Prophylaxis Strategies for Contrast-Induced Nephropathy

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Context Contrast-induced nephropathy is associated with significant economic and clinical consequences, including prolonged hospitalization, the requirement for dialysis, and an increased risk of death.

Objectives To summarize the current state of evidence for prophylaxis of contrast-induced nephropathy, provide evidence-based recommendations regarding management of high-risk patients undergoing angiographic procedures, and identify new avenues for research.

Data Sources Systematic searches of peer-reviewed publications were performed in MEDLINE, EMBASE, and the Cochrane database from 1966 to January 2006. Search terms included *radio contrast nephropathy, contrast media, acetylcysteine, theophylline, sodium bicarbonate, HMG Co-A reductase inhibitors, ascorbic acid, kidney diseases, renal insufficiency, kidney failure, nephropathy, fenoldopam, diuretics,* and *saline or half saline*.

Study Selection Observational studies of risk factors and randomized controlled trials of prophylaxis strategies for contrast-induced nephropathy that specified a definition of contrast-induced nephropathy or postprocedure creatinine level as an outcome measure.

Evidence Synthesis Important patient-related risk factors for contrast-induced nephropathy include chronic kidney disease, diabetes mellitus, heart failure, older age, anemia, and left ventricular systolic dysfunction. Non–patient-related risk factors include high-osmolar contrast, ionic contrast, contrast viscosity, and contrast volume. Practice guidelines recommend obtaining preprocedural serum creatinine levels among patients with renal disease, diabetes, proteinuria, hypertension, gout, or congestive heart failure. Available evidence, largely based on small- to medium-sized trials, supports the use of hydration, bicarbonate, and low volumes of iso- or low-osmolar contrast in patients at risk. *N*-acetylcysteine or ascorbic acid may be of value in very high-risk patients.

Conclusions While several risk factors for contrast-induced nephropathy have been identified, the development of an effective prophylaxis strategy for contrast-induced nephropathy has been limited by our poor understanding of the pathophysiology and the clinical significance of this condition. Future research should focus on correctly identifying higher-risk patients and testing therapies in the setting of large well-powered clinical trials.

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NEPHROPATHY INDUCED BY CONtrast media is a recognized complication of diagnostic and therapeutic procedures requiring parenteral administration of contrast and is the third leading cause of hospital-acquired acute renal failure, accounting for 12% of cases.[1] Contrast-induced nephropathy is associated with significant consequences, including prolonged hospitalization, the requirement for dialysis, and an increased risk of death.[2,3] Clinical outcomes associated with acute renal failure following cardiac catheterization can be catastrophic, with an in-hospital mortality rate of 20% in unselected patients and a 1-year mortality rate of up to 66% in patients with acute myocardial infarction and preexisting renal dysfunction.[3-5]

This review will critically evaluate current evidence for strategies to prevent contrast-induced nephropathy, present an evidence-based approach to this clinically important problem, and identify key areas for future research.

METHODS

A literature search was performed for English-language journal articles reporting risk factors for contrast nephropathy. We searched MEDLINE and EMBASE to identify publications from 1966 to January 2006, using the key terms *radio contrast nephropathy, contrast media, risk, diabetes, nephrotoxicity, creatinine, coronary disease, coronary procedures, dehydration,* and *hypovolemia*. A total of 59 studies were identified by the authors as being potentially relevant.

A separate literature search was performed for English-language clinical trials in contrast nephropathy. We searched MEDLINE and EMBASE to identify trials from 1966 to January 2006, using the key terms *radio contrast ne-*

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Box. Risk Factors for Contrast-Induced Nephropathy

Patient Related

Chronic kidney disease[3,13-19]
Diabetes mellitus[13,16,17,19]
Urgent/elective procedure[16]
Intra-aortic balloon pump[16,17,20]
Congestive heart failure[13,15,17,20]
Age[3,17]
Hypertension[21,22]
Low hematocrit[17,23]
Hypotension[17,22]
Left ventricular ejection fraction <40%[22]

Not Patient Related

Contrast properties
- High osmolar contrast[7,24]
- Ionic contrast[25-28]
- Contrast viscosity[29,30]

Contrast volume[3,13,16-19,31-34]

phropathy, contrast media, acetylcysteine, theophylline, sodium bicarbonate, HMG Co-A reductase inhibitors, ascorbic acid, kidney diseases, renal insufficiency, kidney failure, nephropathy, fenoldopam, saline, and *diuretics*. The citations of existing reviews and trials identified were evaluated by 2 reviewers to identify pertinent trials. Any study considered relevant by one or both reviewers was retrieved for further consideration. A total of 331 studies were identified as potentially relevant, of which 63 were randomized controlled trials (RCTs) of prophylaxis strategies for contrast-induced nephropathy. Criteria for study selection were publication in a peer-reviewed journal, controlled study design, and English language. Quality assessment was based on concealment of treatment allocation, double-blind design, intention-to-treat analysis, and rate of loss to follow-up.

DEFINITIONS AND EPIDEMIOLOGY

Although there is no universally accepted definition, contrast-induced nephropathy refers to the development of acute renal impairment following the intravascular administration of radiocontrast in the absence of other identifiable causes of renal failure. Most studies have used a 25% elevation in serum creatinine (SCr) or an absolute increase of 0.5 mg/dL (44 µmol/L) 2 to 7 days following contrast administration. Although relatively mild, these changes in kidney function are associated with clinically important adverse short- and long-term outcomes.[2,3,6,7] The causal pathway linking the development of contrast-induced nephropathy to adverse cardiovascular outcomes has not been established. Whether contrast-induced nephropathy is directly responsible for the observed increase in mortality, or is simply a marker for illness acuity and/or comorbidity, remains unknown.

Based on these definitions, the incidence of contrast nephropathy in patients undergoing diagnostic interventions requiring contrast is low (1.6%-2.3%).[8] Intra-arterial administration of radiocontrast might be more likely to lead to contrast-induced nephropathy than the intravenous route,[9] although other causes of acute renal failure (such as atheroemboli) may also be triggered by arteriography. The incidence of contrast-induced nephropathy is dependent on the definition and is considerably lower when cases are defined based on a greater absolute increase in SCr level, or if the postprocedure SCr measurement is obtained earlier.[10] Acute renal failure due to contrast-induced nephropathy is generally nonoliguric and reversible. In most cases, the SCr level peaks between 2 and 5 days after contrast exposure and returns to normal within 14 days.[11,12] Registry data report the incidence of contrast-induced nephropathy requiring dialysis treatment to be approximately 0.4%.[13]

RISK FACTORS

The most commonly identified risk factors for contrast-induced nephropathy are listed in the BOX. Most have been identified through retrospective analysis of databases cataloging coronary angiographic procedures. Unfortunately, periprocedural hydration and an accurate assessment of comorbidity have rarely been captured in these data sources, so estimates of the risk attributable to individual factors are unreliable.

Patient-Related Factors

Patients with diabetes and chronic kidney disease appear to be at the highest risk for developing contrast-induced nephropathy. These patients have reported rates of contrast-induced nephropathy that are approximately 4-fold higher than those without diabetes or preexisting renal impairment.[25,35]

Hypovolemia and/or decreased effective circulating volume are well-recognized risk factors for contrast-induced nephropathy, but have never been directly assessed in clinical trials. Indirect evidence comes from studies that show a benefit of intravenous hydration[36,37] and the deleterious effect of diuretics.[38] Conditions resulting in a low effective circulating volume such as cardiogenic shock,[16] use of an intra-aortic balloon pump,[16,17,20] hypotension,[17,22] congestive heart failure (CHF),[13,15,17,20] and ejection fraction less than 40%[22] are also identified risk factors for contrast-induced nephropathy.

Female sex is a frequently cited[14,21,39] but somewhat controversial risk factor for contrast-induced nephropathy. A more recent analysis of 1383 patients[40] suggests that women may have unfavorable baseline characteristics (older age, more frequent hypertension and diabetes, lower baseline kidney function) that put them at risk for contrast-induced nephropathy. After adjustment for these confounders, female sex did not appear to independently increase risk.

Non–Patient-Related Factors

Radiocontrast media are frequently classified on the basis of osmolality, which is determined by the ratio of iodine atoms to osmotically active particles.[41,42] A comparison of commonly

used radiocontrast agents is presented in TABLE 1.

A direct correlation between osmolality and nephrotoxicity is well established in contrast agents with an osmolality greater than 780 mOsm/kg. A 1992 meta-analysis[43] pooling data from 25 randomized trials showed that the risk of contrast nephropathy was significantly greater with high-osmolality (>1400 mOsm/kg) radiocontrast agents in patients with preexisting renal disease.

While the previously publicized findings of a study comparing iohexol (a low-osmolar agent [600-800 mOsm/kg]) with iodixanol (an iso-osmolar agent [290 mOsm/kg]) initially suggested additional nephroprotection with a further reduction in radiocontrast osmolality,[24] the differing physicochemical properties of radiocontrast agents may in fact be a more important mediator of nephrotoxicity. Pooled analyses evaluating the nephrotoxicity of differing contrast agents used in recent randomized interventional trials[29,30] showed that iohexol was associated with a significantly increased risk of developing contrast-induced nephropathy compared with either iopamidol (another agent with similar osmolality) or iodixanol (an iso-osmolar radiocontrast agent) (contrast-induced nephropathy 25% vs 13.5% and 11%, respectively; both $P<.05$). More importantly, there was no significant difference in the reported rates of contrast nephropathy associated with iopamidol and iodixanol, which can perhaps be explained by the increased viscosity of iodixanol relative to many of the low-osmolar agents.

Whether ionic compounds are more nephrotoxic than nonionic compounds remains somewhat controversial, as previous studies are frequently confounded by differences in osmolality. Several randomized trials of ionic vs nonionic contrast showed no difference in rates of contrast-induced nephropathy.[25-28] However, post hoc analysis of one study did demonstrate that patients with preexisting renal dysfunction were less likely to develop contrast-induced nephropathy when nonionic radiocontrast media was used.[25]

Table 1. Properties of Commonly Used Radiocontrast Media

Type	Generic Name	Iodine, mg/mL	Osmolality, mOsm/kg	Viscosity, cps at 37°C
High osmolar				
Ionic monomer	Sodium iothalamate	325	1843	2.75
Ionic monomer	Meglumine diatrizoate	306	1530	5.0
Low osmolar				
Ionic dimer	Meglumine ioxaglate	320	580	7.5
Ionic dimer	Sodium ioxaglate	320	580	7.5
Nonionic monomer	Iopamidol	300	616	4.7
Nonionic monomer	Iohexol	300	640	6.3
Nonionic monomer	Ioversol	300	645	5.5
Nonionic monomer	Iopromide	300	610	4.6
Iso osmolar				
Nonionic dimer	Iotrolan	300	320	8.1
Nonionic dimer	Iodixanol	320	290	11.4

RISK STRATIFICATION

Several attempts have been made to develop a clinical tool for the purposes of risk stratification,[13,15-17,44,45] but none have been validated prospectively or in other databases. In addition, none of the databases captured comorbidity or prophylactic interventions to prevent contrast nephropathy such as the administration of hydration. As all risk scores were derived from patients undergoing coronary angiography, they may not specifically apply to the use of parenterally administered contrast in other settings (ie, intravenous contrast).

Two risk scores[16,17] for contrast-induced nephropathy developed from large interventional cardiology databases may be the most generalizable to this patient population. Bartholomew et al[16] (n=20 479) identified 8 variables that were associated with contrast-induced nephropathy (creatinine clearance <60 mL/min [1.0 mL/s], use of an intra-aortic ballon pump, urgent coronary procedure, diabetes, CHF, hypertension, peripheral vascular disease, contrast volume) and created 4 risk categories based on their analysis. They defined contrast-induced nephropathy as a greater than 1 mg/dL [88.4 µmol/L] rise in SCr with no specified time frame for post SCr measurement. By this definition, contrast-induced nephropathy occurred in 2% of patients. Patients in the highest risk group had a 28% risk of developing contrast nephropathy and a 17% risk of death. Mehran and colleagues[17] (n=8357) identified 3 additional characteristics that were associated with increased risk: older age, the presence of hypotension, and anemia. They used a less stringent definition of contrast-induced nephropathy (change in SCr ≥25% or ≥0.5 mg/dL [44.2 µmol/L] at 48 hours), which may partially account for the higher reported incidence of contrast-induced nephropathy (13.1%).

PROPHYLAXIS STRATEGIES

The mechanism by which contrast agents produce nephrotoxicity is poorly understood but probably includes a reduction in renal perfusion resulting in regional hypoxia, as well as direct tubular toxicity. Therapies studied to date have targeted renal vasoconstriction and hypoxia-induced oxidative stress with limited success.

TABLE 2, TABLE 3, and TABLE 4 summarize all identified RCTs investigating prophylaxis strategies for contrast-induced nephropathy. Most studies were small and were consequently underpowered to detect a clinically significant benefit. Few studies present sample size or power calculations, and most were not double-blinded (TABLE 5). Many were not analyzed as intention to treat, and loss to follow-up was rarely reported (Table 5).

Table 2. Study Demographics and Clinical Characteristics: Hydration and Diuretics, Dopamine, Fenoldopam, and Theophylline/Aminophylline

Source	Osmolality/ Route of Contrast	Intervention Prophylaxis and Regimen	Control Prophylaxis and Regimen	Cointervention and Regimen	No. of Participants	Mean Age, y/ Female, %	Female, %	Diabetic, %	Mean Baseline SCr, mg/dL	Definition of Contrast-Induced Nephropathy
Hydration and Diuretics										
Bader et al,[46] 2004	Low/both IA and IV	Bolus 300 mL during procedure	2000 mL 0.9% saline in total (over 12 h pre/12 h post)	1500-2000 mL po H_20 (12 h pre)	39	65/18	18	26	0.9	>50% decrease in GFR at 48 h
Krasuski et al,[47] 2003	Multiple/IA	Bolus 250 mL saline x 20 min	1 mL/kg/h 0.45% saline (12 h pre)	1 mL/kg/h 0.45% saline (12 h post)	70	68/17	17	54	NR	>0.5 mg/dL in SCr at 48 h
Merten et al,[48] 2004	Low/both IA and IV	3 mL/kg/h IV saline (1 h pre) 1 mL/kg/h IV bolus (6 h post)	3 mL/kg/h IV saline (1 h pre); 1 mL/kg/h IV bolus (6 h post)	None	137	68/25	25	48	1.8	≥25% increase in SCr at 48 h
Mueller et al,[37] 2002	Low/IA	1 mL/kg/h 0.45% saline (same day)	1 mL/kg/h 0.9% saline (same day)	None	1620	64/26	26	16	0.9	≥0.5 mg/dL in SCr at 24 h or 48 h
Solomon et al,[38] 1994	Multiple/IA	Mannitol 25 g (60 min pre); furosemide 80 mg (30 min pre)	Placebo	1 mL/kg/h 0.45% saline (12 h pre/ 12 h post)	78	63/31	31	53	2.1	≥0.5 mg/dL increase in SCr at 48 h
Stevens et al,[49] 1999	Multiple/IA	Furosemide 1 mg/kg (max 100 mg) and mannitol 12.5 g in 250 mL D5W infused x 2 h	Placebo	150 mL/h 0.45% saline (start in laboratory/ 6 h post)	100	70/33	33	53	2.5	Multiple definitions
Taylor et al,[50] 1998	Multiple/IA	1000 mL po H_20 (10 h pre); 0.45% IV saline 300 mL/h (30-60 min pre/ 6 h post)	75 mL/h 0.45% IV saline (12 h pre/ 12 h post)	None	36	70/7	7	14	1.8	≥0.3 mg/dL increase in SCr within 24-48 h
Trivedi et al,[36] 2003	Low/IA	1 mL/kg/h 0.9% saline (12 h pre/ 12 h post)	Unrestricted fluids po	None	53	68/2	2	19	1.2	≥0.5 mg/dL increase in SCr at 48 h
Weinstein et al,[51] 1992	Multiple/IA	Furosemide 1.5 mg/kg (30 min pre)	None	6 mL/kg Hartman's solution x 1 h then 6 mL/kg/h D5W in 0.18% saline (1 h pre/ 2 h post)	18	69/0		25	1.6	None
Dopamine										
Gare et al,[52] 1999	Low/IA	Dopamine 2 µg/kg/min x 48 h	Placebo	≥100 mL/h 0.45% saline (8-12 h pre/ 36-48 h post); 120 mL/h 0.9% saline x 48 h	68	61/23	23	88	1.1	≥40% increase in SCr
Hans et al,[53] 1998	Low/IA	Dopamine 2.5 µg/kg (1 h pre and continued for 12 h)	0.9% Saline (equal volume)	None	55	73/11	11	40	1.9	≥0.5 mg/dL increase in SCr
Weisberg et al,[54] 1994	High/IA	Dopamine 2 µg/kg/min in 0.45% saline at 100 mL/h; ANP 50-µg bolus and 1 µg/min infusion in 0.45% saline at 100 mL/h; mannitol 15 g/dL in 0.45% saline in 100 mL/h	Placebo	100 mL/h 0.45% saline (12 h pre)	50	NR		48	2.5	≥25% increase in SCr within 48 h
Fenoldopam										
Allaqaband et al,[55] 2002	Low/IA	Fenoldopam IV 0.1 µg/kg/min (4 h pre/4 h post); NAC 600 mg po bid (1 d pre/ 1 d post)	0.9% saline	1 mL/kg/h 0.45% saline (12 h pre/ 12 h post)	126	71/42	42	50	2.1	≥0.5 mg/dL increase in SCr at 48 h

(Continued)

Table 2. Study Demographics and Clinical Characteristics: Hydration and Diuretics, Dopamine, Fenoldopam, and Theophylline/Aminophylline (cont)

Source	Osmolality/ Route of Contrast	Intervention Prophylaxis and Regimen	Control Prophylaxis and Regimen	Cointervention and Regimen	No. of Participants	Mean Age, y/ Female, %	Female, %	Diabetic, %	Mean Baseline SCr, mg/dL	Definition of Contrast-Induced Nephropathy
Hydration and Diuretics										
Briguori et al,[56] 2004	Iso osmolar/IA	Fenoldopam 0.1 µg/kg/min (1 h pre/ 12 h post)	NAC 1200 mg po bid (1 d pre/ 1 d post)	1 ml/kg/h 0.45% saline (12 h pre/ 12 h post)	192	68/15	15	51	1.7	≥0.5 mg/dL increase in SCr at 48 h or need for dialysis after procedure
Ng et al,[57] 2006	Low/IA	Fenoldopam 0.1 µg/kg/min (1-2 h pre/ 6 h post)	NAC 600 mg po bid (3 doses pre/ 1 dose post)	1 mL/kg/h 0.9% saline (1-2 h pre/ 6-12 post)	95	68/24	24	42	1.5	>25% increase in SCr or ≥0.5 mg/dL with 24-72 h
Stone et al,[58] 2003	Multiple/IA	Fenoldopam 0.05 µg/kg/min (1.5-0.5 h pre x 12 h) (increased to 0.1 µg/kg/min in 20 min if tolerated)	Placebo	1.5 mL/kg/h 0.45% saline (2-12 h pre)	315	70/34	34	49	1.8	≥25% increase in SCr at 24-96 h, ≥0.5 mg/dL increase in SCr
Tumlin et al,[59] 2002	Multiple/IA	Fenoldopam 0.1 µg/kg/min (1 h pre/4 h post)	Placebo	100 mL/h 0.45% saline (3 h pre/4 h post)	45	63/76	76	53	2.6	≥0.5 mg/dL increase in SCr or ≥25% increase at 48 h
Theophylline/Aminophylline										
Abizaid et al,[60] 1999	Low/IA	Aminophylline 4 mg/kg followed by 0.4 mg/kg/h (2 h pre); dopamine 2.5 ug/kg/min (2 h pre)	1 mL/kg/h 0.45% saline (2 h pre)	1 mL/kg/h 0.45% saline (12 h pre/ 12 h post)	60	75/33	33	57	2.0	≥25% increase in SCr at 48 h
Erley et al,[61] 1994	Low/both IA and IV	Theophylline 5 mg/kg IV in saline (45 min pre)	Placebo	None	39	55/28	28	18	1.2	None
Erley et al,[62] 1999	Low/both IA and IV	Theophylline 10 mg/d po (2 d pre/3 d post)	Placebo	0.45% saline, IV or po (24 h pre/ 24 h post); 2000-2500 mL total	80	64/22	22	30	1.8	≥0.5 mg/dL increase in SCr
Gandhi et al,[63] 1992	Low/IA	Theophylline 125 mg tid (1 d pre/2 d post)	Placebo	None	21	54/33	33	NR	NR	None
Huber et al,[64] 2002	Low/both IA and IV	Theophylline 200 mg (30 min pre)	Placebo	None	100	68/82	82	34	2.0	≥0.5 mg/dL increase in SCr at 48 h
Huber et al,[65] 2003	Low/IA	Theophylline 200 mg (30 min pre)	Placebo	None	100	68/17	17	31	1.7	≥0.5 mg/dL increase in SCr at 48 h
Kapoor et al,[66] 2002	High/IA	Theophylline 200 mg po bid (24 h pre/ 48 h post)	None	1 mL/kg/h 0.9% saline (12 h pre/ 12 h post)	70	53/9	9	100	1.2	≥25% increase in SCr or ≥25% decrease in GFR at 48 h
Katholi et al,[67] 1995	Multiple/IA	Theophylline 2.88 mg/kg po bid (1 h pre x 48 h)	Placebo	1.43 mL/kg/h po H_2O or IV D5W x 72 h	93	61/0		18	1.3	None
Kolonko et al,[68] 1998	High/NR	Theophylline 165 mg (30 min pre)	Placebo	None	58	41/21	21	0	1.0	None

Abbreviations: ANP, atrial natriuretic peptide; bid, twice daily; D5W, 5% dextrose; GFR, measured glomerular filtration rate; IA, intra-arterial; IV, intravenous; NAC, *N*-acetylcysteine; NR, not reported; po, by mouth; SCr, serum creatinine; tid, 3 times per day.
SI conversion: To convert SCr to µmol/L, multiply by 88.4.

Hydration

Early studies evaluating the renal effects of radiocontrast administration in dogs demonstrated a reduction in renal perfusion lasting up to 20 hours after radiocontrast administration.[108] While no RCT has studied the benefits of hydration alone, it seems plausible that adequate hydration may counteract some of the putative hemodynamic effects that may lead to contrast-induced nephropathy.

Table 3. Study Demographics and Clinical Characteristics: Calcium Channel Blockers and *N*-Acetylcysteine (NAC)

Source	Osmolality/ Route of Contrast	Intervention Prophylaxis and Regimen	Control Prophylaxis and Regimen	Cointervention and Regimen	No. of Participants	Mean Age, y/ Female, %	Female, %	Diabetic, %	Mean Baseline SCr, mg/dL	Definition of Contrast-Induced Nephropathy
Calcium Channel Blockers										
Arici et al,[69] 2003	Low/IA	Amlodipine 10 mg/d (6 d pre/ 7 d post)	Placebo	500 mL IV 0.9% saline (2 h pre/4 h post)	29	55/34	34	0	2.1	≥0.5 mg/dL increase in SCr at 24 h
Carraro et al,[70] 1996	Low/IA	Nitrendipine 10 mg po (1 h pre)	Placebo	None	100	66/38	38	14	1.1	≥50% increase in SCr at 24 h
Khoury et al,[71] 1995	Multiple/Both IA and IV	Nifedpine 10 mg po (1 h pre)	None	0.5-1.5 L 0.9% saline (pre); 0.5 L 0.9% saline (4 h post)	111	63/49	49	31	1.0	≥0.5 mg/dL increase at SCr at 24 h
NAC										
Azmus et al,[72] 2005	Multiple/IA	NAC 600 mg po bid (1 d pre/ 1.5 d post)	Placebo	1000 mL 0.9% IV saline (pre/post)	414	67/41	41	50	1.3	≥25% increase in SCr at 48 h or ≥0.5 mg/dL (and SCr ≥1.3 mg/dL 24-48 h post)
Baker et al,[73] 2003	Iso osmolar/IA	NAC 150 mg/kg (30 min pre); NAC 50 mg/kg in 0.9% saline (4 h post)	1 mL/kg/h 0.9% saline (12 h pre/ 12 h post)	None	80	69/13	13	43	1.8	≥25% increase in SCr at 48 h or 96 h
Briguori et al,[74] 2002	Low/IA	NAC 60 mg po bid (1 d pre/ 1 d post)	0.9% Saline	1 ml/kg/h 0.45% saline (12 h pre/ 12 h post)	183	64/14	14	38	1.5	≥25% increase in SCr at 48 h or the need for dialysis after procedure
Diaz-Sandoval et al,[75] 2002	Low/IA	NAC 600 mg po bid (1 dose pre/3 doses post)	Placebo	1 mL/kg/h 0.45% saline (2-12 h pre/ 12 h post)	54	73/20	20	39	1.6	≥0.5 mg/dL or >25% increase in SCr at 48 h
Drager et al,[76] 2004	Low/IA	NAC 600 mg po bid (2 d pre/ 2 d post)	Placebo	2 mg/kg/h saline (4 h pre/4 h post)	30	65/17	17	38	1.8	None
Durham et al,[77] 2002	Low/IA	NAC 1200 mg po (1 h pre/ 3 h post)	Placebo	1 mL/kg/h 0.45% saline (12 h pre/ 12 h post)	81	71/34	34	48	2.3	≥0.5 mg/dL increase in SCr at 48 h
Efrati et al,[78] 2003	Low/IA	NAC 1 g po bid (1 d pre/ 1 d post)	Placebo	1 mL/kg/h 0.45% saline (12 h pre/ 12 h post)	55	67/10	10	53	1.5	>25% increase in SCr from baseline within 24 or 96 h
Fung et al,[79] 2004	Low/IA	NAC 400 mg po tid (1 d pre/ 1 d post)	None	100 mL/h 0.9% saline (12 h pre/12 h post) unless HF	91	68/30	30	53	2.3	≥0.5 mg/dL increase in SCr or ≥25% decrease in MDRD at 48 h
Goldenberg et al,[80] 2004	Low/IA	NAC 600 mg po tid (1 d pre/ 1 d post)	Placebo	1 mL/kg/h 0.45% saline (12 h pre/ 12 h post)	80	70/18	18	44	2.0	≥0.5 mg/dL increase in SCr at 48 h
Gomes et al,[81] 2005	Low/IA	NAC 600 mg po bid (2 doses pre/ 2 doses post)	Placebo	1 mL/kg/h 0.9% saline (12 h pre/ 12 h post)	156	65/41	41	52	1.3	≥44.2 umol/L increase in SCr at 48 h
Gulel et al,[82] 2005	Low/IA	NAC 600 mg po tid (1 d pre/ 1 d post)	None	1 mL/kg/h 0.9% saline (12 h pre/ 12 h post)	50	61/24	24	32	1.7	>0.5 mg/dL increase in SCr at 48 h
Kay et al,[83] 2003	Low/IA	NAC 600 mg po bid (1 d pre/ 1 d post)	Placebo	1 mL/kg/h 0.9% saline (12 h pre/ 6 h post)	200	69/39	39	38	1.3	>25% increase in SCr at 48 h

(Continued)

Table 3. Study Demographics and Clinical Characteristics: Calcium Channel Blockers and *N*-Acetylcysteine (NAC) (cont)

Source	Osmolality/ Route of Contrast	Intervention Prophylaxis and Regimen	Control Prophylaxis and Regimen	Cointervention and Regimen	No. of Participants	Mean Age, y/ Female, %	Female, %	Diabetic, %	Mean Baseline SCr, mg/dL	Definition of Contrast-Induced Nephropathy
Kotlyar et al,[84] 2005	Low/IA	NAC 300 mg IV (1-2 h pre/2-4 h post x 20 min); NAC 600 mg IV (1-2 h pre/ 2-4 h post x 20 min)	Placebo	200 mL/h 0.9% saline (2 h pre/5 h post)	65	67/17	17	27	1.8	≥0.5 mg/dL increase in SCr at 48 h
MacNeill et al,[85] 2003	Low/IA	NAC 600 mg bid (1 dose pre/1 dose 4 h post and 3 additional doses at 12-h intervals post)	Placebo	Inpatients: 1 mL/kg/h 0.45% saline (12 h pre); day-case patients: 2 mL/kg/h 0.45% saline (4 h pre) 75 mL/h 0.45% saline (12 h post)	57	73/14	14	47	1.9	>25% increase in SCr
Miner et al,[86] 2004	Low/IA	NAC 2000 mg/ dose po bid (4000-6000 mg total)	Placebo	75 mL/h 0.45% saline x 24 h from enrollment	180	70/33	33	68	1.4	≥25% increase in SCr at 48-72 h
Ochoa et al,[87] 2004	Multiple/IA	NAC 1000 mg po (1 h pre/ 4 h post)	Placebo	150 mL/h 0.9% saline (4 h pre/6 h post)	105	71/58	58	55	2.0	≥25% increase in SCr or ≥0.5 mg/dL at 48 h
Oldemeyer et al,[88] 2003	Low/IA	NAC 1500 mg po bid x 48 h (beginning the evening pre)	Placebo	1 mL/kg/h 0.45% saline (12 h pre/ 12 h post)	96	76/45	45	45	1.6	≥25% increase in SCr or ≥0.5 mg/dL increase at 24 or 48 h
Rashid et al,[89] 2004	Low/IA	NAC 1 g IV	Placebo	500 mL 0.9% saline (4-6 h pre/ 4-6 post)	103	70/36	36	32	1.3	≥25% increase in SCr or ≥0.5 mg/dL at 48 h
Shyu et al,[90] 2002	Low/IA	NAC 400 mg po bid (1 d pre/ 1 d post)	Placebo	1 mL/kg/h 0.45% saline (12 h pre/ 23 h post)	121	70/32	32	64	2.8	≥0.5 mg/dL increase in SCr at 48 h
Tepel et al,[91] 2000	Low/IV	NAC 600 mg po bid (1 d pre/ 1 d post)	Placebo	1 mL/kg/h 0.45% saline (12 h pre/ 12 h post)	104	65/43	43	33	2.5	≥0.5 mg/dL increase in SCr at 48 h
Webb et al,[92] 2004	Low/IA	NAC 500 mg IV (1 h pre)	Placebo	1.5 mL/kg/h 0.9% saline (6 h post)	487	70/39	39	35	1.6	>5 mL/min decrease in CG
Briguori et al,[93] 2004	Iso osmolar/IA	NAC 1200 mg po bid (1 d pre/ 1 d post)	NAC 600 mg po bid (1 d pre/ 1 d post)	1 mL/kg/h 0.45% saline (12 h pre/ 12 h post)	223	66/18	18	42	1.6	≥0.5 mg/dL increase in SCr at 48 h or need for dialysis after procedure

Abbreviations: bid, twice daily; CG, Cockcroft and Gault formula for creatinine clearance; HF, hemofiltration; IA, intra-arterial; IV, intravenous; po, by mouth; SCr, serum creatinine; tid, 3 times per day.
SI conversion: to convert SCr to µmol/L, multiply by 88.4.

We identified 10 studies that evaluated the effects of various hydration protocols and diuretics in the incidence of contrast-induced nephropathy. Four studies[38,49,51,54] compared forced diuresis (furosemide and/or mannitol) with hydration, of which 3 showed a significant increase in the rate of contrast-induced nephropathy in the groups receiving diuretics. Two studies[46,47] evaluated bolus intravenous infusions of 0.9% saline (250-300 mL) immediately before or during cardiac catheterization vs slow intravenous hydration 12 hours prior to the procedure. Neither found a significant difference between treatment groups; however, both studies were small (n=39 and n=37) and the event rates were low. Two additional studies[36,50] compared oral hydration with prolonged intravenous hydration (12 hours before and after) and found contradictory results. Taylor et al[50] (n=36) found no difference between treatment groups, although the oral hydration group in this study received 6 hours of intravenous hydration in addition to their oral intake. Trivedi et al[36] (n=53) found that oral hydration alone appeared to be inferior to intravenous hydration with respect to the development of contrast-induced nephropathy (34.6% vs 3.7%; *P*=.005) in patients with normal renal function undergoing cardiac catheterization. Interestingly, the incidence of contrast-induced nephropathy in the oral hydration group was much higher than expected in this patient population.

In addition to timing and route of hydration, other factors, such as fluid tonicity and fluid composition, may also play a role. Single studies supporting the use of isotonic vs half isotonic saline[37] and sodium bicarbonate[48] suggest that isotonic fluids may be superior to hypotonic fluids, likely because of their enhanced ability to expand intravascular volume. Sodium

Table 4. Study Demographics and Clinical Characteristics: Hemodialysis, Hemofiltration, and Other

Source	Osmolality/ Route of Contrast	Intervention Prophylaxis and Regimen	Control Prophylaxis and Regimen	Cointervention and Regimen	No. of Participants	Mean Age, y/ Female, %	Female, %	Diabetic, %	Mean Baseline SCr, mg/dL	Definition of Contrast-Induced Nephropathy
Hemodialysis										
Frank et al,[94] 2003	Low/IA	HD 1.3 m^2 (500 mL/min) (10 min pre/ 4 h during)	Hydration	1000 mL 0.9% saline (6 h pre/6 h post)	17	61/18	18	65	4.1	None
Lehnert et al,[95] 1998	Low/IA	HD (on average 63 min post x 3 h)	None	83 mL/h 0.9% saline (12 h pre/ 12 h post); 10 mg nitrendipine (12 h pre) (if no Ca^{2+})	34	62/17	17	43	2.4	≥0.5 mg/dL increase in SCr at 48 h
Sterner et al,[96] 2000	Low/IA	HD 200 mL/min (x 4 h 2-3 h post)	None	10 mg po nifedipine (1 h pre); 2-2.5 L fluid po or IV (12 h pre); 2.5 L fluid po or IV (24 h post)	32	68/0		53	3.3	None
Vogt et al,[97] 2001	Low/both IA and IV	HD 3.1 h on average (30-280 min post)	1 mL/kg/h (12 h post)	1 mL/kg/h 0.9% saline (12 h pre)	113	69/40	40	32	3.5	>1.5 mg/dL SCr increase or >50% SCr at 1-6 d, >0.5 mg/dL SCr increase or >25% SCr
Hemofiltration										
Marenzi et al,[98] 2003	Low/IA	HF (4-6 h pre/ 18-24 h post)	1 mL/kg/h 0.9% saline (6-8 h pre/ 24 h post) (0.5 mL/kg/h if EF<40%)	None	114	69/22	22	30	3.1	≥25% increase in SCr
Marenzi et al,[99] 2006	Low/IA	1 mL/kg/h 0.9% saline (6 h pre); HF (18-24 h post); HF (6 h pre/ 18-24 h post)	1 mL/kg/h 0.9% saline (12 h pre/ 12 h post) (if poorly tolerated, then 0.5 mL/kg/h)	None	92	72/29	29	30	3.6	≥25% increase in SCr
Other										
Albert et al,[100] 1994	Multiple/IA	ATP-$MgCl_2$ 30 mg/kg 20% $MgCl_2$ H_2O 0.1-0.25 mg/kg/min (20 min pre x 120 min)	Placebo	1-1.5 L IV saline (pre); 75-100 mL/h IV saline (4+ h post)	18	62/17	17	22	3.2	>1.0 mg/dL increase in SCr or decrease in renal clearance of DTPA >2 SE
Gupta et al,[101] 1999	High/IA	Captopril 25 mg po tid (1 h pre/ 3 d post) (every 8 h)	None	1 mL/kg/h, saline (3 h pre/6 h post)	71	56/10	10	100	1.4	≥0.5 mg/dL increase in SCr at 24 h
Koch et al,[102] 2000	Multiple/ Both IA and IV	PGE_1 10 ng/kg/min (1 h pre x 6 h); PGE_1 20 ng/kg/min (1 h pre x 6 h) PGE_1 40 ng/kg/min (1 h pre x 6 h)	Placebo	2000 mL saline IV or po fluids (24 h pre/ 24 h post)	130	67/34	34	47	2.2	≥0.5 mg/dL increase in SCr at 48 h post, ≥1.0 mg/dL increase in SCr at 48 h post, ≥1.5 mg/dL increase in SCr at 48 h post
Kurnik et al,[103] 1998	Multiple/ Both IA and IV	Anaritide 0.01 µg/kg/min (30 min pre/ 30 min post); Anaritide 0.05 µg/kg/min (30 min pre/ 30 min post); Anaritide 0.1 µg/kg/min (30 min pre/ 30 min post)	Placebo	1.5 mL/kg/h 0.45% saline (12 h pre/ 12 h post)	249	66/28	28	50	2.1	≥25% increase in SCr or ≥0.5 mg/dL at 48 h

(Continued)

Table 4. Study Demographics and Clinical Characteristics: Hemodialysis, Hemofiltration, and Other (cont)

Source	Osmolality/ Route of Contrast	Intervention Prophylaxis and Regimen	Control Prophylaxis and Regimen	Cointervention and Regimen	No. of Participants	Mean Age, y/ Female, %	Female, %	Diabetic, %	Mean Baseline SCr, mg/dL	Definition of Contrast-Induced Nephropathy
Liss et al,[104] 2005	Low/IA	CO_2 IV 40-50 mL (usually repeated 2-3 times 5 min)	None	300-500 mL saline	82	67/45	45	17	1.4	>25% increase in SCr within 1 wk
Miller et al,[105] 2003	Low/IA	L-Arginine 20 g (20-30 min pre)	Placebo	100 mL/h 0.45% saline (12 h pre/ 12 h post); diazepam 2.5 mg and nitroglycerin 300 µg (pre)	42	71/26	26	26	2.5	None
Russo et al,[106] 1995	Multiple/IV	Captopril 50 mg po (20 min pre); Nifedipine 10 mg sublingual (10 min pre)	None	15 mL/kg po tap water (on d) and "more" tap water (post), depending on urine output	21	51/48	48	0	2.7	None
Spargias et al,[10] 2004	Multiple/IA	Ascorbic acid 3 g po (2 h pre/ 2 g po the night and morning post)	Placebo	50-125 mL/h 0.9% saline (from randomization to 6 h post)	238	66/8	8	25	1.4	≥0.5 mg/dL increase in SCr or ≥25% increase 2-5 d
Wang et al,[107] 2000	Low/IA	SB 209670 100 µg/kg x 10 min and infusion 1.0 µg/kg/min (30-150 min pre)	Placebo	1 mL/kg/h 0.45% saline (2-12 h pre/ 12 h post)	158	66/30	30	63	2.8	≥0.5 mg/dL or ≥25% increase in SCr at 48 h

Abbreviations: ATP-$MgCl_2$, adenosine triphosphate-magnesium chloride; DTPA, diethylenetriamine pentaacetic acid; EF, ejection fraction; HD, hemodialysis; HF, hemofiltration; IA, intra-arterial; IV, intravenous; PGE_1, prostaglandin E_1; po, by mouth; SB 209670, endothelin A and B receptor antagonist; SCr, serum creatinine; tid, 3 times per day.
SI conversion: to convert SCr to µmol/L, multiply by 88.4.

bicarbonate may provide additional renoprotection by alkalinizing renal tubular fluid and thereby minimizing tubular damage.

In summary, there is suggestive, but incomplete, evidence supporting the use of hydration as a prophylaxis measure for contrast-induced nephropathy. Questions still remain about whether all patients benefit equally from this treatment, as well as the optimal type, route, volume, and timing of hydration administration. Although hydration is a generally benign therapy, it is logistically challenging to implement, as most angiographic procedures are performed on outpatients (in whom 6 to 12 hours of preprocedural hydration may not be possible). These issues deserve further study.

Vasodilators

Dopamine/Fenoldopam. The benefits of vasodilation and increased renal blood flow associated with "renal dose" dopamine were studied in 4 RCTs,[52-54,60] evaluating a variety of patients with both normal and impaired baseline renal function. While not directly comparable (all used different definitions of contrast-induced nephropathy), none showed a benefit of dopamine administration. Currently, there is no basis for the use of dopamine in preventing contrast-induced nephropathy.

Fenoldopam, a dopamine-1 receptor agonist with vasodilatory properties, has also been extensively studied. Three randomized trials[55,58,59] (416 participants) have compared fenoldopam with placebo. The relative risk of contrast-induced nephropathy in one trial favored fenoldopam[55] but was not significant. Continued interest in fenoldopam has persisted, despite the lack of benefit shown in the CONTRAST trial.[58] Additional randomized studies comparing fenoldopam with *N*-acetylcysteine[56,57] found no benefit associated with the use of fenoldopam.

Critics argue that the doses of dopamine and fenoldopam used in these trials may have been insufficient to produce renal vasodilation.[109] Despite this, we do not feel that further studies are warranted, given the significant adverse effect profile of these drugs (ie, dopamine: arrhythmias; fenoldopam: systemic hypotension) and the difficulties associated with intravenous administration.

Theophylline. Small studies of theophylline as a potential prophylaxis agent for contrast nephropathy have yielded conflicting results. To date there have been 9 trials[60-68] (601 participants) comparing theophylline or aminophylline with no active treatment. Relative risks for contrast-induced nephropathy ranged from 0.07 to 1.7 (median, 0.25). Three of 5 favored theophylline (one was statistically significant). Differences in mean change from baseline in SCr level between treatment groups ranged from –0.29 to 0 mg/dL (median, –0.14 mg/dL). Six of 8 trials reporting outcomes of contrast-induced nephropathy or a change in SCr favored theophylline/aminophylline therapy (2 were statistically significant).

Meta-analysis has identified considerable heterogeneity among the studies.[110] There was variability in the inclusion criteria, the method and schedule of theophylline/aminophylline administration, hydration protocols, and the type of contrast adminis-

tered. Few of the trials compared the incidence of adverse events between treatment groups. We are unable to recommend theophylline as a prophylaxis agent based on the currently available data.

Calcium Channel Blockers/Other Agents. Three small RCTs of calcium channel blockers vs placebo[69-71] (240

Table 5. Quality Assessment of the Included Studies

Source	Concealed Treatment Allocation	Double-Blind	Intention-to-Treat	Description of Loss to Follow-up	Loss to Follow-up, %	Funding
Abizaid et al,[60] 1999	NR	N	N	Y	0	Public
Albert et al,[100] 1994	NR	Y	Y	N	NR	Public
Allaqaband et al,[55] 2002	NR	N	N	Y	2	NR
Arici et al,[69] 2003	NR	N	N	Partial	7	NR
Azmus et al,[72] 2005	NR	Y	N	Y	4	NR
Bader et al,[46] 2004	NR	N	Y	N	NR	NR
Baker et al,[73] 2003	NR	N	Y	Y	4	Public
Briguori et al,[74] 2002	NR	N	N	N	NR	NR
Briguori et al,[93] 2004	NR	N	N	Y	0.4	NR
Briguori et al,[56] 2004	NR	N	N	Y	2	NR
Carraro et al,[70] 1996	NR	Y	N	Partial	6	NR
Diaz-Sandoval et al,[75] 2002	Y	Y	N	N	NR	NR
Drager et al,[76] 2004	NR	Y	N	Y	20	NR
Durham et al,[77] 2002	NR	N	N	Y	2	NR
Efrati et al,[78] 2003	NR	Y	N	Partial	11	Public
Erley et al,[61] 1994	NR	Y	N	Y	5	NR
Erley et al,[62] 1999	NR	Y	N	Y	20	NR
Frank et al,[94] 2003	NR	N	N	N	NR	Public
Fung et al,[79] 2004	Y	N	Y	Y	0	NR
Gandhi et al,[63] 1992	NR	N	N	N	NR	NR
Gare et al,[52] 1999	Y	Y	N	Y	3	Public
Goldenberg et al,[80] 2004	Y	Y	N	Y	0	NR
Gomes et al,[81] 2005	Y	Y	N	N	NR	NR
Gulel et al,[82] 2005	NR	N	N	N	NR	NR
Gupta et al,[101] 1999	NR	N	N	N	NR	NR
Hans et al,[53] 1998	NR	N	N	N	NR	Public
Huber et al,[64] 2002	NR	Y	N	N	NR	NR
Huber et al,[65] 2003	NR	N	N	N	NR	NR
Kapoor et al,[66] 2002	NR	N	N	N	NR	NR
Katholi et al,[67] 1995	NR	N	N	N	NR	Private
Kay et al,[83] 2003	NR	Y	Y	Y	4	Mixed
Khoury et al,[71] 1995	Y	N	N	Partial	23	Public
Koch et al,[102] 2000	NR	Y	N	Y	10	NR
Kolonko et al,[68] 1998	NR	Y	N	N	NR	NR
Kotlyar et al,[84] 2005	Y	N	N	Partial	8	Mixed
Krasuski et al,[47] 2003	NR	N	N	Y	10	NR
Kurnik et al,[103] 1998	NR	Y	N	Partial	4	Private
Lehnert et al,[95] 1998	NR	N	N	Y	12	Private
Liss et al,[104] 2005	NR	N	Y	N	NR	Public
MacNeill et al,[85] 2003	NR	Y	N	Partial	25	NR
Marenzi et al,[98] 2003	NR	N	N	Y	0	Public
Marenzi et al,[99] 2006	NR	N	N	N	NR	NR
Merten et al,[48] 2004	Y	N	N	Y	13	Public
Miller et al,[105] 2003	NR	Y	N	N	NR	NR
Miner et al,[86] 2004	NR	Y	Y	Partial	14	NR
Mueller et al,[37] 2002	NR	N	N	Y	15	NR
Ng et al,[57] 2006	NR	N	Y	Partial	12	NR
Ochoa et al,[87] 2004	NR	Y	Y	Partial	24	Public
Oldemeyer et al,[88] 2003	NR	Y	N	N	NR	NR
Rashid et al,[89] 2004	Y	Y	N	Partial	9	NR
Russo et al,[106] 1995	NR	N	N	N	NR	Public
Shyu et al,[90] 2002	NR	Y	N	N	NR	Public
Solomon et al,[38] 1994	NR	N	N	Y	0	Private
Spargias et al,[10] 2004	Y	Y	Y	Y	3	NR
Sterner et al,[96] 2000	NR	N	N	N	NR	NR
Stevens et al,[49] 1999	Y	N	Y	Partial	2	Public
Stone et al,[58] 2003	Y	Y	Y	Y	10	Private
Taylor et al,[50] 1998	Y	N	N	Y	0	Public
Tepel et al,[91] 2000	NR	N	Y	N	NR	NR
Trivedi et al,[36] 2003	NR	N	Y	Y	0	Public
Tumlin et al,[59] 2002	Y	Y	N	N	NR	Mixed
Vogt et al,[97] 2001	NR	N	N	Y	7	Public
Wang et al,[107] 2000	Y	Y	N	Partial	16	Private
Webb et al,[92] 2004	Y	Y	Y	Y	18	Mixed
Weinstein et al,[51] 1992	NR	N	N	N	NR	Public
Weisberg et al,[54] 1994	NR	Y	N	Y	0	Public

Abbreviations: Mixed, both public and private funding sources; NR, not reported; N, no; Y, yes.

participants in total) in patients with normal renal function who received contrast media showed no difference between treatment groups. However, these trials lacked sufficient statistical power to detect clinically significant outcomes. Small underpowered trials of other agents with vasodilating properties such as atrial natriuretic peptide,[103] an endothelin antagonist,[107] prostaglandin E_1,[102] angiotensin-converting enzyme inhibitors,[101,106] and L-arginine[105] have shown no benefit, and in some cases, potential harm[107] with the use of these agents.

Antioxidants

N-Acetylcysteine. *N*-acetylcysteine has been the most widely studied of all prophylaxis strategies, although the mechanism for its purported nephroprotective action is unclear. *N*-acetylcysteine might act by scavenging oxygen free radicals[111,112] or by enhancing the vasodilatory effects of nitric oxide.[113]

We identified 22 trials[72-93] (2918 participants) comparing *N*-acetylcysteine with placebo. Relative risks for contrast-induced nephropathy ranged from 0.11 to 1.5 (median, 0.72). Eleven of 20 trials that reported contrast-induced nephropathy and 13 of 20 trials that reported a change in SCr level as an outcome favored *N*-acetylcysteine prophylaxis (5 were statistically significant). Differences in treatment means in change from baseline SCr ranged from –0.6 to 0.1 mg/dL (median, –0.03 mg/dL). Negative values confer lesser reductions or larger improvements in renal function in the *N*-acetylcysteine groups.

Twelve meta-analyses have been published on this topic to date.[114-125] Nine have presented pooled risk estimates suggesting benefit, but most have found significant unexplained heterogeneity in the analyses leading to inconclusive results. Differences in contrast media, definitions of contrast-induced nephropathy, patient selection (undocumented differences in comorbidity), cointerventions, *N*-acetylcysteine dose and route of administration, as well as the timing of the procedure (urgent vs elective) may have contributed to the heterogeneity observed in the pooled analyses. New trials that address these issues are required before a final conclusion can be reached. We believe that the available data do not allow definitive conclusions about the efficacy of *N*-acetylcysteine for prevention of contrast nephropathy.

Ascorbic Acid. The results of a double-blind RCT evaluating the use of the antioxidant ascorbic acid[10] to prevent contrast-induced nephropathy in 231 patients undergoing coronary angiography are encouraging and deserve further study. The authors defined contrast-induced nephropathy by a 25% or higher rise in SCr level 2 to 5 days postprocedure and found that ascorbic acid significantly reduced the risk of this outcome (odds ratio, 0.38; 95% confidence interval, 0.17-0.85).

Extracorporeal Removal of Contrast

Hemodialysis effectively removes radiocontrast[126-128] and has been proposed as a prophylaxis treatment for contrast-induced nephropathy. Four small randomized trials have considered this question in patients with impaired renal function.[94-97] Two found no benefit and the largest (n=113) suggested that hemodialysis was harmful, since more patients in the treatment group required ongoing dialytic support.[97]

On the other hand, one group has reported that hemofiltration dramatically reduces the risk of contrast-induced nephropathy compared with hydration alone in 2 randomized trials of patients with impaired renal function.[98,99] While encouraging, the provision of hemofiltration is invasive and impractical except in those at very high risk of contrast-induced nephropathy. A recent economic analysis[129] suggests that hemofiltration may be cost-effective in patients with a baseline SCr measurement greater than 265 µmol/L if the magnitude of risk reduction seen in these studies is reproducible. The apparent benefits of hemofiltration need to be replicated in another center before it can be widely recommended.

SUGGESTED MANAGEMENT STRATEGY

Given the relatively low incidence of contrast-induced nephropathy, it would be impractical and costly to routinely measure SCr levels for all patients scheduled for diagnostic procedures requiring parenteral contrast administration. Guidelines published by the European Society of Urogenital Radiology suggest that all patients referred for contrast-enhanced diagnostic examinations should be asked about a history of renal disease, diabetes, proteinuria, renal surgery, hypertension, and/or gout.[130] Given the identification of left ventricular function as a predictor of contrast-induced nephropathy in several retrospective analyses,[16,17] we believe that a history of CHF should also be sought. Patients with any of these conditions and all patients undergoing angiographic procedures should have an SCr measurement within 7 days in advance of the scheduled examination. The detection of abnormal renal function with or without diabetes and CHF constitute high risk for contrast-induced nephropathy. In our opinion, those patients requiring urgent procedures before renal function can be measured should also be considered high risk. Our recommended management strategy for patients with risk factors for contrast-induced nephropathy is presented in the FIGURE.

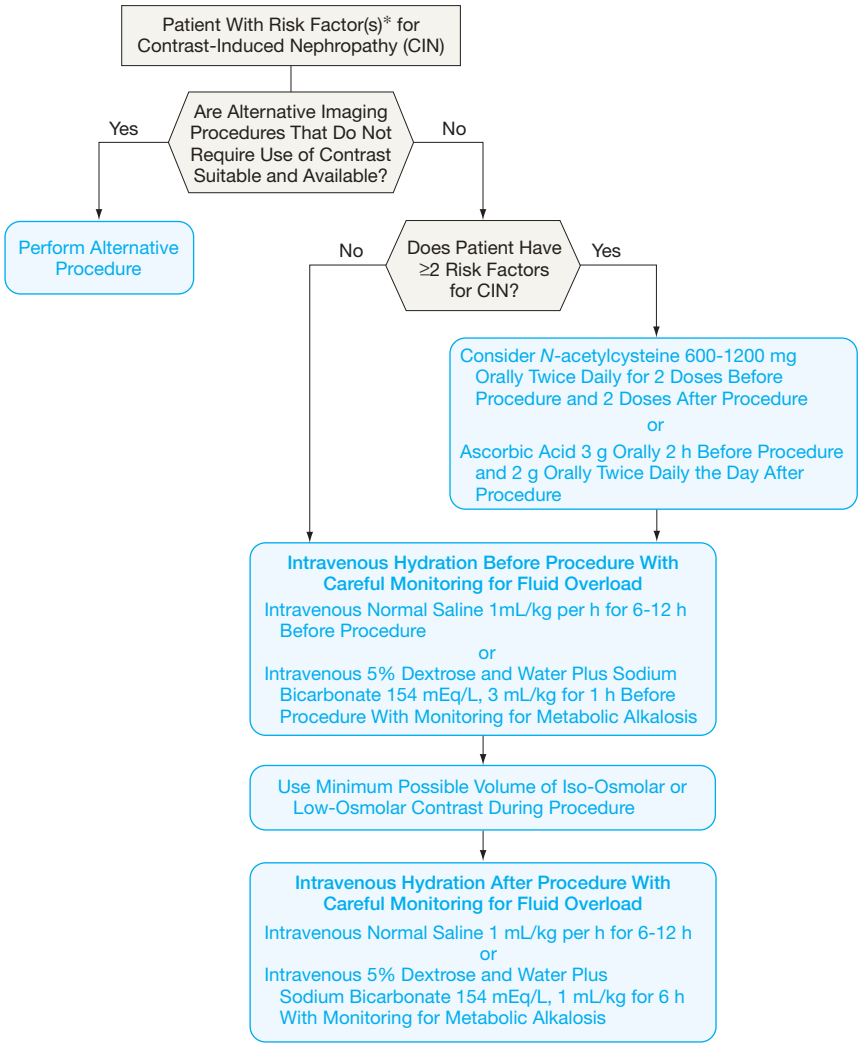
FUTURE DIRECTIONS

The discovery of novel therapies for the prevention of contrast-induced nephropathy has been hampered by an incomplete understanding of its pathophysiology. Experimental and preclinical studies should remain a priority for investigators working in this field. However, existing trials evaluating currently available therapies also have significant limitations. Our review of the literature has identified 4 main problems with the randomized studies to date: (1) variation in the definition of contrast-induced nephropathy; (2) inability to accurately identify high-risk patients; (3) inconsistency in the ad-

ministration of cotherapies like hydration; and (4) small sample sizes with suboptimal study designs.

Perhaps the most problematic issue is the wide variation in the definition of contrast-induced nephropathy. No standard definition has been used in clinical trials, and the clinical relevance of commonly used definitions (such as a 25% or ≥0.5 mg/dL [44.2 µmol/L] increase in SCr) remains unknown. While even modest increases in SCr have been associated with an increase in in-hospital and long-term mortality, it is hard to imagine a pathophysiological link between the two, unless the development of contrast-induced nephropathy is simply a marker for underlying comorbidity. Furthermore, no convincing data demonstrate that reducing the incidence of contrast nephropathy reduces the incidence of adverse outcomes. Therefore, we recommend development and adoption of a consensus definition of contrast-induced nephropathy based on more clinically relevant criteria. One example of such a definition might be the composite of doubling in SCr or the requirement for dialysis.

Figure. Strategy for Management of Patients With Risk Factors for Contrast-Induced Nephropathy



*See Box for listing of risk factors for contrast-induced nephropathy.

Second, study investigators have been unable to accurately identify high-risk patients for enrollment in contrast-induced nephropathy prophylaxis studies. Even among patients with preexisting renal impairment, the reported incidence of contrast-induced nephropathy varies between 20% and 50%. Further studies are required to identify additional risk factors for contrast-induced nephropathy and validate and refine existing risk scores. This information can be used to select high-risk patients for inclusion in future studies, thus increasing statistical power and the likelihood of obtaining useful information.

Third, clinical trials have been inconsistent in the administration of cointerventions such as hydration. In addition, the risk imposed by choice of radiocontrast agent and the route of administration has been largely ignored in clinical trials to date. We recommend that future trials ensure equal use of cointerventions between study groups, and that the type of contrast media be standardized.

Fourth, most studies have been small, often poor in quality (Table 5), and usually underpowered to detect a clinically significant difference in outcome. Future studies should be powered to detect differences in clinically meaningful outcomes such as mortality, the need for dialysis, or resource use. A large-scale multicenter study would likely be needed to accrue a sufficient number of patients. We discourage further attempts at small randomized studies, as they use valuable limited research resources yet generally do not yield definitive results. Unfortunately, there is little incentive for pharmaceutical companies to sponsor large clinical studies, as the interventions that have been proposed are unlikely to generate significant revenue. Further investigation in this area will probably need to be funded by national funding bodies.

CONCLUSIONS

In summary, contrast-induced nephropathy is a common condition that

is associated with adverse outcomes and substantial resource use. Despite the clinical importance of contrast-induced nephropathy, much remains to be known about how best to prevent it. Well-designed and adequately powered randomized trials are urgently needed to study fundamental issues such as the optimal type, route, volume, and timing of hydration, as well as the role of other commonly advocated prophylaxis strategies such as *N*-acetylcysteine and fenoldopam.

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Study concept and design: Pannu, Wiebe, Tonelli.
Acquisition of data: Pannu, Wiebe, Tonelli.
Analysis and interpretation of data: Pannu, Wiebe, Tonelli.
Drafting of the manuscript: Pannu, Wiebe.
Critical revision of the manuscript for important intellectual content: Pannu, Wiebe, Tonelli.
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