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Renal safety evaluation of aspirin plus edaravone in patients with ischaemic stroke: 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 ischaemic 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 patients with ischaemic stroke.

Design A propensity score-matched retrospective cohort study.

Setting A tertiary hospital in China.

Participants Patients with ischaemic stroke were treated with aspirin from February 2007 to May 2018.

Primary and secondary outcome measures Acute kidney injury (AKI, diagnosed by the 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/min/1.73 m^2, especially in eGFR 60–90 mL/min/1.73 m^2. In patients with different complications, the incidence of AKI showed no significant differences in patients with chronic kidney injury, hypertension, anaemia, age above 75 years, except in patients with cardiovascular disease (OR, 2.82; 95% CI 1.50 to 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 ischaemic stroke didn't increase the nephrotoxicity of aspirin, and even had a protective effect on mild renal deterioration. Nevertheless, there is a need to be cautious when patients are in bad pathophysiological conditions and at high risk of bleeding.

Strengths and limitations of this study

- A retrospective study in a tertiary medical centre.
- This study included 3061 patients with ischaemic stroke from the electronic medical record system of a Chinese tertiary hospital.
- The potential confounding factors of acute kidney injury were balanced by propensity score matching.
- Subgroup analyses were conducted according to patients' baseline estimated glomerular filtration rate 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; ischaemic stroke makes up about 70% of all cases. About 13.7 million people suffer from stroke every year and 5.8 million die because 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 ischaemic stroke.[2] Aspirin is recommended to reduce platelet aggregation during the onset of ischaemic stroke and prevent recurrence.[3 4] Edaravone, a free radical scavenger, was approved by the US Food and Drug Administration for amyotrophic lateral sclerosis[5] and is also used to improve the neurological symptoms, daily life and dysfunction associated with acute ischaemic stroke.[6] In recent years, several studies have determined that combination of aspirin and edaravone is a more effective therapy than aspirin or edaravone alone for ischaemic stroke.[6 7]

As we all know, aspirin has been 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 patients with chronic kidney disease (CKD).[8] Furthermore, AKI caused by aspirin is commonly reported.[9 10] Meanwhile, a postmarketing

surveillance system report of 207 cases showed that edaravone aggravated renal dysfunction by altering renal haemodynamics.[11] And a study based on 5195 890 reports found 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 ischaemic 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] Patients with ischaemic stroke are at a high-risk of AKI,[15] and AKI is associated with higher long-term and short-term mortality after ischaemic stroke.[16] No AKI prevention strategy has been proved to be completely effective so far,[17] so the prevention of AKI in patients with ischaemic stroke is of great importance.

Thus, a retrospective matched cohort study was conducted to investigate the renal safety of aspirin and aspirin combined with edaravone in patients with ischaemic stroke, and to provide a reference for clinical medication of ischaemic 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. The medical records were obtained from the electronic medical record system. Inclusion criteria: (1) Patients with ischaemic stroke diagnosed by CT scan; (2) Patients treated with aspirin during hospitalisation; (3) Complete serum creatinine (Scr) records before and after aspirin administration. Exclusion criteria: (1) The duration time of aspirin or edaravone less than 24 hours; (2) The combination time of aspirin and edaravone less than 24 hours; (3) Patients with uraemia; (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 hours; edaravone, 30 mg intravenous infusion, twice a day, lasted at least 24 hours. Medical information including basic information, diagnostic records, laboratory indexes and medication records were collected from the electronic medical record system.

Clinical assessment

Ischaemic stroke was diagnosed by CT scan, and other complications were defined according to the diagnosis in medical records by an investigator blinded to the allocation. Anaemia was defined as haematocrit <36.0% for women, and <39.0% for men. CKD was defined as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2, calculated by the simplified Modification of Diet in Renal Disease formula. Combination therapy: the combined use of aspirin and edaravone lasted for at least 24 hours.

Definition of end points

Primary end point: the occurrence of AKI. AKI was defined according to the criterion of the Acute Kidney Injury Network. Stage 1: Scr increased by 1.5 times or 0.3 mg/dL than baseline Scr; stage 2: Scr increased by two times than baseline; stage 3: Scr increased by three times or ≥4 mg/dL or renal replacement therapy initiated. Any of the above conditions that happened within 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 end points: (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.

Statistical analysis

Statistical analysis was conducted by SPSS V.22.0 (SPSS, Chicago, Illinois, USA). The continuous variables were expressed as mean±SD and categorical variables as percentages. A two-sided t test was used for continuous variables of normal distribution, Mann-Whiney U-test was used for non-normal distribution and the χ^2 test was used for categorical variables. To eliminate bias caused by confounders, we adjusted risk factors of AKI by propensity score analysis. The risk factors of AKI in our subjects were evaluated by univariate logistic analysis, which indicated that risk factors of our patients included age, baseline Scr, uric acid, urea, haematocrit, 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 end points of the two groups. To further verify our results, we conducted subgroup analyses according to patients' baseline renal function (eGFR ≤30 mL/min/1.73 m^2, 30–60 mL/min/1.73 m^2, 60–90 mL/min/1.73 m^2 and ≥90 mL/min/1.73 m^2) and complications (including CKD, hypertension, diabetes mellitus, anaemia, cardiovascular disease (CVD, including angina, myocardial infarction and heart failure), and age ≥75 years). A value of $p<0.05$ 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 online supplemental figure S1. The characteristics of enrolled patients are shown

Table 1 Baseline characteristics of enrolled patients

Characteristics	Aspirin group (n=1641)	Combination group (n=1420)	*P value*
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*
Haematocrit (%), 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*
Anaemia	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

*p <0.05.
ACEI, ACE inhibitor; ARB, angiotensin receptor inhibitor; BUN, blood urea nitrogen; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

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) (online supplemental 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, haematocrit, diabetes, myocardial infarction, heart failure, anaemia, CKD, diuretic, angiotensin receptor inhibitor, cephalosporin and calcium antagonist (online supplemental table S2). Except for anaemia and CKD (we matched baseline Scr and haematocrit), 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 including 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 in 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:

Table 2 Characteristics after propensity score matching

Characteristics	Aspirin group (n=986)	Combination group (n=986)	*P value*
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
Haematocrit (%), 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
Anaemia	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

*p <0.05.
ACEI, ACE inhibitor; ARB, angiotensin receptor inhibitor; BUN, blood urea nitrogen; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

eGFR <30 mL/min/1.73 m^2, 30–60 mL/min/1.73 m^2, 60–90 mL/min/1.73 m^2 and ≥90 mL/min/1.73 m^2. Then, the kidney-related outcomes were compared in the different groups. The combination therapy showed no significant difference in the four groups. However, in the group eGFR 30–60 mL/min/1.73 m^2, the stage 1 AKI was lower in the combination group (A vs C: 9.09% vs 4.62%) and the protective effect was more obvious in the group eGFR 60–90 mL/min/1.73 m^2 (A vs C: 6.14% vs 2.83%) (online supplemental table S3).

As for the incidence of eGFR decline, except group eGFR <30 mL/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 (online supplemental table S4).

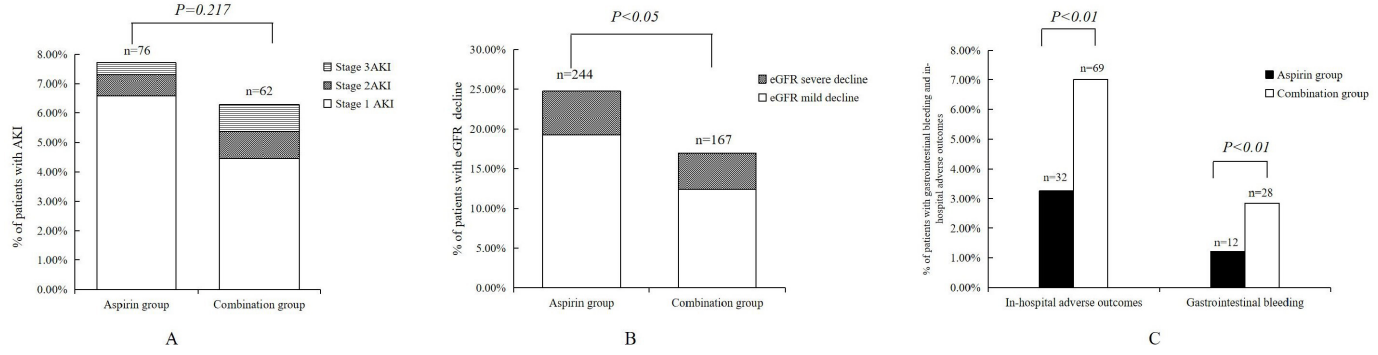

Figure 1 (A) Incidence of AKI after matching. (B) Incidence of eGFR decline after matching. (C) Incidence of gastrointestinal bleeding and in-hospital adverse outcomes after matching. AKI, acute kidney injury ; eGFR, estimated glomerular filtration rate; n, the number of patients.

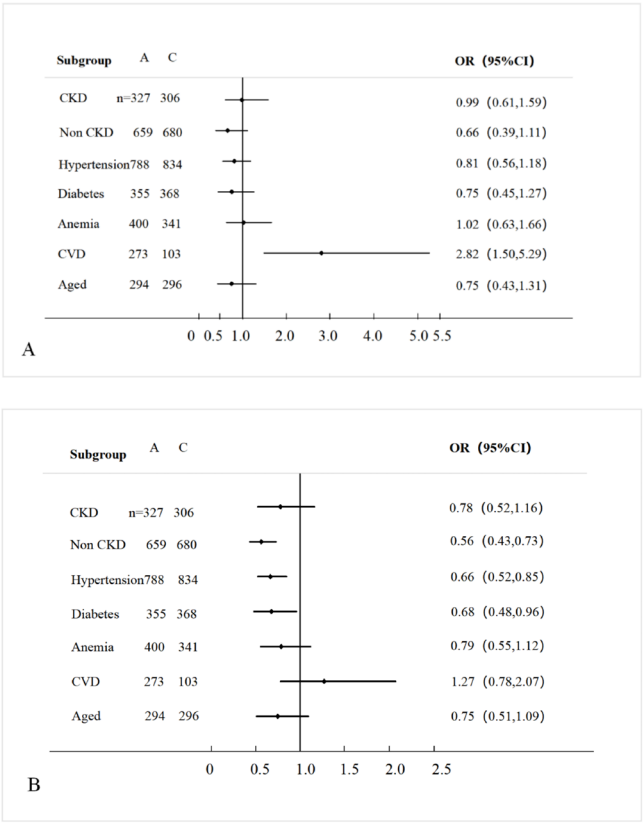

Figure 2 The renal outcome in patients with different complications. (A) The association between the combination therapy and AKI in the subgroups; (B) The association between the combination therapy and eGFR decline in the subgroups. A, aspirin group; C, combination group. Aged: age ≥75 years; AKI, acute kidney injury; CKD: chronic kidney disease; CVD: cardiovascular disease; eGFR, estimated glomerular filtration rate; Non CKD: patients without CKD.

Outcomes of subgroup analysis based on different complications

We further performed a subgroup analysis that included CKD, non-CKD, hypertension, diabetes, anaemia, CVD and people aged ≥75 years. For the incidence of AKI, except in the CVD population (OR, 2.82; 95% CI 1.50 to 5.29; 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, 0.56; 95% CI 0.43 to 0.73; p<0.001), hypertension (OR, 0.66; 95% CI 0.52 to 0.85; p<0.001), diabetes (OR, 0.68; 95% CI 0.48 to 0.96; p=0.028). In contrast, there was a trend towards impairment in patients with CVD 1.(OR, 1.27; 95% CI 0.78 to 2.07; 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 end point.

DISCUSSION

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

Aspirin is widely used in the prevention of cerebrovascular disease, even in patients with CKD. Hsiao *et al* found that aspirin was significantly associated with renal failure in patients with CKD.[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 patients with ischaemic stroke who used aspirin, lower than 13.5%, which is reported by another study in China.[22] It seems that the use of aspirin in patients with ischaemic stroke was related to decreased risk of AKI. The mechanism might be involved in inhibition of tranexamic acid-2(TxA 2); excessive production of TxA 2 is harmful to renal function.[23]

Edaravone has been 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 with the aspirin group. Actually, edaravone has been reported to have protective effects in many animal models of kidney injury, such as ischaemia/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.[13 14 24] Similarly, it has also been found in clinical studies that edaravone might play a protective role in the kidney by exerting antioxidant stress and inhibiting inflammatory levels in patients with paraquat poisoning.[25 26] A study found a negative correlation between edaravone use and AKI in 5689 patients with acute ischaemic stroke,[26] which was consistent with our results.

A subgroup analysis based on baseline renal function indicated that the combination therapy showed the optimum protective effect on 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 patients with severe renal failure, and severe renal failure is a contraindication. In contrast, Kamouchi *et al* have found that edaravone is negatively correlated with the occurrence of AKI,[26] and the baseline eGFR in hospitalised patients cannot accurately predict the deterioration of renal

function after medication.[27] Thus, there are 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 a different basic renal function in the real world. Subgroup analysis based on different complications showed that the combination treatment had no effect on the incidence of AKI in the CKD, hypertension, diabetes, anaemia and aged groups, and even had a protective effect on mild deterioration of renal function in the CKD, anaemia and aged groups. Nevertheless, the combination therapy increased the incidence of AKI in patients with CVD. At present, edaravone is mainly used for cerebrovascular disease rather than CVD. 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 hypoxia-inducible factor-1/heme oxygenase-1(HIF-1/HO-1) pathway.[28] In addition, long-term aspirin is a conventional therapy for patients with CVD, so their renal function may be in the worse baseline condition. Thus, the combination therapy should be cautiously used in patients with CVD.

Although the combination therapy showed good 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 ischaemic stroke.[29] This may restrict the use of combination therapy in patients with ischaemic stroke. However, we only considered the factors 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 ischaemic stroke; (2) We used real-world data, hence the results were more relevant to the actual clinical situation; (3) We conducted propensity score matching to eliminate the influences caused by other confounders; (4) We further stratified patients based on renal function and complications to provide individualised advice to different patients.

Limitations: (1) Due to the limitations of our database, the data regarding clinical severity of the ischaemic stroke for example, the score of National Institutes of Health stroke scale (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, ACE inhibitors, and β-blockers 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-centre retrospective research with its inherent restrictions, and the data were 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 were not considered when matching. Thus, large multicentre randomised trials are needed to further validate our findings.

CONCLUSION

In brief, the combination of aspirin and edaravone didn't cause renal damage in most patients with ischaemic stroke and was even related to delayed mild renal exacerbation in people with baseline eGFR >30 mL/min/1.73 m^2. However, when treating patients with eGFR <30 mL/min/1.73 m^2, CVD and high risk of bleeding, the combination should be weighed.

Contributors X-CZ and KL: conceived and designed the study. H-QY and KL: data acquisition and statistical analyses. W-JY and M-CL: interpretation and discussion of the results. H-QY: prepared the figures and tables. H-QY and KL: drafted the manuscript. All authors approved the final version of the manuscript. H-QY is the guarantor.

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Patient consent for publication Not applicable.

Ethics approval Approval was granted by the Medical Ethical Committee in the Third Xiangya Hospital of Central South University (2020-S342).

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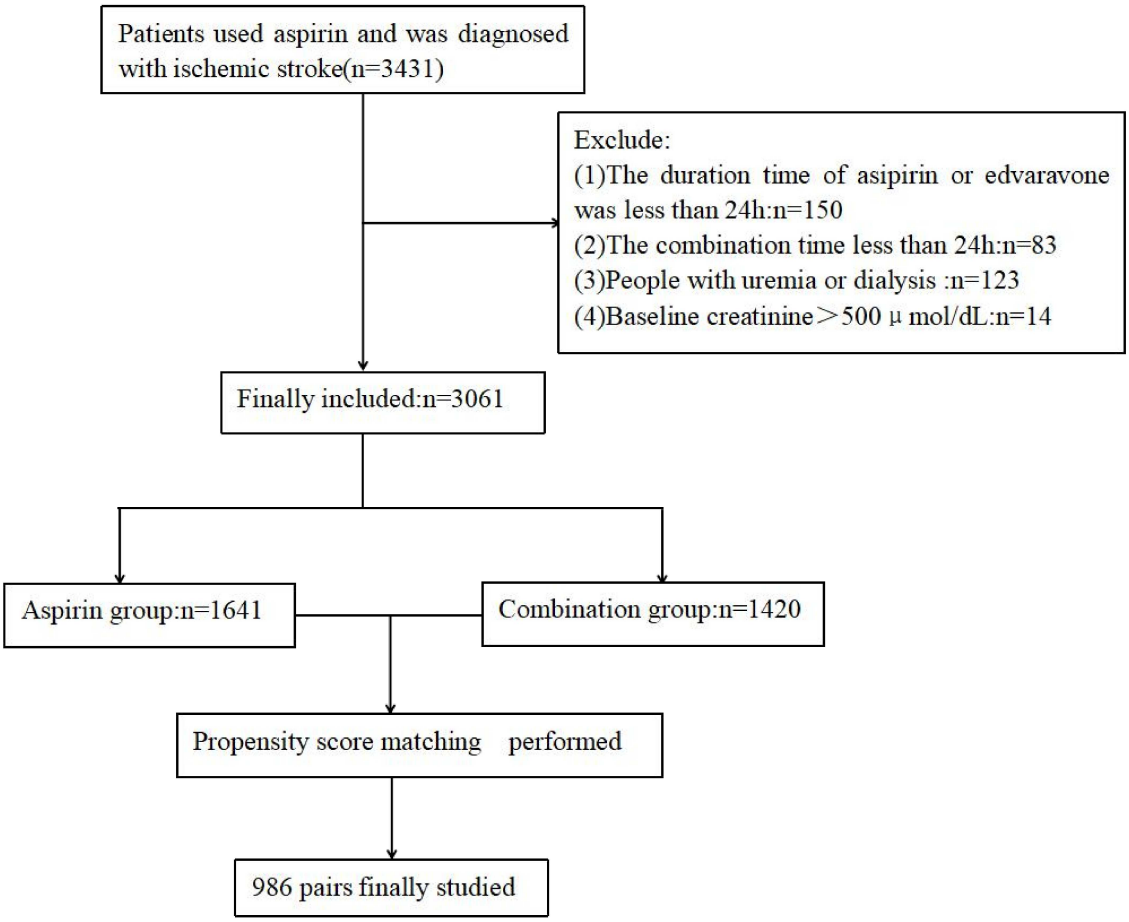

Figure S1. The screening flow chart

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.