 (166.0–226.0)	30.6 (24.6–36.4)	0.8 (0.3–1.7)	130.0 (120.0–135.0)	80.0 (75.0–85.0)
	Post-double-blind period	203.1 (172.9–252.7)	28.0 (21.0–34.3)	1.1 (0.4–2.1)	130.0 (125.0–140.0)	80.0 (75.0–85.0)
	Post-open-label period	206.9 (175.6–253.5)	27.7 (20.6–33.6)	0.9 (0.4–2.1)	130.0 (125.0–135.0)	80.0 (74.0–84.0)

Notes: IQR: interquartile range; eGFR: estimated glomerular filtration rate; Scr: serum creatinine; SBP: systolic blood pressure; DBP: diastolic blood pressure; UPE: urinary protein excretion

groups, respectively (*P*=0.214). There was no significant difference between the two groups in Scr change between 24 and 48 weeks (*P*=0.854). As shown in Figure 2A, after 24 weeks, the median changes in Scr were 0.51% and 6.4%, respectively (*P*=0.01). After 48 weeks, the median changes were 5.6% and 10.3%, respectively (*P*=0.159).

At baseline, after the double-blind period and open-label period, there was no significant difference in the median eGFR between the Niaoduqing and placebo groups (*P*=0.961, 0.083 and 0.161, respectively). However, compared with the baseline value, the eGFR at 24 weeks in the Niaoduqing and placebo groups increased by –0.2 (–4.3–2.7) and –2.21 (–5.7–0.8) mL•min^{-1}•1.73 m^{-2} (*P*=0.016). After 48 weeks, the changes in eGFR compared with the baseline value were –2.3 (–6.4–1.9) and –3.7 (–7.5–1.1) mL•min^{-1}•1.73 m^{-2} in the Niaoduqing and placebo groups (*P*=0.134). Comparing the changes in eGFR between 24 and 48 weeks, there was no significant difference between the two groups (*P*=0.930). As shown in Figure 2B, after 24 weeks, the median changes were –0.63% and –7.4%, respectively (*P*=0.01); and after 48 weeks, the median changes were –6.5% and –11.4%, respectively (*P*=0.159).

Secondary Outcomes

At baseline, post-double-blind period (24-week), and post-open-label period (48-week) treatment, there were no significant differences in median 24-h UPE between the groups (*P*=0.210, 0.409, and 0.805, respectively). Compared with that of the baseline, the 24-h UPE after the double-blind period in the Niaoduqing group increased by 0.06 (–0.3–0.9) g, while the 24-h UPE in the placebo group increased by 0.02 (–0.2–0.6) g (*P*=0.525). Compared with that of the baseline, the 24-h UPE after the open-label period in the Niaoduqing group increased by 0.03 (–0.3–0.5) g, while that in the placebo group increased by 0.08 (–0.2–0.4) g (*P*=0.850).

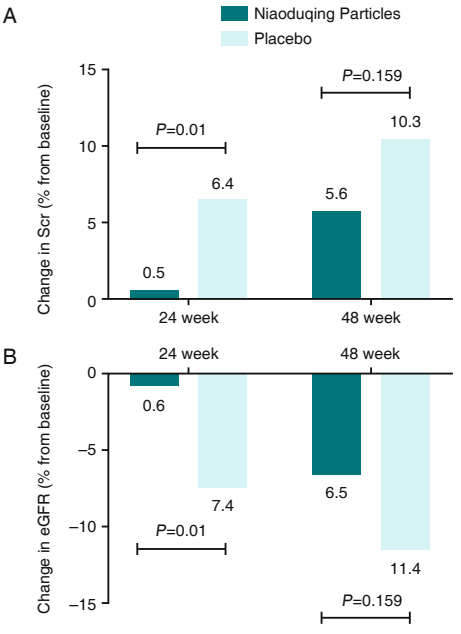

Figure 2. Changes in Kidney Functional Parameters of CKD Patients in Niaoduqing and Placebo Groups

Notes: Scr: serum creatinine; eGFR: estimated glomerular filtration rate

Post-hoc Analysis

We also analyzed the changes in eGFR in the subgroups relative to baseline eGFR, after grouping according to 24-h UPE <1.5 g or ⩾1.5 g (Table 2). In the subgroups of 24-h UPE <1.5 g, there was no difference in eGFR at baseline, 24 and 48 weeks (*P*=0.801, 0.210 and 0.195, respectively). After 24-week treatment, the median eGFR in the Niaoduqing group were not different from baseline (*P*=0.485), but decreased in the placebo group (*P*=0.011). After 48-week treatment, the median eGFR was not different from baseline in the Niaoduqing group (*P*=0.645), but decreased significantly from baseline in the placebo group (*P*<0.001). At 48 weeks, eGFR changes from baseline was significant different

Chin J Integr Med 2019 Mar;25(3):168-174

Table 2. Changes in eGFR when 24-h UPE < or ⩾1.5 g in CKD Patients at Three Periods [mL·min^{-1}·1.73 m^{-2}, Median (IQR)]

24-h UPE	Group	Case	eGFR			Change of eGFR		
			0 week	24 week	48 week	0 *vs*. 24 week	0 *vs*. 48 week	24 *vs*. 48 week
<1.5 g	Niaoduqing	82	30.4 (23.8–37.6)	30.3 (24.4–37.3)	30.0 (24.2–37.3)	0.3 (–3.2–3.8)*	0.0 (–4.3–3.4)*	–0.1 (–3.6–1.5)
	Placebo	100	30.6 (24.6–35.3)	29.3 (22.4–35.0)	28.2 (22.9–34.7)	–0.9 (–5.1–1.8)$^{\triangle}$	–1.9 (–6.6–1.2)$^{\triangle\triangle}$	0.0 (–3.7–1.2)$^{\triangle}$
⩾1.5 g	Niaoduqing	61	31.3 (25.1–37.0)	27.5 (21.5–33.8)	26.2 (20.2–33.1)	–2.8 (–7.4–0.6)$^{\triangle\triangle}$	–4.4 (–10.2–0.0)$^{\triangle\triangle}$	0.0 (–3.7–0.5)$^{\triangle}$
	Placebo	41	31.2 (25.8–37.9)	22.8 (19.0–32.5)	22.3 (17.7–32.4)	–4.7 (–8.7–1.5)$^{\triangle\triangle}$	–4.9 (–10.1–1.5)$^{\triangle\triangle}$	0.0 (–3.2–1.1)

Notes: Because of missing values, the number of participants were not equal in 24-h UPE to total number of FAS. UPE, urinary protein excretion; IQR, interquartile range; eGFR, estimated glomerular filtration rate; $^{*}P$<0.05 *vs*. placebo group; $^{\triangle}P$<0.05, $^{\triangle\triangle}P$<0.01, comparison between different periods

between the two groups (P=0.024). Although there was no statistical difference in eGFR changes in the two groups between 24 and 48 weeks (P=0.893), eGFR in the placebo group deceased significantly from 24 weeks (P=0.036), and no change in the Niaoduqing group was observed (P=0.087).

In the subgroups of 24-h UPE ⩾1.5 g, there was no difference in eGFR at baseline between groups (P=0.856). After the double-blind period treatment (24 weeks), the median eGFR change from baseline decreased 2.8 mL·min^{-1}·1.73 m^{-2} in the Niaoduqing group (P<0.001), and 4.7 mL·min^{-1}·1.73 m^{-2} in the placebo group (P<0.001). After the open-label period treatment (48 weeks), the median eGFR change from baseline decreased 4.4 mL·min^{-1}·1.73 m^{-2} in the Niaoduqing group (P<0.001), and 4.9 mL·min^{-1}·1.73 m^{-2} in the placebo group (P<0.001).

DISCUSSION

Following the cohorts for a total of 48 weeks, including the double-blind period and the open-label period, we observed deferred but still significant eGFR reductions in both treatment groups. However, it is interesting that, comparing the changes in eGFR between the post-double-blind and post-open-label periods, there was no significant difference between the Niaoduqing and placebo groups. Considering that both groups were administered Niaoduqing Particles during the open-label period, our results support our previous conclusion that Niaoduqing Particles can delay renal functional decline in patients with CKD stage 3b and 4.[15] In addition, the group with 48 weeks of Niaoduqing particle treatment had less severe eGFR deterioration compared to that of the group with 24 weeks of Niaoduqing Particle treatment. Although there was no statistical difference, this suggests that early use of Niaoduqing particle could delay renal dysfunction more effectively.

In patients with diabetic nephropathy, RAS blockers and blood pressure maintenance have been reported to reduce eGFR decline to 5–6 mL·min^{-1}·1.73 m^{-2} per year.[10] Similarly, in non-diabetic nephropathy patients with significant proteinuria, eGFR decline was delayed by 6–8 mL·min^{-1}·1.73 m^{-2} per year.[17] In the present study, all participants had blood pressures of less than 140/90 mm Hg, and the median baseline 24-h UPE levels were 1.1 and 0.8 g for the Niaoduqing and the placebo groups (with significant proteinuria), respectively. After 48 weeks of Niaoduqing Particle treatment in our study, the eGFR reduction was 2.3 mL·min^{-1}·1.73 m^{-2} (projected to 2.5 mL·min^{-1}·1.73 m^{-2} per year), significantly less than previous study using RAS blockers.

Overt proteinuria is one the most important risk factor of CKD progression.[18] Le, et al[19] reported that patients with time-average proteinuria (TA-P) > 1.0 g/day were associated with a 9.4-fold higher risk of CKD progression than patients with TA-P < 1.0 g/day (P<0.001). Regarding our participants with overt proteinuria, we did post-hoc analysis according to their 24-h UPE at baseline. We found that in the subgroups with 24-h UPE <1.5 g, there was no difference in eGFR between baseline and 48 weeks of Niaoduqing Particle treatment. However, in the subgroup with 24-h UPE ⩾1.5 g, the median eGFR decreased after 48 weeks of Niaoduqing Particle treatment compared with baseline (P<0.001). Indeed, our results also suggest that it is hard to retard the speed of eGFR reduction with significant proteinuria (e.g., 24-h UPE ⩾1.5 g). The 24-h UPE in both groups was not significantly different between baseline and post-double-blind period treatment. However, the post-hoc analysis showed that Niaoduqing Particle treatment delayed the renal functional reduction more significantly than did placebo in the 24-h UPE <1.5 g subgroup and there was a similar trend in the 24-h UPE ⩾1.5 g

subgroup, despite showing no statistical difference. Our results suggest that the effect of delaying renal functional decline with Niaoduqing Particles was independent of proteinuria reduction.

CKD progression is linked to many pathological mechanisms. Niaoduqing Particles are a compound of multiple plants with multi-targeted renoprotective effects. As a compound CM, Niaoduqing Particles have been discovered to have a wide range of biological activities, including alleviating the symptoms of chronic renal failure, and tubulointerstitial fibrosis, as well as regulating the function of cytokines, synthesis of extracellular matrix, and infiltration of monocytes and macrophages.[20] In addition, the main active ingredients of Niaoduqing Particles include rhubarb that regulates lipopolysaccharide-induced toll-like receptor 4 and reduces the expression of tumor necrosis factor-alpha and interleukin-6, all three of which are synthesized by renal tubular epithelial cells;[21] astragaloside that acts as both an anti-inflammatory and antifibrotic agent;[22,23] and prevents contrast-induced nephropathy in patients with acute coronary syndrome.[24-26]

The strengths of our study include: 1) focusing on a high-risk population with rapid CKD progression and limited treatment; 2) participants were representative of Chinese CKD patients because of the national, multi-center design; 3) using a study cohort that was derived from a randomized trial, and, therefore, the baseline characteristics were well-balanced between both groups.

Our post-trial analysis has some limitations. First, 48-week follow-up was insufficient to assess endpoints, of end-stage renal disease, cardiovascular disease, and death. Second, our study cohort was derived from a randomized trial of patients, and therefore, the results may have limited extrapolation to broader populations. Third, the changes in eGFR classified by baseline 24-h UPE were based on post-hoc analysis, so they must be interpreted with caution.

In conclusion, 48 weeks of Niaoduqing Particles treatment appeared to have long-term efficacy for patients with moderate-to-severe renal dysfunction. Although there was no statistical difference, it is suggested that early use of Niaoduqing Particles improves the deterioration of renal function. Longer and larger population studies are needed to clarify the long-term effects of Niaoduqing Particles on renal and cardiovascular outcomes.

Conflict of Interest

Consun Pharmaceutical Group (Guangzhou, Guangdong, China) provided the Niaoduqing Particles and placebo. The Consun Pharmaceutical Group had no participation or influence on the study design, data collection, statistical analysis, and interpretation of results.

Author Contributions

Chen XM, Cai GY, Yao C, and Hu Z contributed to the conception and design; Zheng Y, Chen XM, Cai GY, and Yao C contributed to the analysis and interpretation of the data; Zheng Y, Chen XM, Cai GY contributed to the writing of the article; WEI RB, He LQ, Lin HL, Wang NS, Chen XH, Wang NS, Jian GH, Liu XS, Liu YN, Ni ZH, Fang JA, Ding HL, Guo W, He YN, Wang LH, Wang YP, Yang HT, Ye ZM, Yu RH, Zhao LJ, Zhou WH, Li WG, Mao HJ, and Zhan YL performed the participant recruitment and data collection; Yao C contributed to the database management and statistical analysis.

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