Prevention of contrast-induced nephropathy

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INTRODUCTION — The administration of radiocontrast media can lead to a usually reversible form of acute kidney injury (AKI) that begins soon after the contrast is administered [1-11]. In most cases, there are no permanent sequelae, but there is some evidence that its development is associated with adverse outcomes [12].

This topic will provide an overview of the relative nephrotoxicity of different iodinated radiocontrast agents and the relative efficacy of various prophylactic strategies. The pathogenesis, clinical features, and diagnosis of radiocontrast media-induced nephropathy and a discussion of acute tubular necrosis, the most common cause of AKI in hospitalized patients, are presented separately. (See "Pathogenesis, clinical features, and diagnosis of contrast-induced nephropathy" and "Etiology and diagnosis of prerenal disease and acute tubular necrosis in acute kidney injury (acute renal failure)" and "Renal and patient outcomes after acute tubular necrosis".)

Types of radiocontrast agents — Iodinated radiocontrast agents are either ionic or nonionic and, at the concentrations required for arteriography or computed tomography (CT), are of variable osmolality [10,13]:

- First-generation agents are ionic monomers; they are highly hyperosmolal (approximately 1400 to 1800 mosmol/kg), compared with the osmolality of plasma.
- Second-generation agents, such as iohexol, are nonionic monomers with a lower osmolality than the first-generation radiocontrast media; however, they still have an increased osmolality (500 to 850 mosmol/kg), compared with plasma. In addition, there is an ionic low-osmolal contrast agent (ioxaglate).
- The newest nonionic contrast agents are iso-osmolal, being dimers with an osmolality of approximately 290 mosmol/kg (iodixanol is the first such agent). Thus, iso-osmolal agents have a lower osmolality than "low-osmolal" second-generation drugs.

The nephrotoxic properties of these agents appear to vary, with low- and iso-osmolal agents being associated with a relatively decreased incidence of renal injury among high-risk patients. (See 'Type of contrast agent' below.)

PREVENTION — There is no specific treatment once contrast-induced acute kidney injury (AKI) develops, and management must be as for any cause of acute tubular necrosis, with the focus on maintaining fluid and electrolyte balance. The best treatment of contrast-induced kidney injury is prevention.

Overview — A variety of preventive measures may reduce the risk of contrast nephropathy [1-3,14]:

- The use, if clinically possible, of ultrasonography, magnetic resonance imaging (MRI) (see 'Contrast-enhanced magnetic resonance imaging as an alternative' below), or computed tomography (CT) scanning without radiocontrast agents, particularly in high-risk patients.
- The use of lower doses of contrast [4-7,15] and avoidance of repetitive studies that are closely spaced (within 48 to 72 hours). Very small amounts of contrast (<10 mL) have been safely used in patients with advanced kidney disease for examination of poorly maturing arteriovenous fistula [16]. Specialized techniques during coronary angiography, such as endovascular ultrasound, can significantly reduce contrast volume.
- Avoidance of volume depletion or nonsteroidal anti-inflammatory drugs (NSAIDs), both of which can increase renal vasoconstriction.

- The administration of intravenous saline or sodium bicarbonate.
- The administration of the antioxidant acetylcysteine.
- The use of selected low- or iso-osmolal nonionic contrast agents.

It is important to appreciate that most of the clinical trials that have evaluated these factors have used small, transient elevations in the serum creatinine concentration (which are of dubious clinical significance) as endpoints (eg, ≥0.5 mg/dL [44.2 micromol/L] or ≥25 to 50 percent above baseline) [14]. Nevertheless, there are an increasing number of reports that contrast-induced nephropathy, defined in this manner, is associated with significant in-hospital and long-term mortality [8,9,17]. (See "Pathogenesis, clinical features, and diagnosis of contrast-induced nephropathy".)

Type of contrast agent — A decreased incidence of contrast nephropathy appears to be associated with nonionic agents, which, as defined above, are either low osmolal (500 to 850 mosmol/kg) or iso-osmolal (approximately 290 mosmol/kg). Most studies have evaluated the relative effectiveness of nonionic low-osmolal agents versus ionic hyperosmolal agents. The ionic low-osmolal agent, ioxaglate, also appears to be associated with a lower risk of contrast nephropathy, compared with ionic hyperosmolal agents (1500 to 1800 mosmol/kg), which are not commonly used for intravascular contrast administration [10].

Nonionic iso-osmolal agents — Iodixanol, the only currently available iso-osmolal nonionic contrast agent (approximately 290 mosmol/kg), has been proposed to be associated with a lower risk of nephropathy than some low-osmolal agents, particularly iohexol, among diabetic patients with chronic kidney disease (CKD) and a reduced glomerular filtration rate (GFR) who are given intra-arterial contrast, mostly for coronary angiography.

In an initial trial that compared iodixanol and iohexol in 129 high-risk patients with diabetes and CKD (mean serum creatinine 1.5 mg/dL [133 micromol/L]) who underwent angiography, iodixanol was associated with a lower incidence of a >0.5 mg/dL (44 micromol/L) rise in serum creatinine (3 versus 26 percent with iohexol) [18]. In contrast, three much larger subsequent trials that compared iodixanol with two other nonionic low-osmolal contrast agents (ioversol and iopamidol) in patients with diabetic and nondiabetic CKD found no difference in the incidence of contrast nephropathy among the different agents [19-21].

A meta-analysis of 16 randomized trials also suggested that iodixanol was associated with a reduction in risk among patients with CKD who received contrast when compared with iohexol (relative risk [RR] 0.19, 95% CI 0.07-0.56), but **not** when compared with other nonionic low-osmolal contrast agents (RR 0.79, 95% CI 0.56-1.12) [22].

In summary, the data support a benefit of iso-osmolal iodixanol compared with low-osmolal iohexol among patients who have diabetes and CKD, but not a benefit for iodixanol compared with other nonionic low-osmolal agents. Thus, the positive findings in the initial trial [18] may represent an adverse effect of iohexol rather than a beneficial effect of nonionic iso-osmolal agents. After considering all of the published data, the American College of Cardiology/American Heart Association (ACC/AHA) guidelines on percutaneous coronary intervention (PCI) were revised to suggest the use of either an iso-osmolal contrast agent or a low-molecular-weight contrast agent other than iohexol or the ionic low-osmolal agent, ioxaglate [23]. The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommended low-osmolal or iso-osmolal rather than high-osmolal contrast agents, but stated that the work group found no reliable evidence upon which to base a recommendation for either low- versus iso-osmolal agents [24].

Carbon dioxide — An alternative contrast agent is carbon dioxide, which can be used alone or with small amounts of iodinated contrast. Satisfactory imaging and procedural results are obtained, particularly with modern imaging technology (digital subtraction angiography), with no or little nephrotoxicity [25-30].

An important limitation is the risk of neurotoxicity when injected close to the cerebral circulation, or if there is a right-to-left intracardiac shunt [31,32]. Thus, it cannot be used for cerebrovascular imaging, and, if to be used, its use should be limited to imaging below the diaphragm [27].

Summary — The iso-osmolal nonionic contrast agent, iodixanol, appears to reduce the risk of contrast nephropathy in high-risk patients, such as diabetic patients with renal insufficiency, compared with the low-osmolal nonionic agent iohexol, but not when compared with other low-osmolal nonionic agents. However, additional randomized, prospective trials comparing iodixanol (or other iso-osmolal agents, if developed) with other low-osmolal ionic or nonionic agents are required before it can be concluded that iso-osmolal contrast agents are uniformly less nephrotoxic than low-osmolal agents as a class, with the exception of iohexol, especially given the substantially greater expense of the only currently available iso-osmolal nonionic agent, iodixanol.

Volume administration, mannitol, and diuretics — Intravenous volume administration is beneficial, and the type of solution may be important [1,2,14,33]. In comparison, the role of diuretics, mannitol, and other renal vasodilators in this setting is uncertain [33-36].

Diuretics — Several small trials have investigated the effect of diuretics. In one trial, 78 patients with stable CKD (mean plasma creatinine concentration 2.1 mg/dL [186 micromol/L]) about to undergo coronary angiography were randomly assigned to one of three regimens [33]:

- One-half isotonic (0.45 percent) saline at a rate of 1 mL/kg per hour for 12 hours before and 12 hours after the angiogram
- One-half isotonic saline plus 25 g of mannitol infused intravenously during the one hour before the procedure
- One-half isotonic saline plus 80 mg of furosemide infused intravenously during the 30 minutes before angiography

The incidence of AKI (defined as a rise in the serum creatinine of at least 0.5 mg/dL [44 micromol/L]) was lowest in the group treated with saline alone. Mannitol was of no added benefit, while there was a suggestion that furosemide therapy slightly increased the risk. Why this might occur is not known since volume depletion from the furosemide could not be definitively excluded.

A subsequent randomized trial that compared mannitol plus furosemide with placebo among 92 patients with moderate renal insufficiency (mean serum creatinine of 2.8 mg/dL [248 micromol/L]) also showed an increased risk associated with diuretics [36]. In this trial, AKI (defined as a 25 percent increase in serum creatinine) occurred more frequently among patients who received mannitol and furosemide, compared with placebo (23 of 46 versus 13 of 46, adjusted odds ratio [OR] 3.73, 95% CI 1.12-12.38). There was no difference in net fluid balance between the groups.

Another study evaluated 50 patients (24 of whom were diabetic) with moderate CKD (mean serum creatinine approximately 2.5 mg/dL or 220 micromol/L) who were about to undergo coronary angiography [35]. The patients were randomly assigned to receive saline or one of three renal vasodilator/diuretic drugs (dopamine [2 mcg/kg per minute], mannitol [15 g/dL in a one-half isotonic saline solution given at 100 mL/hour], or atrial natriuretic peptide). Contrast toxicity was defined as a rise in the creatinine of at least 25 percent.

- Saline hydration was associated with a 40 percent incidence of renal dysfunction in diabetic and nondiabetic patients.
- Dopamine, mannitol, and atrial natriuretic peptide were associated with a much higher incidence of renal dysfunction (75 to 83 percent) in diabetic subjects. On the other hand, there were no cases of contrast toxicity in the nondiabetic patients, suggesting a possible benefit.

In addition to not being of benefit, mannitol use is associated with significant complications, which are discussed in detail separately. (See "Complications of mannitol therapy".)

Intravenous saline — The optimal intravenous solution (isotonic saline, one-half isotonic saline, or isotonic sodium bicarbonate) and its volume and duration of administration pre- and postcontrast for prevention of contrast nephropathy are unclear.

Volume expansion with isotonic saline may be superior to one-half isotonic saline [37]. This was shown in a

prospective, randomized trial of 1620 patients treated with either isotonic or one-half isotonic saline at a rate of 1 mL/kg per hour, started the morning of the procedure and continued until 8 AM the next morning [38]. Baseline serum creatinine concentration was the same in both groups (0.9 mg/dL [81 micromol/L]). Patients in each group received approximately 450, 350, and 1200 mL of fluid prior to, during, and after the procedure. Contrast nephropathy was defined as an increase in serum creatinine of at least 0.5 mg/dL (44 micromol/L) within 48 hours.

The overall incidence of contrast-induced nephropathy was 1.4 percent and was significantly lower in patients given isotonic saline (0.7 versus 2.0 percent). The benefit with isotonic saline was more pronounced in diabetic patients (0.0 versus 5.5 percent) and those given >250 mL of contrast (0 versus 3 percent). However, there was no difference for those with significant renal dysfunction (serum creatinine >1.6 mg/dL [>141 micromol/L], 14 and 17 in the saline and one-half normal saline groups, respectively). This is an important limitation since it is patients with underlying renal dysfunction who are at increased risk for contrast nephropathy. In general, isotonic saline is preferred to one-half isotonic saline since isotonic saline is a more effective volume expander.

Intravenous bicarbonate — Since alkalinization may protect against free radical injury, the possibility that sodium bicarbonate may be superior to isotonic saline has been examined in a number of randomized trials and meta-analyses. The results were conflicting as some showed a significantly lower rate of contrast-induced nephropathy with sodium bicarbonate [39-43], while others found equivalent rates [44-48].

Variations in outcomes with sodium bicarbonate may be due to the significant heterogeneity found in these studies. Several meta-analyses have noted differences due to wide variations in study size, treatment effect, and publication bias [48-50]. In general, studies that have examined outcomes with isotonic sodium bicarbonate versus isotonic sodium chloride have noted either equivalent or better outcomes with sodium bicarbonate. However, one randomized trial published after these meta-analyses comparing a prolonged infusion of isotonic saline (1 mL/kg/hour for at least 12 hours prior to and after the procedure) to briefer infusions of isotonic bicarbonate (3 mL/kg for one hour prior to procedure and 1 mL/kg/hour for six hours after the procedure, or 3 mL/kg over 20 minutes prior to procedure plus oral sodium bicarbonate 500 mg per 10 kg) observed a lower rate of contrast nephropathy with isotonic saline [51]. Thus, the data regarding the use of bicarbonate and the optimal rate of fluid administration remain equivocal.

If there are no contraindications to volume expansion, we recommend isotonic intravenous fluids prior to and continued for several hours after contrast administration. The optimal type of fluid and timing of administration are not well established. We generally use isotonic bicarbonate rather than isotonic saline.

One regimen is to administer a bolus of 3 mL/kg of isotonic bicarbonate for one hour prior to the procedure and continued at a rate of 1 mL/kg per hour for six hours after the procedure. An alternative regimen is to administer 1 mL/kg for 6 to 12 hours pre- and postprocedure [52]. Currently, there are no commercially available isotonic sodium bicarbonate solutions available. To administer isotonic bicarbonate, a solution can be prepared by adding 150 mEq of sodium bicarbonate (three 50 mL ampules of 1 mEq/mL sodium bicarbonate) to 850 mL of sterile water. Although the administration of sodium bicarbonate may be potentially superior to the administration of isotonic saline for the prevention of contrast-induced nephropathy, the 2012 KDIGO guideline work group did not make a specific recommendation for the use of bicarbonate preferentially to saline due to concern for potential harm from errors in compounding of the bicarbonate solutions at point of care or in the hospital pharmacy [24].

Oral hydration — Given that an increasing number of individuals receive contrast as outpatients, three small trials have evaluated the effectiveness of oral hydration or salt loading in preventing contrast nephropathy. The one trial that tested the effect of unrestricted oral fluids (ie, no salt) found a much higher rate of AKI after intra-arterial contrast than those given isotonic saline [53,54]. In this trial, 53 patients were randomly assigned to either unrestricted oral fluids or to normal saline at 1 mL/kg per hour for 24 hours, beginning 12 hours prior to the scheduled catheterization [52]. AKI was significantly more common with oral hydration (35 versus 4 percent).

The two trials that included salt loading as part of the protocol showed no difference in outcome, compared with intravenous saline:

- In one trial, 36 patients with serum creatinine ≥1.4 mg/dL (≥124 micromol/L) who required cardiac catheterization were randomly assigned to an outpatient oral hydration, followed by six hours of intravenous one-half isotonic saline for six hours before the procedure or an inpatient regimen of intravenous one-half isotonic saline [55]. There was no difference in the maximal change in creatinine between the two groups.
- The second trial compared salt loading with tablets (1 g/10 kg per day in two or three doses for two days before contrast) and intravenous saline (15 mL/kg for six hours prior to contrast) in 153 patients with CKD (mean serum creatinine 2.2 mg/dL [200 micromol/L]) [56]. There was no difference in the proportion of patients with an increase in serum creatinine of ≥0.5 mg/dL (44 micromol/L) between the two groups.

Thus, the safety and efficacy of oral hydration or salt loading for the prevention of contrast nephropathy remains uncertain, especially in patients receiving intravenous contrast media.

Methods to guide fluid repletion — The careful repletion of fluid is important in prevention of contrast-induced AKI. Two methods to guide fluid repletion have been studied:

- Using left ventricular (LV) end-diastolic pressure to guide fluid replacement
- RenalGuard system

Left ventricular end-diastolic pressure — A randomized trial tested the benefit of a fluid replacement protocol guided by LV end-diastolic pressure among patients with CKD (estimated GFR [eGFR] <60 mL/min per 1.73 m^2) and other risk factors for contrast-induced AKI (including either diabetes mellitus, history of congestive heart failure, hypertension, or age older than 75 years) [57]. In this trial, 350 patients were assigned to LV end-diastolic pressure-guided fluid management or to a control group. All patients received intravenous isotonic saline 3 mL/kg for one hour prior to cardiac catheterization. LV end-diastolic pressure was determined in all patients prior to administration of contrast.

In the LV end-diastolic pressure-guided group, patients received 5 mL/kg/hour if LV end-diastolic pressure was lower than 13 mmHg, 3 mL/Kg/hour if LV end-diastolic pressure was between 13 and 18 mmHg, and 1.5 mL/Kg/hour if LV end-diastolic pressure was greater than 18 mmHg. The control group received 1.5 mL/kg/hour.

Both groups received intravenous fluid throughout and for four hours following the procedure.

Contrast-induced AKI (defined as >0.5 mg/dL or >25 percent increase in serum creatinine between one and four days after the procedure) occurred less frequently in the LV end-diastolic pressure group, compared with control (6.7 versus 16.3, respectively [RR 0.41, 95% CI 0.22-0.79]).

Three patients in each group stopped intravenous fluids early because of dyspnea; LV end-diastolic pressures were 3, 7, and 26 mmHg in the LV end-diastolic pressure-guided group and 3, 23, and 31 mmHg in the control group.

These data suggest that, among patients who are undergoing cardiac catheterization, an aggressive fluid strategy based upon LV end-diastolic pressure may provide benefit. These findings are of interest, but need confirmation from other centers involving larger numbers of patients before this approach can be recommended.

RenalGuard system — The RenalGuard system is a fluid management device that guides fluid replacement and may minimize the risk of volume depletion in the setting of a forced diuresis [53]. Two studies have evaluated the benefits of furosemide-induced diuresis and matched saline infusion guided by the RenalGuard system among patients undergoing angiography [54,58]. In both trials, forced diuresis and matched volume repletion decreased the incidence of contrast nephropathy. The potential value of the RenalGuard system is that volume infusion and urine output are, per hour, significantly greater than with conventional hydration regimens.

However, high-volume forced diuresis raises some concerns, even in the setting of carefully matched volume replacement. As an example, volume overload may ensue if isotonic saline is used to replace urine, which, following the administration of loop diuretics, generally has the tonicity of approximately half normal saline. In one of the trials cited above, such an increase in intravascular volume may have been sufficient to increase the eGFR in patients undergoing forced diuresis [58].

Additionally, arrhythmia-inducing electrolyte abnormalities such as hypokalemia may result from forced diuresis in a vulnerable population. Additional studies that address these issues are necessary before forced diuresis and matched volume replacement are used clinically.

Summary — The following conclusions can be drawn from the current literature. However, these conclusions may be modified pending additional clinical trials:

- Prophylactic diuretics or mannitol do not appear to be beneficial for the prevention of contrast-induced AKI.
- Intravenous volume administration is superior to oral hydration. Oral hydration with water alone should not be used.
- Intravenous volume administration with isotonic saline solution is superior to one-half normal saline.
- Isotonic sodium bicarbonate is not inferior to isotonic saline, and some data suggest that it may protect against contrast-induced AKI.

For patients at risk for contrast nephropathy, we recommend isotonic intravenous volume administration for prophylaxis. The selection of fluid and rate of administration must take into consideration the patient's ability to tolerate the fluid load (eg, rapid volume expansion may be harmful to individuals with reduced LV function) and the degree of underlying risk for nephropathy. (See "Pathogenesis, clinical features, and diagnosis of contrast-induced nephropathy", section on 'Epidemiology'.)

Since the data suggest that isotonic bicarbonate is not inferior to isotonic saline and since there are selected data that suggest a potential protective effect of bicarbonate, it is reasonable to use isotonic bicarbonate as long as that patient can tolerate alkalinization and provided that errors from pharmacologic constitution of the fluid are avoided.

We do not recommend prophylactic use of diuretics or mannitol. However, diuretics may be required to treat volume overload. (See 'Summary and recommendations' below.)

Acetylcysteine — Acetylcysteine is a thiol compound with antioxidant and vasodilatory properties. Although not well understood, a possible mechanism of benefit in contrast-induced nephropathy involves minimizing both vasoconstriction and oxygen-free radical generation after radiocontrast agent administration.

There are great heterogeneity and conflicting results in the available clinical trials and meta-analyses examining the effectiveness of acetylcysteine in the prevention of contrast nephropathy [59,60]. Given the conflicting data regarding benefit, we cannot make a strong recommendation regarding the use of acetylcysteine. Since the agent is potentially beneficial, well tolerated, and relatively inexpensive, we agree with the 2012 KDIGO guidelines that suggest administration of acetylcysteine to patients at high risk. However, some clinicians may elect not to give this unproven therapy [24]. The joint ACC/AHA guidelines do not recommend acetylcysteine [61].

This must be accompanied by intravenous isotonic fluid administration and use of a low- or iso-osmolal contrast agent. (See "Pathogenesis, clinical features, and diagnosis of contrast-induced nephropathy", section on 'Epidemiology' and 'Volume administration, mannitol, and diuretics' above and 'Type of contrast agent' above.)

Numerous prospective trials examining the prophylactic effect of acetylcysteine in contrast nephropathy have been performed, with substantial inconsistency in reported results [62-75]. A variety of factors probably contribute to these inconsistencies. These include the definition of contrast-induced AKI; baseline risk for AKI (eg, severity of renal dysfunction and proportion with diabetes); acetylcysteine dose and route of administration (eg, oral or intravenous); intravenous volume administration protocols; amount and type of contrast given; and type of procedure performed (eg, contrast CT, cardiac catheterization, or peripheral angiography) [14,76,77].

In the Acetylcysteine for the Prevention of Contrast-Induced Nephropathy (ACT) trial, 2308 patients undergoing angiography received either acetylcysteine (1200 mg orally twice daily) or placebo on the day before and after angiogram [78]. Patients had at least one of the following risk factors: age >70 years, CKD, diabetes mellitus, heart failure or LV ejection fraction <45 percent, or shock. There was no difference in the development of AKI, defined as

a ≥25 percent increase above baseline in serum creatinine within 48 to 96 hours after angiography (12.7 percent in both groups). Secondary endpoints, including death, the need for dialysis, or either at 30 days, were also not different between groups.

There was no difference among groups in several subgroups that were defined after the study ended, including the following:

- Patients with CKD, defined as baseline serum creatinine ≥1.5 mg/dL (n = 367) (6.4 versus 5.6 percent in placebo)
- Patients with stage 3 CKD, defined as an eGFR between 30 and 60 mL/min per 1.73 m^2 (n = 823) (7.1 versus 6.8 percent in placebo)
- Patients with stage 4 CKD, defined as an eGFR <30 mL/min per 1.73 m^2 (n = 104) (10.7 versus 6.3 in placebo)
- Patients with diabetes mellitus

However, this trial has several shortcomings:

- Although 823 patients had CKD as defined by eGFR, only 367 patients had a serum creatinine >1.5 mg/dL. Thus, the majority of patients defined as having CKD had only a mild reduction in eGFR (ie, 45 to 60 mL/min per 1.73 m^2). It is not clear whether such patients are at increased risk for contrast nephropathy. A benefit of acetylcysteine would not be expected to be seen among patients who are not at risk.
- The incidence of AKI in patients with CKD, defined by a serum creatinine >1.5 mg/dL (who are more likely to have eGFR <45 mL/min per 1.73 m^2), was low, suggesting that the trial was underpowered to exclude a benefit of acetylcysteine for patients at highest risk for AKI.
- The baseline creatinine was obtained at any time within three months of angiography and, thus, may not have provided an accurate reference serum creatinine for assessing the postprocedural change.
- Over 20 percent of patients received high-osmolal contrast media, which confers a greater risk for AKI, compared with low- or iso-osmolal media. (See 'Type of contrast agent' above.)

The overall prophylactic efficacy of acetylcysteine has been assessed in multiple meta-analyses. Several meta-analyses have suggested a substantial benefit, reporting risk reductions of up to 50 percent with acetylcysteine, whereas others have reported less substantial, and occasionally nonsignificant, risk reductions [46,78-83]. In general, benefits have been reported in meta-analyses that did not consider the great heterogeneity between the trials [84].

However, benefits have also been noted in some, but not all, meta-analyses that did recognize this heterogeneity [82,83,85,86]. In one meta-analysis that included 41 studies, but was published before the ACT trial, N-acetylcysteine significantly lowered the risk for contrast nephropathy, compared with saline alone (RR 0.62, 95% CI 0.44-0.88) [85].

A potential concern related to the interpretation of clinical trials is that administration of acetylcysteine in typical doses (600 mg twice daily for two days) transiently reduces the serum creatinine [62,63,69,87]. However, the magnitude of the fall in serum creatinine is very small (eg, from 0.85 to 0.82 mg/dL [75 to 72 micromol/L] in a study in normal patients [87]) in comparison with the ≥25 to 50 percent increase used to define contrast nephropathy in clinical trials. Higher doses of acetylcysteine (1200 mg twice daily for two days) also had virtually no effect on serum creatinine among patients with eGFR <60 mL/min per 1.73 m^2 [88].

Dosing — A variety of different dosing regimens for oral acetylcysteine have been studied. The most commonly studied dose is 600 mg orally twice daily. A subgroup analysis of 12 studies that evaluated this regimen reported a summary risk ratio of 0.73 (95% CI 0.46-1.2) [82]. However, studies comparing 600 and 1200 mg twice daily suggested slightly better outcomes with the higher dose [73,74]. A beneficial effect of high-dose acetylcysteine compared with control has also been shown. The best data are from a meta-analysis of 1677

subjects that compared the effect of high-dose acetylcysteine (defined as a daily dose >600 mg or a single preprocedural dose >600 mg) with control [89]. The majority (>70 percent) of subjects had CKD at baseline. The risk of contrast nephropathy was lower among subjects who received high-dose acetylcysteine, compared with those who did not (OR 0.46, 95% CI 0.33-0.64).

Although data regarding the efficacy of acetylcysteine are conflicting, if it is to be used, the preferred dose is 1200 mg administered orally twice daily on the day before and the day of the procedure to patients at risk for contrast nephropathy.

Intravenous therapy — Patients requiring emergent coronary angiography or procedures, in whom preventive therapy with oral acetylcysteine cannot be given the day before, have been treated with intravenous acetylcysteine. The benefit of this approach remains uncertain, and comparison of the various trials is difficult because of differences in patient populations and dosing, or lack of an adequate control group [71-73].

A placebo-controlled study of 487 patients with a mean baseline serum creatinine of 1.6 mg/dL (140 micromol/L), all of whom received isotonic saline (200 mL before the procedure, 1.5 mL/kg per hour for six hours after), found no benefit to therapy with intravenous acetylcysteine (500 mg immediately before the procedure) [71].

In contrast, two trials reported a substantial reduction in the rate of a ≥25 percent increase in serum creatinine with intravenous acetylcysteine, compared with pretreatment with intravenous saline or no pretreatment:

- In a trial of 80 patients with a mean baseline creatinine of 1.8 mg/dL (160 micromol/L), intravenous acetylcysteine (150 mg/kg prior to the procedure, followed by 50 mg/kg over four hours after to the procedure) was compared with isotonic saline (1 mL/kg per hour for 12 hours pre- and postcontrast) [72]. Fewer patients in the acetylcysteine group (5 versus 20 percent in the control group) developed AKI. However, at the high doses used, 7 percent developed anaphylactoid reactions.
- Different intravenous acetylcysteine doses, compared with no acetylcysteine, were studied in 354 patients with acute myocardial infarction [73]. Fewer patients assigned to high-dose (1200 mg) or low-dose (600 mg) intravenous acetylcysteine (followed by the same oral dose twice daily for two days) developed AKI (8 and 15 percent versus 33 percent of those in the placebo group).

However, the lower rate of AKI in the acetylcysteine group in this trial cannot be reasonably ascribed to treatment for the following reasons [73]:

- Most patients had normal kidney function (baseline serum creatinine 1.0 mg/dL [88 micromol/L]), in whom the risk of contrast nephropathy is expected to be negligible. (See "Pathogenesis, clinical features, and diagnosis of contrast-induced nephropathy", section on 'Epidemiology'.)
- A large proportion of patients, particularly in the control group, had severe complications that could explain the AKI (eg, intra-aortic balloon pump, respiratory failure requiring mechanical ventilation).

Based upon the lack of convincing evidence of benefit and the potential risk of anaphylactoid reactions, we suggest not giving intravenous acetylcysteine for the prevention of contrast nephropathy. (See "Acetaminophen (paracetamol) poisoning in adults: Treatment", section on 'Effectiveness of acetylcysteine'.)

Prophylactic hemofiltration and hemodialysis — The potential that removal of the inciting compound from the circulation might prevent contrast-induced AKI led to the examination of the role of prophylactic hemofiltration and hemodialysis in this setting.

Hemofiltration — The effectiveness of hemofiltration in high-risk patients undergoing procedures requiring contrast was compared with intravenous saline in two trials by the same group in Italy [90,91].

- In the first trial, 114 consecutive patients with a mean serum creatinine of 3.0 mg/dL [265 micromol/L] who required a coronary intervention were randomly assigned to isotonic saline infusion (1 mL/kg per hour) or to hemofiltration (1000 mL/hour fluid replacement rate) that was begun four to eight hours **prior** to the procedure

and resumed after the procedure for 18 to 24 hours. Approximately 250 mL of a nonionic, low-osmolality contrast agent were used in each group.

Compared with isotonic saline, patients in the hemofiltration group had significantly lower rates of a serum creatinine elevation >25 percent above baseline (5 versus 50 percent) and a requirement for dialysis (3 versus 25 percent). There were also significant reductions in in-house (2 versus 14 percent) and one-year mortality (10 versus 30 percent).

- A second trial by the same group found that hemofiltration after contrast administration produced intermediate outcomes between hemofiltration before and after contrast and isotonic saline [91].

The reported benefits with hemofiltration in these trials, in terms of increased serum creatinine and requirement for renal replacement therapy, may be explained by other factors, given the following study design flaws and unusual clinical features of these trials:

- Creatinine removal by the hemofiltration procedure may explain the decreased frequency of elevation in the serum creatinine.
- Hemofiltration or hemodialysis was started for oligoanuria persisting for 48 hours or longer, or earlier for overt heart failure. However, oligoanuria alone as an indication for replacement therapy is not usual clinical practice, particularly with contrast nephropathy, since spontaneous resolution within a few days is common. This may have artificially increased the proportion dialyzed in the saline group.
- Patients in the hemofiltration group were cared for in an intensive care unit; their greater intensity of care relative to the control group (of evidently sick patients given the high in-hospital and one-year mortality of the cohort) may explain why hemofiltration was associated with improved short- and long-term survival.
- The hemofiltration group received bicarbonate-containing replacement fluid, which may have conferred a protective effect.

A 2012 meta-analysis that included eight studies of hemodialysis and three studies of hemofiltration/hemodiafiltration showed no benefit of renal replacement therapy [92]. A subset analysis limited to studies of hemofiltration/hemodiafiltration also showed no benefit.

Hemofiltration is expensive, logistically cumbersome, and associated with significant risks; its effectiveness compared with other, less expensive strategies is not well established; and the reported benefits are implausible [93]. We do not currently recommend prophylactic hemofiltration.

Hemodialysis — Another proposed method of protecting high-risk patients from contrast-induced AKI is removal of the contrast agent using prophylactic dialysis. The efficacy of this approach was assessed in a 2006 meta-analysis of eight studies (six randomized), which included 412 patients (with a mean baseline serum creatinine ranging from 2.5 to 4.0 mg/dL [221 to 354 micromol/L]) who were treated with hemodialysis (six studies) or continuous dialysis modalities (two studies), compared with usual medical therapy alone [94]. There was no benefit and a suggestion of possible harm with hemodialysis.

A subsequent trial suggested possible benefit from prophylactic hemodialysis in patients with substantially more severe renal disease than in the trials included in the meta-analysis. In this trial, 82 patients with a stable baseline serum creatinine of 4.9 mg/dL (433 micromol/L) and a measured creatinine clearance of <15 mL/min per 1.73 m^2 (mean 13 mL/min per 1.73 m^2) were randomly assigned to hemodialysis (as soon as feasible after angiography, but within 12 hours) versus no hemodialysis [95].

Compared with the control group, reported benefits with prophylactic hemodialysis included significantly higher creatinine clearance levels on day 4 (12.8 versus 10.4 mL/min), decreased need for temporary hemodialysis (2 versus 35 percent), shorter length of hospital stay (6 versus 13 days), and a lower rate of requiring long-term hemodialysis after discharge (0 versus 13 percent). Of these, the last outcome is the only benefit that may be due

to the removal of contrast rather than performance of the initial dialysis procedure alone.

The lower risk of requiring chronic dialysis in the prophylactic hemodialysis group may have been due to the prevention of the loss of only a few mL/min of glomerular filtration via the removal of contrast. Among patients with such advanced renal disease at baseline, the preservation of even a small amount of renal function can delay the need for initiating chronic hemodialysis.

Support for this hypothesis is also provided by the observation that, among those not requiring chronic hemodialysis, a significantly larger percentage of the control group had a significant increase in serum creatinine (defined as >1 mg/dL [88 micromol/L]) between baseline and discharge (37 versus 5 percent). However, an alternative explanation is that the higher rate of requiring chronic dialysis in the control group may simply reflect the higher rate of requiring temporary dialysis, with a subsequent reluctance to discontinue dialysis in patients with such severe underlying disease.

Overall confidence in these data is limited by the small study size, the lack of rigorous controls utilized, observer bias, and uncertainties about the magnitude of delay in initiating dialysis in the prophylactic dialysis group. Furthermore, the impressive results have not been reproduced.

In the 2012 meta-analysis cited above [92], a subset analysis limited to studies of hemodialysis suggested that hemodialysis was associated with an increased risk of contrast nephropathy. There was no benefit of renal replacement therapy among patients with eGFR <30 mL/min per 1.73 m^2.

Summary — We do NOT recommend routine hemofiltration or hemodialysis for the prevention of contrast nephropathy in patients with CKD.

There is no indication for prophylactic dialysis for the prevention of volume overload in dialysis-dependent patients [96]. Furthermore, there are no studies that support immediate dialysis after intravascular contrast media administration in order to preserve residual renal function or limit the risk of allergic reaction in hemodialysis patients [96-98]. The issue of whether dialysis should be performed within 24 hours following contrast media administration or can safely wait until the next dialysis treatment remains unclear. Whereas some clinicians try to perform a hemodialysis treatment within 24 to 36 hours after intravascular contrast media exposure, others wait 48 to 72 hours, until the next scheduled hemodialysis treatment.

Contrast-enhanced magnetic resonance imaging as an alternative — Paramagnetic contrast agents, usually administered intravenously, have assumed a role in MRI similar to that played by iodinated contrast agents in CT imaging and angiography. Most MR contrast agents in clinical use are chelates of gadolinium, with the urine being the major route of excretion.

However, there are two major concerns with gadolinium-based chelates:

- Among patients with moderate and particularly severe kidney disease, the possible development of the severe syndrome of nephrogenic systemic fibrosis (NSF). This disorder is discussed separately. (See "Nephrogenic systemic fibrosis/nephrogenic fibrosing dermopathy in advanced renal failure".)
- The possible development of nephrotoxicity, similar to that seen with iodinated contrast agents.

Multiple studies have found that MR contrast agents, when used in small doses for MR examinations, have little or no nephrotoxicity [99-102]. This has led some to promote the use of gadolinium-based chelates as an alternative to iodinated radiographic contrast agents for digital subtraction angiography or interventional procedures, particularly in patients with renal insufficiency or iodinated contrast allergy [103-105].

However, there are emerging data from animal experiments, case reports, and small series that gadolinium-based contrast media can be associated with nephrotoxicity when given at high doses (>0.3 mmol/kg) for use as a contrast agent in standard (non-MR) digital subtraction angiography [106-110]. Some have claimed that the nephrotoxic profile of gadolinium is similar to that of diluted iodinated contrast media [107].

In the largest study, renal outcomes were reported for 21 patients with moderate to severe CKD (average serum creatinine concentration of 3.2 mg/dL [283 micromol/L]) undergoing digital subtraction angiography who were randomly assigned to iodinated nonionic contrast media (iohexol) or gadolinium (gadobutrol) [106]. The incidence of nephropathy (defined as a fall of ≥50 percent in baseline GFR) was 50 and 45 percent in the two groups, respectively; the mean fall in eGFR was 9 to 11 mL/min in the two groups.

However, this study has multiple limitations. These include the small number of patients evaluated, use of a high dose of gadolinium (0.34 to 0.90 mmol/kg), absence of clinically significant rises in mean serum creatinine concentration in either group, use of small volumes of iodinated contrast media to measure GFR, and a greater number of diabetics in the gadolinium group.

More importantly, among patients with moderate to severe kidney disease (dialysis dependent or eGFR <30 mL/min), the administration of gadolinium has been associated with the potentially severe syndrome of NSF. In such patients, gadolinium should be avoided, if possible. (See "Nephrogenic systemic fibrosis/nephrogenic fibrosing dermopathy in advanced renal failure".)

Summary — Based upon this limited literature, it is difficult to be certain that gadolinium is completely free of important nephrotoxicity in high-risk azotemic patients [111]. Furthermore, as noted above, gadolinium-based imaging should not be performed, if at all possible, in patients with an eGFR <30 mL/min because of the risk of NSF. In such patients, we prefer the risk of radiocontrast nephropathy with iodinated contrast media, using all of the preventive measures that are available, to the risk of the much more severe complication of NSF.

A separate issue, which has not yet been studied, is the safety of gadolinium-based in patients with an eGFR of 30 to 60 mL/min who also have an increased risk of iodinated contrast nephropathy. No data are available, and opinion among experts differs as to whether or not one would expose such patients to gadolinium if alternative imaging procedures were available. (See "Nephrogenic systemic fibrosis/nephrogenic fibrosing dermopathy in advanced renal failure".)

Inhibition of renal vasoconstriction — The acute reduction in GFR, induced by contrast agents, may be minimized in some patients by agents that prevent vasoconstriction. Such agents include theophylline or aminophylline (presumably via inhibition of the effect of adenosine), nifedipine, captopril, prostaglandin E or I2, low-dose dopamine, or fenoldopam [112-121]. Some [119,121], but not all [122,123], vasodilator agents may reduce the risk. The following studies have examined the effects of different agents:

- A meta-analysis that included 13 studies and 1222 patients demonstrated a theophylline-associated reduction in risk for contrast nephropathy, but not for dialysis or in-house mortality [124]. However, there was significant heterogeneity between studies, which appears to have been due to differences in baseline creatinine and in the quality of studies. On further analysis, a protective effect of theophylline was not observed among high-risk patients when all studies were analyzed, nor in any group of patients when only higher quality studies were analyzed. These results suggest that theophylline has little or no effect on contrast nephropathy [125]. In addition, concurrent administration of the antiplatelet agent dipyridamole may increase contrast toxicity by enhancing the action of adenosine [112].

- The prostacyclin analog, iloprost, was tested in a randomized, placebo-controlled trial of 208 patients undergoing coronary angiography who had a serum creatinine concentration >1.4 mg/dL (123.76 micromol/L) [121]. Intravenous iloprost (1 ng/kg per min) or placebo was given 30 to 90 minutes before and 240 minutes after the procedure. Contrast nephropathy (defined as an increase in serum creatinine >0.5 mg/dL [44.2 micromol/L] or >25 percent, measured two to five days after the procedure) occurred less frequently among patients who received iloprost compared with placebo (8 versus 22 percent, respectively). Severe hypotension required withdrawal of iloprost in three patients. Although iloprost may be effective in the prevention of contrast nephropathy, confirmation of these results in larger definitive trials is necessary before its use can be recommended [126].

- A prospective randomized trial (CONTRAST) assessed the effectiveness of fenoldopam in 315 patients (one-

half diabetic) undergoing a cardiovascular procedure who had CKD with an estimated creatinine clearance <60 mL/min (mean 29 mL/min, with a mean serum creatinine of 1.8 mg/dL [159 micromol/L]) [122]. All patients also received one-half normal saline, as mentioned above, and contrast nephropathy was defined as an increase in serum creatinine of ≥25 percent above baseline in the first four days. There was no reduction in the incidence of contrast nephropathy in the fenoldopam group (34 versus 30 percent with placebo). It has been proposed that direct intrarenal administration may be more beneficial [127].

- A nonselective endothelin receptor antagonist was tested in a multicenter, double-blind, randomized trial of high-risk patients undergoing coronary angiography [123]. Compared with those assigned to placebo, a significantly higher percentage of patients who received active therapy sustained contrast nephropathy (56 versus 29 percent); this observation raises the possibility that endothelin may actually provide an intrinsic protective effect rather than contributing to the development of AKI. Alternatively, selective endothelin receptor antagonists may be required to demonstrate prophylactic value in this setting.

Other interventions — A variety of other interventions have been tried, including remote ischemic preconditioning (RIPC), atrial natriuretic peptide, statins, and ascorbic acid.

Remote ischemic preconditioning — RIPC is a method by which the deliberate induction of transient nonlethal ischemia of an organ protects against subsequent ischemic injury of another organ. Some, but not all, studies have suggested that RIPC prior to cardiac surgery protects against AKI. (See "Possible prevention and therapy of postischemic (ischemic) acute tubular necrosis", section on 'Remote ischemic preconditioning'.)

Some studies have suggested that RIPC prior to contrast administration may protect against contrast nephropathy. As examples:

- In one randomized, double-blind trial, 100 patients with serum creatinine >1.4 mg/dL (124 mmol/L) or eGFR <60 mL/min per 1.73 m^2 were subjected to RIPC or to a sham procedure prior to elective coronary angiography [128]. RIPC was induced by intermittent arm ischemia generated by four cycles of five-minute inflation of a blood pressure (BP) cuff to 50 mmHg above individual systolic pressure within 45 minutes before angiography. The sham procedure consisted of inflation of a BP cuff to individual diastolic pressure, followed by deflation to 10 mmHg. All patients received acetylcysteine and a continuous saline infusion. The incidence of contrast nephropathy (defined as an increase in serum creatinine to ≥25 percent or ≥0.5 mg/dL [44 mmol/L] above baseline within 48 hours) was decreased among patients who underwent RIPC, compared with the sham procedure (6 versus 20, respectively, OR 0.21, 95% CI 0.07-0.57). At six weeks of follow-up, a composite cardiovascular endpoint including death, rehospitalization, or hemodialysis occurred less frequently in the RIPC group, compared with sham (8 versus 19, respectively).

- In a second trial, 225 patients with a non-ST-segment elevation myocardial infarction were randomly assigned to receive RIPC or a sham procedure prior to PCI [129]. RIPC consisted of four cycles of 30-second inflation, followed by 30 seconds deflation of the stent balloon during the PCI procedure; the sham procedure consisted of four cycles of 30-second inflation to only 3 atm pressure, followed by deflation. Contrast nephropathy occurred less frequently in the RIPC group, compared with the sham group (12.4 versus 29.5 percent, respectively, OR 0.34, 95% CI 0.16-0.71). Death or rehospitalization at 30 days was less frequent in the RIPC group, compared with the sham group (22.3 versus 12.4 percent, respectively, OR 0.49, 95% CI 0.22-1.01).

These results require confirmation in larger randomized trials to determine the underlying mechanism of protection and before RIPC can be recommended as a preventive measure for contrast nephropathy [130]. In addition, the safety of repetitive balloon inflations in a coronary artery poststenting remains unclear.

Statins — Statins may improve endothelial function, reduce arterial stiffness (via improved endothelin-mediated vasodilatation), and reduce inflammation and oxidative stress [131,132]. The possibility that statins may reduce the incidence of contrast-induced AKI has been suggested by several observational studies [133-135] and in some randomized trials [136-139]. As examples:

- In a single-center randomized trial, 503 patients with non-ST elevation acute coronary syndrome were randomly assigned to receive rosuvastatin (40 mg on admission, followed by 20 mg daily) or to a control group prior to angiography [138]. All patients received standard therapy including unfractionated heparin, aspirin, and clopidogrel. All patients received isotonic saline (1 mL/kg/hour) and N-acetylcysteine (1200 mg twice daily). Patients were excluded who were already on a statin; who required emergent angiography (within two hours); or who had AKI, end-stage renal disease (ESRD), a serum creatinine ≥3.0 mg/dL, or other significant comorbidities. At discharge, the statin group continued to receive rosuvastatin 20 mg daily, whereas the control received 40 mg rosuvastatin.

  Contrast-induced AKI, defined as an increase in creatinine ≥0.5 mg/dL or ≥25 percent over baseline within 72 hours, occurred less frequently in the statin group, compared with control (6.7 versus 15.1 percent, respectively, with an adjusted OR 0.38, 95% CI 0.20-0.71). In addition, the incidence of adverse cardiovascular or renal events (including death, dialysis, myocardial infarction, stroke, or CKD) was lower in the statin versus control group at 30 days (3.6 versus 7.9 percent, respectively).

- In a second large, randomized trial, 2998 patients with type 2 diabetes and CKD (defined as eGFR between 30 and 89 mL/min per 1.73 m^2) were assigned to receive rosuvastatin or to a control group prior to a diagnostic angiogram with or without percutaneous intervention [139]. Patients assigned to rosuvastatin received 10 mg daily two days prior and three days after the scheduled procedure [139]. Contrast-induced AKI (defined as ≥0.5 mg/dL or ≥25 percent increase in serum creatinine above baseline at 72 hours after contrast exposure) was less common among patients assigned to rosuvastatin, compared with control (2.3 versus 3.9 percent, respectively).

However, one randomized trial that included 304 patients with estimated creatinine clearance <60 mL/min showed no benefit of atorvastatin, compared with placebo [140].

Statins merit further study for the prevention of contrast-induced nephropathy. Among patients who are likely to be started on statins prior to discharge (such as those with acute myocardial infarction), it is reasonable to start the statin prior to angiography, although this suggestion is based on weak evidence. We do not believe there are sufficient data to support the use of statins solely for the prevention of contrast nephropathy.

Oral sodium citrate — One randomized trial has demonstrated a benefit of oral sodium citrate in preventing contrast nephropathy [141]. This trial included 202 patients who were randomly assigned to receive either Na/Citrate (5 g) in 200 mL water or placebo (200 mL water) one hour before and four hours after coronary angiography. All patients received normal saline 1 mL/kg per hour for 2 hours before and 12 hours after angiography. Over 75 percent of patients had a history of diabetes, and over 40 percent had eGFR <60 mL/min per 1.73 m^2. The risk of contrast nephropathy (defined as >25 percent or >44 micromol/L increase in serum creatinine at 48 hours) was lower among patients who received oral citrate, compared with placebo (4 versus 20 percent, respectively). This result requires confirmation by other trials before such an approach is recommended.

Atrial natriuretic peptide — Atrial natriuretic peptide (anaritide) has been considered for prophylaxis in high-risk patients since its administration has been beneficial in animal models of contrast nephropathy [142]. However, **no benefit** was observed in a multicenter, prospective, double-blind, placebo-controlled randomized trial [143]. In this study, 247 patients (with a serum creatinine >1.8 mg/dL [159 micromol/L] or between 1.5 and 1.8 mg/dL [133 to 159 micromol/L]) undergoing radiocontrast administration were randomly assigned to placebo or one of three intravenous doses of anaritide given 30 minutes before and continued for 30 minutes after the procedure. Compared with placebo, active therapy at any dose failed to reduce the incidence of nephropathy in all patient groups, including those with diabetes.

Ascorbic acid — Ascorbic acid can ameliorate renal damage in experimental models of ischemic or toxic injury [144,145], and an initial randomized trial in humans suggested protection against contrast-mediated nephropathy [146]. However, a second, large, well-designed trial found that ascorbic acid did not provide added benefit to a prophylactic regimen of isotonic saline plus acetylcysteine among patients at high risk [40]. (See 'Intravenous

saline' above.)

In summary, data are insufficient to support the use of ascorbic acid for prevention of contrast nephropathy.

Trimetazidine — Trimetazidine, a cellular anti-ischemic agent, provided added protection to isotonic saline from contrast-mediated nephropathy in an initial, small, randomized prospective study [147]. Further study in a larger number of patients is required to better characterize the effectiveness of this agent.

Withholding ACE inhibitors and/or ARBs — Some studies have suggested that patients who are on an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blockers (ARBs) are at higher risk for contrast nephropathy, compared with those who are not [148]. Studies that have examined this issue are discussed elsewhere. (See "Pathogenesis, clinical features, and diagnosis of contrast-induced nephropathy", section on 'Other'.)

However, it is not clear whether holding or withdrawing an ACE inhibitor and/or ARB prior to angiography provides any benefit. In one study, 220 patients who were on ACE inhibitors or ARBs and had an eGFR of 15 to 60 mL/min per 1.73 m^2 were randomly assigned prior to angiography to either an ACE inhibitor/ARB discontinuation group, in which the ACE inhibitor or ARB was held 24 hours prior to procedure, or to a control group, in which these agents were continued [149]. There was no significant difference in the incidence of contrast nephropathy between patients who had the ACE inhibitor and/or ARB withdrawn and those who did not.

The issue of whether to withhold ACE inhibitors and ARBs prior to contrast procedure is not resolved, and further study of this important issue is warranted. At this time, given the insufficient data, we generally do not withhold ACE inhibitors and ARBs prior to angiography. ACE/ARB may protect against contrast-induced nephropathy by blocking renin-angio II vasoconstriction.

SUMMARY AND RECOMMENDATIONS — Optimal therapy to prevent contrast-induced acute kidney injury (AKI) remains uncertain. Patients with near-normal renal function are at little risk, and few precautions are necessary, other than avoidance of volume depletion.

We recommend the following preventive measures for patients at increased risk of contrast nephropathy, which is defined as a serum creatinine ≥1.5 mg/dL (132 micromol/L) or an estimated glomerular filtration rate (eGFR) <60 mL/1.73 m^2, particularly in those with diabetes (see "Pathogenesis, clinical features, and diagnosis of contrast-induced nephropathy", section on 'Epidemiology'):

- Use, if possible, ultrasonography, magnetic resonance imaging (MRI) **without** gadolinium contrast, or computed tomography (CT) scanning **without** radiocontrast agents. (See 'Overview' above.)
- We recommend **not** using high-osmolal agents (1400 to 1800 mosmol/kg) (**Grade 1A**). (See 'Type of contrast agent' above.)
- We recommend the use of iodixanol or nonionic low-osmolal agents, such as iopamidol or ioversol, rather than iohexol (**Grade 1B**). (See 'Nonionic iso-osmolal agents' above.)
- Use lower doses of contrast and avoid repetitive, closely spaced studies (eg, <48 hours apart). (See 'Overview' above.)
- Avoid volume depletion and nonsteroidal antiinflammatory drugs (NSAIDs). (See 'Overview' above.)
- If there are no contraindications to volume expansion, we recommend isotonic intravenous fluids prior to and continued for several hours after contrast administration (**Grade 1B**). The optimal type of fluid and timing of administration are not well established. We suggest isotonic bicarbonate rather than isotonic saline (**Grade 2B**). (See 'Intravenous bicarbonate' above.)

  A suggested regimen is a bolus of 3 mL/kg of isotonic bicarbonate for one hour prior to the procedure, and continued at a rate of 1 mL/kg per hour for six hours after the procedure. This solution can be prepared by

adding 150 mEq of sodium bicarbonate (three 50 mL ampules of 1 mEq/mL sodium bicarbonate) to 850 mL of sterile water. An alternative regimen is to administer 1 mL/kg for 6 to 12 hours pre- and postprocedure. There are no commercially available isotonic sodium bicarbonate solutions available, and, if bicarbonate is used, care must be taken to avoid compounding errors in preparing solutions.

If isotonic saline is chosen, suggested regimens are:

- Isotonic saline at a rate of 1 mL/kg per hour, begun at least 2 and preferably 6 to 12 hours prior to the procedure, and continuing for 6 to 12 hours after contrast administration. The duration of administration of fluid should be directly proportional to the degree of renal impairment (eg, should be longer for individuals with more severe renal impairment). An alternative regimen that may be more convenient for use among outpatients is 3 mL/kg over one hour and 1 to 1.5 mL/kg/hour for four to six hours after the procedure.

- Despite conflicting data, we suggest that acetylcysteine be administered the day before and the day of the procedure, based upon its potential for benefit and low toxicity and cost (**Grade 2B**). If acetylcysteine is administered, we suggest giving 1200 mg orally twice daily rather than 600 mg twice daily the day before and the day of the procedure (**Grade 2B**). (See 'Acetylcysteine' above.)

- Based upon the lack of convincing evidence of benefit and the potential risk of anaphylactoid reactions, we suggest not using intravenous acetylcysteine for the prevention of contrast nephropathy (**Grade 2B**). (See 'Intravenous therapy' above.)

- We recommend **not** using mannitol or other diuretics prophylactically (**Grade 1B**). (See 'Volume administration, mannitol, and diuretics' above.)

- Among patients with stage 3 and 4 chronic kidney disease (CKD), we recommend **not** performing prophylactic hemofiltration or hemodialysis after contrast exposure (**Grade 1B**). (See 'Prophylactic hemofiltration and hemodialysis' above.)

- We do not believe there are sufficient data to support the use of prophylactic hemodialysis following contrast exposure, even among patients with stage 5 CKD who have a functioning hemoaccess. (See 'Hemodialysis' above.)

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