# Oral N-acetylcysteine for prophylaxis of contrast-induced nephropathy in patients following coronary angioplasty: A meta-analysis

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**Abstract.** It is acknowledged that contrast-induced nephropathy (CIN) is a common cause of acute renal insufficiency after cardiac catheterization and affects mortality and morbidity. To date, it is unknown whether oral N-acetylcysteine (NAC) is able to prevent contrast-induced nephropathy (CIN) in patients undergoing coronary angioplasty. A meta-analysis of randomized controlled trials was performed to assess the effects of NAC in the prevention of CIN in patients following coronary angioplasty. A total of 19 studies published prior to January 2015 that investigated the efficacy of oral NAC for the prevention of CIN were collected from Medline, Cochrane and Embase databases and conference proceedings from cardiology and nephrology meetings. The primary point of investigation was CIN, and the secondary points were renal failure requiring dialysis, mortality and length of hospitalization. The meta-analysis was performed using fixed- or random-effect models according to heterogeneity. Up to January 2015, 19 randomized placebo-controlled clinical trials met the inclusion criteria for the meta-analysis, including 4,514 patients. The pooled data showed that oral NAC did not reduce the CIN incidence [relative risk 0.84, 95% confidence interval (CI) 0.65-1.10; P=0.20], without heterogeneity among trials ($I^2$=29%). Thus, the present meta-analysis suggests that oral NAC therapy is not effective as an alternative treatment to prevent CIN in patients following angioplasty. Further high quality randomized clinical controlled trials are required to confirm the usage and availability of this treatment.

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*Key words:* N-acetylcysteine, contrast-induced nephropathy, cardiac catheterization, meta-analysis

## Introduction

At present the incidence of contrast-induced nephropathy (CIN) has been increasing in patients undergoing coronary angioplasty, due to the increasing use of contrast media (1). CIN is usually described as an increase in serum creatinine of 0.5 mg/dl or a 25% increase from the baseline value 48 h following the imaging procedure (2). CIN has been reported to occur in ≥14.5% of unselected patients undergoing coronary angioplasty, and is considered to be the third leading cause of hospital-acquired acute renal failure (3). It is more commonly associated with adverse clinical outcomes, increased medical care costs, prolonged hospitalization, and increased in-hospitality morbidity and mortality (4). The major risk factors of CIN are reduced circulation volume, the type and volume of contrast agent, simultaneous administration of nephrotoxic agents and pre-existing renal dysfunction, particularly that due to diabetic nephropathy (5-8). Since the poor prognosis of patients with diabetic nephropathy could largely attribute to CIN, these patients may benefit greatly from preventive interventions. The precise mechanisms underlying the pathogenesis of CIN have not been well established. However, it is widely speculated that the underlying mechanism of CIN may involve an injury to the renal medulla caused by a combination of reduced blood flow, direct tubular toxicity and an osmotic effect (9). The direct tubular toxicity may be associated with reactive oxygen species (ROS), which are generated following the administration of contrast agent (10). Currently, the preventive treatments for CIN involve reducing contrast exposure, intravenous volume expansion with a saline hydration, and usage of low or iso-osmolarity contrast agent; however, these may provide incomplete prevention of CIN and thus, adjunctive pharmacotherapies in clinical practice have emerged (11). Among these, N-acetylcysteine (NAC) has been of interest since it was initially reported by Tepel *et al* (12). NAC as a direct scavenger of free radicals may improve blood flow via nitric oxide-mediated pathways, and it is a precursor of glutathione synthesis, providing vasodilation and antioxidant activity against CIN (13). Therefore, oral NAC therapy may be an alternative method for CIN prevention, providing safety, low cost and few side effects (14).

It has been reported that oral NAC may more effectively provide protection against CIN compared with intravenous hydration alone (15). Results of the initial study (12) of oral

NAC for the prevention of CIN were encouraging, while the bioavailability of oral NAC may be low and exhibited mixed results; a few trials demonstrated the reduction of CIN incidence by oral NAC therapy (16-21), and most trials revealed no significant CIN prevention (22-34). The aim of the present study was to determine whether oral NAC therapy is beneficial for CIN prevention in clinical practice, using a meta-analysis.

## Materials and methods

*Search strategy and selection criteria*. A comprehensive study was performed to search all published randomized controlled trials (RCT) until January 1, 2015 which concerned oral NAC treatment to prevent CIN in patients undergoing coronary angioplasty, using searching engines such as Medline (https://www.nlm.nih.gov/bsd/pmresources.html), Embase (https://www.elsevier.com/solutions/embase-biomedical-research) and Cochrane (http://uk.cochrane.org/). The search terms were as follows: N-acetylcysteine, acetylcysteine, NAC, cardiac catheterization, coronary angioplasty, coronary angiogram, percutaneous coronary intervention, contrast-induced nephropathy, contrast-induced nephrotoxicity, contrast-medium nephrotoxicity, contrast medium-induced nephropathy and contrast-induced acute kidney injury. RCTs were limited to those with human subjects. A manual search of the results was then performed for the qualifying trials. Abstracts alone or meeting proceedings were excluded. This search strategy was performed comprehensively until no new potential citations were found on review of the reference list of retrieved papers. All of the studies published in English which met the following inclusion criteria were included: Subjects underwent coronary angioplasty, randomization of oral NAC and placebo, and data regarding CIN incidence. Exclusion criteria were as follows: <18 years of age, known allergy or hypersensitivity to NAC, dialysis patients and those with ST-segment elevation myocardial infarction undergoing primary angioplasty.

*Data extraction and quality assessment*. Two investigators (Dr Jing-Xiu Li and Dr Nan-Nan Liu) were assigned independently to assemble the information of each study as follows: First author name, surgery type (coronary angiography or percutaneous coronary intervention), study design (RCT, prospective or not), control types (placebo or not), blinding types (double-blinding or not), NAC regimen, sample size, mean age, percentage of males, the incidence of CIN and length of hospitalization in each group. Disagreements were settled through discussion and consensus.

*Risk of bias*. The majority of selected trials were conducted in randomized sequence generation and allocation concealment, and the participants were divided randomly. All of them were considered to be of low bias risk.

*Statistical analysis*. The relative risk (RR) was estimated with 95% confidence interval (CI) for dichotomous outcomes. Heterogeneity was reported with the $I^2$ statistic, using a fixed-effects model, and >50% of $I^2$ was considered to be statistically significant. Begg and Egger tests were performed for presenting the publication bias, and the potential bias was analyzed with visual inspection of the Begg funnel plots in which the log RRS plotted against their standard errors. $P<0.05$ was considered to indicate a statistically significant difference. All statistical analyses were performed using STATA software, version 12.0 (StataCorp LP, College Station, TX, USA) and RevMan 5.2 (The Nordic Cochrane Centre, Copenhagen, Denmark).

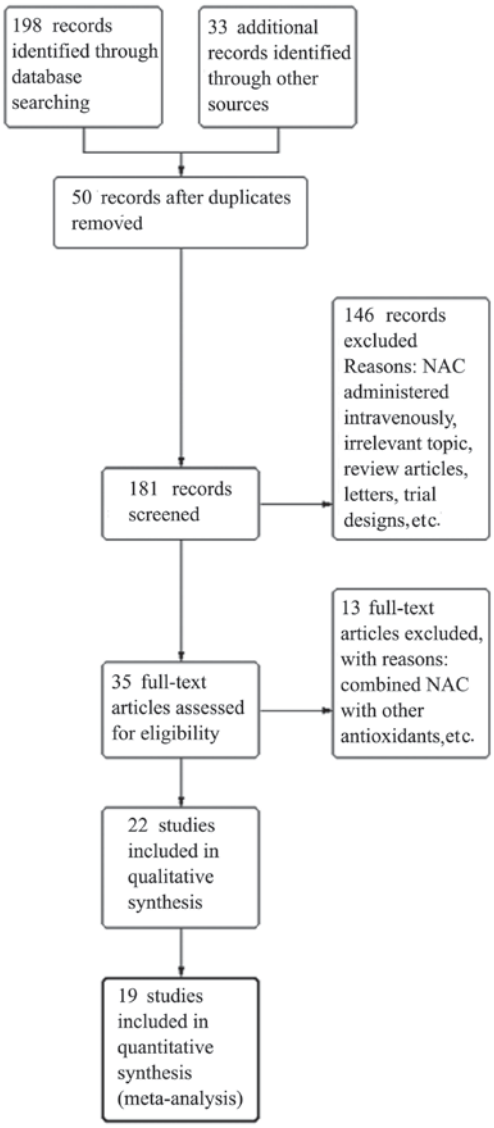


Figure 1. Process of study selection of place-controlled, randomized trials. NAC, N-acetylcysteine.

## Results

*Description of the studies*. A total of 19 placebo-control RCTs were included in this study, consisting of 4,514 patients. The flow of identified studies through the selection process is shown in Fig. 1. The characteristics at baseline and design of the selected studies are shown in Tables I and II. The range of participant number was 36-2,308, including men and women. The range of total NAC dosage was 1,200-12,000 mg. The effects of oral NAC on CIN prevention were also compared.

*Quality assessment of the trials and publication bias*. The selected trials in the meta-analysis were well-designed and

Table I. Characteristic data of studies included in the meta-analysis.

| Authors, year | Patients (I/C) | Renal function for inclusion (mg/dl) | CIN definition (SCr) | Contrast agent | Avg. contrast volume (ml) | Hydration regimen | Cumulative NAC dose (mg) | Diabetes mellitus (%) | Refs. |
|---|---|---|---|---|---|---|---|---|---|
| Ochoa *et al*, 2004 | 80 (36/44) | >1.8 (male) >1.6 (female) | 0.5 mg/dl or ≥25% above baseline after 48 h | Low osmolarity | 155 | 0.9% saline 1,500 ml | 1,000 (1 h before and 4 h after) | 55 | (16) |
| MacNeill *et al*, 2003 | 43 (21/22) | >1.5 | ≥25% above baseline after 72 h | Low osmolarity | 103 | 0.45% 1 ml/kg/h | 600 (bid for 4 doses) | 46.50 | (17) |
| Briguori *et al*, 2002 | 183 (92/91) | >1.2 | ≥25% above baseline after 48 h | Low osmolarity | 140 | 0.45% 1 ml/kg/h | 600 (bid pre/post) | 37.70 | (18) |
| Diaz-Sandoval *et al*, 2002 | 54 (25/29) | >1.4 | 0.5 mg/dl or ≥25% above baseline after 48 h | Low osmolarity | 189 | 0.45% 1 ml/kg/h 2-12 h before, 12 h after | 600 bid for 4 doses | 38.90 | (19) |
| Kay *et al*, 2003 | 200 (102/98) | >1.2 mg/dl | ≥25% above baseline within 48 h | Low osmolarity | 120 | 0.9% 1 ml/kg/h 12 h before, 6 h after | 600 (PO bid pre/post) | 37.50 | (20) |
| Shyu *et al*, 2002 | 121 (60/61) | >2.0 mg/dl | 0.5 mg/dl after 48 h | Low osmolarity | 119 | 0.45% 1 ml/kg/h 12 h before, 12 h after | 400 (PO bid pre/post) | 63.60 | (21) |
| ACT Investigators, 2011 | 2,308 (1,172/1,136) | >1.5 | 0.5 mg/dl 48-96 h | High osmolarity Low osmolarity Iso-osmolar | 100 | 0.9% 1 ml/kg/h 6-12 h before, 6-12 h after | 1,200 (bid pre/post) | 68.45 | (22) |
| Allaqaband *et al*, 2002 | 85 (45/40) | >1.6 | 0.5 mg/dl after 48 h | Low osmolarity | 122 | 0.45% 1 ml/kg/h 12 h before, 12 h after | 600 (bid pre/post) | 48.29 | (23) |
| Amini *et al*, 2009 | 90 (45/45) | >1.5 | 0.5 mg/dl or ≥25% above baseline after 48 h | Low osmolarity Iso-osmolar | 118 | 0.9% saline 1,000 ml | 600 (bid pre/post) | N/A | (24) |
| Baskurt *et al*, 2009 | 145 (73/72) | >1.3 | 0.5 mg/dl or ≥25% above baseline after 48 h | Low osmolarity | 113 | 0.9% 1 ml/kg/h 12 h before, 12 h after | 600 (bid pre/post) | 30.34 | (25) |
| Oldemeyer *et al*, 2003 | 96 (49/47) | >1.2 | 0.5 mg/dl or ≥25% above baseline after 48 h | Low osmolarity | 134 | 0.45% 1 ml/kg/h 12 h before, 12 h after | 1,500 (bid for 4 doses) | 44.79 | (26) |
| Durham *et al*, 2002 | 79 (41/38) | >1.7 | 0.5 mg/dl after 48 h | Low osmolarity | 84 | 0.45% 1 ml/kg/h 12 h before, 12 h after | 1,200 bid pre/post | 48.10 | (27) |

Table I. Continued.

| Authors, year | Patients (I/C) | Renal function for inclusion (mg/dl) | CIN definition (SCr) | Contrast agent | Avg. contrast volume (ml) | Hydration regimen | Cumulative NAC dose (mg) | Diabetes mellitus (%) | Refs. |
|---|---|---|---|---|---|---|---|---|---|
| Ferrario *et al*, 2009 | 200 (99/101) | >1.5 | 0.5 mg/dl or ≥25% above baseline within 72 h | Iso-osmolar | 180 | 0.9% 1 ml/kg/h 12-24 h before, 24 h after | 600 (bid pre/post) | 25 | (28) |
| Fung *et al*, 2004 | 91 (46/45) | >1.5 | 0.5 mg/dl after 48 h | Low osmolarity | 135 | 0.9% saline 100 ml/h 12 h before, 12 h after | 600 (PO, thrice pre/post) | 52.74 | (29) |
| Goldenberg *et al*, 2004 | 80 (41/39) | >1.5 | 0.5 mg/dl after 48 h | Low osmolarity | 111 | 0.45% 1 ml/kg/h 12 h before, 12 h after | 600 (PO, thrice pre/post | 43.75 | (30) |
| Gomes *et al*, 2005 | 156 (77/79) | >1.2 | 0.5 mg/dl after 48 h | Low osmolarity | 102 | 0.9% 1 ml/kg/h 12 h before, 12 h after | 600 (PO, bid pre/post | 51.90 | (31) |
| Kimmel *et al*, 2008 | 36 (19/17) | >1.2 | 0.5 mg/dl or ≥25% above baseline | Low osmolarity | 219 | 0.45% 1 ml/kg/h 12 h before, 12 h after | 600 (PO, bid pre/post) | 30.60 | (32) |
| Ozcan *et al*, 2007 | 176 (88/88) | >1.2 | 0.5 mg/dl or ≥25% above baseline after 48 h | Low osmolarity | 110 | 0.9% 1 ml/kg/h 6 h before, 6 h after | 600 (PO, bid pre/post) | 46.60 | (33) |
| Yang *et al*, 2014 | 318 (157/161) | N/A | ≥25% above baseline within 72 h | Low osmolarity | 124 | 0.9% 1.5 ml/kg/h 6 h before, 6 h after | 600 (PO, bid pre/post) | 25.50 | (34) |

1 mg/dl=88.4 $\mu$mol/l. I/C, interventions/controls; CIN, contrast-induced nephropathy; SCr, serum creatinine; NAC, N-acetylcysteine; N/A, data not available; bid, bis in die (twice a day); PO, oral.

Table II. Baseline and difference in SCr.

| Author, year | CIN (%) | | Acetylcysteine SCr (mg/dl) | | Control SCr (mg/dl) | | Refs. |
|---|---|---|---|---|---|---|---|
| | Acetylcysteine | Control | Baseline | Second SCr | Baseline | Second SCr | |
| Ochoa *et al*, 2004 | 3 | 25 | 2.02±0.56 | 2.10±0.81 | 1.93±0.53 | 2.10±0.74 | (16) |
| MacNeill *et al*, 2003 | 5 | 32 | 1.89±0.38 | 1.90±0.36 | 1.88±0.41 | 2.14±0.87 | (17) |
| Briguori *et al*, 2002 | 6.50 | 11 | 1.54±0.4 | 1.48±0.36 | 1.5±0.4 | 1.53±0.45 | (18) |
| Diaz-Sandoval *et al*, 2002 | 8 | 45 | 1.66±0.06 | 1.53±0.09 | 1.56±0.05 | 1.88±0.09 | (19) |
| Kay *et al*, 2003 | 4 | 12 | 1.35 | 1.22 | 1.36 | 1.38 | (20) |
| Shyu, *et al*, 2002 | 3.30 | 24.60 | 2.8±0.8 | 2.5±1.0 | 2.8±0.8 | 3.1±1.0 | (21) |
| ACT Investigators, 2011 | 12.70 | 12.70 | 1.2±0.5 | N/A | 1.2±0.5 | N/A | (22) |
| Allaqaband *et al*, 2002 | 17.70 | 15.30 | 2.2±0.73 | 2.22±1.00 | 2.03±0.79 | 2.03±0.48 | (23) |
| Amini *et al*, 2009 | 11.10 | 14.30 | 1.736±0.42 | 2.083±0.4 | 1.736±0.17 | 2.185±0.1 | (24) |
| Baskurt *et al*, 2009 | 10 | 6.90 | 1.39±0.24 | 1.47±0.38 | 1.3±0.20 | 1.38±0.34 | (25) |
| Oldemeyer *et al*, 2003 | 8.20 | 6.40 | 1.63±0.81 | N/A | 1.66±0.65 | N/A | (26) |
| Durham *et al*, 2002 | 26.30 | 22 | 2.3±0.5 | N/A | 2.2±0.4 | N/A | (27) |
| Ferrario *et al*, 2009 | 8.10 | 5.9 | N/A | N/A | N/A | N/A | (28) |
| Fung *et al*, 2004 | 17.40 | 13.30 | 2.27±0.54 | 2.45±0.65 | 2.37±0.61 | 2.40±0.70 | (29) |
| Goldenberg *et al*, 2004 | 10 | 8 | 2.0±0.4 | N/A | 1.9±0.3 | N/A | (30) |
| Gomes *et al*, 2005 | 10.40 | 10.10 | N/A | N/A | N/A | N/A | (31) |
| Kimmel *et al*, 2008 | 5.30 | 5.90 | 1.51±0.23 | N/A | 1.65±0.65 | N/A | (32) |
| Ozcan *et al*, 2007 | 12.50 | 13.60 | 1.4 | 1.42 | 1.4 | 1.46 | (33) |
| Yang *et al*, 2014 | 4.46 | 3.11 | N/A | N/A | N/A | N/A | (34) |

CIN, contrast-induced nephropathy; SCr, serum creatinine; N/A, data not available.

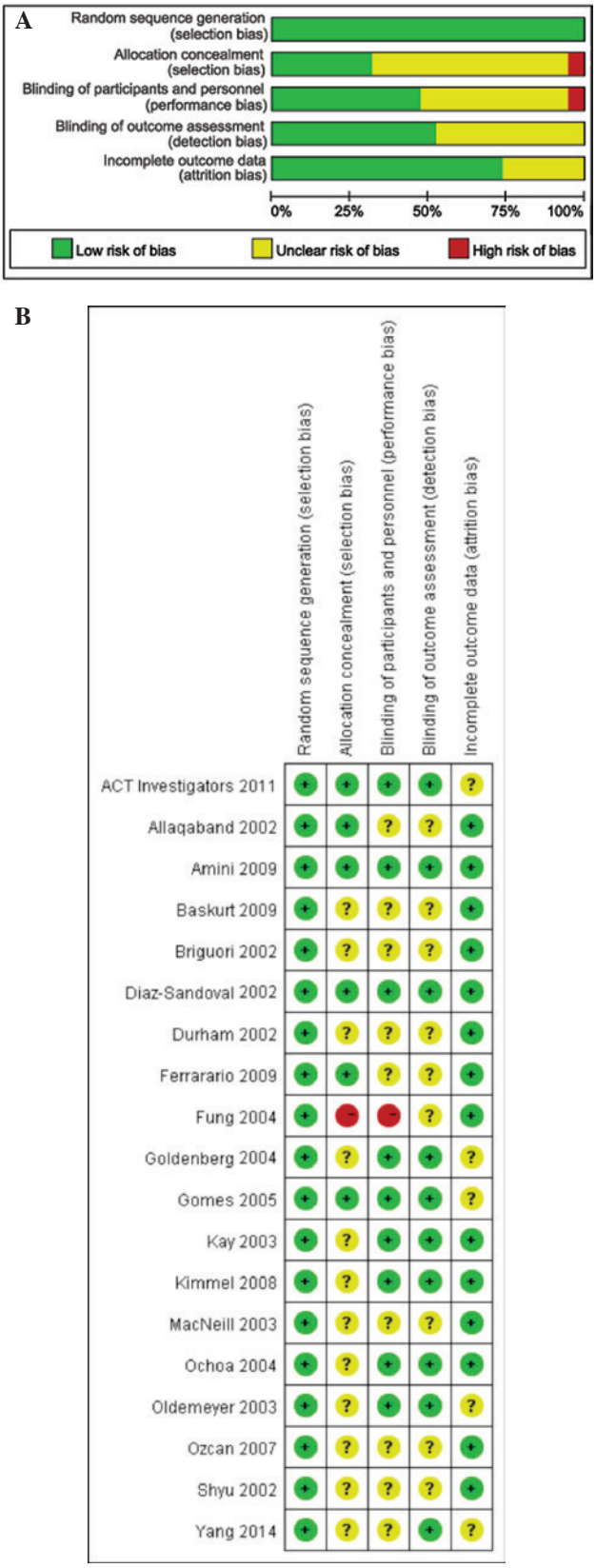


Figure 2. Risk-of-bias analysis. (A) Risk-of-bias summary: Author's judgments about each risk-of-bias item for the included studies. (B) Risk-of-bias graph: Author's judgments concerning each risk-of-bias item across all the included studies.

reasonably conducted, adequately implementing randomized sequence generation and allocation concealment. The

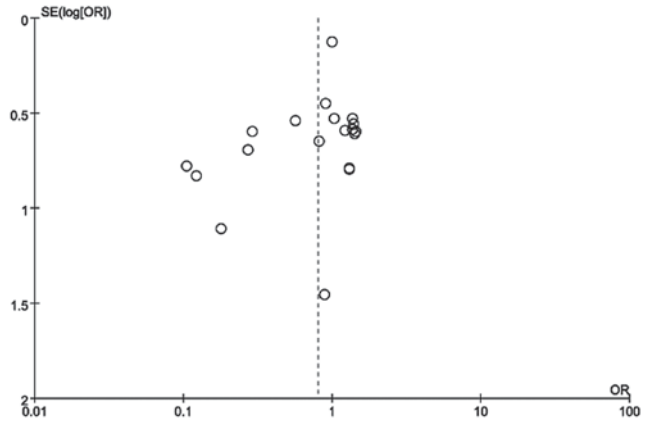


Figure 3. Publication bias for OR of the incidence of contrast-induced neuropathy. SE, standard error; OR, odds ratio.

participants among them were blinded. All of the selected studies had a low risk of bias, and the details are shown in Fig. 2. Publication bias assessed by Egger's test is shown in Fig. 3.

*CIN incidence*. The baseline characteristics revealed no significant difference between history of coexistent disease and routine prophylactic therapies. The CIN incidence was 247 patients in the oral NAC group (n=2,269) and 278 patients in the control group (n=2,245), pooling all of the 19 trials. There was no statistical significance (RR, 0.84; 95% CI, 0.65-1.10; P=0.20, Fig. 4), with no heterogeneity between trials ($I^2$=29%, P=0.12).

## Discussion

In this meta-analysis, 19 RCTs were combined in order to evaluate the effects of oral NAC on CIN prevention in patients undergoing coronary angioplasty. The results showed that oral NAC treatment was not associated with a reduction of CIN incidence, and there was no significant heterogeneity between trials. In addition, it was found that the combined treatments of oral NAC and sodium chloride did not provide additional benefits; therefore, the role of oral NAC therapy is yet to be defined in CIN prevention (11,35,36).

It has been reported that contrast-induced nephropathy occurred in ~14.5% of unselected patients following coronary angioplasty. CIN has been considered as the third common cause of in-hospital acute renal failure after coronary angiography/intervention (37). In present studies, the commonly accepted standard for CIN is according to the absolute or relative change in plasma creatinine concentration (38). In the majority of cases, CIN is defined as an increase in baseline serum creatinine (SCr) concentration of 25% or an absolute increase of at least 44 mmol/l within 48 h (39). It is universally acknowledged that absolute increase in SCr is superior threshold than a relative increase in SCr (40-43). However, it has been shown that SCr may not be an optimal substitute marker for glomerular filtration rate (GFR), as the alteration in renal handling, filtration, secretion and resorption may exert an influence on SCr levels (44). As has been noted previously (45), tubular creatinine secretion may be decreased by contrast media itself. Thus, it may cause a transient increase in SCr

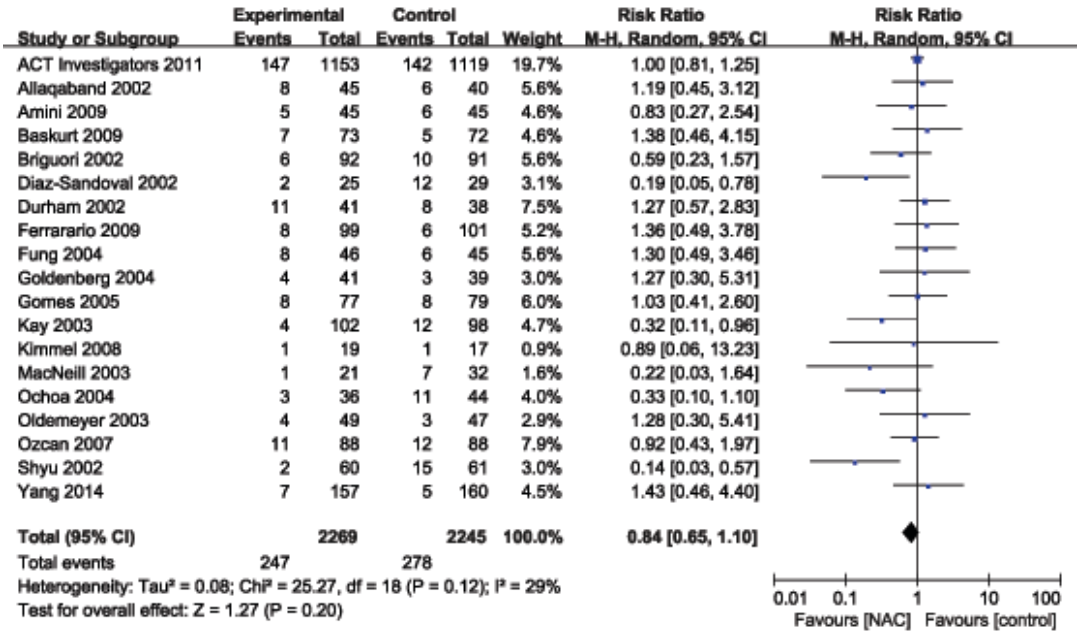


Figure 4. All included studies, relative risk (fixed effect model). CI, confidence interval; M-H, Mantel Haenszel; NAC, N-acetylcysteine.

concentration, independent of the reduction in GFR. Serum cystatin C has been proposed as a sensitive biomarker for the diagnosis of CIN, as cystatin C has been confirmed to reflect contrast medium-induced deterioration in kidney function in a superior manner to serum creatinine (46). A previous study showed that oral NAC did not significantly reduce the incidence of CIN on the basis of the standard disease definition; however, by the cystatin C level disease criteria it may be considered to be efficacious (47). However, at present SCr remains the cheapest and most widely accepted standard of renal function (48). Therefore, the change of absolute or relative SCr concentration remains a key parameter in the diagnosis of CIN. Intravenous saline hydration and the use of low-osmolality contrast medium has been accepted as preventive strategies for CIN (49-51).

In the present meta-analysis, 19 placebo-control RCTs were included, consisting of 4,514 patients. The baseline characteristic revealed no significant difference between history of coexistent disease and routine prophylactic therapies. Each randomize controlled trial utilized intravenous saline hydration. The CIN incidence was 247 patients in the oral NAC group (n=2,269) and 278 patients in the control group (n=2,245), pooling all of the 19 trials. There was no statistically significant difference between the oral NAC group and the control group (RR, 0.84; 95% CI, 0.65-1.10; P=0.20), with no heterogeneity between trials ($I^2$=29%, P=0.12). The results showed that the oral NAC treatment was not associated with a reduction in CIN incidence. A previous study (52) found that intravenous saline hydration with 0.45% saline prior to and following coronary angiography and the proper use of nonionic low osmolar iodine may be renoprotective. Previously, it has been confirmed (51) that normal saline hydration (0.9%) may be more efficacious compared with half-normal saline (0.45%). It is generally accepted that the optimal volume of normal saline hydration may be determined based on body weight, and 1.0-1.5 ml/kg/h is considered to be the normal range (39). In the present meta-analysis, it was found that the combined treatments of oral NAC and sodium chloride did not provide additional benefits, and thus the role of oral NAC therapy not yet to be defined in CIN prevention.

The precise mechanism underlying the pathogenesis of CIN remains unclear. It is widely considered (53-55) that the pathogenesis of CIN may involve injury to the renal medulla caused by reduced renal blood flow and tubular toxicity through ROS, which occurs following the administration of contrast media (1,56). NAC, a thiol-containing antioxidant, has been approved for an increase in the level of plasma glutathione, which is an oxygen-free radical scavenger (13). It has been affirmed (57) that NAC is able to prevent oxidative stress at the location of renal post-ischemia. NAC has received considerable attention in recent years following research by Tepel *et al* (12). In the opinion of Tepel *et al*, the utilization of NAC in conjunction with a fixed volume (75 ml) of low-osmolar contrast medium in patients undergoing computed tomography (CT), may significantly reduce incidence of CIN. It has become increasing recognized that NAC may result in increased nitric oxide production and intensification of nitric oxide binding (58). It has been demonstrated in human testing (59) that NAC treatment may significantly improve endothelium-dependent vasodilation. In a previous study, it was found that pretreatment of vascular smooth muscle cells with NAC clearly reduced ROS formation and prevented the reduction of cell viability (60). In the present meta-analysis, the majority of the selected trials utilized a low dose of NAC (600 mg) twice daily for 48 h in conjunction with intravenous saline hydration. It is known the oral NAC may be absorbed quickly, reaching the peak plasma concentration in 45 min, and having a half-life of 2 h. Thus, pretreatment with NAC more than a few hours prior to contrast exposure or for a prolonged period afterward may not be essential to provide beneficial effects.

There were a number of limitations inherent to this study. First, the asymmetrical appearance of the funnel plot

suggests that publication bias was present. Despite the broad searching databases and manually searching the conference proceedings and reference lists from the identified trials, we could not eliminate that publication bias caused overestimation of the results from the true treatment. Second, all included studies used the endpoint of CIN as the primary outcome. Typically, this has been defined as an increase in baseline serum creatinine level of 25% or an absolute increase of 44 mmol/l. It found that NAC had no effect on preventing CIN on the basis of the standard diagnostic definition, while it showed a preventive effect based on cystatin C levels. Whether a newer urinary biomarker such as cystatin C may identify kidney damage for CIN requires further research. Finally, despite earlier studies having shown the association of CIN with increased in-hospital morbidity and mortality, particularly in patients that require dialysis, insufficient trials have been designed to investigate the effect of NAC on these clinical relevant outcomes. Thus, the present study did not identify sufficient evidence for a meta-analysis to assess the effect of NAC on these relatively rare, but key outcomes.

This meta-analysis of 19 placebo-controlled RCTs indicated that oral NAC did not significantly reduce the incidence of CIN. Also, it revealed that the combination of oral NAC and sodium chloride may not provide additional benefits compared with hydration with sodium chloride alone. Up to now, trials are too inconsistent to warrant a conclusion on efficacy. Recently, it has been found that oral NAC is able to confer a preventive effect of CIN based on cystatin C. Therefore, further high quality RCTs are required to confirm the safety and investigate the effect of oral NAC on clinically relevant outcomes, such as in-hospital morbidity, mortality and cost of medical care, particularly in patients that require dialysis.

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