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Effect of N-acetylcysteine on prevention of contrast-associated acute kidney injury in patients with STEMI undergoing primary percutaneous coronary intervention: a systematic review and meta-analysis of randomised controlled trials

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ABSTRACT

Objective Several studies evaluating the preventive effect of N-acetylcysteine (NAC) on contrast-associated acute kidney injury (CA-AKI) among patients with ST segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PPCI) have suggested inconsistent results and that a systematic review and meta-analysis should be performed.

Design Systematic review and meta-analysis.

Data sources PubMed, MEDLINE, EMBASE, ClinicalTrials.gov and the Cochrane Central databases were searched from inception to 15 November 2019.

Eligibility criteria Randomised controlled trials assessing use of NAC compared with non-use of NAC (eg, placebo) in preventing CA-AKI in patients with STEMI following PPCI were included.

Data synthesis Relative risks with 95% CIs were pooled using a random-effects model. Evidence level of conclusions was assessed by Cochrane GRADE measure.

Results Seven trials including 1710 patients were identified. Compared with non-use of NAC, use of NAC significantly reduced the incidence of CA-AKI by 49% (risk ratio (RR) 0.51, 95% CI 0.31 to 0.82, p<0.01) and all-cause in-hospital mortality by 63% (RR 0.37, 95% CI 0.17 to 0.79, p=0.01). The estimated effects on the requirement for dialysis (RR 0.61, 95% CI 0.11 to 3.38, p=0.24) were not statistically significant. Trial sequential analysis confirmed the true positive of NAC in reducing risk of CA-AKI. Subgroup analyses suggested that the administration of NAC had greater benefits in patients with renal dysfunction and in those receiving oral administration and higher dosage of NAC.

Conclusions NAC intake reduces the risk of CA-AKI and all-cause in-hospital mortality in patients with STEMI undergoing PPCI. The estimated potential benefit of NAC in preventing dialysis was ambiguous, and further high-quality studies are needed.

PROSPERO registration number CRD42020155265.

Strengths and limitations of this study

- This is the first meta-analysis focusing on patients with ST segment elevation myocardial infarction designed to assess the effect of N-acetylcysteine (NAC) on preventing contrast-associated acute kidney injury (CA-AKI) after primary percutaneous coronary intervention.
- This study was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses reporting checklist.
- Trial sequential analysis represents analysis of meta-analytic data, with transparent assumptions and better control of type I and type II errors than the traditional meta-analysis using unadjusted CIs.
- Most of the selected studies were performed at a single centre.
- We did not obtain individual data to confirm the specific effect of NAC on preventing CA-AKI.

INTRODUCTION

Patients with ST segment elevation myocardial infarction (STEMI) are at a substantially higher risk of contrast-associated acute kidney injury (CA-AKI) following primary percutaneous coronary intervention (PPCI), which could increase healthcare costs, adverse renal outcomes and mortality.[1–6] N-acetylcysteine (NAC) may prevent CA-AKI due to its antioxidant properties and its ability to improve renal haemodynamics among patients with acute myocardial infarction (AMI).[7–9] In addition, NAC can be administered intravenously or orally in urgent situations, such as for patients undergoing PPCI.[10 11] Several

studies evaluating the preventive effect of NAC on CA-AKI have suggested inconsistent results among patients with STEMI following PPCI.[12–18] In 2013, a systematic review pointed out that among the six studies on the use of NAC in preventing CA-AKI, only one study showed that the administration of NAC significantly reduced the occurrence of CA-AKI. Further studies are needed before any administration of NAC against CA-AKI can be recommended in routine care of patients undergoing PPCI for STEMI.[19] The benefit of NAC was not demonstrated in a previous general meta-analysis and NAC has not been recommended in recent clinical guidelines.[20 21] However, a systematic review and meta-analysis of the benefit of NAC in CA-AKI in very high-risk patients undergoing PPCI still does not exist. We therefore conducted a systematic review and meta-analysis of randomised controlled trials (RCTs) in patients with STEMI following PPCI to evaluate the effect of NAC on CA-AKI and all-cause in-hospital mortality compared with those in controls not receiving this regimen.

METHODS

We included all RCTs assessing use of NAC compared with non-use of NAC (eg, placebo) in preventing CA-AKI in patients with STEMI following PPCI. We had no restrictions on language or publication status. We considered patients of all ages undergoing percutaneous coronary intervention, as well as research using pre-NAC or post-NAC strategies. The primary endpoint, CA-AKI, was evaluated according to the change in the level of serum creatinine. The secondary endpoints were as follows: all-cause in-hospital mortality (as mentioned by the enrolled studies) and CA-AKI requiring dialysis. We also extracted data on acute pulmonary oedema or heart failure events, according to the study authors' definitions.

Search strategy and data collection

We searched PubMed, MEDLINE, EMBASE, ClinicalTrials.gov and the Cochrane Central databases from inception to 15 November 2019. We had no restrictions on language during the search. The references of the enrolled research and previous meta-analyses exploring similar topic were also evaluated in case these were not screened by the above search strategy. Detailed search terms were as follows: variants of N-acetylcysteine, nephropathy, contrast nephropathy, contrast-induced nephropathy, contrast media, contrast agent, kidney injury, renal and myocardial infarction based on text words and Medical Subject Headings (MeSH) terms (see online supplemental table S1). Various combinations of these terms were used depending on the requirements of the database. Appropriateness evaluation of titles and abstracts and data collection were conducted independently by four persons (ML, LL, ZG and JL). All standardised procedures were unblinded and strictly adhered to a study eligibility and data extraction form based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. We also screened new progress from large-scale cardiology and nephrology conferences within the past 5 years. During data extraction, a fifth person (YX) crosschecked the information for any possible errors. Any divergence was settled by consensus among all authors. We evaluated the quality of included studies based on the Cochrane Handbook for Systematic Reviews of Interventions and Grading of Recommendations Assessment, Development and Evaluation (GRADE).

Statistical analysis

We adhered to the consensus in the Cochrane Handbook for Systematic Reviews of Interventions to evaluate the quality of the included studies. The quantification of endpoint measurement was achieved using a random-effects model to calculate the pooled risk ratio (RR) and 95% CI. A trial sequential analysis (TSA) was conducted for the outcome CA-AKI. We used I^2 statistic to evaluate the heterogeneity among trials, with values 0%–25%, 25%–50% and greater than 50% representing low, moderate and high degrees of heterogeneity, respectively.[22] Sensitivity analyses were conducted to evaluate the robustness of the results by removing one study successively to confirm the impact of individual studies on the pooled effect size. A two-sided p value of <0.05 was deemed statistically significant. Beyond this, to further assess the heterogeneity of clinical significance, subgroup analyses were performed to seek underlying effect adjustment by potential significant factors: dosage of NAC, delivery route of NAC and kidney function on admission. All statistical analyses were performed using Review Manager V.5.2, STATA V.13.0 software and Trial Sequential Analysis V.0.9 Beta software.

Patient and public involvement

No patients were involved in formulating the study question or in the outcome assessment, as well as in the development of the design or implementation of the study. Furthermore, no patients were asked to advise on the interpretation or write-up of the results. Since this study used aggregated data from previous studies, it is not easy to disseminate the results of the study to patients involved directly.

RESULTS

Study selection

The search found a total of 907 citations, of which 452 were selected for full-text review. The study selection flow diagram is shown in figure 1.

Study characteristics

Seven RCTs were included in the primary analysis, all of which mentioned the incidence of CA-AKI. Five studies defined CA-AKI as >25% increase in serum creatinine level, one study defined CA-AKI as either >0.5 mg/dL or 25% increase in serum creatinine level, and one study defined CA-AKI as >0.5 mg/dL increase in serum

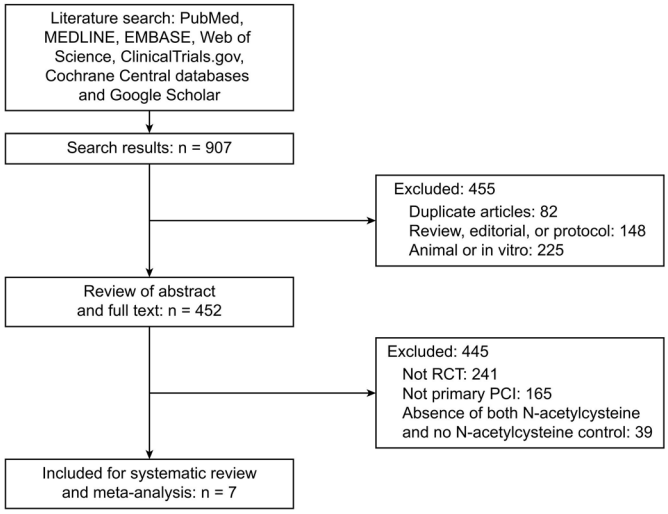

Figure 1 Study selection flow diagram. PCI, percutaneous coronary intervention; RCT, randomised controlled trial.

creatinine level. A total of 2185 participants with STEMI following PPCI were randomised, of whom 475 were not eligible due to the absence of an NAC group or a no-NAC control group. A total of 1710 patients fulfilled all inclusion criteria and were selected for the primary analysis. Individual study characteristics are shown in online supplemental table S2.

Risk of bias and quality of the clinical trials

The quality of the included trials was evaluated and the risk of bias is summarised in online supplemental figure S1. Partial deficiency in confidentiality and blinding in assignments, as well as missing reports on changes in treatment strategies (eg, dose adjustment of NAC) in response to physician recommendations during urgent situations, still existed. The GRADE tool also confirmed the quality of included studies in providing evidence for CA-AKI and all-cause in-hospital mortality (see online supplemental figure S2).

Incidence of CA-AKI

A total of 1710 patients who completed the studies were selected for final analysis, and the incidence of CA-AKI was also reported. NAC was given to 926 patients, while 784 patients were in the control group. The total incidence of CA-AKI in participants receiving NAC was 15.3% (142 of 926) compared with 24.2% (190 of 784) in the control group. Compared with non-use of NAC, the administration of NAC considerably reduced the incidence of CA-AKI by 49% (RR 0.51, 95% CI 0.31 to 0.82, p<0.01; figure 2), using a random-effects model. There was high heterogeneity among the studies (I^2=66%, p=0.007). We performed a sensitivity analysis to assess the stability of the findings. We recomputed the pooled risk estimates by removing one study successively, which led to a small change in the risk estimate, from 0.46 (95% CI 0.34 to 0.61) to 0.58 (95% CI 0.45 to 0.74).

Secondary outcomes

In total, 1.1% (18 of 1710) of the patients needed dialysis and 1.8% (31 of 1710) died in the hospital. Compared with non-use of NAC, the estimated effects of NAC on the requirement for dialysis (RR 0.61, 95% CI 0.11 to 3.38, p=0.10; figure 3) were not statistically significant. The use of NAC largely reduced the incidence of all-cause in-hospital mortality by 63% (RR 0.37, 95% CI 0.17 to 0.79, p=0.01; figure 4).

Subgroup analysis

The following subgroups were examined to assess the consistency of the effect of NAC on CA-AKI: dosage of NAC, delivery route and kidney function on admission. The results are detailed in figure 5. According to the results of the subgroup analysis, the observed association between NAC intake and CA-AKI risk was inconsistent in different subgroups. NAC administration had greater benefit in patients with renal dysfunction (RR 0.35, 95% CI 0.19 to 0.64), in patients who received an oral administration of NAC (RR 0.60, 95% CI 0.40 to 0.89) and in patients who received a high dosage of NAC (RR 0.49, 95% CI 0.30 to 0.80). However, NAC intake was not beneficial in patients without renal dysfunction, patients who received a low dosage of NAC and patients who received an administration of NAC orally and intravascularly, with significant heterogeneity (I^2=0%, p=0.33; I^2=74%, p=0.02; I^2=87%, p<0.01, respectively).

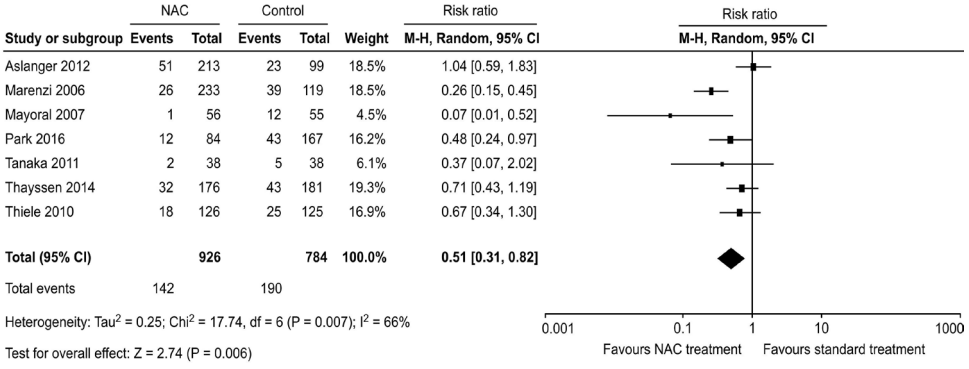

Figure 2 Effects of NAC on lowering the risk of contrast-associated acute kidney injury (NAC vs non-use of NAC). M-H, Mantel-Haenszel; NAC, N-acetylcysteine.

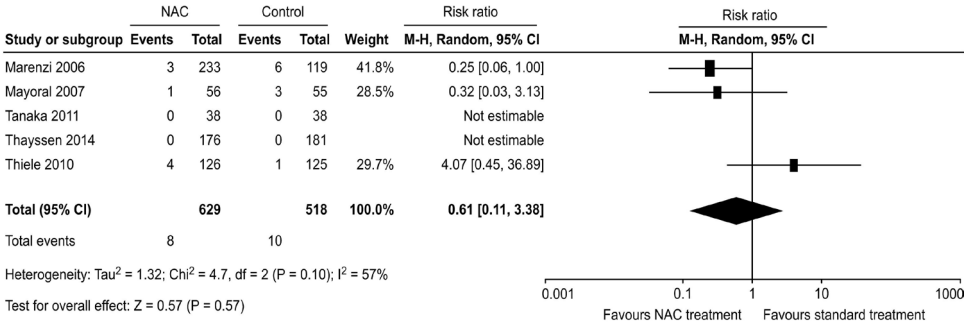

Figure 3 Effects of NAC on lowering the risk of dialysis (NAC vs non-use of NAC). M-H, Mantel-Haenszel; NAC, N-acetylcysteine.

Trial sequential analysis

The cumulative z curve crossed the futility boundary but not the traditional significance boundary or the TSA boundary, supporting the findings of the conventional meta-analysis and also confirming that there is no use to conduct more trials to assess the effect of NAC on CA-AKI (see online supplemental figure S3).

DISCUSSION

This is the first meta-analysis focusing on patients with STEMI designed to assess the effect of NAC on the prevention of CA-AKI following PPCI. Our meta-analysis confirmed a notable reduction in the risk of CA-AKI and all-cause in-hospital mortality associated with NAC. However, the beneficial effects of NAC on the need for dialysis were not statistically significant among participants following PPCI.

Various studies have been conducted to investigate the effect of NAC on preventing CA-AKI and the results were inconsistent. The preventive effect of NAC on CA-AKI was first clarified by Tepel *et al*[23] among patients undergoing enhanced CT scanning as well as among patients undergoing Coronary angiography (CAG).[24] However, a large, observational, prospective cohort study including 90 578 participants following CAG in the USA indicated that NAC was ineffective in the prevention of CA-AKI.[25] In addition, several RCTs have also demonstrated that administration of NAC was not beneficial in preventing CA-AKI.[10 26 27] However, these results should be considered with caution because most of these trials were conducted at a single centre and the conclusions may lack high external generalisation. In 2018, the Prevention of Serious Adverse Events following Angiography (PRESERVE) study showed no benefit of NAC in preventing CA-AKI.[28] However, it is important to mention an earlier high-quality study published in 2006 which concluded that intravenous and oral NAC may prevent contrast medium-induced nephropathy with a dose-dependent effect in patients treated with PPCI and may improve hospital outcome.[13] Although the two studies have opposite conclusions to some extent, note that the patient selection criteria between the two studies were very different. In the earlier study, patients admitted to the centre who underwent PPCI presented with STEMI. In the PRESERVE study, patients involved presented with chronic kidney disease (CKD stage 3–4). Although these two groups of patients can be defined as 'high-risk patients' according to a recent review, NAC has several features that may play a specific role in determining very high-risk patients with STEMI undergoing PPCI but which may not be common in patients with CKD. For example, it can be administered as an intravenous bolus immediately before PPCI, unlike other measures such as intravenous hydration with normal saline, which needs to be initiated many hours before PPCI.

Although the pathophysiological mechanism of renal injury induced by contrast agents has not been fully elucidated, the following mechanisms are generally accepted: direct and indirect renal injury induced by contrast agents and disturbance of haemodynamic stability.[29–31] First,

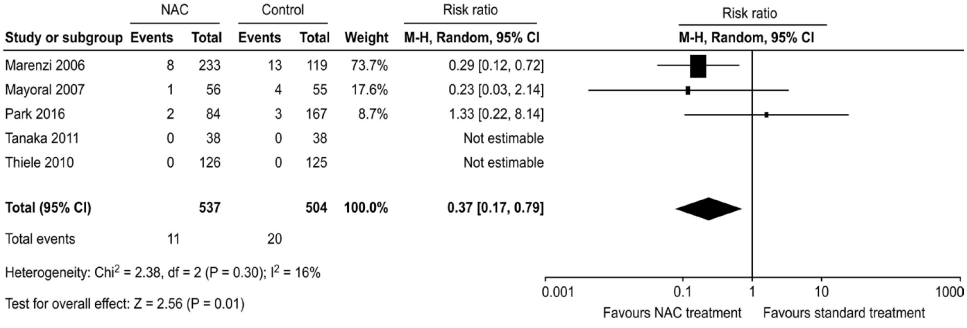

Figure 4 Effects of NAC on lowering the risk of all-cause in-hospital mortality (NAC vs non-use of NAC). M-H, Mantel-Haenszel; NAC, N-acetylcysteine.

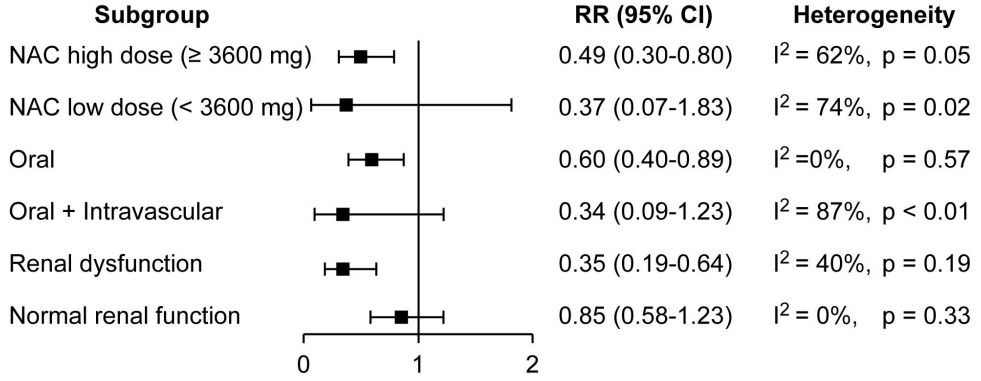

Figure 5 Subgroup analyses of the effect of NAC supplementation versus control on risk of contrast-associated acute kidney injury. NAC, N-acetylcysteine; RR, risk ratio.

intravascular exposure to contrast agents leads to transient systemic vasodilation, followed by intense contractions of the renal vascular bed. Vasoconstriction in the renal medulla results in particularly low baseline oxygen tension, resulting in oxygen supply that does not match demand, leading to ischaemic renal tubular damage. Second, contrast agents are directly toxic to renal tubular epithelial cells. Third, the use of contrast agents leads to reactive oxygen species generation, which accelerates renal tubular cell injury.

Patients with STEMI are prone to hypotension or even cardiogenic shock, a large volume of contrast agent, and an inability to start kidney prophylactic therapy, all of which are closely related to an elevated risk of CA-AKI. Patients with STEMI also commonly have other risk factors for CA-AKI, such as reduced cardiac output or hypotension due to myocardial infarction or a depletion of intravascular volume caused by vomiting, diaphoresis or decreased oral intake. Among patients with STEMI undergoing PPCI, acute renal impairment is multifactorial including exposure to contrast medium. Renal haemodynamic abnormalities may also represent a special type of acute cardiorenal syndrome.[32] Previous studies have explored the effects of NAC on reducing the risk of CA-AKI after exposure to contrast medium in terms of mechanism, and have offered more evidence on the biological interpretability from both internal and external experiments. In internal experiments, administration of NAC was confirmed to dose-dependently prevent cultured renal tubular cells from undergoing a short period of proliferation with extremely high concentrations of low-osmolar and iso-osmolar contrast agents.[33] In external experiments, the results showed that pretreatment of NAC maintained renal medullary vascularity by direct renal vasodilation and the production of prostaglandin E2 and cortical nitric oxide (NO).[34] In participants following CAG, NAC pretreatment reduced the recession in urinary NO final products without affecting lipid peroxidation.[35] In addition, NAC has several specific cardiac protective effects. Its administration in participants with AMI was closely related to less oxidative stress, a tendency towards rapid coronary artery reperfusion, a shrink of the myocardial infarction area and the preservation of left ventricular function.[7]

In both clinical and experimental research of AMI, intravenous administration of NAC has been confirmed to be associated with reduced infarct size and improvement in left ventricular function, possibly due to the antioxidant properties and its scavenging of free radicals. These cardiac effects may be enhanced in patients treated with PPCI, an urgent clinical setting in which oxidative stress and reperfusion injury occur. However, earlier studies were primarily performed to assess the preventive effect on CA-AKI and hence were not powered to evaluate the effect on mortality. Thus, it is possible that some of the observed differences in mortality between the control group and the intervention group using NAC are due to statistical chance. Alternatively, these differences may reflect a potential effect of NAC on preventing renal events that in turn resulted in reduced mortality. In conclusion, the mechanisms associated with improvement in in-hospital clinical outcomes using NAC have not been completely clarified, and research on potential extrarenal effects using NAC is needed.

In this meta-analysis, a subgroup analysis was conducted according to our prespecified clinically significant factors associated with CA-AKI. Baseline kidney insufficiency was deemed to be a significant risk factor for CA-AKI. Administration of NAC has a significantly greater benefit in the prevention of CA-AKI in patients with baseline kidney insufficiency than those without kidney insufficiency. Our findings also showed that patients administered NAC though the oral route would have greater benefits of lowering the risk of CA-AKI. However, intravascular usage of NAC might be more beneficial in patients with STEMI following PPCI owing to its rapid bolus and fluid expansion in such an urgent setting. Thus, further studies will be required to determine the optimal method of NAC administration. We also considered different dosages of NAC and identified that high-dosage NAC intake had an adequate effect on preventing CA-AKI in patients with STEMI undergoing PPCI. Only few trials have evaluated the effect of NAC on lowering CA-AKI risk in subgroups by dosage of contrast medium, or in subgroups complicated by diabetes or anaemia and usage of an intra-aortic balloon pump, which were closely related to the occurrence of CA-AKI in patients with STEMI following PPCI. Furthermore, a

recent study showed that the Kidney Disease Improving Global Outcomes (KDIGO) criteria is more sensitive than the consensus criteria in defining acute kidney injury (AKI) in patients with STEMI and in identifying populations at risk for long-term adverse outcomes.[36] Indeed, the KDIGO criteria allowed the identification of more patients with AKI, which confirmed that even mild elevation of serum creatinine (≥0.3 mg/dL) may also be an important variable that should be considered in subgroup analysis.

The results of the TSA indicated that new opportunities and challenges exist among clinicians. We demonstrated a consistent effect of NAC on lowering the risk of CA-AKI, and as confirmed by TSA future trials are not needed.

Limitations

Our analysis has several limitations that should be acknowledged. First, most of the selected studies were performed at a single centre and the conclusion may lack high external generalisation. However, our study represents the largest available pooled meta-analysis assessing the efficacy of NAC in preventing CA-AKI in patients with STEMI following PPCI. Second, we found unexplainable heterogeneity in both primary and secondary analyses, although our random-effects model did explain for this heterogeneity to some degree. It is probable that the characteristics of the patients contributed to the variation in study effects. However, the studies included in our analysis were all RCTs, with cautious evaluation and verdict by clinical endpoint committees, which assured the quality and accuracy of the data of the included trials. Third, we did not obtain individual data to confirm whether baseline kidney insufficiency and other confounding risk factors influenced the effect of NAC on preventing CA-AKI. Fourth, there was no consensus on the safe dosage of NAC in patients with STEMI following PPCI. Therefore, it was not easy to define the optimal dosage of NAC that would result in the best prevention of CA-AKI with limited side effects. However, the populations in the included trials varied greatly and contained multiple influencing factors for CA-AKI and different dosages of NAC, which assured us to make relatively reasonable conclusions from various patient groups.

CONCLUSIONS

In this analysis of seven RCTs, we confirmed a potential benefit of NAC in the reduction of CA-AKI and all-cause in-hospital mortality in patients with STEMI undergoing PPCI with NAC. However, the effects of NAC on the requirement for dialysis were not significant. Our findings support the administration of NAC, in addition to intravenous hydration, as an alternative in the prevention of CA-AKI in the STEMI setting and highlight the need for further large high-quality RCTs.

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Contributors ZG had full access to all of the data in the manuscript and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: ZG and YoL. Acquisition, analysis or interpretation of data: ZG, JL, LLi, YX, HH, SC, YoL, JT, QX, KW, LZ and J-YC. Drafting of the manuscript: ZG and YL. Critical revision of the manuscript for important intellectual content: ZG, YiL, JL, LLe and YX. Statistical analysis: ZG. Supervision: YiL and JL.

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Patient consent for publication Not required.

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