Contrast-Induced Nephropathy (CIN) Consensus Working Panel: Executive Summary

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With the advances made in radiology and cardiology, greater numbers of patients are expected to undergo exposure to iodinated contrast media in the years to come. Contrast-induced nephropathy (CIN) accounts for a significant number of cases of hospital-acquired renal failure, with adverse effects on prognosis and healthcare costs. The CIN Consensus Working Panel is an international multidisciplinary group convened to address the challenges of CIN. The group reviewed 865 published papers, chosen for potential relevance from a comprehensive literature search that identified over 4000 references. The results were used to compile reviews covering the epidemiology and pathogenesis of CIN, baseline renal function measurement, risk assessment, identification of high-risk patients, contrast medium use, and preventive strategies. In this executive summary, consensus statements and an algorithm for the risk stratification and management of CIN are presented.

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Contrast-induced nephropathy (CIN) is an important complication in the use of iodinated contrast media, accounting for a significant number of cases of hospital-acquired renal failure.[1-4] This iatrogenic condition has an adverse effect on prognosis and adds to healthcare costs. Several factors contribute to the increasing importance of this subject to radiologists, cardiologists, and nephrologists. The numbers of imaging and interventional procedures continue to increase, which inevitably means that more patients

Table 1
Consensus Statements from the CIN Consensus Working Panel

Consensus Statement 1

CIN is a common and potentially serious complication following the administration of contrast media in patients at risk for acute renal injury.

Consensus Statement 2

The risk of CIN is elevated and of clinical importance in patients with chronic kidney disease (particularly when diabetes is also present), recognized by an estimated glomerular filtration rate < 60 mL/min/1.73 m^2.

Consensus Statement 3

When serum creatinine or estimated glomerular filtration rate is unavailable, then a survey may be used to identify patients at higher risk for CIN than the general population.

Consensus Statement 4

In the setting of emergency procedures, where the benefit of very early imaging outweighs the risk of waiting, the procedure can be performed without knowledge of serum creatinine or eGFR.

Consensus Statement 5

The presence of multiple CIN risk factors in the same patient or high-risk clinical scenarios can create a very high risk (~50%) for CIN and acute renal failure requiring dialysis (~15%) after contrast exposure.

Consensus Statement 6

In patients at increased risk for CIN undergoing intra-arterial administration of contrast, ionic high osmolality agents pose a greater risk for CIN than low-osmolality agents. Current evidence suggests that for intra-arterial administration in high-risk patients with chronic kidney disease, particularly those with diabetes mellitus, nonionic, iso-osmolar contrast is associated with the lowest risk of CIN.

Consensus Statement 7

Higher contrast volumes (> 100 mL) are associated with higher rates of CIN in patients at risk. However, even small (~30 mL) volumes of iodinated contrast in very high-risk patients can cause CIN and acute renal failure requiring dialysis, suggesting the absence of a threshold effect.

Consensus Statement 8

Intra-arterial administration of iodinated contrast appears to pose a greater risk of CIN above that with intravenous administration.

Consensus Statement 9

Adequate intravenous volume expansion with isotonic crystalloid (1.0 mL/kg/h to 1.5 mL/kg/h) for 3 to 12 hours before the procedure and continued for 6 to 24 hours afterwards can lessen the probability of CIN in patients at risk. The data on oral fluids as opposed to intravenous volume expansion as a CIN prevention measure are insufficient.

Consensus Statement 10

No adjunctive medical or mechanical treatment has been proven to be efficacious in reducing the risk of CIN. Prophylactic hemodialysis or hemofiltration have not been validated as effective strategies.

CIN, contrast-induced nephropathy; eGFR, estimated glomerular filtration rate.

will be exposed to intravascular iodinated contrast media. At the same time, the incidence and prevalence of chronic kidney disease (CKD), the most important risk factor for CIN, are increasing worldwide; approximately 11% of American adults have some degree of CKD.

The CIN Consensus Working Panel is an international multidisciplinary group convened to address the challenges of CIN.[1] The group systematically reviewed the published evidence on CIN and used these data, together with expert opinion drawn from clinical practice, to compile a series of consensus statements (Table 1) and a management algorithm (Figure 1).

CIN Consensus Working Panel

The Working Panel comprised 2 radiologists, a computed tomography (CT) expert, 2 cardiologists, and 2 nephrologists practicing in Europe and the US.[5] At the first meeting in November 2004, the overall scope and strategy for the project were agreed upon. At the second meeting in September 2005, the Working Panel reviewed and discussed all the evidence and developed a series of consensus statements.

Methodology

A systematic search of the literature was undertaken to identify all

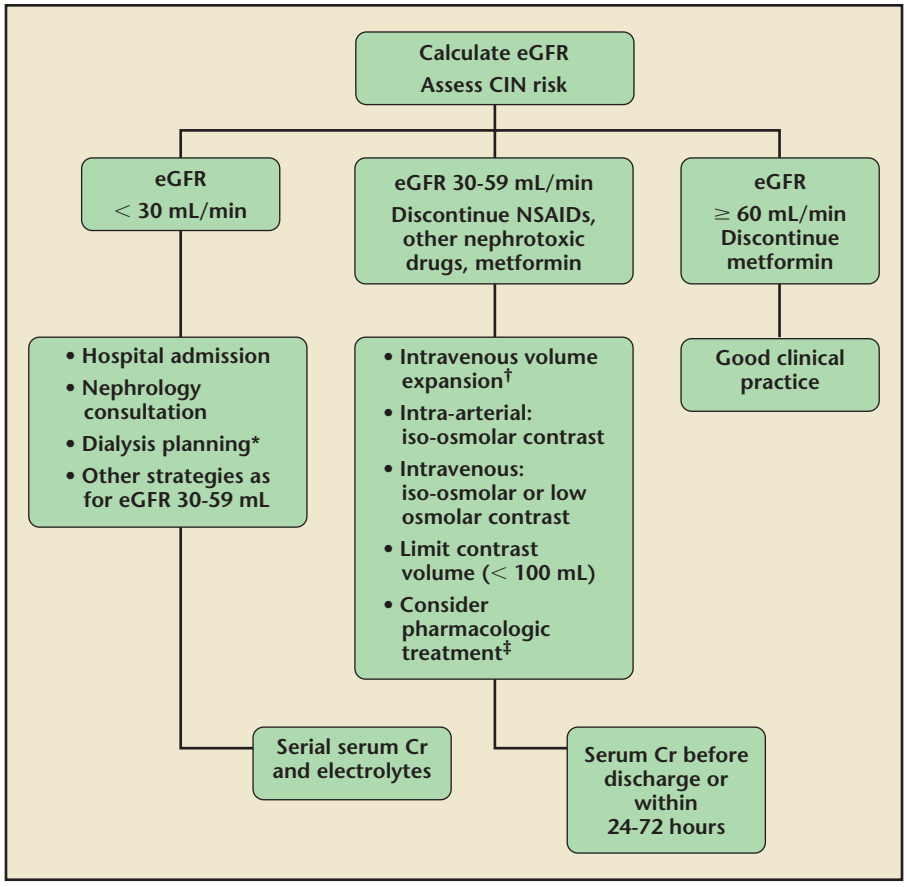

Figure 1. *Algorithm for management of patients receiving iodinated contrast media. *Plans should be made in case CIN occurs and dialysis is required. †Intravenous volume expansion consisting of intravenous isotonic crystalloid 1 mL/kg/h to 1.5 mL/kg/h for 3 to 12 hours before and 6 to 24 hours after the procedure. ‡Consider potential beneficial agents, such as theophylline, 3-hydroxy-3 methylglutaryl coenzyme A reductase inhibitors (statins), ascorbic acid (vitamin C), and prostaglandin E_1 (not approved for this indication). eGFR, estimated glomerular filtration rate; CIN, contrast-induced nephropathy; NSAID, nonsteroidal anti-inflammatory drug; Cr, creatinine.*

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references relevant to the subject of CIN, as a result of which 865 potentially relevant papers were identified and reviewed. The results of the literature search were used to compile reviews covering the epidemiology and pathogenesis of CIN, baseline renal function measurement, risk assessment, identification of high-risk patients, contrast medium use, and preventive strategies.[6]

Epidemiology of CIN

The reported incidence of CIN varies widely across the literature, depending on the patient population and the baseline risk factors. Moreover, as with any clinical event, the incidence also varies depending on the criteria by which it is defined. CIN is typically defined in the recent literature as an increase in serum creatinine typically occurring within the first 24 hours after contrast exposure and peaking up to 5 days afterwards. In most instances, the rise in serum creatinine is expressed either in absolute terms (0.5 mg/dL to 1.0 mg/dL [44.2 μmol/L to 88.4 μmol/L]) or as a proportional rise of 25% or 50% above the baseline value. The most commonly used definitions in clinical trials are a rise of 0.5 mg/dL (44.2 μmol/L) or a 25% increase from the baseline value, assessed at 48 hours after the procedure. Fewer studies used the more stringent definitions of a 1.0 mg/dL (88.4 μmol/L) increase or a 50% increase from the baseline value. Indeed, the review of CIN definitions in the contemporary literature suggests that in the past 5 years, there has been a move toward recognizing CIN at lower threshold levels of serum creatinine, namely at an absolute increase of 0.5 mg/dL or a rise from baseline of 25%. This shift has probably been driven by the desire for more endpoint events in clinical trials to increase the likelihood of the results reaching statistical significance. The Contrast Media Safety Committee of the European Society of Urogenital Radiology (ESUR) defines CIN as impairment in renal function (an increase in serum creatinine of more than 25% or 44.2 μmol/L [0.5 mg/dL]) within 3 days after intravascular administration of contrast medium, without an alternative etiology.[7] Other definitions have been used for CIN, including decreases in the glomerular filtration rate (GFR) or creatinine clearance in addition to increases in serum creatinine[8-10] and increases in blood urea nitrogen (BUN) of 20% to 50%,[11,12] and any increase in serum creatinine.[13] However, defined serum creatinine changes appear to be the universal benchmark measure for the occurrence of CIN.

CIN Frequency

Large-scale studies in general hospital patients provide the best indicator of the healthcare impact of CIN. The frequency of CIN has decreased over the last decade from a general incidence of ~15% to ~7% due to a greater awareness of the problem, better risk prevention measures, and improved iodinated contrast media with less renal toxicity.[14] However, many cases of CIN continue to occur

because of the ever-increasing numbers of procedures requiring contrast medium. Recently, Nash and colleagues[4] found that some degree of renal insufficiency occurred in 7.2% of 4622 general hospital patients. Radiographic contrast media were the third most common cause of hospital-acquired renal failure, after decreased renal perfusion and nephrotoxic medications, and were responsible for 11% of cases. The mortality rate in cases of CIN was 14%. The proportion of cases of hospital-acquired renal failure attributed to contrast media (11%) was almost identical to the 12% proportion reported from an earlier series published in 1979. However, there was a change in the pattern of procedures associated with CIN in the later study, with more cases following cardiac procedures and fewer after non-cardiac angiography.

Using a CIN definition of a 25% rise in serum creatinine, it has been suggested that the previous frequency of CIN after use of contrast media in an unselected group of cardiology patients may be up to 15%.[15,16] In patients with impaired renal function at baseline, the risk is considerably higher. The significance of renal impairment as a risk marker is reviewed later in this article.

Differential Diagnosis

Cholesterol embolism can also be a cause of renal impairment after radiological procedures and may be difficult to distinguish from CIN.[17,18] Atheroembolic renal failure characteristically occurs in elderly patients with cardiovascular disease and risk factors, and is usually accompanied by other indicators, such as cutaneous signs, Hollenhorst plaques, eosinophilia, and hypocomplementemia.[19,20] It may be precipitated by angiography; warfarin use has also been reported as a risk factor. Renal impairment caused by atheroemboli can be mild and asymptomatic or life threatening. The decline in renal function typically occurs over 3 to 8 weeks, unlike the pattern seen with CIN,[19] but the presentation can also be acute or hyperacute.[21]

The mortality rate in cases of contrast-induced nephropathy was 14%.

Increased Mortality Risk

It has been recognized for some time that the development of acute renal failure (ARF) after administration of contrast medium is linked to an increased risk of death. In a large retrospective study of over 16,000 hospital inpatients undergoing procedures requiring contrast medium, a total of 183 subjects developed CIN (defined as a 25% increase in serum creatinine).[22] Although the incidence of CIN in this series was under 2%, the risk of death during hospitalization was 34% in subjects who developed CIN compared with 7% in matched controls who had received contrast medium but did not develop CIN. Even after adjusting for comorbid disease, patients with CIN had a 5.5-fold increased risk of death and a clinical course characterized by complications associated with renal failure.[22] The high risk of in-hospital death associated with CIN has also been noted in a retrospective analysis of 7586 patients, 3.3% of whom developed CIN after exposure to contrast medium. The hospital mortality rate was 22% in the patients who developed CIN, compared with only 1.4% in patients who did not develop ARF.[23] The increased risk of death persisted long term, with significantly higher mortality rates after development of CIN of 12.1% at 1 year and 44.6% at 5 years, compared with rates of 3.7% and 14.5%, respectively, in patients who did not develop CIN ($P < .001$).

Another study confirmed the high mortality in patients who develop CIN: the hospital mortality rate was 7.1% in CIN patients and 35.7% in patients who required dialysis. By 2 years, the mortality rate in patients who required dialysis was 81.2%.[15] In another study of 439 patients with renal impairment (baseline serum creatinine $\geq$ 1.8 mg/dL) undergoing percutaneous coronary intervention (PCI), CIN (defined as an increase $\geq$ 25% in serum creatinine) occurred in 37%.[24] In this group, the hospital mortality rate was 14.9% compared with 4.9% in patients without CIN ($P = .001$). The cumulative 1-year mortality rates were 37.7% and 19.4%, respectively. The 1-year mortality rate was 45.2% for patients with CIN requiring dialysis and 35.4% for those with CIN not requiring dialysis.[24] In patients undergoing primary PCI for myocardial infarction (MI), short- and long-term mortality rates were also significantly higher in those who developed CIN: 16.2% in hospital and 23.3% at 1 year for those with CIN, compared with 1.2% and 3.2%, respectively, for those without CIN ($P < .0001$ for both comparisons).[25] Another study also documented the higher hospital mortality rate for primary PCI patients with CIN: the incidence was 31%, compared with 0.6% in those without CIN ($P = .0001$).[26]

CIN Clinical Course and Outcome

CIN is associated with other adverse outcomes, including late cardiovascular events and increased risk of death. In one registry series of 5967 PCI patients, the development of

CIN was associated with an increased incidence of MI (24% in CIN subjects vs 11.6% in subjects without CIN; $P < .001$) and target vessel revascularization at 1 year (28.8% in CIN subjects vs 20.3% in subjects without CIN; $P < .008$).[27] Another large PCI study from the same group highlighted the links between contrast-induced rises in serum creatinine, post-procedural increases in creatinine kinase MB subfraction (CK-MB), and the risk of late cardiovascular events.[28] The investigators examined risk factors for late mortality and cardiovascular events in a group of 5397 patients and found that a postprocedural rise in serum creatinine was a more powerful predictor of late mortality than CK-MB. Creatinine increases were linked to a 16% rate of death or MI, rising to 26.3% when CK-MB levels were also elevated.[28]

A higher incidence of in-hospital events was observed in patients who developed CIN, regardless of whether they had previous renal dysfunction. Bypass surgery, bleeding requiring transfusion, and vascular complications were all more common in patients with CIN. At 1 year, the cumulative rate of major adverse cardiac events was significantly higher in patients who had developed CIN ($P < .0001$ for patients with and without chronic kidney disease).[29] However, others have observed no difference in the rates of MI and target vessel revascularization in patients with CIN.[24]

Several reports document an association between the development of CIN and a protracted hospital stay. In one series, the postprocedure hospital stay was longer in patients who developed CIN, regardless of baseline renal function (6.8 ± 7.1 days vs 2.3 ± 2.5 days in patients with prior CKD and 3.6 ± 5.1 days vs 1.8 ± 2.4 days in patients without CKD).[29] In a recent study of more than 200 patients undergoing PCI for acute MI, patients who developed CIN had a longer hospital stay than those who did not (13 ± 7 days vs 8 ± 3 days; $P = .001$), and had a more complicated clinical course in addition to a significantly increased risk of death.[26]

Risk of CIN Requiring Dialysis

Although most cases of CIN reflect mild transient impairment of renal function, a small proportion of patients require dialysis. The literature review conducted by the CIN prevention consensus group suggests that the need for dialysis after CIN varies according to the patients' underlying risks at the time of contrast administration but is generally less than 1%.[15,30,31] It was considerably higher, however, in some older studies with high osmolar contrast medium (HOCM).[32,33] In contemporary studies, CIN requiring dialysis developed in almost 4% of patients with underlying renal impairment[34] and 3% of patients undergoing primary PCI for MI.[26] Although CIN requiring dialysis is relatively rare, the impact on patient prognosis is considerable. A group of patients who developed CIN after coronary intervention had a hospital mortality rate of 7.1%, whereas patients with CIN that led to dialysis had a 35.7% hospital mortality rate—and only 19% of these dialysis patients survived 2 years.[15] Similar high mortality rates linked with CIN-associated dialysis were reported in a study of 439 consecutive patients undergoing PCI.[24] This study recorded a hospital mortality rate of 4.9% for patients who did not develop CIN, 14.9% in patients who developed CIN, and 22.6% in the 31 patients who required dialysis as a result of CIN.[24] At 1 year after PCI, the mortality rate in dialysis patients had risen to 45.2%, as compared to 35.4% in CIN patients and 19.4% in patients who did not develop CIN. In a large study involving 1575 patients with diabetes who underwent PCI, 66% of subjects had preserved renal function at baseline, while 31% had baseline evidence of CKD (baseline serum creatinine > 1.5 mg/dL) that did not require dialysis, and 2.3% had CKD that did require dialysis.[34] After PCI, CIN developed in 15% of the patients without CKD and in 27% of patients with CKD. The PCI procedure led to a de novo need for dialysis in 0.1% of diabetic patients with normal renal function and in 3.1% of patients with pre-existing CKD.

At 1 year after percutaneous coronary intervention, the mortality rate in dialysis patients had risen to 45.2%, as compared to 35.4% in contrast-induced nephropathy patients and 19.4% in patients who did not develop contrast-induced nephropathy.

Pathophysiology of Contrast-Induced Renal Injury

The properties of contrast media that could contribute to possible adverse effects on the kidneys include direct chemotoxicity of the molecule (ionicity, iodine content), osmotoxicity, and the possible viscosity-related toxicity of the formulation. The panel concluded that there is insufficient information to make a definitive statement about the relative contributions to renal toxicity. However, it seems clear that the higher osmolality of the contrast medium and, hence, the osmotic load delivered to

the kidneys, appear to play a critical role in the pathogenesis of CIN.

Effects on Renal Blood Flow

In dogs undergoing selective renal angiography, there is a transient increase in renal blood flow (lasting seconds) after contrast medium administration followed by sustained vasoconstriction (lasting minutes to hours).[35] A pronounced decrease in outer medullary blood flow was observed in animals after contrast medium injection.[36] In humans undergoing intravenous pyelography, HOCM infusion was associated with a decrease in renal plasma flow (determined by para-amino hippuric acid clearance), with the greatest effect at 60 minutes and a return to baseline at 120 minutes. The vasoconstrictive effects of higher osmolar agents are greater than those of the low osmolar contrast medium (LOCM).[37,38] Plasma endothelin, in correspondence with intrarenal vasoconstriction, increased within 5 minutes of contrast medium administration and returned to baseline by 30 minutes. Other studies indicate that nitric oxide availability is reduced.[39]

Direct Tubular Toxicity

The term *osmotic nephrosis* has been used to describe the characteristic histological picture observed in renal biopsies from patients with renal impairment after HOCM.[40] The main feature is intense vacuolization of the cytoplasm of the proximal tubules, which can be focal or diffuse. Of 211 patients undergoing renal biopsy within 10 days of renal arteriography or intravenous pyelography, evidence of osmotic nephrosis was found in 47 cases; it was accompanied by tubular atrophy and/or necrosis in 29 cases.[40] Postmortem examination of the kidneys of 34 infants who had died after cardiac catheterization with HOCM showed evidence of medullary necrosis in 3 and vacuolization of the cytoplasm of the proximal tubular epithelium in 4.[41] The toxicity was attributed to osmotic diuresis and renal ischemia. In addition, there may be precipitation of uric acid and plugging of renal tubules with Tamm-Horsfall protein, which add injury to the organ.[42] In patients undergoing selective renal angiography, a transient increase in glomerular permeability led to proteinuria in the first few hours after contrast injection that resolved within 24 hours. The increase in urinary β_2-microglobulin was attributed to a possible overload of tubular resorption.[40] Other toxic effects of iodinated contrast include cellular energy failure, apoptosis, disturbance of calcium, and alterations in tubular cell polarity.

Oxidative Stress

After renal vasoconstriction and direct cellular toxicity, oxidative stress is believed to propagate, if not to play a major role in, renal injury. Increased oxidative stress is present in chronic renal failure and diabetes mellitus and is an important contributor to impaired endothelial function.[43-47] It has been found to mediate age-associated renal cell injury and cell death, particularly apoptosis. Recent studies suggest that oxygen free radicals contribute to enhanced basal vascular tone, tubuloglomerular feedback, and impaired endothelium-dependent relaxation in the diseased kidney.[47] In renal failure caused by other nephrotoxic agents, such as cisplatin or gentamicin, production of oxygen free radicals is associated with death of tubular epithelial cells mediated by caspases and/or endonucleases.[48] It is not surprising therefore that attention has focused on the potential contribution of oxidative stress to CIN, although the evidence is limited. An increase in the ratio of urinary malondialdehyde (a marker of oxidative stress) to creatinine was observed after contrast medium injection, suggesting increased renal production of free radicals.[48] Increased levels of free 3-nitrotyrosine (a marker of peroxynitrite generation from superoxide) in patients undergoing cardiac catheterization indicate that contrast medium administration may increase oxidative stress. Plasma levels of this marker increased slightly but significantly over 72 hours, whereas urinary levels peaked at the end of the procedure and were proportional to contrast medium volume.[49] Urinary levels of F_2-isoprostane, another marker of oxidative stress, also increased immediately after coronary angiography in patients with renal impairment.[50]

Renal Retention of Contrast Media

Many investigators have reported on the association between renal retention of contrast medium and CIN,[51-62] and one study indicated that renal cortical retention at 24 hours (as determined by CT) had better predictive value for the development of CIN than the 24-hour creatinine level.[59] A high incidence of renal cortical retention and CIN was observed in patients who either had impaired renal function or were older than 73 years, or both. A correlation was observed between mean cortical attenuation on CT scan at 22 hours to 26 hours and levels of BUN and serum creatinine.[59] Another study showed that severe renal cortical retention was associated with a higher frequency of CIN than the lesser degrees of retention, but renal cortical retention was not always associated with CIN.[53]

Assessment of Baseline Renal Function

Renal impairment at baseline (estimated glomerular filtration rate

[eGFR] < 60 mL/min/1.73 m^2) is the most important risk marker to predict the risk of CIN in patients receiving iodinated contrast media.[63] Hence, it is important to assess renal function before administration of contrast medium to ensure that appropriate steps are taken to reduce the risk. Serum creatinine alone does not provide a reliable measure of renal function, hence the National Kidney Foundation Kidney Disease Outcome Quality Initiative (K/DOQI) recommends that clinicians use an eGFR calculated from the serum creatinine as an index of renal function rather than measurement of serum creatinine alone, and that laboratories supply clinicians with a report of the eGFR along with the results of the serum creatinine measurement.[64] Laboratory-reported eGFR may be easier for patients and physicians to interpret than serum creatinine levels.[65] The CIN Consensus Working Panel agreed that eGFR should be determined prior to contrast administration. The preferred equation for the calculation of eGFR in adults is the abbreviated Modification of Diet in Renal Disease (MDRD) formula, which is recommended by K/DOQI because it is based on a validated method for measuring GFR (renal clearance of ^{125}I-iothalamate) and on the widely used alkaline picrate method for measuring serum creatinine, and it is suitable for assessment of renal insufficiency. The modified MDRD equation is:

$$\text{GFR (in mL/min/1.73 m}^2\text{)} = 186 \times [\text{serum creatinine}^{-1.154}\ (\mu\text{mol/L})] \times [\text{Age}^{-0.203}] \times [0.742 \text{ if the patient is female}] \times [1.21 \text{ if the patient is black}]$$

The MDRD equation has been validated extensively in different patient populations including Caucasians, African Americans, patients with diabetic and non-diabetic kidney disease, and renal transplant recipients. When a serum creatinine measurement or eGFR is not available, a simple survey or questionnaire can be used before contrast agent administration to identify patients at higher risk of CIN than the general population.[66] In emergency situations, where the benefit of very early imaging outweighs the risk of waiting, the CIN Consensus Working Panel agreed that the procedure can be done without assessment of renal function.

Risk Stratification

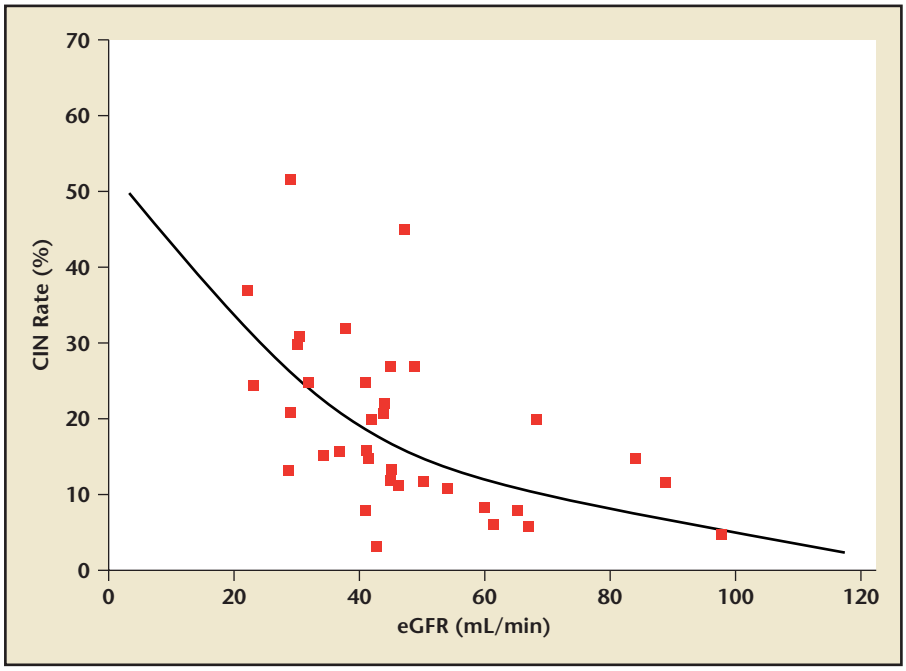
Overview of Major Risk Markers

The panel preferred the use of the term "risk marker" to "risk factor" since many of these indicators are non-modifiable patient characteristics that are not necessarily directly causative. The most important element of risk stratification is baseline renal filtration function, which is a surrogate for reduced nephron mass and renal parenchymal function. In general, CKD defined as an eGFR < 60 mL/min/1.73 m^2 is both necessary and sufficient as a risk marker for CIN. All the other risk markers do not meet both of these tenants.

Impaired Renal Function

Virtually every report describing risk factors for CIN lists abnormal baseline serum creatinine, low GFR, or underlying renal disease as risk factors, and almost every multivariate analysis has shown that pre-existing renal impairment is an independent risk predictor for CIN.[67] Figure 2 shows the incidence of CIN according to baseline renal function, modeled from published data. The consensus view of the group, after reviewing the published data, was that the risk of CIN is increased in patients with an eGFR < 60 mL/minute (equivalent to serum creatinine of

Figure 2. *The risk of contrast-induced nephropathy (CIN) according to the baseline renal function (estimated glomerular filtration rate [eGFR] or creatinine clearance in milliliters per minute, as reported) modeled from published data. The fitted function is a drawn quadratic.* www.medreviews.com



≥ 1.3 mg/dL [115 μmol/L] in men and ≥ 1.0 mg/dL [88.4 μmol/L] in women) and that special precautions should be taken in these patients.

Older Age

Increasing age is associated with a higher prevalence of CIN in many studies, possibly reflecting the decline in renal function with age. However, in some studies, age remains an independent predictor in multivariate analyses.[15,23,33,68] Aging is associated with increased vascular stiffness and a decline in endothelial function resulting in reduced vasodilator responses, as well as a reduced capacity for vascular repair with pluripotent stem cells.[69] These factors may increase the risk of CIN in the elderly patient and reduce the potential for prompt recovery.

Diabetes Mellitus

Most studies have shown that diabetes mellitus is a predictor of CIN, and it remains significant as an independent predictor in most, though not all, multivariate analyses.[15,23,68,70] However, it is not clear whether the risk of CIN is significantly increased in diabetic patients without renal impairment. In a large study in patients with normal baseline serum creatinine levels, diabetes mellitus was an independent predictor of CIN (odds ratio [OR], 1.90; 95% confidence interval [CI], 1.38-2.61).[27] Dangas and colleagues[29] also showed that diabetes mellitus was an independent risk factor for CIN (OR, 1.55; 95% CI, 1.26-1.91) in patients with normal renal function (mean baseline eGFR in CIN patients was 88.0 mL/min/1.73 m^2, and in non-CIN patients it was 81.1 mL/min/1.73 m^2). Among PCI patients with diabetes mellitus, impaired renal function was an independent predictor of CIN; however, CIN also developed in 15% of diabetic patients with preserved renal function (serum creatinine < 1.5 mg/dL or eGFR > 60 mL/min/1.73 m^2).[34] In another retrospective analysis, the presence of diabetes increased the risk of post-PCI renal failure in patients with normal or mildly impaired renal function (serum creatinine < 1.2 mg/dL or 1.2 to 1.9 mg/dL), but it was not associated with a significant additional increase in risk in patients with more severe renal impairment.[23] However, in an older study, the risk of renal impairment after contrast administration in patients with diabetes mellitus without renal insufficiency was no higher than in control patients not receiving contrast.[71] Longer duration of diabetes and the presence of diabetic complications have been reported to increase the risk of CIN.[72] A recent prospective observational study indicated that acute hyperglycemia was a risk factor, with CIN occurring in 42% of 19 diabetic patients with acute hyperglycemia compared with 1 of 19 patients who were normoglycemic at the time of cardiac angiography.[73] The most appropriate characterization of diabetes with respect to CIN is that it acts as a risk multiplier. That is, in the setting of a reduced eGFR < 60 mL/min, diabetes amplifies the risk of CIN and complicates the postprocedure management with respect to glycemic control and management of other comorbidities. Conversely, diabetes alone, in the setting of normal renal function, is neither necessary nor sufficient to result in CIN.

Heart Failure

Heart failure (HF) has frequently been shown to be associated with an increased risk of CIN, although this association has been documented only in patients undergoing cardiac catheterization.[67] Use of digoxin and diuretics (particularly furosemide) has been linked to increased CIN risk, but these agents may be serving as markers for HF because they have not been shown to act independently.[74,75]

Periprocedural Hemodynamic Instability

Several large series of PCI patients have shown an association between CIN and indicators of hemodynamic instability, such as periprocedural hypotension and use of an intra-aortic balloon pump (IABP).[27,29] It is not surprising that hypotension increases the risk of CIN because it increases the likelihood of renal ischemia and is a significant risk factor for ARF in acutely ill patients. The effect of IABP use on CIN risk is probably complex, and several potential mechanisms may contribute, including its significance as a marker of hemodynamic instability, as an indicator of procedural complications, and as a sign of severe atherosclerotic disease. Use of an IABP may also dislodge atheroemboli from aortic lesions, which may compromise renal function. Finally, other markers of an increased risk of CIN include a procedure-related fall in hematocrit[76] and surgical repair of the access site[27] (which could be a surrogate for blood loss and/or hypotension).

Use of digoxin and diuretics (particularly furosemide) has been linked to increased CIN risk, but these agents may be serving as markers for heart failure because they have not been shown to act independently.

Nephrotoxic Drugs

Alamartine and colleagues[77] reported a trend toward a higher incidence of CIN (P = .07) in patients receiving

nephrotoxic drugs (including diuretics, NSAIDs, cyclo-oxygenase-2 inhibitors, aminoglycosides, and amphotericin B). The use of diuretics has been reported to be associated with an increased risk, but this risk may indicate the presence of HF. The evidence on the use of angiotensin-converting enzyme (ACE) inhibitors is conflicting. In patients with preexisting renal insufficiency, ACE inhibitor use was reported to increase the risk of CIN, and there was a trend toward increased risk in patients with prior ACE inhibitor use who received fenoldopam ($P = .08$).[78] However, Dangas and coworkers[29] showed that pre-procedure ACE inhibitor use was associated with a lower risk of CIN in patients with chronic renal disease (OR, 0.61; $P = .005$). One clinical trial showed that periprocedural captopril reduced the risk of CIN compared with an untreated control group.[79] Given the overall long-term beneficial effect of ACE inhibitors and angiotensin II receptor antagonists, many believe these drugs should remain the foundation of treatment for CKD and diabetes, irrespective of contrast administration. In general, these drugs account for a 10% to 25% rise in baseline serum creatinine, and this increase should be kept in mind when evaluating a patient before and after contrast exposure. Cis-platinum causes dose-related and cumulative nephrotoxicity, which is related to tubular epithelial cell necrosis.[80-84] Two cases of ARF (one irreversible) have been reported after contrast administration in patients previously treated with cis-platinum.[82,83]

Other Comorbidities

Anemia. It has recently been shown that a low hematocrit at baseline is a predictor of CIN in patients undergoing PCI.[76] The rate of CIN in the highest hematocrit quintile (23.3%) was more than twice the rate in the lowest quintile (10.3%). Patients with the lowest eGFR and hematocrit had the highest rates of CIN. The threshold hematocrit at which the risk of CIN increased was $< 41.2\%$ in men and $< 34.4\%$ in women. The pO_2 of the outer medulla in the kidney is very low during normal function, and hence the combination of contrast-induced vasoconstriction and anemia may decrease oxygen delivery enough to cause renal medullary hypoxia.[85] Thus, it is intuitive that anemia may play a role in CIN risk.

Liver disease. One study indicated that the risk of CIN was particularly high in patients with the combination of renal and hepatic impairment.[86] However, more recent studies addressing the role of hepatic impairment showed that cirrhosis itself is not a risk indicator.[87,88] One, a retrospective case-control study comparing patients with and without hepatic cirrhosis undergoing CT scans, showed no difference in the incidence of CIN.[87] Other investigators showed prospectively that contrast medium administration had no adverse effects on renal function in patients with cirrhosis.[88] Moreover, no cases of renal failure were attributed to contrast medium among 60 patients with both cirrhosis and renal failure.[88] The situation may be different in patients undergoing transarterial chemoembolization for liver tumors, in whom severe cirrhosis was found to be a risk factor for CIN.[89,90]

Additive Risk

The effect of risk factors is additive, and the likelihood of CIN rises sharply as the number of risk factors increases. This additive risk was first documented by Cochran and colleagues in a study of renal angiography that showed that the risk of CIN was 50% in patients with multiple risk factors.[91] Other researchers have consistently shown a relationship between multiple risk factors and an increased risk of CIN, both in peripheral angiography and in PCI. One study in patients undergoing angiography for peripheral arterial disease documented a 50% risk of CIN when all 4 independent risk factors were present.[92] In patients undergoing primary PCI for acute MI, all patients with 4 or 5 risk factors developed CIN.[26] A similar pattern of additive risk has been documented for nephropathy requiring dialysis. The incidence of CIN requiring dialysis in patients with the highest risk scores has been reported to reach 12.6%[68] and 16%,[30] and another model predicted a probability of 84% in diabetic patients with severe renal impairment.[15] The additive nature of risk has allowed the development of prognostic scores to facilitate risk prediction in clinical practice.

Review of Main Scoring Schemes

A risk model combines 2 or more characteristics to help clinicians make predictions about future health outcomes. The identification of major risk markers for CIN and quantification of the effect of these baseline and periprocedural characteristics on the likelihood of a CIN event among patients undergoing various radiological procedures have allowed the development of risk models. All the recently published models have been originated from large databases of PCI patients, with the data usually divided into a derivation set and a validation set.[14,15,30,68] Hence, they have been validated retrospectively but not in a prospective study. Importantly, no risk models have been developed or validated in patients receiving intravenous contrast medium. Nevertheless, it was the consensus view of the

group that the same pattern of additive effects of risk factors can be extrapolated to patients undergoing contrast-enhanced computed tomography.

High-Risk Scenarios

Coronary Angiography Followed by Coronary Artery Bypass Surgery

ARF is a common complication following cardiac surgery, and up to 5% of patients in a large series may require renal replacement therapy in the postoperative period.[93-95] Angiography to assess the coronary anatomy normally precedes CABG surgery, which therefore raises the question of whether exposure to contrast medium prior to surgery increases the risk of renal failure in the postoperative period. In a prospective study of 649 patients undergoing normothermic CABG or valve surgery, renal dysfunction (≥ 30% increase in serum creatinine) occurred in 17% of patients, and 3.2% required dialysis. Contrast medium administration within the previous 48 hours was an independent predictor of postoperative renal dysfunction.[96] In a larger multicenter study in 2222 patients undergoing CABG with or without valve surgery, 7.7% experienced renal dysfunction and 1.4% required dialysis after surgery. The small subset of patients who had undergone angiography within 24 hours of surgery were at higher risk of postoperative renal dysfunction.[97] However, contrast administration within the previous 5 days was not a significant risk factor for ARF in patients undergoing complex aortic surgery. There was no significant association between recent contrast administration and the occurrence of postoperative acute renal failure.[98]

Liver Disease

A high incidence of ARF that was associated with the severity of cirrhosis has been reported in patients undergoing transarterial chemoembolization (TACE) for hepatocellular carcinoma.[88] Patients with cirrhosis are at an increased risk of developing renal failure and may develop the hepatorenal syndrome, which is characterized by impaired renal function in the absence of specific renal pathology. Systemic and splanchnic vasodilation leads to a fall in arterial pressure with a subsequent activation of compensatory mechanisms leading to intense renal vasoconstriction. This process, in turn, causes a decrease in renal blood flow and a decline in the GFR.[99] This renal failure is functional and potentially reversible after liver transplantation. In view of the compromised renal function in hepatorenal syndrome, it would be expected that the risk of nephropathy after contrast medium administration might be increased, but no relevant reports could be identified in the literature. The consensus view of the panel was that many risk markers for CIN may be present in patients with the hepatorenal syndrome, and these factors should be considered in assessing risk. Transjugular intrahepatic portosystemic shunts (TIPS) are often used in the management of cirrhosis and hepatorenal syndrome, and the procedure is generally associated with an improvement in renal function.[100] Specific data on the effect on renal function are limited, but one study showed that TIPS placement improved renal function and reduced neurohormonal activation in 7 cirrhotic patients with type I hepatorenal syndrome.[101] Transient deterioration of renal function after TIPS placement has been reported, with 17% of patients with previously normal renal function experiencing temporary renal failure in one series.[102]

Radiocontrast image-guided TACE is typically performed in patients with hepatic tumors that are considered unresectable. In a retrospective review of 235 patients with hepatocellular carcinoma treated with TACE (843 treatment sessions), ARF within 7 days after TACE occurred in 23.8%, with a risk of 6.6% per treatment session. Severity of cirrhosis (Child-Pugh class B) and number of sessions were independent risk factors for acute renal failure. Child-Pugh class B and diabetes were risk factors for prolonged renal failure. It was concluded that ARF appeared to be related to the dose of contrast medium and the severity of cirrhosis. A prospective study by the same group evaluating serial changes in renal function also showed that cirrhosis was a risk factor. In 140 patients undergoing TACE for hepatocellular carcinoma, ARF (≥ 50% increase in serum creatinine or absolute increase ≥ 0.5 mg/dL [44.2 μmol/L] to above 1.5 mg/dL [132.6 μmol/L] within 7 days) occurred in 8.6%. Severity of cirrhosis (Child-Pugh class B), number of previous TACE sessions, and occurrence of severe post-embolization syndrome were risk factors.[90] In 24 patients with cirrhosis and hepatocellular carcinoma, neither angiography (8 patients) nor TACE (16 patients) had adverse effects on renal hemodynamics (renal artery pulsatility index).[103] In a series of 180 TACE procedures in 121 patients, almost all with hepatocellular carcinoma, nephropathy occurred after 6% of procedures. Renal cortical retention of contrast medium was detected by CT in 45%.[53] In a similar study in 18 patients with high serum creatinine levels, nephropathy occurred in 39% and renal cortical retention in 89%, whereas nephropathy developed in half the patients with severe renal cortical retention, compared with none of those without retention.[52] It was

concluded that renal cortical retention of contrast medium may be an early indication of nephropathy after TACE.

Renal Transplantation

Renal transplant recipients are potentially at increased risk of CIN because they may have underlying renal impairment from chronic rejection or recurrence of the primary disease and because they may be receiving nephrotoxic immunosuppressive agents, such as cyclosporine. The evidence from recent studies, since the introduction of cyclosporine for immunosuppression, is also conflicting with respect to CIN risk. In a series of 21 transplant patients with stable renal function undergoing either intravenous urography or arteriography with ioxaglate, no changes in serum creatinine, GFR, or renal plasma flow were observed. In addition, there were no cases of CIN.[104] No adverse effects of ioxaglate were observed in the subset treated with cyclosporine or in those with GFR $<$ 60 mL/min, indicating that a LOCM can be used in this population. However, a relatively recent retrospective analysis suggested that transplant recipients do have a higher incidence of CIN, although in this case all patients received HOCM.[105] A total of 44 transplant recipients, most of whom were receiving cyclosporine, underwent intravenous or intra-arterial contrast studies at various intervals after transplantation (mean 56.3 months). The incidence of CIN ($\geq$ 25% increase in serum creatinine) was 21.2%. The incidence was lower in those who received intravenous volume expansion (15.3%) compared with those who received no intravenous fluids (3 out of 7; 42.8%).[105] Another scenario in which a kidney graft may be exposed to contrast medium is through cerebral angiography of the donor to confirm brain death prior to nephrectomy. However, a study in 211 transplant recipients showed that there were no differences in renal function or graft survival between 132 patients receiving kidneys exposed to contrast medium and 79 receiving kidneys not exposed to contrast medium.[106]

Peritoneal Dialysis

Preservation of even a small amount of residual renal function is regarded as an important goal in patients with end-stage renal disease maintained on continuous or intermittent peritoneal dialysis.[107] Surprisingly, in a study of factors affecting loss of renal function in patients on continuous peritoneal dialysis, contrast studies were not significant.[108] In a comment on this report, it was noted that the reason for this is not clear, bearing in mind the importance of chronic renal failure as a predictor of CIN in predialysis patients.[107]

Choice of Contrast Medium

An association between the use of iodinated contrast media and renal impairment was first reported at least 50 years ago with iodopyracet, a diiodinated pyridine derivative.[109-111] This class was soon replaced by triiodinated benzene acid derivatives, which became the standard water-soluble contrast agents for intravascular contrast studies. The first of these were the ionic monomeric compounds, which were described as HOCM because they had an osmolality up to 8 times that of human plasma. These included diatrizoate, metrizoate, ioxithalamate, and iothalamate. Several approaches were taken to develop contrast media with lower osmolality without reducing the iodine content. Osmolality depends on the number of molecules in a solution that can be reduced through the production of non-ionic agents that do not dissociate in solution and by the production of dimeric molecules containing 2 benzoic acid rings. Iohexol, iopamidol, iopentol, iopromide, iomeprol, iobitridol, and ioversol are all nonionic monomers, whereas ioxaglate is the only ionic dimer available for clinical use. These compounds are all classified as LOCM. Nonionic dimers with lower osmolality have been produced: iodixanol is the only agent in this class available for intravascular use and is iso-osmolar to blood at all iodine concentrations. Iodixanol is described as an iso-osmolar contrast medium (IOCM). It is widely acknowledged that the osmolality of HOCM is a major contributor to its adverse effects and that a reduction in osmolality is desirable. There has been considerable discussion of the relative contribution of other properties, such as viscosity, to clinical toxicity but there is no clinical evidence to support an association. The viscosity of contrast media is temperature dependent and lower at higher temperatures.

LOCM Versus HOCM

A meta-analysis was undertaken to compare the relative nephrotoxicity of HOCM and LOCM. This analysis included all trials meeting the specified criteria that were identified by a search of the literature undertaken in 1991.[111] A total of 31 studies comparing HOCM and LOCM were identified, and the pooled data showed that LOCM is significantly less nephrotoxic than HOCM (P = .02). The mean rise in serum creatinine in 24 trials was less with LOCM than with HOCM, but the pooled effect size favoring LOCM, −0.058 standard deviation units (equivalent to a difference in mean serum creatinine of 0.2 μmol/L to 6.2 μmol/L [0.002 mg/dL to 0.07 mg/dL] between

groups), was not significantly different from zero. The pooled odds ratio for the prevalence of CIN events (rise in serum creatinine of > 44.2 μmol/L [> 0.5 mg/dL]) in 25 trials was 0.61 (95% CI, 0.48-0.77), indicating a significant reduction in risk with LOCM. Studies published since the meta-analysis generally support these findings. The largest study was the Iohexol Cooperative study, which was a prospective, randomized, double-blind, multicenter trial comparing iohexol (a non-ionic LOCM) with sodium-meglumine diatrizoate (an ionic HOCM) in 1196 patients undergoing cardiac angiography.[112] The overall incidence of nephrotoxicity, defined as an increase of ≥ 1 mg/dL (88.4 μmol/L) in serum creatinine at 48 to 72 hours, was 3.2% in the iohexol group compared with 7.1% in the diatrizoate group (P = .002). The results were also analyzed in prespecified subgroups according to the presence of diabetes mellitus and/or renal impairment. The reduction in nephrotoxicity was almost completely confined to the high-risk groups with diabetes and renal impairment (11.8% vs 27%) or renal impairment alone (4% vs 7.4%).

IOCM Versus LOCM

A pooled analysis has been undertaken of all patients included in 16 double-blind comparative clinical trials of intra-arterial contrast medium, in which iodixanol was compared with LOCM. This analysis included a total of 2727 patients: 1382 who received iodixanol and 1345 who received LOCM (iohexol, iopromide, iopamidol, or ioxaglate).[113] CIN occurred significantly less often after iodixanol than after LOCM, whether it was defined as an increase of 0.5 mg/dL (44.2 μmol/L) or 1.0 mg/dL (88.4 μmol/L). CIN was also significantly less frequent following iodixanol than after LOCM in the subgroups of patients with renal impairment and with both renal impairment and diabetes mellitus. An additional systematic review by Solomon[114] also found iodixanol to have the lowest risk of contrast nephropathy (OR, 0.262; P = .0019), compared to all other contrast agents. A total of 17 prospective clinical trials (1365 patients) was included. However, only 2 of these trials were randomized comparisons of LOCM and IOCM, and both compared iodixanol and iohexol. The other data came from the placebo arms of 13 trials of preventive strategies for CIN (dopamine, *N*-acetylcysteine, theophylline, hemofiltration) and the LOCM arms of 2 trials comparing LOCM and HOCM. The overall incidence of CIN was 16.8%; the incidence was the lowest with iodixanol (9.5%) as compared to iopamidol (11.3%) and iohexol (21.6%). There was no statistical difference in the incidence of CIN between iodixanol and iopamidol, whereas the difference was significant when considering iodixanol versus iohexol and iopamidol versus iohexol. These were not all head-to-head comparative trials, and the data further support that iodixanol is associated with the lowest rates of CIN in patients entered into randomized trials of contrast media evaluating CIN prevention. Finally, a meta-analysis of the renal tolerability of another iso-osmolar contrast medium, iotrolan 280, provides further evidence that iso-osmolar contrast is associated with a lower risk of postprocedure renal impairment.[115] On the basis of these results, the CIN Consensus Working Panel concluded that in patients with CKD and, particularly, those with diabetes mellitus undergoing angiographic procedures, current evidence suggests that non-ionic, iso-osmolar contrast presents the lowest risk for CIN. This consensus view was incorporated in an algorithm for patient management that indicates that in patients with CKD (eGFR < 60 mL/min/1.73 m^2), IOCM should be used when intra-arterial administration is required. IOCM or LOCM is appropriate for patients requiring intravenous administration and lower risk scenarios with iodinated contrast.

Volume of Contrast Medium

Both the volume of contrast medium and the iodine concentration need to be considered. Contrast media are available at a range of different iodine concentrations, with 300 mg to 370 mg iodine per mL being most commonly used. The iodine content is the determinant of the degree of attenuation and, hence, of the image enhancement achieved. As more complex coronary lesions are managed by PCI, the volumes of contrast medium used for coronary interventions may be high. For CT, with the introduction of multislice CT scanners, there is a trend to use lower volumes of contrast medium with higher intravenous injection rates.[116,117] Doses usually do not exceed 100 mL for coronary CT angiography. However, many patients may require multiple iodinated contrast studies, which can further increase the risk of CIN. Most multivariate analyses have shown that contrast volume is an independent predictor of CIN, both in PCI and peripheral angiography.[34,76] A significant correlation has been observed between postprocedure serum creatinine increase and/or CIN incidence and contrast dose. It has been reported that CIN is infrequent if the contrast volume is below 5 mL/kg divided by the serum creatinine level in mg/dL, and higher above this threshold. In a large registry of more than 16,000 PCI procedures, the contrast volume

adjusted for body weight and renal function was the strongest predictor of nephropathy requiring dialysis.[30] The odds ratio for the development of CIN requiring dialysis was 6.2 (95% CI , 3.0-12.8) in patients receiving more than the "adjusted contrast volume," which is defined as:

Adjusted contrast volume
= (5 mL × body weight [kg])/
baseline serum creatinine

Another group adapted this approach using the ratio of contrast volume to estimated creatinine clearance at baseline, thus adjusting for the effects of age and gender. In a prospective study, CIN occurred in 61% of patients when this ratio was above 6.0 and 1% when it was below 6.0 ($P < .01$).[118]

In patients at risk, the use of volumes of contrast medium above 100 mL is associated with a higher rate of contrast-induced nephropathy.

Even small volumes of contrast medium can have adverse effects on renal function in patients at particularly high risk. A 26% incidence of CIN was reported in patients with diabetes and chronic renal failure (mean serum creatinine 5.9 mg/dL [521.6 μmol/L]) who were receiving less than 30 mL.[119] Nevertheless, those who developed CIN received significantly more contrast medium that those who did not (30 mL vs 20 mL; $P = .004$). After reviewing the evidence, the CIN Consensus Working Panel concluded that, in patients at risk, the use of volumes of contrast medium above 100 mL is associated with a higher rate of CIN. The panel also concluded that there may not be a threshold volume below which CIN does not occur, since even small (~30 mL) volumes of iodinated contrast can cause CIN in patients at very high risk. This consensus view was incorporated into an algorithm for patient management that indicates that a contrast volume of less than 100 mL is preferable in patients with an eGFR < 60 mL/min/1.73 m^2.

Route of Administration

A number of studies have provided circumstantial evidence that the risk of CIN may be higher after intra-arterial administration than after intravenous injection. In 478 patients studied in clinical trials comparing ioxaglate, iohexol, and iopamidol, arterial administration was associated with a greater increase in serum creatinine than peripheral venous administration ($P = .08$).[13] The CIN Consensus Working Panel recognized that there is modest evidence to support a higher risk of CIN after intra-arterial administration compared with intravenous administration, with the pathophysiological basis being that the greater contrast load (concentration) reaching the kidneys occurs when the contrast medium is injected directly into the renal arteries or abdominal aorta. The amount reaching the kidneys is lower after injections into the coronaries and aortic arch because some enters the branches of the aorta, and it is even lower after injection below the origin of the renal arteries because it recirculates to the heart before reaching the kidneys. Similarly, contrast medium injected intravenously mixes with the rest of the venous return to a greater or lesser extent before reaching the kidneys.

Staged Procedures

Situations commonly occur in clinical practice in which further administration of contrast medium is required for diagnostic or therapeutic reasons soon after the index procedure. The most common example is the case of a patient who undergoes diagnostic coronary angiography at a peripheral hospital and is then referred for angioplasty at another hospital. Several analyses of risk factors indicate that repeat contrast administration is a risk factor for CIN.[120-122] One study identified contrast medium administration in the previous 72 hours as an independent risk factor for CIN.[91] A study of serial serum creatinine levels over time showed that renal impairment may persist for at least 10 days after contrast injection and that baseline renal function is a major determinant of the duration of creatinine elevation.[123] This fits with observations that the recovery phase after ischemic acute renal failure—characterized by redifferentiation and repolarization of tubular cells and recovery of GFR—typically begins about 8 days after the ischemic insult.[124] Recognizing that clinicians need practical guidance, the CIN Consensus Working Panel therefore recommended that, when possible, 2 weeks be allowed between procedures, since this duration corresponds to the expected recovery time for the kidney after an acute insult. The panel also recommended that the serum creatinine level be measured again prior to further contrast administration.

Preventive Measures

Volume Expansion

Volume expansion has a well-established role in reducing the risk of CIN, although few studies address this theme directly. Many patients described in early case reports of CIN were dehydrated.[72,125-129] Intravascular volume expansion may increase renal blood flow, reduce intrarenal

vasoconstriction, reduce the dwell time of contrast within the kidney, improve tubular flow of uric acid and cast material, and exert a variety of favorable neurohormonal effects that reduce the rate of CIN in patients. A trial by Mueller and colleagues[130] randomized 1620 patients to receive either 0.9% saline or 0.45% saline, 1 mL/kg/h for 24 hours beginning early on the day of angioplasty. The incidence of CIN (increase in serum creatinine of at least 0.5 mg/dL [44.2 μmol/L] within 48 hours) was significantly lower with 0.9% saline than with 0.45% saline (0.7% vs 2%; $P = .04$). In another randomized trial of 119 patients, intravenous sodium bicarbonate was compared with sodium chloride (154 mEq/L of each; 3 mL/kg/h for 1 hour before and 1 mL/kg/h for 6 hours after the procedure).[131] The risk of CIN (increase of ≥ 25% in serum creatinine within 48 hours) was significantly lower in the group receiving bicarbonate: 1.7% versus 13.6% ($P = .02$). It has been speculated that alkalinizing the urine reduces the nephrotoxicity of iodinated contrast media by changing the redox potential or by decreasing the viscosity of the agents within the vasa recta.

A prospective randomized study showed that intravenous volume expansion (at least 2000 mL saline over 12 hours before and after contrast exposure) was more effective than a 300 mL-saline bolus during contrast administration as shown by the significantly ($P < .05$) lower decline in GFR. The incidence of CIN was also lower.[9] Another randomized trial showed a trend to a lower incidence of CIN with overnight volume expansion rather than bolus fluid.[132] Overnight intravenous volume expansion is not possible for outpatients, and several investigators have evaluated the role of oral regimens. One study showed that an outpatient protocol including oral fluids (1000 mL clear liquid over 10 hours) followed by 6 hours of intravenous fluids (0.45% saline solution at 300 mL/h) beginning just before the procedure was as effective as overnight intravenous volume expansion (0.45% saline solution at 75 mL/h for 12 hours pre- and postcatheterization).[133] However, in this trial, the oral regimen was compared with 0.45% saline, which may be less effective than normal saline. A randomized trial in 53 patients showed that the incidence and severity of CIN was lower in patients who received intravenous normal saline at a rate of 1 mL/kg/h for 12 hours before the procedure than in patients who received unrestricted oral fluids.[134] The CIN Consensus Working Panel agreed that oral fluids may have some benefit; the reference standard should be intravenous volume expansion with an isotonic crystalloid solution. A reasonable protocol to reduce the risk of CIN is 1 to 1.5 mL/kg/h of intravenous isotonic crystalloid initiated 12 hours before the procedure and continued for 6 hours to 24 hours afterwards—a regimen that is achievable in hospitalized patients. Outpatients, in whom this regimen is impractical, should receive intravenous crystalloid for up to 3 hours before the procedure and for up to 12 hours afterwards, depending on the timing of the procedure and the expected discharge time.

Hemofiltration

Although hemodialysis is effective in removing iodinated contrast from the body, once iodinate contrast passes through the kidney, the CIN process has started and hemodialysis directly after contrast exposure has no impact on outcomes. However, hemofiltration for hours before and then immediately after contrast exposure has been a promising approach in patients with severe CKD. One study in 114 subjects showed that in patients with severe chronic renal impairment (serum creatinine > 2 mg/dL [> 176.8 μmol/L]), continuous venovenous hemofiltration (1000 mL/h without weight loss) was more effective than intravenous volume expansion in reducing the risk of CIN (normal saline was 1 mL/kg/h).[135] Hemofiltration and intravenous volume expansion were both started 4 to 8 hours before PCI and continued for 18 to 24 hours afterwards. It is important to note that CIN was defined in this study as a > 25% increase in serum creatinine; this outcome occurred less frequently in the group receiving hemofiltration than in the group treated with intravenous volume expansion (5% vs 50%, $P < .001$). However, since the intervention of hemofiltration itself affected the primary endpoint for the study, it cannot be determined whether there was a beneficial effect of hemofiltration. Although the in-hospital and 1-year mortality rates were significantly lower in the patients who underwent hemofiltration, the flawed nature of the trial design does not allow for definitive conclusions regarding this technique.[135] The CIN Consensus Working Panel concluded that hemofiltration deserves further investigation using endpoints unaffected by the experimental intervention, but the high cost and need for ICU admission also will limit the utility of this prophylactic approach.

Pharmacological Agents

The CIN Consensus Working Panel reviewed published reports describing various pharmacological agents evaluated for reduction in the risk of CIN. Many of the trials have given negative or conflicting results, and

there are no drugs with robust and consistent trial evidence to support clinical use in patients at risk of CIN. The majority of clinical trials of potentially protective agents have been undertaken in patients receiving intra-arterial contrast medium—PCI in most cases—and there are very few trials in patients receiving intravenous contrast media. Moreover, no drugs for prevention of CIN are approved by regulatory authorities anywhere in the world.

For most of the pharmacological agents that have been evaluated for reduction in the risk of CIN, the rationale for use has been based on current understanding of the pathogenesis of CIN. Thus, 3 main groups have been assessed: vasodilators, antagonists of intrarenal mediators, and cytoprotective agents.

After reviewing the evidence, the CIN Consensus Working Panel divided the drugs that have been evaluated in patients at risk of CIN into 3 categories (Table 2):

- Positive results: Potentially beneficial agents that need further evaluation but could be considered for use in patients at risk
- Neutral results: Agents that have not been shown to be consistently effective in reducing the risk of CIN
- Negative results: Potentially detrimental agents

Positive results. *Theophylline/Aminophylline.* Because adenosine is an intrarenal vasoconstrictor and a mediator of the tubuloglomerular feedback mechanism, it was logical to evaluate adenosine antagonists for risk reduction in CIN. Eleven studies were identified evaluating adenosine antagonists in patients at risk of CIN. Of the 9 randomized controlled trials (8 with theophylline, 1 with aminophylline), 3 showed a reduction in the rate of CIN.[136-144] Various oral and intravenous dosage regimens have been evaluated; a single intravenous dose before the procedure is a convenient option.

Table 2
Pharmacologic Agents Evaluated for Contrast-Induced Nephropathy Risk Reduction

Positive results (Potentially beneficial)
- Theophylline/Aminophylline
- Statins
- Ascorbic acid
- Prostaglandin E_1

Neutral results (No consistent effect)
- *N*-acetylcysteine
- Fenoldopam
- Dopamine
- Calcium channel blockers
  - Amlodipine
  - Felodipine
  - Nifedipine
  - Nitrendipine
- Atrial natriuretic peptide
- L-Arginine

Negative results (Potentially detrimental)
- Furosemide
- Mannitol
- Endothelin receptor antagonist

A meta-analysis of 7 trials (480 patients) showed that the administration of theophylline or aminophylline had a statistically significant effect on the decline in renal function following contrast medium administration.[145] The CIN Consensus Working Panel considered that these results were sufficiently positive for clinicians to consider the prophylactic use of theophylline in patients at high risk of CIN, although further studies are required for validation.

Statins. It has been suggested that hydroxymethylglutaryl-CoA inhibitors (statins) may reduce the risk of CIN because they have beneficial effects on endothelial function, maintain nitric oxide production, and reduce oxidative stress.[146,147] A retrospective review of 1002 patients with renal impairment (baseline serum creatinine $\geq$ 1.5 mg/dL [$\geq$ 132.6 μmol/L]) undergoing coronary angiography suggested that the risk of CIN was lower in patients in whom a statin was initiated just before the procedure. The results of a large PCI registry study published after the literature search for this review also support this conclusion; the CIN Consensus Working Panel considered that these findings were of such importance for clinicians that this report should be included. Records of 29,409 patients were reviewed and the results showed that patients who were receiving statin therapy before the procedure had a lower incidence of both CIN and nephropathy requiring dialysis than patients not receiving statin therapy. The incidence of CIN, defined as an increase in serum creatinine of $\geq$ 0.5 mg/dL ($\geq$ 44.2 μmol/L), was 4.37% in the statin group and 5.93% in the non-statin group ($P < .0001$); the incidence of nephropathy requiring dialysis was 0.32% and 0.49%, respectively ($P = .03$).[148] These data reinforce the rationale for the introduction of statin therapy before PCI. However, there is not enough evidence to support the use of statins in radiology patients in whom these drugs are not otherwise indicated.

Ascorbic acid. In view of the possible role of oxidative stress and free radical production in CIN, ascorbic acid was assessed because it is a widely available and well-tolerated antioxidant with an extensive safety record as a dietary supplement. In a double-blind, placebo-controlled trial in 231 patients undergoing cardiac catheterization, the incidence of CIN was significantly lower in patients receiving ascorbic acid.[149]

Prostaglandin E_1. Since renal vasoconstriction is believed to contribute to the pathogenesis of CIN,

preliminary studies have been undertaken with vasodilator prostaglandins. One study showed that misoprostol attenuated the decline in creatinine clearance after radiological procedures,[150] and another showed that the increase in serum creatinine was reduced in patients receiving prostaglandin E_1.[151,152]

Neutral. N-*acetylcysteine*. The possible role of reactive oxygen radicals in the pathogenesis of CIN led to the evaluation of the antioxidant *N*-acetylcysteine (NAC). Twenty-six trials and 9 published meta-analyses were identified, all documenting the significant heterogeneity between studies.[8,10,31,50,153-184] A standard oral regimen of 600 mg twice daily for 24 hours the day before and the day of the procedure has been evaluated in many studies, compared with a placebo group or an untreated control group. However, a number of different dosing regimens have also been evaluated. Briguori and colleagues[160] compared the standard oral dose (600 mg twice daily) with a double dose of NAC (1200 mg twice daily). CIN, defined as an increase in the serum creatinine of ≥ 0.5 mg/dL (≥ 44.2 μmol/L) at 48 hours, occurred in 3.5% of the double-dose group, compared with 11% in the single-dose group ($P = .038$). The difference was significant in patients receiving higher volumes of contrast medium but not in the subgroup receiving less than 140 mL of contrast medium.[160] A beneficial effect on creatinine clearance was observed with 1-g doses in patients with mild renal impairment undergoing coronary angiography. However, in other studies, 1200-mg or 1500-mg doses were not effective.[170]

The largest NAC trial, in which 500 mg NAC was given intravenously immediately before the procedure, was terminated early for futility after the randomization of 487 patients. The primary endpoint, defined as a fall in creatinine clearance from baseline of at least 5 mL/min, occurred in 23.3% in the NAC group and 20.7% in the placebo group ($P = .57$).[10]

The published meta-analyses include different numbers of trials, between 5 and 20, depending on the inclusion criteria adopted and the date on which they were undertaken.[31,177-184] Some included trials that were published only as abstracts or were unpublished, whereas others were confined to trials published in the peer-reviewed literature. All the meta-analyses highlight the heterogeneity in NAC trials that is generally unexplained and limits the conclusions that can be drawn. Some analyses include Begg plots indicating that there may be a publication bias, with smaller negative trials under-represented. A recent study has suggested that the apparent benefit of NAC observed in some trials may be a consequence of an effect on serum creatinine levels that does not reflect a real improvement in GFR. In normal volunteers not receiving contrast medium, NAC treatment was associated with a decrease in serum creatinine levels and an increase in the eGFR calculated from the serum creatinine, but it had no effect on serum levels of cystatin C, a better marker of GFR. It is possible that NAC causes a decrease in serum creatinine through other mechanisms such as renal tubular secretion or increased muscle metabolism.[185]

Fenoldopam/Dopamine. The hypothesis that dopamine might reduce the risk of CIN by causing renal vasodilation and increasing renal blood flow led to its clinical evaluation. A prospective, randomized, double-blind trial showed that low-dose dopamine (2 μg/kg/min) in addition to intravenous 0.45% saline was no more effective than adequate volume expansion in reducing the risk of CIN in patients with mild or moderate renal impairment.[186] In patients with peripheral vascular disease, the increase in serum creatinine was greater in patients receiving dopamine, suggesting a deleterious effect in this subgroup.

Fenoldopam is a selective agonist acting at dopamine A_1 receptors that might in theory selectively increase the blood flow to the renal medulla. However, 2 prospective randomized trials gave negative results.[154] In the first trial, patients were randomized to saline alone or to fenoldopam (0.1 μg/kg/min for 4 hours before and after the procedure); a third arm was treated with *N*-acetylcysteine. The incidence of CIN was similar in fenoldopam (15.7%) and control (15.3%) groups, and there was no benefit over volume expansion alone. A second larger trial also confirmed the lack of benefit with fenoldopam. In this double-blind trial, 315 patients, all hydrated with 0.45% saline, were randomized to fenoldopam (0.05 μg/kg/min titrated to 0.1 μg/kg/min) or placebo starting 1 hour before the procedure and continuing for 12 hours afterwards. There was no significant difference in the incidence of CIN in the 2 groups (fenoldopam 33.6%, placebo 30.1%) or in the rates of dialysis, rehospitalization, or death at 30 days.[187]

Calcium channel blockers. Calcium channel blockers have been evaluated for reduction in the risk of CIN because of their vasodilator properties. Various dihydropyridine calcium antagonists have been evaluated for CIN prophylaxis with no consistent evidence of benefit. Nifedipine,[188-190] nitrendipine,[191-193] felodipine,[194] and amlodipine[195] have all been tested in small studies of patients at risk of CIN, and none have proved beneficial in reducing rates of CIN.

Atrial natriuretic peptide. Atrial natriuretic peptide (ANP) has multiple effects on the kidney and has been shown to be beneficial in animal models of CIN.[196] One study showed no significant difference in the incidence of ARF following contrast medium administration between patients receiving ANP (50 μg bolus, followed by an infusion of 1 (g/min) or mannitol (15%, 100 mL/h) for 2 hours before and during cardiac catheterization. Renal blood flow was maintained in both groups.[196] In a subsequent double-blind, placebo-controlled trial, the incidence of CIN was not reduced by ANP at any of 3 doses (0.01 μg/kg/min, 0.05 μg/kg/min, and 0.1 μg/kg/min for 30 minutes before and 30 minutes after the procedure) compared with placebo.[197] A small hemodynamic study suggested that the use of ANP and other vasodilator agents was associated with an increased risk of CIN in diabetic patients but might be protective in nondiabetic patients.[198]

L-arginine. Theoretically, L-arginine might be renoprotective because it is a substrate for nitric oxide synthesis. However, a single injection of L-arginine (300 mg/kg) administered immediately before coronary angiography did not prevent a decrease in creatinine clearance at 48 hours in patients with mild to moderate renal failure in a randomized, double-blind, placebo-controlled trial.[199]

Negative results. *Furosemide.* In general, studies have not found furosemide to be beneficial because of its effects on reducing intravascular volume and reducing renal blood flow. Although forced diuresis to reduce the renal transit time of iodinated contrast is an attractive hypothesis, testing in a trial that included intravenous crystalloid, mannitol, furosemide, and low-dose dopamine showed no effect on the overall incidence of CIN.[200]

Mannitol. Randomized prospective trials provide no evidence to support a benefit from mannitol in patients at risk of CIN. In one trial, mannitol (25 g just before the procedure) plus saline was less effective than 0.45% saline alone in preventing acute decreases in renal function after cardiac angiography.[201] A forced diuresis regimen including intravenous crystalloid, mannitol, furosemide, and low-dose dopamine had no effect on the overall incidence of CIN. The trial design allowed for the effects of mannitol to be evaluated independently, and the results showed that mannitol provided no additive benefit.[200]

Dual endothelin receptor antagonist. A nonselective dual endothelin A and B receptor antagonist was shown to have a detrimental effect and to exacerbate CIN. The incidence of CIN was 56% in the patients receiving the endothelin receptor antagonist compared with 29% in the control group ($P = .002$).[202]

Conclusion

Ten consensus statements and an accompanying algorithm have been developed; these can be used to guide the management of patients receiving iodinated contrast medium. This consensus program is important as it is the first attempt to systematically review all relevant information on CIN, a common and serious problem. It integrates the viewpoints of cardiologists, nephrologists, and radiologists. Guidelines and quality programs can be developed from this base of work in the future. ■

Main Points

- Contrast-induced nephropathy (CIN) is an important complication of the use of iodinated contrast media that accounts for a significant number of cases of hospital-acquired renal failure.
- Patients with CIN had a 5.5-fold increased risk of death and a clinical course characterized by complications associated with renal failure.
- The preferred equation for the calculation of estimated glomerular filtration rate in adults is the abbreviated Modification of Diet in Renal Disease formula.
- High-risk scenarios for developing CIN include coronary angiography followed by coronary artery bypass surgery, liver disease, renal transplantation, and peritoneal dialysis.
- There is modest evidence to support a higher risk of CIN after intra-arterial administration compared with intravenous administration.
- Iso-osmolar iodixanol is the contrast media of choice when the risk of CIN exceeds 5% (high-risk scenario).
- Agents that could potentially reduce the risk of CIN include theophylline/aminophylline, statins, ascorbic acid, and prostaglandin E_1.

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