Meta-analysis: Effectiveness of Drugs for Preventing Contrast-Induced Nephropathy

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Background: *N*-Acetylcysteine, theophylline, and other agents have shown inconsistent results in reducing contrast-induced nephropathy.

Purpose: To determine the effect of these agents on preventing nephropathy.

Data Sources: Relevant randomized, controlled trials were identified by computerized searches in MEDLINE (from 1966 through 3 November 2006), EMBASE (1980 through November 2006), PubMed, Web of Knowledge (Current Contents Connect, Web of Science, BIOSIS Previews, and ISI Proceedings for the latest 5 years), and the Cochrane Library databases (up to November 2006). Databases were searched for studies in English, Spanish, French, Italian, and German.

Study Selection: Randomized, controlled trials that administered *N*-acetylcysteine, theophylline, fenoldopam, dopamine, iloprost, statin, furosemide, or mannitol to a treatment group; used intravenous iodinated contrast; defined contrast-induced nephropathy explicitly; and reported sufficient data to construct a 2×2 table of the primary effect measure.

Data Extraction: Abstracted information included patient characteristics, type of contrast media and dose, periprocedural hydration, definition of contrast-induced nephropathy, and prophylactic agent dose and route.

Data Synthesis: In the 41 studies included, *N*-acetylcysteine (relative risk, 0.62 [95% CI, 0.44 to 0.88]) and theophylline (relative risk, 0.49 [CI, 0.23 to 1.06]) reduced the risk for contrast-induced nephropathy more than saline alone, whereas furosemide increased it (relative risk, 3.27 [CI, 1.48 to 7.26]). The remaining agents did not significantly affect risk. Significant subgroup heterogeneity was present only for *N*-acetylcysteine. No publication bias was discerned.

Limitations: All trials evaluated the surrogate end point of contrast-induced nephropathy as the primary outcome. The lack of a statistically significant renoprotective effect of theophylline may result from insufficient data or study heterogeneity. True study quality remains uncertain.

Conclusion: *N*-Acetylcysteine is more renoprotective than hydration alone. Theophylline may also reduce risk for contrast-induced nephropathy, although the detected association was not significant. Our data support the administration of *N*-acetylcysteine prophylaxis, particularly in high-risk patients, given its low cost, availability, and few side effects.

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Contrast-induced nephropathy, defined as an increase in serum creatinine greater than 25% or 44.2 μmol/L (>0.5 mg/dL) within 3 days of intravascular contrast administration in the absence of an alternative cause, is the third most common cause of new acute renal failure in hospitalized patients (1, 2). Contrast-induced nephropathy develops in 0% to 10% of patients with normal renal function (3). However, the incidence may be as high as 25% in patients with preexisting renal impairment or certain risk factors, such as diabetes, congestive heart failure, advanced age, and concurrent administration of nephrotoxic drugs (3). Large doses of intravenous contrast and use of high-osmolar contrast agents in patients with renal impairment also increase the risk for contrast-induced nephropathy (4–6). High-osmolar contrast agents are more rarely used now. The risk difference between iso-osmolar agents, such as iodixanol, and low-osmolar agents, such as iopamidol, ioxaglate, or iohexol, is less clear (7–9). Most episodes of contrast-induced nephropathy are not detected clinically because patients are asymptomatic. However, contrast-induced nephropathy may increase the risk for renal failure and is associated with dialysis, prolonged hospital stay, increased health care costs, potentially irreversible reduction in renal function, and death (10).

Use of preprocedural fluids and low-osmolar or iso-osmolar contrast agents has been shown to decrease the risk for contrast-induced nephropathy (11–13). These measures suffice for many patients; however, the risk is reduced but not eliminated in some patients—even when iso-osmolar contrast is used (14, 15). Other studies have evaluated the use of *N*-acetylcysteine, theophylline, fenoldopam, and other agents as preventive strategies in contrast-induced nephropathy; the results have been heterogeneous and are difficult to compare across the different treatment strategies. Given the widespread use of iodinated intravascular contrast agents, an improved understanding of the potential value of these agents has important patient safety and cost implications.

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Audio summary

We conducted a meta-analysis of the literature to quantify the effects of individual strategies on the prevention of contrast-induced nephropathy and to facilitate comparison of preventive effects across strategies.

Context

Contrast-induced nephropathy is a common cause of acute renal failure in hospitalized patients. Clinicians use a variety of contrast agents to reduce the risk for contrast-induced nephropathy, including *N*-acetylcysteine, theophylline, fenoldopam, dopamine, furosemide, mannitol, and bicarbonate.

Contribution

Although all of the agents included in this analysis reduced the risk for contrast-induced nephropathy, this meta-analysis of 33 trials involving 3622 patients found the strongest evidence for the effectiveness of *N*-acetylcysteine, mannitol, and theophylline when compared with periprocedural hydration alone.

Caution

Available studies examined laboratory end points (such as an increase in serum creatinine levels) rather than clinical end points (such as dialysis or death).

—The Editors

Methods

Study Search Strategy

We performed a computerized search by using standard meta-analytic techniques (16) to identify relevant articles in MEDLINE (from 1966 through 3 November 2006), EMBASE (1980 through November 2006), PubMed, Web of Knowledge (Current Contents Connect, Web of Science, BIOSIS Previews, and ISI Proceedings for the latest 5 years), and the Cochrane Library databases. For the MEDLINE search, we used the following combination of keywords: [renal failure or kidney failure to include all subheadings] and [contrast media or iopamidol or iodine or ioxaglic acid or iodine compounds or iohexol or urography or drug hyper sensitivity or tomography, X ray computed or diatrizoate] and [hydration or fluid therapy or water or dehydration or skin or nutritional support or body water] and [clinical trial or randomized controlled trial] and [prospective trial or prospective studies or clinical trials] and [adult or middle aged or aged] and [N-Acetylcysteine or acetylcysteine] or [theophylline] or [mannitol] or [dopamine] or [fenoldopam] or [bicarbonate]. For the PubMed, Cochrane Library Database, and Web of Knowledge searches, we used the search words *renal failure*, *contrast medium*, *hydration*, *randomized controlled trial*, *N acetyl cysteine*, *Theophylline*, *Mannitol*, *Fenoldopam*, *Dopamine* and *Bicarbonate*. We included English-, French-, German-, Spanish- and Italian-language studies and clinical trials and excluded review articles and nonhuman studies. We combined this strategy with a manual search of reference lists from identified articles.

Study Selection

We included a study if 1 of the treatment groups received *N*-acetylcysteine, theophylline, fenoldopam, iloprost, statin, dopamine, trimetazidine, bicarbonate, ascorbic acid, furosemide, or mannitol. Criteria for inclusion were randomized, controlled trials that compared treatment with control; used intravenous iodinated contrast; explicitly defined contrast-induced nephropathy; and sufficiently reported data to construct a 2×2 table and calculate the primary effect measure (relative risk reduction). Where data were missing, we contacted the original authors for the relevant information.

Data Extraction

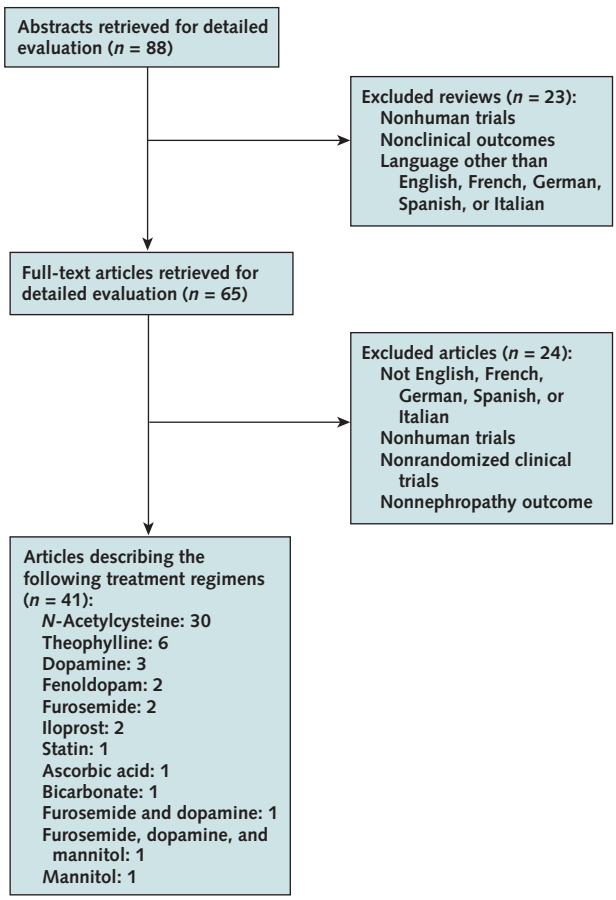
One reviewer examined the abstracts to determine whether the study met the inclusion and exclusion criteria. Two reviewers separately abstracted complete articles according to a standardized form for studies meeting criteria. Abstracted information included patient characteristics (mean age, proportion of men and patients with diabetes mellitus or hypertension, and mean baseline creatinine level), type of radiologic or cardiologic imaging, inclusion and exclusion criteria, type of contrast media and dose used, periprocedural hydration, specific definition of contrast-induced nephropathy, prophylactic agent dose and route, and serum creatinine level at baseline and at 48 hours after contrast injection.

Analysis of Renoprotective Agents

The primary outcome was the development of contrast-induced nephropathy, defined as an absolute increase in baseline serum creatinine greater than 44.2 μmol/L (>0.5 mg/dL) or a relative increase greater than 25% at 48 hours after contrast injection. For trials missing this datum, we contacted the original authors to get the number of patients with this outcome. We calculated individual study relative risks and 95% CIs before aggregation. Subsequently, we obtained overall and subgroup summary risk ratios by random-effects modeling of the binary data from the multiple 2×2 tables. We used the method of DerSimonian and Laird (17), with the estimate of heterogeneity taken from the inverse variance fixed-effect model. We used the *metan* module in Stata, version 9.0 (Stata, College Station, Texas), to perform data synthesis.

We performed subgroup evaluation of each therapeutic regimen. In studies comparing 2 dosage regimens of the same intervention with a single control group (18–20), we considered the same-study dosage groups as representing a single intervention to avoid double-counting of shared control observations. When we identified only 1 study that examined a given therapy, we assigned that study to a group termed "other" and pooled data from all such studies together. This group included 1 study each on the use

Figure 1. **Trial identification, inclusion, and exclusion.**



of iloprost; trimetazidine; mannitol; bicarbonate; ascorbic acid; and combinations of furosemide, dopamine, and mannitol and furosemide and dopamine. We used relative risk ratios to estimate the treatment effects.

Assessment of Methodological Quality

Criteria for quality assessment included concealment of allocation, similarity of both groups at baseline regarding prognostic indicators, eligibility criteria, blinding of patient, blinding of care provider, blinding of outcome assessor, point estimates and measures of variability for the primary outcome measure, and inclusion of an intention-to-treat analysis (21). Any disagreements in abstracted data between the reviewers were adjudicated by a third reviewer. We explored potential heterogeneity in estimates of treatment efficacy attributable to each quality criterion by using meta-regression.

Assessment of Heterogeneity

We used Forest plots to visualize the extent of heterogeneity among studies. We also examined I^2, a standard test for heterogeneity that measures the degree of inconsistency across studies. I^2 values, which range from 0% to 100%, describe the proportion of variation in treatment effect estimates that is due to genuine variation rather than sampling error (22). A value of 0% indicates no observed heterogeneity. Higgins and colleagues (22) suggest describing I^2 values of 25%, 50%, and 75% as low, moderate, and high, respectively. We obtained the group-specific and overall I^2 as standard output of the *metan* program.

We performed an Egger precision-weighted linear regression test as a statistical test of funnel plot asymmetry and publication bias (23).

All statistical analyses were performed with Stata.

RESULTS

Study Identification

Our initial search yielded 619 citations and references. We excluded 531 studies on the basis of our criteria, including nonclinical trials; trials not conducted on humans; trials not reported in English, French, German, Spanish, or Italian; trials reporting only nonnephropathy outcomes; and trials using nonclinical outcome measures, leaving 88 studies that met the inclusion criteria (**Figure 1**). We reviewed abstracts from the 88 articles and excluded an additional 23 trials, including nonrandomized clinical trials; trials not conducted on humans; trials not reported in English, French, German, Spanish, or Italian; trials reporting only nonnephropathy outcomes; and trials that used nonclinical outcome measures, leaving 65 studies for full publication review. The full articles were then reviewed, and a further 24 studies were excluded for reasons similar to those just mentioned. After the final screening, 41 randomized clinical trials met our inclusion criteria (18–20, 24–59), involving 6379 patients who had elective radiographic procedures involving contrast agents.

Study Characteristics

The trials were published between 1994 and 2006, and the **Table** shows their characteristics. Fifteen trials were performed in the United States (9, 20, 24, 25, 30–32, 34, 44, 48, 49, 51, 52, 58, 59), and 26 trials were performed elsewhere (18, 19, 26–29, 33, 35–43, 45–47, 50, 53–57, 59). Thirty-four trials evaluated patients with impaired renal function (9, 19, 20, 24–29, 32–46, 48–52, 56–59), defined as serum creatinine levels greater than 106.1 to 132.6 μmol/L (>1.2 to 1.5 mg/dL). We had insufficient data to separately evaluate patients with normal renal function. Only 3 trials evaluated patients with normal and impaired renal function, and 2 trials evaluated only patients with normal renal function (30, 31, 47, 53, 54). One trial evaluated patients having computed tomography (58); the rest evaluated patients having cardiac catheterization. The average age of the study patients was greater than 65 years in all but 8 studies (9, 18, 29, 37, 40, 41, 45, 48), and all studies included patients with diabetes. Dosing regimens for each trial are detailed in the **Table**. The outcome measure of contrast-induced nephropathy was reported in all studies. Changes in serum creatinine levels were reported at 48 hours in most trials (9, 18–20,

Table. **Study Characteristics***

Study, Year (Reference)	Total Patients, *n*	Patients in the Prophylactic Agent Group, *n*	Treatment	Patients in the Saline-Only Group, *n*	Enrollment Criteria	Hydration Protocol
Dopamine						
Abizaid et al., 1999 (24)	60	20 (dopamine) 20 (aminophylline)	Dopamine, 2.5 μg/kg per min Aminophylline, 4 mg/kg	20	CAD, CRI	0.45% normal saline
Diez et al., 1999 (31)	50	25 (dopamine)	Dopamine, 2 μg/kg per min, from 30 min before until end of study	25	Normal renal function	0.45% normal saline IV, 1.5 mL/kg per min, for 6 h before and after
Fenoldapam						
Allaqaband et al., 2002 (25)	123	38 (fenoldopam) 45 (*N*-acetylcysteine)	Fenoldopam, 0.1 μg/kg per min *N*-Acetylcysteine orally, 600 mg twice daily for 2 d	40	Cr >141.4 μmol/L (>1.6 mg/dL) or CrC ≤1 mL/s (≤60 mL/min)	0.45% normal saline, 1 mg/kg per h
Stone et al., 2003 (57)	315	157 (fenoldopam)	Fenoldopam, 0.05 μg/kg per min, increased to 0.10 μg/kg per min in 20 min if tolerated	158	CrC <1 mL/s (<60 mL/min)	0.45% normal saline IV, 1.5 mL/kg per h (or 1.0 mL/kg per h with cardiac failure), for 2 to 12 h before allocation
Furosemide						
Dussol et al., 2006 (35)†	235	80 (theophylline) 79 (furosemide)	Theophylline orally, 5 mg/kg, 1 h before Furosemide IV, 3 mg/kg, just before procedure	77	CrC between 0.25 and 1 mL/s (15 and 60 mL/min)	0.9% NaCl IV, 15 mL/kg, for 6 h before
Solomon et al., 2006 (9)	78	25 (furosemide) 25 (mannitol)	Furosemide, 80 mg Mannitol, 25 mg	28	Cr >141.4 μmol/L (>1.6 mg/dL) or CrC <1 mL/s (<60 mL/min)	0.45% normal saline, 1 mL/kg per h, for 12 h before and after angiography
***N*-Acetylcysteine**						
Allaqaband et al., 2002 (25)	123	45 (*N*-acetylcysteine) 38 (fenoldopam)	*N*-Acetylcysteine orally, 600 mg twice daily, for 2 d Fenoldopam, 0.1 μg/kg per min	40	Cr >141.4 μmol/L (>1.6 mg/dL) or CrC ≤1 mL/s (≤60 mL/min)	0.45% normal saline, 1 mg/kg per h
Azmus et al., 2005 (26)	397	196 (*N*-acetylcysteine)	*N*-Acetylcysteine orally, 600 mg twice daily, on the day before, day of, and day after	201	CRI	All patients: Saline, 1 L, before and after if tolerated
Baker et al., 2003 (27)	80	41 (*N*-acetylcysteine)	*N*-Acetylcysteine, 150 mg/kg in 500 mL normal saline, 30 min before, and 50 mg/kg in 500 mL normal saline over 4 h	39	Cr >120.2 μmol/L (>1.36 mg/dL) or CrC <1 mL/s (<60 mL/min)	1 mL/kg per h for 12 h before and after procedure
Balderramo et al., 2004 (28)†	61	33 (*N*-acetylcysteine)	*N*-Acetylcysteine orally, 1200 mg, 3 h before and 3 h after	28	Cr >132.6 μmol/L (>1.5 mg/dL) or CrC <0.83 mL/s (<50 mL/min)	0.9% saline IV, 4 mL/kg per h, for 3 h before, and 2 mL/kg per h, for 6 h after
Briguori et al., 2002 (29)	183	92 (*N*-acetylcysteine)	*N*-Acetylcysteine orally, 600 mg twice daily, 12 h before and after	91	Cr >106.1 μmol/L (>1.2 mg/dL) or CrC <1.17 mL/s (<70 mL/min)	0.45% saline IV, 1 mL/kg per h, for 12 h before and after
Coyle et al., 2006 (30)	137	68 (*N*-acetylcysteine)	*N*-Acetylcysteine, 600 mg every 12 h for 4 doses	69	Diabetic and scheduled to have angiography	0.45% saline IV, 300 mL/h, for 6 h
Diaz-Sandoval et al., 2002 (32)	54	25 (*N*-acetylcysteine)	*N*-Acetylcysteine orally, 600 mg twice daily	29	CRI	0.45% saline IV, 1 mL/kg per h

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Table—Continued

Study, Year (Reference)	Total Patients, *n*	Patients in the Prophylactic Agent Group, *n*	Treatment	Patients in the Saline-Only Group, *n*	Enrollment Criteria	Hydration Protocol
Drager et al., 2004 (33)	24	13 (*N*-acetylcysteine)	*N*-Acetylcysteine, 600 mg twice daily, 2 d before and after	11	Cr between 123.8 and 442.0 μmol/L (1.4 and 5.0 mg/dL) or CrC <1.17 mL/s (<70 mL/min)	All patients: Saline, 2 mL/kg, for 4 h before and 4 h after
Durham et al., 2002 (34)	79	38 (*N*-acetylcysteine)	*N*-Acetylcysteine, 1200 mg, 1 h before and 3 h after cardiac catheterization	41	CRI	All patients: 0.45% saline, 1 mL/kg per h, up to 12 h before and 12 h after contrast administration
El Mahmoud et al., 2003 (36)	120	60 (*N*-acetylcysteine)	*N*-Acetylcysteine, 600 mg twice daily, on the day before and day of angiography	60	Cr >120.2 μmol/L (>1.36 mg/dL)	All patients: 0.9% saline, 1 mL/kg per h, for 12 h before and after
Fung et al., 2004 (38)	91	46 (*N*-acetylcysteine)	*N*-Acetylcysteine orally, 400 mg 3 times daily, on the day before and day of procedure	45	CRI	All patients: Saline, 100 mL/h, from 12 h before to 12 h after
Goldenberg et al., 2004 (39)	80	41 (*N*-acetylcysteine)	*N*-Acetylcysteine orally, 600 mg 3 times daily, on the day before and day after	39	CRI	All patients: 0.45% saline, 1 mL/kg per h, for 1 d before and after
Gomes et al., 2005 (40)	156	77 (*N*-acetylcysteine)	*N*-Acetylcysteine, 600 mg twice daily, on the day before and day after procedure	79	Diabetes, Cr >106.1 μmol/L (>1.2 mg/dL), or CrC <0.83 mL/s (<50 mL/min)	Saline IV, 1mL/kg per h, for 12 h before and 12 h after
Kay et al., 2003 (46)	200	102 (*N*-acetylcysteine)	*N*-Acetylcysteine, 600 mg twice daily, on the day before and day after	98	CRI	0.9% saline IV, 1 mL/kg per h, for 12 h before and 6 h after
Kefer et al., 2003 (47)	104	53 (*N*-acetylcysteine)	*N*-Acetylcysteine before and after contrast	51	Normal renal function, CRI	Moderate hydration protocol
MacNeill et al., 2003 (48)	43	21 (*N*-acetylcysteine)	Two 600-mg doses of *N*-acetylcysteine before and 4 h after catheterization	22	Cr ≥132.6 μmol/L (≥1.5 mg/dL)	All received 0.45% saline, 1 or 2 mL/kg per h, before and 75 mL/h after procedure
Marenzi et al., 2006 (18)	352	115 (*N*-acetylcysteine)	*N*-Acetylcysteine IV, 600 mg, before angioplasty, and 600 mg twice daily for 48 h after	119	Patients having angioplasty	0.9% saline, 1 mL/kg per h (or 0.5 mL/kg per h with cardiac failure)
		118 (double-dose *N*-acetylcysteine)	*N*-Acetylcysteine IV, 1200 mg, before angioplasty, and 1200 mg twice daily for 48 h after			
Namgung et al., 2005 (50)	48	25 (*N*-acetylcysteine)	*N*-Acetylcysteine orally, 600 mg twice daily for 2 d	23	CRI	0.45% saline solution IV before and after procedure
Ochoa et al., 2004 (51)	80	36 (*N*-acetylcysteine)	*N*-Acetylcysteine, 1000 mg (5 mL), in diet cola	44	CRI	5 mL of 0.9% saline in diet cola
Oldemeyer et al., 2003 (52)	96	49 (*N*-acetylcysteine)	*N*-Acetylcysteine, 1500 mg twice daily, for 4 doses starting evening before	47	CRI	All patients: 0.45% saline, 1 mL/kg per h, for 12 h before and after
Rashid et al., 2004 (53)	94	46 (*N*-acetylcysteine)	*N*-Acetylcysteine, 1 g	48	Normal and CRI	Normal saline, 500 mL, over 4 to 6 h for 6 to 12 h before and after angiography

Table—Continued

Study, Year (Reference)	Total Patients, *n*	Patients in the Prophylactic Agent Group, *n*	Treatment	Patients in the Saline-Only Group, *n*	Enrollment Criteria	Hydration Protocol
Sandhu et al., 2006 (54)†	116	53 (*N*-acetylcysteine)	*N*-Acetylcysteine, 600 mg twice daily, on the day before and day after procedure	53	Patients referred for diagnostic angiography	Standard hydration
Shyu et al., 2002 (56)	121	60 (*N*-acetylcysteine)	*N*-Acetylcysteine orally, 400 mg twice daily, on the day before and day of procedure	61	Cr between 176.8 and 530.4 μmol/L (2.0 and 6.0 mg/dL) or CrC between 0.13 and 0.66 mL/s (8 and 40 mL/min)	All patients received 0.45% saline IV, 1 mL/kg per h
Sinha et al., 2004 (56)†	70	35 (*N*-acetylcysteine)	*N*-Acetylcysteine orally, 600 mg twice daily on the day before and day of angiography	35	Stable Cr >141.4 μmol/L (>1.6 mg/dL) or CrC <1 mL/s (<60 mL/min)	All patients: 0.45% saline IV, 1.5 mL/kg per h, for 8 h before and after angiography
Tepel et al., 2000 (58)†	83	41 (*N*-acetylcysteine)	*N*-Acetylcysteine orally, 600 mg twice daily, on the day before and day of computed tomography	42	Cr >106.1 μmol/L (>1.2 mg/dL) or CrC <0.83 mL/s (<50 mL/min)	All patients: 0.45% saline IV, 1 mL/kg per h, for 12 h before and after
Webb et al., 2004 (60)	447	242 (*N*-acetylcysteine)	*N*-Acetylcysteine IV, 500 mg in 50 mL of 5% dextrose saline	245	Screening GFR <50 mL/min per 1.73 m^2	All patients: 200 mL saline IV before and saline, 1.5 mL/kg per h, for 6 h or until discharge
Other‡						
Jo et al., 2005 (44)	70	34 (simvastatin)	Simvastatin, 40 mg twice daily	36	CrC <1 mL/s (<60 mL/min)	Half-normal saline IV, 1 mL/kg per h, for 8 h before and after contrast in both groups
Merten et al., 2004 (49)	119	69 (bicarbonate)	154 mEq/L of sodium bicarbonate in 5% dextrose and water	68	Cr ≥97.2 μmol/L (≥1.1 mg/dL)	154 mEq/L of NaCl in 5% dextrose and water
Solomon et al., 2006 (9)	78	25 (mannitol) 25 (furosemide)	Mannitol, 25 mg Furosemide, 80 mg	28	Cr >141.4 μmol/L (>1.6 mg/dL) or CrC <1 mL/s (<60 mL/min)	0.45% saline, 1 mL/kg per h, for 12 h before and after angiography
Spargias et al., 2004 (59)	231	118 (ascorbic acid)	Ascorbic acid, 3 g, at least 2 h before and 2 g in the night and morning after the procedure	113	Cr >106.1 μmol/L (>1.2 mg/dL)	Isotonic hydration
Spargias et al., 2006 (19)	45	15 (iloprost, 1 ng) 15 (iloprost, 2 ng)	Iloprost IV, 1 ng/kg per min, for 30 min before and 4 h after Iloprost IV, 2 ng/kg per min, for 30 min before and 4 h after	15	Cr >106.1 μmol/L (>1.2 mg/dL)	Saline IV, 1.5 mL/kg per h, for 4 h before and 12 h after
Stevens et al., 1999 (20)	98	21 (furosemide and dopamine) 22 (furosemide, dopamine, and mannitol)	Dopamine, 3 μg/kg per min, and furosemide, 1 mg/kg, up to 100 mg Above plus mannitol, 12.5 g, in 250 mL of 5% dextrose	55	Cr >159.1 μmol/L (>1.8 mg/dL)	All patients: 0.45% saline IV, 150 mL/h
Theophylline						
Abizaid et al., 1999 (24)	60	20 (aminophylline) 20 (dopamine)	Aminophylline, 4 mg/kg Dopamine, 2.5 μg/kg per min, and aminophylline, 4 mg/kg	20	CAD, CRI	0.45% normal saline

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Table—Continued

Study, Year (Reference)	Total Patients, *n*	Patients in the Prophylactic Agent Group, *n*	Treatment	Patients in the Saline-Only Group, *n*	Enrollment Criteria	Hydration Protocol
Dussol et al., 2006 (35)†	235	80 (theophylline) 79 (furosemide)	Theophylline orally, 5 mg/kg, 1 h before Furosemide IV, 3 mg/kg, just before procedure	77	CrC between 0.25 and 1 mL/s (15 and 60 mL/min)	0.9% NaCl IV, 15 mL/kg, for 6 h before
Erley et al., 1999 (37)	64	35 (theophylline)	Theophylline orally, 810 mg daily, 2 d before and 3 d after	29	Patients had to receive ≥80 mL of low-osmolar contrast agent	All hydration, 2000–2500 mL of fluid from 24 h before to 24 h after
Huber et al., 2002 (42)	100	50 (theophylline)	Theophylline, 200 mg	50	Cr ≥114.9 μmol/L (≥1.3 mg/dL)	Hydration, 2 L/d, advised for all patients
Huber et al., 2003 (43)	100	50 (theophylline)	Theophylline IV, 200 mg	50	Cr ≥114.9 μmol/L (≥1.3 mg/dL)	Hydration was advised for all patients
Kapoor et al., 2002 (45)	70	35 (theophylline)	Theophylline orally, 200 mg twice daily, 24 h before and 48 h after	35	Diabetes, Cr <265.2 μmol/L (<3 mg/dL)	All patients: Normal saline IV, 1 mL/kg per h, starting 12 h before to 12 h after

* All studies evaluated nephropathy after IV angiography except where indicated. CAD = coronary artery disease; Cr = creatinine; CrC = creatinine clearance; CRI = chronic renal impairment; GFR = glomerular filtration rate; IV = intravenous; NaCl = sodium chloride.
† Study evaluated computed tomography.
‡ This category comprised all studies that were the only included studies for a given therapy.

24–47, 49–59), although we used outcomes reported at 72 hours for 1 trial (48).

Analysis of Renoprotective Agents

Of the evaluated agents, *N*-acetylcysteine significantly decreased the risk for contrast-induced nephropathy compared with saline alone (relative risk, 0.62 [95% CI, 0.44 to 0.88]) (**Figure 2**). Although seemingly renoprotective, the effects of theophylline on nephropathy prevention were not significant (relative risk, 0.49 [CI, 0.23 to 1.06]). In the heterogeneous group of treatments for which only a single study was identified (labeled "other"), only ascorbic acid (relative risk, 0.46 [CI, 0.23 to 0.90]) and bicarbonate (relative risk, 0.12 [CI, 0.02 to 0.95]) significantly reduced contrast-induced nephropathy. Furosemide (relative risk, 3.27 [CI, 1.48 to 7.26]) increased the risk for contrast-induced nephropathy.

Assessment of Methodological Quality

The **Appendix Table** (available at www.annals.org) presents the quality characteristics of each study. Most studies included patients with similar baseline characteristics (94%) or specific inclusion characteristics (90%). Most also presented variance estimates of treatment effects (59%) or blinding of patients to treatment (51%). Fewer than half of the studies reported concealment of allocation (47%) or blinding of care providers to treatment (43%). Few studies noted outcome evaluation by individuals blinded to treatment assignment (6%) or an intention-to-treat design (8%). In exploratory analysis, only the quality characteristic of explicitly stating specific inclusion criteria ($P = 0.007$) independently contributed to heterogeneity across study efficacies.

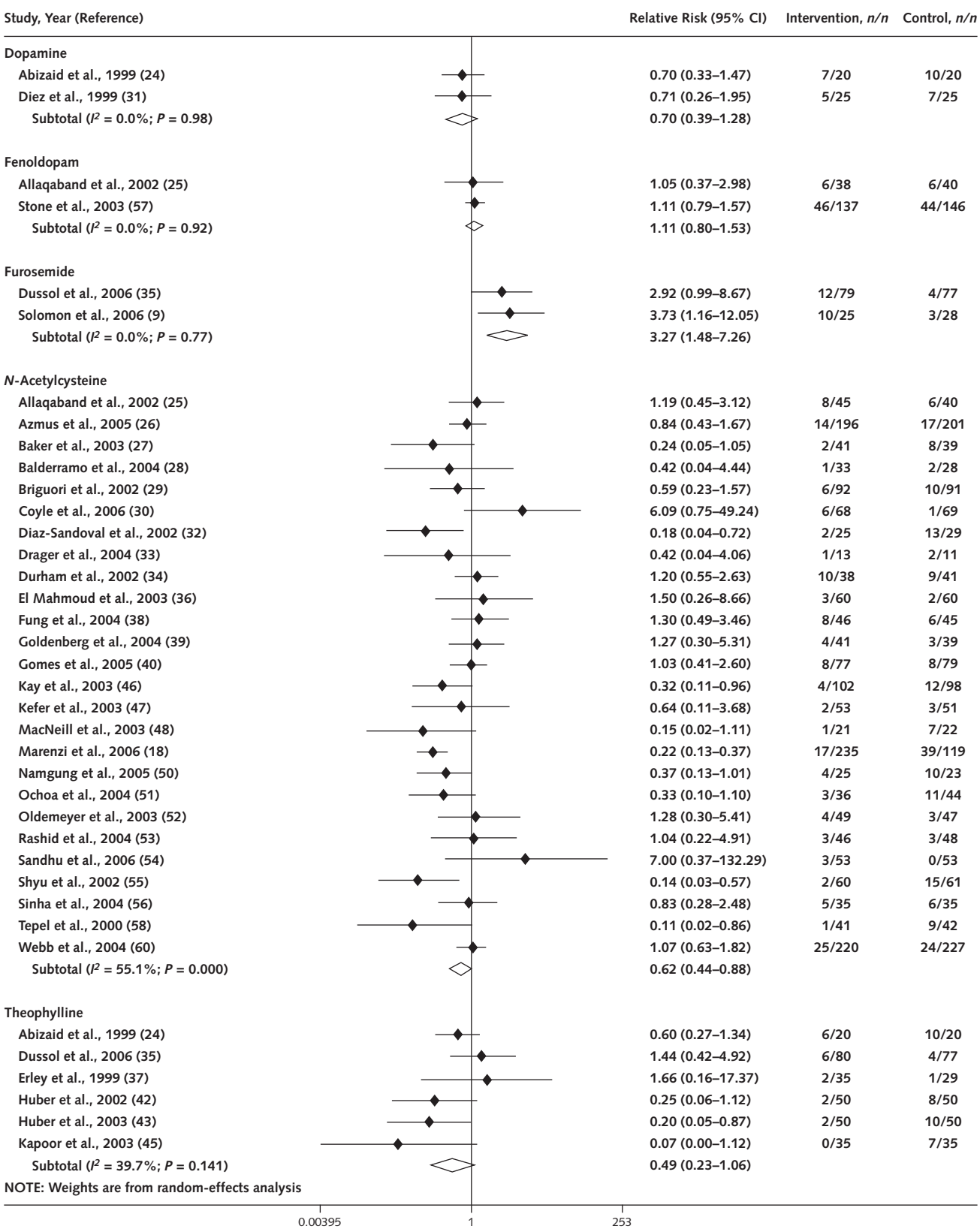
Assessment of Within-Group Heterogeneity and Publication Bias

Treatment effect estimates within the *N*-acetylcysteine group showed moderate heterogeneity ($I^2 = 55\%$; $P < 0.001$). As expected, we found a moderate to high level of heterogeneity among the pooled studies that each examined a different therapy (labeled "other") ($I^2 = 61\%$; $P = 0.024$). No other groups demonstrated significant within-group heterogeneity (**Figure 2**). No significant publication bias was discerned (bias coefficient, −0.55; $P = 0.20$).

Discussion

In our meta-analysis of 41 randomized trials, we found that preprocedural treatment with *N*-acetylcysteine effectively reduced the risk for contrast-induced nephropathy. Theophylline also produced larger risk reductions than previously mentioned; however, the effects of this agent were not significant. Not all agents analyzed had beneficial effects—fenoldopam; furosemide; mannitol; and the combination of furosemide, dopamine, and mannitol had odds ratios greater than 1. Our findings for *N*-acetylcysteine support previous studies (60–63). To date, no meta-analyses have studied preprocedural dopamine or statins for the prevention of contrast-induced nephropathy. Our findings

Figure 2. **Forest plot describing relative risk for contrast-induced nephropathy, by treatment agent.**



The intervention and control columns show the number of events among the total number of participants randomly assigned to the group for each study. We estimated heterogeneity within subgroups by using the I^2 statistic.

for theophylline support previous studies that showed a risk reduction (64). However, the effects of theophylline were not statistically significant in our study. In contrast, Ix and colleagues (64) found borderline statistical significance when they limited their analysis to studies using concomitant intravenous fluids or contrast volumes greater than 100 mL and no statistical significance when their analysis was limited to studies of only coronary angiography patients or where the theophylline was given within 1 hour of the procedure. Bagshaw and Ghali (65), however, did not find a statistically significant effect, similar to our findings.

N-Acetylcysteine is extremely inexpensive at 23 cents for a 500-mg tablet (price as of 17 January 2007 at www.shopping.com), is readily available, and is easily administered. Side effects and drug interactions are very rare with continued use and are highly unlikely to result from the limited use for renal protection. Therefore, although no formal cost-effective analysis has been performed to date, these findings support the use of *N*-acetylcysteine in selected at-risk patients.

Hydration and iso-osmolar or low-osmolar contrast agents, such as iodixanol, are all associated with a decreased incidence of contrast-induced nephropathy in patients with renal impairment (creatinine clearance <1 mL/s [<60 mL/min]) (44). In a recent meta-analysis, McCullough and colleagues (15) found that although low-osmolar contrast agents reduced the risk for contrast-induced nephropathy by two thirds, they did not totally eliminate the risk. Thus, protective agents must still be considered for patients with severe renal impairment who are to receive large volumes of contrast agents.

Our meta-analysis has several limitations. All included trials evaluated the surrogate end point of contrast-induced nephropathy as the primary outcome. Contrast-induced nephropathy was defined as an increase in serum creatinine of more than 44.2 μmol/L (>0.5 mg/dL) or 25% from baseline values, which represents a minor deterioration in renal function in patients with chronic renal failure. Even in high-risk patients, contrast-induced nephropathy is almost always transient and only rarely requires dialysis. Only the trial by Kay and colleagues (46) examined length of hospital stay as an end point and found a significant reduction in length of stay among patients given *N*-acetylcysteine. Despite the reported association of contrast-induced nephropathy with impaired outcomes, no trial has examined clinical end points, such as dialysis dependency or in-hospital morbidity and mortality. The clinical relevance of the renoprotective effects of *N*-acetylcysteine, dopamine, and other agents is therefore debatable, whereas periprocedural hydration is of proven benefit (66). In addition, it is possible that we did not detect a significant effect for theophylline because of study heterogeneity or insufficient data.

Because we primarily identified and used published studies, our results are weighted on the findings of published trials. The exclusion of unpublished data is generally associated with an overestimate of the true effect in meta-analysis (67). The single most common reason for inability to publish a trial is the lack of statistical significance, although some have suggested that the quality of unpublished data is not comparable to that accepted by peer-reviewed journals (68). In addition, many of the included studies did not have high quality scores, and many did not specify that they met the quality criteria, with the true quality remaining uncertain.

Strengths of our study include the comprehensive search strategy and the careful statistical methods used. We identified 41 trials with a total of 6379 patients and evaluated multiple therapeutic agents within 1 analysis framework, allowing side-by-side comparison of the efficacies across agents.

Our meta-analysis shows that *N*-acetylcysteine is the most effective agent for preventing contrast-induced nephropathy in patients with chronic renal insufficiency. Whether this risk reduction translates into a benefit in clinical outcomes remains to be proven. The reported association of contrast-induced nephropathy with increased morbidity, mortality, and hospital stay might justify the use of *N*-acetylcysteine as a routine intervention for prophylaxis of contrast-induced nephropathy, given that *N*-acetylcysteine is readily available and inexpensive and has a favorable side effect profile.

The results of this meta-analysis should be evaluated in head-to-head empirical studies of active agents to identify the most efficacious regimen for preventing contrast-induced nephropathy. However, our findings indicate that the use of such oral agents as *N*-acetylcysteine is reasonable in high-risk patients who are to receive large or repeated volumes of contrast agents. We believe that the lack of significant side effects and the low cost justifies use of these agents while empirical data on clinical outcomes mature.

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Appendix Table. **Summary of Study Quality Characteristics**

Study, Year (Reference)	Concealed Allocation	Similar Baseline	Specific Inclusion Criteria	Blinded Outcome Assessor	Blinded Care Provider	Blinded Patient	Estimate Variability of Outcomes	Intention-to-Treat Analysis
Abizaid et al., 1999 (24)	No	No	Yes	No	No	No	No	No
Allaqaband et al., 2002 (25)	No	No	Yes	No	No	No	No	No
Azmus et al., 2005 (26)	Yes	Yes	Yes	Yes	No	Yes	Yes	No
Baker et al., 2003 (27)	No	Yes	Yes	No	No	No	No	No
Briguori et al., 2002 (29)	No	Yes	Yes	No	No	No	Yes	No
Coyle et al., 2006 (30)	No	Yes	Yes	No	No	No	Yes	No
Diez et al., 1999 (31)	No	Yes	Yes	No	No	No	No	No
Diaz-Sandoval et al., 2002 (32)	No	Yes	Yes	No	Yes	Yes	Yes	No
Balderramo et al., 2004 (28)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Drager et al., 2004 (33)	No	Yes	Yes	No	Yes	Yes	No	No
Durham et al., 2002 (34)	No	Yes	Yes	No	No	Yes	No	No
Dussol et al., 2006 (35)	No	Yes	Yes	No	No	No	Yes	No
El Mahmoud et al., 2003 (36)	No	Yes	Yes	No	No	No	No	No
Erley et al., 1999 (37)	No	Yes	Yes	No	Yes	Yes	No	No
Fung et al., 2004 (38)	No	Yes	Yes	No	No	No	No	No
Goldenberg et al., 2004 (39)	No	Yes	Yes	No	Yes	Yes	Yes	No
Gomes et al., 2005 (40)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Huber et al., 2002 (42)	No	Yes	Yes	No	Yes	Yes	No	No
Huber et al., 2003 (43)	No	Yes	Yes	No	No	No	No	No
Jo et al., 2005 (44)	No	Yes	Yes	No	No	No	Yes	No
Kapoor et al., 2002 (45)	No	Yes	Yes	No	No	No	No	No
Kay et al., 2003 (46)	No	Yes	Yes	No	Yes	Yes	Yes	No
Kefer et al., 2003 (47)	No	Yes	Yes	No	No	Yes	Yes	No
MacNeill et al., 2003 (48)	No	Yes	Yes	No	Yes	Yes	No	No
Marenzi et al., 2006 (18)	No	Yes	Yes	No	No	No	Yes	No
Merten et al., 2004 (49)	No	Yes	Yes	No	No	No	Yes	Yes
Namgung et al., 2005 (50)	No	Yes	Yes	No	No	No	Yes	No
Ochoa et al., 2004 (51)	No	Yes	Yes	No	Yes	Yes	No	No
Oldemeyer et al., 2003 (52)	No	Yes	Yes	No	Yes	Yes	No	No
Rashid et al., 2004 (53)	No	Yes	Yes	No	Yes	Yes	No	No
Sandhu et al., 2006 (54)	Yes	Yes	Yes	No	No	No	Yes	No
Shyu et al., 2002 (55)	No	Yes	Yes	No	No	No	No	No
Sinha et al., 2004 (56)	No	Yes	Yes	No	No	No	Yes	No
Solomon et al., 2006 (9)	No	Yes	Yes	No	No	Yes	Yes	Yes
Spargias et al., 2004 (59)	Yes	Yes	Yes	No	No	No	Yes	No
Spargias et al., 2006 (19)	Yes	Yes	Yes	No	Yes	Yes	Yes	No
Stevens et al., 1999 (20)	No	Yes	Yes	No	No	Yes	Yes	Yes
Stone et al., 2003 (57)	Yes	Yes	Yes	No	Yes	Yes	Yes	No
Tepel et al., 2000 (58)	No	Yes	Yes	No	No	No	No	Yes
Webb et al., 2004 (60)	No	Yes	Yes	No	No	No	No	No