Minimizing the Renal Toxicity of Iodinated Contrast

Peter A. McCullough, MD, MPH, FACC, FACP, FAHA, FCCP
Chief Academic and Scientific Officer
St. John Providence Health System
Detroit, MI USA
Outline

• Terms and definitions
• Pathophysiology
• Risk prediction
• Strategies to improve safety
• Differences in iodinated contrast agents
Outline

• Terms and definitions
• Pathophysiology
• Risk prediction
• Strategies to improve safety
• Differences in iodinated contrast agents
Change of terms:

Contrast Induced Acute Kidney Injury (CI-AKI)

replaces

Contrast-Induced Nephropathy (CIN)
Contrast-induced AKI

Definition

New-onset or exacerbation of renal dysfunction after contrast administration without other identifiable causes:

**Recognized as a change in baseline SCr**
Increase by >25%

or

Absolute \( \uparrow \geq 0.5 \text{ mg/dL} (>44.2 \text{ \( \mu \)mol/L})

**Conventional Definition**

Absolute \( \uparrow \geq 0.3 \text{ mg/dL} \text{ with oliguria} (>26.5 \text{ \( \mu \)mol/L})

**Occurs 24–48 h post contrast exposure, with creatinine peaking 5–7 days later and normalizing within 7–10 days in most cases**

# Acute Kidney Injury Network Classification/Staging System for AKI

<table>
<thead>
<tr>
<th>Stage</th>
<th>SCr criteria</th>
<th>Urine output criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>Baseline ↑ SCr ≥0.3 mg/dL or ≥150% to 200% (1.5–2-fold)</td>
<td>&lt;0.5 mL/kg/h for &gt;6 h</td>
</tr>
<tr>
<td>Stage 2</td>
<td>Baseline ↑ SCr ≥200% to 300% (≥2–3-fold)</td>
<td>&lt;0.5 mL/kg/h for &gt;12 h</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Baseline ↑ SCr &gt;300% (&gt;3-fold) or SCr 4.0 mg/dL with an acute ↑ ≥0.5 mg/dL</td>
<td>&lt;0.3 mL/kg/h for 24 h or anuria for 12 h</td>
</tr>
</tbody>
</table>

Mehta RL et al. *Crit Care.* 2007;11:R31
1-Year Kaplan-Meier Survival Curves Stratified by Creatinine Clearance (CrCl) Levels After Primary Coronary Intervention in CADILLAC

# Mortality Rates Stratified by the Development of CIN

<table>
<thead>
<tr>
<th></th>
<th>Contrast-induced nephropathy (n=86)</th>
<th>No contrast-induced nephropathy (n=1798)</th>
<th>Relative risk (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-day mortality (%)</td>
<td>16.2</td>
<td>1.2</td>
<td>13.8 (7.3-26.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1-year mortality (%)</td>
<td>23.3</td>
<td>3.2</td>
<td>7.4 (4.7-11.7)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Impact of Dialysis Following AKI on Clinical and Economic Outcomes

- **Mean Hospital Days**: 15.5
- **Mean ICU Days**: 7.3
- **In-hospital Mortality (%)**: 25.5
- **1-Year Mortality (%)**: 54.6
- **Dialysis at Discharge (%)**: 31
- **Dialysis at 1 Year (%)**: 23

**Dialysis-requiring ARF**: $128,000 per QALY saved

**Chronic dialysis**: $51,000/year
**Transplantation**: $18,000/year

In-patient expenses: $1,227/day

**n=12,054; QALY, quality-adjusted life years**
Outline

• Terms and definitions
• **Pathophysiology**
• Risk prediction
• Strategies to improve safety
• Differences in iodinated contrast agents
Anatomical and Physiologic Features of the Renal Cortex and Medulla

Proximal Tubular Cell Normal Structure and Function
Proximal Tubular Cell Injury with Iodinated Contrast

Acute kidney injury

Adapted Courtesy Herget-Rosenthal 2010
73 Year Old With Multiple Myeloma
Cr 2.3 mg/dL, CrCl=23 mL/min, Cr rise 0.3 mg/dL


Fig. 1. Axial CT scan of the patient with i.v. administration 0.5 g /kg bw of iodixanol (A) and serial unenhanced CT scans (B-D) following 3 (B), 8 (C), and 17 days (D) after administration of iodixanol. Dense and regular attenuation of both renal cortices as a sign of persistent renal retention of contrast medium is noted at day 3, with subsequent vanishing of the cortical abnormalities over time.
Outline

• Terms and definitions
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• **Risk prediction**
• Strategies to improve safety
• Differences in iodinated contrast agents
Case Example

• 76-year old Caucasian female with type 2 diabetes hospitalized with chest pain
• Equivocal stress test for ischemia – needs diagnostic coronary angiography
• SCr 124 µmol/L (1.4 mg/dL)
  – eGFR=39 mL/min/1.73 m² (MDRD) = Stage 3 CKD
• Hgb 10.2 g/dL
• Mild arthritis, treated with ibuprofen
What Is This Patient’s Risk of AKI After Coronary Angiography?

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Integer score</th>
<th>Patient A’s score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>IABP</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>CHF</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Age &gt;75 y</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>CM volume</td>
<td>1 per 100 mL</td>
<td></td>
</tr>
<tr>
<td>SCr &gt;1.5 mg/dL (133 µmol/L) or</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>eGFR &lt;60 mL/min/1.73 m²</td>
<td>2 for 40-60</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 for 20-39</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>6 for &lt;20</td>
<td></td>
</tr>
</tbody>
</table>

Risk score = 14

Risk Score: Impact of Multiple Risk Factors

Patient risk score = 14
Contrast-induced AKI risk = ~26%
Risk of dialysis = 1%
Outline

• Terms and definitions
• Pathophysiology
• Risk prediction
• **Strategies to improve safety**
• Differences in iodinated contrast agents
Bicarbonate for Volume Expansion: New Trial

MEENA Trial
(N=303)

<table>
<thead>
<tr>
<th></th>
<th>NaHCO$_3$</th>
<th>NaCl</th>
</tr>
</thead>
<tbody>
<tr>
<td>AKI incidence (%)</td>
<td>13.6</td>
<td>13.5</td>
</tr>
<tr>
<td></td>
<td>16.3</td>
<td>15.4</td>
</tr>
</tbody>
</table>

$P=0.97$  $P=0.82$

CI-AKI Definition:  
≥25% ↓ GFR  
≥25% ↑ SCr

The PREVENT trial: Subjects

3569 Patients screened
- 3146 Excluded
  - 423 Eligible
    - 41 Denied
  - 382 Randomized
    - 189 Randomized to Saline
      - 187 Included in primary contrast-induced nephropathy analysis
        - 2 Excluded because did not have laboratory data after angiography
      - 189 Included in 30-day clinical FU
      - 188 Included in 6-month clinical FU
    - 193 Randomized to Bicarbonate
      - 188 Included in primary contrast-induced nephropathy analysis
        - 5 Excluded because did not have laboratory data after angiography
      - 193 Included in 30-day clinical FU
      - 192 Included in 6-month clinical FU

TCT 2010 Abstract
The PREVENT trial: Study Protocol

- 1:1 randomization, open label design
- 9 cardiac centers in Korea
- Independent event committee and data management
- Sponsored by CardioVascular Research Foundation, Seoul, Korea
Study Protocol

- **Bicarbonate group**: Sodium bicarbonate 154mEq/L: 3 mL/kg for 1 hour prior, decreased to 1 mL/kg/hr during and 6 hours after the procedure.

- **Saline group**: Isotonic saline 0.9% NaCl: 1 mL/kg/hr for 12 hours before and 12 hours after.

- All patients received oral N-acetylcysteine 1200 mg twice daily for 2 days, prior to procedure.

- If ejection fraction < 45%, hydration rate was reduced to 0.5mL/kg/hr in both arms.
Primary End Point
- Occurrence of CIN -

Saline Group

Bicarbonate Group

P=0.17

Saline Group

Bicarbonate Group

10/187
17/188

5.3 %
9.0 %

TCT 2010 Abstract
Rates of Dialysis

Saline Group

Bicarbonate Group

\[ P=0.69 \]

2/187

4/188

1.1

2.1
Meta-analysis: Effectiveness of Drugs for Preventing Contrast-Induced Nephropathy

Aine M. Kelly, MD, MS; Ben Dwamena, MD; Paul Cronin, MD, MS; Steven J. Bernstein, MD, MPH; and Ruth C. Carlos, MD, MS

**Background:** N-Acetylcysteine, theophylline, and other agents have shown inconsistent results in reducing contrast-induced nephropathy.

**Purpose:** To determine the effect of these agents on preventing nephropathy.

**Data Sources:** Relevant randomized, controlled trials were identified by computerized searches in MEDLINE (from 1966 through 3 November 2006), EMBASE (1980 through November 2006), PubMed, Web of Knowledge (Current Contents Connect, Web of Science, BIOSIS Previews, and ISI Proceedings for the latest 5 years), and the Cochrane Library databases (up to November 2006). Databases were searched for studies in English, Spanish, French, Italian, and German.

**Study Selection:** Randomized, controlled trials that administered N-acetylcysteine, theophylline, fenoldopam, dopamine, iloprost, statin, furosemide, or mannitol to a treatment group; used intravenous iodinated contrast; defined contrast-induced nephropathy explicitly; and reported sufficient data to construct a 2 × 2 table of the primary effect measure.

**Data Extraction:** Abstracted information included patient characteristics, type of contrast media and dose, periprocedural hydration, definition of contrast-induced nephropathy, and prophylactic agent dose and route.

**Data Synthesis:** In the 41 studies included, N-acetylcysteine (relative risk, 0.62 [95% CI, 0.44 to 0.88]) and theophylline (relative risk, 0.49 [CI, 0.23 to 1.06]) reduced the risk for contrast-induced nephropathy more than saline alone, whereas furosemide increased it (relative risk, 3.27 [CI, 1.48 to 7.26]). The remaining agents did not significantly affect risk. Significant subgroup heterogeneity was present only for N-acetylcysteine. No publication bias was discerned.

**Limitations:** All trials evaluated the surrogate end point of contrast-induced nephropathy as the primary outcome. The lack of a statistically significant renoprotective effect of theophylline may result from insufficient data or study heterogeneity. True study quality remains uncertain.

**Conclusion:** N-Acetylcysteine is more renoprotective than hydration alone. Theophylline may also reduce risk for contrast-induced nephropathy, although the detected association was not significant. Our data support the administration of N-acetylcysteine prophylaxis, particularly in high-risk patients, given its low cost, availability, and few side effects.
**Meta-analysis: N-Acetylcysteine Prophylaxis Prior to Contrast Exposure**

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Relative Risk (95% CI)</th>
<th>Intervention, n/n</th>
<th>Control, n/n</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>N</em>-Acetylcysteine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allaqaband et al., 2002 (25)</td>
<td>1.19 (0.45–3.12)</td>
<td>8/45</td>
<td>6/40</td>
</tr>
<tr>
<td>Azmus et al., 2005 (26)</td>
<td>0.84 (0.43–1.67)</td>
<td>14/196</td>
<td>17/201</td>
</tr>
<tr>
<td>Baker et al., 2003 (27)</td>
<td>0.24 (0.05–1.05)</td>
<td>2/41</td>
<td>8/39</td>
</tr>
<tr>
<td>Balderramo et al., 2004 (28)</td>
<td>0.42 (0.04–4.44)</td>
<td>1/33</td>
<td>2/28</td>
</tr>
<tr>
<td>Briguori et al., 2002 (29)</td>
<td>0.59 (0.23–1.57)</td>
<td>6/92</td>
<td>10/91</td>
</tr>
<tr>
<td>Coyle et al., 2006 (30)</td>
<td>6.09 (0.75–49.24)</td>
<td>6/68</td>
<td>1/69</td>
</tr>
<tr>
<td>Diaz-Sandoval et al., 2002 (32)</td>
<td>0.18 (0.04–0.72)</td>
<td>2/25</td>
<td>13/29</td>
</tr>
<tr>
<td>Drager et al., 2004 (33)</td>
<td>0.42 (0.04–4.06)</td>
<td>1/13</td>
<td>2/11</td>
</tr>
<tr>
<td>Durham et al., 2002 (34)</td>
<td>1.20 (0.55–2.63)</td>
<td>10/38</td>
<td>9/41</td>
</tr>
<tr>
<td>El Mahmoud et al., 2003 (36)</td>
<td>1.50 (0.26–8.66)</td>
<td>3/60</td>
<td>2/60</td>
</tr>
<tr>
<td>Fung et al., 2004 (38)</td>
<td>1.30 (0.49–3.46)</td>
<td>8/46</td>
<td>6/45</td>
</tr>
<tr>
<td>Goldenberg et al., 2004 (39)</td>
<td>1.27 (0.30–5.31)</td>
<td>4/41</td>
<td>3/39</td>
</tr>
<tr>
<td>Gomes et al., 2005 (40)</td>
<td>1.03 (0.41–2.60)</td>
<td>8/77</td>
<td>8/79</td>
</tr>
<tr>
<td>Kay et al., 2003 (46)</td>
<td>0.32 (0.11–0.96)</td>
<td>4/102</td>
<td>12/98</td>
</tr>
<tr>
<td>Kefer et al., 2003 (47)</td>
<td>0.64 (0.11–3.68)</td>
<td>2/53</td>
<td>3/51</td>
</tr>
<tr>
<td>MacNeill et al., 2003 (48)</td>
<td>0.15 (0.02–1.11)</td>
<td>1/21</td>
<td>7/22</td>
</tr>
<tr>
<td>Marenzi et al., 2006 (18)</td>
<td>0.22 (0.13–0.37)</td>
<td>17/235</td>
<td>39/119</td>
</tr>
<tr>
<td>Namgung et al., 2005 (50)</td>
<td>0.37 (0.13–1.01)</td>
<td>4/25</td>
<td>10/23</td>
</tr>
<tr>
<td>Ochoa et al., 2004 (51)</td>
<td>0.33 (0.10–1.10)</td>
<td>3/36</td>
<td>11/44</td>
</tr>
<tr>
<td>Oldemeyer et al., 2003 (52)</td>
<td>1.28 (0.30–5.41)</td>
<td>4/49</td>
<td>3/47</td>
</tr>
<tr>
<td>Rashid et al., 2004 (53)</td>
<td>1.04 (0.22–4.91)</td>
<td>3/46</td>
<td>3/48</td>
</tr>
<tr>
<td>Sandhu et al., 2006 (54)</td>
<td>7.00 (0.37–132.29)</td>
<td>3/53</td>
<td>0/53</td>
</tr>
<tr>
<td>Shyu et al., 2002 (55)</td>
<td>0.14 (0.03–0.57)</td>
<td>2/60</td>
<td>15/61</td>
</tr>
</tbody>
</table>

Subtotal ($I^2 = 55.1\% ; P = 0.000$)  

## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Acetylcysteine (1172)</th>
<th>Placebo (1136)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age – yr</strong></td>
<td>68.0 ± 10.4</td>
<td>68.1 ± 10.4</td>
</tr>
<tr>
<td><strong>Female sex</strong></td>
<td>38.0%</td>
<td>39.3%</td>
</tr>
<tr>
<td>Patients fulfilling inclusion criteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic Renal Failure*</td>
<td>15.4%</td>
<td>16.0%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>61.2%</td>
<td>59.7%</td>
</tr>
<tr>
<td>Heart failure</td>
<td>9.9%</td>
<td>9.2%</td>
</tr>
<tr>
<td>Shock</td>
<td>0.3%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>35.8%</td>
<td>35.1%</td>
</tr>
<tr>
<td>Coronary diagnostic angiography</td>
<td>67.1%</td>
<td>68.7%</td>
</tr>
<tr>
<td>Percutaneous coronary intervention</td>
<td>30.1%</td>
<td>28.5%</td>
</tr>
<tr>
<td>Glomerular filtration rate</td>
<td>60.2 (45.4 to 84.5)</td>
<td>61.4 (45.2 to 83.3)</td>
</tr>
</tbody>
</table>
Results

Acetylcysteine (N=1172)  Placebo (N=1136)

RR = 1.00 (0.81-1.25)  RR = 1.04 (0.69-1.57)  RR = 0.74 (0.36-1.52)
p = 0.97  p = 0.85  p = 0.41

% of patients

Primary Endpoint

CIN

Elevation ≥0.5mg/dL in serum creatinine

Doubling in serum creatinine

12.7  12.7

3.9  3.8

1.1  1.5
## Meta-analysis: Other Pharmacologic Agents for the Prevention of CI-AKI

### Study, Year (Reference)

<table>
<thead>
<tr>
<th>Meta-Analysis</th>
<th>Year (Reference)</th>
<th>Relative Risk (95% CI)</th>
<th>Intervention, n/n</th>
<th>Control, n/n</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dopamine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Abizaid et al., 1999 (24)</td>
<td>0.70 (0.33–1.47)</td>
<td>7/20</td>
<td>10/20</td>
</tr>
<tr>
<td></td>
<td>Diez et al., 1999 (31)</td>
<td>0.71 (0.26–1.95)</td>
<td>5/25</td>
<td>7/25</td>
</tr>
<tr>
<td></td>
<td>Subtotal (I² = 0.0%; P = 0.98)</td>
<td>0.70 (0.39–1.28)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fenoldopam</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Allaqaband et al., 2002 (25)</td>
<td>1.05 (0.37–2.98)</td>
<td>6/38</td>
<td>6/40</td>
</tr>
<tr>
<td></td>
<td>Stone et al., 2003 (57)</td>
<td>1.11 (0.79–1.57)</td>
<td>46/137</td>
<td>44/146</td>
</tr>
<tr>
<td></td>
<td>Subtotal (I² = 0.0%; P = 0.92)</td>
<td>1.11 (0.80–1.53)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Furosemide</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dussol et al., 2006 (35)</td>
<td>2.92 (0.99–8.67)</td>
<td>12/79</td>
<td>4/77</td>
</tr>
<tr>
<td></td>
<td>Solomon et al., 2006 (9)</td>
<td>3.73 (1.16–12.05)</td>
<td>10/25</td>
<td>3/28</td>
</tr>
<tr>
<td></td>
<td>Subtotal (I² = 0.0%; P = 0.77)</td>
<td>3.27 (1.48–7.26)</td>
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<tr>
<td><strong>Theophylline</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Abizaid et al., 1999 (24)</td>
<td>0.60 (0.27–1.34)</td>
<td>6/20</td>
<td>10/20</td>
</tr>
<tr>
<td></td>
<td>Dussol et al., 2006 (35)</td>
<td>1.44 (0.42–4.92)</td>
<td>6/80</td>
<td>4/77</td>
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<tr>
<td></td>
<td>Erley et al., 1999 (37)</td>
<td>1.66 (0.16–17.37)</td>
<td>2/35</td>
<td>1/29</td>
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<tr>
<td></td>
<td>Huber et al., 2002 (42)</td>
<td>0.25 (0.06–1.12)</td>
<td>2/50</td>
<td>8/50</td>
</tr>
<tr>
<td></td>
<td>Huber et al., 2003 (43)</td>
<td>0.20 (0.05–0.87)</td>
<td>2/50</td>
<td>10/50</td>
</tr>
<tr>
<td></td>
<td>Kapoor et al., 2003 (45)</td>
<td>0.07 (0.00–1.12)</td>
<td>0/35</td>
<td>7/35</td>
</tr>
<tr>
<td></td>
<td>Subtotal (I² = 39.7%; P = 0.141)</td>
<td>0.49 (0.23–1.06)</td>
<td></td>
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</tr>
</tbody>
</table>

Hemofiltration works to ensure:
- adequate intravascular volume
- reduce uremic toxins which may worsen AKI
- provides stability to the high risk patient after the procedure reducing the risks of oliguria, volume overload, and electrolyte imbalance that are associated with short-term mortality.

- Double lumen catheter is placed in a jugular or femoral vein for blood withdrawal and reinfusion and connected with an extracorporeal circuit.
- 6 hours before contrast: peristaltic pump (e.g. Prisma hemofiltration pump) at 100 mL/min. Isotonic replacement fluid (post-dilution hemofiltration) at 1000 mL/h, and is matched with the rate of ultrafiltrate production so that no net fluid loss occurs.
- 5000 IU heparin bolus before initiation followed by a continuous heparin infusion of 500 to 1000 IU/h through the inflow side of the catheter.
- At the time of the cardiac procedure, the hemofiltration treatment should be stopped, and the circuit temporarily filled with a saline solution and short-circuited to exclude the patient without interruption of the flow.
- Immediately after the procedure the hemofiltration should be restarted for 12-18 hours.
RenalGuard System

RenalGuard

Urine Output

![Urine Output Graph]

The RenalGuard System is designed to monitor and control urine output in medical settings. The graph shows the urine flow rate over time, with each unit representing 15 minutes.
MYTHOS Trial: Primary Outcome

- **sCr ≥25% or ≥0.5 mg/dl**
  - Controls: 14% (8/57)
  - RenalGuard: 4.0% (2/48)

- **sCr ≥25%**
  - Controls: 14% (8/57)
  - RenalGuard: 4.0% (2/48)

- **sCr ≥0.5 mg/dl**
  - Controls: 7% (4/57)
  - RenalGuard: 4.0% (2/48)

Outline

• Terms and definitions
• Pathophysiology
• Risk prediction
• Strategies to improve safety
• Differences in iodinated contrast agents
Ultra-low CM Volumes Can Reduce Rate of CIN in Patients With CKD

Patient Characteristics
- N=185
- 36% DM
- Mean age = 71 y
- Mean SCr = 2.1 mg/dL
- Mean eGFR = 31 10 mL/min/1.73 m²

# The Evolution of Contrast Media

<table>
<thead>
<tr>
<th>Molecular Structure</th>
<th>Era</th>
<th>Examples</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="https://example.com/structure.png" alt="Ionic monomer" /> COO⁻Na⁺/Meg⁺</td>
<td>1950s</td>
<td>Ionic monomer</td>
<td>High osmolality, 5–8 × blood</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diatrizoate</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Iothalamate</td>
<td></td>
</tr>
<tr>
<td><img src="https://example.com/structure.png" alt="Nonionic monomer" /></td>
<td>1980s</td>
<td>Nonionic monomer</td>
<td>Low osmolality, 2–3 × blood, improved</td>
</tr>
<tr>
<td></td>
<td></td>
<td>lopamidol</td>
<td>hydrophilicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>lohexol</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ioversol</td>
<td></td>
</tr>
<tr>
<td><img src="https://example.com/structure.png" alt="Ionic dimer" /> COO⁻Na⁺/Meg⁺</td>
<td>1980s</td>
<td>Ionic dimer</td>
<td>Low osmolality, ~2× blood</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ioxaglate</td>
<td></td>
</tr>
<tr>
<td><img src="https://example.com/structure.png" alt="Nonionic dimer" /></td>
<td>1990s</td>
<td>Nonionic dimer</td>
<td>Isosmolality</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Iodixanol</td>
<td>Osmolality = blood</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Iotrolan)</td>
<td></td>
</tr>
</tbody>
</table>
Fig. 1. Changes in the renal resistance index (RRI) after intra-arterial administration of iopamidol and iodixanol. Following iopamidol, a statistically significant increase was observed in the RRI 1 min after the start of the injection, which returned to the basic value after 30 min (± 2.3) on average. Administration of iodixanol did not result in renal vasoconstriction, as expressed by constant values of the RRI.
Effects of Intra-Arterial and Intravenous Iso-Osmolar Contrast Medium (Iodixanol) on the Risk of Contrast-Induced Acute Kidney Injury: A Meta-Analysis

Peter A. McCullough\textsuperscript{a} Jeremiah R. Brown\textsuperscript{b}

\textsuperscript{a}St. John Providence Health System, Providence Hospital and Medical Centers, Providence Park Clinical Research, Providence Park Heart Institute, Detroit and Novi, Mich., and
\textsuperscript{b}Dartmouth Institute for Health Policy and Clinical Practice, and Section of Cardiology, Department of Medicine, Dartmouth Medical School, Lebanon, N.H., USA
Fig. 2. Meta-analysis of the incidence of CI-AKI (defined as ≥0.5 mg/dl increase in sCr from baseline) in trials reporting this outcome comparing IA iodixanol (IOCM) with LOCM.

<table>
<thead>
<tr>
<th>Study, year</th>
<th>IOCM</th>
<th>LOCM</th>
<th>Rel. Wt.</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chalmers [29], 1999</td>
<td>54</td>
<td>48</td>
<td>6.88</td>
<td>0.356 (0.072–1.752)</td>
</tr>
<tr>
<td>Jakobsen [30], 1996</td>
<td>8</td>
<td>8</td>
<td>3.32</td>
<td>0.333 (0.016–7.140)</td>
</tr>
<tr>
<td>Wessely [32], 2009</td>
<td>162</td>
<td>162</td>
<td>11.00</td>
<td>0.801 (0.548–1.173)</td>
</tr>
<tr>
<td>Hardiek [15], 2008</td>
<td>54</td>
<td>48</td>
<td>9.49</td>
<td>0.625 (0.258–1.512)</td>
</tr>
<tr>
<td>Solomon [16] (CARE), 2007</td>
<td>210</td>
<td>204</td>
<td>10.59</td>
<td>1.265 (0.730–2.193)</td>
</tr>
<tr>
<td>Juergens [35], 2009</td>
<td>91</td>
<td>100</td>
<td>10.75</td>
<td>1.196 (0.733–1.951)</td>
</tr>
<tr>
<td>Nie [37], 2008</td>
<td>106</td>
<td>102</td>
<td>9.04</td>
<td>0.398 (0.145–1.092)</td>
</tr>
<tr>
<td>Han [25] (abstract), 2010</td>
<td>828</td>
<td>828</td>
<td>11.23</td>
<td>0.147 (0.114–0.190)</td>
</tr>
<tr>
<td>Feldkamp [34], 2006</td>
<td>105</td>
<td>116</td>
<td>9.38</td>
<td>1.246 (0.500–3.109)</td>
</tr>
<tr>
<td>Hernández [38], 2009</td>
<td>118</td>
<td>132</td>
<td>8.08</td>
<td>0.301 (0.085–1.063)</td>
</tr>
<tr>
<td>Mehran [40] (ICON), 2009</td>
<td>72</td>
<td>74</td>
<td>10.24</td>
<td>0.657 (0.337–1.280)</td>
</tr>
</tbody>
</table>

Fig. 5. Compilation of pooled odds ratios for IA, IV, and mixed IA and IV meta-analyses of the incidence of CI-AKI (defined as ≥0.5 mg/dl increase in sCr vs. baseline) demonstrating a leftward shift in pooled estimates moving from IV, to mixed IV/IA, and IA trials. Pooled odds ratios from meta-analyses by Heinrich et al. [9], Reed et al. [10] and From et al. [11].
Contrast-induced acute kidney injury in renal transplant recipients after cardiac catheterization

V. Agrawal¹, A. Swami¹, R. Kosuri¹, M. AlSabbagh¹, M. Agarwal¹, D. Samarakunegavan², L.L. Rocher² and P.A. McCullough³

Table 3. Predictors of contrast-induced AKI in exact logistic regression model.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio (95% confidence intervals)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osmolarity of contrast (low-osmolar vs. iso-osmolar)</td>
<td>7.747 (1.101 – ∞)</td>
<td>0.0381</td>
</tr>
<tr>
<td>Use of N-acetylcysteine (yes vs. no)</td>
<td>0.291 (0.043 – 1.780)</td>
<td>0.2234</td>
</tr>
</tbody>
</table>

Figure 2. Contrast-induced AKI stratified by baseline estimated glomerular filtration rate of renal allograft (p = 0.441).
Calculate eGFR or CrCl
Assess contrast-induced AKI risk

- eGFR <30 mL/min
  - Start/continue statin
  - Discontinue NSAIDs, other nephrotoxic drugs, metformin

- Hospital admission
- Other strategies as for eGFR 30-59 ml
- **Isosmolar contrast**
- Nephrology consultation*
- Consider hemofiltration pre- and post-procedure

- Serum Cr before discharge or 24-72 h expectant care

- eGFR 30-59 mL/min
  - Start/continue statin
  - Discontinue NSAIDs, other nephrotoxic drugs, metformin

  - **IV isotonic (NaCl/NaHCO₃)**
    - 1.0-1.5 mL/kg/min 3-12 h pre and 6-24 h post
    - Ensure urine flow rate > 150 mL/h

  - **Isosmolar contrast**
    - DM, ACS, other added risks

  - Low osmolar contrast
    - No other added risks

  - Limit contrast volume
    - < 30 cc diagnostic
    - <100 cc diagnostic + intervention

  - Consider adjunctive medications as part of clinical trial†

- eGFR ≥60 mL/min
  - Discontinue metformin

  - Good clinical practice

* Plans should be made in case AKI occurs and dialysis is required.
† Potentially beneficial agents NAC in higher doses or longer course, deferiprone, others

Adapted from McCullough PA. J Am Coll Cardiol 2008;51:1419–28)
Improve Renal Blood Flow

Reduce Extravasation into Peritubular Space

Attenuate Inflammation/Oxidation

Reduce Direct Cellular Toxicity in Nephron

Current Preventive Strategies

1) Improve Renal Blood Flow - Pre-procedure IV NS or NaHCO₃
2) Minimize Contrast Volume

1) Reduce Tubular and Peritubular Contrast Stasis with Post-procedure IV NS or NaHCO₃
2) Antioxidant Tubular Protection with NAC or Ascorbic acid

1) Anticipate Volume Overload in ESRD and Dialyze Same Day
2) Pre-emptive Hemofiltration for Near Dialysis CKD Patients Before and After PCI

*Potential MOA's for Captisol+Iohexol
Pivotal Question

Reduce rates of “clinically meaningful events”
- Death
- Dialysis
- Rehospitalization (renal, cardiac, other)
- Heart failure
- Acute coronary syndromes
- Arrhythmias
- Stroke

Prevent contrast-induced AKI

Change long-term prognosis?
By what mechanisms?