Contrast-induced nephropathy (CIN) is one of the most common causes of hospital-acquired acute renal failure.\textsuperscript{1,2} The development of CIN after diagnostic coronary angiography and/or percutaneous coronary intervention (PCI) is associated with prolonged hospitalisation and a remarkable increase in morbidity, early and late mortality and costs.\textsuperscript{3-6} CIN is an absolute (≥0.5 mg/dl) or relative (≥25%) increase in serum creatinine compared with baseline after exposure to a contrast agent when alternative explanations for renal impairment have been excluded. The Contrast-induced Nephropathy Consensus Panel recommended using a relative increase in serum creatinine to define CIN given that this definition is independent of baseline renal function.\textsuperscript{7} CIN typically develops within 24–72 hours post-exposure to contrast medium, with renal function returning to baseline level in two weeks.\textsuperscript{8-10} The overall incidence of CIN in the general population is <2%.\textsuperscript{1,11} In high-risk patients, including the elderly population and patients with chronic renal impairment, diabetes, congestive heart failure and anaemia, the incidence of CIN is much higher (≥20%).\textsuperscript{9,10,12,13} Several risk factors have been described for CIN.\textsuperscript{6,14} To reliably assess the risk of CIN, a simple risk score (see Figure 1) that can be quickly calculated based on readily available information is strongly recommended.\textsuperscript{15}

Pathogenesis of Contrast-induced Nephropathy
The pathogenesis of CIN is not entirely understood. Several pathways of CIN development have been proposed, including altered rheological properties of blood, medullary hypoxia, impaired immunological mechanisms and direct toxic effects of contrast medium on renal epithelial cells and oxidative stress.\textsuperscript{16-20} Iodinated contrast is known to provoke acute vasoconstriction due to a release of adenosine, endothelin and other renal vasoconstrictor agents. Apoptosis has also been implicated as a contributing factor.\textsuperscript{21,22}

Prevention of Radiocontrast Nephropathy
The unfavourable prognostic implications of CIN in high-risk populations make preventing this condition of paramount importance.\textsuperscript{20}

Hydration
Volume supplementation results in plasma volume expansion followed by suppression of the renin–angiotensin–aldosterone system and downregulation of tubuloglomerular feedback, leading to the attenuation of renal cortical vasoconstriction and tubular obstruction triggered by contrast agents.\textsuperscript{23,24} The positive effect of adequate hydration in reducing CIN rates was first established in the randomised study by Solomon et al.\textsuperscript{25} In patients with mild to moderate renal insufficiency, 0.45% saline administration at a rate of 1 ml/kg/hour for 12 hours pre- and post-procedure was more effective in the prevention of CIN than a combination of 0.45% saline and mannitol or furosemide (10.7 versus 28.0 versus 40.0%, respectively; p=0.02 for the comparison with the saline group alone). The randomised comparison of two hydration regimens in a total of 1,620 patients undergoing coronary angioplasty in the study by Mueller et al. showed the superiority of isotonic versus half-isotonic saline in reducing rates of CIN (0.7 versus 2%, respectively).\textsuperscript{26} Although a randomised study by Taylor et al. demonstrated that in high-risk patients different modes of fluid administration (intravenous versus oral) had similar renoprotective effects,\textsuperscript{27} this was not confirmed in another randomised study by Trivedi et al.,\textsuperscript{28} which showed a significantly lower incidence of acute renal failure in patients who received normal saline at a rate of 1 ml/kg/hour for 24 hours starting 12 hours before contrast exposure compared with a protocol of unrestricted oral fluids. In studies by Bader et al. and Krasuski et al.,\textsuperscript{29} rates of CIN were lower in patients who received hydration with saline for 12 hours before and after exposure to contrast medium compared with patients who were administered 250–300 ml saline bolus immediately before or during contrast media exposure. To conclude, volume supplementation with saline should be considered in all patients undergoing contrast medium exposure during diagnostic or therapeutic coronary procedures. Patients with chronic kidney disease and impaired left ventricular function should receive cautious hydration. In the presence of chronic kidney disease, for patients with a normal ejection fraction we recommend hydration with isotonic saline 1 cc/kg/hour for at least 12 hours pre- and post-procedure, while for patients with moderately/severely reduced left ventricular ejection fraction a hydration regimen should be performed with 0.45% saline matching urine output to maintain a euvoletic state.
**Sodium Bicarbonate**

Three prospective, randomised trials showed that preventative hydration with sodium bicarbonate provides better protection against CIN than an alternative hydration regimen with or without other prophylactic medications. In the single-centre study by Merten et al., 119 patients with baseline serum creatinine levels of at least 1.1mg/dl were randomised before exposure to iopamidol to receive a 154mEq/l infusion of either sodium chloride (n=59) or sodium bicarbonate (n=60) in a bolus of 3ml/kg/hour for one hour followed by an infusion of 1ml/kg/hour for the duration of the procedure and for six hours post-procedure. The primary end-point of CIN (increase of ≥25% in serum creatinine within two days of contrast exposure) occurred significantly less frequently in patients hydrated with sodium bicarbonate compared with patients hydrated with sodium chloride (1.7 versus 13.6%, respectively; p=0.02). The subsequent larger, dual-centre, randomised, double-blind study by Briguori et al. compared three different strategies for preventing CIN in 326 patients with chronic kidney disease (baseline serum creatinine ≥2.0mg/dl and/or estimated glomerular filtration rate [GFR] <60ml/minute/1.73m²) who underwent coronary or peripheral angiography and/or angioplasty. The patients were randomly assigned to prophylactic administration of 0.9% saline infusion plus N-acetylcysteine (NAC), (n=111), sodium bicarbonate infusion (using the protocol proposed by Merten et al.) plus NAC (n=108) or 0.9% saline plus ascorbic acid plus NAC (n=107). The rate of CIN (increase of ≥25% of serum creatinine concentration) was significantly (p=0.01) lower in the bicarbonate plus NAC group (1.9%) than in the saline plus NAC group (9.9%), while the rate of CIN was practically identical in the saline plus NAC group and the saline plus ascorbic acid plus NAC group (9.9 versus 10.3%; p=1).

In a randomised study by Ozcan et al. of 264 patients with a baseline creatinine level >1.2mg/dl assigned to one of three prophylactic regimens (infusion of sodium bicarbonate, sodium chloride or sodium chloride plus oral NAC), the incidence of CIN was significantly lower in the sodium bicarbonate group (4.5%) compared with the sodium chloride alone group (13.6%; p=0.036) and tended to be lower than in the combination group (12.5%; p=0.059). However, in the largest randomised trial by Brar et al., which included 353 patients with baseline eGFR ≤60ml/minute/1.73m² and at least one risk factor for CIN (diabetes, hypertension, history of chronic heart failure or age >75 years), hydration with sodium bicarbonate provided no benefit compared with hydration with 0.9% normal saline in terms of the primary end-point of a ≥25% decrease in eGFR (13.6 versus 13.5%; p=0.97) or a secondary end-point of a ≥25% increase in serum creatinine (16.3 versus 15.4%; p=0.82). Rates of dialysis (0 versus 0.3%) and 30-day mortality (2.0 versus 1.3%; p=0.60) were also close between the two groups. Moreover, in a retrospective cohort analysis by the Mayo Clinic, after adjustment for several variables the use of sodium bicarbonate alone was associated with an increased risk of CIN compared with no treatment (odds ratio [OR] 3.10; p<0.001).

**N-acetylcysteine**

There has been ongoing debate as to whether NAC is effective for preventing CIN. NAC, a potent antioxidant that scavenges a wide variety of oxygen-derived free radicals, may be capable of preventing CIN by improving renal haemodynamics and diminishing oxidative tissue damage. In the first randomised placebo-controlled study of 83 patients exposed to contrast media, prophylactic oral administration of NAC along with hydration was superior to hydration alone in preventing CIN in patients with elevated baseline creatinine levels. The rates of CIN in this study were 2% in the NAC group compared with 21% in controls (p=0.01). The subsequent Acetylcysteine to Prevent Angiography-related Renal Tissue Injury (APART) trial, which included 54 patients and used a similar design, confirmed these results: CIN occurred in 8% of patients in the oral NAC group versus 45% in the placebo group. However, in a randomised study lacking placebo control of 183 patients, oral NAC plus hydration failed to show a significant difference in CIN rates compared with hydration alone. Similarly, in the largest randomised study to date assessing the efficacy of NAC to prevent CIN (487 patients), intravenous NAC 500mg did not provide renal protection in patients with impaired renal function compared with placebo. Data of several meta-analyses are also contradictory and are limited by the heterogeneity of the included studies. In the most recent meta-analysis of 41 studies involving a total of 6,379 patients, by Kelly et al., the combination of hydration with NAC was more renoprotective than hydration alone.

**Other Prophylactic Regimens**

Due to its dilatory effect on the renal vasculature and ability to increase renal blood flow and glomerular filtration rate (GFR), dopamine was thought to be useful in the prevention of CIN. However, the results of clinical studies are conflicting. Moreover, in patients with peripheral vascular disease and CIN, the effect of dopamine on renal function was found to be deleterious. Fenoldopam, a selective dopamine-1 receptor agonist known to produce both systemic and renal arteriolar vasodilatation, was shown to blunt the decline in renal blood flow and GFR in animals exposed to contrast media. In the largest randomised radiocontrast study to date, the Controlled Multicenter Trial Evaluating Fenoldopam Mesylate for the Prevention of Contrast-induced Nephropathy (CONTRAST) trial, 315 patients undergoing invasive cardiac procedures with a calculated creatinine clearance rate <60ml/minute were hydrated and then randomised to either placebo or fenoldopam starting one hour before catheterisation and continuing for 12 hours post-catheterisation. CIN occurred in 33.6% of the fenoldopam group versus...
Diagnostics and Imaging

30.1% of control patients (p=0.54). Thus, fenoldopam cannot be recommended for prophylactic use in patients at high risk of CIN. Theophylline, an adenosine A1-receptor antagonist, may attenuate the decrease in renal blood flow and GFR induced by exposure to contrast media. Some randomised studies have shown that the prophylactic intravenous administration of theophylline reduces the incidence of CIN in patients with chronic kidney disease,65,66 while other studies failed to demonstrate any benefit in favour of theophylline compared with placebo.60,65,66 Still, in two meta-analyses of published studies, the prophylactic administration of theophylline was protective in preventing a radiocontrast-induced decline in kidney function.67,68

Some retrospective series analysed the efficacy of pre-treatment with statins on the development of CIN in patients undergoing cardiac catheterisation.60,61 In a large series of 29,409 patients exposed to contrast media during diagnostic and therapeutic procedures, studied by Khanal et al., pre-treatment with statins was associated with a lower incidence of CIN (4.4 versus 5.9%; p<0.0001) and requirement for dialysis (0.32 versus 0.49%; p=0.03).60 However, in the double-blind, placebo-controlled, randomised Simvastatin Prevents the Contrast Induced Acute Renal Failure in Patients Undergoing Coronary Angiography (PROMISS)61 trial of 247 patients with chronic renal insufficiency undergoing coronary angiography pre-treatment with simvastatin 40mg orally every 12 hours starting the evening before and ending the morning after the procedure, the incidence of CIN was similar in the treatment and placebo arms (2.5 versus 3.4%, respectively; p=1.00).

**Dialysis and Haemofiltration**

Several studies have assessed the effect of haemodialysis immediately after exposure to contrast media in preventing renal function deterioration in patients with pre-existing chronic kidney disease. In two of these studies, prophylactic haemodialysis failed to diminish the rates of CIN1,63 and even had negative effects in another study.64 However, in a recent randomised study conducted by Lee et al.,4 prophylactic haemodialysis improved renal outcomes in 82 patients with chronic kidney disease undergoing coronary angiography. In this study, patients were randomised to receive either hydration with normal saline intravenously and prophylactic haemodialysis post-procedure or hydration alone. Prophylactic haemodialysis was associated with a smaller decrease in creatinine clearance within 72 hours of contrast exposure (0.4 versus 2.2ml/minute/1.73m²; p<0.001), a lower level of serum creatinine at day 4 (5.1 versus 6.3mg/dl; p=0.01) and lower rates of temporary renal replacement therapy (2 versus 35%; p=0.001). One randomised study investigated the role of haemofiltration performed for six hours before and for 18-24 hours after contrast exposure in preventing CIN in patients with chronic kidney disease (creatinine clearance ≤30ml/minute) undergoing coronary interventions.65 Among 92 patients, CIN developed significantly less frequently in patients treated with haemofiltration compared with routine hydration (3 versus 40%; p=0.0013). Haemofiltration requirements were also lower in the haemofiltration group (0 versus 30%, respectively; p=0.002).

**Other Treatment Modalities**

Targeted renal therapy is a novel catheter-based approach aimed at delivering renal vasodilator agents such as fenoldopam and neuretidin (a B-type natriuretic peptide) directly to the kidneys via the renal arteries using the Benephit™ Infusion System (FlowMedica, Inc.) to maximise the beneficial renal effects of the drugs while minimising systemic side effects.66 Ongoing trials are addressing the issue of whether local drug delivery may reduce CIN rates in patients undergoing contrast media exposure.

**Contrast Medium Use**

Contrast media are categorised according to their ionicity (ionic or non-ionic), their chemical structure (monomeric or dimeric molecules) and their osmolality (high osmolal [HOCM] ~2,000mOsm/kg, low-osmolal [LOCM] 600-800mOsm/kg and isoosmolal [IOCM] 290mOsm/kg). Numerous studies comparing different contrast agents have been conducted. In a meta-analysis by Barrett et al.67 of 31 randomised trials comparing LOCM and HOCM, LOCM were shown to significantly reduce the risk of a rise in serum creatinine of >0.5mg/dl in comparison with HOCM in patients with renal impairment (OR 0.5; confidence interval [CI] 0.36–0.68), but not in patients with normal renal function (OR 0.75; CI 0.52–1.1).67 In a prospective, randomised, double-blind, multicenter trial by Rudnick et al. comparing the LOCM iohexol with the HOCM diatrizoate in 1,196 patients undergoing cardiac angiography, renal function deterioration (increase in serum creatinine of >1mg/dl at 48–72 hours post-procedure) was observed in 7% of patients receiving diatrizoate compared with 3% of patients receiving iohexol (p=0.002).68 Differences in nephrotoxicity between the two contrast groups were again confined to patients with previous renal insufficiency or renal insufficiency and diabetes.

A number of studies have evaluated whether an IOCM might provide a similar benefit over the LOCM agents, but no consensus has emerged on this point. In a pooled analysis of 16 double-blind, randomised, controlled trials (2,727 patients) comparing the IOCM ioxaglate with LOCM,65 CIN occurred less frequently in the ioxaglate group than in the LOCM comparator group in all analysed patients (1.4 versus 3.5%; p<0.001). However, the majority of patients in these trials did not have chronic kidney disease (CKD), and most subjects received one of only two LOCM: ioxaglate or iopamidol.

In the Renal Toxicity Evaluation and Comparison Between Visipaque (iodixanol) and Hexabrix (ioxaglate) in Coronary Angiography in Renal Insufficiency (RECOVER) and A Prospective, Randomized, Placebo-controlled Trial of Ioxaglate versus Iodixanol in Patients at Increased Risk for Contrast Nephropathy (ICON) trials, high-risk patients with renal impairment were randomly assigned to either the IOCM ioxaglate or the IOCM ioxaglate. In the RECOVER trial, using a composite end-point the incidence of CIN was significantly lower with ioxaglate than with ioxaglate (7.9 versus 17.0%; p=0.021),70 while in the ICON trial in-hospital acute renal failure occurred with similar incidences in the ioxaglate and the ioxaglate groups (18.4 versus 22.2%; p=0.80).71 There was no difference in mean increase in serum creatinine (0.20mg/dl in the ioxaglate group versus 0.35mg/dl in the ioxaglate group; p=0.140).

More recent trials comparing the IOCM with other LOCM agents (iopamidol, iomeprol and ioversol) in patients with pre-existing renal dysfunction have failed to show a benefit to the use of the iso-osmolar agent. In the randomised Cardiac Angiography in Renally Impaired Patients (CARE) study, rates of CIN (defined by multiple end-points) were similar in 414 angiography patients randomised to ioxaglate or iopamidol (p=0.44), although mean changes in serum creatinine were higher in patients receiving the iso-osmolar agent (0.12 versus 0.07mg/dl; p=0.03).71 In the COntrast media and NephroToxicity following coronary Revascularization by AngioplaSTy (CONTRAST) study, CIN was seen in
The CARE study found no statistically significant difference between Isovue® (iopamidol injection 76%) and Visipaque™ (iodixanol injection) in the rate of CIN in high-risk patients undergoing cardiac angiography or PCI.

The CARE study is the largest, prospective, randomized, double-blind comparison of iso-osmolar iodixanol-320 with low-osmolar iopamidol-370 in high-risk patients.1

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Nonionic iodinated contrast media inhibit blood coagulation, in vitro, less than ionic contrast media. Clotting has been reported when blood remains in contact with syringes containing nonionic contrast media. Serious, rarely fatal, thromboembolic events causing myocardial infarction and stroke have been reported during angiographic procedures with both ionic and nonionic contrast media. Therefore, meticulous intravascular administration technique is necessary, particularly during angiographic procedures, to minimize thromboembolic events.

As with all injectable contrast agents, the possibility of severe reactions should be borne in mind, regardless of the patient’s pre-existing medical history.

Please see brief summary of Prescribing Information on the following page.

*CIN defined as a) an absolute increase ≥0.5 mg/dL, b) a relative increase ≥25% in serum creatinine or c) a ≥25% decrease in eGFR from baseline to 45–120 hours postcontrast.

†P value is not statistically significant.

Reference: 1. Solomon RJ, Natarajan MK, Doucet S, et al, and the Investigators of the CARE study. The CARE (Cardiac Angiography in REnally Impaired Patients) study: a randomized, double-blind trial of contrast-induced nephropathy in high-risk patients. Circulation. 2007;115:3189-3196.
**NOT FOR INTRAVENOUS USE**

**SOVUS-200**, **SOVUS-300** and **SOVUE-370** are not for INTRAVENOUS use. See indications, and Drug Administration sections for further details on how use.

**Radiographic Contrast Material**

**BRACCO DIAGNOSTICS**

Rx only

Please see full prescribing information. A brief summary follows.

**SOVUS-200**, **SOVUS-300** and **SOVUE-300** are Iopamidol Injection 41%, 56% and 76% respectively.**SOVUE-200** and **SOVUE-300** are Iopamidol Injection 41% and 56% respectively.

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**SOVUS-200**, **SOVUS-300** and **SOVUE-300** are Iopamidol Injection 41%, 56% and 76% respectively.
22.7% of the 162 patients randomised to ioxanol and in 27.7% of the 162 patients randomised to the low osmolar agent iomeprol (p=0.25).73

Most recently, in the Visipaque Angiography/Interventions with Laboratory Outcomes in Renal insufficiency (VALOR) study, the incidence of CIN in 299 patients with angiography with CKD was 21.8% after ioxanol and 23.8% after the low osmolar agent ioversol (p=0.78).74 These results suggest that the LOMC agents cannot be thought of as a class when it comes to renal tolerability and that the potential benefit ascribed to the iso-osmolar agent has been overestimated based on earlier trials.

**Conclusion**

Although rare in the general population, CIN is highly prevalent in patients with well-known risk factors, including older age, chronic renal insufficiency and diabetes. The best approach to prevent CIN is to identify the patients at risk, provide adequate peri-procedural hydration and minimise the amount of contrast administered. The role of various drugs in the prevention of CIN is still controversial and warrants future studies. So far, no single agent has shown a consistent benefit above and beyond hydration in preventing CIN. Study results are mixed as to whether prophylactic oral NAC reduces the incidence of CIN, although its use is generally recommended given its low cost and favourable side effect profile. Prophylactic haemodialysis and haemofiltration may represent an important option to prevent CIN in the highest-risk cohort, although further studies of these invasive modalities are needed. Several novel pharmacological agents and devices offer promise in preventing CIN and are currently undergoing investigation. Despite the remaining uncertainty regarding the degree of nephrotoxicity produced by various contrast agents, in current practice non-ionic low-osmolar contrast media may be preferred in high-risk patients for CIN.