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N-Acetyl Cysteine Therapy Does Not Prevent Renal Failure in High-Risk Patients Undergoing Open-Heart Surgery

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ABSTRACT

Background: Renal dysfunction is a common complication after cardiovascular surgery. Controversial issues have been discussed regarding the role of N-acetyl cysteine in the prevention of postoperative renal dysfunction. The purpose of this meta-analysis is to assess whether N-acetyl cysteine offers any protection against the development of acute renal dysfunction after cardiac surgery.

Methods: Multiple databases were searched for randomized trials comparing the role of N-acetyl cysteine and placebo in human patients undergoing cardiac surgery. Endpoints studied were: the incidence of acute renal failure, hemodialysis, early mortality, duration of hospital stay, and maximal change in creatinine values. Dichotomous variables were compared using the risk difference (RD) calculated with inverse weighting; continuous data was pooled as (standardized) mean difference. Results are presented with 95% confidence interval ($P < .05$ is significant); results are presented within 95% confidence interval.

Results: Thirteen randomized trials (713 and 707 patients in the N-acetyl cysteine and control groups, respectively) were included in the present analysis; nine dealing with patients at high-risk for acute renal failure. The incidence of postoperative acute renal dysfunction was 23% and 36% in the N-acetyl cysteine and control cohorts, respectively. N-acetyl cysteine therapy did not reduce acute renal dysfunction in the high-risk cohort [RD -0.03 (-0.09 to 0.02); $P = .22$; $I^2 = 24\%$]. Maximal change in creatinine levels after surgery was also comparable [standardized mean difference 0.07 (-0.23, 0.09); $P = .39$]. Early mortality was 2.9% and 3.7% in the N-acetyl cysteine and control cohorts respectively; [RD 0 (-0.03 to 0.02); $P = .63$; $I^2 = 20\%$]. Hospital stay (mean length of stay 10.4 and 10.1 days in the N-acetyl cysteine and control cohorts, respectively) was also similar in both cohorts [WMD 0.17 (-0.02 to 0.37) days; $P = .81$].

Conclusion: Prophylactic N-acetyl cysteine therapy does not reduce the incidence of renal dysfunction in high-risk patients undergoing cardiac surgery.

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INTRODUCTION

Acute renal dysfunction (ARD) is a serious postoperative complication after cardiac surgery. The frequency of ARD after cardiac surgery ranges from 0.7% to 7.7%; almost one-third of patients may subsequently need dialysis [Barr 2008]. This adverse outcome prolongs hospital stay and increases mortality, especially in patients who are dialysis dependent [Sisillo 2008].

Many pharmacologic agents have been used as prophylaxis with varying results [Sisillo 2008]. N-acetyl cysteine (NAC) was initially implemented for its benefit in preventing contrast-induced nephropathy [Tepel 2000]. This protective role of NAC is through the buffering activity against the oxygen free radicals as well as the renal vasodilatation mechanisms [Sisillo 2008].

Various studies have reported differing conclusions about the role of NAC in ameliorating the risk of kidney injury after cardiac surgery [Sisillo 2008]. While an earlier systematic review demonstrated that NAC does not have beneficial effect [Adabag 2009], some new randomized trials have been published since then [Adabag 2009; Song 2015; Prasad 2010; Santana-Santos 2014]. We thus chose to present an updated meta-analysis on this topic.

MATERIAL AND METHODS

PubMed (Inception–December 2014), Embase (Inception–December 2014) and the Cochrane database of trials were systematically searched to identify randomized controlled trials comparing the efficacy of NAC and placebo in the prevention of acute renal failure in adult human subjects undergoing cardiac surgery. Three authors (AMR, SVD, and SEA) independently reviewed the selected abstracts and promising full-text articles were retrieved. Promising full-text articles were then evaluated for inclusion in our systematic review. Disagreement was resolved by consensus. Case

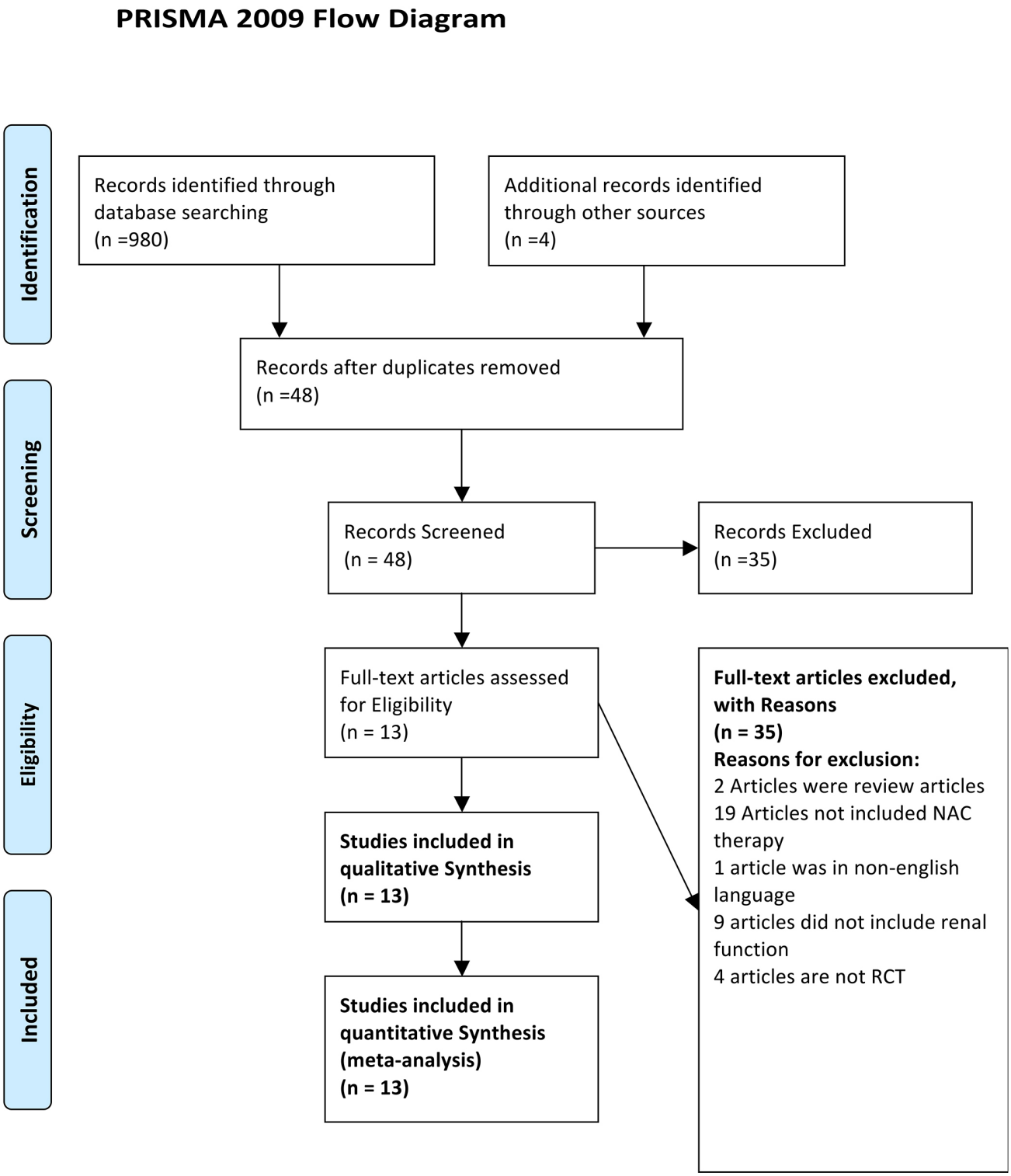

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Figure 1. Flow chart depicting study selection for meta-analysis.

Preoperative Demographic Data for Patients Included in Our Meta-Analysis

Name of Study (Year)	Country	Type of Study	Number of Patients		Age (Year)		Male (%)	
			NAC	Control	NAC	Control	NAC	Control
Barr et al (2008)	USA	RCT	20	19	73.8 ± 2.2	72.4 ± 2.0	75	68.4
Burns et al (2005)	Canada	RCT	148	147	68.9 ± 8.9	69.2 ± 9.7	78.4	79.6
El-Hamamsi et al (2006)	Canada	RCT	50	50	59.8 ± 7.8	61.3 ± 7.4	86	92
Fischer et al (2005)	Germany	RCT	20	20	NA	NA	NA	NA
Haase et al (2007)	Australia	RCT	30	30	68.9 ± 9.7	68.3 ± 9.3	77	70
Adabag et al (2008)	USA	RCT	50	52	70 ± 9	72 ± 9	NA	NA
Praasad et al (2010)	India	RCT	35	35	55.60 ± 10.24	57.77 ± 9.36	71	80
Song et al (2014)	Korea	RCT	57	60	68 ± 10	69 ± 8	70	72
Santana-Santos et al (2014)	Brazil	RCT	35	35	65.0 ± 8.2	64.0 ± 9.0	57	86
Orhan et al (2006)	Turkey	RCT	10	10	59.6 ± 5.48	61.8 ± 4.32	70	60
Ristikankare et al (2006)	Finland	RCT	38	39	72 (44-87)	69 (51-81)	73.7	87.2
Sisillo et al (2007)	Italy	RCT	129	125	73 ± 6	72 ± 6	50	48
Wijeysundera et al (2007)	Canada	RCT	88	87	74 (8)	73 (9)	60	59

CABG indicates coronary artery bypass grafting; CR, creatinine; LV, left ventricular; LVEF, left ventricular ejection fraction; mGFR, mean glomerular filtration

reports, editorials, and letters to the editor were excluded. We also excluded studies that presented only data on NAC cohort without a control group. The reference sections of prior systematic reviews were manually searched to ensure that studies were not missed. Two authors (SEA, AMR) collected data independently using a pre-specified form. Study author, year, nationality, and event rates in both cohorts were obtained from included studies.

The primary end-point studied was the incidence of acute renal failure, as defined by each individual study. Secondary end-points included were: the maximum change in creatinine levels, early mortality and total in-hospital stay duration. This systematic review has not been registered elsewhere. All aspects of the study were performed adhering to the PRISMA guidelines; the PRISMA checklist has been included in the reference section [Liberati 2009]. Study quality has been evaluated using recommended guidelines [van Tulder 2003].

Statistical Analysis

Statistical analysis was performed using Stata 12.0 (StataCorp, College Station, TX, USA). Categorical data was presented as a risk difference (RD) with a 95% confidence interval. The random inverse variance weighted model was implemented. Continuous variables are presented as the mean difference (MD) or standardized mean difference (SMD), as appropriate. The mean (standard deviation) was obtained from the median (range) using accepted formulae. The results are graphically presented using forest plots. The forest plots provide the calculated risk difference (with 95% CI), weight of each included study, and the overall pooled result. Sensitivity analysis was performed by pooling together studies that included high-risk patients according to preoperative criteria.

A funnel plot was constructed to identify publication bias. This was formally tested by applying the Egger`s linear regression method.

Heterogeneity was evaluated by obtaining the Egger's I^2 for each pooled analysis. This calculated value provides an estimate of the variance between studies that cannot be attributed to chance alone. Heterogeneity was graded as low (25-50%), moderate (51-75%) and high (>75%).

RESULTS

From an initial 984 titles, 48 abstracts were screened from which 35 were excluded. Finally, 13 articles were included in our systematic review. The detailed review process is outlined

Diabetes		mGFR or Creatinine		Dose of NAC	LVEF	
NAC	Control	NAC	Control	NAC	NAC	Control
5 (25%)	8 (42.1%)	35.3 ± 2.2	33.5 ± 2.1	600 mg p.o. b.i.d. x 4	2 (10%) <35%	2 (10.5%) <35%
66 (44.6%)	63 (42.9%)	CR: 32 (21.6%) >1.4	CR: 36 (24.5%) >1.4	600 mg p.o. b.i.d. x 4	34 (23.0) <35%	29 (19.7) <35%
NA	NA	NA	NA	600 mg p.o. x 1 150 mg/kg i.v. x 1 12.5 mg/kg/h i.v. x 24 h	8%/LV dysfunction	12%/ LV dysfunction
NA	NA	CR: 92.3 ± 31.3	CR: 93.1 ± 35.4	100 mg/kg i.v. x 1 20 mg/kg/h x 75 min	NA	NA
2 (7%)	3 (10%)	78.6 ± 25.7	77.7 ± 22.3	CABG 150 mg/kg i.v. x 1 CABG + valve 50 mg/kg i.v.x 1 Valve 100 mg/kg x 1	2 (7%) <30%	2 (7%) <30%
26 (52%)	30 (56%)	40 ± 10	39 ± 11	600 mg p.o. b.i.d x 14	53 ± 12	51 ± 11
9 (26%)	12 (34%)	79 (29)	73 (20)	600 mg p.o. b.i.d. x 4	50.54 (9.47)	49.43 (9.34)
43 (75%)	41 (68%)	CR 1.20 ± 0.66	CR 1.22 ± 0.61	150 mg/kg i.v. x 2	7 (12%) <35%	5 (8%) <35%
22 (63)	18 (51)	45.9 ± 9.2	44.7 ± 12	150 mg/kg x 1 50 mg/kg x 1	56.8 ± 11.9	50.5 ± 14.0
5 (50%)	3 (30%)	NA	NA	50 mg/kg x 1	70.7 ± 15.7	67.6 ± 20.11
13 (34.2%)	15 (38.5%)	CR 127 (26)	CR 134 (45)	CABG 150 mg/kg i.v. x 1 CABG + valve 50 mg/kg i.v. x 1 Valve 100 mg/kg x 1	45 (1.2)	47 (1.5)
26 (20%)	26 (21%)	46 ± 7	46 ± 9	1200 mg x 4 i.v.	46.48 ± 0.78	43.79 ± 1.04
31 (35%)	26 (30%)	42 (11)	45 (11)	100 mg/kg x 1 20 mg/kg/hr	13 (15%) <40%	21 (24%) <40%

rate; NA, not available; NAC, N-acetyl cysteine; RCT, randomized controlled trial.

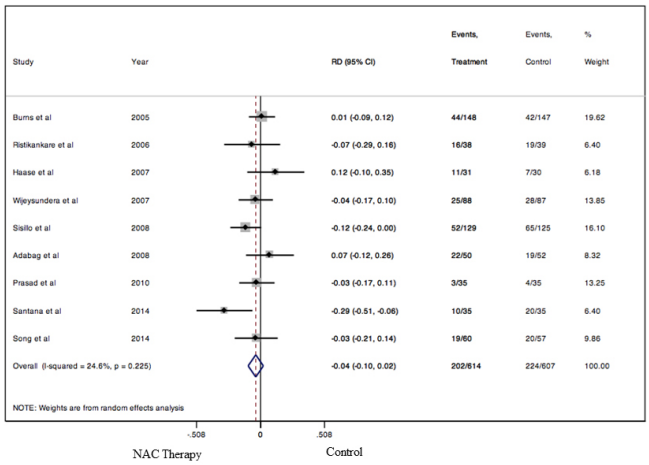
in Figure 1. The Table provides an overview of the NAC and control cohorts.

From the selected articles, 6 studies [Song 2015; Prasad 2010; Santana-Santos 2014; Orhan 2006; El-Hamamsy 2007; Fischer 2005] included only coronary artery bypass grafting surgery; two among them specifically included only patients undergoing off-pump coronary artery bypass surgery [Song 2015; Prasad 2010]. Seven studies [Barr 2008; Sisillo 2008; Adabag 2008; Burns 2005; Haase 2007; Ristikankare 2006; Wijeysundera 2007] included cohorts who had combined valvular and coronary artery bypass surgery. Nine studies [Barr 2008; Sisillo 2008; Song 2015; Prasad 2010; Santana-Santos 2014; Adabag 2008; Burns 2005; Haase 2007; Wijeysundera 2007] included cohorts who are considered to be at a higher risk of acute renal failure due to patient-related factors such as age >70 years, preexisting renal dysfunction, diabetes mellitus, left ventricular dysfunction, redo surgery, or New York Heart Association Class III & IV. Two studies included patients who had NAC administered only orally [Barr 2008; Burns 2005]; nine studies had NAC administered intravenously [Sisillo 2008; Prasad 2010; Santana-Santos 2014; Orhan 2006; Fischer 2005; Burns 2005; Haase 2007; Ristikankare 2006; Wijeysundera 2007]; and two studies had NAC administered intravenously and orally [Song 2015; El-Hamamsy 2007]. Considerable variation in the timing, dose, and duration was noticed among the included studies. The number of patients included in each study varies between studies. Orhan et al [Orhan 2006] included only a total of 20 patients for both cohorts, while the highest volume was noticed in the Burns et al group [Burns 2005], who included a total of 295 patients in both cohorts.

Acute Renal Dysfunction (ARD) (Figure 2, A and B)

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 five days after surgery [Sisillo 2008; Prasad 2010; Adabag 2008; Burns 2005; Haase 2007; Ristikankare 2006; Wijeysundera 2007].

Other authors even defined this outcome as an increase of 0.3 mg/dL from baseline, or to 50% from baseline, or an oliguria less than 0.5 mL/kg/h for more than 6 hours, within two days after surgery [Song 2015], while others [Santana-Santos 2014] defined this outcome according to the Acute Kidney Injury Network Classification [Mehta 2007].



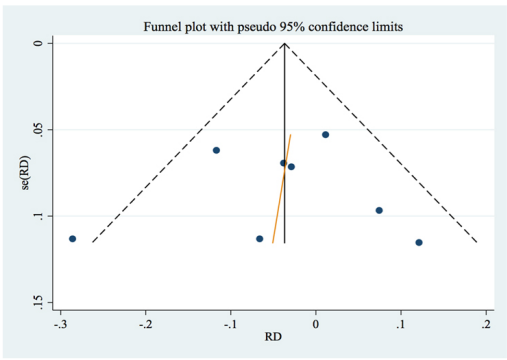


Figure 2. A, The pooled results demonstrate that patients treated with NAC had comparable risk of acute renal failure as control cohort. B, The symmetrical funnel plot demonstrated lack of publication bias.

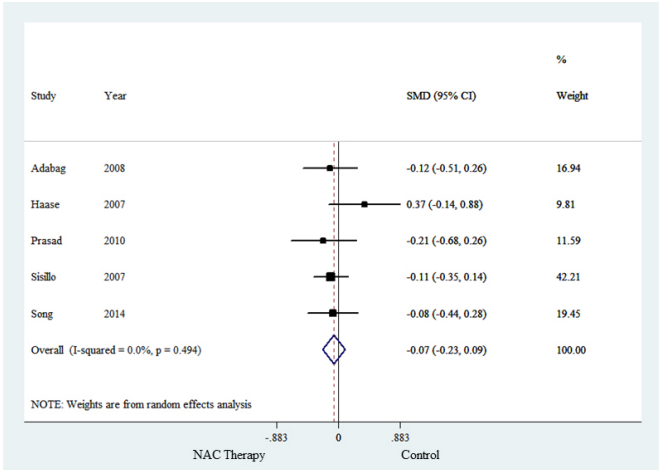
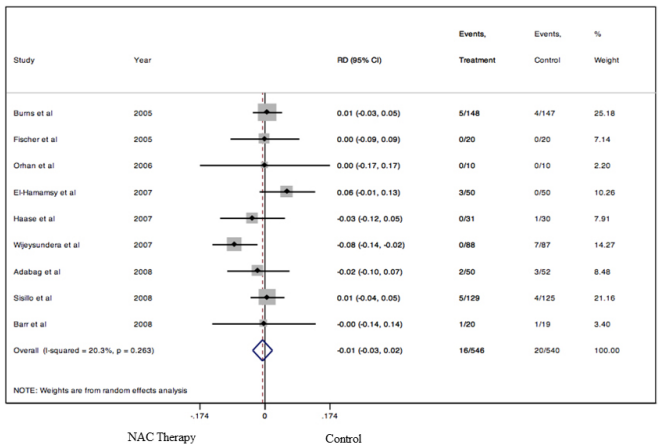


Figure 3. The pooled results demonstrate that both cohorts are comparable in developing maximum change in creatinine levels.



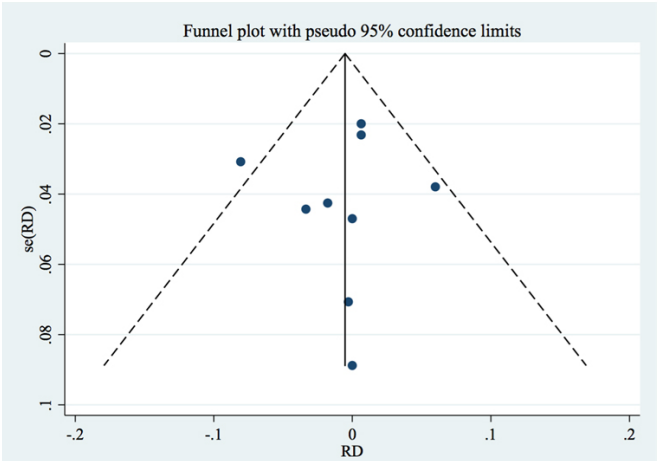


Figure 4. A, Pooled results for early mortality demonstrate that this outcome is comparable between the two cohorts. B, The symmetrical funnel plot demonstrated lack of publication bias.

The incidence of ARD was reported in nine studies [Sisillo 2008; Song 2015; Prasad 2010; Santana-Santos 2014; Adabag 2008; Burns 2005; Haase 2007; Ristikankare 2006; Wijeysundera 2007]. One study reported the absolute difference in creatinine clearance using change scores [Barr 2008]; Fischer and colleagues reported the change in creatinine clearance and serum creatinine levels [Fischer 2005]; El-Hamamsy and colleagues reported the changes in renal function [El-Hamamsy 2007]; while Orhan and colleagues reported no clinical outcomes in their study [Orhan 2006]. The pooled incidence of ARD was 23% and 36% in the NAC and control cohorts, respectively. One study [Fischer 2005] reported the maximum change in serum creatinine level from the baseline; hence this was not included in our pooled result. The combined analysis demonstrated that the incidence of ARD was similar in both cohorts [RD -0.03 (-0.09 to 0.02); P = .22; I2 = 24%). The symmetrical funnel plot demonstrated lack of publication bias (P = .91).

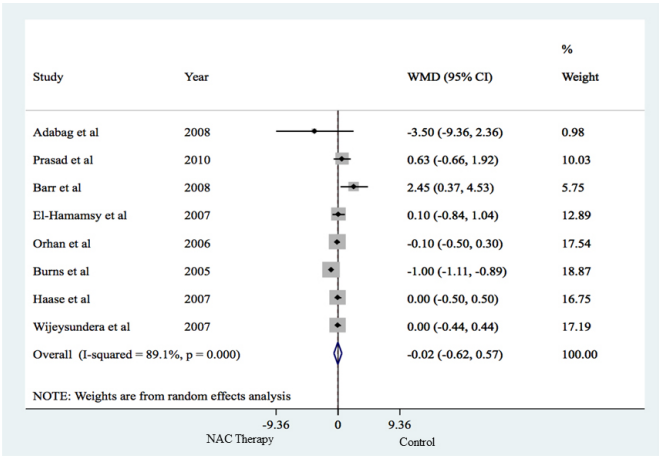


Figure 5. The pooled results demonstrate that the total in-hospital stay period was comparable between the two cohorts.

Maximal Change in Creatinine (Figure 3)

Maximal change in serum creatinine levels before and after surgery was reported in six studies [Fischer 2005; Adabag 2008; Haase 2007; Sisillo 2008; Song 2015; Prasad 2010]. The standardized mean difference in creatinine increase was not different between the two cohorts [SMD 0.07 (-0.23, 0.09); $P = .39$]. This result did not demonstrate any heterogeneity ($I^2 = 0\%$).

Early Mortality (Figure 4, A and B)

This outcome was reported in 11 studies [Barr 2008; Sisillo 2008; Santana-Santos 2014; Orhan 2006; El-Hamamsy 2007; Fischer 2005; Adabag 2008; Burns 2005; Haase 2007; Ristikankare 2006; Wijeysundera 2007]. The incidence of early mortality was 2.9% and 3.7% in the NAC and control cohorts respectively; our pooled analysis did not show a favorable effect of NAC therapy in decreasing early mortality among the treated groups compared to the control groups [RD 0 (-0.03 to 0.02); $P = .63$; $I^2 = 20\%$]. The funnel plot demonstrates lack of publication bias for the results ($P = .60$).

Total In-Hospital Stay Period (Figure 5)

This outcome was reported in nine studies [Barr 2008; Song 2015; Prasad 2010; Orhan 2006; El-Hamamsy 2007; Adabag 2008; Burns 2005; Haase 2007; Wijeysundera 2007]. The mean length of stay was 10.4 and 10.1 days in the NAC and control cohorts respectively. Our pooled analysis showed that this outcome is comparable between the two groups [WMD 0.17 (-0.02 to 0.37) days; $P = .81$].

DISCUSSION

We conducted this meta-analysis to study the potential role of perioperative NAC therapy in preventing acute renal failure after cardiac surgery. While an earlier meta-analysis [Adabag 2009] failed to demonstrate any benefit with NAC therapy, a recent randomized study [Santana-Santos 2014] reported that NAC did reduce the risk of renal dysfunction after cardiac surgery. Our present updated meta-analysis of thirteen randomized trials fails to demonstrate any clinical benefit for NAC therapy in patients undergoing open-heart surgery.

NAC is a thiol compound that has antioxidant, vasodilatory, and free-oxygen reduction properties [Santana-Santos 2014]. It was initially implemented in patients undergoing intravenous contrast administration, since it reduced the incidence of contrast-induced nephropathy [Mehta 2007]. The antioxidant and vasodilatory properties of the agent were considered to be important factors in preventing renal failure in these patients.

The proposed mechanisms for acute renal dysfunction after cardiac surgery are many and include: ischemia-reperfusion injury, oxidative stress, systemic inflammation, and hypotension [Adabag 2009]. Its reno-protective effect was demonstrated in rats that underwent cardiopulmonary bypass [Zhu 2007]. The proposed benefit of NAC in cardiac surgery was thought to be due to its ability to reduce the oxygen free radicals [van Tulder 2003; Zhu 2007]. The absence of beneficial effects of NAC in preventing acute kidney dysfunction despite its powerful anti-inflammatory and antioxidant roles reflects that other mechanisms may play a major role in the pathogenesis of acute kidney dysfunction after cardiac surgery, which could not be counteracted by NAC therapy.

While cardiopulmonary bypass does play an important role in the pathogenesis of acute renal dysfunction, other aspects are also equally important. This is demonstrated by the fact that NAC failed to improve this outcome even in patients who underwent off-pump coronary artery bypass surgery.

There was wide variation in the dose, timing, duration, and route of administration among the included studies. NAC was administered via the intravenous route in moderate to high dose in the peri- and early postoperative period. In one study [Adabag 2008] the period of therapy was extended until one week after surgery to ameliorate the process of ongoing kidney dysfunction in the postoperative period; despite this prolonged course therapy, it did not protect against kidney dysfunction.

Our results are comparable to other studies that investigated the role of NAC in patients undergoing major non-cardiac procedures [Ho 2009].

Strengths And Limitations

We accept that our meta-analysis presents some limitations. All the included studies have significant heterogeneity in the dose and route of administration of the NAC. While various open-heart surgical procedures were included, coronary artery bypass grafting was the most common. Variation in operative technique, conduct of cardiopulmonary bypass, and postoperative patient care will naturally vary between institutions. However, we have included only randomized controlled trials. Our results do not have significant heterogeneity or publication bias. Our meta-analysis is also the largest to date on this subject.

Conclusion

Our pooled analysis of thirteen randomized controlled trials demonstrates that N-acetyl cysteine therapy does not prevent acute renal failure after open-heart surgery.

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