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Use of angiotensin-converting enzyme inhibitors or receptor blockers is associated with reduced mortality in patients with post-acute kidney injury: meta-analysis

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Abstract. – OBJECTIVE: To investigate the association between the use of ACEis or ARBs and outcomes in patients recovering from AKI.

MATERIALS AND METHODS: We searched PubMed, MEDLINE, Cochrane Database, Web of Science and Embase databases from inception to May 2021 and performed a systematic review and meta-analysis using the "meta" package in R 4.0.3.

RESULTS: Five cohort studies, published from 2018 to 2021 with 153174 participants and approximately 39081 mortalities, were included in our meta-analysis. The meta-analysis showed that the use of ACEis/ARBs in patients with post-AKI is associated with a significantly lower risk of death (HR 0.80; 95% CIs, 0.72-0.90) and subgroup analysis showed a significant result in ACEi/ARB users with over 1-year of follow-up (HR 0.86; 95% CIs, 0.77-0.95).

CONCLUSIONS: The use of ACEi/ARB in patients with post-AKI is associated with a significantly lower risk of death.

Key Words:
ACEI, ARB, Mortality, Post-AKI.

Abbreviations
AKI: Acute kidney injury; ACEi: Angiotensin-converting enzyme inhibitors; ARB: Angiotensin-receptor blockers; RCTs: Randomized controlled trials; Cis: Confidence intervals; HR: Hazard ratio.

Introduction

Acute kidney injury (AKI) is an important clinical syndrome associated with increased mortality, a prolonged hospital stay, and the risk of chronic kidney disease[1-3]. According to a 2013 cross-sectional survey in China, the detection rate of AKI was 0.99% by the KDIGO criteria and 2.03% by the expanded criteria[4]. Patients discharged after an episode of AKI have an 80% increased risk of death after hospitalization compared with patients who do not develop AKI[5]. There are currently no known effective therapies for AKI, and little is known about the specific processes of care that could improve outcomes after episodes of AKI.

There has been increasing recognition of the renoprotective effect of angiotensin-converting enzyme inhibitors (ACEis) or angiotensin-receptor blockers (ARBs) in chronic kidney disease (CKD)[6-9], hypertension[10,11], COVID-19[12-14], heart failure[15,16], diabetes[6], and pregnacy[17]. Despite their frequent use, exposure to ACEis or ARBs might exacerbate AKI through vasodilatation of the efferent arterioles and the resultant reduction in glomerular filtration pressure[18] and the use of ACEis or ARBs have long been regarded as a cause of AKI in patients with dehydration, cardiovascular decompensation or infections[19]. Slagelse et al[20] found that current users of ACEi or ARB may have a small increase in mortality rate compared with patients with postoperative AKI; however, Gayat et al[21] reported that an ACEi or ARB prescription in patients discharged alive from the ICU after AKI was associated with a decrease in 1-year mortality. Therefore, the relationship between ACEi or ARB prescriptions and the mortality of patients recovering from AKI remains controversial. In this study, we evaluated whether the use of ACEis or ARBs was associated with better outcomes in patients with post-AKI.

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Materials and Methods

Literature Search

We searched the PubMed, Medline, Embase, Cochrane, and Web of Science for epidemiological studies published up to May 2021. We used the keywords combined with "AND" & "OR". The search string was: (((("angiotensin-converting enzyme inhibitors"[MeSH Terms]) OR ("angiotensin-receptor blockers"[MeSH Terms]) OR ("renin-angiotensin-aldosterone system"[MeSH Terms])) AND (("acute kidney injury"[MeSH Terms]) AND (("mortality" [MeSH Terms]) OR ("death" [MeSH Terms])))). Moreover, we searched reference lists of the relevant articles and reviews to identify additional studies. The search was limited to human studies. PROSPERO registration number: CRD42021253828.

Study Selection

We framed the inclusion criteria according to the PICOS (population, intervention, comparison, outcome, and study design). The following criteria were used for each domain: (1) Population: Adult patients (>18 years of age) with post-AKI. (2) Intervention: use of ACEis/ARBs (patients who had taken any ACEis/ARBs for over 14 days within 6 months after the hospital discharge date of the index AKI episode). (3) Comparison: non-users of ACEis/ARBs or patients who had taken any ACEis/ARBs for less than 14 days within 6 months after the hospital discharge date of the index AKI episode. (4) Outcome: death. (5) Study design: randomized controlled trial (RCTs), cohort studies, or case-control studies. Studies were excluded if (1) they did not provide original data, or hazard ratio, or their 95% confidence intervals (CIs), or information allowing us to compute them; (2) they did not have full-text availability; or (3) they were low-quality studies (the Newcastle-Ottawa scale was less than 4 stars).

Data Extraction

The initial study selection was performed by pairs of reviewers (Heng Shi and Qin Peng; Xian-Ling Zhou and Shi-Ping Zhu) independently screening the titles and abstracts. The full-texts of potentially relevant studies were obtained for detailed evaluation. Three investigators (Heng Shi, Qin Peng, Xian-Ling Zhou) independently extracted the following information from each included article: (1) name of first author, year of publication; (2) study design and location; (3) patient characteristics, period of follow-up; (5) mortality rate by ACEis or ARBs intake status, and its 95% confidence intervals (CIs). Data extracted from the studies were independently checked for accuracy by two reviewers (Shi-Ping Zhu and Sheng-Yun Sun). Discrepancies in data extraction were resolved by consensus, referring to the original article.

Methodological Quality Assessment

The included observational studies were assessed based on the Newcastle-Ottawa Scale for the quality of non-randomized studies. The Newcastle-Ottawa Scale contains eight items that were categorized into three categories: selection (four items including the representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, and outcome of interest was not present at start of study, one star each), comparability (one item including the control for important factor or additional factor, up to two stars), and exposure/outcome (three items including the assessment of outcome, follow-up long enough for outcomes to occur, and adequacy of follow-up of cohorts, one star each). A "star" presents a "high-quality" design feature. A score of over 4 stars is defined as high-quality research and the other studies were defined as low-quality research.

According to the *Cochrane Handbook*, publication bias can be assessed in reviews with a sufficient number (>10) of included studies. Since only 5 articles were included in our meta-analysis, we did not assess the publication bias.

Statistical Analysis

The overall analysis, including all eligible studies, was performed based on study design and period of follow-up when appropriate data were available. The hazard ration (HR) was transformed to its natural logarithm before pooling, and the variance was calculated by ((ln (upper CI HR) - ln (lower CI HR))/3.92). Pooled HR estimates and corresponding 95% CIs were calculated by the inverse-variance-weighted random-effects model.

Heterogeneity was assessed using the Higgins I-squared statistic (I^2). I^2 values of 25, 50, and 75% suggest low, moderate, and high degrees of heterogeneity, respectively. The random-effects model was used for data analysis when I^2>50%; otherwise, the fixed-effects model was used. Sensitivity analysis was carried out to characterize potential sources of statistical heterogeneity, by excluding studies one-by-one and analyzing the homogeneity and effect size for all the remaining

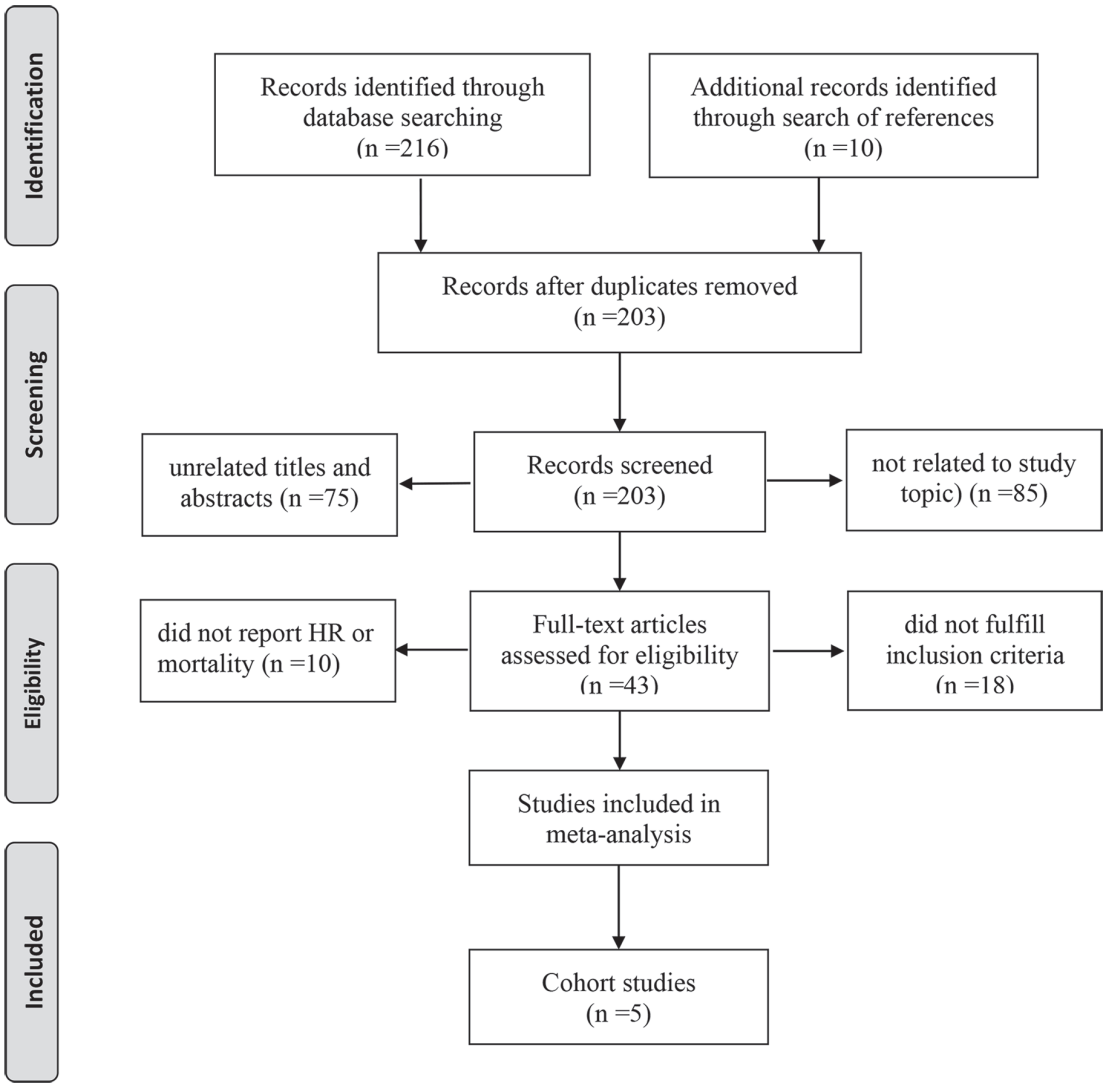

Figure 1. Flow diagram of study selection according to PRISMA guideline.

studies. All *p*-values were two tailed, and *p*-values < 0.05 were considered statistically significant. The "meta" package in R 4.0.3. was used for the statistical analysis.

Results

Study Selection

Figure 1 illustrates the process of study selection. A total of 226 references were identified by electronic and hand searches, and 43 potentially relevant studies were selected for full-text review after screening the titles and abstracts. A total of 5 cohort studies with available full-text met the inclusion criteria.

Study Characteristics

Table I summarizes the study characteristics and the corresponding HRs with 95% CIs. These 5 cohort studies[21-25], involving 153174 participants and approximately 39081 mortalities, were published between 2018 and 2021. The cohort studies, which evaluated ACEi/ARB use and mortality risk, were controlled for potential confounders by adjustments or matching. These studies were conducted in various countries and reported a variety of follow-up periods, and patient population.

Table II summarizes the quality scores of the cohort studies. The Newcastle-Ottawa Scale scores ranged from 3 to 9, while all the full-text published studies scored 5 or more, suggesting a generally excellent quality of the evidence base.

Table I. Study characteristics.

References	Study countries	Patient population	Period of follow-up	ACEis/ARBs prescriptions (n=)	Controls	All-cause mortality (A/C)	Adjusted HR with 95% CI
Gayat et al[21] 2018	France & Belgium	Patients discharged alive from ICU	1 year	109	502	20/153	0.48, 0.27-0.85
Brar et al[22] 2018	Canada	Alberta Kidney Disease Network population-based database	2-7 years	22193	24060	3713/4781	0.85, 0.81-0.89
Yang et al[23] 2020	China	Taiwan Health Insurance Research Database	4.4years (mean)	3885	4673	4841 (Total)	0.93, 0.87-0.98
Siew et al[25] 2020	America	National Corporate Data Warehouse comprising veterans 18 years and older hospitalized	1 year	53235	43748	13110/12368	0.76, 0.71-0.79
Brar et al[24] 2021	America	Patients discharged from hospitals	4.9 years (median)	386	383	95/Not reported	0.62, 0.46-0.84

Abbreviation: ACEis/ARBs = angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers; A/C = angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers groups/control groups; HR = hazard ratio; CIs = confidence intervals.

Table II. Methodological quality of included cohort studies based on the Newcastle-Ottawa Scale.

	Selection				Comparability	Outcome			
Cohort study	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome of interest was not present at start of study	Control for important factor or additional factor	Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow-up of cohort	Score
Gayat et al[21]	☆	☆	☆	☆	☆ ☆	-	☆	☆	8
Brar et al[22]	☆	☆	☆	☆	☆ ☆	☆	☆	☆	9
Yang et al[23]	☆	☆	☆	☆	☆ ☆	☆	☆	☆	9
Siew et al[25]	☆	☆	☆	☆	☆ ☆	☆	☆	☆	9
Brar et al[24]	☆	☆	☆	☆	☆ ☆	☆	☆	☆	9

Abbreviation: ACEis/ARBs = angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers; A/C = angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers groups/control groups; HR = hazard ratio; CIs = confidence intervals.

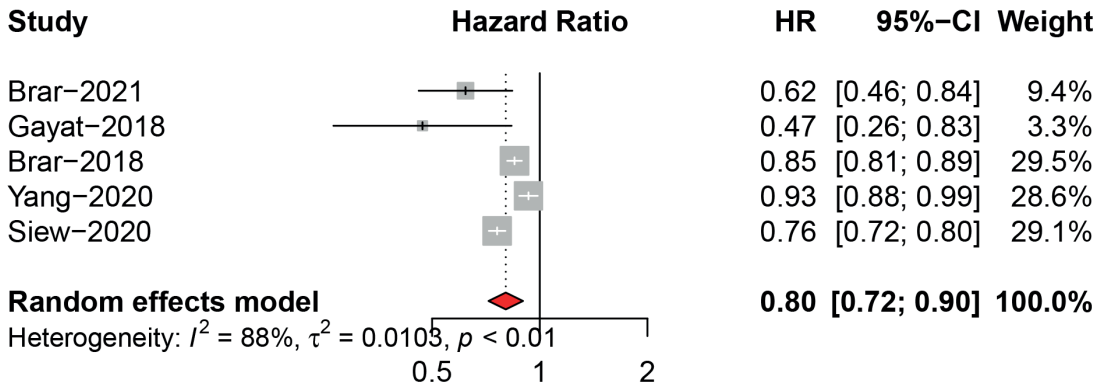

Figure 2. Forrest plot: overall meta-analysis of ACEi/ARB use and mortality risk. Pooled risk ratio and its 95 % confidence intervals were calculated by the random-effects model.

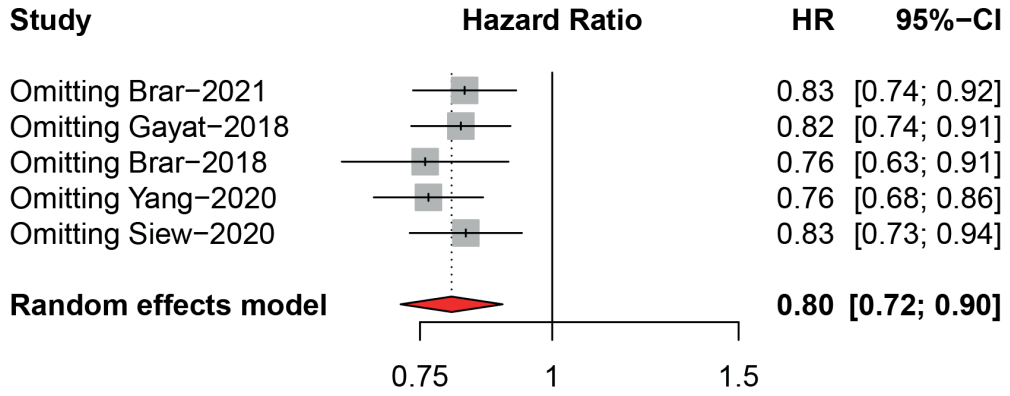

Figure 3. Forrest plot of sensitivity.

Overall Meta-Analysis

Figure 2 shows the forest plot of HR estimates with 95% Cls from individual studies and the overall meta-analysis. In the overall meta-analysis, the pooled results showed a significant decrease in mortality in ACEi/ARB users with post-AKI (HR 0.80; 95% CIs, 0.72-0.90; $p < 0.05$). Meanwhile, high heterogeneity was observed among all the studies ($I^2 = 88\%$), so we used the random-effects model.

Sensitivity analyses, conducted by excluding studies one-by-one and analyzing the homogeneity and effect size for the remaining studies, showed that omitting any included one study did not alter the direction or magnitude of the observed effect (Figure 3).

Subgroup Analysis

The subgroup analysis of studies with a 1-year follow-up showed a nonsignificant decrease in the risk of mortality in patients with post-AKI among all users of ACEi/ARB (HR 0.65, 0.42-1.01) (Figure 4), while a significant result was found in studies with over 1-year ACEi/ARB follow-up (HR 0.86, 0.77-0.95) (Figure 5). Meanwhile, the I^2 values were 81% and 63% respectively, so the random-effect model was used.

We defined severe AKI as AKI stage 2 or 3. The use of ACEi/ARB showed a nonsignificant decrease in the risk of mortality in patients with post-AKI (HR 0.44, 0.08-2.56) (Figure 6). The I^2 value was 81%, so the random-effect model was used.

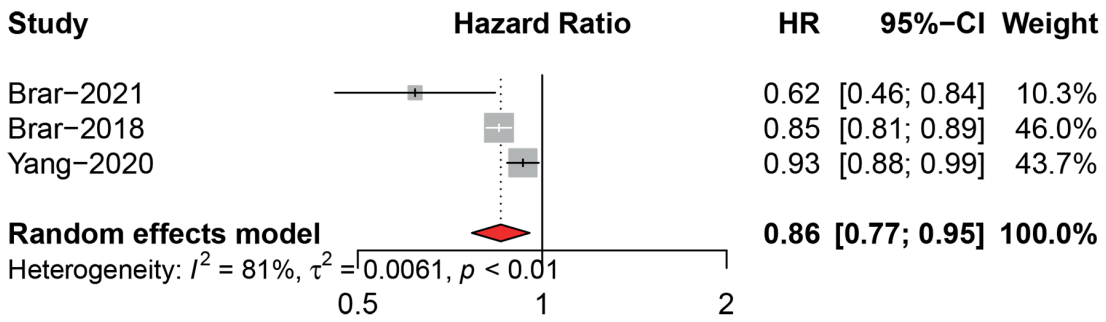

Figure 4. Forrest plot: subgroup analysis of ACEi/ARB use with 1-year follow-up and mortality risk. Pooled risk ratio and its 95 % confidence intervals were calculated by the random-effects model.

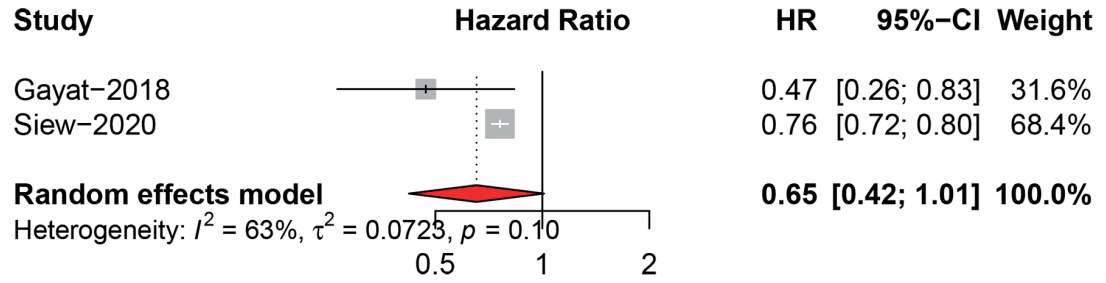

Figure 5. Forrest plot: subgroup analysis of ACEi/ARB use with over 1-year follow-up mortality risk. Pooled risk ratio and its 95 % confidence intervals were calculated by the random-effects model.

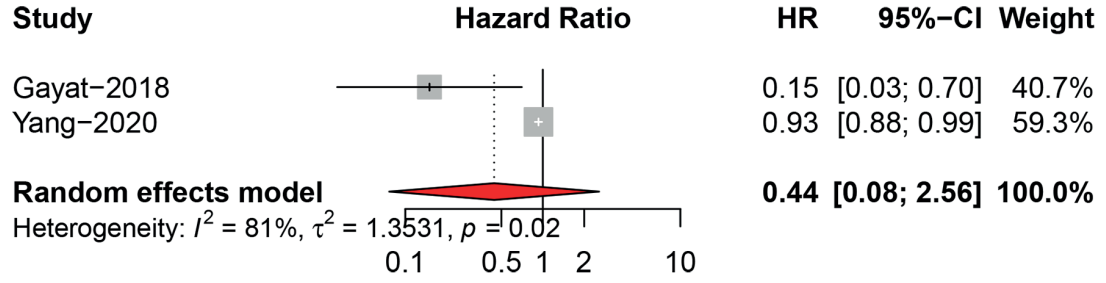

Figure 6. Forrest plot: subgroup analysis of ACEi/ARB use and mortality risk in severe AKI. Pooled risk ratio and its 95 % confidence intervals were calculated by the random-effects model.

Discussion

The beneficial effect of ACEis/ARBs in diabetic kidney disease and proteinuric nondiabetic kidney disease is well known[26,27]. However, many physicians withhold ACEis/ARBs, afraid of the increased risk of developing AKI[28,29]. Therefore, better evaluation and management of patients with post-AKI has been recognized as an important clinical and public health priority[30]. This present meta-analysis included 5 cohort studies, involving 153174 participants and approximately 39081 mortalities. Overall, we found significant evidence for an association between the use of ACEis/ARBs and reduced mortality in patients with post-AKI (HR 0.80; 95% CIs, 0.72-0.90; p <

0.05). Similar results were found in the subgroup analysis of studies with over 1-year of follow-up in ACEis/ARBs users (HR 0.86, 0.77-0.95), whereas there was a nonsignificant decrease in the risk of mortality in patients who used ACEis/ARBs for 1 year (HR 0.65, 0.42-1.01) and patients with severe AKI.

In the present meta-analysis, significant heterogeneity was observed among all studies (I^2 = 88%), therefore, the inverse-variance-weighted random-effects model, which provides a more conservative estimate of the pooled effect size, was employed to determine the pooled HR estimates in our meta-analysis. Moreover, sensitivity analysis showed that omitting of any study did not alter the magnitude of the observed effects, suggesting the stability of our findings.

A previous clinical study, conducted by Qiao et al[31], reported that 3909 individuals receiving ACEi or ARB treatment who experienced an eGFR decrease to below 30 mL/min/1.73 m^2 had a lower risk of mortality, without progressing to end-stage kidney disease. In addition, Gosmanova et al[32] reported that longer predialysis ACEi/ARB exposure was associated with lower postdialysis mortality. Another study conducted by Hines et al[33] found that exposure to an ACEi/ARB during the index hospitalization with AKI did not seem to affect kidney recovery. ACEis/ARBs can reduce tubular damage by improving peritubular capillary perfusion via efferent arteriolar vasodilation, which might reduce tubular ischemia and thus reduce the risk of developing AKI[34]. In a mouse model, Cheng et al[35] showed angiotensin II type 1a receptor signaling was one of the underlying mechanisms by which ACEis/ARBs could reduce mortality after functional recovery from AKI. These findings are in line with the results of our meta-analysis. Although there is much interest in improving care after AKI, there is scant evidence to guide physicians about the most appropriate care. Based on these clinical studies, we believe our data are therefore reassuring and contribute to painting a picture of a favorable risk-benefit profile for ACEis/ARBs after AKI that can inform clinical practice until there is more definitive evidence from RCTs.

Our study also has certain limitations. First, we did not examine the association of the dosage of ACEis/ARBs therapy post-AKI with outcomes such as the development or progression of chronic kidney diseases because of the limited data in the included studies. Second, patients who have chronically been on ACEi/ARB for years before the AKI episode may continue to benefit from their renoprotective effects. Third, all the studies included in our meta-analysis were observational, so the level of evidence is insufficient. However, some researchers believe that well-designed observational studies could yield comparable outcomes to RCTs[36]. Fourth, as with most observational studies, there is the possibility of residual confounding in the Cox and propensity-matched analysis.

Overall, this is the first meta-analysis to evaluate the relationship between the use of AECis/ARBs and mortality in patients with post-AKI. Many patients with relatively long follow-up times and high-quality studies were included in our meta-analysis, which makes our results more credible.

Conclusions

In conclusion, we found that the use of ACEis/ARBs in patients with post-AKI was associated with a significantly lower risk of death. These results need to be validated in future RCTs.

Author Contributions

Heng Shi acquired the data, analyzed and interpreted the data, drafted the article, and provided final approval; Qin Peng acquired the data, and analyzed and interpreted the data; Xian-Ling Zhou acquired the data, and analyzed and interpreted the data; Shi-Ping Zhu interpreted the data, and revised the article; Sheng-Yun Sun conceived and designed the study, critically revised the manuscript, and provided final approval.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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