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N-Acetylcysteine in Cardiovascular-Surgery–Associated Renal Failure: A Meta-Analysis

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Background. Clinical trials with N-acetylcysteine (NAC) in perioperative cardiovascular settings have shown inconsistent effects for renal endpoints. We aimed to systematically review these trials to ascertain its role in prevention of post–cardiovascular surgery acute renal failure.

Methods. We searched MEDLINE, EMBASE, Cochrane Renal Health Library, and Google Scholar for randomized controlled studies that evaluated NAC in adult patients undergoing cardiovascular surgery. Acute renal failure, acute renal failure requiring dialysis, and mortality were the primary outcomes. Additional outcomes studied were length of intensive care unit stay, postoperative serum creatinine, creatinine clearance, renal biomarkers, and adverse effects of NAC.

Results. Twelve studies comprising 1,324 patients were found to be eligible. Meta-analytic estimates showed that NAC was not associated with reduction in acute renal failure (odds ratio [OR]: 0.89, 95% confidence interval [CI]: 0.68 to 1.15), acute renal failure requiring dialysis (OR: 1.09, 95% CI: 0.57 to 2.09) or mortality (OR: 0.95, 95% CI: 0.53 to 1.71). N-acetylcysteine was well tolerated but was not associated with any reduction in the length of intensive care unit stay. It had inconsistent effects on postoperative serum creatinine, creatinine clearance, and renal biomarkers. Subgroup analysis restricted to studies using intravenous NAC preparation showed a nonsignificant trend toward reduction in acute renal failure (OR: 0.81, 95% CI: 0.61 to 1.08) without any significant change in other outcomes.

Conclusions. Overall analysis of the existent literature shows that NAC is not beneficial in the prevention of post–cardiovascular surgery renal dysfunction. Routine use of NAC for this indication should be avoided.
gical procedures, acute renal failure, acute kidney failure, ARF, acute renal insufficiency, acute kidney insufficiency, acute kidney injury, AKI, acute tubular necrosis, and ATN. In addition, we studied reference lists and bibliographical data from all retrieved articles and reviews for any additional relevant material. There was no language restriction.

To be included, the studies had to report at least one of the following renal outcomes: incidence of acute renal failure, incidence of acute renal failure requiring dialysis, postoperative serum creatinine, creatinine clearance, glomerular filtration rate, or renal biomarkers. Studies evaluating role of NAC in noncardiovascular surgical settings (such as radiocontrast nephropathy, sepsis, and so forth) and those that did not report the specified renal outcomes were excluded.

Data Extraction and Quality Assessment
Two authors (S.U.N., P.K.) independently assessed the studies for eligibility and extracted relevant data regarding study design and setting, participant characteristics, and outcome measures using a standardized data extraction form. We accepted the outcome definitions used by the original researchers. Descriptions such as “no major complications were observed in the study” were not considered as zero events. Only explicit descriptions of outcome events were tabulated.

The results of the individual studies were reported in many different ways, including mean and standard deviation (SD), standard error of the mean (SEM), or interquartile range (IQR). We converted SEMs and IQRs to SD, using appropriate formulas. We considered IQR to be 1.35 times the SD. Standard deviation was calculated as square root of sample size times the SEM. All data were converted to uniform measurements; thus, serum creatinine is presented as mg/dL and creatinine clearance as mL/min.

The method of all included studies was rated by means of the validated scale by Jadad and colleagues [14]. This scale considers randomization, blinding, and withdrawal/dropouts. Studies were considered of low quality if the Jadad score was from 0 to 2, of moderate quality if the score was from 3 to 4, and of high quality if the score was 5.

Outcome Measures
The primary outcomes of interest for the current review were acute renal failure, acute renal failure requiring dialysis, and mortality. Secondary outcomes analyzed included duration of intensive care unit stay, postoperative serum creatinine, creatinine clearance/glomerular filtration rate, and indicators of renal injury, for example, urine N-acetyl glucosaminidase and urine albumin to creatinine ratio. We also abstracted data regarding any adverse effects of NAC reported in the included studies, such as bleeding complications (assessed by the amount of blood loss, postoperative blood transfusion requirement, and incidence of reoperation).

Data Analysis and Quantitative Data Synthesis
We analyzed data according to guidelines in the Cochrane Reviewers’ Handbook [15]. All the analyses were performed using RevMan 4.2.10 (Cochrane Collaboration, Oxford, United Kingdom). Dichotomous data outcomes from individual studies were analyzed according to the Mantel-Haenszel model to compute individual odds ratio (OR) with 95% confidence intervals (CI). Where continuous scales of measurement were used to assess the effects of treatment, the weighted mean difference was used. Statistical significance was set at the two-tailed 0.05 level for hypothesis testing. Statistical heterogeneity was analyzed using heterogeneity $I^2$ (Cochrane Q) statistic and $I^2$ test [15, 16]. The $I^2$ values of 25%, 50%, and 75% correspond to low, medium, and high levels of statistical heterogeneity. Treatment effects were analyzed with the random-effects model. If there was a significant heterogeneity ($I^2 >25$%), then we explored possible sources of heterogeneity (for example, participants, study quality, and so forth).

We performed the following subgroup analyses: (1) to explore the effect of nondialysis-dependent preexisting renal insufficiency, we performed an analysis from studies that specifically included patients with preexisting renal insufficiency; (2) to explore the effect of underlying surgery, we performed an analysis for cardiac versus vascular surgical studies; (3) to explore the effect of different formulations of NAC, we performed a separate analysis for studies using only intravenous preparations; and (4) to explore the effect of dose of NAC preparations, we performed a separate analysis for studies using high-dose NAC preparations. Studies included in the high-dose category were those that administered a cumulative dose of $>150$ mg/kg of NAC.

Sensitivity Analysis
We assessed the robustness of findings from the primary analysis to the effects of study population and baseline risk of any of the primary outcomes through sensitivity analyses by switching from random-effect to fixed-effect models, computing relative risks and repeating the analyses to assess the influence of study quality.

Results
Details of the flow of study identification are reported in Figure 1. Database searches and snowballing yielded a total of 108 citations. Excluding 89 nonrelevant titles and abstracts, we retrieved 19 studies in complete form and assessed them according to the selection criteria. A total of seven studies were further excluded for the following reasons: studies did not report the specified renal outcomes ($n = 3$), surgery involved use of radiocontrast exposure ($n = 1$), and duplicate publication ($n = 3$). Our analysis finally identified 12 eligible studies comprising 1,324 patients (668 NAC group; 656 control group) [17–28]. Characteristics of the included studies are summarized in Table 1. Mean age of the patients was 69 years, and 22% patients were female. Nine studies (1,191 patients) evaluated NAC in patients undergoing cardiac surgery [17–22, 25–27], and three studies (153 patients) evaluated NAC in patients undergoing...
aortic aneurysm repair [23, 24, 28]. One study involved patients undergoing thoracoabdominal aortic aneurysm repair [24], and two other studies included patients undergoing abdominal aneurysm repair [23, 28]. Five studies (694 patients) were designed to assess the effects of NAC in patients with impaired preoperative renal function [17, 18, 25–27]. Eight studies used intravenous NAC preparations [19, 21–23, 25–28], two studies used oral NAC preparations [17, 18], and two studies used combined oral and intravenous preparations [20, 24]. NAC was administered only during the surgery in one study [21], and in other studies, it was administered during and after the surgery, mostly for as long as 24 to 48 hours. In one study, NAC was administered for an extended duration of as long as 6 days [17]. Eight studies administered NAC at a cumulative dose of more than 150 mg/kg and were included in the high-dose category [20–25, 27, 28]. In one study, NAC was administered as a part of antioxidant regimen that also included allopurinol, vitamin C, vitamin E, and mannitol [28]. In a study by Barr and colleagues [18], there were two arms that received NAC; one arm received NAC only and the other received NAC along with fenoldopam [18]. We analyzed data from these two arms separately.

Jadad scores for the included studies are outlined in Table 1. Eight studies were of high quality, three studies were of moderate quality, and one study was of low quality.

**Primary Outcomes**

Acute renal failure and acute renal failure requiring dialysis were reported in seven and 11 studies, respectively. Meta-analytic estimate showed that the use of NAC was not associated with reduction in acute renal failure (OR: 0.89, 95% CI: 0.68 to 1.15; Fig 2) and acute renal failure requiring dialysis (OR: 1.09, 95% CI: 0.57 to 2.09; Fig 3). Mortality was reported in all studies, and meta-analytic estimate showed that NAC was not associated with any reduction in mortality (OR: 0.95, 95% CI: 0.53 to 1.71; Fig 4). There was no statistical heterogeneity among the studies for any of the primary outcomes.

**Secondary Outcomes**

Duration of intensive care unit stay was reported in eight studies, and it was not different between the NAC and placebo groups (weighted mean difference, 0.34 days; 95% CI: –0.56 to 1.25). There was a significant heterogeneity among the studies for this outcome (I^2 = 82.7%, p < 0.001), which may have been due to differences in individual institution criteria for intensive care unit requirement and differences in baseline characteristics of the patients.

Ten studies reported postoperative serum creatinine values [17, 19–27], four studies reported estimated creatinine clearance or glomerular filtration rate [18, 21, 26, 27], and one study reported 24-hour creatinine clearance [28]. Fischer and colleagues [21], Barr and associates [18], and Winjen and colleagues [28] demonstrated that the postoperative decrease in creatinine clearance was significantly attenuated by NAC, without any other significant difference between the NAC and control groups.

![Fig 1. Flow chart of study identification.](image)

![Fig 2. Meta-analytic estimates of acute renal failure comparing N-acetylcysteine (NAC) to control. (CI = confidence interval; OR = odds ratio.)](image)
<table>
<thead>
<tr>
<th>Study, Year [Reference]</th>
<th>Population</th>
<th>Intervention and Control</th>
<th>Number of Patients Randomized per Group</th>
<th>Baseline Renal Functiona</th>
<th>Outcomes</th>
<th>Study Definition of Acute Renal Failure</th>
<th>Jadad Score</th>
</tr>
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<tbody>
<tr>
<td>Adabag [17]</td>
<td>Elective cardiac surgery patients with reduced estimated glomerular filtration rate (&lt;60 mL/min)</td>
<td>NAC 600 mg orally twice daily starting on preoperative day 1 and then postoperative for total 14 doses (3 doses before surgery); placebo solution matched in volume, color, consistency, transparency</td>
<td>50 52</td>
<td>1.9 ± 0.7 1.9 ± 0.6</td>
<td>Acute renal failure, dialysis, mortality, ICU stay length, maximal change in postoperative serum creatinine from baseline and adverse events (nausea, delirium, diarrhea)</td>
<td>Increase of &gt;0.5 mg/dL or ≥25% in serum creatinine from baseline within the first 5, 7, and 30 postoperative days</td>
<td>5</td>
</tr>
<tr>
<td>Barr (a) [18]b</td>
<td>Elective, urgent, or emergent cardiac surgery patients with reduced creatinine clearance (&lt;40 mL/min)</td>
<td>NAC 600 mg orally twice daily on preoperative day 1, then on morning of surgery and one dose at night after surgery; placebo solution matched for taste</td>
<td>20 19</td>
<td>35 ± 2 35 ± 2</td>
<td>Dialysis, mortality, ICU stay length, difference between preoperative and postoperative creatinine clearance, adverse events (hypotension)</td>
<td>Not reported</td>
<td>4</td>
</tr>
<tr>
<td>Barr (b) [18]b</td>
<td>Elective, urgent or emergent cardiac surgery patients with reduced creatinine clearance (&lt;40 mL/min)</td>
<td>NAC 600 mg orally twice daily on preoperative day 1, then on morning of surgery and one dose at night after surgery along with intravenous fenoldopam 0.1 μg/kg/min at surgical induction and for 48 hours after surgery; placebo solution matched for taste along with intravenous normal saline</td>
<td>21 19</td>
<td>35 ± 2 35 ± 2</td>
<td>Dialysis, mortality, ICU stay length, difference between preoperative and postoperative creatinine clearance, adverse events (hypotension)</td>
<td>Not reported</td>
<td>4</td>
</tr>
<tr>
<td>Burns [19]</td>
<td>Elective or urgent coronary artery bypass surgery patients with high risk for postoperative renal dysfunction</td>
<td>NAC 600 mg 4 intravenous doses (1st after anesthesia induction, 2nd on weaning from cardiopulmonary bypass, and 3rd and 4th doses at 12 and 24 hours after first dose); placebo 5% dextrose solution</td>
<td>148 147</td>
<td>1.1 ± 0.3 1.2 ± 0.4</td>
<td>Acute renal failure, dialysis, mortality, ICU stay length, maximal change in postoperative serum creatinine from baseline and adverse events (nausea, vomiting, hypotension, surgical reoperation)</td>
<td>Increase of ≥25% or an absolute increase ≥0.5 mg/dL in serum creatinine within the first 5 postoperative days</td>
<td>5</td>
</tr>
<tr>
<td>El-Hamamsy [20]</td>
<td>Elective primary coronary artery bypass patients</td>
<td>NAC 150 mg/kg infusion immediately before skin incision followed by infusion of 12.5 mg/kg/h for 24 hours along with 600 mg oral NAC the day before and morning of operation; placebo not described</td>
<td>50 50</td>
<td>Not available</td>
<td>Dialysis, mortality, postoperative serum creatinine, and adverse events (surgical reoperation)</td>
<td>Not reported</td>
<td>3</td>
</tr>
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</table>

a Baseline creatinine values in mg/dL (μmol/L).
<table>
<thead>
<tr>
<th>Study, Year [Reference]</th>
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<th>Intervention and Control</th>
<th>Number of Patients Randomized per Group</th>
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<th>Jadad Score</th>
</tr>
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<tbody>
<tr>
<td>Fischer [21]</td>
<td>Elective or urgent coronary artery bypass patients</td>
<td>NAC 100 mg/kg into cardiopulmonary bypass prime followed by 20 mg/kg/h until end of cardiopulmonary bypass; placebo 0.9% normal saline</td>
<td>20/20</td>
<td>1.1 ± 0.4/1.0 ± 0.4</td>
<td>Dialysis, mortality, postoperative serum creatinine and creatinine clearance change</td>
<td>Not reported</td>
<td>5</td>
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<tr>
<td>Haase [22]</td>
<td>Patients at high risk of postoperative renal dysfunction undergoing elective or urgent cardiac surgery necessitating cardiopulmonary bypass</td>
<td>NAC 150 mg/kg loading infusion followed by 50 mg/kg over 4 hours, then 100 mg/kg over 20 hours; placebo 5% dextrose solution</td>
<td>31/30</td>
<td>1.0 ± 0.3/1.0 ± 0.3</td>
<td>Acute renal failure, dialysis, mortality, ICU stay, increase in postoperative serum creatinine and cystatin C from baseline to peak, and adverse events (surgical reoperation)</td>
<td>Increase of ≥25% or an absolute increase ≥0.5 mg/dL in serum creatinine within first 5 postoperative days</td>
<td>5</td>
</tr>
<tr>
<td>Hynninen [23]</td>
<td>Elective abdominal aneurysm repair surgery patients</td>
<td>NAC 150 mg/kg loading infusion followed by 150 mg/kg for 24 hours; placebo 5% dextrose solution</td>
<td>34/35</td>
<td>0.8 ± 0.3/0.8 ± 0.2</td>
<td>Dialysis, mortality, ICU stay length, postoperative urine N-acetyl glucosaminidase/creatinine ratio, urine albumin/creatinine ratio, serum creatinine and cystatin C, and adverse events (anaphylactoid reaction, blood transfusion requirement, surgical reoperation)</td>
<td>Not reported</td>
<td>5</td>
</tr>
<tr>
<td>Macedo [24]</td>
<td>Elective abdominal or thoracoabdominal aneurysm repair surgery patients</td>
<td>NAC 1200 mg orally twice daily 24 hour before surgery followed by 600 mg infusion for 48 hours after surgery; placebo oral starch and identical infusion</td>
<td>18/24</td>
<td>1.2 ± 0.3/1.4 ± 0.5</td>
<td>Acute renal failure, dialysis, mortality, ICU stay length, postoperative peak and maximal increase in serum creatinine</td>
<td>Increase of ≥25% in serum creatinine within the first 3 postoperative days</td>
<td>5</td>
</tr>
<tr>
<td>Study, Year [Reference]</td>
<td>Population</td>
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<tr>
<td>Ristikankare [25]</td>
<td>Elective open heart surgery with cardiopulmonary bypass patients with serum creatinine ≥ 1.1 mg/dL</td>
<td>NAC 150 mg/kg loading infusion followed by 50 mg/kg for 4 hours, then 100 mg/kg for 16 hours; placebo 0.9% normal saline</td>
<td>40 40</td>
<td>1.4 ± 0.3 1.5 ± 0.5</td>
<td>Acute renal failure, dialysis, mortality, ICU stay length, postoperative increase in urine N-acetyl glucosaminidase/creatinine ratio, serum creatinine and cystatin C and adverse events (hypotension, blood loss, blood transfusion requirement)</td>
<td>Increase of ≥25% or an absolute increase ≥0.5 mg/dL serum creatinine or increase in urine N-acetyl glucosaminidase/creaseatinine ratio 30% above baseline or increase in serum cystatin C level over 1.4 mg/L within first 5 postoperative days</td>
<td>4</td>
</tr>
<tr>
<td>Sisillo [26]</td>
<td>Elective cardiac surgery patients with reduced creatinine clearance (&lt;60 mL/min)</td>
<td>NAC 1200 mg 4 intravenous doses (1st after anesthesia induction, followed by 3 additional doses at 12-hour intervals in intensive care unit); placebo 0.9% normal saline</td>
<td>127 129</td>
<td>1.2 ± 0.4 1.3 ± 0.3</td>
<td>Acute renal failure, dialysis, mortality, maximal change in postoperative serum creatinine and creatinine clearance adverse events (blood loss requiring blood transfusion requirement, surgical re-operation)</td>
<td>Increase of &gt;25% in serum creatinine within the first 3 postoperative days</td>
<td>5</td>
</tr>
<tr>
<td>Wijeysundera [27]</td>
<td>Elective cardiac surgery patients with reduced estimated glomerular filtration rate (&lt;60 mL/min)</td>
<td>NAC 100 mg/kg intravenous loading dose after anesthesia induction, then 20 mg/kg/h until 4 hours after cardiopulmonary bypass; placebo 5% dextrose solution</td>
<td>89 89</td>
<td>1.5 ± 0.5 1.4 ± 0.4</td>
<td>Acute renal failure, dialysis, mortality, ICU stay length, postoperative change in serum creatinine, estimated glomerular filtration rate, and adverse events (bronchospasm, urticaria, facial edema, nausea, vomiting)</td>
<td>Increase of ≥25% or an absolute increase ≥0.5 mg/dL in serum creatinine within the first 3 postoperative days</td>
<td>5</td>
</tr>
<tr>
<td>Wijnen [28]</td>
<td>Elective infrarenal abdominal aneurysm repair patients</td>
<td>NAC 150 mg/kg intravenous before start of surgery, then 200 mg/kg over 12 hours along with oral allopurinol, oral vitamin E, oral vitamin C, and intravenous mannitol; Placebo not described</td>
<td>20 22</td>
<td>1.1 ± 0.1 1.2 ± 0.1</td>
<td>Mortality, postoperative change in urine albumin/creatinine ratio, creatinine clearance, and adverse events (surgical reoperation)</td>
<td>Not reported</td>
<td>2</td>
</tr>
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</table>

<sup>a</sup> Renal function reported as mean serum creatinine ± SD (mg/dL) except in Barr (a) and Barr (b) studies, where mean creatinine clearance ± SD (mL/min) is reported.  
<sup>b</sup> Study by Barr et al had two intervention arms with N-acetylcysteine (NAC): one intervention was only NAC [Barr (a)] and the other intervention was NAC along with fenoldopam [Barr (b)].  

ICU = intensive care unit.
Postoperative urine albumin to creatinine ratio [23, 28], urine N-acetyl glucosaminidase/creatinine ratio [23, 25], and serum cystatin C values [22, 23, 25] were not significantly different between the NAC and control groups.

Adverse Effects
We analyzed the adverse effects profile of NAC as reported in individual studies. Incidence of adverse effects such as nausea, headache, anaphylaxis, and hypotension was not different in the NAC group compared with the control group (OR: 0.90, 95% CI: 0.55 to 1.48). Amount of blood loss during the first 24 hours after the surgery was reported in one study, and it was significantly more in the NAC group compared with the control group; however, that did not translate into increased requirement of blood transfusion [25]. Similarly, Hynninen and coworkers [23] and Sisillo and associates [26] reported no difference between the NAC and control groups for the perioperative blood transfusion requirement. Risk of surgical reoperation was reported in 6 studies, and it was not different between the NAC and control groups (OR: 1.16, 95% CI: 0.62 to 2.17).

Subgroup Analyses
To explore the effect of nondialysis-dependent preexisting renal insufficiency on outcomes, we performed a

Fig 3. Meta-analytic estimates of acute renal failure requiring dialysis comparing N-acetylcysteine (NAC) to control. (CI = confidence interval; OR = odds ratio.)

Fig 4. Meta-analytic estimates of mortality comparing N-acetylcysteine (NAC) to control. (CI = confidence interval; OR = odds ratio.)
subgroup analysis on studies that specifically included patients with preexisting renal insufficiency (nondialysis dependent). Restricting the analysis to these studies did not change the effects of NAC on acute renal failure (OR: 0.79, 95% CI: 0.57 to 1.10), acute renal failure requiring dialysis (OR: 1.26, 95% CI: 0.62 to 2.58), or mortality (OR: 0.57, 95% CI: 0.25 to 1.30). After restricting the analysis to cardiac surgical patients, the effects of NAC on acute renal failure (OR: 0.86, 95% CI: 0.66 to 1.13), acute renal failure requiring dialysis (OR: 1.03, 95% CI: 0.53 to 2.00), and mortality (OR: 0.77, 95% CI: 0.39 to 1.50) remained nonsignificant. Restricting the analysis to studies that used intravenous NAC only did not change the effects on acute renal failure (OR: 0.81, 95% CI: 0.61 to 1.08), acute renal failure requiring dialysis (OR: 1.04, 95% CI: 0.37 to 2.94), and mortality (OR: 0.58, 95% CI: 0.24 to 1.41). Restricting the analysis to studies that administered high-dose NAC did not change the effects on acute renal failure (OR: 0.89, 95% CI: 0.57 to 1.39), acute renal failure requiring dialysis (OR: 0.75, 95% CI: 0.17 to 3.23), and mortality (OR: 0.92, 95% CI: 0.28 to 3.08).

Sensitivity Analysis
Sensitivity analyses performed by switching from random-effect to fixed-effect models, computing relative risks did not change the overall results for the primary outcomes. Restricting the analysis to studies of high quality did not change the effects of NAC on primary outcomes.

Comment
Acute renal failure after cardiovascular surgery is a major cause of postoperative morbidity and mortality [1, 4, 5]. Many pharmacologic interventions have been tried to provide renal protection in the perioperative period [1]. In a recent review by Zacharias and coworkers [29], investigators systematically analyzed available agents to prevent postsurgical acute renal failure and reported that there are no effective pharmacologic interventions to prevent acute renal failure after major surgeries including cardiovascular surgeries. However, this review analyzed dopamine, diuretics, calcium channel blockers, angiotensin-converting enzyme inhibitors, and hydration fluids but did not address the role of NAC.

Our meta-analysis assessed whether NAC, an inexpensive medicine with antioxidant properties, would be beneficial in improving renal outcomes in patients undergoing cardiovascular surgery. We found that the prophylactic use of NAC was overall well tolerated but was not beneficial in improving acute renal failure, dialysis requirement, and mortality in the cardiovascular surgical setting when radiocontrast dye is not used. In our review, NAC did not reduce the length of intensive care unit stay and did not have consistent beneficial effects on surgery serum creatinine, creatinine clearance, and renal injury markers (urine N-acetyl glucosaminidase and urine albumin to creatinine ratio) after surgery.

Several mechanisms are thought to be playing a role in the development of post–cardiovascular surgery renal dysfunction. Release of reactive free oxygen radicals and neutrophil activation leading to increased levels of tumor necrosis factor-α and interleukin-8 are known to contribute to this renal dysfunction along with other factors such as hypovolemia, ischemia-reperfusion, neurohumoral activation, and aortic cross-clamping [11, 30]. In experimental studies, NAC has attenuated renal dysfunction through different anti-inflammatory and antioxidant effects such as antagonism of tumor necrosis factor-α and inhibition of the vascular cell adhesion molecule expression [30]. In radiocontrast nephropathy, NAC has been demonstrated to provide renal protection by acting as an antioxidant and arteriolar vasodilator through the nitrous oxide pathway [31]. Furthermore, NAC has been shown to prevent cardiopulmonary bypass pump–induced inflammatory response [32]. Despite these positive experimental and clinical findings, it is intriguing to see NAC was not found to be beneficial in the prevention of renal dysfunction in cardiovascular surgical setting. There may be several possible explanations for this. Mechanisms other than those inhibited by NAC possibly contribute more toward the pathogenesis of post–cardiovascular surgery acute renal failure. Antioxidant and vasodilatory actions of NAC are not enough to negate these other mechanisms. Although our review included studies involving NAC doses well above those used for radiocontrast nephropathy prevention [33], the optimal dose of NAC needed to prevent postcardiovascular surgery renal dysfunction is unknown and may well be much higher than used so far in any study. The route of administration of NAC might have played role as bioavailability of oral NAC may be unpredictable in the perioperative setting. In subgroup analysis, however, we did not observe any benefit from intravenous NAC preparations.

Our systematic review has limitations. Some of the studies included patients undergoing cardiac surgery using off-pump technique and that could have attenuated the potential beneficial effects of NAC as cardiopulmonary bypass pump is known to induce a significant inflammatory response, which has been previously shown to be reduced by NAC [32]. In fact, Sisillo and colleagues [26] reported in their study that the use of NAC was associated with statistically significant reduction in acute renal failure when analysis was restricted to patients who underwent cardiac surgery using on-pump technique. However, NAC was not consistently beneficial in studies that specifically excluded patients who underwent cardiac surgery using off-pump technique. Individual study definitions of acute renal failure were not reported in some studies and varied among those that reported them, and that reduces the validity of the meta-analytic estimate for this outcome. Future studies related to acute renal failure should use standard definitions such as the one proposed by the Acute Kidney Injury Network [34]. The outcomes considered in our review were not necessarily the primary outcomes of interest to the study authors, and hence, the included studies were underpowered to detect any significant difference, especially for outcomes such as acute renal failure requiring dialysis and mortality. For definitive evaluation of outcome such as acute renal failure requiring dialysis, the sample size required will be approximately 2,400 (two-sided alpha 0.05,
80% power [35]. Because the required sample size is large, it is unlikely that a future single randomized controlled trial will be able to address the role of NAC in this setting, and the findings of our comprehensive review provide the best available evidence to address its role in the prevention of post-cardiovascular surgery renal dysfunction.

In conclusion, overall analysis of the existing literature shows that the perioperative use of NAC is not beneficial in the prevention of post-cardiovascular surgery acute renal failure, and the routine use of NAC for this indication should be avoided.

The authors would like to thank Miss Cathy Carey for her valuable help as a librarian.

References
