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N-Acetylcysteine for Preventing of Acute Kidney Injury in Chronic Kidney Disease Patients Undergoing Cardiac Surgery: A Metaanalysis

Guiyuan He, MM,[1,3] Qi Li, MM,[2,3] Wenxin Li, MD,[1,3] Li Wang, MD,[1,3] Jun Yang, MD,[2,3] Fanjun Zeng, MM[1,3]

[1]Department of Respiratory Medicine, The First College of Clinical Medical Sciences, Yichang Central People's Hospital, China Three Gorges University, Yichang, Hubei province, China; [2]Department of Cardiology, The First College of Clinical Medical Sciences, Institute of Cardiovascular Diseases, China Three Gorges University, Yichang, Hubei province, China; [3]Institute of Evidence-Based and Translational Medicine, China Three Gorges University, Yichang, Hubei province, China

ABSTRACT

Objective: The aim of this study was to determine whether N-acetylcysteine (NAC) has an effect on acute kidney injury (AKI) in chronic kidney disease patients undergoing cardiac surgery.

Methods: We reviewed literature through PubMed, Medline through PubMed and OVID, The Cochrane Library, Wan Fang Database, China Biology Medicine Database, Chinese Periodical Database, China Knowledge Resource Integrated Database, and Chinese Clinical Trial Registry (1980 to July 10, 2018). Two investigators independently collected the data and assessed the quality of each study. RevMan 5.3 was used for the present metaanalysis.

Results: A total of 5 RCTs (N = 678 participants) were included in the primary analysis. Pooled analysis showed that intravenous infusion of NAC significantly reduced the incidence of AKI (RR = 0.77, 95% = 0.63 to 0.94, $P < .01$) and that NAC could decrease the adverse cardiac events (RR = 0.83, 95% = 0.70 to 0.97, $P < .05$), but that it may increase the length of stay in the ICU (mean difference [MD] = 2.1, 95% CI = 1.61 to 2.60, $P < .01$). There were no statistically significant differences between the 2 groups in the requirement for renal replacement therapy(RRT) (RR = 1.33, 95% = 0.63 to 2.81, $P = .45$) and all-cause mortality (RR = 0.51, 95% = 0.25 to 1.06, $P = .07$).

Conclusion: Our study shows that intravenous infusion of NAC could prevent postoperative AKI in preexisting-renal-failure patients undergoing cardiac surgery.

INTRODUCTION

Acute kidney injury (AKI) is a common serious complication after cardiopulmonary bypass (CPB), associated with infections, prolonged hospital stays, high mortality, and increased hospitalization costs [LaPar 2013; Zheng 2016]. Despite advances in surgical and perioperative care, there are still serious challenges [Bucaloiu 2012]. Patients with heart disease often have chronic renal insufficiency. During CPB, nonpulsating blood flow and renal perfusion were reduced, and mean arterial pressure was reduced by approximately 30%. For patients with previous renal insufficiency, CPB may cause more severe kidney injury than for patients with normal renal function [Mehta 2007; Song 2015]. Therefore, complications after cardiac surgery are still very frequent. Among them, the incidence of AKI is as high as 18%-30% [Rosner 2006]. The underlying mechanisms of CPB-triggered AKI may be associated with the activation of the neurohormonal and sympathetic nervous systems, oxidative stress, activation of inflammatory cascade, release of various proinflammatory cytokines, and ischemia-reperfusion (I/R) injury [Thiele 2015; Chen 2018].

Although many potential mechanisms of cardiac surgery–induced AKI have been explored, viable preventive or therapeutic regimens are still lacking. In the clinic, dopamine, mannitol, diuretics, fenoldopam, enalaprilat, dexamethasone, and other drugs have been used for renal protection during cardiac operations [Wang 2016]. N-acetylcysteine (NAC), a cysteine prodrug and glutathione (GSH) precursor, has been used for several decades in clinical therapeutic practices as a mucolytic agent and for the treatment of disorders associated with GSH deficiency. It is known that NAC is a thiol compound possessing antioxidant and vasodilatory properties and reduces oxygen free-radical production. And NAC is also a nonantibiotic compound possessing antimicrobial property. Furthermore, NAC can alter the levels of acetaminophen (APAP) metabolites, and APAP is an analgesic and antipyretic drug that can induce oxidative stress–mediated hepatotoxicity at high doses [Abdel-Daim 2018]. Owing to its anti-inflammatory and antioxidant properties, NAC attenuates several mechanisms of kidney injury during cardiac surgery, namely the systemic inflammatory response, free radical injury, and ischemia [Burns 2005]. Recently, some studies showed that perioperative administration of NAC could prevent the development of postoperative AKI after cardiac surgery [Gaffney 2015; Lee 2018].

Much metaanalysis about NAC preventing AKI in patients after surgery or cardiac surgery existed [Ozaydin 2014; Hu

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G.H. and Q.L. contributed equally to this work.

Correspondence: Fanjun Zeng, MM, Department of Respiratory Medicine, The First College of Clinical Medical Sciences, Yichang Central People's Hospital, China Three Gorges University, Yiling Road 183, Yichang 443000, Hubei Province, China; 86-15507206059; (e-mail: yczengfanjun@163.com).

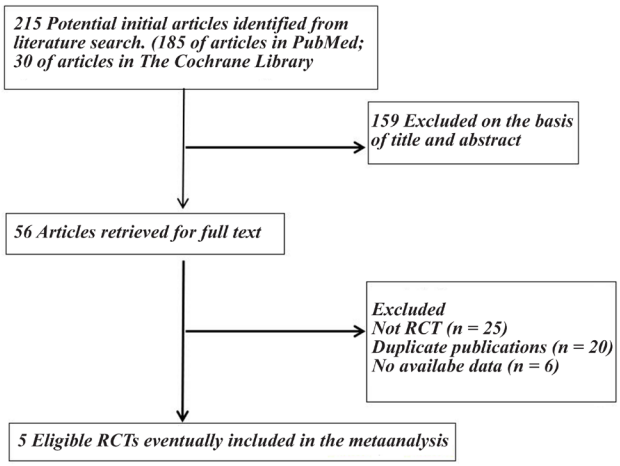


Figure 1. Flow diagram of the study selection process in the metaanalysis.

2016], but no one had considered chronic kidney disease (CKD) patients. Randomized controlled studies (RCTs) evaluating the role of NAC in the CKD patients after cardiac surgery have been underpowered and produced conflicting results. The purpose of this study was to undertake a systematic analysis of RCTs to investigate the influence of perioperative NAC administration on the incidence of AKI. Our research object is the preexisting–renal-dysfunction adult who undergoing cardiac surgery. In the treatment group, any dose of NAC was administered intravenously or orally immediately before, during or after cardiac surgery.

METHODS

Data Sources and Searches

We systematically searched the literature through PubMed, Medline through PubMed and OVID, The Cochrane Library, Wan Fang Database, Chinese Periodical Database, China Biology Medicine Database, China Knowledge Resource Integrated Database, and Chinese Clinical Trial Registry. During the electronic database search, we used the Boolean operator "AND" with the following key words: ("N-acetylcysteine" or "acetylcysteine" or "mucosolvin" or "ambroxol hydrochloride") AND ("acute kidney injury" or "renal injury" or "kidney injury") AND ("chronic kidney disease" or "chronic renal failure" or "pre-existing moderate renal insufficiency" or "renal dysfunction") AND ("cardiac surgery" or "cardiopulmonary bypass"). Peer-reviewed published articles up to July 10, 2018 were retrieved. References of retrieved metaanalyses were searched individually for additional relevant publications. Results were filtered for RCTs. We identified additional citations from reference lists of review articles, from conferences, and through experts.

Study Inclusion and Selection Criteria

The inclusion criteria are revealed as follows: (1) study design: randomized controlled trial; (2) type of participants:

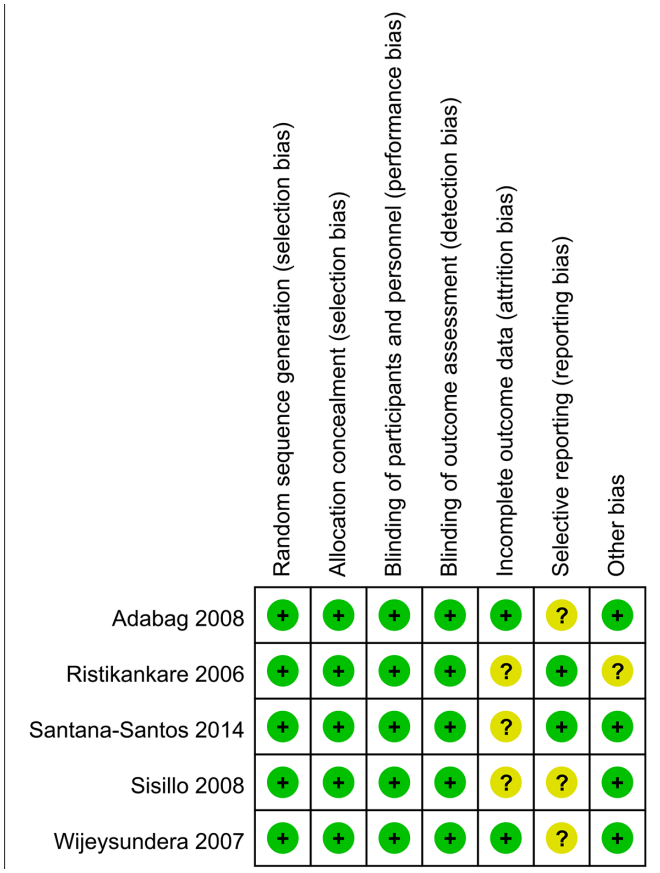


Figure 2. Risk of bias summary: review authors' judgments about each risk of bias item for each included study. For authors' names and the years, they indicate the corresponding item in the "References."

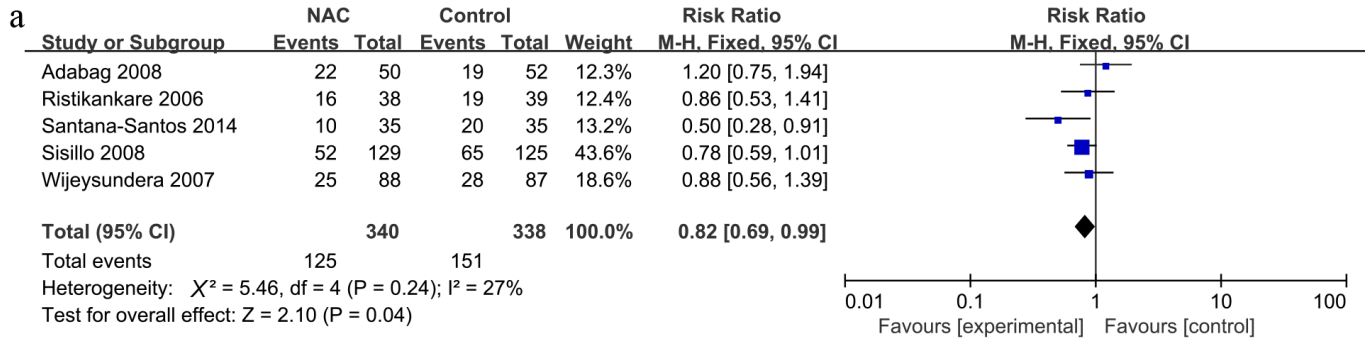
patients with CKD undergoing cardiac surgery, who are older than 18 years and (3) for whom the intervention is NAC, while the control is placebo. Studies were excluded from the analysis if (1) one was unable to extract the concrete data from the published results, such as in comments, letters, case reports, abstracts, reviews; (2) if they are pediatric, animal, or cell studies; (3) if they are studies that did not provide the related outcomes; (4) if they are studies that had been duplicated in other publications; and (5) if they are studies with small-sized groups (<20 patients).

Study Outcomes and Definitions

The primary outcome of interest was the incidence of AKI. This outcome was defined as "per each study" and included either an absolute increase of serum creatinine level of 0.5 mg/dL or a relative increase of 25%, from the baseline value within 48-72 hours after cardiac surgery [Finn 2006; Mukete 2016]. The secondary outcomes were the opportunity of renal replacement therapy, all-cause mortality, adverse cardiac events, and the length of stay in the ICU.

Quality Scoring and Risk of Bias Assessment

The quality of all eligible trials was evaluated according to the modified Jadad scale (a numerical score between zero



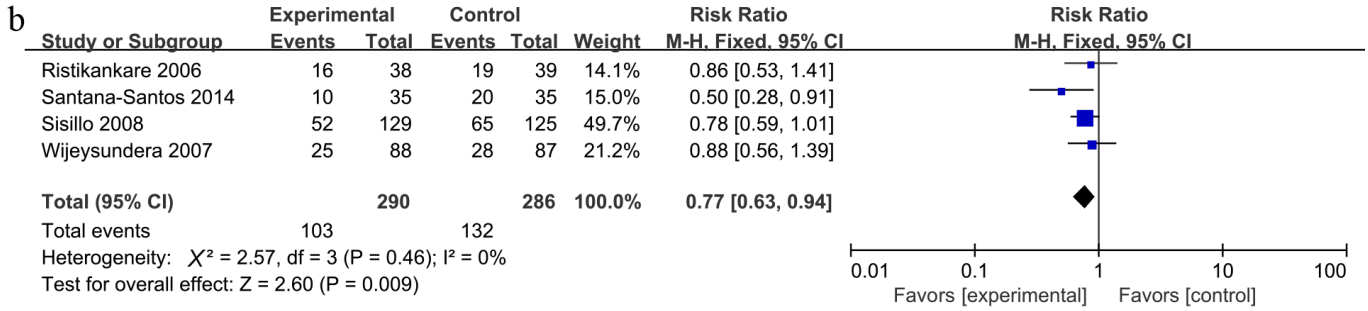


Figure 3. (A), Risk ratio of acute kidney injury in CKD patients undergoing CPB (risk ratio between NAC and saline). (B), Risk ratio of acute kidney injury in CKD patients undergoing CPB (risk ratio between intravenous NAC and saline). CKD, chronic kidney disease; CPB, cardiopulmonary bypass; NAC, *N*-acetylcysteine; CI, confidence interval. For authors' names and the years, they indicate the corresponding item in the "References."

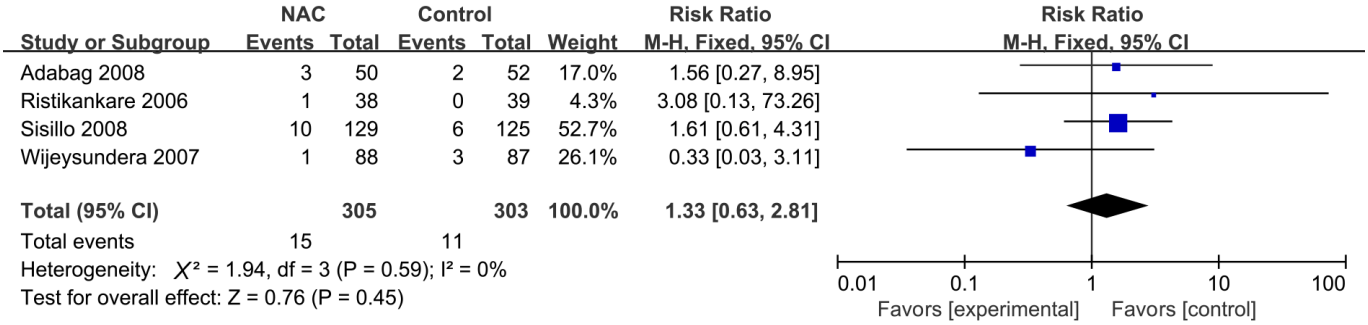


Figure 4. Risk ratio of the opportunity of renal replacement therapy in CKD patients undergoing CPB (risk ratio between NAC and saline). CKD, chronic kidney disease; CPB, cardiopulmonary bypass; NAC, *N*-acetylcysteine; CI, confidence interval. For authors' names and the years, they indicate the corresponding item in the "References."

and 7, with zero being the weakest and 7 being the strongest). Details of the quality assessment included the methodology of randomization, the adequacy of allocation concealment, whether a blind or double-blind method was used, whether an intention-to-treat analysis was utilized along with descriptions of withdrawals, and follow-up. The total score of 4-7 indicated a high quality [Jadad 1996]. A risk of bias assessment was performed in accordance with guidelines outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* [Higgins 2011]. Two authors (G.Y.H. and Q.L.) reviewed all studies and subjectively assigned a value of "high," "low," or "unclear" to the following: selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome), reporting bias (selective outcome reporting), and inclusion of intention-to-treat analysis (other bias). The 2 trained reviewers (W.X.L. and L.W.) assessed the quality of the trials and the risk of bias and independently resolved differences by consensus.

Data Processing and Statistical Analyses

Metaanalysis was conducted by using RevMan 5.3 software (The Cochrane Collaboration, Oxford, UK). The identification of titles and abstracts and the extraction of data were independently screened by 2 reviewers (G.Y.H. and Q.L.).

Table 1. Characteristics of the Clinical Trials Included in the Metaanalysis*

Reference, Year, Country of Origin	Participant Nos. (N/C)	Age of Participants (N/C)	Participant Nos. by Gender (M/F)	NYHA	LVEF, % (N/C)	Serum Creatinine (N/C)	Comorbidities (N/C)
Adabag et al, 2008, America†	50/52	70 ± 9/72 ± 9	50/52	I-IV	53 ± 12/51 ± 11	1.90 ± 0.7/1.90 ± 0.6 (mg/dL)	Hypertension, hyperlipidemia, chronic lung disease, peripheral arterial disease, cerebrovascular disease
Ristikankare et al, 2005, Finland†	38/39	72/69	62/15	III-IV	45/47	1.4/1.5 (mg/dL)	Diabetes, hypertension, peripheral vascular disease
Wijeysundera et al, 2007, Canada	89/88	74/73	106/71	Unclear	Unclear	1.4/1.5 (mg/dL)	Hypertension, diabetes mellitus requiring medication, peripheral vascular disease, cerebrovascular disease, COPD
Sisillo et al, 2008, Italy	129/125	73 ± 6/72 ± 6	125/131	I-IV	56 ± 12/54 ± 12	1.27 ± 0.3/1.24 ± 0.4 (mg/dL)	Hypertension, diabetes mellitus, peripheral vascular disease
Santana-Santos et al, 2013, Brazil†	35/35	65 ± 8.2/64 ± 9	50/20	I-IV	56.8 ± 11.9/50.5 ± 14	1.27/1.28 (mg/dL)	Hypertension, peripheral vascular disease, dyslipidemia

*N, *N*-acetylcysteine groups; C, control groups; NYHA, New York Heart Association; COPD, chronic obstructive pulmonary disease.
†The difference in year between what is here and what is in the "References" may be attributed to one being the date of the study and the other being the date of the article.

W.X.L. and L.W. were responsible for the potential of disagreement between the 2 reviewers. For outcomes, the raw data were extracted by using mean, median, and standard deviations for continuous outcomes, and event rate for dichotomous outcomes[Lewicki 2015]. The Mantel-Haenszel (M-H) test is used with dichotomous, whereas inverse-variance (I-V) weighting is used for continuous. For dichotomous variables (eg, the incidence of AKI, the requirement for renal replacement therapy(RRT), all-cause mortality, and the adverse cardiac events), we calculated the risk ratio (RR) and 95% confidence interval (CI) of every trial and estimated the pooled values of both. For continuous variables (eg, the length of stay in the ICU), we calculated the standard estimation of the MD. I^2 Statistics and the χ^2 test were applied to estimate heterogeneity. If there was significant heterogeneity ($P \leq .10$ for χ^2 test or $I^2 \geq 50\%$), the random-effects model was used. If there was no significant heterogeneity, the fixed-effects model was used. Both the M-H test and I-V weighting were applied. $P < .05$ was considered statistically significant. Funnel plots were used to detect the potential publication bias. The sensitivity analysis was conducted by taking each single study away from the total and reanalyzing the remainder.

RESULTS

Search Results and Study Characteristics

There were 215 relevant reports identified by the search. After reviewing the abstracts, 56 trials were retrieved for a full-text review. Of which, 51 trials were excluded because they did not meet the inclusion criteria. In total, 5 RCTs [Ristikankare 2006; Wijeysundera 2007; Adabag 2008; Sisillo 2008; Santana-Santos 2014] enrolling 678 participants satisfying the inclusion criteria were finally analyzed. Figure 1 shows the flow diagram of the study selection process in this metaanalysis. Patient-oriented baseline clinical characteristics are described in Table 1, with no significant difference between the 2 groups. Also, detailed research data about inclusion and exclusion criteria and about intervention and surgical procedures are revealed in Table 2.

Design Methods and Trial Quality

All trials were treatment with NAC alone and were randomized. All included trials used random sequence generation to avoid selection bias and were double-blind trials. Placebos were used in 5 trials as the control group. According to the Jadad quality scale, all trials included are of high quality as is shown in Table 3, and the Jadad score for 3 of these studies is 7. The risk of bias for each study was evaluated according to the methods that were described in the *Cochrane Handbook* [Higgins 2011], and the details of the results are presented in Figure 2.

Acute Kidney Injury

The incidence of AKI was reported in 5 studies. From the metaanalysis, we can find that AKI developed in 276 patients, 125 in the NAC group and 151 in the control group. The combined analysis demonstrated that NAC significantly reduced the incidence of AKI (RR = 0.82, 95% = 0.69 to 0.99, $P < .05$, $I^2 = 27\%$, Figure 3A). According to the different methods of administration, subgroup analysis was carried out.

Table 2. Research Data of the Clinical Trials Included in the Metaanalysis*

Reference, Year, Country of Origin	Participants, Inclusion and Exclusion Criteria	Intervention	Surgery
Adabag et al, 2008, America†	Inclusion: participants had CKD; patients scheduled for cardiac surgery Exclusion: dialysis before the surgery; renal transplantation; an intravenous contrast agent within 4 days	600 mg PO twice daily for a total of 14 doses	CABG,CPB
Ristikankare et al, 2005, Finland†	Inclusion: patients had preoperative plasma creatinine values above the upper range limit (>100 μmol/L), received open-heart surgery with CPB. Exclusion: patients had preoperative plasma creatinine level above 400 μmol/L, chronic renal replacement therapy, kidney transplantation, allergy to NAC.	150 mg/kg IV (load); 20 mg/kg IV	CABG, CPB
Wijeysundera et al, 2007, Canada	Inclusion: age ≧18 y; preexisting moderate renal insufficiency; elective CABG and/or valve surgery with CPB. Exclusion: preoperative hemodynamic instability; NAC or angiographic contrast within 24 h before surgery; planned off-pump surgery; planned deep hypothermic circulatory arrest; prior adverse reaction to NAC.	100 mg/kg bolus (load); 20 mg·kg-1·h-1 IV up to 4 h	CPB
Sisillo et al, 2008, Italy	Inclusion: patients scheduled for cardiac surgery; having at least moderate (stage 3 nephropathy) renal insufficiency. Exclusion: creatinine clearance ≧60 mL/min; treat for chronic peritoneal or hemodialysis allergy to NAC; received NAC for contrast-induced nephropathy prevention in the previous 7 days or contrast agents in the previous 72 h (in elective cases).	1200 mg IV (load); 1200 mg IV 8 h up to 24 h	CABG, CPB
Santana-Santos et al, 2013, Brazil†	Inclusion: glomerular filtration rate of 15 or greater and less than 60 $mL{\cdot}min^{-1}{\cdot}1.73\ m^{-2}$; scheduled to undergo elective CABG. Exclusion: dialysis; serum creatinine ≥4 mg/dL; allergy to NAC; participating in other studies; refusal to participate.	150 mg/kg IV 2 h before surgery; 50 mg/kg IV up to 6 h	CABG, CPB

*PO, orally; CABG, coronary artery bypass disease; CPB, cardiopulmonary bypass; IV, intravenously; y, year; h, hour; NAC, N-acetylcysteine.
†The difference in year between what is here and what is in the "References" may be attributed to one being the date of the study and the other being the date of the article.

Metaanalysis showed a statistically significant intravenous infusion of NAC (RR = 0.77, 95% = 0.63 to 0.94, P <.01, I^2 = 0%, Figure 3B).

Renal Replacement Therapy

The result indicated no statistical significance in the 2 groups for the outcome of the renal replacement therapy (RR = 1.33, 95% = 0.63 to 2.81, P = .45, Figure 4). This result did not demonstrate any heterogeneity (I^2 = 0%).

All-Cause Mortality

All included trails reported all-cause mortality. There was a total of 30 postoperative deaths. Ten patients in the NAC group died of cardiac infraction. Myocardial infarction and respiratory failure were the main causes of death in the control group. NAC treatment did not influence all-cause mortality between the 2 groups (RR = 0.51, 95% = 0.25 to 1.06, P = .07, Figure 5). This result did not demonstrate any heterogeneity (I^2 = 0%).

Adverse Cardiac Events

Four of the trials comprised 576 patients reporting lung adverse events. Adverse cardiac events occurred in 119 of 290 patients treated with NAC and 141 of 286 patients treated with saline. There was significance difference in adverse cardiac events (RR = 0.83, 95% = 0.70 to 0.97, P <.05, Figure 6). This result did not demonstrate any heterogeneity (I^2 = 0%).

Length of Stay in the ICU

Two RCTs (179 patients) evaluated the effect of NAC on the length of stay in the ICU. The metaanalysis using the random effects model showed that the NAC could increase the length of stay in the ICU (MD = 2.10, 95% CI = 1.61 to 2.60, P <.01, I^2 = 82%, Figure 7).

Sensitivity Analysis

Metaanalysis showed that there was a statistically significant heterogeneity for the length of stay in the ICU (I^2 = 82%). Therefore, we performed sensitivity analysis. The

Table 3. Summary of the Quality Evaluation by the Jadad Scale for the Included Trials

Trials	Random Sequence Generation	Allocation Concealment	Double Blinding	Description of Withdrawals and Dropouts	Score
Adabag et al, 2008, America*	2	2	2	1	7
Ristikankare et al, 2005, Finland*	2	1	1	1	5
Wijeysundera et al, 2007, Canada	2	2	2	1	7
Sisillo et al, 2008, Italy	2	2	2	1	7
Santana-Santos et al, 2013, Brazil*	2	2	1	1	6

*The difference in year between what is here and what is in the "References" may be attributed to one being the date of the study and the other being the date of the article.

sensitivity analysis showed that exclusion of any single study did not alter the overall conclusion. We considered that this heterogeneity was probably related to the great difference among studies.

DISCUSSION

The development of CPB was one of the greatest medical breakthroughs of the 20th century [Evans 2018]. It makes it possible for more than 2 million coronary artery bypass graft procedures or valve replacement or repair procedures performed annually worldwide. However, the incidence of AKI after global cardiac surgery is increasing; therefore, strategies to prevent AKI are extremely important [Sgouralis 2017].

Previous clinical studies have shown that NAC reduces the incidence of contrast-induced nephropathy by activity against the oxygen free radicals and by dilation of renal blood vessels, so it was initially implemented in patients undergoing intravenous contrast administration [Shimizu 2017]. Currently, researches on NAC are mainly concentrated on normal renal function patients after cardiac surgery [Rababa'h 2016; Mei 2018]. Preexisting renal failure is one of the recognized risk factors of postoperative renal failure [Adabag 2009], so we discussed whether NAC protected kidney function in CKD patients undergoing CPB.

NAC has been reported to be associated with reducing the incidence of AKI. A recent randomized controlled trial has demonstrated a positive result for NAC in reducing the risk of AKI following cardiac surgery in patients with preexisting moderate renal insufficiency. The metaanalysis of Mei et al [Mei 2018] found that the association of NAC treatment with the occurrence of cardiac surgery–associated acute kidney injury (CSA-AKI) decreased with increasing baseline eGFR. Adabag et al [Adabag 2009]. also observed a trend towards reduced occurrence of CSA-AKI with NAC treatment in high-risk patients with baseline CKD. The biggest difference with respect to these articles is that we directly discussed AKI in patients with chronic renal insufficiency after CPB. In our metaanalysis, NAC could prevent the postoperative AKI in patients with preexisting renal failure undergoing cardiac surgery. The mechanism of AKI caused by CPB after cardiac surgery is still unclear and may be related to the following points. First of all, during CPB, perfusionists monitor mixed venous saturation of hemoglobin with oxygen and maintain it at 70%-80%. This level of venous oxygenation is not adequate for the kidneys and, therefore, promotes hypoxia in the kidneys and leads to acute kidney damage. Second, hemodilution could reduce the oxygen-carrying capacity of blood and, therefore, the quantity of renal oxygen delivery. Third, inflammation and oxidative stress would lead to renal vasoconstriction, as would activation of the sympathetic and renin–angiotensin systems. Furthermore, the rewarming phase of CPB increases metabolic activity, thereby increasing oxygen consumption caused by tissue temperature [Tossios 2003;Mauricio 2017; Evans 2018]. Moreover, previous studies have shown that NAC could inhibit reactive oxygen species (ROS)/ERS/apoptosis signal pathway activation and reduce the production of ROS against AKI.

In addition, Savluk et al [Savluk 2017] found that prophylactic use of intravenous NAC had a protective effect on renal function compared with oral NAC. Oral administration of NAC may reduce its effectiveness, because the half-life of NAC is very short, only 2.2 hours [Pei 2018]. Similarly, Sucu et al [Sucu 2004] reported that intravenous infusion of NAC decreased the pump-induced oxide-inflammatory response during CPB. In our metaanalysis, except for the use of oral administration by Adabag et al [Adabag 2008], the other 4 were administered intravenously. We attempted to exclude this study and found that intravenous administration of NAC significantly reduced the incidence of AKI with a lower heterogeneity. Therefore, we indicated that use of intravenous NAC had a protective effect on renal function in CKD patients undergoing CPB.

Similar to other investigations, our study revealed that NAC could be used as an adjuvant therapy to decrease cardiovascular adverse events after CPB. Adverse cardiac events, eg, acute myocardial infarction, hypotension, shock, are the major cause of mortality. Actually, the more adverse events, the higher the mortality; but mortality does not seem to be associated with adverse events in this metaanalysis. NAC played an important role in decreasing adverse cardiac events. But NAC could not reduce the all-cause mortality; this finding is in accordance with previous publications [Ho 2009;

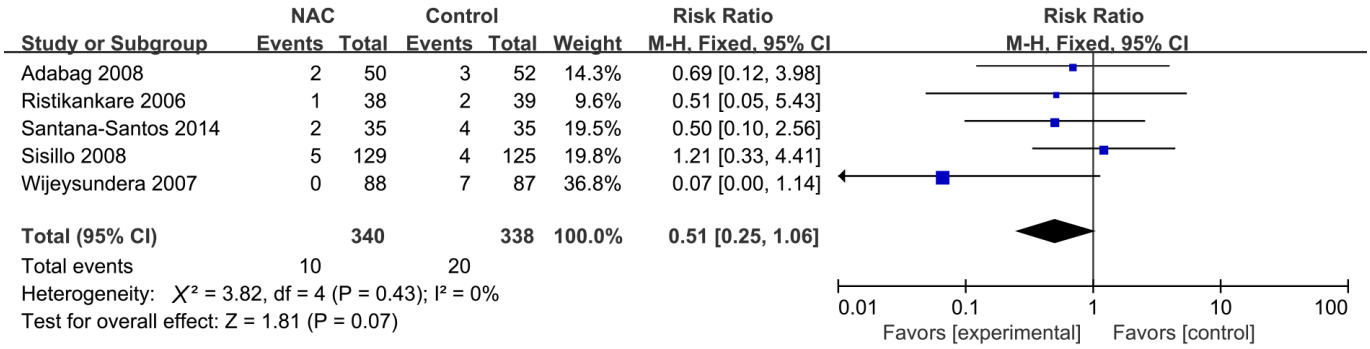


Figure 5. Risk ratio of all-cause mortality in CKD patients undergoing CPB (risk ratio between NAC and saline). CKD, chronic kidney disease; CPB, cardiopulmonary bypass; NAC, *N*-acetylcysteine; CI, confidence interval. For authors' names and the years, they indicate the corresponding item in the "References."

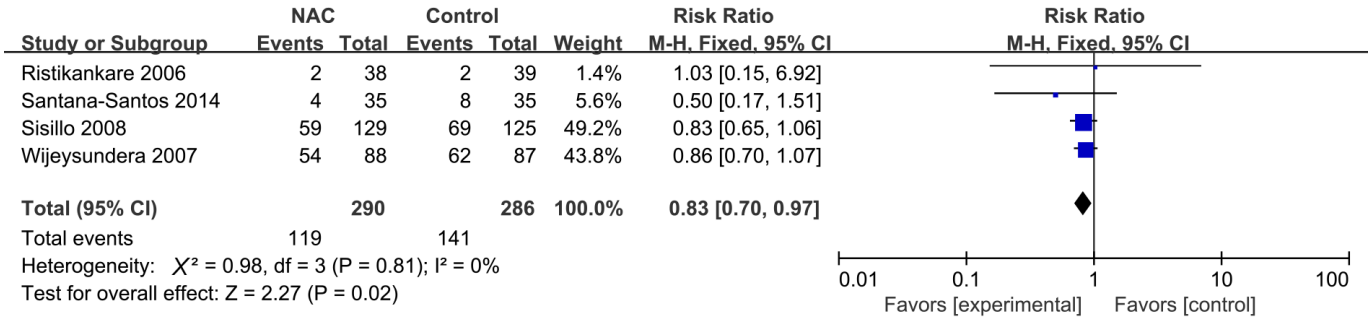


Figure 6. Risk ratio of adverse cardiac events in CKD patients undergoing CPB (risk ratio between NAC and saline). CKD, chronic kidney disease; CPB, cardiopulmonary bypass; NAC, *N*-acetylcysteine; CI, confidence interval. For authors' names and the years, they indicate the corresponding item in the "References."

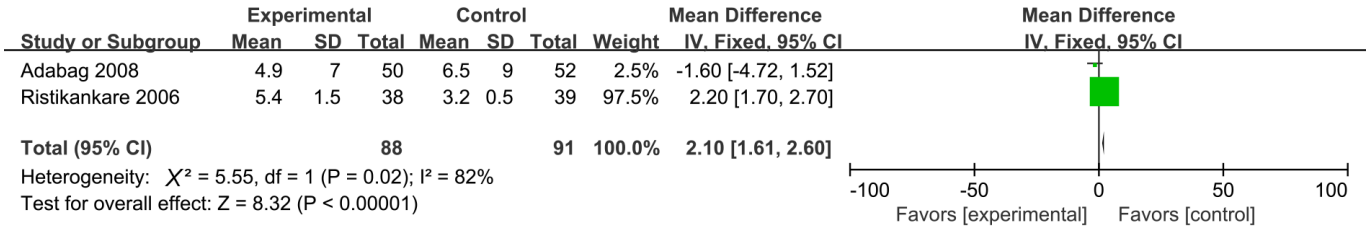


Figure 7. Risk ratio of the length of stay in the ICU in CKD patients undergoing CPB (risk ratio between NAC and saline). CKD, chronic kidney disease; CPB, cardiopulmonary bypass; NAC, *N*-acetylcysteine; CI, confidence interval.

Ataei 2015]. Some researchers hold the view that low-dose NAC did not reduce mortality after cardiac surgery, although high-dose NAC might be effective [Devlin 1997]. Ristikankare [Ristikankare 2006] used a higher dose of NAC, which was 9 times larger than that used by Sisillo and colleagues [Sisillo 2008]. Previous studies have showed that the antioxidant and anti-inflammatory effects of NAC are related to high doses [Devlin 1997]. Rank et al [Rank 2000] found that a large dose of NAC has been effective in organ protection in a number of studies performed in hepatic failure. But Magder [Magder 2006] showed that high-dose NAC may have diminished the level of ROS, thereby attenuating their potentially positive role in the regulation of intracellular signaling. This seems to indicate that high doses of NAC do not necessarily play an active role. In our metaanalysis, though, the treatment dosage of NAC seems to be unconcerned with mortality. To date, no consensus has been reached on the most effective doses for identifying NAC administration associated with significant renal protection in patients undergoing CPB. But high-quality RCTs comparing different dosages of NAC are required in order to answer these questions. In addition, our research found that NAC not only does not reduce the length of stay in the ICU, but also increases the time. But our study excluded statistical observations and included high-quality RCTs with statistically significant results. However, it should not be overlooked that the research of Ristikankare et

al [Ristikankare 2006] has a large weight in the results of this analysis (weight = 97.5%), which may result in a wide CI caused by a single research institute and a low event rate. The results are statistically significant and should be treated with caution.

STUDY LIMITATIONS

There are a number of limitations in the metaanalysis. First, most of the included RCTs were small (only one trial had more than 200 patients), so the results were relatively stable and reliable. Second, the definition of adverse cardiac events varies in different trials; therefore, the number of adverse events may have error. Third, the randomization methods were not clearly stated in most trials which causing some heterogeneity.

CONCLUSION

Despite the limitation of this metaanalysis of RCTs, the findings of this study confirm that intravenous NAC may reduce the incidence of AKI. NAC also decreased major adverse cardiac events. NAC could not reduce all-cause mortality and the requirement for renal replacement therapy (RRT). This drug may provide an effective therapy for CKD patient undergoing cardiac surgery.

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The authors declare that there are no conflicts of interest.

The identification of titles and abstracts and extracting of data were independently screened by G.Y.H. and Q.L. W.X.L. and L.W. were responsible for the potential of disagreement between G.Y.H. and Q.L. J.Y. solved the problem of RevMan software All authors contributed to the writing of the draft and have read and approved the final version of the manuscript prior to submission. The corresponding author, F.J.Z., contributed to the development of the protocol and prepared the manuscript.

REFERENCES

Abdel-Daim M, Abushouk AI, Reggi R, Yarla NS, Palmery M, Peluso I. 2018. Association of antioxidant nutraceuticals and acetaminophen (paracetamol): friend or foe? J Food Drug Anal 26(2S):S78-87.

Adabag AS, Ishani A, Koneswaran S, et al. 2008. Utility of N-acetylcysteine to prevent acute kidney injury after cardiac surgery: a randomized controlled trial. Am Heart J 155:1143-9.

Adabag AS, IshaniA, Bloomfield HE, Ngo AK, Wilt TJ. 2009. Efficacy of N-acetylcysteine in preventing renal injury after heart surgery: a systematic review of randomized trials. Eur Heart J 30:1910-7.

Ataei S, Hadjibabaie M, Moslehi A et al. 2015. A double-blind, randomized, controlled trial on N-acetylcysteine for the prevention of acute kidney injury in patients undergoing allogeneic hematopoietic stem cell transplantation. Hematol Oncol 33:67-74.

Bucaloiu ID, Kirchner HL, Norfolk ER, Hartle JE 2nd, Perkins RM. 2012. Increased risk of death and de novo chronic kidney disease following reversible acute kidney injury. Kidney Int 81:477-85.

Burns KE, Chu MW, Novick RJ, et al. 2005. Perioperative N-acetylcysteine to prevent renal dysfunction in high-risk patients undergoing CABG surgery: a randomized controlled trial. JAMA 294:342-50.

Chen X, Huang T, Cao X, Xu G. 2018. Comparative efficacy of drugs for preventing acute kidney injury after cardiac surgery: a network meta-analysis. Am J Cardiovasc Drugs 18:49-58.

Devlin J, Ellis AE, McPeake J, Heaton N, Wendon JA, Williams R. 1997. N-acetylcysteine improves indocyanine green extraction and oxygen transport during hepatic dysfunction. Crit Care Med 25:236-42.

Evans RG, Lankadeva YR, Cochrane AD, et al. 2018. Renal haemodynamics and oxygenation during and after cardiac surgery and cardiopulmonary bypass. Acta Physiol (Oxf) 222:e12995.

Finn WF. 2006. The clinical and renal consequences of contrast-induced nephropathy. Nephrol Dial Transplant 21:i2-10.

Gaffney AM, Sladen RN. 2015. Acute kidney injury in cardiac surgery. Curr Opin Anaesthesiol 28:50-9.

Higgins JP, Green S, editors. 2011. Cochrane handbook for systematic reviews of interventions. Version 5.1.0. [London]: The Cochrane Collaboration; [updated 2011 Mar 20; accessed 2018 Nov 16]. Available from: http://handbook.cochrane.org.

Ho KM, Morgan DJ. 2009. Meta-analysis of N-acetylcysteine to prevent acute renal failure after major surgery. Am J Kidney Dis 53:33-40.

Hu J, Chen R, Liu S, Yu X, Zou J, Ding X. 2016. Global incidence and outcomes of adult patients with acute kidney injury after cardiac surgery: a systematic review and meta-analysis. J Cardiothorac Vasc Anesth 30:82-9.

Jadad AR, Moore RA, Carroll D, et al. 1996. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 17:1-12.

LaPar DJ, Crosby IK, Rich JB, et al. 2013. A contemporary cost analysis of postoperative morbidity after coronary artery bypass grafting with and without concomitant aortic valve replacement to improve patient quality and cost-effective care. Ann Thorac Surg 96:1621-7.

Lee CC, Chang CH, Chen SW, et al. 2018. Preoperative risk assessment improves biomarker detection for predicting acute kidney injury after cardiac surgery. PLoS One 13:e0203447.

Lewicki M, Ng I, Schneider AG. 2015. HMG CoA reductase inhibitors (statins) for preventing acute kidney injury after surgical procedures requiring cardiac bypass. Cochrane Database Syst Rev (3):CD010480.

Mehta RL, Kellum JA, Shah SV, et al. 2007. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care 11:R31.

Mukete BN, Riehl RA, Alonso A, Samson R, Jaiswal A, Le Jemtel TH. 2016. Multivessel revascularization does not increase contrast-induced acute kidney injury incidence in acute myocardial infarction: a meta-analysis. Am J Cardiovasc Drugs 16:419-26.

Mei M, Zhao HW, Pan QG, Pu YM, Tang MZ, Shen BB. 2018. Efficacy

of N-acetylcysteine in preventing acute kidney injury after cardiac surgery: a meta-analysis study J Invest Surg 31:14-23.

Mauricio Del Rio J, Nicoara A, Swaminathan M. 2017. Neuroendocrine stress response: implications for cardiac surgery-associated acute kidney injury. Rom J Anaesth Intensive Care 24:57-63.

Magder S. 2006. Reactive oxygen species: toxic molecules or spark of life? Crit Care 10:208.

Ozaydin M, Peker T, Akcay S, et al. 2014. Addition of N-acetyl cysteine to carvedilol decreases the incidence of acute renal injury after cardiac surgery. Clin Cardiol 37:108-14.

Pei Y, Liu H, Yang Y, et al. 2018. Biological activities and potential oral applications of N-acetylcysteine: progress and prospects. Oxid Med Cell Longev 2018:2835787.

Rababa'h AM, Deo SV, Altarabsheh SE, et al. 2016. N-acetyl cysteine therapy does not prevent renal failure in high-risk patients undergoing open-heart surgery. Heart Surg Forum 19:E16-22.

Rank N, Michel C, Haertel C, et al. 2000. N-acetylcysteine increases liver blood flow and improves liver function in septic shock patients: results of a prospective, randomized, double-blind study. Crit Care Med 28:3799-807.

Ristikankare A, Kuitunen T, Kuitunen A, et al. 2006. Lack of renoprotective effect of i.v. N-acetylcysteine in patients with chronic renal failure undergoing cardiac surgery. Br J Anaesth 97:611-6.

Rosner MH, Okusa MD. 2006. Acute kidney injury associated with cardiac surgery. Clin J Am Soc Nephrol 1:19-32.

Santana-Santos E, Gowdak LH, Gaiotto FA, et al. 2014. High dose of N-acetylcystein prevents acute kidney injury in chronic kidney disease patients undergoing myocardial revascularization. Ann Thorac Surg 97:1617-23.

Savluk OF, Guzelmeric F, Yavuz Y, et al. 2017. N-acetylcysteine versus dopamine to prevent acute kidney injury after cardiac surgery in patients with preexisting moderate renal insufficiency. Braz J Cardiovasc Surg 32:8-14.

Sgouralis I, Evans RG, Layton AT. 2017. Renal medullary and urinary oxygen tension during cardiopulmonary bypass in the rat. Math Med Biol 34:313-33.

Shimizu MH, Gois PH, Volpini RA, et al. 2017. N-acetylcysteine protects against star fruit-induced acute kidney injury. Ren Fail 39:193-202.

Sisillo E, Ceriani R, Bortone F, et al. 2008. N-acetylcysteine for prevention of acute renal failure in patients with chronic renal insufficiency undergoing cardiac surgery: a prospective, randomized, clinical trial. Crit Care Med 36:81-6.

Song JW, Shim JK, Soh S, Jang J, Kwak YL. 2015. Double-blinded, randomised controlled trial of N-acetylcysteine for prevention of acute kidney injury in high risk patients undergoing off-pump coronary artery bypass. Nephrology (Carlton) 20: 96-102.

Sucu N, Cinel I, Unlu A, et al. 2004. N-acetylcysteine for preventing pump-induced oxidoinflammatory response during cardiopulmonary bypass. Surg Today 34:237-42.

Thiele RH, Isbell JM, Rosner MH. 2015. AKI associated with cardiac surgery. Clin J Am Soc Nephrol 10:500-14.

Tossios P, Bloch W, Huebner A, et al. 2003. N-acetylcysteine prevents reactive oxygen species-mediated myocardial stress in patients undergoing cardiac surgery: result of a randomized, double-blind, placebo-controlled clinical trial. J Thorac Cardiovasc Surg 126:1513-20.

Wang HB, Yang J, Ding JW, et al. 2016. RNAi-Mediated down-regulation of CD47 protects against ischemia/reperfusion-induced myocardial damage via activation of eNOS in a rat model. Cell Physiol Biochem 40:1163-74.

Wijeysundera DN, Beattie WS, Rao V, Granton JT, Chan CT. 2007. N-acetylcysteine for preventing acute kidney injury in cardiac surgery patients with pre-existing moderate renal insufficiency. Can J Anaesth 54:872-81.

Zheng Z, Jayaram R, Jiang L, et al. 2016. Perioperative rosuvastatin in cardiac surgery. N Engl J Med 374:1744-53.