Iodixanol Versus Low-Osmolar Contrast Media for Prevention of Contrast Induced Nephropathy
Meta-analysis of Randomized, Controlled Trials

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Background—Contrast-induced nephropathy (CIN) is associated with significant morbidity and mortality. The objective of our meta-analysis was to assess the efficacy of iodixanol compared with low-osmolar contrast media (LOCM) for prevention of CIN.

Methods and Results—We searched MEDLINE, the Cochrane Central Register of Controlled Trials, and internet sources of cardiology trial results for individual and relevant reviews of randomized, controlled trials, for the terms contrast media, contrast nephropathy, renal failure, iodixanol, Visipaque, and low-osmolar contrast media. All studies reported an incidence rate of CIN for each study group; there was no restriction on the definition of CIN. There were no restrictions on journal type or patient population. Overall, 36 trials were identified for analysis of aggregated summary data on 7166 patients; 3672 patients received iodixanol and 3494 patients received LOCM. Overall, iodixanol showed no statistically significant reduction in CIN incidence below that observed with heterogeneous comparator agents (P=0.11). Analysis of patient subgroups revealed that there was a significant benefit of iodixanol when compared with iohexol alone (odds ratio, 0.25; 95% confidence interval, 0.11 to 0.55; P<0.001) but not when compared with LOCM other than iohexol or with other ionic dimers or among patients receiving intra-arterial contrast injections or among patients undergoing coronary angiography with or without percutaneous intervention.

Conclusions—Analysis of aggregated summary data from multiple randomized, controlled trials of iodixanol against diverse LOCMs for heterogeneous procedures and definitions of CIN show an iodixanol-associated reduction that is suggestive but statistically nonsignificant. (Circ Cardiovasc Interv. 2010;3:351-358.)

Key Words: Visipaque ■ iodixanol ■ low-osmolar contrast media ■ contrast-induced nephropathy

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Contrast-induced nephropathy (CIN) is associated with significant morbidity and mortality,\(^1\)\(^-\)\(^3\) thus, multiple strategies to adjust modifiable risk factors associated with CIN have been explored.\(^4\)\(^-\)\(^8\) Controversy remains whether certain contrast media types, with various osmolalities, are associated with a lower risk of CIN. Lower osmolality is thought to be associated with a reduced incidence of CIN.\(^9\) Iodixanol has the lowest osmolality of all available contrast media (290 mOsm/kg H\(_2\)O), which represents a nearly two-thirds reduction in osmolality compared with low-osmolar contrast agents such as iohexol (844 mOsm/kg H\(_2\)O).\(^9\) Many prospective trials have evaluated the efficacy of iodixanol compared with various low osmolar contrast media (LOCM). These studies show mixed results. An attempt to analyze several of these randomized trials by McCullough et al\(^1\)\(^0\) showed a significantly protective benefit of iodixanol at reducing the incidence of CIN, whereas other analyses have shown no such benefit.\(^1\)\(^1\)\(^,\)\(^1\)\(^2\) Since the publication of this study, several new randomized trials have been performed to better elucidate the role of iodixanol in radiographic procedures.\(^1\)\(^3\)\(^-\)\(^1\)\(^5\) The goal of our meta-analysis was to assess the efficacy of iodixanol compared with LOCM for prevention of CIN. We hypothesized that in a large analysis without exclusion of trials based on procedure type or population studied, the incidence of CIN would be reduced by iodixanol when compared with LOCM.

Criteria for Study Selection

We restricted our meta-analysis to (1) randomized controlled trials that (2) compared iodixanol to any LOCM, (3) provided a definition of CIN, and (4) reported the incidence of CIN in both arms. There was no restriction on the definition of CIN or on the time elapsed before CIN occurred. When a trial report omitted data based on its internal definition of CIN, we substituted incidence of creatinine...
increase ≥0.5 mg/dL after contrast exposure, which was commonly reported, in the meta-analysis. There were no restrictions to journal type or population studied.

Data Sources
We searched MEDLINE (from 1966 through December 2009), the Cochrane Central Register of Controlled Trials and Web of Knowledge for randomized trials using the search terms: contrast media, contrast nephropathy, renal failure, iodixanol, Visipaque and low-osmolar contrast media. In addition, relevant reviews from major medical journals published within the last 5 years were identified and assessed for possible information on trials of interest. Internet-based sources of information on the results of clinical trials in cardiology (http://www.theheart.org and http://www.tctmd.com) were also searched. The search was conducted by 2 independent investigators (A.M.F. and F.J.A.); discrepancies were resolved by consensus.

Statistical Analysis
All analyses were performed with review manager software (RevMan Analyses Version 5.0.4 Copenhagen; The Nordic Cochrane Center, The Cochrane Collaboration, 2008). The meta-analysis was performed using the random-effects models because statistically significant heterogeneity was detected with respect to the primary outcome. Subgroup analyses for comparisons between iodixanol and specific types of low osmolar contrast (eg, iohexol) and specific groups of patients (ie, those receiving arterial injection and those undergoing coronary angiography) were outlined before data collection. Post hoc subgroup analyses of studies stratified by the definition of contrast nephropathy reported (ie, ≥0.5 mg/dL or ≥25% increase in baseline creatine value), and by those that report results based on baseline diabetes and kidney function were performed when data were available. Publication bias and skewness were assessed graphically using a funnel plot. Heterogeneity between studies was analyzed by means of I² assessed graphically using a funnel plot. Heterogeneity between studies measured the postprocedure creatinine value at 1, 2, or 3 days (n=24). In 6 trials, data on contrast nephropathy were not reported in the published report.19,27,32,40,44,46 In these studies, the incidence of contrast nephropathy was obtained from the cited meta-analysis by McCullough et al.10

Among 33 studies (6293 patients) with data on sex, 74% of patients who received iodixanol were male compared with 73% of patients who received LOCM. Among 19 studies (5143 patients) with data on diabetes mellitus, 48% of patients who received iodixanol were diabetic compared with 46% of patients who received LOCM. Average preprocedure creatinine values were available in 20 studies (3211 patients), the average prior creatinine ranged from 0.9 to 6.3 mg/dL for patients who received iodixanol compared with 0.9 to 7.8 mg/dL for patients who received LOCM (Table 2). Study quality characteristics as defined by the previously published PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement are shown in Table 3.49

As shown in Figure 2, the Funnel Plot for all trials where at least 1 patient developed CIN suggests there was little publication bias. Figure 3 shows the results for all trials with at least 1 outcome in either group with the corresponding odds ratios. As shown in Figure 3, the test for the overall effect using the random-effects model showed a nonsignificant protective trend toward decreased rates of CIN for iodixanol compared with heterogeneous LOCM comparator agents (odds ratio [OR], 0.77; 95% confidence interval [CI], 0.56 to 1.09; P=0.11). Multiple subgroup analyses were performed as shown in Table 4.

Because the subgroup analysis revealed a significant reduction in the incidence of CIN when iodixanol was compared with iohexol but a nonsignificant reduction when compared with all other LOCM (Table 4), we performed an interaction analysis using previously described interaction testing methods50 to determine the relative risk reduction in CIN of other LOCM compared with iohexol. We compared the subgroup of studies where iohexol was used as a control to the subgroup of studies where all other LOCM agents were used as the control agents. This interaction test revealed that other LOCM have a relative risk reduction of 3.52 (95% CI, 1.53 to 8.12; P=0.003) compared with iohexol.

Discussion
The major findings of this meta-analysis of randomized, controlled trials are that (1) Overall, iodixanol was associated with a reduction in the incidence of CIN that was not statistically significant when compared with LOCM. (2) The incidence of CIN was lower with iodixanol when compared only with iohexol. (3) Analysis of patient subgroups revealed that there was no significant benefit of iodixanol when compared with LOCM other than iohexol, other ionic dimers, or among patients receiving intra-arterial contrast injections or among patients undergoing coronary angiography with or without percutaneous intervention.

The findings of our overall analysis are consistent with other meta-analyses by Heinrich et al11 and Reed et al.12 However, the results of our analysis contradict a much earlier meta-analysis performed by McCullough et al.10 which shows a significant reduction in CIN with iodixanol among all
patients. We should point out, as stated, that we used the published text by McCullough as a secondary source of data for 6 trials; these data were originally obtained directly from the manufacturer of iodixanol and have not been subject to independent review. Despite the potential for bias by inclusion of this information, our overall analysis extends prior analyses and sometimes challenges their conclusions, probably because it reflects the variation seen in general clinical practice, where strict definitions of contrast nephropathy are usually not used and heterogeneous groups of patients are treated.

We analyzed several subgroups. The subgroups defined before data collection (ie, type of contrast, route of administration, or type of radiographic study) are based on uniformly reported information. Among these subgroups, we found that iodixanol is associated with significant renal protection only when compared with iohexol. Heinrich et al11 report a similar finding. The difference between these 2 agents may relate to the differences in their molecular structure. The iodixanol molecule is composed of 2 benzoic acid rings attached to 6 molecules in solution (thus, lower osmolality) compared with 3 iodine atoms. This molecular configuration allows for fewer ions per molecule is composed of 2 benzoic acid rings attached to 6 molecules in solution (thus, lower osmolality) compared with 3 iodine atoms. This molecular configuration allows for fewer ions per

Table 1. Characteristics of Trials

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Type of Study</th>
<th>Patient Characteristics</th>
<th>N</th>
<th>Definition of CIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schmid13</td>
<td>2007</td>
<td>Cardiac and peripheral angiography</td>
<td>Cre ≥2.5</td>
<td>216</td>
<td>Any Cre increase</td>
</tr>
<tr>
<td>Thomsen14</td>
<td>2008</td>
<td>CT dialyzer</td>
<td>Cre ≥1.5; CrCl=10 to 59</td>
<td>148</td>
<td>Cre increase ≥0.5</td>
</tr>
<tr>
<td>Andersen17</td>
<td>1993</td>
<td>Coronary angiography</td>
<td>No exclusions</td>
<td>74</td>
<td>CrCl decrease ≥25%</td>
</tr>
<tr>
<td>Barrett18</td>
<td>2006</td>
<td>CT of liver or peripheral vessels</td>
<td>Cre ≥1.5</td>
<td>153</td>
<td>Cre increase ≥0.5</td>
</tr>
<tr>
<td>Bertrand19</td>
<td>2000</td>
<td>Coronary intervention</td>
<td>No exclusions</td>
<td>1314</td>
<td>Cre increase ≥0.5</td>
</tr>
<tr>
<td>Carraccio20</td>
<td>1998</td>
<td>Intravenous urography</td>
<td>Cre=1.5 to 3.0</td>
<td>64</td>
<td>Cre increase ≥50%</td>
</tr>
<tr>
<td>Chalmers21</td>
<td>1999</td>
<td>peripheral angiography</td>
<td>no exclusions</td>
<td>102</td>
<td>Cre increase ≥25%</td>
</tr>
<tr>
<td>Chuang22</td>
<td>2009</td>
<td>Intravenous pyelography</td>
<td>Cre ≥1.5</td>
<td>50</td>
<td>Cre increase ≥25%</td>
</tr>
<tr>
<td>Davidson23</td>
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<td>Coronary intervention</td>
<td>Cr ≥2.0</td>
<td>815</td>
<td>renal failure requiring medication</td>
</tr>
<tr>
<td>Feldkamp24</td>
<td>2006</td>
<td>Coronary angiography</td>
<td>CrCl &gt;50</td>
<td>221</td>
<td>Cre increase ≥25%</td>
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<tr>
<td>Grossman25</td>
<td>1996</td>
<td>Intracranial CT</td>
<td>No exclusions</td>
<td>148</td>
<td>Cre increase ≥40%</td>
</tr>
<tr>
<td>Hardiek26</td>
<td>2008</td>
<td>Coronary angiography</td>
<td>DM; Cre ≤2</td>
<td>102</td>
<td>Cre increase ≥0.5</td>
</tr>
<tr>
<td>Hill27</td>
<td>1994</td>
<td>Coronary angiography</td>
<td>No exclusions</td>
<td>200</td>
<td>Cre increase ≥0.5</td>
</tr>
<tr>
<td>Jakobsen28</td>
<td>1995</td>
<td>Coronary angiography</td>
<td>No DM; GFR &lt;25</td>
<td>16</td>
<td>Cre increase ≥25%</td>
</tr>
<tr>
<td>Jo29</td>
<td>2006</td>
<td>Coronary angiography +/- PCI</td>
<td>CrCl ≤60</td>
<td>275</td>
<td>Cre increase ≥25% or ≥0.5</td>
</tr>
<tr>
<td>Jorgensen30</td>
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<td>None (Phase I Trial)</td>
<td>healthy male volunteers</td>
<td>60</td>
<td>Significant change in Cre</td>
</tr>
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<td>Juergens31</td>
<td>2008</td>
<td>Coronary intervention</td>
<td>Cre &gt;1.5; CrCl &lt;60</td>
<td>145</td>
<td>Cre increase ≥25% or ≥0.5</td>
</tr>
<tr>
<td>Klow32</td>
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<td>Coronary angiography</td>
<td>Cre ≤1.4</td>
<td>72</td>
<td>Cre increase ≥50%</td>
</tr>
<tr>
<td>Kuhn33</td>
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<td>CT head and body</td>
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<td>Cre increase ≥25%</td>
</tr>
<tr>
<td>Laskey34</td>
<td>2009</td>
<td>Coronary angiography +/- PCI</td>
<td>DM; Cre ≥1.7 (M); Cre ≥1.5 (F)</td>
<td>418</td>
<td>Cre increase ≥0.5</td>
</tr>
<tr>
<td>Lee35</td>
<td>1996</td>
<td>CT body</td>
<td>No exclusions</td>
<td>126</td>
<td>Cre increase ≥0.5</td>
</tr>
<tr>
<td>Mehran36</td>
<td>2009</td>
<td>Coronary angiography +/- PCI</td>
<td>Cre =1.5 to 3.0</td>
<td>145</td>
<td>Cre increase ≥25% or ≥0.5</td>
</tr>
<tr>
<td>Nio37</td>
<td>2008</td>
<td>Coronary angiography +/- PCI</td>
<td>CrCl ≤60</td>
<td>208</td>
<td>Cre increase ≥25% or ≥0.5</td>
</tr>
<tr>
<td>Nguyen38</td>
<td>2008</td>
<td>CT</td>
<td>Cre &gt;1.5; CrCl &lt;60</td>
<td>117</td>
<td>Cre increase ≥0.5</td>
</tr>
<tr>
<td>Poirier39</td>
<td>1996</td>
<td>Cerebral angiography</td>
<td>No exclusions</td>
<td>49</td>
<td>Cre ≥0.5 (applied)</td>
</tr>
<tr>
<td>Pugh40</td>
<td>1993</td>
<td>Femoral angiography</td>
<td>No exclusions</td>
<td>95</td>
<td>Cre ≥0.5 (applied)</td>
</tr>
<tr>
<td>Rosenblum41</td>
<td>1996</td>
<td>Aortography and peripheral angiography</td>
<td>No exclusions</td>
<td>46</td>
<td>Clinically significant change in Cre</td>
</tr>
<tr>
<td>Rudnick42</td>
<td>2008</td>
<td>Coronary angiography +/- PCI</td>
<td>Cre ≥1.7 (M); Cre ≥1.5 (F)</td>
<td>299</td>
<td>Cre increase ≥0.5</td>
</tr>
<tr>
<td>Siegel43</td>
<td>1996</td>
<td>Renal and abdominal Angiography</td>
<td>No exclusions</td>
<td>54</td>
<td>Cre ≥0.5</td>
</tr>
<tr>
<td>Singh44</td>
<td>1993</td>
<td>Abdominal angiography</td>
<td>No exclusions</td>
<td>59</td>
<td>Cre increase ≥0.5</td>
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<tr>
<td>Solomon45</td>
<td>2007</td>
<td>Coronary angiography</td>
<td>CrCl=20 to 59</td>
<td>414</td>
<td>Cre increase ≥0.5</td>
</tr>
<tr>
<td>Tele46</td>
<td>1994</td>
<td>Coronary angiography</td>
<td>No exclusions</td>
<td>102</td>
<td>Clinically significant change in Cre</td>
</tr>
<tr>
<td>Verow47</td>
<td>1995</td>
<td>Aorto-femoral angiography</td>
<td>No exclusions</td>
<td>133</td>
<td>Clinically significant change in Cre</td>
</tr>
<tr>
<td>Wessely48</td>
<td>2009</td>
<td>Coronary intervention</td>
<td>Cre ≥1.5; CrCl &lt;60</td>
<td>324</td>
<td>Cre increase &gt;1.0</td>
</tr>
<tr>
<td>Fischbach48</td>
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<td>Intravenous angiography</td>
<td>Cre &lt;1.2</td>
<td>117</td>
<td>Clinically significant change in Cre</td>
</tr>
<tr>
<td>Aspelin52</td>
<td>2003</td>
<td>Coronary and aorto-femoral angiography</td>
<td>DM; Cre=1.5 to 3.5</td>
<td>129</td>
<td>Cre increase ≥0.5</td>
</tr>
</tbody>
</table>

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Table 2. Characteristics of Trials

<table>
<thead>
<tr>
<th>Author</th>
<th>Route of Administration</th>
<th>LOCM and Concentration (mg I/mL)</th>
<th>Concentration of Ioxanol (mg I/mL)</th>
<th>% Male Patients</th>
<th>% Diabetic Patients</th>
<th>Follow-Up, d</th>
<th>Quantity of Ioxanol Delivered, mL</th>
<th>Quantity of LOCM Delivered, mL</th>
<th>Prior Creatinine in Ioxanol Group*</th>
<th>Prior Creatinine in LOCM Group*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schmid13</td>
<td>Arterial</td>
<td>Iomeprol (350) or (300)</td>
<td>320</td>
<td>71.3%</td>
<td>NA</td>
<td>7</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Thomsen14</td>
<td>Venous</td>
<td>Iomeprol (400)</td>
<td>320</td>
<td>70.3%</td>
<td>20.3%</td>
<td>3</td>
<td>125 ± 0</td>
<td>100 ± 0</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Andersen17</td>
<td>Arterial</td>
<td>Ioxaglate (320)</td>
<td>320</td>
<td>70.3%</td>
<td>NA</td>
<td>2</td>
<td>107 (85–153)</td>
<td>106 (84–253)</td>
<td>1.1 ± 0.1</td>
<td>0.9 ± 1</td>
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<tr>
<td>Barrett16</td>
<td>Venous</td>
<td>Iopamidol (370)</td>
<td>320</td>
<td>68.6%</td>
<td>23.5%</td>
<td>3</td>
<td>644 ± 646</td>
<td>552 ± 497</td>
<td>1.5 ± 0.5</td>
<td>1.6 ± 0.4</td>
</tr>
<tr>
<td>Bertrand19</td>
<td>Arterial</td>
<td>Ioxaglate (320)</td>
<td>320</td>
<td>77.0%</td>
<td>18.0%</td>
<td>2</td>
<td>212 ± 99</td>
<td>229 ± 109</td>
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<td>NA</td>
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<tr>
<td>Carraro20</td>
<td>Venous</td>
<td>Iopromide (300)</td>
<td>320</td>
<td>85.9%</td>
<td>NA</td>
<td>2</td>
<td>148 ± 21.3</td>
<td>152.8 ± 24.4</td>
<td>1.7 ± 0.2</td>
<td>1.7 ± 0.2</td>
</tr>
<tr>
<td>Chalmers21</td>
<td>Arterial</td>
<td>Iohexol (300)</td>
<td>270 or 320</td>
<td>70.6%</td>
<td>33.3%</td>
<td>7</td>
<td>60 (40–100)</td>
<td>23 (42–102)</td>
<td>3.1 (2.3–4.4)</td>
<td>3.4 (2.4–5.5)</td>
</tr>
<tr>
<td>Chuang22</td>
<td>Venous</td>
<td>Iohexol (NA)</td>
<td>NA</td>
<td>68.0%</td>
<td>38.0%</td>
<td>7</td>
<td>57.2 ± 8</td>
<td>60.1 ± 10.7</td>
<td>1.36 ± 0.42</td>
<td>1.34 ± 0.45</td>
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<td>Davidson23</td>
<td>Arterial</td>
<td>Ioxaglate (320)</td>
<td>320</td>
<td>67.5%</td>
<td>27.0%</td>
<td>In-hospital</td>
<td>345 ± 165</td>
<td>364 ± 175</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Feldkamp24</td>
<td>Arterial</td>
<td>Iopromide (320)</td>
<td>320</td>
<td>67.5%</td>
<td>100%</td>
<td>2</td>
<td>141.5 ± 76.4</td>
<td>142.2 ± 67.2</td>
<td>1.04 ± 0.18</td>
<td>1.03 ± 0.19</td>
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<td>Venous</td>
<td>Iohexol (300)</td>
<td>270 or 320</td>
<td>56.9%</td>
<td>100%</td>
<td>7</td>
<td>103 ± 15</td>
<td>98 ± 17</td>
<td>0.9 ± 0.6</td>
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<td>Arterial</td>
<td>Iopamidol (370)</td>
<td>320</td>
<td>43.5%</td>
<td>NA</td>
<td>3</td>
<td>103 ± 46</td>
<td>103 ± 37</td>
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<td>Iohexol (350)</td>
<td>320</td>
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<td>5</td>
<td>87 (60–125)</td>
<td>56 (53–72)</td>
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<td>7.8 (5.9–8.8)</td>
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<td>Arterial</td>
<td>Ioxaglate (NA)</td>
<td>NA</td>
<td>56.0%</td>
<td>35.3%</td>
<td>2</td>
<td>204.6 ± 159.2</td>
<td>194.8 ± 123.9</td>
<td>1.4 ± 0.6</td>
<td>1.3 ± 0.5</td>
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<td>Jorgensen29</td>
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<td>Iopamidol (300) or Iopamidol (300)</td>
<td>320</td>
<td>100%</td>
<td>0.0%</td>
<td>5</td>
<td>215 ± 123</td>
<td>204 ± 108</td>
<td>1.86 ± 0.34</td>
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<td>Juergens31</td>
<td>Arterial</td>
<td>Iopamidol (370)</td>
<td>320</td>
<td>75.9%</td>
<td>40.8%</td>
<td>7</td>
<td>101 ± 60</td>
<td>116 ± 65</td>
<td>1.6 ± 0.4</td>
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<tr>
<td>Klów32</td>
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<td>Iohexol (550)</td>
<td>320</td>
<td>NA</td>
<td>NA</td>
<td>2</td>
<td>175 ± 15</td>
<td>174 ± 15</td>
<td>1.0 ± 0.1</td>
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<td>Kuhn33</td>
<td>Venous</td>
<td>Iopamidol (370)</td>
<td>320</td>
<td>43.1%</td>
<td>100%</td>
<td>3</td>
<td>102 ± 24</td>
<td>107 ± 26</td>
<td>1.4 ± 0.4</td>
<td>1.5 ± 0.4</td>
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<td>Laskay34</td>
<td>Arterial</td>
<td>Iopamidol (370)</td>
<td>320</td>
<td>64.6%</td>
<td>100%</td>
<td>3</td>
<td>121 ± 85.1</td>
<td>112.6 ± 67.6</td>
<td>1.6</td>
<td>1.51</td>
</tr>
<tr>
<td>Leop35</td>
<td>Venous</td>
<td>Iohexol (300)</td>
<td>270 or 320</td>
<td>55.5%</td>
<td>NA</td>
<td>3</td>
<td>116 ± 30</td>
<td>120 ± 24</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Mehran36</td>
<td>Arterial</td>
<td>Ioxaglate</td>
<td>NA</td>
<td>87.6%</td>
<td>44.8%</td>
<td>3</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Nie37</td>
<td>Arterial</td>
<td>Iopramide (370)</td>
<td>320</td>
<td>77.9%</td>
<td>26.9%</td>
<td>3</td>
<td>150 ± 01</td>
<td>158 ± 102</td>
<td>1.5 ± 0.6</td>
<td>1.5 ± 0.5</td>
</tr>
<tr>
<td>Nguyen38</td>
<td>Venous</td>
<td>Iopromide (270)</td>
<td>320</td>
<td>70.9%</td>
<td>28.2%</td>
<td>3</td>
<td>NA</td>
<td>NA</td>
<td>1.8 ± 0.2</td>
<td>1.8 ± 0.3</td>
</tr>
<tr>
<td>Porier39</td>
<td>Arterial</td>
<td>Iohexol (300)</td>
<td>320</td>
<td>46.9%</td>
<td>NA</td>
<td>3</td>
<td>90 ± 38</td>
<td>88 ± 39</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Pugh40</td>
<td>Arterial</td>
<td>Iopromide (300) or (150)</td>
<td>150 or 320</td>
<td>63.2%</td>
<td>NA</td>
<td>2</td>
<td>NA</td>
<td>NA</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>Rosemblum41</td>
<td>Arterial</td>
<td>Ioxaglate (320)</td>
<td>320</td>
<td>52.2%</td>
<td>NA</td>
<td>3</td>
<td>201 ± 41</td>
<td>187 ± 52</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Rudnick42</td>
<td>Arterial</td>
<td>Ioversol (320)</td>
<td>320</td>
<td>60.2%</td>
<td>51.8%</td>
<td>7</td>
<td>118 ± 84</td>
<td>130 ± 81</td>
<td>2.0 ± 0.6</td>
<td>1.9 ± 0.6</td>
</tr>
<tr>
<td>Siegel43</td>
<td>Arterial</td>
<td>Ioxaglate (320)</td>
<td>320</td>
<td>63.0%</td>
<td>NA</td>
<td>1</td>
<td>180 ± 57</td>
<td>150 ± 60</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Singh44</td>
<td>Arterial</td>
<td>Iomeprol (300)</td>
<td>270</td>
<td>69.5%</td>
<td>NA</td>
<td>1</td>
<td>236 (120–300)</td>
<td>255 (140–300)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Solomon45</td>
<td>Arterial</td>
<td>Iopamidol (370)</td>
<td>320</td>
<td>64.0%</td>
<td>41.1%</td>
<td>3</td>
<td>136 ± 72</td>
<td>134 ± 74</td>
<td>1.4 ± 0.4</td>
<td>1.5 ± 0.4</td>
</tr>
<tr>
<td>Tveit46</td>
<td>Arterial</td>
<td>Ioxaglate (320)</td>
<td>320</td>
<td>79.4%</td>
<td>NA</td>
<td>2</td>
<td>135 (95–289)</td>
<td>139 (84–260)</td>
<td>1.0 ± 0.2</td>
<td>1.0 ± 0.2</td>
</tr>
<tr>
<td>Verow47</td>
<td>Arterial</td>
<td>Iopamidol (300)</td>
<td>270</td>
<td>NA</td>
<td>NA</td>
<td>1</td>
<td>96 ± 44</td>
<td>87 ± 48</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Wesely53</td>
<td>Arterial</td>
<td>Iomeprol (350)</td>
<td>320</td>
<td>72.5%</td>
<td>37.5%</td>
<td>365</td>
<td>366 ± 158</td>
<td>367 ± 170</td>
<td>1.36 ± 0.51</td>
<td>1.37 ± 0.33</td>
</tr>
<tr>
<td>Fischbach58</td>
<td>Venous</td>
<td>Iopamidol (370)</td>
<td>320</td>
<td>76.9%</td>
<td>NA</td>
<td>3</td>
<td>183 ± 57</td>
<td>201 ± 45</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Aspelén52</td>
<td>Arterial</td>
<td>Iohexol (350)</td>
<td>320</td>
<td>59.9%</td>
<td>100%</td>
<td>3</td>
<td>163 ± 88</td>
<td>162 ± 82</td>
<td>1.5 ± 0.53</td>
<td>1.6 ± 0.52</td>
</tr>
</tbody>
</table>

Cre indicates creatinine; CrCl, creatinine clearance; CT, computerized tomography; PCI, percutaneous coronary intervention; NA, not available; and L, iodine.

*Values reported as mean ± SD or median (interquartile range) as per the original manuscript from which the data were abstracted.

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confined to diabetics, with 26% incidence of CIN, higher than seen in any arm of any other study and far higher than seen in any other study involving iohexol, even in mixed samples including diabetics. Therefore, it may be difficult to make a general conclusion regarding iohexol versus iodixanol.

Because there is much debate over the utility of isoosmolar contrast materials in patients with kidney dysfunction or diabetes mellitus, we did attempt to stratify results on the basis of these comorbid conditions. The literature seems to show benefit of isoosmolar contrast media in patients with diabetes and/or kidney dysfunction. For example, the NEPHRIC Study (NePHRotoxIC effects in high-risk patients undergoing angiography) by Aspelin et al enrolled patients with both diabetes and decreased renal function and showed a clearly protective benefit of iodixanol. On the other hand, studies by Hardiek et al26 and Jakobsen et al,28 which enrolled

Table 3. Study Quality Characteristics

<table>
<thead>
<tr>
<th>Author</th>
<th>Randomization Described?</th>
<th>Method for Concealment of Allocation</th>
<th>Blinding of Health Care Providers and Participants?</th>
<th>% of Randomized Patients Not Analyzed</th>
<th>Power Calculation Reported?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schmid13</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>0.0%</td>
<td>No</td>
</tr>
<tr>
<td>Thomsen14</td>
<td>No</td>
<td>Unclear</td>
<td>Yes</td>
<td>19.1%</td>
<td>No</td>
</tr>
<tr>
<td>Andersen17</td>
<td>No</td>
<td>Unclear</td>
<td>NA</td>
<td>2.6%</td>
<td>No</td>
</tr>
<tr>
<td>Barrett19</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>7.8%</td>
<td>No</td>
</tr>
<tr>
<td>Bertrand19</td>
<td>No</td>
<td>Unclear</td>
<td>Yes</td>
<td>9.0%</td>
<td>No</td>
</tr>
<tr>
<td>Carraro20</td>
<td>No</td>
<td>Unclear</td>
<td>NA</td>
<td>0.0%</td>
<td>No</td>
</tr>
<tr>
<td>Chalmers21</td>
<td>No</td>
<td>Unclear</td>
<td>NA</td>
<td>17.7%</td>
<td>No</td>
</tr>
<tr>
<td>Chuang22</td>
<td>No</td>
<td>Unclear</td>
<td>NA</td>
<td>NA</td>
<td>No</td>
</tr>
<tr>
<td>Davidson23</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>4.8%</td>
<td>No</td>
</tr>
<tr>
<td>Feldkamp24</td>
<td>Yes</td>
<td>Yes</td>
<td>NA</td>
<td>NA</td>
<td>No</td>
</tr>
<tr>
<td>Grossman25</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>1.3%</td>
<td>No</td>
</tr>
<tr>
<td>Hardiek26</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>7.3%</td>
<td>No</td>
</tr>
<tr>
<td>Hill27</td>
<td>Yes</td>
<td>Yes</td>
<td>NA</td>
<td>0.0%</td>
<td>No</td>
</tr>
<tr>
<td>Jakobsen28</td>
<td>No</td>
<td>Unclear</td>
<td>NA</td>
<td>NA</td>
<td>No</td>
</tr>
<tr>
<td>Jo29</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>8.3%</td>
<td>Yes</td>
</tr>
<tr>
<td>Jorgensen30</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>0.0%</td>
<td>Yes</td>
</tr>
<tr>
<td>Juergens31</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>5.4%</td>
<td>Yes</td>
</tr>
<tr>
<td>Klow32</td>
<td>No</td>
<td>Unclear</td>
<td>NA</td>
<td>NA</td>
<td>No</td>
</tr>
<tr>
<td>Kuhn33</td>
<td>No</td>
<td>Unclear</td>
<td>Yes</td>
<td>2.4%</td>
<td>No</td>
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<td>Laskey34</td>
<td>No</td>
<td>Unclear</td>
<td>Yes</td>
<td>22.6%</td>
<td>Yes</td>
</tr>
<tr>
<td>Lee35</td>
<td>No</td>
<td>Unclear</td>
<td>Yes</td>
<td>0.8%</td>
<td>No</td>
</tr>
<tr>
<td>Mehran36</td>
<td>Yes</td>
<td>Yes</td>
<td>NA</td>
<td>0.0%</td>
<td>Yes</td>
</tr>
<tr>
<td>Niel37</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>3.7%</td>
<td>Yes</td>
</tr>
<tr>
<td>Nguyen38</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>7.1%</td>
<td>No</td>
</tr>
<tr>
<td>Pointer39</td>
<td>No</td>
<td>Unclear</td>
<td>Yes</td>
<td>2.0%</td>
<td>No</td>
</tr>
<tr>
<td>Pugh40</td>
<td>No</td>
<td>Unclear</td>
<td>NA</td>
<td>5.0%</td>
<td>No</td>
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<tr>
<td>Rosenblum41</td>
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<td>Yes</td>
<td>NA</td>
<td>35.2%</td>
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</tr>
<tr>
<td>Rudnick42</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>11.3%</td>
<td>Yes</td>
</tr>
<tr>
<td>Siegel43</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>NA</td>
<td>No</td>
</tr>
<tr>
<td>Singh44</td>
<td>No</td>
<td>Unclear</td>
<td>NA</td>
<td>1.7%</td>
<td>No</td>
</tr>
<tr>
<td>Solomon45</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>11.2%</td>
<td>Yes</td>
</tr>
<tr>
<td>Tveit46</td>
<td>No</td>
<td>Unclear</td>
<td>NA</td>
<td>1.9%</td>
<td>No</td>
</tr>
<tr>
<td>Verow47</td>
<td>No</td>
<td>Unclear</td>
<td>Yes</td>
<td>4.3%</td>
<td>No</td>
</tr>
<tr>
<td>Wessely48</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>0.0%</td>
<td>Yes</td>
</tr>
<tr>
<td>Fischbach49</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>2.5%</td>
<td>No</td>
</tr>
<tr>
<td>Aspelin52</td>
<td>No</td>
<td>Unclear</td>
<td>Yes</td>
<td>4.4%</td>
<td>Yes</td>
</tr>
</tbody>
</table>

NA indicates not available.

Figure 2. Funnel plot of studies. This funnel plot represents each study’s treatment effect on the x-axis versus the standard error of the study, determined by study size, on the y-axis. The symmetrical shape of the inverted funnel suggests that publication bias based on trial result is unlikely.
patients with diabetes only and no baseline kidney dysfunction or included patients with baseline kidney dysfunction alone without diabetes mellitus, respectively, showed an equivocal effect of ioxanol on the development of CIN compared with LOCM. We found no difference for ioxanol compared with LOCM among these groups, but we do recognize that outcome data were not uniformly available among patients with baseline renal dysfunction or diabetes. A possible explanation for our findings and the findings in the literature could be that improved procedural technique, in-

**Table 4. Subgroup Analyses**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Studies</th>
<th>No. of Patients</th>
<th>CIN Iodixanol</th>
<th>CIN LOCM</th>
<th>OR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iodixanol vs ionic dimer</td>
<td>8</td>
<td>2,978</td>
<td>34/1412 (2.4%)</td>
<td>51/1413 (3.6%)</td>
<td>0.62</td>
<td>0.39–1.01</td>
<td>0.05</td>
</tr>
<tr>
<td>Iodixanol vs iohexol</td>
<td>10</td>
<td>951</td>
<td>3/753 (1.3%)</td>
<td>25/414 (6.0%)</td>
<td>0.25</td>
<td>0.11–0.55</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Iodixanol vs LOCM other than iohexol</td>
<td>26</td>
<td>3215</td>
<td>170/3135 (5.4%)</td>
<td>186/3080 (6.0%)</td>
<td>0.88</td>
<td>0.70–1.10</td>
<td>0.25</td>
</tr>
<tr>
<td>Intra-arterial contrast</td>
<td>26</td>
<td>5935</td>
<td>157/2997 (5.2%)</td>
<td>192/2938 (6.5%)</td>
<td>0.74</td>
<td>0.52–1.06</td>
<td>0.10</td>
</tr>
<tr>
<td>Coronary angiography ± PCI</td>
<td>17</td>
<td>5052</td>
<td>152/2542 (6.0%)</td>
<td>169/2510 (6.7%)</td>
<td>0.85</td>
<td>0.62–1.17</td>
<td>0.33</td>
</tr>
<tr>
<td>Definition of contrast nephropathy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine increase ≥0.5 mg/dL</td>
<td>13</td>
<td>3368</td>
<td>99/1711 (5.8%)</td>
<td>104/1657 (6.3%)</td>
<td>0.82</td>
<td>0.51–1.32</td>
<td>0.42</td>
</tr>
<tr>
<td>Creatinine increase &gt;25%</td>
<td>12</td>
<td>1447</td>
<td>50/729 (6.9%)</td>
<td>80/718 (11.1%)</td>
<td>0.58</td>
<td>0.40–0.85</td>
<td>0.0006</td>
</tr>
<tr>
<td>Patients at high risk of CIN*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any diabetes or renal dysfunction</td>
<td>17</td>
<td>3205</td>
<td>169/1657 (9.6%)</td>
<td>194/1548 (11.5%)</td>
<td>0.81</td>
<td>0.54–1.20</td>
<td>0.29</td>
</tr>
<tr>
<td>Diabetes and renal dysfunction</td>
<td>8</td>
<td>1172</td>
<td>64/549 (9.3%)</td>
<td>75/623 (12.0%)</td>
<td>0.68</td>
<td>0.30–1.54</td>
<td>0.36</td>
</tr>
<tr>
<td>Diabetes without renal dysfunction</td>
<td>3</td>
<td>148</td>
<td>5/101 (11.5%)</td>
<td>10/47 (21.3%)</td>
<td>0.83</td>
<td>0.22–3.15</td>
<td>0.78</td>
</tr>
<tr>
<td>Nondiabetic with renal dysfunction</td>
<td>7</td>
<td>677</td>
<td>27/395 (11.5%)</td>
<td>39/282 (12.5%)</td>
<td>0.68</td>
<td>0.38–1.19</td>
<td>0.18</td>
</tr>
</tbody>
</table>

NS indicates not significant; n, number with CIN; and N, total number of patients within the group.

*Diagnosis of diabetes was made by the included study’s authors; in most studies, no clear definition of diabetes mellitus was outlined. Baseline renal dysfunction was identified if baseline creatinine was >1.5 mg/dL or baseline creatinine clearance was <60 mL/min.
increased knowledge about risk factors for CIN and advances in strategies for CIN prevention may have, over time, limited the differences in incidence of CIN and contrast agents among high risk patients.

**Study Limitations**

The major limitation of our study is that the results are based on the combined data of many heterogeneous randomized, controlled trials. The included trials utilized different radiographic procedures, different contrast loads, various definitions of CIN, and different populations of patients (high-risk or healthy). We have attempted to account for these differences by performing several subgroup analyses and by including both published and unpollished trials. Furthermore, the subgroup analyses of definition of contrast nephropathy and baseline kidney or renal function may be less valid because the data for these groups were dependent on the authors’ decision to report stratified results and data for these subgroups were not uniformly available in all studies.

**Conclusion**

Analysis of aggregated summary data from multiple randomized, controlled trials of ioxixanol against diverse LOCMs, for heterogeneous procedures and definitions of CIN, show an ioxixanol-associated reduction that is suggestive of a lower incidence of CIN, but is statistically nonsignificant. The incidence of CIN was significantly lower with ioxixanol when compared with iohexol but not when compared with LOCM other than iohexol or other ionic dimers. There was no difference in the incidence of CIN with ioxixanol among patients receiving intra-arterial contrast injections, those with diabetes and/or kidney dysfunction, or among patients undergoing coronary angiography with or without percutaneous intervention.

**Disclosures**

None.

**References**


**CLINICAL PERSPECTIVE**

Because contrast-induced nephropathy is associated with significant morbidity and mortality, we performed a meta-analysis of 36 trials to assess the efficacy of iodixanol compared with low-osmolar contrast media. In this study, iodixanol showed no statistically significant reduction in contrast-induced nephropathy incidence below that observed with heterogeneous comparator agents. We were unable to show a significant benefit in any high-risk subgroups; there was a significant benefit of iodixanol when compared with iohexol alone. The heterogeneity of the studies included reflects the variation seen in general clinical practice and suggests that a general benefit of iodixanol relative to low-osmolar contrast media has not been established. Although the results could be applied to patients undergoing any contrast requiring radiographic procedure, we believe that the study is most applicable to patients undergoing cardiac angiography because the majority of studies included in our analysis were performed in cardiac patients.
Iodixanol Versus Low-Osmolar Contrast Media for Prevention of Contrast Induced Nephropathy: Meta-analysis of Randomized, Controlled Trials
Aaron M. From, Firas J. Al Badarin, Furman S. McDonald, Brian J. Bartholmai, Stephen S. Cha and Charanjit S. Rihal

_Circ Cardiovasc Interv._ 2010;3:351-358; originally published online July 20, 2010; doi: 10.1161/CIRCINTERVENTIONS.109.917070
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