Contrast-induced nephropathy (CIN) is the third most common reason for hospital-acquired acute kidney injury. In-hospital and long-term mortality and morbidity (e.g., stroke, myocardial infarction and vessel re-occlusion) incidences are higher in patients who develop CIN as opposed to patients without CIN. Evolving diagnostic and interventional procedures make CIN a more serious problem than it was previously. Accordingly, efforts to reduce CIN incidence have received particular attention in recent years, and many studies have been published regarding this issue. In this article, we conduct a systematic literature search of the most recent evidence available from 2000 to 2010, with the purpose of providing practical suggestions for prevention of CIN.

**Definition, incidence & clinical significance**

Although there is no widely accepted definition for contrast-induced nephropathy (CIN), it is generally defined as an absolute (≥0.5 mg/dl) or relative (≥25%) increase in serum creatinine (SCr) with respect to baseline within 48–72 h of contrast media administration in the absence of alternative causes. The incidence of CIN varies, ranging from almost zero to over 50% [1–4]. The reasons for this high variance result from the CIN definition not being standardized in studies (i.e., if 1 mg/dl is used instead of 0.5 mg/dl for SCr, the incidence obviously decreases), as well as risk factors and CM type and quantity.

Contrast-induced nephropathy is the third most common reason for hospital-acquired acute kidney injury. In-hospital and 1- and 5-year mortality and morbidity (e.g., stroke, myocardial infarction and vessel re-occlusion) incidences are higher in patients who develop CIN as opposed to patients without CIN [5–9]. It is not known whether this can be attributed to CIN that directly causes the increased mortality or to the fact that patients who develop CIN have more serious and mortal comorbidities.

**Clinical features & risk factors**

Contrast-induced nephropathy can be detected from an increase in SCr level beginning within the 12–24 h after intake of CM; however, the increased SCr level may not be detected until 72–96 h post-intake. In many of the cases, oliguria is not detected. Renal dysfunction is frequently mild and transient, but sometimes may be as severe as to require hemodialysis.

For the development of CIN, chronic kidney disease (CKD) is the most important risk factor (Figure 1) [10] (CKD is defined as SCr ≥1.5 mg/dl or estimated glomerular filtration rate <60 ml/min/1.73 m²). For those who have cardiovascular disease (especially for elderly or obese patients), the modification of diet in renal disease (MDRD) formula for estimated glomerular filtration rate gives a more precise result than the Cockcroft–Gault formula [11,12]. For the MDRD formula, the SCr, age, gender and race (being African or not) are required whereas weight is not. The alternative MDRD formula that also includes blood urea and albumin values can be used, but the result will be similar. Current Personal Digital Assistants have built-in programs for this complex formula.

Other important risk factors are diabetes mellitus, hypovolemia, hypotension, advanced age (>70 years), chronic heart failure (CHF), anemia, nephrotic drug use (e.g., gentamycin and nonsteroidal anti-inflammatory drugs), hyperuricemia and recent (within 10 days, especially the first 3 days) and overdose of CM. The greater number of risk factors, especially elevation of baseline SCr value, the greater the probability of CIN.

In oliguric hemodialysis patients, CM may reduce glomerular filtration rate and lead to reduced urine output and accordingly quality of life may be disturbed. In these cases, CM...
Interv. Cardiol. (2010) 2(2) should be avoided as much as possible. However, according to some authors, if the chronic hemodialysis patient is anuric, CIN is not a matter of concern since there is nothing to lose for residual kidney function, and any type of CM can be used without apprehension [13]. However, whether anuria itself has an effect on quality of life is somewhat doubtful [14].

In order to diagnose CIN accurately, other causes of renal dysfunction such as sepsis and renal atheroemboli should also be considered (Box 1) [15]. During coronary angiography (CAG) or percutaneous coronary intervention (PCI), microatheroemboli may detach from the atherosclerotic aortic wall while catheterizing, and travel to the kidney.

The route of CM administration is also important regarding CIN risk [16]. It is thought that CIN risk is higher when CM is administered via a supra-renal arterial route (e.g., coronary angiography [CAG] or PCI) than via an intravenous route (e.g., computerized tomography or intravenous pyelography). This may be caused by a higher concentration of CM within kidney after the intra-arterial rather than intravenous injection. However, renal atheroemboli in the intra-arterial route may be the other cause of increased SCr levels.

Pathophysiologic mechanisms

The pathophysiology of CIN is not clearly known owing to the fact that it is generally transient, and histopathologic changes caused by underlying renal dysfunction complicate biopsy assessment. For this reason, current data are mostly obtained from animal experiments.

The most important mechanisms are renal vasoconstriction (e.g., reduced medullary blood flow) and acute tubular injury. Reduced medullary blood flow is caused, in part, by contrast-induced release of vasoconstrictor agents such as endothelin, by blockage of vasodilator agents such as nitric oxide and prostaglandins, and by increased viscosity of the vascular bed by high osmolar CM (HOCM). The other mechanism, acute tubular injury, is possibly caused either by a direct toxic effect of CM, triggering of oxygen free radical formation by CM, or both. Acute tubular injury may also be exacerbated by renal vasoconstriction. High oxygen demands due to increased workload make the residual functioning tubuli in CKD more susceptible to injury caused by all these effects.

Contrast media

The first manufactured CM were ionic and had high osmolality (>1500 mOsm/kg-water); however, because this increased the osmotic load of the kidney the risk of nephropathy was quite high. For this reason, nonionic CM were developed. As these also had relatively lower osmolality with respect to older HOCM versions, these CM were named as low osmolality CM (LOCM). Despite their name being LOCM, they still have higher osmolality than blood (blood: 290, LOCM: <850 mOsm/kg-water) (Table 1). After discovering that a reduction of osmolality was less nephrotoxic; iodixanols having the same osmolality as blood were developed, and classified as iso-osmolar CM.

Prevention strategies

Once CIN develops, the therapy is conservative. Fluid and electrolyte balance should be maintained and the patient should be followed-up with serial blood tests, whether or not he or she is proceeding to dialysis. However, the best treatment is to prevent CIN. To date, many studies have been conducted about prevention of CIN. Owing to numerous contradicting studies, and for clarity in order to simplify the true approach to CIN, we are going to review only randomized controlled studies’ results from 2000 to 2010.

Figure 1. Correlation between estimated glomerular filtration rate and contrast-induced nephropathy. Please note that CIN risk increases as estimated glomerular filtration rate decreases (especially for the values less than 60 ml/min/1.73 m2, CIN risk increased exponentially). CIN: Contrast-induced nephropathy.

Adapted from [16].
**Type & quantity of contrast media**

High osmolar CM began to be substituted with LOCM in practice owing to CIN risk, allergy, bradycardia, asystole and myocardial depressive effects. The lowering of LOCM prices down close to HOCM prices has had an important role in this alternation.

Iodixanol is equivalent to other LOCMs in terms of reduction of CIN risk in 11 studies [17–27], superior in four [28–31] and inferior in two [32,33]. In a meta-analysis, iodixanol, although having a partially lower risk of CIN, hemodialysis and death compared with iohexol and ioxaglate, was similar regarding risks when other LOCMs (iopamidol, ioversol, iopromide and iomeprol) were taken altogether [34].

Whether the CM is a monomer or dimer does not affect our selection. Another key point is that HOCMs are possibly not more nephrotoxic when compared with LOCMs in patients with no risk factors [35–37].

It can be estimated that if the amount of CM has increased, the CIN risk would also have increased [38,39]. A retrospective study on this subject suggests that for diagnostic procedures, 30 ml of CM should not be exceeded, and for interventional procedures the maximum level is 100 ml [40], whereas some others suggest definite amounts of CM to be given on the basis of weight [41]. However, owing to the complexity and unpredictability of PCI, and since it would be impractical in the real-world to interrupt the procedure, these values have often been exceeded, the most practical method is to complete the procedure with the least amount of CM possible. This can be assured by utilization of biplane or rotational devices, working with small-sized catheters, avoidance of ventriculography (despite the intense pressure by some surgeons before coronary artery bypass grafting) for the cases whose left ventricular and valvular functions are clearly assessed by echocardiography or MRI, and administration of the least amount of CM – just enough for a complete wash of coronary vessels. At this point, even though gadolinium-enhanced MRI was considered to be an interesting alternative to prevent CIN, newly defined nephrogenic systemic fibrosis, which is irreversible and a more serious problem than CIN, revealed that gadolinium is not so harmless [42–44].

In fact, the best way to administer the least amount of CM is not to use it at all; that is, not to proceed with an unnecessary procedure. If it is expected to produce the same results or unlikely to change the therapeutical approach, a preference for echocardiography use instead of catheterization, MRI without gadolinium, CT without contrast, myocardial perfusion scintigraphy, and avoiding unnecessary CAG or PCI are important procedures to consider. As an alternative contrast agent, carbon dioxide can be considered in digital subtraction angiography to be applied in subdiaphragmatic vessels. Carbon dioxide, however, is not to be nephrotoxic; its disadvantage is the probability of being neurotoxic (in the presence of right-to-left shunt or in supradiaphragm imaging) [45–48].

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**Table 1. Radiographic contrast media.**

<table>
<thead>
<tr>
<th>Osmolality (mOsm/kg-water)</th>
<th>Ionic status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High-osmolality contrast media</strong></td>
<td></td>
</tr>
<tr>
<td>Sodium diatrizoate</td>
<td>1690</td>
</tr>
<tr>
<td>Sodium meglumine diatrizoate</td>
<td>1940</td>
</tr>
<tr>
<td><strong>Low-osmolality contrast media</strong></td>
<td></td>
</tr>
<tr>
<td>Ioxaglate</td>
<td>600</td>
</tr>
<tr>
<td>Iohexol</td>
<td>844</td>
</tr>
<tr>
<td>Iopamidol</td>
<td>796</td>
</tr>
<tr>
<td>Ioxilan</td>
<td>695</td>
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<tr>
<td>Iopromide</td>
<td>774</td>
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<tr>
<td>Ioversol</td>
<td>792</td>
</tr>
<tr>
<td>Iomeprol</td>
<td>726</td>
</tr>
<tr>
<td>Iodixanol (iso-osmolar)</td>
<td>290</td>
</tr>
</tbody>
</table>

Osmolality of blood = 290 mOsm/kg-water. Please also note that iso-osmolar iodixanol is actually a subclass of low-osmolality contrast media.

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**Box 1. Clinical features in favor of renal atheroemboli rather than contrast-induced nephropathy.**

- Serum creatinine increase delayed for days to weeks after the procedure.
- Little or no recovery of renal function.
- Livedo reticularis or other embolic lesions (especially at fingertips).
- Transient eosinophilia
In the case of stable angina pectoris in particular, as the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) study stressed, keeping in mind that there is no long-term mortality difference between medical therapy and PCI; trying medical therapy before deciding upon CAG will probably prevent much more CIN in the real-world compared with application of all the preventive strategies mentioned in this article. On the other hand, certain procedures should not be avoided whenever necessary, even if there is a CIN risk. For example; in obstructive coronary artery disease patients who have CKD, the PCI procedure has been shown to provide a better prognosis than no PCI in a registry [49]. The same situation may also apply to patients with heart failure. As a result, the physician should consider the case globally, and carefully assess the necessary therapeutric options by weighting profit and loss, even if the therapy is risky.

■ Hydration

The most effective prophylactic strategy in reducing the risk of CIN is hydration. It is a low-cost and low-risk strategy for most patients. It dilutes CM and decreases contact time within kidney, increases diuresis, and suppresses production of endogen vasoconstrictor agents. There are several studies investigating different fluids. However, because alkalinization is known to reduce free radical production, studies regarding hydration with fluids that have alkali properties, such as sodium bicarbonate, have been performed, and fluids with sodium bicarbonate were compared with isotonic sodium chloride. Five of six prospective studies showed that isotonic sodium bicarbonate caused fewer incidences of CIN than isotonic sodium chloride [50–54], where in one study there was no difference [55]. However, in a retrospective cohort study consisting of 7977 patients, sodium bicarbonate caused more CIN than sodium chloride [56]. Furthermore, there are conflicting results between meta-analyses [57–61]. For this reason, well-designed studies are awaited to decide which one should be the first choice (sodium bicarbonate solution is prepared by adding three 50 mL doses of 8.4% mEq/l sodium bicarbonate to either 850 mL of 5% dextrose or sterile water).

Administration of volume replacement in the form of infusion pre- or post-procedure was seen to be more effective than oral fluid replacement or if given in the form of bolus during procedure [62–64]. In addition, in one study the combination of 0.45% sodium chloride and 5% dextrose prevented less CIN in comparison to isotonic sodium chloride [65]. However, it must be considered that this study did not control for the amount of sodium administered: the difference between the isotonic sodium chloride and 0.45% sodium chloride is that you have to give twice as much of the latter to give the same amount of sodium as the former.

Hydration is problematic for patients with CHF. It is rational to appraise the clinical signs for volume status, and hydrate only the hypovolemic patients with CHF meticulously. Patients with CHF should not be hydrated routinely. It is suggested that patients are given sodium bicarbonate 1 h before the procedure as 3 mL/kg/h, or isotonic sodium chloride 6–12 h before the procedure as 1 mL/kg/h. After the procedure, hydration (whichever you have chosen) should continue with 1 mL/kg/h dose for 6–12 h (with a longer time in hot weather or for advanced CKD cases).

■ N-acetylcysteine

Owing to antioxidant and vasodilatation effects, there have been many studies conducted considering the possible potential of N-acetylcysteine (NAC) to prevent CIN. Results of 31 studies are as follows: in nine studies, administering NAC is superior to not administering [66–73], more harmful in one [74] and indifferent in others [75–95]. Several meta-analyses and even overview have been made in this area and the results have differed [96–99]. To dispel this confusion, a well-designed (multicenter, prospective, randomized, controlled and large scale) acetylcysteine for contrast-induced nephropathy (ACT) trial is still ongoing [100]. Until the release of the results, we suggest applying this prophylaxis, which is at least known to be inexpensive and harmless. Despite the controversies regarding the administration dose and route, the most widely accepted mode is to give NAC 1200 mg orally, 1 day before and 1 day after the procedure, and twice-daily from then on [96]. Superiority of the intravenous route to oral is controversial owing to lack of evidence and risk of anaphylaxis. It should be emphasized that all NAC studies were conducted in patients whose hydration is maintained, that is, NAC is not an alternative to hydration.

■ Hemodialysis/hemofiltration

Owing to the capability of eliminating more than half of the volume of CM by hemodialysis, three studies were conducted. In one of them, hemodialysis prevented CIN [101], and in the other two it unexpectedly increased CIN risk [81,102]. Here it is necessary to distinguish prophylactic
hemodialysis (just after CM administration, yet before CIN development), of which benefit was not clearly demonstrated from therapeutic hemodialysis implemented for acute kidney injury, the most advanced state of CIN.

In two studies on hemofiltration, CIN risk was reduced provided hemofiltration was initiated before CM administration [103,104]. However, the obtained benefit may have been a pseudo-effect resulting from bicarbonate administered simultaneously or direct clearance of SCr by hemofiltration. Accordingly, although it may be useful for very high-risk patients (e.g., stage 5 CKD), it is difficult to justify hemofiltration in view of its cost, invasiveness and aforementioned reasons. With all these data, expensive, invasive and ineffective prophylactic hemodialysis cannot be recommended for prevention of CIN. However, hemofiltration may be used for very high-risk patients, but there is a need to conduct further investigations in order to provide more supported recommendations.

**Angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers & metformin**

In the results of some studies, angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers increased the risk of CIN [105,106]. In other studies they decreased the risk of CIN [107,108]. Accordingly, at present, the issue of whether to discontinue before the procedure is not clear.

Metformin is important not for being nephrotoxic but for the risk of lactic acidosis if CIN develops. There are five guidelines regarding the use of metformin in diabetic patients receiving CM, and these guidelines have inconsistent recommendations owing to the low level of evidence for ceasing metformin therapy [109]. It seems reasonable to discontinue metformin before 2 days of CM administration and remain off for 2 days after CM if renal dysfunction presents (SCr ≥ 1.5 mg/dl or estimated glomerular filtration rate <60 ml/dl/1.73 m²) [43]. If renal function is normal, it may not be necessary to stop taking metformin, owing to the low risk of developing lactic acidosis.

**Other methods**

Endothelin-receptor antagonists and phenoldopam, a renal vasodilator, increased CIN incidence, contrary to expectations [75,110–113]. Dopamine, furosemide, mannitol, calcium-channel blockers and theophylline showed no benefit [40,45,114–117]. The effect of statins, ascorbic acid, erythropoietin, prostacyclin analogs and trimetazidine should be assessed after large-scale studies [118–126]. In brief, according to our present knowledge, the agents mentioned in this paragraph cannot be recommended to prevent CIN.

**Future perspective**

The incidence of CIN has been increasing gradually. An increase in incidence of diabetes mellitus, hypertension, advanced age and CKD in the population play an important role. Awareness about the presence and severity of nephrogenic systemic fibrosis caused by gadolinium-enhanced MRI appears to have led to an increase in the number procedures utilizing CM. This makes us believe that CIN will be a more serious problem in the future. Therefore, the requirement of well-designed studies that do not bear the drawbacks of most of the present studies will increase (Box 2).

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**Box 2. What a well-designed prevention study regarding contrast-induced nephropathy should entail.**

- It should be large-scale, multicenter, prospective, randomized and double blind.
- The definition of contrast-induced nephropathy should be standardized.
- Other reasons for nephropathy (especially renal atheroemboli) should be considered.
- Nonionic low osmolality contrast media should be used, and each case should be given the same type of contrast media in equal amount.
- Stability of serum creatinine (SCr) should be ensured, that is, values of at least 2 weeks previously, and just before the procedure these values should be the same. SCr should be measured just before the hydration to avoid dilution effect. Postprocedure SCr measurements should not be random but standardized at exactly 48 h (additional measurements may increase the quality).
- Estimated glomerular filtration rate should be calculated (preferably with the modification of diet in renal disease formula).
- Patients’ risk profile (especially diabetes mellitus) should be clearly stated. Only patients with estimated glomerular filtration rate <60 ml/dl/1.73 m² or SCr ≥ 1.5 mg/dl should be recruited for the study so as not to disturb statistical importance since contrast-induced nephropathy risk is low in the normal population.
- Isotonic sodium bicarbonate or isotonic sodium chloride infusion should be preferred for hydration.
- Administration route (intravenous or intra-arterial) should be similar.
- Long term mortality rates and need for chronic dialysis should be hardly stated.

*If percentage increase is 25% by definition, the increase, which is probably not important, may be wrongly assessed in low SCr values. (e.g., elevation of SCr from 0.6 to 0.75 mg/dl) [127].*
Executive summary

Definition & importance
- Contrast-induced nephropathy is generally defined as an absolute (≥0.5 mg/dl) or relative (≥25%) increase in serum creatinine with respect to baseline within 48 to 72 h of contrast media administration in the absence of alternative causes.
- It is related to short- and long-term mortality and morbidity, and is the third most common reason for hospital-acquired acute kidney injury.

Risk factors
- The most important one is chronic kidney disease (CKD; serum creatinine ≥1.5 mg/dl or estimated glomerular filtration rate <60 ml/dl/1.73 m²; for estimated glomerular filtration rate, the ‘modification of diet in renal disease’ formula is preferred to the Cockcroft–Gault formula).
- Other risk factors include diabetes mellitus, hypovolemia, hypotension, advanced age, chronic heart failure, anemia, nephrotoxic drug use, hyperuricemia and high quantity or recent (within 10 days) use of contrast media.
- The greater the number of risk factors a person has, the greater their risk for CIN.

Prevention strategies
- For people with no risk factors it would probably be enough to prevent only volume depletion and make a note of contrast media amount.
- Our suggestions for people with any risk factors are:
  - Prefer echocardiography, computerized tomography without contrast, magnetic resonance imaging without gadolinium or myocardial perfusion scintigraphy to the procedure using contrast media, if appropriate.
  - Do not give contrast media redundantly; always strive to finish the procedure with the least amount of contrast media. Avoid ventriculography if it is unlikely to provide extra information.
  - Consider if coronary angiography or percutaneous coronary intervention are really necessary scientifically; in some situations (especially heart failure or refractory angina) do not abandon the procedure despite contrast-induced nephropathy risk. If possible avoid a second procedure (e.g., percutaneous coronary intervention) within 10 days of the first procedure (e.g., coronary angiography). If this is not practical for your institute, wait at least 3 days.
  - Discontinue nonsteroidal antinflammatory drugs and other nephrotoxic drugs. Discontinue metformin for 2 days before and after the procedure if renal dysfunction exists (angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers are controversial and to be used at the physician’s discretion).
  - Do not use high osmolar contrast media; use iso- or low-osmolar contrast media (except ioxaglate and iohexol).
  - Avoid volume depletion; give fluid infusion (except in chronic heart failure). Prefer isotonic solutions (isotonic sodium chloride or isotonic sodium bicarbonate) to hypotonic ones (5% dextrose and 0.45% sodium chloride).
  - Administer N-acetylcysteine 1200 mg pre- and post-24 h, twice-daily. The oral route is preferable to intravenous.
  - Do not use prophylactic hemodialysis. Hemofiltration should only be considered for stage 5 chronic kidney disease patients.
  - Check postprocedural 48-h serum creatinine value.

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Papers of special note have been highlighted as:

Contrast-induced nephropathy: a contemporary & simplified review


*Meta-analysis of important studies comparing iso-osmolar ioxidanol with other low-osmolar contrast media.*


A study to prevent contrast-induced nephropathy with sodium bicarbonate. Despite the low number of patients it was quite well designed in other aspects.


A retrospective study that demonstrated nonsuperiority of sodium bicarbonate, contrary to all prospective studies that showed the superiority of sodium bicarbonate to sodium chloride. However, the high number of patients is remarkable.


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or N-
A randomized controlled trial comparing Heart percutaneous coronary intervention.
angiography with or without concomitant
and hydration versus placebo and hydration
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a randomized controlled trial of intravenous in vascular patients undergoing angiography:
Prevention of contrast-induced nephropathy – a randomized controlled study.
Nephrol. Dial. Transplant
Williams RG: Efficacy of:
et al.
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Trials
Kock M:
and review of the current literature.
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* This article questioned different contrast-induced nephropathy definitions that have hindered the comparison of to-date contrast-induced nephropathy studies.