Intravenous Contrast Medium–induced Nephrotoxicity: Is the Medical Risk Really as Great as We Have Come to Believe?1

That acute renal dysfunction may be caused by intravenously administered radiologic contrast media (CM) has become axiomatic in the practice and literature of modern medicine (1). Thus, these CM are often withheld when computed tomography (CT) is performed (2). This may reduce the diagnostic accuracy of the examination and can lead to less-than-ideal disease management. Contrast medium–induced nephropathy (CIN) is not common in patients with normal preexisting renal function; rather, it occurs more frequently in patients with renal impairment and is possibly exacerbated when the impairment is due to diabetic nephropathy. In most studies, controls for concurrent disease have been almost completely lacking (3), variation in serum creatinine (SCr) levels has been interpreted as indicating nephrotoxicity even though such variation occurs without CM administration (4), and the risks of intravenous CM injection and intraarterial CM injection during angiocardiology have been unjustifiably equated (5). In this editorial, we will (a) analyze clinical experiences in which researchers compared variations in renal function between patients who underwent contrast medium–enhanced (CE) CT and control subjects who underwent CT without CM administration, (b) analyze random variations in the SCr level of hospitalized patients, and (c) discuss the comparison of rates and adverse outcomes of CIN in prospective clinical trials between outpatient and inpatient cohorts that underwent CE CT and cardiac catheterization procedures. We believe that the risk of CIN with CE CT is overstated and that a more accurate assessment of the risk of CIN could lead to wider CM use, more accurate diagnoses, and better clinical treatment.

Implications from Studies Assessing Random Variations in Renal Function

One reason the incidence of CIN has been overestimated is the failure to consider fluctuations in SCr level that may occur naturally or in response to acute medical instability. A major concern lies in the nearly universal assumption that any decline in renal function that follows administration of CM is caused by the CM itself; this is an example of the classic post hoc, ergo propter hoc (after this, therefore because of this) logical fallacy. Any valid assessment of the risk of CIN must include a group of subjects who do not receive CM as a control.

SCr levels are determined by the dynamic interplay of endogenous creatinine production, the glomerular filtration rate (GFR), and a small component of tubular secretion. These change for a variety of reasons beyond the effects of CM administration, and there is the further possibility of a laboratory error that may further increase the observed variations (6,7). Temporal variations in the creatinine clearance rate of healthy subjects have been well documented (8,9), as have hour-to-hour variations in GFR.

Linear changes in GFR are related to nonlinear changes in SCr level, as shown in the Figure. It is important to note that in the lower ranges of baseline renal function, there is an asymptotic increase in the observed changes in SCr level, with relatively small decreases in GFR. This has led some to suggest that the increased incidence of CIN in patients with baseline renal insufficiency is possibly artifactual overestimated (10). There are greater random variations in SCr level in subjects with a high initial creatinine level and diabetes mellitus, increasing the effect of changes in GFR on SCr level at low GFRs. Precept and practice reinforce the concept that patients with diabetes are more likely to experience an increase in creatinine level after CM administration than are patients without diabetes; however, patients with diabetes have wider swings...
in GFR (6,7,11) and SCr level than do patients without diabetes. The finding that creatinine levels increase after CM administration in patients with diabetes might simply reflect this phenomenon rather than any risk that CM might pose to kidney function in patients with diabetes.

Data revealing the day-to-day variations in SCr level in a large group of patients who presumably had the same prevalence of risks to kidney function, including diabetes, as any large randomly chosen population of hospitalized patients (4) show that the range of such variations is just as large as those variations attributed to CM administration in nearly all published series and is even more striking when one assesses recent prospective clinical trials in patients with renal insufficiency. As will be discussed, the overall rate of CIN in at-risk patients with renal insufficiency in these studies is in the range of 5% (5).

Newhouse et al (4) investigated whether increases in SCr level after intravenous CM administration could represent random variations similar in frequency to those in patients who did not receive CM. In 32161 patients whose SCr level was measured on each of 5 consecutive days and who did not receive CM, Newhouse et al determined the fraction of patients who had an increased SCr level was equal to commonly used thresholds for CIN as a function of the initial SCr level. They found that the higher the initial SCr level, the greater the fraction of patients who reached the thresholds. They compared their results with 19 published reports of patients who received intravenous CM and were evaluated for increased SCr levels after CM administration. The fraction of patients in the 24 studies whose increased creatinine level exceeded the various thresholds was within the same range of the fraction of patients in the Newhouse et al study whose increased creatinine level exceeded the same thresholds. Indeed, in 14 of the 19 studies, the patients who received CM had an increased creatinine level that exceeded the thresholds less often than did patients who did not receive CM. Patients in three of the remaining five studies had significant increases (55%–76%) in SCr level after CM administration; however, patients in these series had renal failure, diabetes, or initial SCr level above 2.0 mg/dL (176.8 μmol/L). The authors’ opinion was that the random increases observed in their surveys were not different from the incidences attributed to CIN in previously published reports.

Imlications from Studies in Which Control Subjects Were Compared with Patients Who Underwent CE CT

Findings of studies performed in patients suspected of being affected by the nephrotoxic effects of CM have been published repeatedly; however, a distressingly small number of these studies have included control subjects. To our knowledge, for intravenous CM administration, there have been only six such studies. Of these, five were clinical trials (12–16) that revealed no significant difference in SCr variations between the control subjects and the patients who received CM (Table 1). In a retrospective assessment, Bruce et al (17), showed there was no difference between control and study subjects for one of two specific CM and only a small difference between control and study subjects for another contrast medium. The only significant difference (P < .05) occurred between control subjects and patients with stage 3 chronic kidney disease (estimated GFR, 30–59 mL/min) who received iohexol (10.2% vs 8.0%, respectively).

Cramer et al (12) assessed SCr levels before and 2 days after CE CT in 193 patients and after nonenhanced CT in 233 control subjects. A high-osmolar contrast medium was administered, with a dose range of 60–350 mL. Renal dysfunction after CT, defined as an increase in the SCr level to more than 1.2 mg/dL (106 μmol/L) and to a level at least 50% higher than the baseline level, developed in four (2.1%) patients who received the contrast medium and three (1.3%) subjects who did not receive any CM. The difference in renal dysfunction was not meaningful. CIN occurred in none of the 19 patients with preexisting renal insufficiency who received a high-osmolar contrast medium and in two (4.3%) of the 46 patients with preexisting renal insufficiency who received no CM (12). We acknowledge, however, that a relatively stringent criterion for CIN was used, and there may have been a lack of comparability between the control subjects and the patients who received the contrast medium because the decision to perform unenhanced CT in them may have been based partly on the perceived risk of CIN.

Heller et al (13) examined 292 inpatients who received high-osmolar CM and 405 patients who did not receive CM. Renal impairment was defined as a maximal increase of at least 50% or as an increase of more than 0.5 mg/dL (44.2 μmol/L) from the baseline SCr value on at least one of the subsequent 4 days and was noted in 12 (4%) patients who received CM and 16 (4%) patients who received no CM. There
was no difference in the incidence of CIN between the subjects who received high-osmolar CM and the control subjects. An acute increase in the SCr level was seen in seven (10%) of 68 patients with preexisting renal insufficiency who received CM and in six (7%) of 88 patients with preexisting renal insufficiency who did not receive CM. Admittedly, there may have been a selection bias factor in that the subjects who did not receive CM were known to be at greater risk for CIN than were those who did not receive high-osmolar CM, indicating a negative selection (selective use in the low-risk patients). However, in both the Heller et al study (12) and the Cramer et al study (13), in the subset of high-risk subjects, there was no significant difference in the rate of subsequent renal fluctuation between subjects who received CM and those who did not.

Langner et al (14) compared changes in SCr level on days 3 and 7 after administration of 60 mL of ioxixanol in 100 inpatients with changes in SCr level who were not exposed to any CM. After CM administration, seven (7%) patients had a relative increase in the SCr level of 25% or more compared with the baseline SCr level. In the control group, a relative increase in the SCr level of 25% or more was seen in 12 (12%) patients. This difference was not significant. Of those subjects who received CM, seven (7%) had a baseline SCr level of at least 1.5 mg/dL (132.6 μmol/L), and none experienced a significant decline in renal function. In the control group, 13 patients had a baseline SCr level of at least 1.5 mg/dL (132.6 μmol/L), and one patient had a significant decline in renal function.

Oleinik et al (15) compared patients who had experienced a stroke and who subsequently underwent CT. They found that 14% of 130 patients who received no CM, 5% of 124 patients who underwent one CE CT examination, and 6% of 244 patients who underwent more than one CE CT examination developed acute nephropathy (SCr value increase of at least 25% or 0.5 mg/dL [44.2 μmol/L]) increase in SCr level to at least 1.5 mg/dL [132.6 μmol/L]).

In 2009, Bansal and Darby (16) compared pre- and postprocedure (median, 3.8 days after CM administration) SCr values in patients with renal insufficiency who underwent CE CT and compared these with pre- and postprocedure SCr values in control subjects who did not receive CM. Of the 63 patients who received CM, 12% had an individual SCr value increase of either 25% or 0.05 mg/dL [44.2 μmol/L]; 13% of the 52 control patients had such an increase.

Overall comparisons between the CE CT and control groups in the Cramer et al, Heller et al, Langner et al, Oleinik et al, and Bansal and Darby studies suggest there is no clear difference in SCr changes between these groups (Table 1) (12–16).

In a small retrospective study of 95 patients, Tremblay et al (18) showed that in patients with trauma, the fraction of patients who did not receive CM and who had an increased creatinine level was just as large as the fraction of patients who did receive CM and who had an increased creatinine level; furthermore, preexisting chronic renal failure and diabetes were risk factors for an elevated creatinine level among patients who did not receive CM. Three percent of 56 patients who received CM and 16% of 39 control subjects had a transient increase of 25% in the SCr value within 48 hours of the imaging procedures. Since procedures were not separated into those in which intrarterial CM were injected during angiography and those in which CM were administered intravenously, we have not combined the data with the data presented in Table 1. However, the findings support our hypothesis that random variations, underlying disease, and treatment must be taken into consideration to truly determine the risk of CIN.

Bruce et al (17) retrospectively analyzed 11588 patients (13274 encounters) who underwent both CE CT and unenhanced CT over a 7-year period. Patients who underwent CE CT received either a low-osmolar contrast medium (iohexol) or an iso-osmolar contrast medium (ioxixanol). CIN was defined as an increase in SCr concentration of at

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Table 1

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients Who Underwent CE CT</th>
<th>No. of Control Subjects</th>
<th>CIN Criteria</th>
<th>Study Type</th>
<th>Contrast Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cramer et al (12) (1985)</td>
<td>4/193 (2)</td>
<td>3/233 (1)</td>
<td>≥50% increase in SCr level and SCr level &gt;1.2 mg/dL</td>
<td>Prospective</td>
<td>HOCM</td>
</tr>
<tr>
<td>Heller et al (13) (1991)</td>
<td>12/292 (4)</td>
<td>16/405 (4)</td>
<td>≥50% increase in SCr level, SCr level &gt;0.5 mg/dL</td>
<td>Prospective</td>
<td>HOCM</td>
</tr>
<tr>
<td>Langner et al (14) (2009)</td>
<td>7/100 (7)</td>
<td>12/100 (12)</td>
<td>≥25% increase in SCr level</td>
<td>Prospective</td>
<td>LOCM</td>
</tr>
<tr>
<td>Oleinik et al (15) (2009)</td>
<td>6/124 (5)</td>
<td>18/130 (14)</td>
<td>≥25% increase in SCr level or SCr level &gt;0.5 mg/dL</td>
<td>Retrospective</td>
<td>LOCM</td>
</tr>
<tr>
<td>Bansal and Darby (16) (2009)</td>
<td>8/65 (12)</td>
<td>7/52 (14)</td>
<td>≥25% increase in SCr level</td>
<td>Retrospective</td>
<td>LOCM</td>
</tr>
<tr>
<td>Summary of comparative rates of SCr level fluctuation</td>
<td>37/774 (5)</td>
<td>56/920 (6)</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

Note.—Data in parentheses are percentages, except in the Study column. To convert milligrams per deciliter to micromoles per liter, multiply by 88.4. HOCM = high-osmolar contrast medium, LOCM = low-osmolar contrast medium, NA = not applicable, RI = renal insufficiency.
least 0.5 mg/dL (44.2 μmol/L) or a 25% or greater decrease in estimated GFR. They found no significant difference in the overall incidence of CIN between the group that received the iso-osmolar contrast medium (average, 8.2%; range, 0.0%–18.5%) and the control group (average, 5.9%; range, 1.3%–9.0%) for all baseline creatinine values. The overall incidence of CIN in the low-osmolar contrast medium group (2.1%–10.4%) paralleled that in the control group (1.3%–8.6%) up to an SCr level of 1.8 mg/dL (159.1 μmol/L). Increases above this level were associated with a higher incidence of acute kidney injury in the low-osmolar contrast medium group. It is interesting to note that the incidence of SCr value increases that were diagnostic of CIN increased with increasing baseline creatinine concentrations in all three groups, including the group of subjects who did not receive CM. This appears to support the nonlinear relationship between GFR and SCr level, which was noted previously in this article and is depicted in the Figure. Bruce et al (17) concluded that SCr elevations occur even in patients who do not receive CM during CT examinations and that the risk of CIN might have been overstated. They suggested that much of the SCr elevation in these patients could be attributed to background fluctuation disease or treatment.

The study by Bruce et al (17) is the largest evaluation to date of the incidence of acute kidney injury in a control population receiving no CM in comparison with a population receiving CM. However, the Bruce et al (17) and Newhouse et al (4) studies were retrospective and nonrandomized. Such study designs may have excluded a large number of cases and introduced a selection bias for patients who presumably had clinical reasons for having their SCr concentration followed up. However, it has been clearly shown that large background fluctuations in SCr concentration are common, and researchers rarely have taken them into consideration when assessing the true rates of CIN.

An additional perspective on this issue is highlighted in the study by Rahimi et al (19). In their study, patients with renal failure were carefully chosen to have no simultaneous acute disease, nephrotoxic medications, or procedures that might exacerbate renal failure. None of these patients experienced deterioration of renal function after CM administration.

All of these data underscore the danger in quantifying CIN risk by measuring creatinine concentration variability, as well as the crucial need for a control group of subjects who do not receive CM if the real risk of CIN is to be established.

Intravenous Contrast Medium–induced Nephrotoxicity

Katzberg and Newhouse

We believe that the incidence of CIN with intravenous administration of CM has been overstated not only because of the extrapolation of the cardiology experience with percutaneous catheterization, ventriculography, and coronary intervention but also because of CE CT with intravenous CM administration.

Angiography has long been recognized as a procedure that might be followed by acute renal dysfunction (20,21). The relative risks of nephropathy after angiography, peripheral arteriography, and studies involving intravenous CM are hard to evaluate conclusively. However, as early as 1979 (22) study results indicated that intravenous CM were less risky than intraarterial CM (23), particularly if the arterial injection was suprarenal (24). Khoury et al (25) found that intravenous injection posed a significantly lower risk to kidney function than did renal arterial injection, and Gomes et al (26) found that for aortography, the closer to the renal arteries the injection occurred, the higher the risk of CIN. Albert et al (27) found that after systemic arteriography in patients with chronic renal failure, creatinine clearance declined. Manske et al (28) found that among patients with diabetes and chronic renal failure, patients who underwent coronary angiography were significantly more likely to experience acute renal dysfunction than were patients who did not. Moore et al (29) and Katzberg and Barrett (5) found that angiography led to a higher risk of postprocedure nephrotoxicity than did intravenous CM administration.

It is interesting to note that a significant increase in the reported incidence of CIN, such as the one reported by Mudge (30), was recognized in numerous reports appearing primarily in the cardiology literature. This is surprising, since in that era, high-osmolar CM were still the primary contrast agents used, and there were few, if any, reports of CIN occurring with use of intravenous contrast agents. On the other hand, cardiac catheterization became more prevalent in the mid-1970s. The beginning of widespread use of low-osmolar CM occurred in the early to mid-1980s, and multiple clinical trials in which these CM were administered intravenously yielded little evidence of CIN, death, or dialysis (30).

More recent prospective investigations (albeit ones without control subjects), including those conducted by 'Tepel et al (31), Becker and Reiser (32), Barrett et al (33), Thomsen et al (34), Kuhn et al (35), Nguyen et al (36), and Weishord et al (37) (Table 2), have shown low rates of CIN with use of low- and iso-osmolar CM for CE CT, approximating an overall rate of 5.4%, even in patients with baseline renal insufficiency (19–24). On the other hand, in the cardiology literature, overall rates of CIN in patients with chronic kidney disease and diabetes are in the range of 33%, as noted by Rudnick et al in the Iohexol Cooperative Study, a large randomized trial (38). In comparison with this study, in a prospective study by Kuhn et al (35), the incidence of CIN with use of low-osmolar CM for CE CT in patients with renal insufficiency and diabetes mellitus was 5.2% (13 of 248 patients).

The difference in the rates of serious adverse outcomes between patients undergoing cardiac catheterization and those undergoing CE multidetector CT is even more striking. For example, in a retrospective cardiac catheterization observational study in 439 patients with renal insufficiency, Gruenberg et al (39) found a 37.7% rate of CIN, including a 7.0%
The report by Levy et al. (40) is widely quoted, and their results markedly deviated from the previously reported morbidity and mortality rates after intravenous administration of CM. In their study, Levy et al. used a matched-pairs cohort design to retrospectively analyze morbidity and mortality in 16248 inpatients who underwent CE procedures (half of the patients underwent angiography, while the other half underwent CT and other miscellaneous CE procedures) between 1987 and 1989 at a large academic hospital. A total of 174 patients developed CIN. These index subjects with acute kidney injury were matched with control subjects who did not have an acute kidney injury on the basis of age, baseline SCr concentration, and type of CE procedure performed. The mean SCr value was 1.6 mg/dL (141.4 μmol/L) in index and control subjects. However, when compared with control subjects, index subjects had significantly more acute comorbid conditions, and the in-hospital mortality rate was 34% for index patients and only 7% for matched subjects (P ≤ .001). As noted by Rudnick and Feldman (41), the clinical course of CIN was atypical, with 29% of patients having oliguria and 12% needing renal replacement therapy. Rudnick and Feldman emphasized two conflicting conclusions suggested by the results of Levy et al.: The first was that although all of the case subjects had an acute kidney injury, “most could not be considered to have CIN, since other risk factors for renal failure (both comorbid and iatrogenic) were present.” The second was that acute kidney injury in this setting was directly associated with increased mortality, even when one adjusted for comorbidities.

CIN has long been portrayed as particularly dangerous by publications that describe elevated risks of morbidity and mortality among patients with CIN (42), despite the fact that the most common manifestation of CIN is an asymptomatic small-amplitude transient elevation of the creatinine value (43). However, there is a strong possibility that renal dysfunction of any cause is responsible for such risks; if nephropathy after intravenous administration of CM is not caused by CM, it cannot be held that CM increases those risks; if nephropathy after intravenous administration of CM is not caused by CM, it cannot be held that CM increases those risks. Rudnick and Feldman (41) propose that CIN may be a marker for increased mortality risk rather than a contributing cause of death. They performed a literature review that focused on observational studies in which researchers assessed factors associated with mortality in patients with CIN, most of which were derived from the cardiac catheterization literature. The observational studies assessed showed that short- and long-term

Table 2
Prospective Studies on CIN in Patients with Renal Insufficiency without Control Subjects

<table>
<thead>
<tr>
<th>Study</th>
<th>Contrast Agent*</th>
<th>Prospective Design</th>
<th>CIN Criteria</th>
<th>No. of Patients with Renal Insufficiency†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tepel et al (31) (2000)</td>
<td>LOCM</td>
<td>Yes</td>
<td>Increased SCr level ≥ 0.5 mg/dL</td>
<td>9/42 (21)</td>
</tr>
<tr>
<td>Becker and Reiser (32) (2005)</td>
<td>LOCM</td>
<td>Yes</td>
<td>Increased SCr level ≥ 0.5 mg/dL</td>
<td>9/100 (0)</td>
</tr>
<tr>
<td>Barrett et al (33) (2006)</td>
<td>LOCM</td>
<td>Yes</td>
<td>Increased SCr level ≥ 0.5 mg/dL</td>
<td>2/153 (1.3)</td>
</tr>
<tr>
<td>Thomsen et al (34) (2008)</td>
<td>LOCM</td>
<td>Yes</td>
<td>Increased SCr level ≥ 0.5 mg/dL</td>
<td>5/148 (3.4)</td>
</tr>
<tr>
<td>Kuhn et al (35) (2008)†</td>
<td>LOCM</td>
<td>Yes</td>
<td>SCr concentration ≥ 25%</td>
<td>13/248 (5.2)</td>
</tr>
<tr>
<td>Nguyen et al (36) (2008)</td>
<td>LOCM</td>
<td>Yes</td>
<td>Increased SCr level ≥ 0.5 mg/dL</td>
<td>13/117 (11.1)</td>
</tr>
<tr>
<td>Weisbord et al (37) (2008)</td>
<td>LOCM</td>
<td>Yes</td>
<td>Increased SCr level ≥ 0.5 mg/dL</td>
<td>13/367 (3.5)</td>
</tr>
</tbody>
</table>

Note.—A subtotal of 64 (5.4%) of 1175 patients had renal insufficiency. To convert milligrams per deciliter to micromoles per liter, multiply by 88.4.

* LOCM = low-osmolar contrast medium.
† Data in parentheses are percentages.
‡ All patients had renal insufficiency and diabetes.

Table 3
Serious Adverse Outcomes after CE CT

<table>
<thead>
<tr>
<th>Study</th>
<th>Dialysis</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tepel et al (31) (2000)</td>
<td>0/42</td>
<td>0/42</td>
</tr>
<tr>
<td>Becker and Reiser (32) (2005)</td>
<td>0/100</td>
<td>0/100</td>
</tr>
<tr>
<td>Barrett et al (33) (2006)</td>
<td>0/153</td>
<td>0/153</td>
</tr>
<tr>
<td>Thomsen et al (34) (2008)</td>
<td>0/148</td>
<td>0/148</td>
</tr>
<tr>
<td>Kuhn et al (35) (2008)</td>
<td>0/248</td>
<td>0/248</td>
</tr>
<tr>
<td>Nguyen et al (36) (2008)</td>
<td>0/117</td>
<td>0/117</td>
</tr>
<tr>
<td>Weisbord et al (37) (2008)</td>
<td>0/367</td>
<td>0/367</td>
</tr>
<tr>
<td>Total</td>
<td>0/1175</td>
<td>0/1175</td>
</tr>
</tbody>
</table>

Note.—All studies were prospective and included patients with renal insufficiency, with or without diabetes.
mortality is increased in patients who develop CIN. In most of these studies, researchers assessed the relationship between CIN and downstream events of morbidity and mortality. This assessment clearly showed that patients with CIN had more comorbidities at the time of CM administration than did patients who did not experience CIN. Independent predictors of in-hospital mortality included age, congestive heart failure, emergency procedures, multivessel procedures, preprocedural shock, peripheral vascular disease, intraprocedural balloon pump, non-Q wave infarction, creatinine kinase-MB fraction, and liver disease, among other factors. This raises the question of whether these multiple comorbidities are independent causes of death and whether CIN is, in fact, a contributing factor or simply a marker. More importantly, putative mechanisms for how CIN is able to cause death or other serious complications have not been elucidated.

**Role of Nonionic Low- or Iso-osmolar CM in CE CT in Individuals at Risk for CIN**

Studies in which intravenous CM were used in patients with renal insufficiency and diabetes mellitus have provided new insights into the relative rates of CIN in patients being evaluated with CE CT (Table 2). The studies by Barrett et al (33), Thomsen et al (34), Kuhn et al (35), and Nguyen et al (36) have been highlighted since they were prospective in nature, the criteria for CIN were uniform, and head-to-head comparisons were made between commonly used nonionic low- and iso-osmolar CM. All subjects had renal insufficiency, and the researchers ensured that enrolled patients had baseline stable renal function. The percentage of patients with concomitant diabetes ranged from 20.2% to 100%.

Barrett et al (33) compared the effects of a nonionic monomer, iopromide 370 (Ultravist; Bayer, Berlin, Germany), on renal function in patients with renal impairment who underwent CE CT in a single-center, double-blind randomized parallel group study. A total of 153 patients with stable, moderate, or severe chronic renal disease (SCr level ≥1.5 mg/dL [132.8 µmol/L], creatinine clearance rate of 10–59 mL/min, or both) were enrolled, and CIN was defined as an absolute increase of 0.5 mg/dL (44.2 µmol/L) or more in the SCr value. The two study groups were comparable with regard to all baseline characteristics. An absolute increase of at least 0.5 mg/dL (44.2 µmol/L) in the SCr level was observed in two (3%) of 76 patients who received iopromide 370 and in none (0%) of the seven patients who received iopamidol 370 (95% confidence interval: −6.2%, 1.0%; P = .3). The authors concluded that the rate of CIN in patients with moderate to severe kidney disease who received a nonionic monomer was not significantly different from that in patients who received a nonionic dimer. In this study, 36 (23.5%) of 153 subjects with renal insufficiency also had diabetes mellitus.

Thomsen et al (34) compared the effects of a nonionic monomer, iomeprol 400 (Iomeron 400; Bracco Imaging, Milan, Italy) with those of a nonionic dimer, iodixanol 320 (Visipaque 320; GE Healthcare, Chalfont St Giles, England), on renal function in patients with renal impairment who underwent CE CT in a similar multicenter, double-blind randomized parallel group study. Five (6.9%) of the 72 patients who received iodixanol 320 and none of the patients who received iomeprol 400 had an increase of 0.5 mg/dL (44.2 µmol/L) or more from the baseline SCr level (P = .025; 95% confidence interval: −12.8%, −1.1%). The mean SCr change from baseline was significantly higher (P = .017) after iodixanol 320 administration than after iomeprol 400 administration. Thomsen et al (34) concluded that the incidence of CIN was significantly higher after intravenous administration of iodixanol 320 than after intravenous administration of iomeprol 400. The overall rate of CIN in all study groups was 3.4% (five of 148 patients). In this study, 30 (20.2%) of 148 subjects had diabetes.

Kuhn et al (35) compared the effects of a nonionic monomer, iopamidol 370 (Isovue; Bracco Diagnostics), with those of a nonionic dimer, iodixanol 320 (Visipaque; GE Healthcare), on renal function in patients with both renal impairment and diabetes mellitus who underwent CE CT in another multicenter, double-blind randomized parallel group study. CIN was defined as an increase in the SCr value of at least 25% from the baseline value after CM administration. The overall rate of CIN was 5.2% (13 of 248 patients). Increases in SCr values of 25% or more occurred in seven (5.6%) patients who received iopamidol 370 and in six (4.9%) patients who received iodixanol 320 (95% confidence interval: −4.8%, 6.3%; P > .999, not statistically significant).

Nguyen et al (36) reported findings from a single-center, randomized double-blind prospective study involving 117 patients with decreased renal function who underwent CE CT with either the nonionic monomer iopamidol 370 (Ultravist; Bayer, Berlin, Germany) or the nonionic dimer iodixanol 320 (Visipaque; GE Healthcare). A comparative outcome measure included an increase of at least 0.5 mg/dL (44.2 µmol/L) in SCr level for 3 days after CE CT. There were fewer patients with an increase of 0.5 mg/dL (44.2 µmol/L) or more in SCr level in the iodixanol group (three [5.1%] of 61) than in the iopamidol group (10 [18%] of 56) (P = .037). Diabetes mellitus was present in 33 (28.2%) of 117 patients.

In these head-to-head trials, there appears to have been no consistent difference between nonionic low osmolar CM and nonionic iso-osmolar CM (33–36). Diabetes mellitus was not found to be an independent risk factor for CIN.

**Summary**

From the multiple perspectives described, it is our belief that the risk of CIN with CE CT has been exaggerated. Clinical rates and adverse outcomes from cardiac catheterization and intervention cannot be extrapolated to the clinical experience with CE CT. It appears that all currently used nonionic CM have similar safety profiles.

We believe that modern CM pose only a small risk to renal function and that
thresholds of creatinine above which CM are withheld for CT should be increased to improve the accuracy of CT examinations. The population of patients with mild to moderate renal dysfunction who would then receive CM should be analyzed carefully to determine whether the thresholds subsequently can be increased further. International radiologic professional organizations, such as the American College of Radiology, should revisit the basis of their practice guidelines to reduce their implications about the danger of CIN with CE CT.

References


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Katzberg and Newhouse


