Contrast nephropathy (CN) is the third leading cause of hospital-acquired acute renal failure accounting for 10% of all cases (1) and contributing to prolonged hospital stay and increased medical costs (1,2). Renal failure after contrast administration requiring in-hospital dialysis is associated with poor outcome including 36% in-hospital mortality and 19% two-year survival (3,4). Patients with renal insufficiency carry an inherent risk of developing atherosclerosis (5), and thus will be frequently referred for angiography. On the other hand, patients with cardiovascular disease often have concomitant impairment of renal function or receive medication associated with an increased risk of CN while undergoing angiography, such as angiotensin-converting enzyme inhibitors (ACEI). Therefore, even the most careful patient selection cannot avoid that a high number of patients at risk will be exposed to a contrast agent.

**RISK FACTORS**

The most important risk factor for CN is preexisting renal dysfunction (2–4). The presence of diabetes mellitus has significant impact on the incidence of CN in patients with mild-to-moderate renal insufficiency (creatinine <2.0 mg/dl), whereas, in patients with advanced renal insufficiency (creatinine ≥2.0 mg/dl), the incidence of CN in patients with diabetic and nondiabetic nephropathy does not differ (2). The degree of pre-existing renal impairment is the most powerful predictor of CN, and patients with atherosclerosis and reduced effective circulating arterial volume are at particular risk (Table 1). Peripheral vascular disease, bypass graft intervention, and the need for an intra-aortic balloon pump probably are surrogates of more severe atherosclerosis, advanced and long-lasting coronary artery disease. Procedures with bypass angiography and intervention may be associated with higher complexity, longer duration, and limited success, thus indicating an unstable postprocedural period with impaired cardiac output. In addition, older age, hypertension, repeated exposure to contrast medium, and nephrotoxic medication, such as aminoglycosides, as well as drugs impairing the renovascular autoregulation such as non-steroidal anti-inflammatory drugs (NSAID) and ACEI were reported to be risk factors (6).

Contrast nephropathy is rare in patients with normal renal function in the absence of diabetes mellitus (2,7). Rihal et al. (2) found a 2% incidence of CN in nondiabetic patients with a baseline creatinine ≤1.1 mg/dl. On the other hand, 50% of patients with diabetic nephropathy and a mean serum creatinine of 5.9 mg/dl had a >25% increase after coronary angiography (8).

**CONTRAST AGENTS**

Contrast agents are classified according to their osmolality, which depends on the ratio of iodine atoms to osmotically active particles (Table 2). High osmolar contrast agents (about 2,000 mOsm/kg H₂O) are considerably hyperosmolar compared with plasma. Diatrizoate is a tri-iodinated...
benzoate and thus a ratio 1.5 agent, because the substance dissociates into two osmotically active particles for each three iodine atoms. The so-called low osmolality contrast agents have a lower osmolality (about 600 to 900 mOsm/kg H₂O), but are still hyperosmolal to plasma. These substances are either nonionic monomers with three iodine atoms for each osmotically active particle or ionic dimers with six iodine atoms for each two osmotically active particles, respectively (ratio 3 agents). Iodixanol is a non-ionic dimer with six iodine atoms for each osmotically active particle (ratio 6 agent) and iso-osmolal to plasma (9).

**PATHOGENESIS**

The pathogenesis of CN is not completely understood. Disturbances in renal hemodynamics and direct cytotoxicity have been identified as key factors (10). The renal medulla has an extremely low oxygen tension due to high transport activity of the medullary thick ascending limb and, therefore, is especially susceptible to ischemia (10). In animal models of renal insufficiency, selective medullary injury after contrast administration has been shown, mediated by vasoconstrictors such as endothelin, vasopressin, and adenosine (10,11).

As renal function declines, a number of abnormalities develop including endothelial dysfunction, changes in coagulation and fibrinolysis, and advanced vascular and valvular calcification, all of which contribute to the acceleration of cardiovascular disease (12). Worsening cardiac and vascular function, in turn, may lead to decreased cardiac output and subsequently reduced effective circulating arterial blood volume and activation of the renin-angiotensin-aldosterone system. Although antagonism of the renin-angiotensin-aldosterone system has been proven to slow the long-term progression of the disease in patients with cardiorenal risk (13,14), in presence of acute contrast-induced reduction of renal blood flow, blunting of the vasoconstrictor effects of angiotensin II on the efferent arteriola may be deleterious due to reduction of intra-glomerular pressure. The concomitant use of NSAIDs leading to withdrawal of the relaxing effects on the afferent arteriola by prostaglandins will further reduce glomerular filtration rate, thus precipitating acute renal failure.

Furthermore, a direct toxic effect of contrast media on renal epithelial cells has been shown (15), as well as an increased red cell aggregation, possibly further impairing oxygen delivery (16). Experimental studies on the role of osmolality per se in the pathogenesis of CN have provided conflicting data (16–18). Clinical trials indicate a lower incidence of CN when using low-osmolality compared with high-osmolality contrast agents (7,19), and when using

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**Table 1. Independent Predictors for the Development of Contrast Nephropathy**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>Reference*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contrast nephropathy†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-existing renal failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preprocedural creatinine 2.0–2.9 mg/dl</td>
<td>7.37</td>
<td>4.78–11.39</td>
<td>(2)</td>
</tr>
<tr>
<td>Preprocedural creatinine ≥3 mg/dl</td>
<td>12.82</td>
<td>8.01–20.54</td>
<td>(2)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.61</td>
<td>1.21–2.16</td>
<td>(2)</td>
</tr>
<tr>
<td>Creatinine 0–1.1 mg/dl</td>
<td>1.86</td>
<td>1.20–2.89</td>
<td>(2)</td>
</tr>
<tr>
<td>Creatinine 1.2–1.9 mg/dl</td>
<td>2.42</td>
<td>1.54–3.79</td>
<td>(2)</td>
</tr>
<tr>
<td>Creatinine 2.0–2.9 mg/dl</td>
<td>1.00</td>
<td>0.48–2.08</td>
<td>(2)</td>
</tr>
<tr>
<td>Creatinine ≥3.0</td>
<td>1.36</td>
<td>0.63–2.92</td>
<td>(2)</td>
</tr>
<tr>
<td>Preprocedure shock</td>
<td>1.19</td>
<td>0.72–1.96</td>
<td>(2)</td>
</tr>
<tr>
<td>Myocardial infarction ≥24 h</td>
<td>1.85</td>
<td>1.31–2.63</td>
<td>(2)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1.53</td>
<td>1.21–2.10</td>
<td>(2)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>1.71</td>
<td>1.23–2.37</td>
<td>(2)</td>
</tr>
<tr>
<td>Contrast volume</td>
<td>1.12</td>
<td>1.02–1.23</td>
<td>(2)</td>
</tr>
<tr>
<td>Contrast nephropathy requiring dialysis†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic renal insufficiency</td>
<td>20.25</td>
<td>11.48–35.71</td>
<td>(3)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3.34</td>
<td>1.92–5.81</td>
<td>(3)</td>
</tr>
<tr>
<td>Contrast volume</td>
<td>5.47</td>
<td>1.40–21.32</td>
<td>(4)</td>
</tr>
<tr>
<td>Intra-aortic balloon pump</td>
<td>1.10</td>
<td>1.0003–1.22</td>
<td>(3)</td>
</tr>
<tr>
<td>Bypass graft intervention</td>
<td>1.94</td>
<td>1.08–3.49</td>
<td>(3)</td>
</tr>
</tbody>
</table>

*Data are mainly derived from two studies (2,3) restricted to patients undergoing percutaneous coronary interventions but not only diagnostic angiography; †defined as increase in serum creatinine ≥0.5 mg/dl from preprocedural values; ‡defined as the presence of previously documented renal insufficiency or a baseline creatinine level of at least 1.8 mg/dl (159.1 μmol/l).
Cystatin C is a cationic non-glycosylated low-molecular-weight cysteine protease that is produced by all nucleated cells at a constant rate, is not metabolized in the serum, and is freely filtered by the renal glomeruli (38,39). Serum concentration of cystatin C has been reported to be superior to serum creatinine with regard to assessment of glomerular filtration rate (38), and to be independent of age, gender, and muscle mass (39). A recent study provides evidence for the usefulness of cystatin C as a marker of CN (39). Cystatin C levels peaked at 24 h after contrast administration and reached baseline levels within 48 h, whereas creatinine levels continued to increase at 48 h. Unfortunately, there are other factors than renal function influencing cystatin C levels (e.g., malignant tumors [40] or elevation of C-reactive protein [41]).

DEFINITION AND DIAGNOSIS

In clinical trials CN was defined as an increase in serum creatinine >0.5 mg/dl within 48 to 72 h) in the iohexol group (12.2%) than in the diatrizoate group (27%). This effect was even more evident in patients with both renal dysfunction and diabetes (7). The incidence of CN (defined as an increase in serum creatinine >0.5 mg/dl within three days) in patients with both diabetes and pre-existing renal dysfunction was recently reported to be markedly lower when using the iso-osmolar contrast agent ioxilan (3%) compared with iohexol (26%) (20).

ROLE OF PROPHYLACTIC INTERVENTIONS

Hydration. Relying on the observation of a higher incidence of CN in dehydrated patients and the beneficial effect of hydration compared with vasodilators and mannitol as adjuncts to hydration (44), the periprocedural administration of fluids has become standard. In most studies, a uniform protocol with half-isotonic (0.45%) saline at a rate of 1 ml/kg/h before and after contrast exposure was employed (23–30). One study compared the administration of isotonic to half-isotonic saline in 1,383 patients undergoing coronary angiography (21). Contrast nephropathy occurred in 0.7% of the patients assigned to 0.9% saline, and in 2.0% of those assigned to half-isotonic saline (p = 0.04). Three subgroups demonstrated particular benefit: women, diabetics, and those receiving high volumes of contrast (≥250 ml). Because only 20% of the study population had pre-existing renal insufficiency, conclusions about the optimal hydration protocol in high-risk patients are limited. In this study intravenous fluids were initiated only a few hours before angiography, relying on the data of a small trial showing non-inferiority of a combination of oral and intravenous pre-catheterization hydration (1,000 ml clear liquid over 10 h followed by saline 0.45% 300 ml/h over 6 h) compared with overnight intravenous hydration (saline 0.45% 75 ml/h) in patients with mild-to-moderate renal dysfunction undergoing angiography (postcatheterization hydration with saline 0.45% 75 ml/h over 12 h for all patients) (45). However, unrestricted oral periprocedural fluid intake with-
out additional intravenous administration seems to be inferior to intravenous hydration (46).

Based on the hypothesis that alkalizing renal tubular fluid with bicarbonate may reduce free radical formation and thus reduce injury, a prospective, single-center trial evaluated an alternative hydration protocol with sodium bicarbonate (47). Patients with pre-existing renal insufficiency scheduled for different procedures (mainly cardiac catheterization) were randomized to receive either 154 mEq/l sodium bicarbonate (n = 60; creatinine 1.89 ± 0.69 mg/dl) or equiosmolar sodium chloride (n = 59; creatinine 1.71 ± 0.42 mg/dl), both given as an intravenous bolus (3 ml/kg/h for 1 h) immediately before administration of iopamidol, followed by an infusion at a rate of 1 ml/kg/h for 6 h after the procedure. The incidence of CN (defined as an increase of ≥25% of baseline creatinine within two days) was markedly lower in the bicarbonate group (1.7%) than in the sodium chloride group (13.6%; p = 0.02). These very promising results are hampered only by the fact that a 7-h instead of a 24-h hydration period was used, which does not allow direct comparison with previous studies. Therefore, further studies are required to clarify the role of sodium bicarbonate hydration in the prevention of CN.

Diuretics. Relying on the idea that inducing and maintaining a post-contrast diuresis and blocking of the oxygen-demanding active transport processes of the medullary thick ascending limb would prevent CN, furosemide was given as prophylaxis. However, the landmark trial of Solomon et al. (22) rejected the hypothesis that the administration of furosemide or mannitol plus hydration would more efficiently prevent CN than hydration alone. The failure of furosemide can probably be explained by loop diuretic-induced hypovolemia. In current practice diuretics usually are withdrawn before contrast exposure whenever possible.

Dopamine and fenoldopam. Dopamine at “low dose” (<5 μg/kg/min) stimulates dopamine and possibly beta-receptors, thereby increasing renal blood flow and glomerular filtration (48). However, studies comparing saline plus low-dose dopamine to hydration alone disclosed negative (49) or neutral (48) effects. Abizaid et al. (49) studied 60 patients (creatinine ≥1.5 mg/dl) undergoing coronary angiography randomized to saline (0.45% 1 ml/kg/h for 12 h before and after the procedure) alone, or dopamine (2.5 μg/kg/min) plus saline, or amilor- phyline (4 mg/kg followed by a drip of 0.4 mg/kg/h) plus saline. There was a non-significant trend toward a higher incidence of CN in patients receiving dopamine. The failure of dopamine may be, at least in part, due to hypovolemia and tachyarrhythmia induced by diuretic, potassium-wasting, and pro-arrhythmogenic effects, both leading to reduced cardiac output and reduced effective circulating arterial volume, thereby blunting the positive inotropic properties of dopamine. The adverse effect of dopamine was further explained by unselective stimulation of both dopamine-1 and -2 receptors (48). In contrast, dopamine-1 stimulation with the selective dopamine-1 agonist fenoldopam was shown to prevent the diatrizoate-induced reductions in the glomerular filtration rate in anesthetized volume-depleted dogs (50). The promising results of a prospective pilot study (51) evaluating fenoldopam as an adjunct to hydration were not confirmed. In contrast, a recent multicenter study (52) comparing fenoldopam plus intravenous hydration to placebo plus hydration in patients with a creatinine clearance <60 ml/min undergoing coronary angiography demonstrated a trend in favor of placebo (CN in 30.1% of patients assigned to placebo vs. 33.6% of the fenoldopam group; p = NS).

Vasodilators. In a canine model of renal insufficiency (subtotal nephrectomy), adenosine was shown to act as a vasoconstrictor after iohexol administration, whereas vasodilation was induced in sham-operated dogs (11). These differences were explained by contrast-induced adenosine-2-receptor-mediated vasodilation in dogs with normal function, and conversely both early adenosine-2-receptor-mediated vasodilation and sustained and overwhelming adenosine-1-receptor-mediated vasoconstriction in dogs with impaired renal function. Two studies evaluating the effect of the adenosine antagonist theophylline either as a single intravenous bolus of 200 mg (53) or as oral intake of 200 mg twice a day starting 24 h before and continuing 48 h after coronary angiography in addition to saline hydration (54) were promising. A contradictory study found no benefit of the oral administration of 810 mg theophylline during five days and (not uniform) hydration compared with hydration alone in patients with chronic renal insufficiency undergoing either computed tomography or digital subtraction angiography (55).

In a recently published trial (6), 100 patients were randomly assigned to receive either placebo (creatinine 1.72 ± 0.69 mg/dl) or theophylline 200 mg intravenously (creatinine 1.65 ± 0.41 mg/dl) 30 min before coronary angiography resulting in a significantly lower incidence of CN in the theophylline group (4% vs. 20% in the saline group; p = 0.0138). Unfortunately, hydration was not uniform, but patients were given fluids “according to clinical examination, X-ray, and central venous pressure” (6). Because data are conflicting and theophylline has a narrow therapeutic range and may be associated with adverse effects (e.g., tachycardia), it is not a prophylactic agent of first choice.

Among theoretically possible candidates to prevent CN, neither atrial natriuretic peptide (56), nor a mixed endothelin antagonist (57), nor dihydropyridine calcium channel blockers (58) led to favorable results in clinical studies.

**N-acetylcysteine (NAC).** Relying on the assumption that reactive oxygen species might be involved in the pathogenesis of CN, Tepel et al. (59) compared the oral administration of the antioxidant NAC (600 mg twice a day on the day before and day of examination) plus standard hydration to hydration alone in 83 patients (creatinine 2.4 ± 1.3 mg/dl) undergoing computed tomography with intravenous administration of 75 ml of nonionic, low-osmolality contrast agent. The authors were able to demonstrate a significantly lower incidence of CN in the NAC group (2%) compared with the placebo group (21%; p = 0.01). However, this trial
is hampered by the fact that the incidence of CN in the control group was much higher compared with the control group in the trial of Solomon et al. (22), although the patients in the latter study underwent angiography instead of computed tomography; received higher doses; and 32% of patients received high-osmolality contrast agents compared with nonionic, low-osmolality contrast agents received by all patients in the study by Tepel et al. (59).

Several trials designed to confirm the benefit of NAC in patients with chronic renal insufficiency undergoing angiography provided conflicting results (23–34). There were marked differences concerning grade of renal insufficiency of included patients, NAC regime, and type and amount of contrast agent administered, as shown in Table 3. The authors of a recent meta-analysis excluding several studies for various reasons (e.g., intravenous NAC administration) found a benefit of NAC prophylaxis and recommended it for high-risk patients (60), whereas the authors of two other meta-analyses released in 2004 (61,62) stated that general conclusions about a benefit of NAC to prevent CN are impossible due to inconsistent study design in the analyzed trials.

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (n)</th>
<th>Baseline Serum Creatinine (mg/dl)†‡</th>
<th>NAC Regimen</th>
<th>Uniform Hydration Protocol Employed§</th>
<th>Contrast Agent</th>
<th>Amount of Contrast Agent (ml)</th>
<th>CN Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective trials showing no beneficial effect of NAC prophylaxis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Durham et al.*</td>
<td>79</td>
<td>NAC: 2.2 ± 0.4 Placebo: 2.3 ± 0.5</td>
<td>Yes Iohexol</td>
<td>NAC: 77.4 ± 35.9 Placebo: 84.7 ± 42.1</td>
<td>NAC: 26.3%</td>
<td>Placebo: 22.0%</td>
<td>p = NS</td>
</tr>
<tr>
<td>Boccalandro et al.*</td>
<td>179</td>
<td>NAC: 1.8 ± 0.6 Placebo: 1.9 ± 0.6</td>
<td>Yes Iodixanol</td>
<td>NAC: 192 ± 142 Placebo: 191 ± 120</td>
<td>NAC: 13%</td>
<td>Placebo: 12%</td>
<td>p = NS</td>
</tr>
<tr>
<td>Allaqaband et al.*</td>
<td>85</td>
<td>NAC: 2.2 ± 1.0 Placebo: 2.0 ± 0.8</td>
<td>Yes Ioversol</td>
<td>NAC: 122 ± 65 Placebo: 122 ± 75</td>
<td>NAC: 17.7%</td>
<td>Placebo: 15.3%</td>
<td>p = NS</td>
</tr>
<tr>
<td>Goldenberg et al.*</td>
<td>80</td>
<td>NAC: 2.0 ± 0.4 Placebo: 1.9 ± 0.3</td>
<td>Yes Iopamidol</td>
<td>NAC: 111 ± 43 Placebo: 121 ± 49</td>
<td>NAC: 10%</td>
<td>Placebo: 8%</td>
<td>p = NS</td>
</tr>
<tr>
<td>Briguori et al.*</td>
<td>183</td>
<td>NAC: 1.5 ± 0.4 Placebo: 1.5 ± 0.4</td>
<td>Yes Iopromide</td>
<td>NAC: 194 ± 127 Placebo: 200 ± 144</td>
<td>NAC: 6.5%</td>
<td>Placebo: 11%</td>
<td>p = NS</td>
</tr>
<tr>
<td>Oldenmeyer et al.</td>
<td>96</td>
<td>NAC: 1.6 ± 0.8 Placebo: 1.7 ± 0.7</td>
<td>Yes Iopamidol</td>
<td>NAC: 134 ± 71 Placebo: 127 ± 73</td>
<td>NAC: 8.2%</td>
<td>Placebo: 6.4%</td>
<td>p = NS</td>
</tr>
</tbody>
</table>

*, Study included in the meta-analysis by Goldenberg et al. (26); †mean values ± SD or median (interquartile range); ‡to convert from mg/dl to μmol/l, multiply serum creatinine values by 88.4; §a uniform hydration protocol was used, saline 0.4% at a rate of 1 ml/kg/h 12 h before and 12 h after the procedure (23,25–27,29,32), saline 0.45% at 75 ml/h prior to procedure; No = 50% above baseline level 48 h after contrast exposure; *defined as increase in serum creatinine concentration >25% above the baseline level 24, 48, or 72 h after contrast exposure; ¶defined as increase in serum creatinine concentration >25% above the baseline level 48 h after contrast exposure; #defined as increase in serum creatinine concentration >25% above the baseline level 48 h after contrast exposure; **defined as increase in serum creatinine concentration >25% above the baseline level 48 h after contrast exposure; t.i.d. = twice a day; CN = contrast nephropathy; IV = intravenously; NAC = N-acetylcysteine; NS = not significant; t.i.d. = three times a day.

Table 3. Summary of Prospective Trials Published as Full-Text Articles Until March 2004 Comparing N-Acetylcysteine Plus Hydration to Hydration for the Prevention of Contrast Nephropathy in Patients Undergoing Angiography (23–27,29–34)
In one of the most recent trials on the subject, 80 patients (creatinine clearance <50 ml/min) undergoing coronary angiography with iopamidol were randomized to receive either NAC 600 mg three times a day for 48 h starting 24 h before contrast administration plus hydration (0.45% saline at 1 ml/kg/h for 12 h before and after contrast exposure) or placebo plus hydration (26). The incidence of CN did not differ between the NAC group (10%) and the placebo group (8%; p = 0.52).

A meta-analysis of eight prospective studies comprising 1,023 patients (23–27,29–31) in the same paper (26) found an overall benefit of NAC (odds ratio 0.53 [95% confidence interval 0.35 to 0.78]). However, the authors pointed out that two of the three studies favoring NAC administration were using a nonuniform or incomplete hydration protocol as well as slightly different definitions of CN (25% instead of 0.5 mg/dl increase above baseline creatinine), and they, therefore, concluded that NAC administered as adjunct to a uniform 24-h hydration protocol provides no additional benefit.

Although the available data do not allow conclusions about the usefulness of NAC in general, some of these trials dealing with subgroups of patients provide interesting results. Of special importance is the study by Shyu et al. (27), which compared NAC plus hydration to hydration alone in patients with the highest ever NAC trial-tested creatinine levels (2.8 ± 0.8 mg/dl) and found a markedly lower incidence of CN in the NAC group (3.3%) than in the hydration group (24.6%; p < 0.001). Baker et al. (34) for the first time evaluated the intravenous administration of NAC combined with a shortened hydration protocol (Table 3) resulting in a significantly lower incidence of CN in the NAC group (5%) than in the saline group (21%; p = 0.045). Briguori et al. (28) compared a standard NAC dose (SD group, 600 mg twice a day) to a double NAC dose (DD group, 1,200 mg twice a day) in addition to intravenous saline 0.45% (1 ml/kg/h) for 12 h before and after coronary or peripheral angiography in patients with chronic renal insufficiency (creatinine >1.5 mg/dl and/or creatinine clearance <60 ml/min). Contrast nephropathy occurred in 11% of patients in the SD group and in 3.5% of patients in the DD group (p = 0.038). In the subgroup with the contrast dose ≥140 ml, CN was more frequent in the SD group (18.9%) than in the DD group (5.4%; p = 0.039), whereas no difference was found in the low-dose (<140 ml) subgroup.

**Hemodialysis and hemofiltration.** The hypothesis that hemodialysis might prevent CN by removing contrast media from the circulation was not confirmed in clinical trials (63,35). The largest study on this subject included 113 patients with advanced renal insufficiency (creatinine 3.5 ± 1.2 mg/dl) undergoing different procedures with administration of nonionic, low-osmolality contrast agent (35). Patients were given either periprocedural hydration (saline at 1 ml/kg/h for 12 h before and after contrast exposure) or preprocedural hydration (saline at 1 ml/kg/h for 12 h) followed by a 3-h hemodialysis. Nine patients in the non-hemodialysis group and 13 in the hemodialysis group (p = NS) developed CN (maximum increase in creatinine >1.5 mg/dl or >50% above baseline). There was no benefit of hemodialysis in the subgroup receiving >150 ml of contrast agent.

Marenzi et al. (64) studied 114 patients (creatinine >2 mg/dl) undergoing coronary angiography with nonionic, low-osmolality contrast agent, who were randomly assigned to either venovenous hemofiltration in an intensive care unit starting 4 to 6 h before the coronary procedure and continuing for 18 to 24 h (hemofiltration group, creatinine clearance 26 ± 9 ml/min) or infusion of isotonic saline at a rate of 1 ml/kg/h for 6 to 8 h before and 24 h after the procedure (control group, creatinine clearance 26 ± 8 ml/min). Three patients in the hemofiltration group (5%) developed CN compared with 28 patients in the control group (50%; p < 0.001). In 10 control patients, emergency hemodialysis was required, but in no patient of the hemofiltration group. In-hospital mortality was significantly lower in the hemofiltration group (2% vs. 14%; p = 0.02). These impressive results were questioned due to the following reasons: the exceptionally high mortality of the control group and the fact that heparin administration and intensive care might have considerably added to the mortality difference. Furthermore, incorporation of this study into clinical practice will raise important logistical issues.

**CONCLUSIONS AND THERAPEUTIC RECOMMENDATIONS**

All patients undergoing angiography should receive hydration. Guidelines (65) recommend at least 100 ml oral intake or intravenous administration per hour starting 4 h before to 24 h after contrast exposure. We suggest the use of an intravenous hydration regime (saline 0.45%, at least 1 ml/kg/h 12 h before and after contrast exposure, if tolerated 0.9% saline) for all patients with impaired renal function. Alternatively, a combination of oral and intravenous preprocedural hydration followed by postprocedural intravenous hydration according to the protocol of Taylor et al. (45) can be used. However, this regime might be unsuitable for patients with congestive heart failure. If the hydration period has to be shortened for any reason, the use of sodium bicarbonate instead of sodium chloride has to be considered. Diuretics, ACEIs, angiotensin receptor blockers, NSAIDs, and other nephrotoxic drugs should be withdrawn at least 24 h before contrast exposure. We discourage using dopamine, fenoldopam, and theophylline. The smallest possible amount of a nonionic, low-osmolal or iso-osmolal contrast agent should be given, and repeated contrast administration within a short period of time should be avoided. Concerning the use of NAC, we agree with experts (66) who recently suggested that in patients with high creatinine levels (>2.5 mg/dl) and in those receiving large contrast doses (>140 ml), high-dose NAC (2 × 1,200 mg) should be given. Because the contrast dose in complex coronary interventions may easily exceed 140 ml, and because NAC is inexpensive and has virtually no side effects, we suggest that all patients with chronic renal insufficiency (creatinine >1.5 mg/dl or creatinine clearance <60 ml/min) and all diabetics
should receive high-dose NAC. Further large prospective studies are warranted to clarify the debate about the benefit of NAC in all other patients.

A possible algorithm to choose the optimal prophylactic strategy in an individual patient is given in Figure 1. It has to be emphasized that there are no studies about the best approach in patients undergoing emergency procedures. In these patients it will not be possible to start preventive

Figure 1. Suggested algorithm for therapeutic recommendations to prevent contrast nephropathy. *Angiotensin-converting enzyme inhibitors, angiotensin receptor blocking agents, non-steroidal anti-inflammatory drugs, diuretics, aminoglycosides, calcineurin inhibitors; †chronic renal insufficiency, diabetes, multiple myeloma, congestive heart failure, or age >70 years. b.i.d. = twice a day; IV = intravenous.
measures including drug withdrawal, hydration, and NAC intake 12 to 24 h before contrast exposure. We suggest beginning as soon as possible and adequately lengthening the postcontrast period (e.g., for hydration: start immediately before angiography, duration until 24 h after angiography). However, these suggestions are not evidence-based and await confirmation in future clinical trials.

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REFERENCES


