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The renal safety evaluation of aspirin plus edaravone in ischemic stroke patients: a retrospective cohort study

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ABSTRACT

BACKGROUND AND OBJECTIVE: Aspirin combined with edaravone is more effective than aspirin or edaravone alone in treatment of ischemic stroke. Aspirin is defined as a nephrotoxic drug while the renal safety of edaravone is controversial. We aimed to evaluate whether edaravone will increase the nephrotoxicity of aspirin in ischemic stroke patients.

DESIGN: A propensity score matched retrospective cohort study.

SETTING: A tertiary hospital in China.

PARTICIPANTS: Ischemic stroke patients treated with aspirin from February 2007 to May 2018.

PRIMARY AND SECONDARY OUTCOME MEASURES: Acute kidney injury (AKI), decreased estimated glomerular filtration rate (eGFR, >10%), gastrointestinal bleeding and in-hospital adverse outcomes (defined as died or gave up treatment in hospital). AKI was diagnosed and staged based on acute kidney injury network (AKIN) .

RESULTS: Of the 986 pairs patients enrolled, the incidence of AKI between the aspirin group and the combination group showed no significant difference (7.71% vs 6.29%, p =0.217). While the incidence of grade 1 AKI (6.59% vs 4.46%, p =0.039) and eGFR decline (24.75% vs 16.94%, p <0.001) were significantly lower in the combination group. The protective effect was significant in patients with baseline eGFR 60-90mL/ (min1.73

m^2). In patients with different complications, the incidence of AKI showed no significant differences in patients with chronic kidney injury, hypertension, anemia, aged above 75 years, except in patients with cardiovascular disease (OR, 2.82; CI 1.50-5.29; p =0.001). However, the incidence of gastrointestinal bleeding (1.22% vs 2.84%, p =0.011) and in-hospital adverse outcomes (3.25% vs 7.00%, p <0.001) were significantly higher in the combination group.

CONCLUSIONS: Our study indicated that edaravone in patients with ischemic stroke didn't increase the nephrotoxicity of aspirin, and even had a protective effect on mild renal deterioration. Nevertheless, it should be cautious when patients in bad pathophysiological condition and at high risk of bleeding.

Key words: aspirin · edaravone · combination therapy · ischemic stroke · acute kidney injury

Strengths and limitations of this study

Our study firstly evaluated the renal safety of aspirin combined with edaravone in ischemic stroke patients.

We provide a reference for the treatment of patients with ischemic stroke through the large cohort study.

We conducted a propensity score matching to eliminate the influences caused by other confounders.

The data of NIHSS score were missing, so the efficacy couldn't be evaluated.

Introduction

Stroke is one of the most serious public health problems today, of which ischemic stroke makes up about 70%, about 13.7 million people occurred stroke a year, and 5.8 million die of it [1]. Acute stroke is not only one of the top causes of mortality, but also a leading cause of long-term disability [1].

Aspirin and edaravone are recommended for ischemic stroke [2]. Aspirin is recommended to reduce platelet aggregation during the onset of an ischemic stroke and prevent recurrence [3, 4]. And edaravone, a free radical scavenger, was approved by the U.S. Food and Drug Administration (FDA) for amyotrophic lateral sclerosis [5], and is also used to improve the neurological symptoms, daily life and dysfunction associate with acute ischemic stroke [6]. Recent years, several researches showed that the combination of aspirin and edaravone was a more effective therapy than aspirin or edaravone alone for the ischemic stroke [6, 7].

As we all know, aspirin is a considered as a nephrotoxic drug for a long time, while the renal safety of edaravone is controversial at present. According to the instructions, both of aspirin and edaravone may relate to the occurrence of acute kidney injury (AKI). A retrospective study showed that even low-dose aspirin was significantly associated with an increased risk of renal failure in chronic kidney disease (CKD) patients [8]. Furthermore, it's common to see the case reports about AKI caused by aspirin [9, 10]. As for edaravone, a post-marketing surveillance system report of 207 cases showed that

edaravone aggravated renal dysfunction by altering renal hemodynamics [11]. And a study based on 5,195,890 reports found out that AKI caused by edaravone was one of the most commonly reported [12]. Whereas, some studies have shown that edaravone had a protective effect in various kidney injury animal models [13, 14]. Therefore, the renal safety of aspirin combined with edaravone for ischemic stroke treatment needs to be addressed.

In addition, acute brain dysfunction is able to affect renal function, including functional changes and electrolyte disorders [15]. AKI is a common complication after acute cerebrovascular events, with an overall prevalence of about 11.6% [15]. The ischemic stroke patients are high risk population of AKI [15], and AKI is associated with higher long-term and short-term mortality after ischemic stroke [16]. No AKI prevent strategy have proved to be completely effective so far [17], so the prevention of AKI in ischemic stroke patients is of great importance.

Given that, a retrospective, matched cohort study was conducted to investigate the renal safety of aspirin and aspirin combined with edaravone in ischemic stroke patients, and to provide reference for the clinical medication of ischemic stroke.

Methods

Subjects

This retrospective cohort study included inpatients admitted to the Third Xiangya Hospital from February 2007 to May 2018. It was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Medical Ethical Committee in the Third Xiangya Hospital of Central South University (2020-S342). The medical records were obtained from the electronic medical record system. Inclusion criteria: (1) Ischemic stroke patients diagnosed by CT scan; (2) patients treated with aspirin during hospitalization; (3) complete serum creatinine (Scr) records before and after aspirin administration. Exclusion criteria: (1) The duration time of aspirin or edaravone was less than 24 h; (2) the combination time of aspirin and edaravone was less than 24 h; (3) patients with uremia; (4) baseline Scr >500 μmol/dL. Patients were divided into two groups, combination group (combination therapy of aspirin and edaravone) and aspirin group (aspirin used alone). Aspirin 100mg/day (97%), oral placebo, lasted at least 24h; edaravone, 30mg intravenous infusion, twice a day, lasted at least 24h. Medical information including basic information, diagnostic records, laboratory indexes and medication records was collected from the electronic medical record system.

Clinical assessment

Ischemic stroke was diagnosed by CT scan, and other complications were defined according to the diagnosis in medical records by an investigator blindly to the allocation. Anemia was defined as hematokrit <36.0% for women, and <39.0% for men. CKD was defined as eGFR <60 mL/(min 1.73 m^2) , calculated by simplified Modification of Diet in Renal Disease (MDRD) formula. Combination therapy: the combined using of aspirin and edaravone lasted for at least 24 h.

Definition of endpoints

Primary endpoint: the occurrence of AKI. AKI was defined according to the criterion of the acute kidney injury network (AKIN) based on Scr. Grade 1: Scr increased by 1.5 times or 0.3 mg/dL than baseline Scr; grade 2: Scr increased by 2 times than baseline; grade 3: Scr increased by 3 times or ≥4 mg/dL or initiate renal replacement therapy. Any of the above conditions happened in 14 days of the onset of therapy was defined as ANY AKI in this study. The latest Scr level within 14 days prior to aspirin or edaravone was defined as baseline, and the largest Scr in 14 days was used to define AKI.

Secondary endpoints: (1) eGFR decline (decrease ≥10%) included mild decline: eGFR decreased 10%-30% from baseline, and severe decline: eGFR decreased over 30%. (2) In-hospital gastrointestinal bleeding. (3) In-hospital adverse outcomes: defined as died or gave up treatment in hospital.

Statistically analysis

Statistical analysis was conducted by SPSS 22.0 (SPSS, Inc., Chicago, IL). The continuous variables were expressed as mean ± SD and categorical variables as percentages. The two-sided t test was used for continuous variables of normal distribution, Mann-Whiney U-test was used for non-normal distribution, and the chi-square test was used for categorical variables. In order to eliminate the bias caused by confounders, the risk factors of AKI in our subjects were evaluated by a univariate logistic analysis. The risk factors were matched by 1:1 propensity score, with a matching tolerance of 0.02, and the incidence of endpoints of the two groups were then compared. Subgroup analyses according to patients' baseline renal function [(eGFR ≤30, 30-60, 60-90 and ≥90 mL/ (min 1.73 m^2)] and complications [including CKD, hypertension, diabetes mellitus, anemia, cardiovascular disease (CVD, including angina, myocardial infarction and heart failure) , and age ≥75 years] were conducted. P <0.05 was considered statistically significant.

Results

Patient characteristics

We finally included 3061 patients in our study, 1641 in the aspirin group and 1420 in the combination group, the details are showed Figure S1. The characteristics of enrolled patients are shown in Table 1. A total of 235 (7.68%) patients developed AKI in the enrolled patients, the incidence of AKI was significantly lower in the combination group (A vs C: 9.69% vs 5.35%, p <0.001) (Table 1).

Propensity score matching according to univariate logistic regression analysis

The univariate logistic regression analysis showed that the risk factors for AKI in the subjects included age, baseline Scr, uric acid, urea, hematokrit, diabetes, myocardial infarction, heart failure, anemia, CKD, diuretic, angiotensin receptor inhibitor, cephalosporin and calcium antagonist (Table S1). Except anemia and CKD (we matched baseline Scr and hematokrit), the other risk factors were matched by 1:1 propensity score, and 986 pairs were finally obtained (Table 2). After matching, the risk factors included age, baseline creatinine, diabetes, heart failure and so on, were comparative between the two groups.

Association between combination therapy and outcomes after matching

The incidence of grade 1 AKI in the combination group was still significantly lower (A vs C: 6.59% vs 4.46%, p =0.039), but the incidence of ANY AKI (A vs C: 7.71% vs

6.29%, p =0.217), grade 2 AKI (A vs C: 0.71% vs 0.91%, p =0.616), or grade 3 AKI (A vs C: 0.41% vs 0.91%, p =0.614) showed no significant difference (Figure 1A).

The incidence of the eGFR decline (A vs C: 24.75% vs 16.94%, p <0.001) and eGFR mild decline (A vs C: 19.27% vs 12.37%, p <0.001) were significantly lower in the combination group, while the incidence of eGFR severe decline (A vs C: 5.48% vs 4.56%, p =0.353) had no statistical difference (Figure 1B). However, gastrointestinal bleeding (A vs C: 1.22% vs 2.84%, p =0.011) and in-hospital adverse outcomes (A vs C: 3.25% vs 7.00%, p <0.001) were significantly higher in the combination group (Figure 1C).

Outcomes of subgroup analysis based on different baseline renal function

Considering that the occurrence of AKI is relate to baseline renal function, we assessed the effect of baseline renal function on AKI, and divided patients into four groups according to their baseline eGFR: eGFR <30, 30-60, 60-90 and ≥90 mL/ (min 1.73 m^2). Then, the kidney-related outcomes were compared in different group. The combination therapy showed lower incidence of grade 1 AKI (A vs C: 6.14% vs 2.83%, p =0.026) in group 60≤ eGFR <90 mL/ (min 1.73 m^2), while showed no significant difference in group eGFR <30, 30≤ eGFR <60 and eGFR ≥90 mL/ (min 1.73 m^2) (Table S2).

As for the incidence of eGFR decline, except group eGFR <30mL/ (min 1.73 m^2), the incidence of mild eGFR decline with the combination therapy was lower in all groups, while the incidence of severe eGFR decline showed no significant differences (Table S3).

Outcomes of subgroup analysis based on different complications

We further performed a subgroup analysis that included CKD, non-CKD, hypertension, diabetes, anemia, CVD, and people age ≥75 years. For incidence of AKI, except CVD population [odds ratio (OR), 2.818; 95% confidence interval (CI) 1.500-5.294; p =0.001], the combination therapy didn't increase the risk of AKI in any other population (Figure 4).

For incidence of eGFR decline, the combination therapy was significantly lower in patients without CKD (OR, 0.560; CI 0.430-0.729; p <0.001), hypertension (OR, 0.662; CI 0.518-0.846; p =0.001), diabetes (OR, 0.675; CI 0.476-0.958; p =0.028). While in patients with CVD (OR, 1.268; CI 0.775-2.074; p =0.345), there was an injury trend. In other populations (aged and CKD), combination therapy had no significant relationship with eGFR decline. The results were approximately similar to the primary endpoint (Figure 2).

Discussion

Our study firstly investigated the effect of edaravone combined with aspirin on renal function in patients with ischemic stroke. In generally, aspirin combined with edaravone didn't increase the incidence of AKI in patients with ischemic stroke. Furthermore, the combination therapy was statistically significant in reducing the incidence of mild AKI in hospitalized ischemic stroke patients, especially in patients with baseline eGFR 60-90 mL/ (min 1.73 m^2). Unfortunately, the gastrointestinal bleeding and in-hospital adverse outcomes in hospital were positively associated with the combination therapy.

Aspirin is widely used in the prevention of cerebrovascular disease, even in patients with CKD. Hsiao KC et al. found that aspirin was significantly associated with renal failure in CKD patients [18]. Hovever, several studies found that aspirin had no effect on renal function [19], and even could slow down the deterioration process [20, 21]. The prevalence of AKI was 7.67% in our ischemic stroke patients who used aspirin, lower than 13.5%, which reported by another study in China [22]. It seems that use of aspirin in ischemic stroke patients was related to decreased risk of AKI. The mechanism might involve in inhibition of TxA 2, excessive production of TxA 2 is harmful to renal function [23].

Edaravone is defined as a nephrotoxic drug in a long time, and is reported to be one of the most common drug related to AKI [12]. Nevertheless, our study showed that the combination therapy didn't increase the incidence of AKI, but decrease the mild renal

deterioration, compared to the aspirin group. Actually, edaravone has been reported to have protective effects in many animal models of kidney injury, such as ischemia/reperfusion, cisplatin and diabetic nephropathy. The mechanisms might involve in scavenging free radicals, inhibiting lipid peroxidation, inhibiting inflammatory factors, protecting renal mitochondria, inhibiting cell apoptosis and reducing oxidative stress [14, 24, 25]. Similarly, it has also been found in clinical study that edaravone might play a protective role in kidney by exerting antioxidant stress and inhibiting inflammatory levels in patients with paraquat poisoning [26, 27]. A study found a negative correlation between edaravone use and AKI in 5689 patients with acute ischemic stroke [27], which was consistent with our results.

The subgroup analysis based on the baseline renal function indicated that the combination therapy showed optimum protective effect to eGFR decline in patients with baseline eGFR 60-90 mL/ (min 1.73 m^2), while in patients with eGFR <30 mL/ (min 1.73 m^2), the combination had no protective effect and even a non-significant aggravate trend. This is consistent to its instruction: edaravone may aggravate renal failure in severe renal failure patients, and severe renal failure is a contraindication. In contrast, Kamouchi M et.al have found that edaravone is negatively correlated with the occurrence of AKI [27], and the baseline eGFR in hospitalized patients cannot accurately predict the deterioration of renal function after medication [28]. Thus, there are a few off-label use of edaravone in patients with eGFR <30mL/ (min 1.73 m^2), and we enrolled these patients to evaluate the

combination therapy in patients with different basic renal function in the real world. The subgroup analysis based on different complications showed that the combination treatment had no effect on the incidence of AKI in CKD, hypertension, diabetes, anaemia and aged groups, and even had protective effect on the mild deterioration of renal function in CKD, anaemia and aged groups. Nevertheless, the combination therapy increased the incidence of AKI in CVD patients. At present, edaravone is mainly used for cerebrovascular disease rather than cardiovascular disease. The safety of edaravone on patients with CVD hasn't been studied yet. However, edaravone has been reported to improve septic heart function in rats by inducing the HIF-1/HO-1 pathway [28]. In addition, long-term aspirin is a conventional therapy to the CVD patients, so their renal function may in worse baseline condition. Thus, the combination therapy should be cautious in CVD patients.

Although the combination therapy showed well renal safety, our data indicated that the combination therapy might relate to higher risk of gastrointestinal bleeding and in-hospital mortality. As we all known, gastrointestinal bleeding is a common adverse reaction of aspirin, and gastrointestinal bleeding is highly related to the recurrence of ischemic stroke [30]. This may restrict the use of combination therapy in ischemic stroke patients. However, we only considered the factor related to AKI when matching, this result may be biased. The risk of bleeding and influence on mortality of the combination therapy needs to be further studied.

Strengths: (1) To our knowledge, this is the first study that evaluated the safety of aspirin in combination with edaravone in patients with ischemic stroke; (2) The data we used was from real world, hence the results were more relevant to the actual clinical situation; (3) We conducted a propensity score matching to eliminate the influences caused by other confounders; (4) We further stratified patients based on renal function and complications to provide individualized advice to different patients.

Limitations: (1) Due to the limitations of our database, the data regarding clinical severity of the ischemic stroke e. g NIHSS, couldn't be obtained to evaluate the efficacy of the combination therapy. Thus, we mainly focused on the renal safety of the combination therapy in this study; (2) Even the hypertension, angina, contrast agents, ACEI, β-blocker were sill significantly diffenrent between the two groups after matching, but they were not risk factors to AKI in our population while the risk factors were comparative between the two groups; (3) This is a retrospective research, the data was from the real world, hence the duration of our therapy and the detailed types of stroke couldn't been restricted. Thus, large multicenter randomized trials are needed to further validate our findings.

Conclusion

In brief, combination of aspirin and edaravone didn't cause renal damage to most ischemic stroke patients, and even related to decreased incidence of grade 1 AKI, especially in patients with baseline eGFR 60-90mL/ (min1.73 m^2). It was related to

delayed mild renal exacerbation in people with baseline eGFR >30mL/ (min1.73 m^2). However, when patients with eGFR <30mL/ (min1.73 m^2), CVD and high risk of bleeding, the combination should be weighed.

Statements

Author Contributions XZ and KL conceived and designed the study. HY and KL performed data acquisition and statistically analyses. WY and ML contributed the interpretation and discussion of the results. HY prepared the figures and tables. HY and KL drafted the manuscript. All authors approved the final version of the manuscript.

Conflict of interest The authors declare that they have no conflict of interest.

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Patient consent for publication All subjects were anonymized, thus the provision of informed consent was not required.

Data availability statement Data are available upon reasonable request.

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Medical Ethical Committee in the Third Xiangya Hospital of Central South University (2020-S342).

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Tables

Characteristics	Aspirin group(n=1641)	Combination group(n=1420)	p
Age (years)	69.52±10.45	65.40±12.05	<0.001*
Sex (male)	1069(65.14%)	915(64.44%)	0.683
eGFR [mL/ (min 1.73 m^2)]	68.50±32.62	81.81±33.84	<0.001*
Baseline creatinine (μmol/L)	116.03±72.18	96.01 ±57.39	<0.001*
Uric acid (μmol/L)	371.40±129.94	329.54±121.94	<0.001*
BUN (mmol/L)	7.29±3.90	6.00±3.15	<0.001*
Hematokrit (%)	37.64±6.04	39.74±5.75	<0.001*
Complication			
Hypertension	1336(81.41%)	1134(79.86%)	0.277
Diabetes	693(42.23%)	442(31.13%)	<0.001*
Angina	297(18.10%)	22(1.55%)	<0.001*
Myocardial infarction	302(18.40%)	27(1.90%)	<0.001*
Heart failure	214(13.04%)	78(5.49%)	<0.001*
Anemia	795(48.45%)	434(30.56%)	<0.001*
CKD	678(41.32%)	349(24.58%)	<0.001*
Nephrotoxic drug			

Contrast agents	461(28.09%)	200(14.08%)	<0.001*
Diuretic	366(22.30%)	190(13.38%)	<0.001*
ACEI	539(32.85%)	93(6.55%)	<0.001*
ARB	342(20.84%)	143(10.07%)	<0.001*
Calcium antagonists	743(45.28%)	647(45.56%)	0.874
β-blocker	539(32.85%)	93(6.55%)	<0.001*
Cephalosporin	275(16.76%)	312(21.97%)	<0.001*
Statins	1258(76.66%)	1061(74.72%)	0.211
Endpoint			
eGFR mild decline	338(20.60%)	178(12.54%)	<0.001*
eGFR severe decline	97(5.91%)	64(4.51%)	0.083
eGFR decline	435(26.51%)	242(17.04%)	<0.001*
Grade 1 AKI	143(8.71%)	55(3.87%)	<0.001*
Grade 2 AKI	9(0.55%)	11(0.77%)	0.439
Grade 3 AKI	7(0.43%)	10(0.70%)	0.303
ANY AKI	159(9.69%)	76(5.35%)	<0.001*

Table 1. Baseline characteristics of our patients.

Abbreviations: BUN, blood uric nitrogen; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor inhibitor.

*p <0.05.

Characteristics	Aspirin group(n=986)	Combination group(n=986)	p
Age (years)	68.10±10.88	67.94±10.76	0.739
Sex (male)	618(62.68%)	601(60.95%)	0.431
eGFR (mL/ (min 1.73 m^2))	74.37±32.05	75.04±30.73	0.630
Baseline creatinine (μmol/L)	103.09±57.34	102.96±62.43	0.962
Uric acid (μmol/L)	345.53±117.87	355.56±119.75	0.066
BUN (mmol/L)	6.52±3.12	6.51±3.45	0.932
Hematokrit (%)	38.74±5.71	39.15±5.68	0.095
Complication			
Hypertension	788(79.92%)	834(84.58%)	0.007*
Diabetes	355(36.00%)	368(37.32%)	0.544
Angina	202(20.49%)	15(1.52%)	<0.001*
Myocardial infarction	32(3.25%)	27(2.74%)	0.509
Heart failure	70(7.10%)	72(7.30%)	0.862
Anemia	400(40.57%)	341(34.58%)	0.006*
CKD	327(33.16%)	306(31.03%)	0.311
Nephrotoxic drug			
Contrast agents	266(26.98%)	126(13.78%)	<0.001*

Diuretic	150(15.21%)	140(14.20%)	0.525
ACEI	306(31.03%)	71(7.20%)	<0.001*
ARB	128(12.98%)	132(13.39%)	0.790
Calcium antagonists	467(47.36%)	499(50.61%)	0.149
β-blocker	306(31.03%)	71(7.20%)	<0.001*
Cephalosporin	172(17.44%)	159(16.13%)	0.433
Statins	729(73.94%)	750(76.06%)	0.275

Table 2. Characteristics after propensity-score matching.

Abbreviations: BUN, blood uric nitrogen; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor inhibitor.

Risk factors include age, baseline Scr, uric acid, urea, hematokrit, diabetes, myocardial infarction, heart failure, diuretic, angiotensin receptor inhibitor, cephalosporin and calcium antagonist were matched.

*p <0.05.

Figures

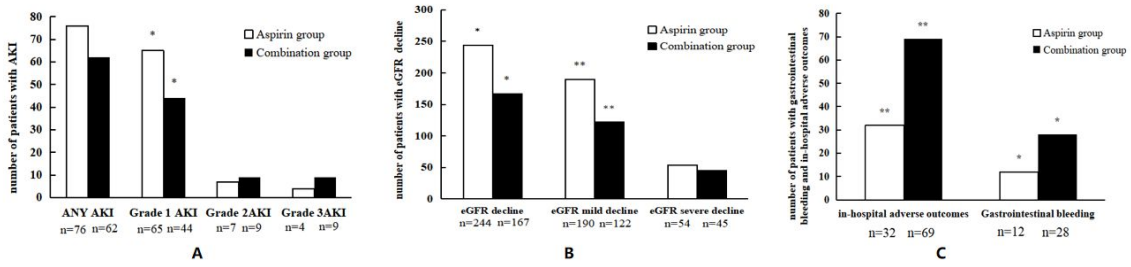

Figure 1

A:Incidence of AKI after matching

*p <0.05

B:Incidence of eGFR decline after matching

*p <0.001; **p <0.001. eGFR decline: eGFR decreased >10% from baseline eGFR; mild decline: decreased 10%-30% from baseline eGFR; severe decline: decreased >30% from baseline eGFR.

C:Incidence of gastrointestinal bleeding and in-hospital adverse outcomes after matching

*p <0.05; **p <0.001. In-hospital adverse outcomes, died or gave up treatment in hospital.

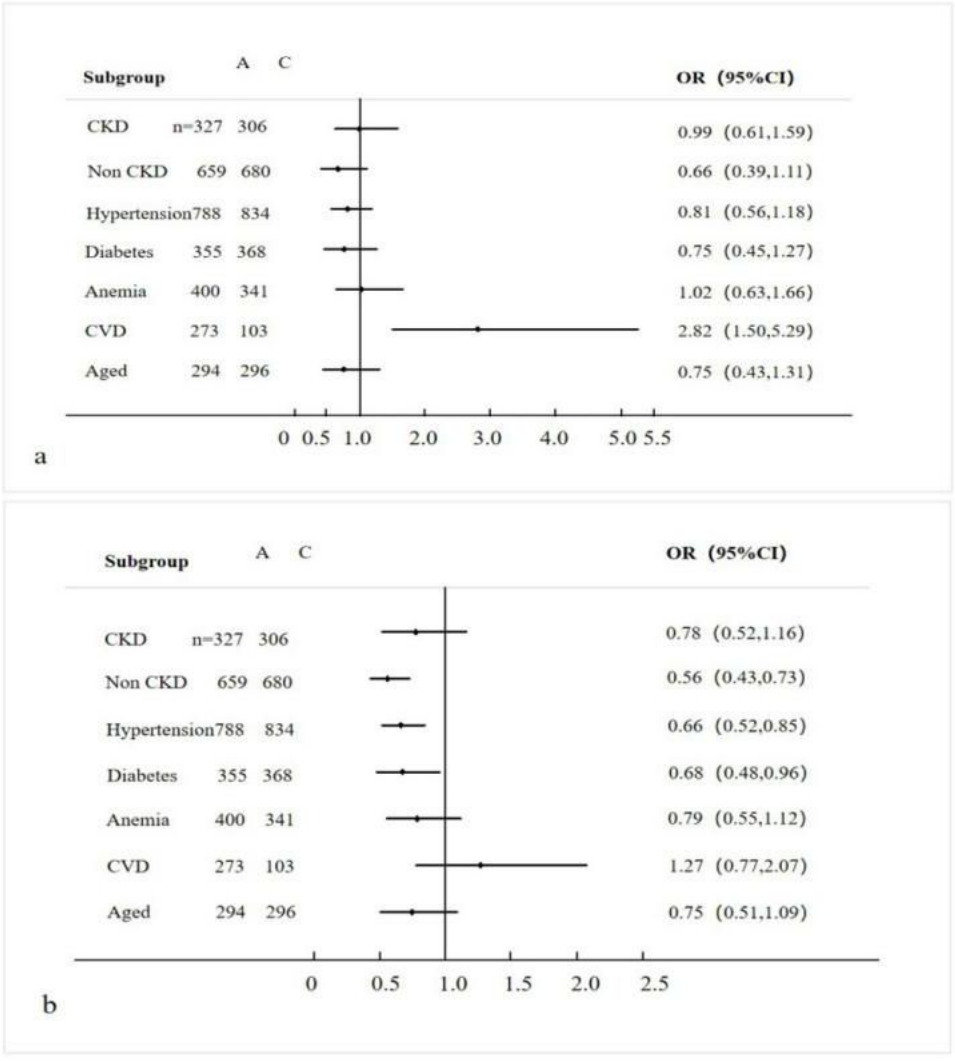

Figure 2 The renal outcome of patients with different complication

CKD: patients with chronic kidney injury; Non CKD: patients without CKD; CVD: patients with cardiovascular disease; Aged: age ≥75 years.

OR, odds ratio; CI, 95%confidence interval.

a, the association between the combination therapy and AKI in the subgroups;

b, the association between the combination therapy and eGFR decline in the subgroups. A, aspirin group; C, combination group.

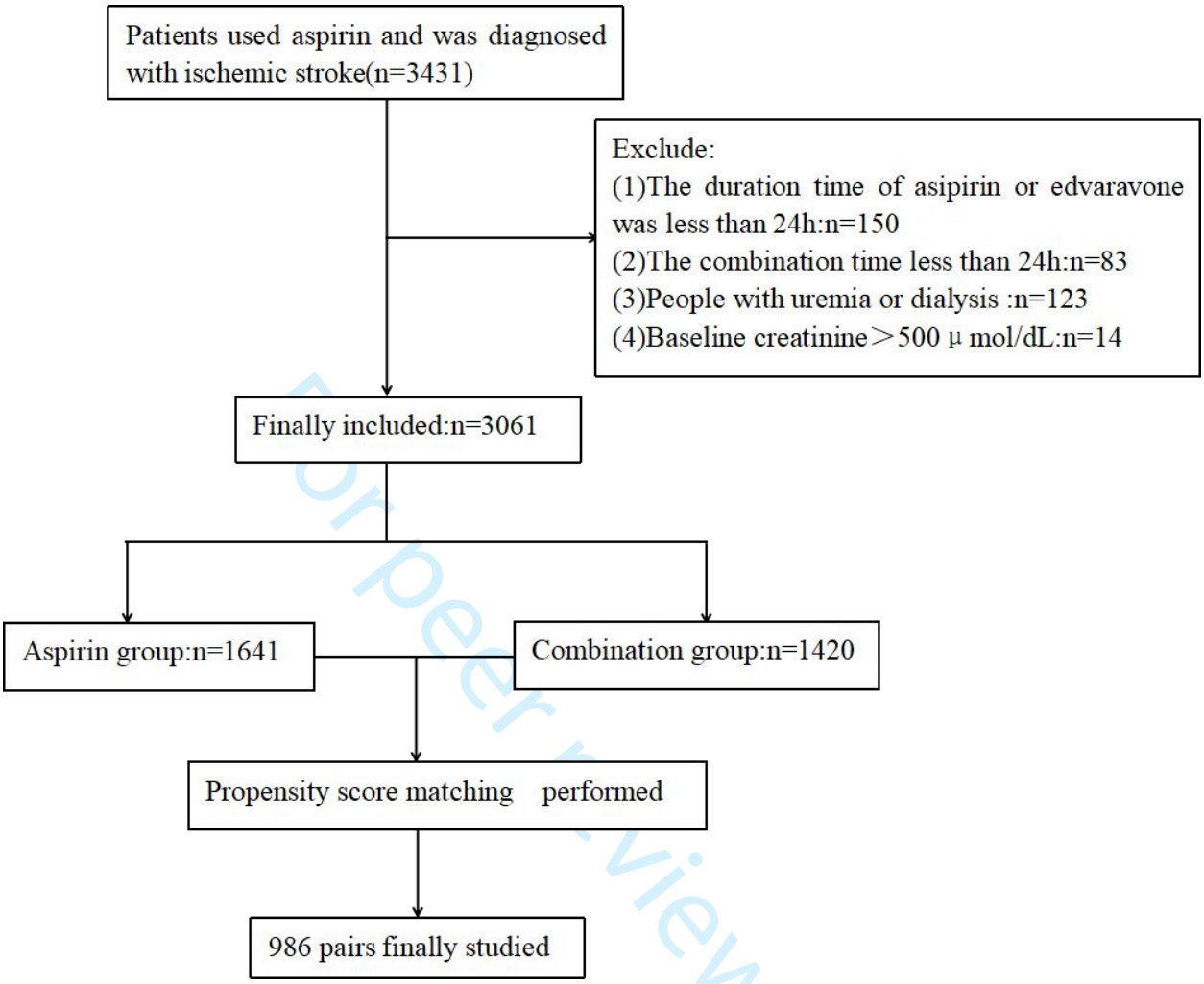

Figure S1 The screening flow chart

Variable	OR	Lower 95%CI	Upper 95%CI	p
Sex (male)	1.035	0.782	1.369	0.811
Age (years)	1.021	1.008	1.034	0.001*
Uric acid (μmol/L)	1.002	1.001	1.003	0.001*
BUN (mmol/L)	1.147	1.116	1.179	0.000*
Baseline creatinine (μmol/L)	1.009	1.007	1.010	0.000*
Hematokrit (%)	0.923	0.903	0.942	0.000*
Hypertension	1.400	0.966	2.028	0.076
Diabetes	1.761	1.348	2.300	0.000*
Angina	0.696	0.424	1.142	0.151
Myocardial infarction	2.255	1.601	3.177	0.000*
Heart failure	3.244	2.328	4.520	0.000*
Anemia	2.351	1.792	3.083	0.000*
CKD	3.349	2.548	4.401	0.000*
Contrast agents	0.875	0.626	1.222	0.434
Diuretic	4.604	3.495	6.065	0.000*
ACEI	1.071	0.775	1.480	0.677
ARB	1.403	1.006	1.958	0.046*

Calcium antagonists	1.402	1.074	1.831	0.013*
β-blocker	1.071	0.775	1.480	0.677
Cephalosporin	1.533	1.128	2.083	0.006*
Statins	0.906	0.668	1.227	0.523

Table S1. Univariate logistic regression analysis for risk factors of AKI before matching

Abbreviations: BUN, blood uric nitrogen; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor inhibitor. OR, odds ratio; 95%CI, confdence interval.

*p <0.05.

Baseline eGFR	AKI grade	Aspirin group	Combination group	p
	ANY AKI	14(22.22%)	19(27.94%)	0.451
<30	Grade 1	13(20.63%)	18(26.47%)	0.432
Aspirin: (n=)63	Grade 2	0	0	-
Edaravone: 68	Grade 3	1(1.59%)	1(1.47%)	0.957
	ANY AKI	26(9.85%)	18(7.56%)	0.366
30≤ eGFR <60	Grade 1	24(9.09%)	11(4.62%)	0.050
Aspirin: 264	Grade 2	1(0.38%)	4(1.68%%)	0.142
Edaravone: 238	Grade 3	1(0.38%)	3(1.26%)	0.267
	ANY AKI	29(7.42%)	17(4.37%)	0.071
60≤ eGFR <90	Grade 1	24(6.14%)	11(2.83%)	0.026*
Aspirin: 391	Grade 2	3(0.77%)	3(0.77%)	0.995
Edaravone: 389	Grade 3	2(0.51%)	3(0.77%)	0.650
	ANY AKI	7(2.61%)	8(2.75%)	0.920
90≤	Grade 1	4(1.49%)	4(1.37%)	0.907
Aspirin: 268	Grade 2	3(1.12%)	2(0.69%)	0.588
Edaravone: 291	Grade 3	0	2(0.69%)	0.174

Table S2.Incidence of AKI in diffenrent baseline eGFR groups between the two therapies.

*p <0.05.

Baseline eGFR	eGFR decline	Aspirin group	Combination group	p
<30	decline	15(23.81%)	21(30.88%)	0.365
Aspirin: (n=)63	mild decline	12(19.05%)	14(20.59%)	0.825
Edaravone: 68	severe decline	3(4.76%)	7(10.29%)	0.233
30≤ eGFR <60	decline	52(19.70%)	30(12.61%)	0.032*
Aspirin: 264	mild decline	39(14.77%)	19(7.98%)	0.017*
Edaravone: 238	severe decline	13(4.92%)	11(4.62%)	0.874
60≤ eGFR <90	decline	79(20.20%)	40(10.28%)	0.000*
Aspirin: 391	mild decline	57(14.58%)	26(6.68%)	0.000*
Edaravone: 389	severe decline	22(5.63%)	14(3.60%)	0.177
90≤	decline	98(36.57%)	76(26.12%)	0.008*
Aspirin: 268	mild decline	82(30.60%)	63(21.65%)	0.016*
Edaravone: 291	severe decline	16(5.97%)	13(4.47%)	0.424

Table S3.Incidence of eGFR decline in diffenrent baseline eGFR groups between the two therapies.

eGFR decline: eGFR decreased >10% from baseline eGFR; mild decline: decreased 10%-30% from baseline eGFR; severe decline: decreased >30% from baseline eGFR.

*p <0.05.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	7-8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6-8*
Bias	9	Describe any efforts to address potential sources of bias	7-8

Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	7-8
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	9
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	9-10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-10

		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-11
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	12-15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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The renal safety evaluation of aspirin plus edaravone in ischemic stroke patients: a retrospective cohort study

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ABSTRACT

BACKGROUND AND OBJECTIVE: Aspirin combined with edaravone is more effective than aspirin or edaravone alone in the treatment of ischemic stroke. Aspirin is defined as a nephrotoxic drug while the renal safety of edaravone is controversial. We aimed to evaluate whether edaravone will increase the nephrotoxicity of aspirin in ischemic stroke patients.

DESIGN: A propensity score-matched retrospective cohort study.

SETTING: A tertiary hospital in China.

PARTICIPANTS: Ischemic stroke patients were treated with aspirin from February 2007 to May 2018.

PRIMARY AND SECONDARY OUTCOME MEASURES: Acute kidney injury (AKI, diagnosed by acute kidney injury network), decreased estimated glomerular filtration rate (eGFR, >10%), gastrointestinal bleeding, and in-hospital adverse outcomes (defined as dying or giving up treatment in our hospital).

RESULTS: We included 3061 patients, and 986 pairs were successfully matched. Of the 986 pairs of patients included, the incidence of AKI between the aspirin group and the combination group showed no significant difference (7.71% vs 6.29%, p =0.217). While the incidence of eGFR decline (24.75% vs 16.94%, p <0.001) was significantly lower in the combination group. The protective effect was significant in patients with baseline eGFR >30 mL/ (min1.73 m^2), especially in eGFR 60-90 mL/ (min1.73 m^2). In patients with different complications, the incidence of AKI showed no significant differences in

patients with chronic kidney injury, hypertension, anemia, aged above 75 years, except in patients with cardiovascular disease (OR, 2.82; CI 1.50-5.29; p <0.001). However, the incidence of gastrointestinal bleeding (1.22% vs 2.84%, p =0.011) and in-hospital adverse outcomes (3.25% vs 7.00%, p <0.001) were significantly higher in the combination group.

CONCLUSIONS: Our study indicated that edaravone in patients with ischemic stroke didn't increase the nephrotoxicity of aspirin, and even had a protective effect on mild renal deterioration. Nevertheless, it should be cautious when patients are in bad pathophysiological conditions and at high risk of bleeding.

Key words: aspirin · edaravone · combination therapy · ischemic stroke · acute kidney injury

Strengths and limitations of this study

A retrospective study in a tertiary medical center.

This study included 3061 ischemic stroke patients from the electronic medical record system of a Chinese tertiary hospital.

The potential confounding factors of AKI were balanced by propensity score matching.

Subgroup analyses were conducted according to patients' baseline eGFR and complications.

The NIHSS score and risk factors of gastrointestinal bleeding, and in-hospital adverse outcomes couldn't be acquired due to limitations of our database.

Introduction

Stroke is one of the most serious public health problems today, of which ischemic stroke makes up about 70%, about 13.7 million people occurred stroke a year, and 5.8 million die of it [1]. Acute stroke is not only one of the top causes of mortality, but also a leading cause of long-term disability [1].

Aspirin and edaravone are recommended for ischemic stroke [2]. Aspirin is recommended to reduce platelet aggregation during the onset of the ischemic stroke and prevent recurrence [3, 4]. And edaravone, a free radical scavenger, was approved by the U.S. Food and Drug Administration (FDA) for amyotrophic lateral sclerosis [5] and is also used to improve the neurological symptoms, daily life, and dysfunction associated with acute ischemic stroke [6]. In recent years, several studies determined that the combination of aspirin and edaravone was a more effective therapy than aspirin or edaravone alone for the ischemic stroke [6, 7].

As we all know, aspirin is considered a nephrotoxic drug for a long time, while the renal safety of edaravone is controversial at present. According to the instructions, both aspirin and edaravone may relate to the occurrence of acute kidney injury (AKI). A retrospective study showed that even low-dose aspirin was significantly associated with increased risk of renal failure in chronic kidney disease (CKD) patients [8]. Furthermore, AKI caused by aspirin is commonly reported [9, 10]. Meanwhile, edaravone, a post-marketing surveillance system report of 207 cases showed that edaravone aggravated renal dysfunction by altering renal hemodynamics [11]. And a study based on

5,195,890 reports found out that AKI caused by edaravone was one of the most commonly reported drug-induced AKI [12]. Whereas, some studies have shown that edaravone had a protective effect in various kidney injury animal models [13, 14]. Therefore, the renal safety of aspirin combined with edaravone for ischemic stroke treatment needs further study.

In addition, acute brain dysfunction can affect renal function, including functional changes and electrolyte disorders [15]. AKI is a common complication after acute cerebrovascular events, with an overall prevalence of about 11.6% [15]. The ischemic stroke patients is a high-risk population of AKI [15], and AKI is associated with higher long-term and short-term mortality after ischemic stroke [16]. No AKI prevent strategy has been proved to be completely effective so far [17], so the prevention of AKI in ischemic stroke patients is of great importance.

Given that, a retrospective, matched cohort study was conducted to investigate the renal safety of aspirin and aspirin combined with edaravone in ischemic stroke patients, and to provide a reference for the clinical medication of ischemic stroke.

Methods

Subjects

This retrospective cohort study included inpatients admitted to the Third Xiangya Hospital from February 2007 to May 2018. It was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Medical Ethical Committee in the Third Xiangya Hospital of Central South University (2020-S342). The medical records were obtained from the electronic medical record system. Inclusion criteria: (1) Ischemic stroke patients diagnosed by CT scan; (2) patients treated with aspirin during hospitalization; (3) complete serum creatinine (Scr) records before and after the aspirin administration. Exclusion criteria: (1) The duration time of aspirin or edaravone was less than 24 h; (2) the combination time of aspirin and edaravone was less than 24 h; (3) patients with uremia; (4) baseline Scr >500 μmol/dL. Patients were divided into two groups, combination group (combination therapy of aspirin and edaravone, 'C' for short) and aspirin group (aspirin used alone, 'A' for short). Aspirin 100 mg/day (97%), oral placebo, lasted at least 24 h; edaravone, 30mg intravenous infusion, twice a day, lasted at least 24 h. Medical information including basic information, diagnostic records, laboratory indexes, and medication records were collected from the electronic medical record system.

Clinical assessment

Ischemic stroke was diagnosed by CT scan, and other complications were defined according to the diagnosis in medical records by an investigator blindly to the allocation.

Anemia was defined as hematocrit <36.0% for women, and <39.0% for men. CKD was defined as eGFR <60 mL/ (min 1.73 m^2), calculated by simplified Modification of Diet in Renal Disease (MDRD) formula. Combination therapy: the combined use of aspirin and edaravone lasted for at least 24 h.

Definition of endpoints

Primary endpoint: the occurrence of AKI. AKI was defined according to the criterion of the acute kidney injury network (AKIN). Stage 1: Scr increased by 1.5 times or 0.3 mg/dL than baseline Scr; stage 2: Scr increased by 2 times than baseline; stage 3: Scr increased by 3 times or ≥4 mg/dL or initiate renal replacement therapy. Any of the above conditions that happened 14 days of the onset of therapy were defined as AKI in this study. The latest Scr level within 14 days prior to aspirin or edaravone was defined as the baseline, and the largest Scr in 14 days was used to define AKI.

Secondary endpoints: (1) eGFR decline (decrease ≥10%) included mild decline: eGFR decreased 10%-30% from baseline, and severe decline: eGFR decreased over 30%. (2) In-hospital gastrointestinal bleeding. (3) In-hospital adverse outcomes: defined as dying or giving up treatment in hospital.

Statistically analysis

Statistical analysis was conducted by SPSS 22.0 (SPSS, Inc., Chicago, IL). The continuous variables were expressed as mean ± SD and categorical variables as percentages. The two-sided t test was used for continuous variables of normal distribution, Mann-Whiney U-test was used for non-normal distribution, and the

chi-square test was used for categorical variables. To eliminate the bias caused by confounders, we adjusted the risk factors of AKI by a propensity score analysis. The risk factors of AKI in our subjects were evaluated by a univariate logistic analysis, which indicated that risk factors of our patients included age, baseline Scr, uric acid, urea, hematocrit, diabetes, myocardial infarction, heart failure, diuretic, angiotensin receptor inhibitor, cephalosporin, and calcium antagonist. All these risk factors between the two groups were matched by 1:1 genetic matching, with a matching tolerance of 0.02. We then compared the baseline characteristics and incidence of endpoints of the two groups. To further verify our results, we conducted subgroup analyses according to patients' baseline renal function [(eGFR ≤30, 30-60, 60-90 and ≥90 mL/ (min 1.73 m^2)] and complications [including CKD, hypertension, diabetes mellitus, anemia, cardiovascular disease (CVD, including angina, myocardial infarction and heart failure), and age ≥75 years]. p <0.05 was considered statistically significant.

Results

Patient characteristics

We finally included 3061 patients in our study, 1641 in the aspirin group and 1420 in the combination group, the details are shown in Figure S1. The characteristics of enrolled patients are shown in Table 1. A total of 235 (7.68%) patients developed AKI in the enrolled patients, the incidence of AKI was significantly lower in the combination group (A vs C: 9.69% vs 5.35%, p <0.001) (Table S1).

Propensity score matching according to univariate logistic regression analysis

The univariate logistic regression analysis showed that the risk factors for AKI in the subjects included age, baseline Scr, uric acid, urea, hematocrit, diabetes, myocardial infarction, heart failure, anemia, CKD, diuretic, angiotensin receptor inhibitor, cephalosporin, and calcium antagonist (Table S2). Except for anemia and CKD (we matched baseline Scr and hematocrit), the other risk factors were matched by a 1:1 propensity score, and 986 pairs were finally obtained (Table 2). After matching, the risk factors included age, baseline creatinine, diabetes, heart failure, and so on, were balanced between the two groups.

Association between combination therapy and outcomes after matching

After matching, the incidence of AKI (A vs C: 7.71% vs 6.29%, p =0.217) showed no significant difference (Figure 1A). And the stage 1 AKI in the combination group was still lower than the aspirin group (A vs C: 6.59% vs 4.46%) (Figure 1A). Furthermore, the incidence of eGFR decline (A vs C: 24.75% vs 16.94%, p <0.001) was significantly

lower in the combination group (Figure 1B). However, as shown in Figure 1C, the risk of gastrointestinal bleeding (A vs C: 1.22% vs 2.84%, p =0.011) and in-hospital adverse outcomes (A vs C: 3.25% vs 7.00%, p <0.001) were significantly higher in the combination group.

Outcomes of subgroup analysis based on different baseline renal function

Considering that the occurrence of AKI is related to baseline renal function, we assessed the effect of baseline renal function on AKI, and divided patients into four groups according to their baseline eGFR: eGFR <30, 30-60, 60-90, and ≥90 mL/ (min 1.73 m^2). Then, the kidney-related outcomes were compared in different groups. The combination therapy showed no significant difference in the four groups. However, in group eGFR 30-60 mL/ (min 1.73 m^2), the stage 1 AKI was lower in combination group (A vs C: 9.09% vs 4.62%) and the protective effect was more obvious in group eGFR 60-90 mL/ (min 1.73 m^2) (A vs C: 6.14% vs 2.83%) (Table S3).

As for the incidence of eGFR decline, except group eGFR <30mL/ (min 1.73 m^2), the incidence of mild eGFR decline with the combination therapy was lower in all groups, while the incidence of severe eGFR decline showed no significant differences (Table S4).

Outcomes of subgroup analysis based on different complications

We further performed a subgroup analysis that included CKD, non-CKD, hypertension, diabetes, anemia, CVD, and people aged ≥75 years. For the incidence of AKI, except CVD population [odds ratio (OR), 2.818; 95% confidence interval (CI)

1.500-5.294; p =0.001], the combination therapy didn't increase the risk of AKI in any other population (Figure 2a).

For incidence of eGFR decline, the combination therapy was significantly lower in patients without CKD (OR, 0.560; CI 0.430-0.729; p <0.001), hypertension (OR, 0.662; CI 0.518-0.846; p =0.001), diabetes (OR, 0.675; CI 0.476-0.958; p =0.028). In contrast, there was a trend toward impairment in patients with CVD (OR, 1.268; CI 0.775-2.074; p =0.345). In other populations (aged and CKD), combination therapy had no significant relationship with eGFR decline (Figure 2b). The results were approximately similar to the primary endpoint.

Discussion

Our study firstly investigated the effect of edaravone combined with aspirin on renal function in patients with ischemic stroke. In general, aspirin combined with edaravone didn't increase the incidence of AKI in patients with ischemic stroke. Furthermore, the combination therapy was statistically significant in reducing the incidence of mild AKI in hospitalized ischemic stroke patients, especially in patients with baseline eGFR 60-90 mL/ (min 1.73 m^2). Unfortunately, gastrointestinal bleeding and in-hospital adverse outcomes in the hospital were positively associated with the combination therapy.

Aspirin is widely used in the prevention of cerebrovascular disease, even in patients with CKD. Hsiao KC et al. found that aspirin was significantly associated with renal failure in CKD patients [18]. However, several studies found that aspirin did not affect renal function [19], and even could slow down the deterioration process [20, 21]. The prevalence of AKI was 7.67% in our ischemic stroke patients who used aspirin, lower than 13.5%, which reported by another study in China [22]. It seems that the use of aspirin in ischemic stroke patients was related to decreased risk of AKI. The mechanism might involve in inhibition of TxA 2, excessive production of TxA 2 is harmful to renal function [23].

Edaravone is defined as a nephrotoxic drug for a long time and is reported to be one of the most common drugs related to AKI [12]. Nevertheless, our study showed that the combination therapy didn't increase the incidence of AKI, but decreased the mild renal deterioration, compared to the aspirin group. Actually, edaravone has been reported to

have protective effects in many animal models of kidney injury, such as ischemia/reperfusion, cisplatin, and diabetic nephropathy. The mechanisms might involve scavenging free radicals, inhibiting lipid peroxidation, inhibiting inflammatory factors, protecting renal mitochondria, inhibiting cell apoptosis, and reducing oxidative stress [14, 24, 25]. Similarly, it has also been found in clinical studies that edaravone might play a protective role in kidney by exerting antioxidant stress and inhibiting inflammatory levels in patients with paraquat poisoning [26, 27]. A study found a negative correlation between edaravone use and AKI in 5689 patients with acute ischemic stroke [27], which was consistent with our results.

The subgroup analysis based on the baseline renal function indicated that the combination therapy showed the optimum protective effect to eGFR decline in patients with baseline eGFR 60-90 mL/ (min 1.73 m^2), while in patients with eGFR <30 mL/ (min 1.73 m^2), the combination had no protective effect and even a non-significant aggravate trend. This is consistent with its instruction: edaravone may aggravate renal failure in severe renal failure patients, and severe renal failure is a contraindication. In contrast, Kamouchi M et.al have found that edaravone is negatively correlated with the occurrence of AKI [27], and the baseline eGFR in hospitalized patients cannot accurately predict the deterioration of renal function after medication [28]. Thus, there is a few off-label uses of edaravone in patients with eGFR <30 mL/ (min 1.73 m^2), and we enrolled these patients to evaluate the combination therapy in patients with different basic renal function in the real world. The subgroup analysis based on different complications showed that the

combination treatment had no effect on the incidence of AKI in CKD, hypertension, diabetes, anemia, and aged groups, and even had a protective effect on the mild deterioration of renal function in CKD, anemia and aged groups. Nevertheless, the combination therapy increased the incidence of AKI in CVD patients. At present, edaravone is mainly used for cerebrovascular disease rather than cardiovascular disease. The safety of edaravone on patients with CVD hasn't been studied yet. However, edaravone has been reported to improve septic heart function in rats by inducing the HIF-1/HO-1 pathway [29]. In addition, long-term aspirin is a conventional therapy for CVD patients, so their renal function may be in the worse baseline condition. Thus, the combination therapy should be cautious in CVD patients.

Although the combination therapy showed well renal safety, our data indicated that the combination therapy might relate to a higher risk of gastrointestinal bleeding and in-hospital mortality. As we all know, gastrointestinal bleeding is a common adverse reaction of aspirin, and gastrointestinal bleeding is highly related to the recurrence of ischemic stroke [30]. This may restrict the use of combination therapy in ischemic stroke patients. However, we only considered the factor related to AKI when matching, this result may be biased. The risk of bleeding and influence on mortality of the combination therapy needs to be further studied.

Strengths: (1) To our knowledge, this is the first study that evaluated the safety of aspirin in combination with edaravone in patients with ischemic stroke; (2) The data we used was from real-world, hence the results were more relevant to the actual clinical

situation; (3) We conducted a propensity score matching to eliminate the influences caused by other confounders; (4) We further stratified patients based on renal function and complications to provide individualized advice to different patients.

Limitations: (1) Due to the limitations of our database, the data regarding clinical severity of the ischemic stroke e. g NIHSS, couldn't be obtained to evaluate the efficacy of the combination therapy. Thus, we mainly focused on the renal safety of the combination therapy in this study; (2) Even hypertension, angina, contrast agents, ACEI, and β-blocker were still significantly different between the two groups after matching, but they were not risk factors to AKI in our population while the risk factors were balanced between the two groups; (3) This is a single-center retrospective research with its inherent restriction, and the data was from the real world, hence the duration of our therapy and the detailed types of stroke couldn't be restricted; (4) We focused on the renal safety of the combination therapy, and the risk factors related to bleeding or death didn't consider when matching. Thus, large multicenter randomized trials are needed to further validate our findings.

Conclusion

In brief, the combination of aspirin and edaravone didn't cause renal damage in most ischemic stroke patients and was even related to delayed mild renal exacerbation in people with baseline eGFR >30 mL/ (min1.73 m^2). However, when patients with eGFR <30 mL/ (min1.73 m^2), CVD, and high risk of bleeding, the combination should be weighed.

Statements

Author Contributions X-C Z and K L conceived and designed the study. H-Q Y and K L performed data acquisition and statistically analyses. W-J Y and M-C L contributed the interpretation and discussion of the results. H-Q Y prepared the figures and tables. H-Q Y and K L drafted the manuscript. All authors approved the final version of the manuscript.

Conflict of interest The authors declare that they have no conflict of interest.

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Patient consent for publication All subjects were anonymized, thus the provision of informed consent was not required.

Patient and Public Involvement Not applicable.

Data availability statement Data are available upon reasonable request.

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Medical Ethical Committee in the Third Xiangya Hospital of Central South University (2020-S342).

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Tables

Characteristics	Aspirin group(n=1641)	Combination group(n=1420)	*p*
Age (years), mean±SD	69.52±10.45	65.40±12.05	<0.001*
Sex (male)	1069(65.14%)	915(64.44%)	0.683
eGFR [mL/ (min 1.73 m^2)], mean±SD	68.50±32.62	81.81±33.84	<0.001*
Baseline creatinine (μmol/L), median (IQR)	95(73-128)	82(65-105)	<0.001*
Uric acid (μmol/L), mean±SD	371.40±129.94	329.54±121.94	<0.001*
BUN (mmol/L), median (IQR)	6.32(4.79-8.42)	5.26(4.08-6.82)	<0.001*
Hematokrit (%), mean±SD	37.64±6.04	39.74±5.75	<0.001*
Complication			
Hypertension	1336(81.41%)	1134(79.86%)	0.277
Diabetes	693(42.23%)	442(31.13%)	<0.001*
Angina	297(18.10%)	22(1.55%)	<0.001*
Myocardial infarction	302(18.40%)	27(1.90%)	<0.001*
Heart failure	214(13.04%)	78(5.49%)	<0.001*
Anemia	795(48.45%)	434(30.56%)	<0.001*
CKD	678(41.32%)	349(24.58%)	<0.001*
Nephrotoxic drug			
Contrast agents	461(28.09%)	200(14.08%)	<0.001*
Diuretic	366(22.30%)	190(13.38%)	<0.001*
ACEI	539(32.85%)	93(6.55%)	<0.001*
ARB	342(20.84%)	143(10.07%)	<0.001*
Calcium antagonists	743(45.28%)	647(45.56%)	0.874
β-blocker	539(32.85%)	93(6.55%)	<0.001*

Cephalosporin	275(16.76%)	312(21.97%)	<0.001*
Statins	1258(76.66%)	1061(74.72%)	0.211

Table 1. Baseline characteristics of enrolled patients.

Abbreviations: BUN, blood uric nitrogen; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor inhibitor.

*p <0.05.

Characteristics	Aspirin group(n=986)	Combination group(n=986)	*p*
Age (years), mean±SD	68.10±10.88	67.94±10.76	0.739
Sex (male)	618(62.68%)	601(60.95%)	0.431
eGFR (mL/ (min 1.73 m^2)), mean±SD	74.37±32.05	75.04±30.73	0.630
Baseline creatinine (μmol/L), median (IQR)	87(68-117)	85.5(68-112)	0.962
Uric acid (μmol/L), mean±SD	345.53±117.87	355.56±119.75	0.066
BUN (mmol/L), median (IQR)	5.85(4.58-7.60)	5.62(4.37-7.58)	0.932
Hematokrit (%), mean±SD	38.74±5.71	39.15±5.68	0.095
Complication			
Hypertension	788(79.92%)	834(84.58%)	0.007*
Diabetes	355(36.00%)	368(37.32%)	0.544
Angina	202(20.49%)	15(1.52%)	<0.001*
Myocardial infarction	32(3.25%)	27(2.74%)	0.509
Heart failure	70(7.10%)	72(7.30%)	0.862
Anemia	400(40.57%)	341(34.58%)	0.006*
CKD	327(33.16%)	306(31.03%)	0.311
Nephrotoxic drug			
Contrast agents	266(26.98%)	126(13.78%)	<0.001*
Diuretic	150(15.21%)	140(14.20%)	0.525
ACEI	306(31.03%)	71(7.20%)	<0.001*
ARB	128(12.98%)	132(13.39%)	0.790
Calcium antagonists	467(47.36%)	499(50.61%)	0.149
β-blocker	306(31.03%)	71(7.20%)	<0.001*
Cephalosporin	172(17.44%)	159(16.13%)	0.433

Statins	729(73.94%)	750(76.06%)	0.275

Table 2. Characteristics after propensity-score matching.

Abbreviations: BUN, blood uric nitrogen; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor inhibitor.

*p <0.05.

Figures

Figure 1

A:Incidence of AKI after matching

B:Incidence of eGFR decline after matching

C:Incidence of gastrointestinal bleeding and in-hospital adverse outcomes after matching

n, the number of patients

Figure 2 The renal outcome of patients with different complication

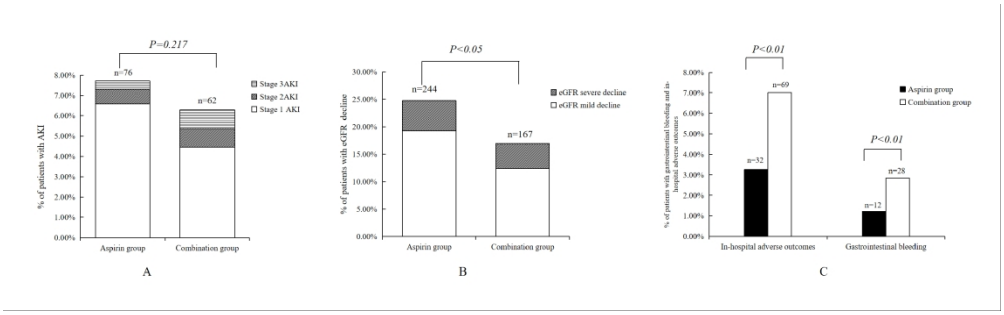
CKD: patients with chronic kidney injury; Non CKD: patients without CKD; CVD: patients with cardiovascular disease; Aged: age ≥75 years.

OR, odds ratio; CI, 95%confidence interval.

a, the association between the combination therapy and AKI in the subgroups;

b, the association between the combination therapy and eGFR decline in the subgroups.

A, aspirin group; C, combination group.



A:Incidence of AKI after matching
B:Incidence of eGFR decline after matching
C:Incidence of gastrointestinal bleeding and in-hospital adverse outcomes after matching
n, the number of patients

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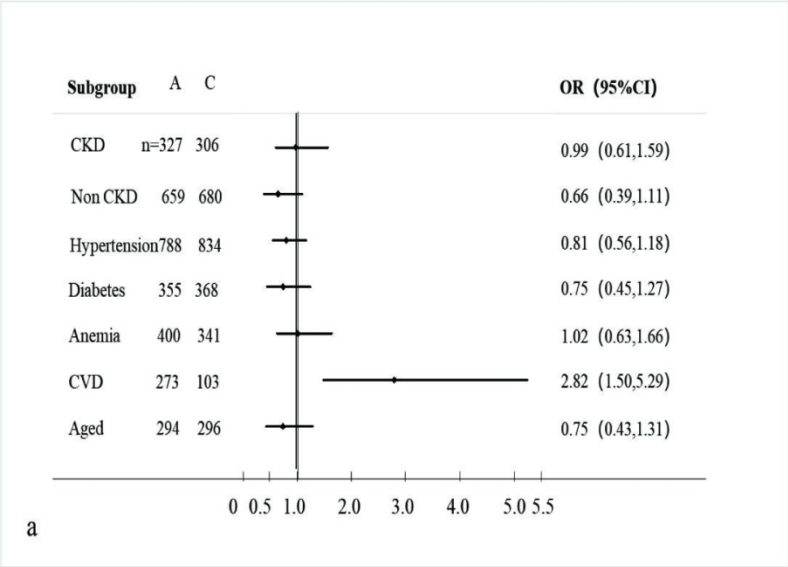

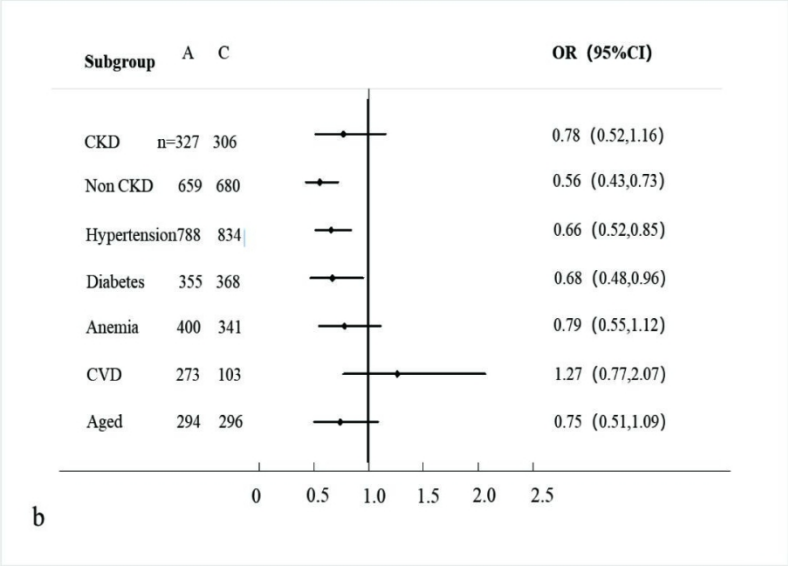

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a, the association between the combination therapy and AKI in the subgroups;
b, the association between the combination therapy and eGFR decline in the subgroups. A, aspirin group; C, combination group.

92x139mm (300 x 300 DPI)

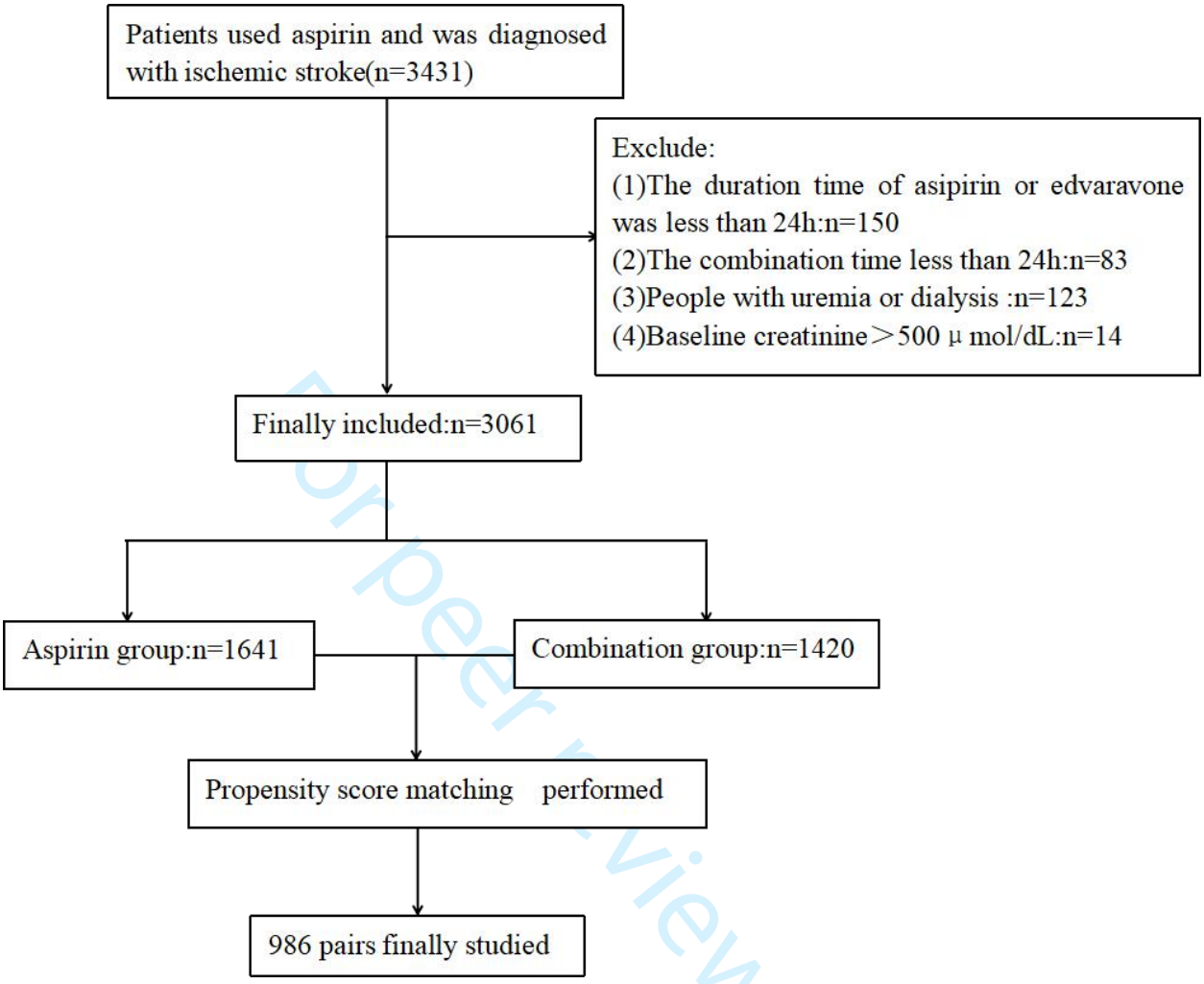

Figure S1. The screening flow chart

Endpoint	Aspirin group(n=1641)	Combination group(n=1420)	*p*
eGFR decline	435(26.51%)	242(17.04%)	<0.001*
eGFR mild decline	338(20.60%)	178(12.54%)	
eGFR severe decline	97(5.91%)	64(4.51%)	
AKI(AKIN stage ≥1)	159(9.69%)	76(5.35%)	<0.001*
Stage 1 AKI	143(8.71%)	55(3.87%)	
Stage 2 AKI	9(0.55%)	11(0.77%)	
Stage 3 AKI	7(0.43%)	10(0.70%)	

Table S1. Incidence of AKI and eGFR decline in patients before matching
*p <0.05.

Variable	OR	Lower 95%CI	Upper 95%CI	*p*
Sex (male)	1.035	0.782	1.369	0.811
Age (years)	1.021	1.008	1.034	0.001*
Uric acid (μmol/L)	1.002	1.001	1.003	0.001*
BUN (mmol/L)	1.147	1.116	1.179	0.000*
Baseline creatinine (μmol/L)	1.009	1.007	1.010	0.000*
Hematokrit (%)	0.923	0.903	0.942	0.000*
Hypertension	1.400	0.966	2.028	0.076
Diabetes	1.761	1.348	2.300	0.000*
Angina	0.696	0.424	1.142	0.151
Myocardial infarction	2.255	1.601	3.177	0.000*
Heart failure	3.244	2.328	4.520	0.000*
Anemia	2.351	1.792	3.083	0.000*
CKD	3.349	2.548	4.401	0.000*
Contrast agents	0.875	0.626	1.222	0.434
Diuretic	4.604	3.495	6.065	0.000*
ACEI	1.071	0.775	1.480	0.677
ARB	1.403	1.006	1.958	0.046*
Calcium antagonists	1.402	1.074	1.831	0.013*
β-blocker	1.071	0.775	1.480	0.677
Cephalosporin	1.533	1.128	2.083	0.006*
Statins	0.906	0.668	1.227	0.523

Table S2. Univariate logistic regression analysis for risk factors of AKI before matching

Abbreviations: BUN, blood uric nitrogen; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor inhibitor. OR, odds ratio; 95%CI, confdence interval.

*p <0.05.

Baseline eGFR	AKIN stage	Aspirin group	Combination group	*p*
eGFR<30mL/		N=63(%)	N=68(%)	
(min1.73 m^2)	AKI (Stage ≥1)	14(22.22%)	19(27.94%)	0.451
				0.463
	0	49(77.78%)	49(72.06%)	
	Stage 1	13(20.63%)	18(26.47%)	
	Stage 2	0	0	
	Stage 3	1(1.59%)	1(1.47%)	
30≤ eGFR		N=264(%)	N=238(%)	
<60mL/	AKI (Stage ≥1)	26(9.85%)	18(7.56%)	0.366
(min1.73 m^2)				0.417
	0	238(90.15%)	220(92.44%)	
	Stage 1	24(9.09%)	11(4.62%)	
	Stage 2	1(0.38%)	4(1.68%%)	
	Stage 3	1(0.38%)	3(1.26%)	
60≤ eGFR		N=391(%)	N=389(%)	
<90mL/	AKI (Stage ≥1)	29(7.42%)	17(4.37%)	0.071
(min1.73 m^2)				0.077
	0	362(92.58%)	372(95.63%)	
	Stage 1	24(6.14%)	11(2.83%)	
	Stage 2	3(0.77%)	3(0.77%)	
	Stage 3	2(0.51%)	3(0.77%)	
90≤eGFRmL/		N=268(%)	N=291(%)	
(min1.73 m^2)	AKI (Stage ≥1)	7(2.61%)	8(2.75%)	0.920
				0.913
	0	261(97.39%)	283(97.25%)	

Stage 1	4(1.49%)	4(1.37%)
Stage 2	3(1.12%)	2(0.69%)
Stage 3	0	2(0.69%)

Table S3.Incidence of different stages AKI in diffenrent baseline eGFR groups between the two therapies.

*p <0.05.

Baseline eGFR	eGFR decline	Aspirin group	Combination group	*p*
<30mL/ (min1.73		N=63(%）	N=68(%)	
m^2)	decline	15(23.81%)	21(30.88%)	0.365
				0.309
	0	48(76.19%)	47(69.12%)	
	mild decline	12(19.05%)	14(20.59%)	
	severe decline	3(4.76%)	7(10.29%)	
30≤ eGFR		N=264(%)	N=238(%)	
<60mL/ (min1.73	decline	52(19.70%)	30(12.61%)	0.032*
m^2)				0.040
	0	212(80.30%)	208(87.39%)	
	mild decline	39(14.77%)	19(7.98%)	
	severe decline	13(4.92%)	11(4.62%)	
60≤ eGFR		N=391(%)	N=389(%)	
<90mL/ (min1.73	decline	79(20.20%)	40(10.28%)	0.000*
m^2)				0.000
	0	312(79.80%)	349(89.72%)	
	mild decline	57(14.58%)	26(6.68%)	
	severe decline	22(5.63%)	14(3.60%)	
90≤eGFRmL/		N=268(%)	N=291(%)	
(min1.73 m^2)	decline	98(36.57%)	76(26.12%)	0.008*
				0.009
	0	170(63.43%)	215(73.88%)	
	mild decline	82(30.60%)	63(21.65%)	
	severe decline	16(5.97%)	13(4.47%)	

Table S4.Incidence of eGFR decline in diffenrent baseline eGFR groups between the two

therapies.

eGFR decline: eGFR decreased >10% from baseline eGFR; mild decline: decreased 10%-30% from baseline eGFR; severe decline: decreased >30% from baseline eGFR; eGFR didn't decrease or decreased ≤10%.

*p <0.05.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	7-8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*6-8*
Bias	9	Describe any efforts to address potential sources of bias	7-8
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	7-8
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	9
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	9-10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-10
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-11
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	12-15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.