Iodinated Contrast Media and the Kidney

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One of the principal complications of radiographic procedures utilizing intravascular iodinated contrast media is acute kidney injury. Although several clinical and procedural factors impact a patient's risk for contrast-induced acute kidney injury (CIAKI), substantial attention has been focused on the relationship between the type of contrast agent used and renal injury. Multiple contrast agents are available for clinical use, each defined by a series of physicochemical properties. The evolution from high osmolal to low osmolal and, more recently, iso-osmolal contrast media has led to several clinical trials and meta-analyses comparing the nephrotoxicity of different contrast agents. This article summarizes the physicochemical properties that define and differentiate iodinated contrast media, discusses the purported relationship between these properties and kidney injury, and describes the salient findings of clinical trials and meta-analyses that have compared the nephrotoxic effects of contrast agents. Although ongoing and future studies will further elucidate our understanding of the relationship between iodinated contrast and risk for CIAKI, a sound understanding of the currently available data will help inform evidence-based decisions on the use of these agents in clinical practice.

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Contrast-induced acute kidney injury (CIAKI) is a well-recognized and potentially serious complication of intravascular iodinated contrast administration.[1-3] A series of epidemiological, clinical, and technological factors suggest that this iatrogenic condition will continue to be an important clinical entity. First, the patient population is growing in size and living longer

with chronic illness, suggesting that a greater number of patients will have clinical indications for radiographic procedures that use intravascular radiocontrast. Second, chronic kidney disease, which is the principal risk factor for CIAKI, and diabetes mellitus, which amplifies risk for CIAKI in patients with baseline renal impairment, are increasing in prevalence.[4] Third, recent recognition of the association of gadolinium with nephrogenic systemic fibrosis in patients with advanced and end-stage kidney disease may lead to less use of MRI and greater reliance on imaging modalities that utilize iodinated radiocontrast.[5] Finally, advancements in modern imaging technology have led to an increasing array of diagnostic and therapeutic radiographic procedures that employ iodinated contrast. Unfortunately, despite intense investigation, few pharmacologic measures have been conclusively found to prevent the development of CIAKI. As a result, a great deal of attention has been paid to the few interventions that do impact risk for CIAKI, including choice of contrast agent.

Iodinated contrast media are characterized and differentiated by a series of physicochemical properties, including ionicity, osmolality, and viscosity, each of which has been studied in respect to risk for CIAKI. Considerable controversy surrounds the relative importance of each of these characteristics in regard to risk for kidney injury. Nonetheless, since iodinated contrast media became available decades ago, significant advancements have been made in our understanding of how to most effectively and safely use these agents.

Physicochemical Properties

Ionicity

Iodinated contrast media can be divided into ionic and nonionic agents. Ionic compounds are those that contain ions, or charged particles. Early iodinated contrast agents were ionic monomers, comprised of a single benzene ring and containing a cation (sodium or meglumine) that dissociated in aqueous solution (Figure 1). The presence of the cation and dissociation of these agents into charged particles (triiodinated anion and cation) in blood define these compounds as ionic. In addition, ionic monomeric compounds are also characterized as high osmolal, with osmolalities of approximately 5 to 8 times that of human plasma. However, it is important to note that all ionic contrast agents are not high osmolal. Ioxaglate is a dimeric molecule consisting of 2 benzene rings and a sodium atom. It is ionic, yet low osmolal, with an osmolality of approximately twice that of plasma. Ioxaglate is the sole ionic, low osmolal agent currently available for use in the clinical arena. Therefore, ionicity and osmolality, although related properties, should not be considered synonymous.

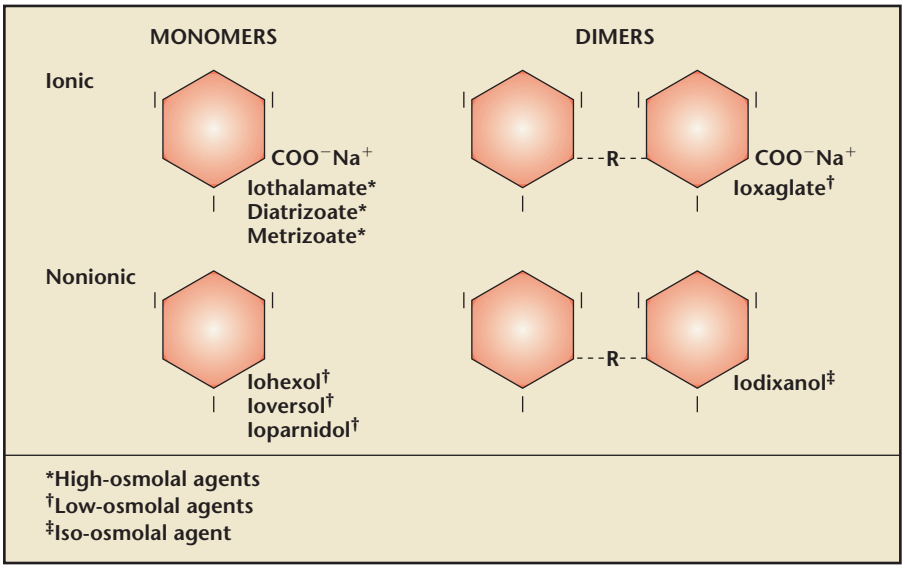

Figure 1. *Contrast agents. Reprinted with permission from Rudnick MR[26] (adapted with permission from Rudnick MR[28]).*

Osmolality

Perhaps the most widely recognized physicochemical property of iodinated contrast media is osmolality, which refers to the number of particles in solution, measured as milliOsmoles per kilogram of water (mOsm/kg water). Contrast agents are typically divided into 3 distinct categories of osmolality: high osmolal, low osmolal, and iso-osmolal. High osmolal contrast media (HOCM), including diatrizoate, iothalamate, metrizoate, and ioxithalamate, were the most widely used agents into the 1980s, with osmolalities ranging from approximately 1500 mOsm/kg to greater than 2000 mOsm/kg. The next generation of contrast agents was referred to as low osmolal contrast media (LOCM) and had osmolalities of approximately 600 to 1000 mOsm/kg. These agents were developed by either producing nonionic compounds that did not dissociate in solution or creating dimeric molecules linking 2 benzene rings through a common side chain. The term *low osmolal* was coined based on the lower osmolality of these agents

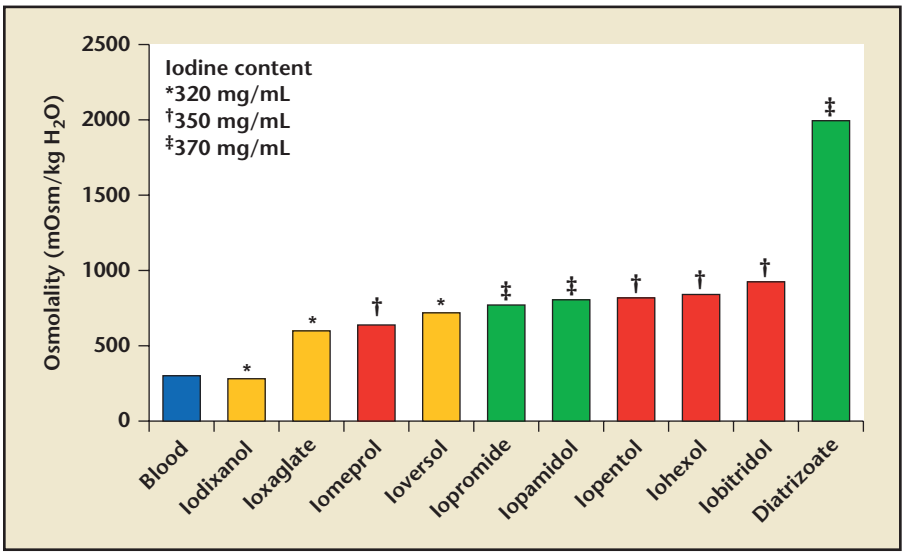

Figure 2. *Osmolalities of contrast agents. Reprinted from Davidson C et al,[27] with permission from Elsevier.*

relative to conventional HOCM. However, low osmolal is a misnomer. These contrast media are in fact, hyperosmolal to human plasma, and this terminology has unfortunately led to significant confusion. Lastly, the most recent generation of contrast media is iso-osmolal contrast (IOCM); appropriately named based on an osmolality that approximates plasma (~ 290 mOsm/kg) (Figure 2).

An alternative approach to categorizing the different osmolality contrast media is based on the ratio of iodine atoms to dissolved particles. HOCM, which are monomers made up of a single benzene ring containing 3 iodine atoms and an attached cation, have 3 iodine atoms to 2 particles in solution, or a ratio of 1.5:1. LOCM, other than ioxaglate, are nonionic monomers with 3 iodine atoms, reflecting a ratio of 3:1. The chemical structure of IOCM (of which the only available agent for clinical use in the United States is iodixanol) is a nonionic dimer, comprised of 2 benzene rings and 6 iodine atoms. Therefore, the ratio of iodine atoms to dissolved particles is 6:1 (Figure 1). Higher ratios of iodine atoms to osmotically active particles in solution are associated with greater radiographic attenuation. Advancements in the development of contrast media were based on generating nonionic, lower-osmolal molecules that would reduce untoward side effects and improve tolerability, while simultaneously preserving iodine concentration and radiographic opacification.

Viscosity

A rheologic property of contrast media that has recently gained increasing attention is viscosity, which refers to the resistance of a fluid to flow. Viscosity is expressed in milliPascal second (mPa × s). Although several factors affect the viscosity of contrast media, HOCM and LOCM have lower viscosities than IOCM, particularly at room temperature. However, the viscosity of contrast media is highly dependent on and inversely related to temperature. As a result, a clinical approach that is commonly used to lower the viscosity of contrast media prior to injection is preheating of the fluid.

Physicochemical Properties and the Pathophysiology of CIAKI

The evolution of contrast media over the past 3 decades has been accompanied by substantial debate on the importance of ionicity, osmolality, and viscosity in regard to the pathogenesis of CIAKI. Animal studies support the role of multiple pathophysiologic mechanisms in the pathogenesis of CIAKI. Principal among these are direct tubular cell toxicity of contrast media and hypoxia of the outer medullary region of the kidney. The medulla is characterized by a relatively low PO_2 and high oxygen demand, making it an area of the kidney particularly susceptible to mismatch in oxygen demand and delivery. A series of studies in animal models have demonstrated that the administration of iodinated contrast media leads to altered renal microcirculation and medullary hypoxia. These pathogenic processes have in part, been the basis for investigation of the associations of osmolality and viscosity of contrast media with the development of CIAKI.

Ionic contrast media, specifically high osmolal agents, have been associated with an increased risk for CIAKI; however, it has been difficult to disentangle the relationship between iconicity and osmolality with regard to nephrotoxic effects. Therefore, much of the work on contrast and the pathogenesis of CIAKI has focused on osmolality. There are a series of hypotheses for the association of increased osmolality with CIAKI. It has been proposed that differential effects on tubular metabolic activity, vasodilatory mediators, and renal hemodynamics of contrast media of differing osmolality might explain an association between osmolality and

CIAKI. Administration of contrast media leads to an osmotic diuresis. The increased solute delivery to distal segments of the renal tubule would be expected to lead to an augmentation in metabolic activity. The resultant increase in oxygen demand, could, in the setting of vasoconstriction and medullary hypoxia, contribute to renal injury. Studies in animals have reported a direct association of diuresis/natriuresis with osmolality.[6] However, conclusive data supporting this association and its effect on renal injury are lacking. In experimental models, HOCM and LOCM reduced production of the vasodilator nitric oxide in smooth muscle cells, whereas IOCM did not impact nitric oxide production.[7] In patients with chronic kidney disease, HOCM has been shown to result in a greater reduction in renal plasma flow and glomerular filtration rate than LOCM.[8] Conversely, other studies have found that IOCM results in a more pronounced reduction in renal blood flow and single nephron glomerular filtration than hyperosmolal contrast.[9,10] Thus, there are conflicting data on the impact of osmolality on renal hemodynamics.

Administration of contrast media leads to an osmotic diuresis.

Similarly, there are a series of hypotheses underlying the association of contrast agent viscosity and risk for renal injury. Studies in animal models have documented that more viscous contrast may delay transit time of the contrast medium in the renal tubule, increase tubular hydrostatic pressure, and decrease glomerular filtration.[11] It has also been suggested that higher viscosity leads to a greater degree of erythrocyte aggregation and reduced erythrocyte velocity in the medullary circulation.[6] Although these reported effects of viscosity appear to provide biologic plausibility for a link between higher viscosity of contrast agent and risk for CIAKI, some of the potentially adverse effects associated with higher viscosity may be attenuated by preheating.[9] Moreover, past clinical studies that demonstrated lower rates of CIAKI with iodixanol than certain LOCM do not support a strong relationship between viscosity and risk for CIAKI.

It is important to note that many of the studies to date examining the role and importance of specific physicochemical properties of contrast and renal injury have been based on in vitro experiments and animal models. Unfortunately, such studies cannot provide conclusive evidence of the precise pathophysiologic processes in humans following the injection of intravascular radiocontrast. However, they provide a scientific context from which to discuss clinical trials that have compared the nephrologic effects of iodinated contrast media.

Clinical Trials of Contrast Agents

HOCM versus LOCM

Although more expensive than HOCM, LOCM were found to be associated with greater tolerability and fewer adverse cardiovascular and pseudoallergic effects. The balance between cost and clinical benefit led to a series of studies comparing the nephrotoxicity of these agents. Following several trials that were underpowered and/or enrolled inadequate numbers of high-risk participants and were therefore unable to provide consensus on the superiority of LOCM, Barrett and Carlisle[12] conducted a meta-analysis comparing LOCM with HOCM. Among 25 trials for which there were evaluable data, the pooled odds of CIAKI, defined by a rise in serum creatinine (SCr) greater than 0.5 mg/dL, was 0.61 (95% CI, 0.48-0.77) with the use of LOCM. The odds of CIAKI with LOCM decreased to 0.5 (95% CI, 0.36-0.68) among patients with abnormal kidney function, suggesting an even greater benefit among this patient subgroup. This meta-analysis provided preliminary evidence that LOCM decreased the risk of renal injury among patients with impaired baseline kidney function.

Following the publication of this meta-analysis, Rudnick and colleagues[13] reported the results of the Iohexol Cooperative Study, a multicenter clinical trial of 1196 patients undergoing nonemergent coronary angiography. Participants were randomized to receive high osmolal diatrizoate or low osmolal iohexol. The primary study outcome was the development of CIAKI, defined by an increase in SCr greater than or equal to 1.0 mg/dL within 48 to 72 hours following angiography. The overall incidence of CIAKI was lower among patients who received iohexol compared with diatriazoate (3.2% vs 7.1%; $P = .002$). Using a less robust increase in SCr of 0.5 mg/dL or more to define renal injury, iohexol was also associated with a lower overall incidence of CIAKI than diatrizoate (13.4% vs 21.1%; $P < .001$). The beneficial effects of iohexol were limited to patients with baseline renal insufficiency and were pronounced among participants with kidney disease and concomitant diabetes mellitus. This study, the data of which were included in the meta-analysis by Barrett and Carlisle,[12] confirmed that iohexol was less nephrotoxic than diatrizoate in "at risk" patients. Furthermore, it demonstrated that

among patients with chronic kidney disease, coexistent diabetes mellitus substantially amplifies the risk for CIAKI. Collectively, both of these studies established an evidence basis for the widespread use of LOCM, particularly among patients with abnormal baseline kidney function.

LOCM versus IOCM

Over the past decade, several trials have been conducted to evaluate the relative nephrotoxicity of LOCM and IOCM. However, many were performed in very small patient populations and/or enrolled inadequate numbers of patients at increased risk for CIAKI, rendering the results of unclear clinical significance. More recent randomized clinical trials that enrolled larger numbers of patients and/or focused on patients at increased risk for CIAKI form much of the current evidence basis on the relative nephrotoxicity of LOCM and IOCM, and fuel the ongoing controversy on the comparative effects of these agents (Table 1).

In 1998, Carraro and coworkers[14] published one of the first studies comparing LOCM with IOCM in patients with underlying kidney disease. This clinical trial enrolled patients with baseline SCr between 1.5 and 3.0 mg/dL who were undergoing intravenous urography, and randomized patients to receive iso-osmolal iodixanol (32 patients) or low osmolal, nonionic iopromide (32 patients). The primary study endpoint was the development of CIAKI defined by an increase in SCr of 50% within 24 hours of contrast administration. Only 1 study patient (who received iodixanol) developed CIAKI, and the SCr reportedly returned to baseline within 48 hours. Although this study demonstrated no significant differences in CIAKI between the 2 contrast agents, there were certain methodological limitations to this trial. First, the patient population was quite small, which significantly limited the study's power to detect differences between groups. Second, although all participants had chronic kidney disease, very few had comorbid diabetes mellitus, which likely rendered the study population at moderate rather than high risk for CIAKI. Lastly, CIAKI was defined by a substantial increase in SCr within just 24 hours following the procedure, which may not have allowed sufficient time to determine whether renal injury had occurred. Although serologic evidence of CIAKI may manifest within 24 hours of contrast administration, a substantial proportion of patients may not have biochemical evidence of

Although serologic evidence of contrast-induced acute kidney injury may manifest within 24 hours of contrast administration, a substantial proportion of patients may not have biochemical evidence of renal injury for 2 to 3 days.

Table 1
Select Clinical Trials of Low and Iso-Osmolal Contrast in Patients at Risk for CIAKI

Study	Patients (n)	Contrast Agents	Procedure	Baseline SCr (mg/dL)	Incidence of CIAKI (%)		*P* Value
					LOMC	IOCM	
Carraro M et al[14]	64	Iopromide Iodixanol	IV urography	1.69-1.7	0	3.1	NS
Chalmers N and Jackson RW[15]	102	Iohexol Iodixanol	Angiography	3.05-3.34	31	15	< .05
Aspelin P et al[16]	129	Iohexol Iodixanol	Angiography	1.49-1.6	26*	3*	.002
Jo SH et al[17]	275	Ioxaglate Iodixanol	Coronary angiography	1.3-1.38	17	7.9	.02
Barrett BJ et al[18]	153	Iopamidol Iodixanol	Computed tomography	1.5-1.6	0*	2.6	.2
Solomon RJ et al[19]	414	Iopamidol Iodixanol	Coronary angiography	1.44-1.46	4.4*	6.7*	.39

CIAKI, contrast-induced acute kidney injury; IOCM, iso-osmolal contrast media; IV, intravenous; LOCM, low osmolal contrast media; SCr, serum creatinine.
*Based on an increase in SCr ≥ 0.5 mg/dL.

renal injury for 2 to 3 days. It should also be noted that contrast was administered intravenously in this study, which has been associated with less risk for CIAKI than intra-arterial administration.

In 1999, Chalmers and Jackson[15] reported the results of a clinical trial that randomized hospitalized patients with moderately advanced kidney disease (SCr > 1.7 mg/dL) who were undergoing angiography to receive iohexol or iodixanol. Of 48 patients who received iohexol, 15 (31%) demonstrated a rise in SCr greater than 10% compared with 8 of 54 (15%) who received iodixanol ($P < .05$). Five patients (10%) in the iohexol group manifested an increase in SCr of more than 25% as compared with 2 subjects (3.7%) in the iodixanol group (P = NS). These findings provided preliminary evidence that iodixanol might be less nephrotoxic in high-risk patients. The primary strength of this trial was the enrollment of patients with moderately advanced chronic kidney disease. However, the study sample was relatively small and it remains unclear whether a postprocedure rise in SCr of more than 10% is a sufficiently specific definition of CIAKI, or whether it represents a clinically meaningful change in kidney function.

The Nephrotoxic Effects in High-Risk Patients Undergoing Angiography (NEPHRIC) study[16] was a randomized, double-blind, multicenter study comparing iodixanol and iohexol in 129 diabetic patients with baseline renal impairment undergoing coronary or aortofemoral angiography.[16] The primary study endpoint was the peak increase in SCr by day 3 following the procedure. Secondary endpoints included increases in SCr greater than or equal to 0.5 mg/dL and greater than or equal to 1.0 mg/dL, as well as the change in SCr from day 0 to day 7. Iodixanol was found to result in a smaller peak increase in SCr by day 3 than iohexol (0.13 mg/dL vs 0.55 mg/dL; $P = .001$). Only 3% of patients who received iodixanol manifested a rise in SCr greater than or equal to 0.5 mg/dL compared with 26% of patients who received iohexol ($P = .002$), whereas none of the patients who received iodixanol developed a change in SCr of greater than or equal to 1.0 mg/dL as compared with 15% of patients in the iohexol group ($P = .001$). Mean peak increase in SCr at 7 days was also lower with iodixanol. This study, published in 2003, was the largest trial up until that time to compare LOCM and IOCM in high-risk patients. Enrollment of patients at particularly high risk for CIAKI, all of whom had chronic kidney disease and diabetes mellitus, was one of the strengths of this study. Additionally the protocolized assessment of renal function out to the seventh day postprocedure facilitated the comparison of study groups on a series of biochemically defined outcomes. Conversely, the sample size estimate was based on a continuous outcome, which likely allowed for the enrollment of a smaller number of patients. Although there were substantial differences in categorical outcomes, all of which favored iodixanol, the propensity for a type 1 error with such outcomes increases with smaller sample size. Notwithstanding these limitations, the findings in the NEPHRIC provided supportive data that iodixanol was less nephrotoxic than iohexol.

In 2006, Jo and colleagues[17] reported their findings of the Renal Toxicity Evaluation and Comparison Between Visipaque and Hexabrix in Patients With Renal Insufficiency Undergoing Coronary Angiography (RECOVER) study, a clinical trial of patients with baseline kidney disease (baseline creatinine clearance ≤ 60 mL/min) undergoing coronary angiography with or without percutaneous intervention. Overall, 275 patients were randomized to receive iodixanol or the low osmolal ionic agent ioxaglate and had evaluable follow up data. A definition of CIAKI based on an increase in SCr of greater than or equal to 25% or 0.5 mg/dL within 2 days was the primary study endpoint. The incidence of CIAKI using this definition was lower among patients who received iodixanol than those who received ioxaglate (7.9% vs 17%; $P = .021$). When 2 different definitions of CIAKI, increases in SCr of greater than or equal to 0.5 mg/dL and greater than or equal to 1.0 mg/dL were each analyzed, the differences between contrast agents were not statistically different. Subgroup analyses of patients with advanced baseline kidney disease (creatinine clearance < 30 mL/min) and patients with diabetes demonstrated a lower incidence of CIAKI with iodixanol. Among subgroups of older patients and those with significantly reduced ejection fraction, there were no differences in CIAKI. Finally, there were no differences between the groups in the composite safety outcome that included need for dialysis and death. Strengths of this study included the recruitment of a larger study population and the exclusion of patients without baseline kidney disease. However, less than 40% of patients were diabetic, rendering the patient population at lower risk than participants in the NEPHRIC study. Moreover, the relatively small number of patients included in many of the subgroup analyses significantly limited the power of these comparisons. Nonetheless, by recognizing the higher viscosity of iodixanol than iohexol and ioxaglate, the NEPHRIC

and RECOVER studies and the trial by Chalmers and Jackson[15] suggested that osmolality is a more important property than viscosity in regard to risk for CIAKI.

There have been a series of trials that have not demonstrated differences in risk for CIAKI between IOCM and certain LOCM. In 2006, Barrett and colleagues[18] published the results of the Isovue-370 and Visipaque-320 in renally IMpaired PAtients undergoing Computed Tomography (IMPACT) study, a multicenter clinical trial of patients with baseline kidney disease undergoing multidetector CT with intravenous contrast. Patients in this study were randomized to receive iso-osmolal iodixanol or low osmolal iopamidol. An increase in SCr greater than or equal to 0.5 mg/dL was observed in 2 of 76 (2.6%) patients who received iodixanol compared with none of the 77 (0%) who received iopamidol ($P = .2$). An increment in SCr of greater than or equal to 25% developed in 4.0% of patients who received iodixanol and 3.9% of those who were administered iopamidol ($P = 1.0$). These results supported a similar risk for CIAKI with iodixanol and iopamidol among patients with chronic kidney disease undergoing multidetector CT. This was a methodologically sound trial that achieved comparability between the study groups in several clinical factors that have known associations with CIAKI. Nonetheless, the overall size of the study population was small, raising questions on the study's power to detect subtle differences between the groups. Moreover, less than 25% of participants were diabetic and most had less advanced baseline kidney disease. It is therefore not surprising that the observed rates of CIAKI were quite low. It is also important to note that this study involved intravenous contrast administration, which may be associated with a lower risk for CIAKI than intra-arterial administration. Nonetheless, one conclusion drawn from the results was that there are no differences in risk for CIAKI between iodixanol and iopamidol among patients at moderate risk for this condition who receive intravenous contrast. Finally, although it is difficult to compare results across trials and study populations, this study also raised the possibility of potential differences in risk for CIAKI among the different clinically available LOCM.

Most recently, Solomon and coworkers[19] reported the results of the Cardiac Angiography in Renally Impaired Patients (CARE) study. This multicenter, double-blind, randomized trial was a comparison of iodixanol and iopamidol in patients with chronic kidney disease undergoing coronary angiography, with or without percutaneous intervention. Among 210 evaluable patients who received iodixanol, 14 (6.7%) manifested a rise in SCr of 0.5 mg/dL or more and 26 (12.4%) had a rise of 25% or more, compared with 4.4% and 9.8%, respectively, among patients who received iopamidol (P = NS for each comparison). In analyses among subgroups defined by the presence or absence of diabetes, no statistically significant differences in CIAKI were seen between the 2 study groups. Collectively these results supported the findings of the IMPACT study that iodixanol and iopamidol were comparable in their risk for CIAKI. The principal strength of this randomized clinical trial was the enrollment of a larger number of patients. However, 34% of study participants had only mild kidney disease (baseline estimated glomerular filtration rates, 50-59 mL/min/1.73 m^2), and less than half were diabetic, raising important questions on the true underlying level of risk for CIAKI in much of the study population. Interestingly, there also appeared to be differences in the incidence of CIAKI based on the timing of the postprocedure SCr. A higher incidence of CIAKI was observed with iodixanol among patients with postprocedure SCr assessments at 45 to 71 hours, yet among patients with postprocedure assessments at 71 to 96 hours, iopamidol was associated with a higher rate of CIAKI. However, these analyses, as with the other subgroup analyses in this trial and the RECOVER study, had less power to discern meaningful differences.

Trial data comparing high osmolal contrast media with low osmolal contrast media in higher-risk patients appear to suggest that osmolality may have a stronger relationship with risk for contrast-induced acute kidney injury than viscosity.

These 6 studies constitute much of the evidence base on the nephrotoxic effects of IOMC and LOCM in patients at increased risk for CIAKI. Three studies suggest a lower risk for renal injury with iodixanol than certain LOCM agents (eg, iohexol, ioxaglate), whereas 3 trials found no differences between iodixanol and either iopamidol or iopromide. There are certain limitations to each of these studies, which need to be carefully considered when interpreting the results and conclusions. Collectively the findings of these trials, when viewed in light of the trial data comparing HOMC with LOCM in higher-risk patients, appear to suggest that osmolality may

have a stronger relationship with risk for CIAKI than viscosity. However, it is also possible that some of the benefit achieved by decreasing osmolality from low osmolal to iso-osmolal is offset by the higher viscosity of IOCM. Recently completed studies, the results of which have yet to be published, should shed further light on the comparability of LOCM and IOCM in high-risk patients.

Pooled Analyses, Meta-Regression Analyses, and Meta-Analyses of LOCM and IOCM

A lack of consensus on the relative risks for CIAKI of LOCM and IOCM led to a series of analyses that combined data from several different clinical trials in order to identify a summary effect of contrast type on CIAKI. It should be noted that data from the RECOVER, IMPACT, and CARE studies were not included in these analyses.

In 2005, Sharma and Kini[20] reported the findings of an analysis in which trial-level results of prospective studies of contrast agents were pooled to generate summary relative risk estimates for CIAKI with iodixanol and low osmolal contrast agents. Based on a study sample of 560 patients, the investigators found that both iodixanol and iopamidol were associated with a lower risk for CIAKI than iohexol, yet identified no difference in risk when comparing iodixanol with iopamidol. Although novel in the approach to the question of osmolality and CIAKI, this study had a relatively small sample size, did not include studies published before 2002, and did not formally account for statistical heterogeneity among the included studies.

In a subsequent study, Solomon[21] published the results of a meta-regression analysis that pooled the findings of 17 studies including direct comparisons of iodixanol with LOCM, as well as the control arms of trials that investigated other interventions for the prevention of CIAKI. A total of 1365 patients were included, and in logistic regression analyses, iodixanol and iopamidol were similar in their risk for CIAKI; yet both were associated with a lower risk than iohexol. This study supported the findings of Sharma and Kini,[20] yet included the control arms of studies that investigated preventive interventions other than contrast, rather than data from all of the participants in these trials. The selective inclusion of patients from trials that addressed a different clinical question could have confounded the results. A subsequently published meta-regression analysis by Solomon and DuMouchel[22] that included 3112 patients from 22 trials also reported a higher rate of CIAKI with iohexol than iopamidol, and a generally comparable risk of CIAKI with iodixanol and iopamidol. However, the findings of these 2 later studies were based on the use of trial rather than patient-level data and heterogeneity among the included studies was managed by trial-level meta-regression techniques. This is a less robust approach to pooled analyses than utilizing patient level data.

Finally, McCullough and coworkers[23] conducted a meta-analysis comparing the renal safety of iodixanol and LOCM, of which several agents were considered collectively. Individual-level data from 2727 patients was pooled from 16 clinical trials, all of which were head-to-head comparisons of iodixanol and LOCM in angiography. Outcomes, based on both the maximal change in SCr, and CIAKI defined by an increase in SCr of at least 0.5 mg/dL were reported for the overall population, as well as subgroups of patients at high and low risk for CIAKI. The investigators assessed study heterogeneity and used this assessment to guide their regression analyses. Iodixanol was associated with a smaller rise in SCr in the overall population and among each of the subgroups. Similarly, iodixanol was associated with a lower risk for CIAKI than LOCM in the overall population, among patients with chronic kidney disease, and among diabetics with chronic kidney disease. However, no differences in the risk for CIAKI between iodixanol and LOCM were found among patients without chronic kidney disease, whether diabetic or nondiabetic, or among nondiabetic patients with chronic kidney disease. These findings suggested that among patients at lower risk for CIAKI, there is little difference between agents. However, among patients at higher risk for CIAKI, iodixanol appears less nephrotoxic. This study was strengthened by the inclusion of only those studies that were head-to-head comparisons of contrast agents, a large number of patients, and the utilization of patient rather than trial-level data. It is, however, important to note that only 69 of 1345 (5%) in the LOCM group received iopamidol, which was the low osmolal agent that had been reported in the other pooled analyses to be less nephrotoxic than iohexol. Therefore, differences between iodixanol and iopamidol could not be meaningfully assessed in this meta-analysis.

These 4 analyses provide further data that there are differences between and among IOCM and LOCM; consistently demonstrating that iohexol is associated with a greater risk for CIAKI among higher-risk patients. When LOCM are considered collectively, they appear to

pose a greater risk for CIAKI than iodixanol in higher-risk patients, specifically those with chronic kidney disease and diabetes. However, the results of some of these trials and pooled analyses dispute the notion that all LOCM are equivalent in regard to renal safety, suggesting that iopamidol is a less nephrotoxic low osmolal agent. These conflicting findings are reflected in recent guidelines for the use of contrast agents. The American College of Cardiology/American Heart Association guidelines recommend the use of IOCM in patients with chronic kidney disease undergoing angiography, whereas the European Society of Urogenital Radiology recommends the use of either LOCM or IOCM in patients at increased risk of CIAKI.[24,25] Future studies will clearly be needed to elucidate the differences among the different LOCM, and between LOCM and IOCM.

Conclusions

Iodinated contrast agents have greatly facilitated the diagnosis and treatment of many diseases, and their use is likely to continue to increase in the future. A series of physicochemical properties define and differentiate currently available contrast media, and a growing understanding of the relationships between these properties and adverse effects have led to improvements in the tolerability and safety of these agents. Although it is clear that additional studies will be needed to elucidate which contrast agent poses the lowest risk for CIAKI, a sound appreciation for the current evidence basis will enable providers to use these agents in the safest and most efficacious manner. ■

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Main Points

- One of the principal complications of radiographic procedures utilizing intravascular iodinated contrast media is acute kidney injury. Although several clinical and procedural factors impact a patient's risk for contrast-induced acute kidney injury (CIAKI), substantial attention has been focused on the relationship between the type of contrast agent used and renal injury.
- Patients at risk for CIAKI include those with chronic kidney disease and diabetes mellitus.
- Low osmolal contrast media were found to be associated with greater tolerability and fewer adverse cardiovascular and pseudoallergic effects than high osmolal contrast media.

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