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Sodium Bicarbonate Plus N-Acetylcysteine Prophylaxis: A Meta-analysis

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Abstract

Objectives: We sought to conduct a meta-analysis to compare N-acetylcysteine in combination with sodium bicarbonate for the prevention of contrast-induced acute kidney injury (AKI).

Background: Contrast-induced AKI is a serious consequence of cardiac catheterizations and percutaneous coronary interventions (PCI). Despite recent supporting evidence for combination therapy, not enough has been done to prevent the occurrence of contrast-induced AKI prophylactically.

Methods: Published randomized controlled trial data were collected from OVID/PubMed, Web of Science, and conference abstracts. The outcome of interest was contrast-induced AKI, defined as a ≥25% or ≥0.5 mg/dL increase in serum creatinine from baseline. Secondary outcome was renal failure requiring dialysis.

Results: Ten randomized controlled trials met our criteria. Combination treatment of N-acetylcysteine with intravenous sodium bicarbonate reduced contrast-induced AKI by 35% (RR: 65; 95%CI: 0.40, 1.05). However, the combination of N-acetylcysteine plus sodium bicarbonate did not significantly reduce renal failure requiring dialysis (RR: 0.47; 95%CI: 0.16, 1.41).

Conclusions: Combination prophylaxis with N-acetylcysteine and sodium bicarbonate significantly reduced the occurrence of contrast-induced AKI overall, but not dialysis-dependent renal failure. Combination prophylaxis should be incorporated for all high-risk patients (emergent

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Disclosures

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cases or patients with chronic kidney disease) and should be strongly considered for all interventional radio-contrast procedures.

Keywords

acute kidney injury; renal pharmacology; contrast; epidemiology; meta-analysis

Introduction

Contrast-induced acute kidney injury (AKI) is a serious consequence of the more than 1.3 million cardiac catheterizations and percutaneous coronary interventions (PCI) in the United States each year. Researchers hypothesize contrast-induced AKI results from direct toxicity to the renal tubules by contrast medium or renal hemodynamic changes.(1,2) Up to fifteen percent of patients develop contrast-induced AKI following PCI with a 5-fold increased risk of in-hospital(3) and long-term mortality.(4)

Contrast-induced AKI is commonly defined as a 25% increase or 0.5 mg/dL increase in serum creatinine from baseline within 48 hours of exposure.(4–7) Rihal and Chertow, showed that contrast-induced AKI was associated with an increased risk of in-hospital mortality.(8,9) Patients with contrast-induced AKI had a 22% mortality rate compared to 1.4% for those without AKI.(9) Patients admitted to the hospital for all causes and developing contrast-induced AKI were 6.5-times more likely to die in the hospital compared to patients not developing AKI; on average these patients had 3.5 more days in the hospital and $7,500 additional hospital costs.(8)

Variation exists in prophylactic strategies and there is a lack of consensus on prevention tactics according to a recent taskforce.(10) Despite the ease of identifying patients at risk,(11,12) preventive measures to reduce contrast-induced AKI have not been consistent.(13) However, two recent randomized controlled trials (RCT) among high-risk patients using N-acetylcysteine and sodium bicarbonate(14,15) demonstrated the combination of N-acetylcysteine and sodium bicarbonate were significantly effective at preventing the contrast-induced AKI. Both N-acetylcysteine and sodium bicarbonate are oxygen-derived free radical scavengers and therefore block injury to the renal tubules.(16–21) There has been no formal synthesis of the combination prophylactic trial data. Consequently, there are no consensus protocols for prophylactic strategies or contrast dosing to prevent contrast-induced AKI. These gaps have identified opportunities to adopt effective evidence-based measures to reduce contrast-induced AKI.

Therefore, we sought to synthesize randomized controlled trial evidence for prophylactic combination strategies incorporating oral or intravenous N-acetylcysteine and intravenous sodium bicarbonate in cardiac catheterization or PCI.

Materials and Methods

Data and Sources of Searches

We conducted a meta-analysis of randomized controlled trials using combination prophylaxis of N-acetylcysteine and sodium bicarbonate among patients undergoing

catheterization or percutaneous coronary intervention. MEDLINE (OVID and Pubmed, 1960 through February 2009), Web of Knowledge, Cochrane Library databases and conference abstracts (American Heart Association, American College of Cardiology, Transcatheter Cardiovascular Therapeutics, National Kidney Foundation, American Society of Nephrology Renal Week) were used to identify published randomized controlled trials from 2006 through February 2009.

Study Selection

Key words used to search included: (N-acetylcysteine) and (sodium bicarbonate) and (catheterization or angiography or percutaneous coronary intervention or PCI). The search yielded ten published human randomized controlled trials (Figure 1, Table 1).(14,15,22–29) We searched ClinicalTrial.gov; we found one additional trial: CONTRAST (Singapore). However, the trial is still enrolling patients and has not reported the interim results.

Data Abstraction and Quality Assessment

We abstracted data from the trials on contrast-induced AKI (defined as ≥25%, ≥0.5 mg/dL, ≥25% and ≥0.5 mg/dL increase in creatinine from baseline) and renal failure (new onset of dialysis). We followed the appropriate methods for conducting a meta-analysis as stipulated in the QUORUM statement.(30) Two independent reviewers (JB, CB) selected trials for information outcomes and recorded data on spreadsheets. The Jadad criteria were used to assess study quality and reported with study the characteristics (Table 1).(31)

Data Synthesis and Analysis

All outcome comparisons and treatment effects were calculated using the Cochrane Collaborative software, RevMan 4.2.8. We calculated the I^2 to evaluate the percentage of heterogeneity among all the trials incorporated in the summary estimate.(32) Heterogeneity was observed in the three comparisons; therefore, we used random effects modeling. For all comparisons, a fixed effects relative risk (RR) and 95%CI was calculated for each independent study and for the summary statistic. Methods for the calculation of the above statistics have been reported previously.(33,34)

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Ten trials met our eligibility criteria for combination therapy including sodium bicarbonate plus N-acetylcysteine before and after contrast administration (Table 1). All studies reported contrast-induced AKI as ≥25% increase in serum creatinine; four reported contrast-induced AKI separately by ≥0.5 (mg/dL) increase in serum creatinine. Nine studies compared combination treatment (sodium bicarbonate and N-acetylcysteine) with N-acetylcysteine and hydration with normal saline; one study compared combination therapy with N-acetylcysteine alone; one study compared combination therapy with N-acetylcysteine with normal saline and a separate arm with N-acetylcysteine and ascorbic acid (we have included this arm in the analysis).

Contrast-induced AKI was defined in three ways. The first analysis with contrast-induced AKI defined as a ≥25%ΔCr (Figure 2A) demonstrated the combination of N-acetylcysteine plus sodium bicarbonate did not significantly reduce contrast-induced AKI (≥25%ΔCr) by 33% with the combined RR of 0.67 (95%CI: 0.42, 1.07), however, this effect demonstrated a strong trend towards protection against contrast-induce AKI. Alternatively, when using an alternative definition for contrast-induced AKI (≥0.5Cr: Figure 2B), a statistically significant benefit was observed for combination treatment with a significant 69% reduction (RR: 0.31; 95%CI: 0.11, 0.87). When using the greater of the two definitions (≥25%ΔCr and ≥0.5: Figure 2C), the results were similar to the ≥25%ΔCr definition with a non-significant 35% reduction in contrast-induced AKI (RR: 65; 95%CI: 0.40, 1.05).

Dialysis (Figure 3): When the combination of N-acetylcysteine and sodium bicarbonate was compared to controls or head-to-head with N-acetylcysteine, the combination treatment did not significantly reduce dialysis dependent renal failure (RR: 0.47; 95%CI: 0.16, 1.41).

Discussion

We conducted a meta-analysis on the clinical effectiveness of N-acetylcysteine in combination with intravenous sodium bicarbonate compared to N-acetylcysteine. We found ten randomized controlled trials that met our criteria. Collectively, combination treatment of N-acetylcysteine with intravenous sodium bicarbonate reduced contrast-induced AKI by 35% (RR: 65; 95%CI: 0.40, 1.05). Therefore, combination treatment with N-acetylcysteine plus sodium bicarbonate prevented contrast-induced AKI in 4 out of 10 patients over N-acetylcysteine alone. However, the combination of N-acetylcysteine plus sodium bicarbonate did not significantly reduce renal failure requiring dialysis (RR: 0.47; 95%CI: 0.16, 1.41), although only five patients (0.7%) receiving the combination therapy went on dialysis compared with eleven (1.6%) receiving N-acetylcysteine.

Multiple strategies have been used independently to reduce contrast-induced AKI: hydration alone, sodium bicarbonate alone, N-acetylcysteine alone, and others. However, there has been a lack of consensus about the implementation of these strategies in practice, likely due to much confusion about their clinical efficacy.

Hydration:

In a small prospective randomized control trial (RCT), hydration with 0.45% normal saline for 12 hours before and after angiography has been shown to be effective in reducing contrast-induced AKI by 65%.(35) In a large prospective RCT, hydration with half isotonic (0.45%) or isotonic (0.9%) saline for the morning before elective PCI and immediately prior to emergency PCI reduced contrast-induced AKI by 0.7% and 2.0%, respectively.(36)

Sodium Bicarbonate ($NaHCO_3$):

Isotonic sodium bicarbonate through the alkalinization of renal tubular fluid and subsequent reduction in free oxygen radicals has shown beneficial results (although mixed) in reducing contrast-induced AKI. Merten reported patients receiving isotonic (154 mEq/L) infusion of sodium bicarbonate before and after contrast administration (370 mg iodine/mL) had an 89% reduction in contrast-induced AKI compared with patients that received hydration with

isotonic sodium chloride.(37) Four recent meta-analyses evaluating the protective effects of hydration with sodium bicarbonate compared with hydration with normal saline have shown sodium bicarbonate to be more effective in preventing contrast-induced AKI by 54–63%: RR: 37 (95%CI: 0.18, 0.74);(38) RR: 0.45 (95%CI: 0.26, 0.79);(39) RR: 0.46 (95%CI: 0.26, 0.82);(40) and RR: 0.52 (95%CI: 0.34, 0.80).(41)

N-acetylcysteine:

N-acetylcysteine is postulated to act as a free radical scavenger. Tepel was the first to report a protective effect of N-acetylcysteine (600 mg twice daily on the day before and day of intervention with half isotonic saline) in reducing contrast-induced AKI by 91%.(42) Seven meta-analyses of N-acetylcysteine have shown beneficial treatment effects in reducing contrast-induced AKI.(43–49) However, five meta-analyses were inconclusive. (50–54) Marenzi et al., demonstrated a dose-dependent effect of N-acetylcycsteine (600 mg IV before and 600 mg orally twice daily for 48hrs post), whereby both single and double doses of N-acetylcysteine reduced contrast-induced AKI and in-hospital mortality with the more beneficial treatment being the double dose of N-acetylcysteine in patients undergoing primary PCI.(55) Unfortunately, N-acetylcysteine might cause an artificial transient decline in serum creatinine without changing renal function and therefore additional markers of renal function should be incorporated to confirm these effects, such as Cystatin C.(45,56) Recently, Kelly et al., performed a meta-analysis of N-acetylcyteine compared to hydration alone. They found oral or intravenous N-acetylcysteine significantly reduced contrast-induced AKI by 38% when compared with hydration controls (RR: 0.62; 95%CI: 0.44–0.88).(57) Current systematic reviews and meta-analyses have identified a statistically significant benefit for either hydration with sodium bicarbonate and prophylaxis with N-acetylcysteine. Our meta-analysis focus on the question of combined hydration and prophylaxis with both sodium bicarbonate and N-acetylcysteine, demonstrating a significant benefit for combination prophylaxis over N-acetylcysteine with or without hydration alone.

Other pharmacological strategies have been used over the years. Theophylline causes arrythmias and therefore is not useful for cardiac patients. In a recent meta-analysis, Kelly et al., showed theophylline with a non-significant, but impressive, 51% reduction in contrast-induced AKI (RR: 0.49; 95%CI: 0.23–1.06); this report suggests a promising protective effect for theoplylline.(57) Prostaglandins can cause severe hypotension. Other agents include antioxidant ascorbic acid and trimetazidine; but, limited evidence has been reported on these agents for preventing contrast-induced AKI.(58) Hypoperfusion of the kidney through vasoconstriction might play a role in contrast-induced AKI; however, vasodilators have not been shown to be successful reducing contrast-induced AKI. All four RCTs for dopamine showed no benefit in reducing contrast-induced AKI.(59–62) Two trials have reported on fenoldopam, neither showing a protective effect against contrast-induced AKI. (57,63,64) A meta-analysis demonstrated renal replacement therapy does not reduce the risk of contrast-induced AKI (0.97; 95%CI: 0.44, 2.14).(65) Continuous veno-venus hemofiltration (CVVH) following PCI in one study was not shown to protect renal function. (66) However, a recent trial by Lee et al., reported that prophylactic hemodialysis resulted in a 95% reduction in post-catheterization dialysis for chronic kidney disease patient undergoing coronary angiography.(67)

There have been several hypotheses generated around the pharmacodynamics of N-acetylcysteine and sodium bicarbonate. Merten et al., postulated that alkalizing the renal tubule fluid with sodium bicarbonate might reduce acute tubule necrosis brought on by nephrotoxic contrast media.(37) In a recent study examining renal cell apoptosis by contrast agents, Romano et al., proposed sodium bicarbonate scavanges free-radicals and the presence of bicarbonate in the proximal convoluted tubules might work to either buffer the production of H+ from cellular hypoxia or to drive Na^+ reabsorption.(68) However, they reported sodium bicarbonate did not raise the pH of the media *in vitro* compared to contrast alone and postulated the protective action of sodium bicarbonate works through a different mechanism than N-acetylcysteine and ascorbic acid and therefore provides an additive effect.(68) Romano et al., were able to demonstrate that N-acetylcysteine and ascorbic acid works *in vitro* on the proximal renal tubule and prevents renal cell apoptosis, but not sodium bicarbonate.(68) This finding was supported by an earlier report by Briguori et al., showing N-acetylcysteine works in a dose-dependent manner.(69) Our meta-analysis compares the additive effect of sodium bicarbonate compared to the use of N-acetylcysteine or ascorbic acid and demonstrates a distinct advantage in reducing CI-AKI; while the mechanism of the prophylactic effect of sodium bicarbonate in the renal tubules is not confirmed, based on the summary of evidence, there does appear to be an additive effect either through more regimented hydration or through free radical scavenging in the renal tubules.

The barriers to reducing contrast-induced AKI following PCI have been due to inconsistencies in the randomized controlled trial evidence and meta-analysis reporting either N-acetylcysteine or sodium bicarbonate. Cardiology and Nephrology historically have compartmentalized patient care within each discipline. These barriers create a chasm between current practice and the best evidence-based care for patients.

Additional trials are needed to comment on the clinical effectiveness of combination protocols for the prevention of contrast-induced AKI. Recommendations differ surrounding the prevention of contrast-induced AKI and not enough has been done to establish a working protocol to prevent contrast-induced AKI among all patients. Until a large-scale RCT can be conducted to evaluate the clinical effectiveness of these prophylactic strategies, clinical action must be taken on the evidence that exists. We recommend a comprehensive prophylactic protocol needs to be incorporated into practice to prevent contrast-induced AKI incorporating both sodium bicarbonate and N-acetylcysteine. We encourage institutions to form a multi-disciplinary team of nephrologists, cardiologists, and epidemiologists to work together to develop evidence-based benchmarks for high quality care and standardize their prophylactic strategies in preventing contrast-induced AKI.

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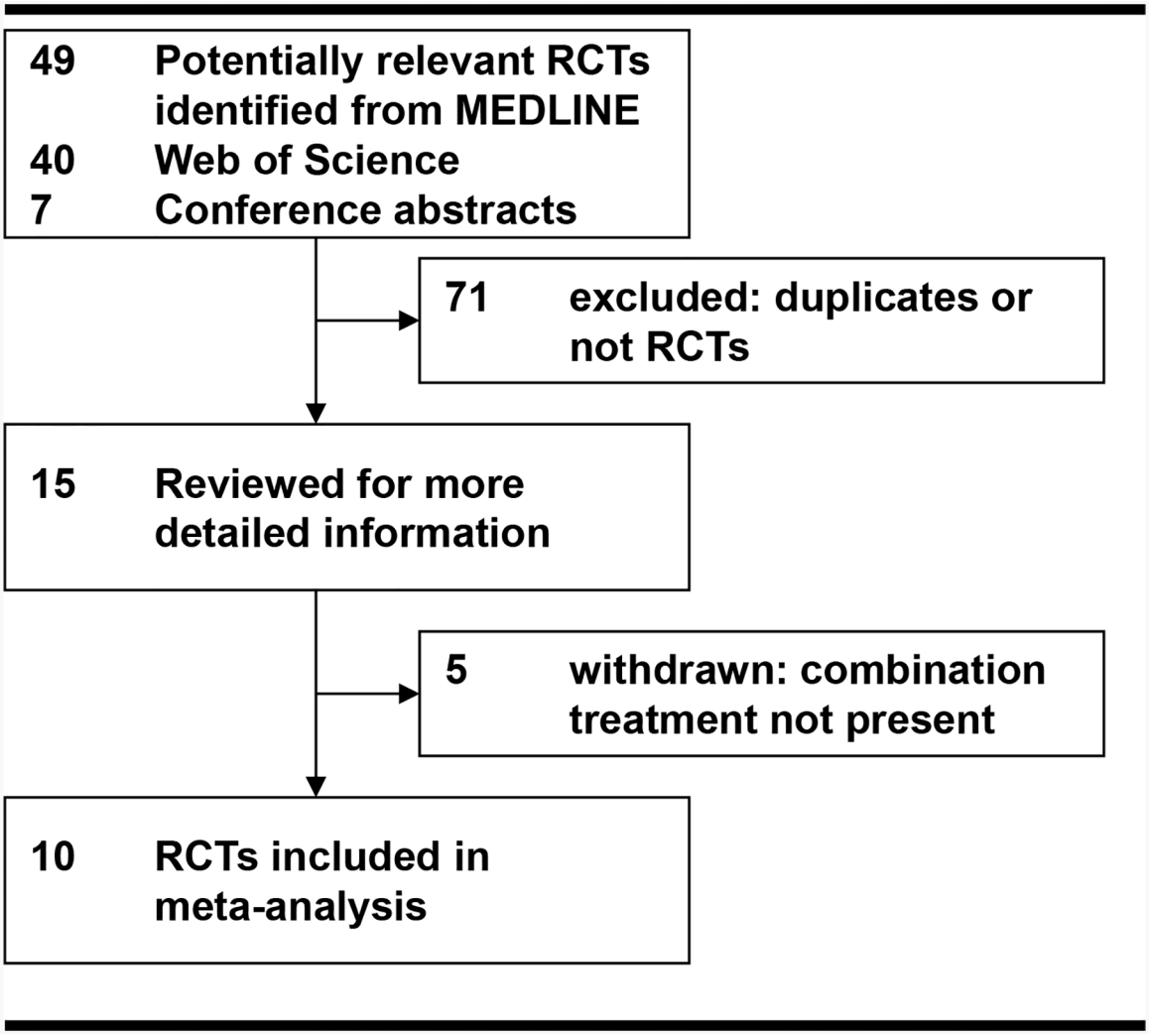

Figure 1: Study Selection.

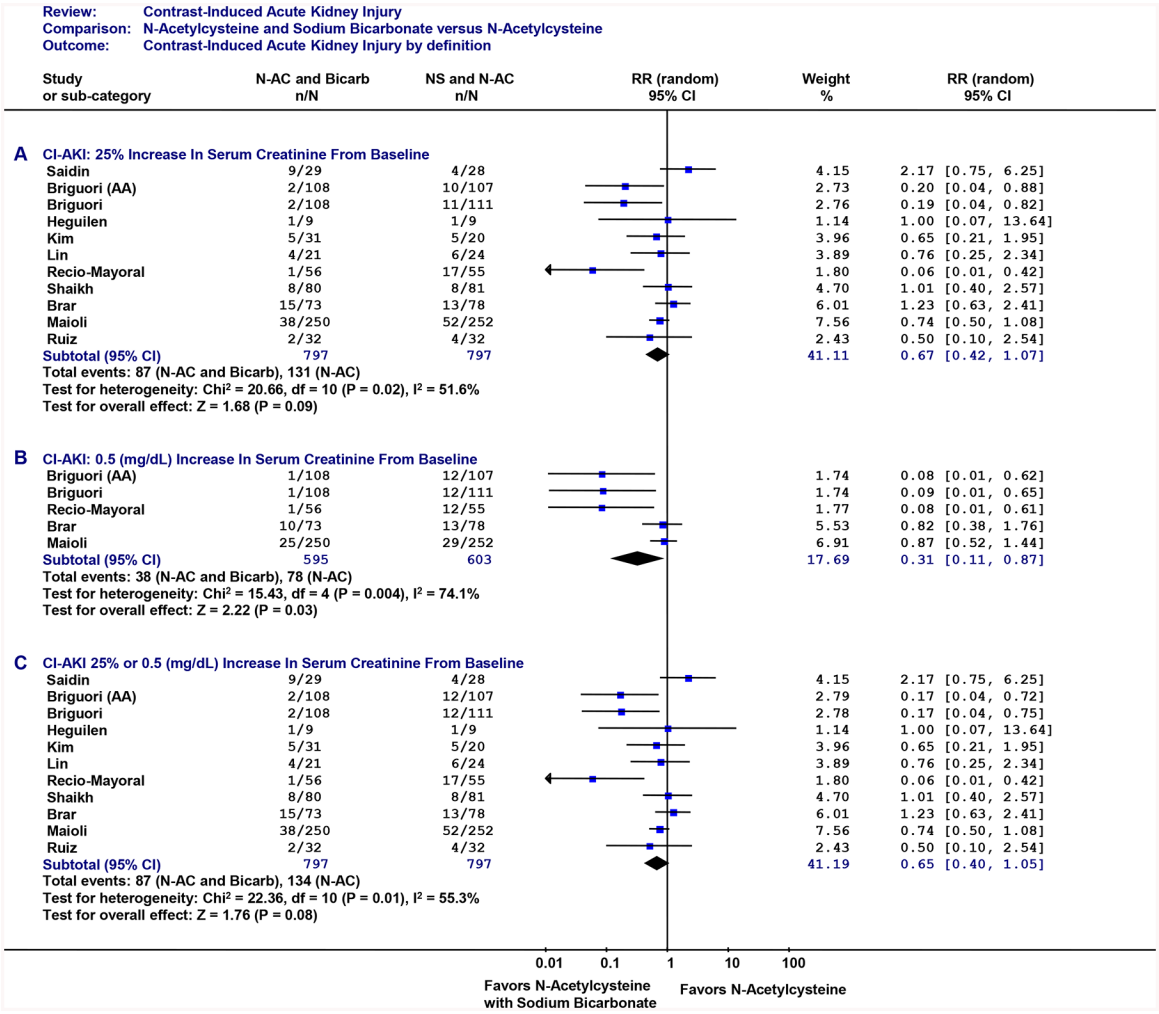

Figure 2: Contrast-Induced AKI.

Individual randomized controlled trials are listed in order by year of publication. Outcome is contrast-induced AKI. Figure 2A: contrast-induced AKI (25% relative increase in serum creatinine from baseline). Figure 2B: contrast-induced AKI (≥0.5 mg/dL increase in serum creatinine from baseline). Figure 2C: contrast-induced AKI (≥25% or ≥0.5 mg/dL increase in serum creatinine from baseline). CI: 95 percent confidence interval. The size of each square denotes the weight of each trial's relative risk in calculating the combined relative risk. The diamond represents the combined relative risk at the center; opposing points of the diamond represent the 95% confidence intervals. Treatment: N-acetylcysteine plus sodium bicarbondate. AA: N-acetylcysteine plus ascorbic acid.

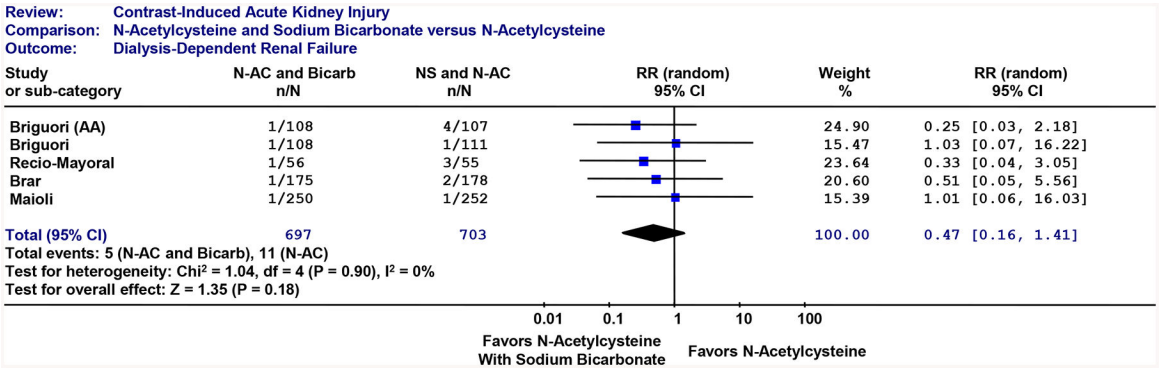

Figure 3: Renal Failure Requiring Dialysis.

Individual randomized controlled trials are listed in order by year of publication. Outcome is dialysis. CI: 95 percent confidence interval. The size of each square denotes the weight of each trial's relative risk in calculating the combined relative risk. The diamond represents the combined relative risk at the center; opposing points of the diamond represent the 95% confidence intervals. Treatment: N-acetylcysteine plus sodium bicarbondate. AA: N-acetylcysteine plus ascorbic acid.

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Table 1.

Study Characteristics*

Trial (Year)	Total Patients	Treatment Group, N	Treatment Protocol	Control Group, N	Control Protocol	Enrollment Criteria	Blinding	Jadad[23] Score
Saidin[28] (2006)	57	29	**Oral N-acetylcysteine plus sodium bicarbonate.** Oral N-acetylcysteine plus sodium bicarbonate 2 hours before and 6 hours after procedure.	28	**Oral N-acetylcysteine plus normal saline.** Oral N-acetylcysteine plus normal saline 2 hours before and 6 hours after procedure.	Coronary angiography or angioplasty, CKD stages 2–4.	Double-Blind	2
Brigouri[14] (2007)	351	10 8	**Oral N-acetylcysteine plus sodium bicarbonate.** Isotonic saline (0.9%) IV at 1 mL/kg/hr (0.5mL/kg/hr for EF<40) for 12 hours before and 12 hours after contrast exposure. Oral 1,200mg N-acetylcysteine twice a day for day before and after procedure with 154 mEq/L sodium bicarbonate in dextrose and H_2O (Merten Protocol[29]): initial IV bolus 3mL/kg/h for 1 hour immediately prior to contrast; during and for 6 hours after contrast exposure with same dose at 1mL/kg/hr.	111	**Oral N-acetylcysteine plus IV hydration.** Isotonic saline (0.9%) IV at 1 mL/kg/hr (0.5mL/kg/hr for EF<40) for 12 hours before and 12 hours after contrast exposure. Oral 1,200mg N-acetylcysteine twice a day for day before and after procedure.	Coronary and/or peripheral angiography and/or angioplasty with chronic kidney disease, Creatinine ≥2mg/dL or eGFR<40 mL min^{-1} 1.73m^{-2}, age ≥18.	Double-Blind	3
				107	**Oral N-acetylcysteine plus IV hydration plus IV ascorbic acid.** Isotonic saline (0.9%) IV at 1 mL/kg/hr (0.5mL/kg/hr for EF<40) for 12 hours before and 12 hours after contrast exposure. Oral 1,200mg N-acetylcysteine twice a day for day before and after procedure with 3g IV ascorbic acid 2 hours before contrast and 2g the night and morning after contrast.		Double-Blind	3
Heguillen[23] (2007)	27	9	**Oral N-acetylcysteine plus sodium bicarbonate.** Oral 600mg N-acetylcysteine twice a day for day before and of procedure with 154 mEq/L sodium bicarbonate at 3mL/kg/h for 1 hour immediately prior to procedure; and at 1mL/kg/h for 6 hours after procedure.	9	**Oral N-acetylcysteine plus normal saline.** Oral 600mg N- acetylcysteine twice a day for day before and of procedure with 154 mEq/L normal saline at 3mL/kg/h for 1 hour immediately prior to procedure; and at 1mL/kg/h for 6 hours after procedure.	Coronary angiography or angioplasty, serum creatinine >1.25 (mg/dL), eGFR<50 mL min-1 1.73m-2, age ≥18.	Single-Blind	2
Kim[24] (2007)	100	31	**Oral N-acetylcysteine plus sodium bicarbonate.** Oral 600mg N-acetylcysteine twice a day for two days with 80 mEq/L sodium bicarbonate at 1mL/kg/h for 12 hour prior to procedure and for 12 hours after procedure.	20	**Oral N-acetylcysteine plus normal saline.** Oral 600mg N- acetylcysteine twice a day for two days with 80 mEq/L normal saline at 1mL/kg/h for 12 hour prior to procedure	Elective coronary angiography, serum creatinine >1.5 (mg/dL), proteinurea>5 00 mg/day.	Single-Blind	1

Trial (Year)	Total Patients	Treatment Group, N	Treatment Protocol	Control Group, N	Control Protocol	Enrollment Criteria	Blinding	Jadad[23] Score
					and for 12 hours after procedure.			
Lin[25] (2007)	45	21	**Oral N-acetylcysteine plus sodium bicarbonate.** Oral 600mg N-acetylcysteine twice a day for day of and day after procedure with 154 mEq/L sodium bicarbonate at 3mL/kg/h for 1 hour prior to procedure and for 6 hours after procedure.	24	**Oral N-acetylcysteine plus normal saline.** Oral 600mg N- acetylcysteine twice a day for day of and day after procedure with 154 mEq/L normal saline at 3mL/kg/h for 1 hour prior to procedure and for 6 hours after procedure.	Coronary angiography, angioplasty, serum creatinine <2.0 (mg/dL).	Single-Blind	1
Recio- Mayoral[15] (2007)	111	56	**IV N-acetylcysteine plus sodium bicarbonate.** Initial IV bolus 5mL/kg/hr alkaline saline with 154 mEq/L sodium bicarbonate in 5% glucose and H_2O plus 2,400mg N- acetylcysteine in same solution over 1 hour. Following contrast, same fluids continued without N-acetylcysteine at 1.5 mL/kg/hr for 12 hours plus 2 oral doses of 600mg N-acetylcysteine the day after contrast.	55	**Oral N-acetylcysteine plus hydration.** Isotonic saine (0.9%) at 1mL/kg/hr for 12 hours after contrast plus 2 oral doses of 600mg N-acetylcysteine the day after contrast.	Patients with MI undergoing primary or rescue PCI or high-risk non- STEMI requiring urgent PCI.	Single-Blind	2
Shaikh[29] (2007)	320	80	**IV N-acetylcysteine plus sodium bicarbonate.** IV N-acetylcysteine with 154 mEq/L sodium bicarbonate at 3mL/kg/h for 1 hour prior to procedure and 1mL/kg/h for 6 hours after procedure.	81	**IV N-acetylcysteine plus normal saline.** IV N-acetylcysteine with 154 mEq/L normal saline at 3mL/kg/h for 1 hour prior to procedure and 1mL/kg/h for 6 hours after procedure.	High risk catheterization.	Single-Blind	1
Brar[22] (2008)	353	73	**Oral N-acetylcysteine plus sodium bicarbonate.** Oral 600mg N-acetylcysteine twice a day for day before and day of the procedure with sodium bicarbonate at 3mL/kg/h for 1 hour prior to procedure and 1.5mL/kg/h during and for 6 hours after procedure.	78	**Oral N-acetylcysteine plus normal saline.** Oral 600mg N- acetylcysteine twice a day for day before and day of the procedure with normal saline at 3mL/kg/h for 1 hour prior to procedure and 1.5mL/kg/h during and for 6 hours after procedure.	Coronary angiography eGFR<60 mL min^{-1} $1.73m^{-2}$, age ≥18, 1 + of either diabetes, congestive heart failure, hypertension, or age>75 years.	Single-Blind	3
Maioli[26] (2008)	502	25 0	**Oral N-acetylcysteine plus sodium bicarbonate.** Oral 600mg N-acetylcysteine twice a day for day before and after procedure with 154 mEq/L sodium bicarbonate in dextrose and H_2O (Merten Protocol[29]): initial IV bolus 3mL/kg/h for 1 hour immediately prior to	252	**Oral N-acetylcysteine plus normal saline.** Isotonic saline (0.9%) IV at 1 mL/kg/hr for 12 hours before and 12 hours after contrast exposure. Oral 600mg N-acetylcysteine twice a day for day before and after procedure.	Coronary angiography eGFR<60 mL min^{-1} $1.73m^{-2}$, age ≥18, 1 + of either diabetes, congestive heart failure, hypertension, or age>75 years.	Single-Blind	3

Trial (Year)	Total Patients	Treatment Group, N	Treatment Protocol	Control Group, N	Control Protocol	Enrollment Criteria	Blinding	Jadad[23] Score
			contrast; during and for 6 hours after contrast exposure with same dose at 1mL/kg/hr.					
Ruiz[27] (2008)	128	32	**Oral N-acetylcysteine plus sodium bicarbonate.** Methods not described.	32	**Oral N-acetylcysteine plus normal saline.** Methods not described.	Coronary and/or peripheral angiography, angioplasty, creatinine >1.5 (mg/dL) or diabetics creatinine >1.2 (mg/dL).	Single-Blind	1

*All studies investigating combination of N-acetylcysteine plus sodium bicarbonate were included. IV: intravenous; EF: ejection fraction (%); MI: myocardial infarction; STEMI: ST-elevation MI; PCI: percutaneous coronary intervention; eGFR: estimated glomerular filtration rate using MDRD equation.