Contrast-induced nephropathy: Pharmacological prophylaxis

C Briguori[1,2] and G Marenzi[3]

[1]Laboratory of Interventional Cardiology, Clinica Mediterranea, Naples, Italy; [2]Laboratory of Interventional Cardiology, 'Vita e Salute' University School of Medicine, San Raffaele Hospital, Milan, Italy and [3]Centro Cardiologico Monzino, Institute of Cardiology, University of Milan, Milan, Italy

Contrast media-associated acute renal failure represents the third most common cause of in-hospital renal function deterioration after decreased renal perfusion and post-operative renal insufficiency. Although generally benign, this complication is associated with a mortality rate ranging from 3.8 to 64%, depending on the increase of creatinine concentration. Multiple drugs have been tested in an attempt to prevent this complication. Central to the pathophysiology of contrast-induced nephrotoxicity (CIN) is an alteration in renal hemodynamics. In an effort to reverse these hemodynamic changes, vasodilators and diuretics have been tested as prophylactic drugs. However, their effectiveness has not been confirmed. Recently, considerable interest has resulted from the initial positive data on the effectivess of prophylactic administration of antioxidant compounds, such as acetylcysteine and ascorbic acid. In this review, we focus on the effectiveness of pharmacologic therapies for preventing CIN.

Kidney International (2006) **69,** S30–S38. doi:10.1038/sj.ki.5000372

KEYWORDS: contrast media; kidney; prevention; complications

Correspondence: *C Briguori, Interventional Cardiology, Clinica Mediterranea, Via Orazio, 2, I-80121, Naples, Italy. E-mail: briguori.carlo@hsr.it*

ANTIOXIDANT STRATEGY

In the last years, many clinical studies have been conducted with the use of antioxidant compounds in an attempt to prevent contrast-induced nephrotoxicity (CIN). The two most investigated drugs are (a) acetylcysteine and (b) ascorbic acid.

N-acetylcysteine

N-acetylcysteine (NAC), a potent antioxidant that scavenges a wide variety of oxygen-derived –free radicals, may be capable of preventing CIN, both by improving renal hemodynamics and by preventing direct oxidative tissue damage.[1–3] NAC is classically known as a mucolytic agent, which is used to thin mucus, especially in patients with respiratory problems such as emphysema and bronchitis and cystic fibrosis. Animal experiments have shown that NAC inhibits the renal ischemia-induced reduction of c-fos and c-jun expression and the renal ischemia-induced increase of Jun NH_2 terminal kinase activity.[1] A potential mechanism of NAC in preventing CIN is the prevention of direct oxidative tissue damage by scavenging reactive oxygen species; this antioxidant effect seems to be dose-dependent. Efrati *et al.*[4] demonstrated that treatment with NAC results in an increase in nitric oxide production as compared to the decrease observed in the control group after contrast agent administration. Renal vasoconstriction, possibly mediated by alterations in nitric oxide, and a direct toxic effect of contrast media agents have been implicated in the pathogenesis of CIN. Contrast agents can cause a direct tubular injury, leading to the generation of oxygen-free radicals, which in turn react with nitric oxide to produce peroxynitrite. Peroxynitrite is a potent oxidant that further decreases nitric oxide bioavailability and results in more tissue injury.

Tepel *et al.*[5] first reported that NAC (600 mg orally twice daily) plus hydration before and after administration of contrast agent is more effective than hydration alone in preventing CIN in patients with chronic renal insufficiency who were undergoing computed tomography with a constant dose (75 ml) of a nonionic, low-osmolality contrast agent. In a prospective study using the contrast agent, 83 patients with chronic renal insufficiency (average serum creatinine (sCr) concentration of 2.5 mg/dl or 216 μmol/l) were randomized

Table 1 | Clinical studies on the prophylactic use of NAC to prevent CIN

Author	Number of pateints	Design	Baseline sCr (mg/dl)	NAC dose and route of administration	CIN in the NAC group (%)	CIN in the control group (%)	Effect of NAC	Volume of Contrast dye (ml)
Tepel[5]	83	RPCT	2.5±1.3	600 mg b.i.d. OS, day before and after	2	21	+	75
Diaz-Sandoval[6]	54	BRPCT	1.6±0.4	600 mg b.i.d. OS 1 dose before and 3 after	8	45	+	184±10
Shyu[7]	121	RPCT	2.8±0.8	400 mg b.i.d. OS, day before and after	3.3	24.6	+	117±25
Kay[8]	200	BRPCT	1.25[a] (0.70–3.30)	600 mg b.i.d. OS, day before and after	4	12	+	125 (70–320)[a]
Briguori[9]	183	RCT	1.5±0.4	600 mg b.i.d. OS, day before and after	6.5	11	Null	197±135
Allaqaband[10]	123	RCT	2.1±0.8	600 mg b.i.d. OS, day before and after	17.7	15.3	Null	125±65
Durham[11]	79	RPCT	1.6±0.7	1200 mg b.i.d. OS, 1 h before and 3 h after	26.3	22	Null	81±39
Webb[12]	447	BRPCT	2.2±0.4	500 mg i.v., 1 h before	7.3	5.7	Null	120 (80–175)[a]
Boccalandro[13]	181	CT	1.8±0.5	600 mg b.i.d. OS day before and after	13	12	Null	191±130
Goldenberg[14]	80	BRPCT	2.0±0.4	600 mg b.i.d. OS day before and after	10	8	Null	116±45
Oldemeyer[15]	96	BRPCT	1.6±0.7	1500 mg b.i.d. OS, day before and after	8.2	6.4	Null	130±72
Baker[16]	80	RCT	1.8±0.5	150 mg/kg over 30 min immediately before and 50 mg/kg over 4 h	5	21	+	230±158
Miner[20]	180	BRPCT	1.4±0.6	2000 mg OS, one dose before and and two doses after	9.6	22.2	+	347±199

BRPCT=double-blinded, randomized, placebo-controlled trial; RPCT=randomized, placebo-controlled trial; RCT=randomized-controlled trial, placebo-controlled trial; CT=controlled trial; NAC=*N*-acetylcysteine; CIN=contrast-induced nephrotoxicity.
[a]median (interquatile range); sCr=serum creatinine concentration.

to either NAC (600 mg p.o. b.i.d. administered the day before and the day of the procedure) plus intravenous saline (0.45% at 1 ml/kg per hour for 12 h before and 12 h after the procedure) or to placebo plus saline. At 48 h after the administration of non-ionic low-osmolality contrast media, an elevation of the serum creatinine $\geqslant$0.5 mg/dl (44 μmol/l) was much less common in the NAC group (2 versus 21%, $P=0.01$). Gastrointestinal discomfort and dizziness, the only adverse effects found, were reported in both randomized groups. Other studies eventually confirmed[5–8] and refuted[9–15] this preliminary observation (Table 1). Some data also exist on the beneficial effect of a rapid protocol of intravenous NAC (150 mg/kg in 500 ml normal saline over 30 min immediately before contrast, followed by 50 mg/kg in 500 ml normal saline over 4 h).[16]

It has been pointed out that the advantage of NAC administration was based on a decrease in sCr concentration. This decrease in sCr concentrations might reflect either an increase in creatinine excretion or a decrease in creatinine production attributable to NAC or interference by NAC with the method of creatinine determination. Hoffmann *et al.*[17] demonstrated an effect of NAC on creatinine levels and estimated glomerular filtration rate, surrogate markers of renal injury, without any effect on cystatin C levels (another surrogate marker of renal injury). In contrast, Izzedine *et al.*[18] reported that the effect of NAC on contrast media nephrotoxicity was not related to an analytical interaction between creatinine and NAC.

Some evidence exists that the effect of NAC on CIN is dose-dependent.[19–20] Briguori *et al.*,[19] in a prospective, randomized trial enrolling 223 patients with baseline creatinine level $\geqslant$1.5 mg/dl, referred for coronary procedures and randomly administered NAC at the standard dose (600 mg orally twice daily; SD group) or at a double dose (1200 mg orally twice daily; DD group) before and after a non-ionic, low-osmolality contrast dye administration. CIN occurred in 12/109 patients in the SD group (11%) and 4/114 patients in the DD group (3.5%) ($P=0.038$; odds ratio (OR) = 0.29; 95% confidence interval (95% CI) 0.09–0.94).

Owing in part to these controversies, the overall prophylactic efficacy of NAC has been assessed in multiple meta-analyses.[21–26] Birck *et al.*[21] reported a primary analysis performed among eight randomized controlled trials that enrolled 885 patients. Compared with hydration alone, NAC plus hydration significantly reduced the risk of developing CIN after contrast administration among those with chronic renal insufficiency (OR = 0.41, 95% CI 0.22–0.79). However, this overall effect must be viewed in the context of the marked variability in individual risk. In the meta-analysis by

Alonso *et al.*[22] including eight randomized trials and 885 patients, the authors concluded that NAC appears to be a beneficial preventive agent for CIN. However, this benefit was observed only in patients with a mean baseline creatinine level <1.9 mg/dl or administered more than 140 ml of contrast media. A third meta-analysis by Pannu *et al.*[23] included 14 studies encompassing a total of 1776 patients, and demonstrated a borderline significant risk reduction for CIN associated with NAC treatment (OR = 0.65; 95% CI 0.43–1.00; $P = 0.049$). In the meta-analysis by Kshirsagar *et al.*,[24] 16 randomized trials with a total of 1538 patients were included. They concluded that the heterogeneity of the current literature limits any meaningful conclusion on the benefit of NAC for CIN. In the meta-analysis by Isenbarger *et al.*,[25] seven studies selected from 19 were included, involving 805 study subjects. Excluded studies were either not randomized clinical trials ($n = 10$) or published only as abstracts (not peer-reviewed, $n = 2$). The odds of developing CIN were significantly lower in the NAC group (summary OR = 0.37; 95% CI 0.16–0.84). The summary risk difference was −0.11 (95% CI −0.19 to −0.03), which corresponds to a number of needed-to-treat patients of nine (95% CI 5–33). In other words, nine patients would have to be treated with NAC to prevent one episode of CIN.

Ascorbic acid

Additional evidence of the effectiveness of an antioxidant strategy comes from the recent observation by Spargias *et al.*,[27] who investigated the impact of ascorbic acid in preventing CIN. The antioxidant ascorbic acid has been shown to attenutate renal damage caused by a variety of insults, such as post-ischemic stress, cisplatin, aminoglycosides, and potassium bromate in animals and has an extensive safety record as a dietary supplement in humans. Spargias *et al.* conducted a randomized, double-blind, placebo-controlled trial of ascorbic acid in 231 patients with a sCr concentration $\geqslant 1.2$ mg/dl who underwent coronary angiography and/or intervention. Ascorbic acid, 3 g at least 2 h before the procedure and 2 g the night and the morning after the procedure, or placebo was administered orally. Hydration with 50–125 ml/h i.v. normal saline was started in all patients from randomization until at least 6 h after the procedure. CIN (defined by an absolute increase of serum creatinine $\geqslant 0.5$ mg/dl or a relative increase of $\geqslant 25\%$, measured 2–5 days after the procedure) occurred in 11 of the 118 patients (9%) in the ascorbic acid group and in 23 of the 113 patients (20%) in the placebo group (OR = 0.38; 95% CI 0.17–0.85; $P = 0.02$). The mean sCr concentration increased significantly in the placebo group (from 1.36 ± 0.50 to 1.50 ± 0.54 mg/dl, $P < 0.001$) and non-significantly in the ascorbic acid group (from 1.46 ± 0.52 to 1.52 ± 0.64 mg/dl, $P = 0.07$). The mean increase in sCr concentration was greater in the placebo group than in the ascorbic acid group (difference of 0.09 mg/dl; 95% CI, 0.00–0.17; $P = 0.049$). The authors conclude that prophylactic oral administration of ascorbic acid may protect against CIN in high-risk patients undergoing a coronary procedure.

INHIBITION OF RENAL VASOCONSTRICTION

Owing to the potential role of hemodynamic effects induced by contrast agents, numerous vasodilators drugs have been tested for prevention of acute reduction in renal function. The possible importance of endothelin-induced renal vasoconstriction led to the evaluation of a non-selective *endothelin receptor antagonist* in a multicenter, double-blind randomized trial of high-risk patients undergoing coronary angiography.[28] Compared with those randomized to placebo, a significantly higher percentage of patients who received active therapy sustained CIN (56 versus 29%; $P = 0.002$). However, this study evaluated a mixed endothelin A and B receptor antagonist, and this disappointing result may tentatively be explained by endothelin B receptor inhibition that favors vasoconstriction. To date, it is unknown whether selectìve endothelin A blockade may be beneficial in preventing CIN.

Atrial natriuretic peptide has been considered for prophylaxis in high-risk patients as its administration has been associated with benefits in animal models of CIN.[29] However, no benefit was observed with the intravenous administration of this agent in a large multicenter, prospective, double-blind, placebo-controlled randomized trial.[30]

Calcium channel blockers (Table 2) such as verapamil, diltiazem,[31] and amlodipine[32] have been found to attenuate the renal vasoconstrictor response to radiocontrast media, and to inhibit CIN in rats. A randomized, placebo-controlled study of 35 patients with renal insufficiency has shown that oral nitrendipine (20 mg/day for 3 days) is effective for preventing the decrease in glomerular filtration rate.[33] In contrast, other studies with nitrendipine,[34] felodipine,[35] and amlodipine[36] did not confirm the beneficial effects of calcium antagonists in prevention of CIN. However, it must be emphasized that only dihydropyridine calcium channel blockers have been clinically tested so far.[33–41] These agents have a more potent peripheral vasodilating effect than verapamil and diltiazem. Therefore, a possible protective renal effect from calcium channel inhibition might be offset by the hypotensive effect caused by these drugs with resulting lower renal perfusion pressure. Further investigation is needed to evaluate possible effects of using different calcium channel antagonist agents. Currently, the use of calcium channel blockers to prevent CIN is not recommended. However, their discontinuation at the time of contrast exposure is not required in patients taking these drugs for other indications.

Prostaglandin E_1 (PGE) has vasodilatory effects and may be promising as a prophylactic agent against CIN, but further studies are needed to confirm the effectiveness of this agent. In one study, 130 patients with renal insufficiency (sCr $\geqslant 1.5$ mg/dl) were randomly assigned to receive either placebo or one of three doses of PGE (10, 20, and 40 ng/kg/min for 6 h) in addition to intravenous hydration before and after contrast exposure.[42] The increase in sCr was smaller in all the three PGE groups than in placebo group, but the difference was significant only in the medium-dose PGE

Table 2 | Clinical studies on the prophylactic use of CCBs to prevent CIN

Author, year	Number of patients	Randomized	Baseline sCr (mg/dl)	CCB and dose	CIN in the CCBs group (%)	CIN in the control group (%)	Effect of CCBs	Comment
Pourrat, 1984[39]	53	No	Normal	Nifedipine, 30-60 mg/day	NA	–	+	Evaluation at 24 h
Cacoub, 1988[40]	27	No	2.70	Nifedipine, 40 mg/day	36	37.5	Null	Retrospective
Neumayer, 1989[33]	35	Yes	1.23	Nitrendipine, 20 mg/day (3 days)	NA	NA	+	Protection on GFR and enzymuria on day 2 only
Russo, 1990[41]	30	Yes	Normal	Nifedipine, 10 mg/sublingual	NA	NA	+	Evaluation only at 30, 60, and 120 min
Russo, 1995[37]	14	Yes	2.60	Nifedipine, 10 mg/sublingual	NA	NA	+	Protection versus rise in sCr at 24, 48, and 72 h
Khoury, 1995[38]	85	Yes	1.05	Nifedipine, 10 mg orally, 1 h before	0	4.6	Null	
Spangberg-Viklund, 1996[35]	27	Yes	1.56	Felodipine, 10 mg orally	NA	NA	Null	
Carraro, 1996[34]	121	Yes	1.20	Nitrendipine, 10 mg (or 20 mg)	6.5	8.3	Null	
Arici, 2003[36]	29	Yes	0.90	Amlodipine, 500 mg i.v., 1 h before	6.7	7.1	Null	

CCBs=calcium channel blockers; CIN=contrast-induced nephrotoxicity; GFR=glomerular filtration rate, sCr=serum creatinine concentration, NA=not available; +=favors use of CCBs; Null=does not favor use of CCBs.

Table 3 | Clinical studies on the prophylactic use of AAs to prevent CIN

Author, year	Number of patients	Randomized	Baseline sCr (mg/dl)	AAs and dose	CIN in the AAs group (%)	CIN in the control group (%)	Effect of AAs	Comment
Gandhi, 1992[45]	21	Yes	NA	Theophylline, 125 mg for 3 days	15.4	12.5	Null	Nephrotoxicity not defined
Erley, 1994[46]	39	Yes	1.20	Theophylline, 5 mg/kg i.v., 45 min before	NA	NA	+	Prevention of acute and delayed decline in GFR
Katholi, 1995[44]	93	Yes	1.25	Theophylline, 2.88 mg/kg/12 h for four times	NA	NA	+	Prevention of decline in GFR
Kolonko, 1998[47]	58	Yes	1.0	Theophylline, 165 mg i.v.	NA	NA	+	Prevention of increase in sCr
Abizaid, 1999[48]	60	Yes	1.9	Aminophylline, 4 mg/kg/h	35	30	Null	Coronary angioplasty
Erley, 1999[49]	80	Yes	1.9	Theophylline, 810 mg/day for 5 days	5.7	3.4	Null	CIN defined as rise in sCr >0.5 mg/dl
Shammas, 2001[51]	52	No	1.6	Aminophylline, 200 mg i.v. before procedure	11.5	11.5	Null	
Huber, 2001[50]	78	No	1.47	Theophylline, 200 mg i.v. 30 min before procedure	4	14	+	Control series
Huber, 2002[52]	100	Yes	2.07	Theophylline, 200 mg i.v. 30 min before procedure	4	16	+	ICU patients
Kapoor, 2002[53]	70	Yes	1.16	Theophylline, 200 mg twice daily for 3 days	0	20	+	Diabetic patients
Huber, 2003[54]	100	Yes	1.65	Theophylline, 200 mg i.v. 30 min before procedure	4	20	+	

Aa=adenosine antagonists; CIN=contrast-induced nephrotoxicity; GFR=glomerular filtration rate; sCr=serum creatinine concentration; NA=not available; +=favors use of AAs; Null=does not favor use of AAs.

group. In another study, Gurkowski *et al.*[43] showed that repeated treatment with the PGE analog misoprostol (four times a day starting from 3 days before and 2 days after contrast exposure) significantly attenuates the decrease in creatinine clearance induced by the contrast administration.

Contrast media stimulate the intrarenal secretion of adenosine, which binds to the renal adenosine receptor and acts as a potent vasoconstrictor, primarily in the efferent arterioles, reducing renal blood flow. As this vasoconstrictive response can be blunted with theophylline in experimental animals, multiple investigators have evaluated the competitive *adenosine antagonists (aminophylline and theophylline)* as a potential means of reducing the risk of CIN in human subjects (Table 3[44–54]). However, these studies have been limited by small sample size, variation in timing and dosage of drug administration, and variation in the definition of CIN. Two prospective randomized trials evaluated the administration of intravenous theophylline.[48,49] In the first

Table 4 | Clinical studies on the prophylactic use of dopamine (DA) and fenoldopam (FE) to prevent CIN

Author, year	Number of patients	Randomized	Baseline sCr (mg/dl)	DA/FE dose	CIN in the DA/FE group	CIN in the control group	Effect of DA/FE	Comment
Hans, 1990[57]	60	Yes	1.97	DA 2.5 μg/kg/min for 12 h	NA	NA	+	Small CrCl improvement at day 1
Hall, 1992[58]	222	No	3.0	DA 3.0 μg/kg/min from the evening before to the next day	0	NA	+	No control group
Weisberg, 1993[56]	30	Yes	2.37	DA 2.0 μg/kg/min for 120 min	33	40	Null	
Kapoor, 1996[59]	40	Yes	1.5	DA 5.0 μg/kg/min from 30 min before to 6 h after	0	50	+	
Hans, 1998[60]	55	Yes	1.97	DA 2.5 μg/kg/min 1 h before and 12 h after	NA	NA	+/Null	Benefit after 24 h only in pts with sCr ≥ 2 mg/dl
Abizaid, 1999[48]	60	Yes	1.9	DA 2.5 μg/kg/min for 2 h before	50	30	Null	More patients in DA group required HD
Gare, 1999[61]	66	Yes	1.1	DA 2.0 μg/kg/min for 36–48 h after	12	6	Null	CIN defined as >40% increase in sCr
Madyoon, 2001[65]	46	No	2.4	FE 0.1 μg/kg/min for 2 h before and >4 h after	13	38	+	Historical controls
Kini, 2002[64]	260	No	2.08	FE 0.1 μg/kg/min 15–20 min before and 6 h after	3	NA	+	Retrospective study
Chamsuddin, 2002[66]	29	No	2.55	FE 0.1 μg/kg/min for 2 h before and >4 h after	7	NA	+	Retrospective study
Tumlin, 2002[67]	45	Yes	2.61	FE 0.1 μg/kg/min for 2 h before and >4 h after	21	41	Null	
Stone, 2003[68]	315	Yes	1.82	FE 0.1 μg/kg/min for 2 h before and 12 h after	33.6	30.1	Null	
Allaquaband, 2002[10]	123	Yes	1.94	FE 0.1 μg/kg/min for 2 h before and 4 h after	15.7	15.3	Null	
Briguori, 2004[69]	192	Yes	1.75	FE 0.1 μg/kg/min for 2 h before and 12 h after	13.7	4.1	Null	

CIN=contrast-induced nephrotoxicity; GFR=glomerular filtration rate; sCr=serum creatinine concentration; NA=not available; +=favors use of DA/FE; Null=does not favor use of DA/FE; HD=hemodialysis.

of these two studies, 80 patients with chronic renal failure were evaluated, but no benefit was observed in patients who received theophylline.[49] Similarly, in the second randomized trial of patients undergoing coronary angioplasty, in which aminophylline, dopamine, and saline were compared, no clinically significant reduction in the incidence of CIN with the use of aminophylline was observed.[48] In contrast, Huber *et al.*[50] observed a reduction in the incidence of CIN (from 20 to 4%) in a series of 100 patients with chronic renal dysfunction treated with oral theophylline. A recent meta-analysis suggests that theophylline may be helpful,[55] so that further studies are needed to definitely determine its efficacy, safety, and utility.

Although theoretically justified, studies testing the effectiveness of low (<2 μg/kg/min) doses of *dopamine* showed negative or neutral results (Table 4[48,56–61]). The failure of dopamine may be due to hypovolemia and tachyarrhythmia induced by diuretic and pro-arrhythmogenic effects, both leading to reduced cardiac output and reduced effective circulating arterial volume. Furthermore, the unselective stimulation of both dopamine-1 and -2 receptors may have an important role.

Fenoldopam is a parenteral, selective dopaminergic agent approved in 1997 for the treatment of systemic hypertension. In contrast to dopamine, fenoldopam is a selective dopamine-1 receptor agonist with systemic and renal arterial vasodilatory properties that does not stimulate dopamine-2 or adrenergic receptors, even when administered in higher doses. Low dosage of fenoldopam, which did not decrease blood pressure, in dogs produced dopamine-1 receptor-mediated dose-related renal vasodilation, diuresis, and natriuresis when administered directly into the renal artery. Intravenous infusion of fenoldopam (0.025–0.5 μg/kg/min) causes small decreases in diastolic blood pressure in healthy volunteers and dose-related increase in heart rate, without altering systolic blood pressure.[62] Fenoldopam significantly increases renal blood flow and decreases renal vascular resistance, without altering glomerular filtration rate. In healthy volunteers, an intravenous infusion of fenoldopam 0.025–0.5 μg/kg/min increased renal plasma flow (by 12–57%) and decreased renal vascular resistance (by 19–42%) in a generally dose-related manner.[62,63] Following preliminary studies showing a benefit of fenoldopam in reducing CIN, more recent prospective, randomized trials suggested negative results (Table 4[10,64–69]). Kini *et al.*[64] found that fenoldopam has a protective effect against renal ischemic injury during percutaneous coronary intervention. Intravenous fenoldopam should be started at least 1 h before the procedure at a rate of 0.1 μg/kg/min and be continued during the percutaneous intervention and for 4–6 h after procedure if the patient's blood pressure is stable. In the study by Kini *et al.* including 269 patients with baseline creatinine

concentration $\geqslant 1.5$ mg/dl (mean $= 2.08 \pm 0.71$), an increase of $\geqslant 25\%$ in creatinine level occurred in 3.8% of cases, whereas urgent dialysis was seen in 0.77%. Of note, it seems that fenoldopam extends its renoprotective benefit in patients with diabetes mellitus and baseline creatinine concentration > 2.0 mg/dl. The Evaluation of Corlopam in Patients at Risk for Renal Failure – A Safety and Efficacy Trial (CONTRAST)[68] is a randomized, multicenter, double-blind, placebo-controlled study of an i.v. infusion of fenoldopam in 315 patients with creatinine clearance < 60 ml/min, at risk for developing CIN, and undergoing diagnostic and/or interventional cardiology procedures. The CONTRAST trial suggests that fenoldopam mesylate is ineffective in preventing further renal function deterioration in patients with chronic renal insufficiency receiving iodinated contrast. All patients received 0.45% saline for hydration. A non-ionic contrast agent was administered to all patients and 90% of the patients received a low-osmolality contrast agent. Fenoldopam mesylate infusion was started at least 1 h before the procedure at 0.05 μg/kg/min and then increased to 0.10 μg/kg/min in 20 min, if tolerated. The infusion was continued during the procedure and for 12 h post procedure. NAC was administered before the procedure in 49.6% of the Fenoldopam group and 54.1% of patients in the placebo group. Premature discontinuation of the study drug because of hypotension occurred in 21% of the Fenoldopam group compared to 11% in the placebo group. The incidence of CIN at 48 h was 19.9% in the Fenoldopam group versus 15.9% in the control group ($P = 0.45$), and at 96 h 33.6 versus 30.1%, respectively ($P = 0.61$). No statistical difference was evident between the two treatment groups. In addition, no interaction between fenoldopam and NAC was evident. Briguori *et al.*[69] compared the effectiveness of fenoldopam versus NAC. Patients with chronic impairment of renal function (sCr concentration $\geqslant 1.5$ mg/dl and/or creatinine clearance < 60 ml/min) were randomly assigned to receive intravenous saline plus NAC (NAC group) or fenoldopam mesylate (Fenoldopam group) before and after administration of iodixanol, a non-ionic, iso-osmolality contrast agent. Saline (0.45%) was given intravenously at a rate of 1 ml/kg of body weight per hour (0.5 ml/kg for patients with left ventricular ejection fraction $< 40\%$) for 12 h before and 12 h after administration of the contrast agent. NAC was given orally at a dose of 1200 mg twice daily in the NAC Group on the day before and on the day of administration of the contrast agent, for a total of 2 days. Fenoldopam infusion was started at least 1 h before the procedure at 0.10 μg/kg/min, maintained during the procedure and continued for 12 h post procedure. The dosage was downtitrated or discontinued in case of hypotension or tachycardia. Severe hypotension was defined as a systolic blood pressure < 90 mm Hg. Three patients experienced side effects in the Fenoldopam group necessitating premature drug infusion discontinuation: two patients had severe hypotension (one patient 2 h and the other 4 h after the procedure), and one patient had allergic reaction (skin rash and vomiting) before the procedure. A trend to a greater absolute decrease in systolic blood pressure was found in the Fenoldopam group than in the NAC group (-17 ± 20 versus 11 ± 25 mm Hg; $P = 0.068$). In contrast, decrease in diastolic (-9 ± 11 versus -9 ± 14 mm Hg; $P = 1.00$) and mean (-11 ± 12 vs. -8 ± 15 mm Hg; $P = 0.30$) blood pressure was similar in the two groups. CIN occurred in 4/97 patients in the NAC Group (4.1%) and in 13/95 patients in the Fenoldopam Group (13.7%) ($P = 0.019$; OR $= 0.27$; 95% CI $= 0.08$–0.85). Contrast-associated nephrotoxicity occurred in 5/11 (45.5%) patients with serum creatinine level > 2.5 mg/dl in the Fenoldopam group versus 1/9 (11%) patients in the NAC group ($P = 0.095$). In the 98 diabetic patients, renal function deterioration occurred in 4/49 (8.2%) in Fenoldopam Group and in 3/49 (6.1%) in the NAC Group ($P = 0.72$). In the 23 patients with left ventricular ejection fraction $< 40\%$, renal function deterioration occurred in 4/13 (13.3%) in Fenoldopam group and in none of the 10 patients in the NAC group ($P = 0.23$). In patients with left ventricular ejection fraction $\geqslant 40\%$, renal function deterioration occurred in 9/72 (12.5%) in Fenoldopam group and in 4/87 (4.5%) in the NAC group ($P = 0.085$). No case of CIN were observed in the 16 diabetic patients with left ventricular ejection fraction $< 40\%$ (seven patients in the Fenoldopam group and nine in the NAC group). In the Fenoldopam group, mean blood pressure lowering was similar in patients with and without contrast-associated nephrotoxicity (-11 ± 11 versus -11 ± 10 mm Hg; $P = 0.95$), and in patients with left ventricular ejection fraction < 40 and $\geqslant 40\%$ (-13 ± 9 versus -10 ± 12 mm Hg; $P = 0.39$). Renal failure requiring dialysis occurred in one patient enrolled in the Fenoldopam group (1.1%): this patient subsequently experienced in-hospital death. Length of in-hospital stay (from admission to discharge) was longer in the Fenoldopam Group than NAC Group (5.0 ± 10 versus 2.9 ± 2.7 days; $P = 0.049$).

On the basis of the results of these studies, fenoldopam should not be used as a prophylactic measure to prevent further renal function deterioration in patients at risk for CIN.

DIURETICS: MANNITOL AND FUROSEMIDE

Up to the mid-1990s a common approach to the patient at risk for contrast nephropathy was pretreatment with saline hydration with mannitol and furosemide. Furosemide inhibits sodium–potassium–chloride cotransport in the thick ascending limb of the loop of Henle. This segment of the nephron is at greatest risk of ischemic injury attributable to the combination of high metabolic demand and low oxygen delivery. It has been postulated that inhibition of active ion transport in this nephron segment would reduce oxygen utilization and decrease the risk of nephrotoxicity resulting from contrast-stimulated vasoconstrition. In the study by Solomon *et al.*,[70] there were no beneficial effects of the osmotic diuretic mannitol when added to saline hydration in either diabetic or nondiabetic patients, and there was an actual exacerbation of contrast-induced renal dysfunction with the use of the loop diuretic furosemide with saline hydration.

The prospective Randomized Trial of Prevention Measures in Patient at High-risk for Contrast Nephropathy study found no benefit to forced diuresis with intravenous crystalloid, furosemide, mannitol, and low-dose dopamine over hydration alone.[71] Mannitol increases the intrarenal secretion of adenosine, a potent renal vasoconstrictor, resulting in a reduction of renal blood flow. Furthermore, the active transport process that is responsible for excretion of this osmotically active compound also increases tubular mitochondrial oxygen consumption. Furosemide-induced diuresis may result in hypovolemia, which may actually increase the risk of contrast-induced tubular injury.

Many other pharmacologic approaches have been investigated in attempts to decrease the incidence and severity of CIN, but the results with these agents must be considered preliminary and inconclusive. In one study, the *nitric oxide* substrate L-arginine was used, on the theory that CIN is related to impaired endothelial function, but it did not have a protective effect.[72] In several studies and review articles, angiotensin-converting enzyme *(ACE) inhibitors* have been identified as a risk factor for CIN because of their potential to reduce renal function. Gupta *et al.*[73] challenged this concept by evaluating the use of captopril before contrast administration. They hypothesized that the reduction of renal blood flow that occurs following administration of contrast may be because of the rennin–angiotensin system causing constriction of the afferent arterioles, and they suggested that by using ACE inhibitors, this response may be attenuated. Indeed, in their study, the incidence of CIN was lower in patients treated with captopril than in controls (6 versus 29%; $P = 0.002$). Even though the results of this study are interesting, more studies need to be performed to better understand the role of ACE inhibitors in relation to contrast administration. Finally, a recent study investigated the usefulness of *statins* in CIN. Khanal *et al.*[74] retrospectively evaluated 29 409 patients undergoing cardiac catheterization. Among them, 10 831 (38%) patients were on statin therapy before the procedure, and 18 040 (62%) were not. Patients on a pre-procedure statins had a lower incidence of CIN (4.37 versus 5.93%; $P < 0.0001$) and nephropathy requiring dialysis (0.32 versus 0.49%; $P = 0.03$). These promising preliminary results on a protective role of statins against CIN should be confirmed by a randomized, prospective trial.

RECOMMENDATIONS

Saline hydration throughout all studies has repeatedly been shown to provide effective and safe prophylaxis for CIN. With the onset of newer therapies regarding the pathophysiology behind CIN, *N*-acetylcysteine has been targeted as a potentially new pharmacologic answer to this growing problem. Because of the low incidence of adverse effects and the nominal cost of acetylcysteine, it appears that little harm can be incurred by a patient receiving this drug. Therefore, it may be at least acceptable to include this drug in prophylactic protocols for patients at high risk. We suggest the dose of 1200 mg b.i.d. the day before and the day of the procedure. Additional data are necessary to clarify the role of different hydration protocol (in particular sodium bicarbonate) and of the type of antioxidant compound (*N*-acetylcysteine or ascorbic acid).

The major studies of fenoldopam strongly point to the lack of value provided by this drug when administered systemically. The risk of hypotension (21%) and the additional cost make it an impractical choice for the prevention of contrast-associated nephrotoxicity. Because of the negative or inconclusive data, theophylline, calcium antagonists, atrial natriuretic peptide, adenosine, and endothelin receptor antagonits are not recommended to prevent contrast nephrotoxicity.

CONCLUSIONS

(1) *N-acetylcysteine*: *N*-acetylcysteine has been targeted as a potentially new pharmacologic answer to this growing problem. Because of the low incidence of adverse effects and the nominal cost of acetylcysteine, it appears that little harm can be incurred by a patient receiving this drug. Therefore, it may be at least acceptable to include this drug in prophylactic protocols for patients at high risk. We suggest the dose of 1200 mg b.i.d. the day before and the day of the procedure.

(2) *Ascorbic acid:* Additional data are necessary to clarify the role of ascorbic acid.

(3) *Dopamine*: Dopamine should not be used as a prophylactic measure to prevent further renal function deterioration in patients at risk for CIN.

(4) *Fenoldopam mesylate*: Fenoldopam should not be used as a prophylactic measure to prevent further renal function deterioration in patients at risk for CIN.

(5) *Diuretics*: Furosemide-induced diuresis may result in hypovolemia, which may actually increase the risk of contrast-induced tubular injury.

(6) *Theophylline*: A recent meta-analysis suggests that theophylline may be helpful, so further studies are needed to definitely determine its efficacy, safety, and utility.

(7) *Calcium antagonists*: Further investigation is needed to evaluate possible effects of using different calcium channel antagonist agents. Currently, the use of calcium channel blockers to prevent CIN is not recommended. However, their discontinuation at the time of contrast exposure is not required in patients taking these drugs for other indications.

(8) *Atrial natriuretic peptide*: Not recommended.

(9) *Endothelin receptor antagonists*: To date, it is unknown whether selectìve endothelin A blockade may be beneficial in preventing CIN.

(10) *ACE inhibitors*: More studies need to be performed to better understand the role of ACE inhibitors in relation to contrast administration.

(11) *PGE*: May be promising as a prophylactic agent against CIN, but further studies are needed to confirm the effectiveness of this agent.

REFERENCES

1. DiMari J, Megyesi J, Udvarhelyi N *et al.* *N*-acetylcysteine ameliorates ischemic renal failure. *Am J Physiol* 1997; **272**: F292–F298.
2. Heyman SN, Goldfarb M, Shina A *et al.* *N*-acetylcysteine ameliorates renal microcirculation: studies in rats. *Kidney Int* 2003; **63**: 634–641.
3. Tariq M, Morais C, Sobki A *et al.* *N*-acetylcysteine attenuates cyclosporin-induced nephrotoxicity in rats. *Nephrol Dial Transplant* 1999; **14**: 923–929.
4. Efrati S, Dishy V, Averbukh M *et al.* The effect of *N*-acetylcysteine on renal function, nitric oxide, and oxidative stress after angiography. *Kidney Int* 2003; **64**: 2182–2187.
5. Tepel M, Van der Giet M, Schwarzfeld C *et al.* Prevention of radiographic-contrast-agent-induced reductions in renal function by acetylcysteine. *N Engl J Med* 2000; **343**: 180–184.
6. Diaz-Sandoval LJ, Kosowsky BD, Losordo DW. Acetylcysteine to prevent angiography-related renal tissue injury (the APART trial). *Am J Cardiol* 2002; **89**: 356–358.
7. Shyu KG, Cheng JJ, Kuan P. Acetylcysteine protects against acute renal damage in patients with abnormal renal function undergoing a coronary procedure. *J Am Coll Cardiol* 2002; **40**: 1383–1388.
8. Kay J, Chow WH, Chan TM *et al.* Acetylcysteine for prevention of acute deterioration of renal function following elective coronary angiography and intervention: a randomized controlled trial. *JAMA* 2003; **289**: 553–558.
9. Briguori C, Manganelli F, Scarpato P *et al.* Acetylcysteine and contrast-agent associated nephrotoxicity. *J Am Coll Cardiol* 2002; **40**: 298–303.
10. Allaqaband S, Tumuluri R, Malik AM *et al.* Prospective randomized study of *N*-acetylcysteine, fenoldopam, and saline for prevention of radiocontrast-induced nephropathy. *Cathet Cardiovasc Interv* 2002; **57**: 279–283.
11. Durham JD, Caputo C, Dokko J *et al.* A randomized controlled trial of *N*-acetylcysteine to prevent contrast nephropathy in cardiac angiography. *Kidney Int* 2002; **62**: 2202–2207.
12. Webb JG, Pate GE, Humphries KH *et al.* A randomized controlled trial of intravenous *N*-acetylcysteine for the prevention of contrast-induced nephropathy after cardiac catheterization: lack of effect. *Am Heart J* 2004; **148**: 422–429.
13. Boccalandro F, Amhad M, Smalling RW, Sdringola S. Oral acetylcysteine does not protect renal function from moderate to high doses of intravenous radiographic contrast. *Catheter Cardiovasc Interv* 2003; **58**: 336–341.
14. Goldenberg I, Shechter M, Matetzky S *et al.* Oral acetylcysteine as an adjunct to saline hydration for the prevention of contrast-induced nephropathy following coronary angiography. A randomized controlled trial and review of the current literature. *Eur Heart J* 2004; **25**: 212–218.
15. Oldemeyer JB, Biddle WP, Wurdeman RL *et al.* Acetylcysteine in the prevention of contrast-induced nephropathy after coronary angiography. *Am Heart J* 2003; **146**: E23.
16. Baker CSR, Wragg A, Kumar S *et al.* A rapid protocol for the prevention of contrast-induced renal dysfunction: the RAPPID study. *J Am Coll Cardiol* 2003; **41**: 2114–2118.
17. Hoffmann U, Fischereder M, Kruger B *et al.* The value of *N*-acetylcysteine in the prevention of radiocontrast agent-induced nephropathy seems questionable. *J Am Soc Nephrol* 2004; **15**: 407–410.
18. Izzedine H, Guerin V, Launay-Vacher V *et al.* Effect of *N*-acetylcysteine on serum creatinine level. *Nephrol Dial Transplant* 2001; **16**: 1514–1515.
19. Briguori C, Colombo A, Violante A *et al.* Standard vs double dose of *N*-acetylcysteine to prevent contrast agent associated nephrotoxicity. *Eur Heart J* 2004; **25**: 206–211.
20. Miner SES, Dzavik V, Nguyen-Ho P *et al.* *N*-acetylcysteine reduces contrast-associated nephropathy but not clinical events during long-term follow-up. *Am Heart J* 2004; **148**: 690–695.
21. Birck R, Krzossok S, Markowetz F *et al.* Acetylcysteine for prevention of contrast nephropathy: meta-analysis. *Lancet* 2003; **362**: 598–603.
22. Alonso A, Lau J, Jaber BL *et al.* Prevention of radiocontrast nephropathy with *N*-acetylcysteine in patients with chronic kidney disease: a meta-analysis of randomized, controlled trials. *Am J Kidney Dis* 2004; **43**: 1–9.
23. Pannu N, Manns B, Lee H, Tonelli M. Systematic review of the impact of *N*-acetylcysteine on contrast nephropathy. *Kidney Int* 2004; **65**: 1366–1374.
24. Kshirsagar AV, Poole C, Mottl A *et al.* *N*-acetylcysteine for the prevention of radiocontrast induced nephropathy: a meta-analysis of prospective controlled trials. *J Am Soc Nephrol* 2004; **15**: 761–769.
25. Isenbarger DW, Kent SM, O'Malley PG. Meta-analysis of randomized clinical trials on the usefulness of acetylcysteine for prevention of contrast nephropathy. *Am J Cardiol* 2003; **92**: 1454–1458.
26. Nallamothu B, Shojania KG, Saint S *et al.* Is acetylcysteine effective in preventing contrast-related nephropathy? A meta-analysis. *Am J Med* 2004; **117**: 938–947.
27. Spargias K, Alexopoulos E, Kyrzopoulos S *et al.* Ascorbic acid prevents contrast-mediated nephropathy in patients with renal dysfunction undergoing coronary angiography or intervention. *Circulation* 2004; **110**: 2837–2842.
28. Wang A, Holcslaw T, Bashore TM *et al.* Exacerbation of radiocontrast nephrotoxicity by endothelin receptor antagonism. *Kidney Int* 2000; **57**: 1675–1680.
29. Margulies KB, McKinley LJ, Cavero PG, Burnett Jr JC. Induction and prevention of radiocontrast-induced nephropathy in dogs with heart failure. *Kidney Int* 1990; **38**: 1101–1108.
30. Kurnik BR, Allgren RL, Genter FC *et al.* Prospective study of atrial natriuretic peptide for the prevention of radiocontrast-induced nephropathy. *Am J Kidney Dis* 1998; **31**: 674–680.
31. Wang YX, Jia YF, Chen KM, Morcos SK. Radiographic contrast media induced nephropathy: experimental observations and the protective effect of calcium channel blockers. *Br J Radiol* 2001; **74**: 1103–1108.
32. Duan SB, Liu FY, Luo JA *et al.* Nephrotoxicity of high- and low-osmolar contrast media. The protective role of amlodipine in a rat model. *Acta Radiol* 2000; **41**: 503–507.
33. Neumayer HH, Junge W, Kufner A, Wenning A. Prevention of radiocontrast-media-induced nephrotoxicity by the calcium channel blocker nitrendipine: a prospective randomized clinical trial. *Nephrol Dial Transplant* 1989; **4**: 1030–1036.
34. Carraro M, Mancini W, Artero M *et al.* Dose effect of nitrendipine on urinary enzymes and microproteins following non-ionic radiocontrast administration. *Nephrol Dial Transplant* 1996; **11**: 444–448.
35. Spangberg-Viklund B, Berglund J, Nikonoff T *et al.* Does prophylactic treatment with felodipine, a calcium antagonist, prevent low-osmolar contrast-induced renal dysfunction in hydrated diabetic and nondiabetic patients with normal or moderately reduced renal function? *Scand J Urol Nephrol* 1996; **30**: 63–68.
36. Arici M, Usalan C, Altun B *et al.* Radiocontrast-induced nephrotoxicity and urinary alpha-glutathione *S*-transferase levels: effect of amlodipine administration. *Int J Urol Nephrol* 2003; **35**: 255–261.
37. Russo D, Minutolo R, Cianciaruso B *et al.* Early effects of contrast media on renal hemodynamics and tubular function in chronic renal failure. *J Am Soc Nephrol* 1995; **6**: 1451–1458.
38. Khoury Z, Schlicht JR, Como J *et al.* The effect of prophylactic nifedipine on renal function in patients administered contrast media. *Pharmacotherapy* 1999; **15**: 59–65.
39. Pourrat JP, Douste-Blazy P. Renal side effects of nifedipine. *Clin Cardiol* 1984; **7**: 29–30.
40. Cacoub P, Deray G, Baumelou A *et al.* No evidence for protective effects of nifedipine against radiocontrast induced acute renal failure. *Clin Nephrol* 1988; **29**: 215–216.
41. Russo D, Testa A, Della Volpe L *et al.* Randomised prospective study on renal effects of two different contrast media in humans: protective role of a calcium channel blocker. *Nephron* 1990; **55**: 254–257.
42. Koch JA, Plum J, Grabensee B, Modder U. Prostaglandin E1: a new agent for the prevention of renal dysfunction in high risk patients caused by radiocontrast media? *Nephrol Dial Transplant* 2000; **15**: 43–49.
43. Gurkowski L, MacDougall M, Wiegmann T. Effects of misoprostol on contrast-induced renal dysfunction. *Am J Ther* 1995; **2**: 837–842.
44. Katholi RE, Taylor GJ, McCann WP *et al.* Nephrotoxicity from contrast media: attenuation with theophylline. *Radiology* 1995; **195**: 17–22.
45. Gandhi MR, Brown P, Romanowski CAJ *et al.* The use of theophylline, an adenosine antagonist, in the prevention of contrast media induced nephropathy. *Br J Radiol* 1992; **65**: 838 (letter).
46. Erley CM, Duda SH, Schlepckow S *et al.* Adenosine antagonist theophylline prevents the reduction of glomerular filtration rate after contrast media application. *Kidney Int* 1994; **45**: 1425–1431.
47. Kolonko A, Wiecek A, Kokot F. The nonselective adenosine antagonist theophylline does prevent renal dysfunction induced by radiographic contrast agents. *J Nephrol* 1998; **11**: 151–156.
48. Abizaid A, Clark CE, Mintz GS *et al.* Effects of dopamine and aminophylline on contrast-induced acute renal failure after coronary angioplasty in patients with preexisting renal insufficiency. *Am J Cardiol* 1999; **83**: 260–263.
49. Erley CM, Duda SH, Rehfuss D *et al.* Prevention of radiocontrast-media-induced nephropathy in patients with pre-existing renal insufficiency by hydration in combination with the adenosine antagonist theophyllline. *Nephrol Dial Transplant* 1999; **14**: 1146–1149.

50. Huber W, Jeschke B, Page M *et al.* Reduced incidence of radiocontrast-induced nephropathy in ICU patients under theophylline prophylaxis: a prospective comparison to series of patients at similar risk. *Intens Care Med* 2001; **27**: 1200–1209.
51. Shammas NW, Kapalis MJ, Harris M *et al.* Aminophylline doe not protect against radiocontrast nephropathy in patients undergoing percutaneous angiographic procedures. *J Invas Cardiol* 2001; **13**: 738–740.
52. Huber W, Ilgmann K, Page M *et al.* Effect of thephylline on contrast material-induced nephropathy in patients with chronic renal insufficiency: controlled, randomized, double-blinded study. *Radiology* 2002; **223**: 772–779.
53. Kapoor A, Kumar S, Gulati S *et al.* The role of theophylline in contrast-induced nephropathy: a case–control study. *Nephrol Dial Transplant* 2002; **17**: 1936–1941.
54. Huber W, Schipak C, Ilgmann K *et al.* Effectiveness of theophylline prophylaxis of renal impairment after angiography in patients with chronic renal insufficiency. *Am J Cardiol* 2003; **91**: 1157–1162.
55. Ix JH, McCulloch CE, Chertow GM. Theophylline for the prevention of radiocontrast nephropathy: meta-analysis. *Nephrol Dial Transplant* 2004; **19**: 2747–2753.
56. Weisberg LS, Kurnik PB, Kurnik BR. Dopamine and renal blood flow in radiocontrast-induced nephropathy in humans. *Ren Fail* 1993; **15**: 61–68.
57. Hans B, Hans SS, Mittal VK *et al.* Renal functional response to dopamine during and after arteriography in patients with chronic renal insufficiency. *Radiology* 1990; **176**: 651–654.
58. Hall KA, Wong RW, Hunter GC *et al.* Contrast-induced nephrotoxicity: the effects of vasodilator therapy. *J Surg Res* 1992; **53**: 317–320.
59. Kapoor A, Sinha N, Sharma RK *et al.* Use of dopamine in prevention of contrast induced acute renal failure. A randomized study. *Int J Cardiol* 1996; **53**: 233–236.
60. Hans SS, Hans BA, Dhillon R *et al.* Effect of dopamine on renal function after arteriography in patients with pre-existing renal insufficiency. *Am Surg* 1998; **64**: 432–436.
61. Gare M, Haviv YS, Ben-Yehuda A *et al.* The renal effect of low-dose dopamine in high-risk patients undergoing coronary angiography. *J Am Coll Cardiol* 1999; **34**: 1682–1688.
62. Mathur V, Swan S, Lambrecht L *et al.* The effects of fenoldopam, a selective dopamine receptor agonist, on systemic and renal hemodynamic in normotensive subjects. *Crit Care Med* 1999; **27**: 1832–1837.
63. Bakris G, Lass NA, Glock D. Renal hemodynamics in radiocontrast medium-induced renal dysfunction: a role for dopamine-1 receptors. *Kidney Int* 1999; **56**: 206–210.
64. Kini AS, Mitre CA, Kamran M *et al.* Changing trends in incidence and predictors of radiographic contrast nephropathy after percutaneous coronary intervention with use of fenoldopam. *Am J Cardiol* 2002; **89**: 999–1002.
65. Madyoon H, Croushore L, Weaver D, Mathur V. Use of fenoldopam to prevent radiocontrast nephropathy in high-risk patients. *Cathet Cardiovasc Interv* 2001; **53**: 341–345.
66. Chamsuddin AA, Kpwalik KJ, Bjarnason H *et al.* Using a dopamine tupe 1a receptor agonist in high-risk patients to ameliorate contrast associated nephropathy. *Am J Roentgenol* 2002; **179**: 591–596.
67. Tumlin JA, Wang A, Murray PT, Mathur VS. Fenodopam mesylate blocks reduction in renal plasma flow after radiocontrast dye infusion: a pilot trial in the prevention of contrast nephropathy. *Am Heart J* 2002; **143**: 894–903.
68. Stone GW, McCullough PA, Tumlin JA *et al.* Fenoldopam mesylate for the prevention of contrast-induced nephrotoxicity. *JAMA* 2003; **290**: 2284–2291.
69. Briguori C, Colombo A, Airoldi F *et al. N*-acetylcysteine versus fenoldopam mesylate to prevent contrast agent-associated nephrotoxicity. *J Am Coll Cardiol* 2004; **44**: 762–765.
70. Solomon R, Werner C, Mann D *et al.* Effects of saline, mannitol, and furosemide on acute decreases in renal function induced by radiocontrast agents. *N Engl J Med* 1994; **331**: 1416–1420.
71. Stevens MA, McCullough PA, Tobin KJ *et al.* A prospective randomized trial of prevention measures in patients at high risk for contrast nephropathy: results of the PRINCE study. *J Am Coll Cardiol* 1999; **33**: 403–411.
72. Miller HI, Dascalu A, Rassin TA *et al.* Effects of an acute dose of L-arginine during coronary angiography in patients with chronic renal failure: a randomized, parallel, double-blind clinical trial. *Am J Nephrol* 2003; **23**: 91–95.
73. Gupta RK, Kapoor A, Tavani S *et al.* Captopril for the prevention of contrast media-induced nephropathy in diabetic patients: a randomized study. *Indian Heart J* 1999; **51**: 521–526.
74. Khanal S, Attallah N, Smith DE *et al.* Statin therapy reduces contrast-induced nephropathy: an analysis of contemporary percutaneous interventions. *Am J Med* 2005; **118**: 843–849.