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Randomized Trial of Contrast Media Utilization in High-Risk PTCA
The COURT Trial

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Background—Previous in vitro and in vivo studies have suggested an association between thrombus-related events and type of contrast media. Low osmolar contrast agents appear to improve the safety of diagnostic and coronary artery interventional procedures. However, no data are available on PTCA outcomes with an isosmolar contrast agent.

Methods and Results—A multicenter prospective randomized double-blind trial was performed in 856 high-risk patients undergoing coronary artery intervention. The objective was to compare the isosmolar nonionic dimer iodixanol (n=405) with the low osmolar ionic agent ioxaglate (n=410). A composite variable of in-hospital major adverse clinical events (MACE) was the primary end point. A secondary objective was to evaluate major angiographic and procedural events during and after PTCA. The composite in-hospital primary end point was less frequent in those receiving iodixanol compared with those receiving ioxaglate (5.4% versus 9.5%, respectively; P=0.027). Core laboratory defined angiographic success was more frequent in patients receiving iodixanol (92.2% versus 85.9% for ioxaglate, P=0.004). There was a trend toward lower total clinical events at 30 days in patients randomized to iodixanol (9.1% versus 13.2% for ioxaglate, P=0.07). Multivariate predictors of in-hospital MACE were use of ioxaglate (P=0.01) and treatment of a de novo lesion (P=0.03).

Conclusions—In this contemporary prospective multicenter trial of PTCA in the setting of acute coronary syndromes, there was a low incidence of in-hospital clinical events for both treatment groups. The cohort receiving the nonionic dimer iodixanol experienced a 45% reduction in in-hospital MACE when compared with the cohort receiving ioxaglate. (Circulation. 2000;101:2172-2177.)

Key Words: contrast media □ angioplasty □ myocardial infarction

Coronary angioplasty has undergone dramatic evolution during the last several years. With the introduction of intracoronary stents and intravenous antiplatelet therapy, both acute and long-term clinical outcomes have improved.1–4 The contribution of contrast media to major complications during PTCA has been debated.5–8 Compared with high osmolar ionic contrast agents, nonionic low osmolar contrast agents have been shown to decrease the incidence of major complications associated with diagnostic cardiac catheterization.9–11 In vitro studies have shown that nonionic low osmolar agents possess less inherent anticoagulant activity than do ionic agents.12,13 However, large-scale clinical studies have not clearly demonstrated that nonionic agents are associated with more adverse clinical consequences during diagnostic cardiac catheterization.14

Despite the use of intravenous antiplatelet therapy, patients with evolving acute myocardial infarction (MI), unstable angina, and post-MI ischemia experience higher rates of thrombus-related complications.4 The pathophysiology underlying these events is most likely related to increased thrombogenicity that is due to endothelial damage. The relation of contrast media to these events, if any, remains unclear.

Ioxaglate, a low osmolar ionic dimer, has been thought to confer the benefits of low osmolar agents in addition to the greater anticoagulant properties of ionic agents.7 Several
small single-center clinical trials comparing ioxaglate and nonionic low osmolar agents in PTCA have supported the conclusion that ioxaglate confers some benefits.\textsuperscript{5,15} Iodixanol is a nonionic contrast agent that is hyposmolar with blood.\textsuperscript{16} Sodium and calcium are added to the final product to achieve isosmolarity with blood. In vitro data have demonstrated that iodixanol, unlike other nonionic contrast agents, exhibits less platelet activation with degranulation.\textsuperscript{17} The clinical relevance of this in vitro effect is unknown.\textsuperscript{18}

The purpose of this multicenter prospective randomized trial was to compare the incidence of major adverse cardiac events in patients receiving iodixanol or ioxaglate during PTCA for acute coronary syndromes. Another objective was to compare the incidence of angiographic and procedural events during and at 30 days after PTCA.

Methods

Study Population

A double-blind phase IV randomized trial of contrast media utilization in high-risk PTCA (the COURT Trial) was conducted at 13 clinical sites in the United States from May 25, 1997, to July 24, 1998. Patients undergoing PTCA for acute coronary syndromes with any Food and Drug Administration–approved device were eligible.

High-risk patients were defined as patients who had ≥1 of the following conditions: (1) angina at rest (Braunwald classification IIIb or IIIc) within the previous 48 hours, (2) evolving Q wave or non–Q wave MI within 72 hours, including patients who failed thrombolytics, or (3) post-MI ischemia documented either by angina during the current hospitalization or within 2 weeks of an MI or by a positive functional study within 2 weeks of an MI.

Exclusion criteria were as follows: participation in an investigational drug or device trial within 30 days; a history of significant medication allergies, including iodinated contrast media; severe renal impairment, defined as a serum creatinine >2.0 mg/dL; contraindication to heparin, aspirin, ticlopidine, or abciximab therapy; or receiving additional contrast media within 24 hours before the intervention or scheduled to receive iodinated contrast media within 48 hours after the intervention. Also excluded were females of child-bearing potential in which the potential risk of trial participation exceeded the benefit.

Patients were randomly assigned to receive either iodixanol (Visipaque-320, Nycomed-Amersham) or ioxaglate (Hexabrix-320, Mallinkrudt). A third party–blind procedure was followed for randomization of contrast media. This was accomplished by covering all bottles of contrast agents with a sleeve, which prevented identification by the physician of the contrast media being used. Blinding was performed by a nurse or technician in the laboratory who was not involved in the data collection.

All angiograms were evaluated at the investigation site for angiographic and procedural events during and after the procedure. Additionaly, the angiographic core laboratory at the Washington Hospital Center conducted blinded morphological and quantitative angiographic (CMS-GFT, MEDIS) assessment of all angiograms.\textsuperscript{19} Patients were administered aspirin (325 mg) before and after the intervention. Ticlopidine (250 mg twice a day) was administered in all patients undergoing stent implantation. The use of abciximab was left to the discretion of the operating physician. Heparin was administered as a weight-adjusted dose according to prespecified guidelines. When abciximab was used, the heparin anticoagulation regimen and activating clotting time guidelines were as described in the low-dose heparin arm of the EPILOG trial.\textsuperscript{1}

Study End Points

The primary composite end point for the comparison of iodixanol and ioxaglate included the occurrence of at least 1 of 7 major clinical adverse events during the hospital stay. Clinical outcomes were assessed at hospital discharge. Major clinical adverse events that were evaluated included the following: emergency recatheterization (for documented ischemic ECG changes) or repeat PTCA; documented abrupt closure of the target vessel; stroke; systemic arterial thromboembolic event; periiprocedural nonfatal MI, defined as a postprocedure elevation of total creatine kinase enzyme at least 3 times the upper limit of normal with positive creatine kinase-MB and normal creatine kinase levels before PTCA; unplanned coronary artery bypass surgery; or cardiac death.

A secondary end point of the trial was to evaluate the occurrence of a core laboratory–defined major angiographic or procedural complications during or immediately after the interventional procedure. Major angiographic or procedural complications were defined as abrupt closure of the target vessel, development of moderate to large thrombi, distal embolization, side branch occlusion of vessel >1.0 mm, no reflow of the target vessel (requiring treatment other than nitroglycerin), unplanned use of an intra-aortic balloon pump for clinical deterioration, unplanned use of intravenous antplatelet therapy, or failure to obtain procedural success. Procedural success was defined as postprocedural stenosis ≤50% with a >20% decrease in absolute stenosis and TIMI-3 flow. Procedural variables of unplanned intra-aortic balloon pump and unplanned abciximab were assessed at the investigational site. Ablution closure site assessment was performed because not all closures were documented on the core angiogram for core laboratory analysis. All other angiographic complications were validated by blinded analysis at the core angiographic laboratory.

Secondary end points were obtained to compare the in-hospital incidence rates of noncardiac death, clinically significant arrhythmia requiring therapy, symptoms of angina with ECG changes, hypotension requiring intervention, renal failure requiring medical intervention or prolonging hospitalization, or bleeding complications. Bleeding was defined as a groin site complication requiring vascular repair, ultrasound-guided compression, or transfusion. Evaluation of clinical outcomes at 30 days was by telephone follow-up.

Data were independently monitored at each study site. An adjudication committee was used to ensure consistency in evaluating end points. The committee conducted a blinded review of all major primary and secondary clinical outcomes before any data analysis. No investigator reviewed patients enrolled at his own study site.

Statistical Analysis

Continuous variables were summarized by use of descriptive statistics. Categorical variables were summarized by counts and percentages. All evaluable subjects were included in the analyses of the primary and secondary end points. For those angiographic or procedural complications assessed by both the site investigator and the core laboratory, the assessment by the core laboratory was used for the end point, except for abrupt closure. Comparison between iodixanol and ioxaglate for the occurrence of major clinical complications or major angiographic or procedural complications was tested with a 2-sided comparison of the incidence rates with the use of standard normal approximations.

Composite outcome obtained from the hospital stay for adjudicated assessments of all evaluable subjects was considered the primary end point for the multivariate analysis. A multivariate stepwise logistic regression model was used to identify those variables independently predictive of the primary composite major adverse clinical event.

Results

The study began on May 25, 1997, and ended on July 24, 1998, with a total of 1489 patients enrolled at 13 clinical sites. The enrollment scheme of patients is shown in the Figure, and baseline characteristics of the study population are shown in Table 1. Patients were randomized before contrast administration. Therefore, all patients undergoing diagnostic catheterization without PTCA were placed into a separate registry. No further efficacy analyses were performed on these patients.
The trial included 856 patients who underwent PTCA and were randomized and a total of 815 patients who were evaluable; 405 patients received iodixanol and 410 received ioxaglate. The 2 treatment groups were similar with regard to demographics and medical history. Patients were excluded if the activating clotting time was not within 15% of the prespecified target (n = 24), if another contrast agent was administered within 48 hours after the index PTCA (n = 4), or if patients did not meet criteria as defined in the study entrance criteria (n = 13) (Figure). Clinical presentation was unstable angina in 208 (51%) and 232 (57%) patients, evolving acute MI occurred in 140 (35%) and 125 (30%) patients, and postinfarction ischemia occurred in 56 (14%) and 53 (13%) patients of the iodixanol and ioxaglate groups, respectively.

Treatment device selection was similar for both groups. Balloon PTCA was the primary treatment device in the majority (iodixanol 61%, ioxaglate 60%; Table 2). Location of the primary treated lesion was similar for both groups; percentages were as follows for iodixanol versus ioxaglate groups, respectively: left anterior descending coronary artery, 30% versus 34%; left circumflex coronary artery, 23% versus 25%; right coronary artery, 33% versus 32%; and saphenous vein graft, 7% versus 10%. Systemic anticoagulation was similar for both groups. The mean highest activating clotting times for the procedure were similar for the iodixanol group and for the ioxaglate group with use of either the Hemochron (International Technique Corp, Edison, NJ) or the Hemotec device (Hemotech Systems Inc, Hopkins, MN) (318 ± 68 versus 320 ± 74 seconds and 262 ± 64 versus 297 ± 62 seconds), respectively.

Administered contrast volume was similar for both groups. In those undergoing only coronary intervention, the mean volume was 250 ± 114 mL for the iodixanol group compared with 285 ± 134 mL for the ioxaglate group. For patients who had combined diagnostic and interventional procedures, the mean volume of contrast media was 346 ± 165 and 364 ± 175 mL for iodixanol and ioxaglate, respectively.

There was a low incidence of in-hospital clinical outcomes for both treatment groups (Table 3). However, the iodixanol cohort experienced the primary composite clinical outcomes less frequently than did the ioxaglate group (5.4% versus 9.5%, respectively; P = 0.027). The reduction in abrupt closure (0.7% versus 2.4%, P = 0.05) and nonfatal MI (2.0% versus 4.4%, P = 0.05) were the components that accounted for the difference.
for the majority of benefit in the iodixanol cohort versus the ioxaglate cohort, respectively. In-hospital data analyses were also performed on an intention-to-treat basis. When all 856 patients were evaluated on an intention-to-treat basis, the composite end point remained significantly less frequent in the iodixanol group (22 of 421, 5.2%) than in the ioxaglate group (40 of 435, 9.2%) ($P=0.025$).

In-hospital cardiac death occurred in 5 patients in the iodixanol group and 1 patient in the ioxaglate group. In the iodixanol group, 3 deaths were due to progressive congestive heart failure and left ventricular dysfunction within 30 days of the procedure, 1 was due to ventricular arrhythmia 11 days after acute anterior MI, and 1 death was due to acute mitral regurgitation at 5 days after MI. In the ioxaglate group, 1 death was due to ventricular arrhythmia 2 days after abrupt closure and unsuccessful repeat PTCA.

### TABLE 5. Angiographic and Procedural Outcome

<table>
<thead>
<tr>
<th></th>
<th>Iodixanol (n=400)</th>
<th>Ioxaglate (n=396)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abrupt closure</td>
<td>2 0.5</td>
<td>7 1.8</td>
<td>0.09</td>
</tr>
<tr>
<td>Prolonged no-reflow</td>
<td>3 0.8</td>
<td>3 0.8</td>
<td>0.99</td>
</tr>
<tr>
<td>Distal embolization</td>
<td>2 0.5</td>
<td>1 0.3</td>
<td>0.57</td>
</tr>
<tr>
<td>Side-branch occlusion</td>
<td>6 1.5</td>
<td>6 1.5</td>
<td>0.99</td>
</tr>
<tr>
<td>Development of moderate to large thrombus</td>
<td>0 0 0 0 ...</td>
<td>0 0</td>
<td>0.37</td>
</tr>
<tr>
<td>Dissection</td>
<td>18 4.5</td>
<td>25 6.3</td>
<td>0.25</td>
</tr>
<tr>
<td>Unplanned IABP</td>
<td>4 1.0</td>
<td>7 1.8</td>
<td>0.37</td>
</tr>
<tr>
<td>Unplanned abciximab†</td>
<td>29 7.3</td>
<td>32 8.1</td>
<td>0.66</td>
</tr>
<tr>
<td>Procedural success</td>
<td>369 92.2</td>
<td>340 85.9</td>
<td>0.004</td>
</tr>
<tr>
<td>&gt;20% Absolute decrease</td>
<td>375 93.9</td>
<td>355 90.0</td>
<td>...</td>
</tr>
<tr>
<td>&lt;50% Residual stenosis</td>
<td>389 97.3</td>
<td>379 94.9</td>
<td>...</td>
</tr>
<tr>
<td>TIMI-3 flow</td>
<td>397 99.3</td>
<td>391 98.8</td>
<td>...</td>
</tr>
<tr>
<td>Composite outcome</td>
<td>69 17.3</td>
<td>87 22.0</td>
<td>0.093</td>
</tr>
</tbody>
</table>

†One patient with unplanned abciximab had missing angiographic core laboratory data.

### TABLE 6. Secondary In-Hospital Clinical Outcomes: Adjudicated Assessments

<table>
<thead>
<tr>
<th></th>
<th>Iodixanol (n=405)</th>
<th>Ioxaglate (n=410)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noncardiac death</td>
<td>0 0.0</td>
<td>0 0.0</td>
<td>0</td>
</tr>
<tr>
<td>Arrhythmia requiring therapy</td>
<td>6 1.5</td>
<td>9 2.2</td>
<td>0.45</td>
</tr>
<tr>
<td>Angina with ECG changes</td>
<td>15 3.7</td>
<td>21 5.1</td>
<td>0.33</td>
</tr>
<tr>
<td>Hypotension with intervention</td>
<td>34 8.4</td>
<td>41 10.0</td>
<td>0.43</td>
</tr>
<tr>
<td>Renal failure requiring medication</td>
<td>2 0.5</td>
<td>2 0.5</td>
<td>0.99</td>
</tr>
<tr>
<td>Post PTCA bleeding</td>
<td>17 4.2</td>
<td>16 3.9</td>
<td>0.83</td>
</tr>
<tr>
<td>Composite outcome</td>
<td>63 15.6</td>
<td>73 17.8</td>
<td>0.39</td>
</tr>
</tbody>
</table>

Overall clinical events after discharge to 30 days were similar for both treatment groups (iodixanol 3.8% versus ioxaglate 3.8%, $P=0.94$; Table 4). However, cumulative in-hospital and 30-day composite major events tended to be less in the group that received iodixanol (9.1% versus 13.4% for ioxaglate, $P=0.07$).

The angiographic and procedural outcomes are shown in Table 5. The overall angiographic success rate (defined as final stenosis <50%, reduction in stenosis >20%, and TIMI-3 flow) was higher in the group receiving iodixanol (iodixanol 92.2% and ioxaglate 85.9%; $P=0.004$). The predefined composite end point of angiographic and procedural complications tended to be less frequent for the iodixanol group compared with the ioxaglate group (17.3% versus 22%, respectively; $P=0.093$).

Abciximab was used in 345 patients with a similar frequency in both groups (Table 2). In those receiving abciximab, the composite primary clinical outcomes occurred in 18 (10.5%) of the iodixanol cohort and 20 (11.5%) of the ioxaglate cohort ($P=0.77$). However, in patients who did not receive abciximab, the primary clinical outcome occurred in only 4 (1.7%) of the iodixanol group compared with 19 (8.1%) of the ioxaglate group ($P=0.001$). This difference was primarily related to a nonsignificant reduction in nonfatal MI (0.9% [iodixanol] versus 3% [ioxaglate], $P=0.09$) and emergent recatheterization or repeat PTCA (0.9% [iodixanol] versus 3.4% [ioxaglate], $P=0.06$). Thus, the lowest event rate was noted in patients who received iodixanol but did not receive abciximab.

Secondary in-hospital complications were similar for both cohorts (Table 6). Noncardiac death, arrhythmia, angina with ECG changes, significant hypotension, nephrotoxicity, bleeding, or the composite outcomes occurred in equal frequencies for each group.

Demographic, clinical, and procedural factors were evaluated in the multivariate analysis. Significant multivariate predictors of the primary in-hospital major adverse clinical events were use of ioxaglate (odds ratio 2.1, 95% CI 1.2 to 3.6; $P=0.01$) and treatment of a de novo lesion (odds ratio 3.7, 95% CI 1.1 to 12.3; $P=0.03$).

### Discussion

When Robertson observed blood clot formation in angiographic syringes filled with a mixture of contrast media and
blood, concerns were raised regarding the potential thrombogenicity of contrast media.2 Since that time, in vitro studies have indicated that whereas all contrast media possess anticoagulant properties, the low osmolar nonionic contrast media confer less of an anticoagulant effect than do ionic anticoagulant properties, the low osmolar nonionic contrast media have indicated that whereas all contrast media possess antithrombogenicity of low osmolar nonionic contrast media.20 Despite the in vitro data, clinical data have failed to demonstrate any difference in thromboembolic complications with the use of nonionic agents during diagnostic cardiac catheterization or PTCA.14,22 Several small trials have reported findings that support concerns about the use of low osmolar nonionic agents in PTCA.5,15

In 1996, the first nonionic isosmolar dimer, iodixanol, was approved for use in the United States. In vitro work has shown that nonionic agents during diagnostic cardiac catheterization or PTCA.14,22 Several small trials have reported findings that support concerns about the use of low osmolar nonionic agents in PTCA.5,15

The Contrast Media Utilization in High Risk PTCA (COURT) Trial demonstrates that the use of iodixanol, compared with ioxaglate, is associated with a significant reduction in adverse clinical outcomes during PTCA for acute coronary syndromes. The predefined composite clinical end point was significantly less frequent in patients who received iodixanol than in patients who received ioxaglate. At hospital discharge, there was a 45% reduction in the primary clinical composite end point with iodixanol. Multivariate analysis further confirmed these results, demonstrating that the type of contrast agent is independently predictive of patient outcomes.

Previous clinical trials comparing low osmolar nonionic and ionic contrast media in patients undergoing PTCA have yielded conflicting results.5,6,15,22 Some have shown that the incidences of rethrombosis,21 guidewire platelet deposition,6,7 and post-PTCA ischemic complications5 were lower with the ionic contrast media. However, others have demonstrated no difference in major ischemic complications.22 The present study is the largest multicenter trial evaluating isosmolar contrast media in high-risk patients undergoing PTCA. A recent prospective randomized trial comparing iodixanol and ioxaglate and including both low- and high-risk patients was performed.23 In that study, no significant difference in major adverse cardiac events was observed. Overall events were low in both groups (4.7% for iodixanol and 3.9% for ioxaglate).

The present study used contemporary PTCA techniques, including stents and abciximab. Device selection was at the discretion of the operator. In the multivariate analysis, there did not appear to be a device-dependent effect. The majority of patients received abciximab as planned therapy. No significant difference in clinical outcomes was observed between the iodixanol and ioxaglate groups when abciximab was used. However, in those that did not receive abciximab, there were significantly less adverse clinical outcomes in the iodixanol cohort (1.7% versus 8.1% in the ioxaglate cohort, P=0.009). These data suggest that abciximab, a potent antplatelet agent, may “neutralize” the platelet activation and degranulation observed in vitro with ioxaglate.

Angiographic analysis confirmed the results observed in clinical outcomes. Although individual angiographic events were similar for both groups, the procedural success assessed by the angiographic core laboratory was significantly better in the iodixanol group (P=0.004). The composite angiographic and procedural outcome also tended to be less frequent in the iodixanol group.

Comparison With In Vitro Data

In vitro data have suggested that the degree of osmolality of the contrast media may be the most important factor in its interaction with the subsequent degranulation of platelets17 and that the effects of osmolality may be modulated downward by ionicity. Other in vitro work has shown that iodixanol produces less platelet degranulation than does low osmolar ionic contrast media.24,25 The interaction of the various effects of contrast media on anticoagulation, platelet activation, and endothelial interaction in vivo are unknown. It was previously unclear whether these in vitro data translate into any important clinical effects.

Limitations

The present study focused on acutely ischemic patients because they are at greater risk of developing thromboembolic complications from interventional procedures. Because this study population did not include stable patients, extrapolation of these results to that population is not possible. Also, the present study allowed abciximab use as deemed clinically necessary by each investigator. Because there were no protocol-specified guidelines for abciximab use, any comparisons regarding the relative benefits of iodixanol versus abciximab are speculative.

Conclusions

In the present era, the incidences of major in-hospital clinical outcomes and major angiographic complications are reduced in high-risk patients undergoing coronary intervention with the nonionic isosmolar dimer iodixanol compared with the low osmolar ionic dimer ioxaglate.

Acknowledgment

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References


