PCI in Chronic Kidney Disease: RECOVER, CARE, LOCM-Related Studies, and Meta-Analysis

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Disclosures: Roxana Mehran

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How to Assess Renal Function?

**Abbreviated Modification of Diet in Renal Disease (MDRD) equation:**

\[
eGFR, \text{ ml/min/}1.73 \text{ m}^2 = 186 \times (\text{Serum Creatinine [mg/dL]})^{-1.154} \times (\text{Age} - 0.203 \times (0.742 \text{ if female}) \times (1.210 \text{ if African American}) \times \text{Body Weight [kg]}^{-1}
\]

**Cockcroft-Gault equation:**

\[
\text{Creatinine Clearance, ml/min} = \frac{(140 - \text{age}) \times \text{Body Weight [kg]}^*}{\text{Serum Creatinine mg/dL} \times 72}
\]

* Multiple by 0.8 in female
## Predictors of All-Cause Mortality to 7 Years BARI Trial + Registry

<table>
<thead>
<tr>
<th>Predictor</th>
<th>RR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD (baseline Cr &gt; 1.5 mg/dl)</td>
<td>2.31</td>
<td>1.63-3.28</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex, female vs. male</td>
<td>0.91</td>
<td>0.75-1.10</td>
<td>0.32</td>
</tr>
<tr>
<td>Race, black vs. non-black</td>
<td>1.40</td>
<td>1.04-1.89</td>
<td>0.028</td>
</tr>
<tr>
<td>Age, y</td>
<td>1.05</td>
<td>1.04-1.06</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral hypoglycemics</td>
<td>1.63</td>
<td>1.29-2.06</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Insulin</td>
<td>1.80</td>
<td>1.26-2.58</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PTCS vs. CABG</td>
<td>1.04</td>
<td>0.87-1.25</td>
<td>0.67</td>
</tr>
<tr>
<td>Interaction between PTCA and insulin-treated diabetics</td>
<td>1.73</td>
<td>1.11-2.69</td>
<td>0.02</td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior tobacco use</td>
<td>1.30</td>
<td>1.06-1.59</td>
<td>0.01</td>
</tr>
<tr>
<td>Tobacco use at baseline</td>
<td>1.82</td>
<td>1.42-2.33</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Major Causes of Acute Renal Failure In Cardiac Patients

1) Contrast Induced Nephropathy (CIN)

2) Acute Renal Failure after Cardiopulmonary Bypass Procedures
Contrast-Induced Nephropathy

Definition

• New onset or exacerbation of renal dysfunction after contrast administration in the absence of other causes:

increase by > 25%

or

absolute ↑ of > 0.5 mg/dL

from baseline serum creatinine

Occurs 24 to 48 hrs post–contrast exposure, with creatinine peaking 5 to 7 days later and normalizing within 7 to 10 days in most cases.
Preventive Trials
Strategies
Prevention of Contrast Induced Nephropathy

Hydration
Sodium Bicarbonate
NAC
Hemodialysis
Intrarenal Infusion

CIN Prevention

Brar, SS
1937 Patients Screened

317 Ineligible or No Consent

1620 Randomized

809 Received 0.9% Saline

124 Excluded From Primary End Point Analysis
Repeat Catheterization (n=78)
Incomplete Data (n=46)

685 for Primary End Point Analysis

811 Received 0.45% Sodium Chloride

113 Excluded From Primary End Point Analysis
Repeat Catheterization (n=59)
Incomplete Data (n=53)
Bypass Grafting (n=1)

698 for Primary End Point Analysis
Optimal Hydration
0.9% NS vs 0.45% NS

Mueller et al Arch Intern Med 2002
RenalGuard™ for CI-AKI prevention is designed to:

- Create and maintain high urine output
- Prevent contrast agents from clogging tubules
- Limit toxin exposure in kidneys
- Automated matched fluid replacement in real-time to reduce side effects associated with over- or under-hydration
## Results

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients who developed CIN</td>
<td>2/21 (9.5%)</td>
</tr>
<tr>
<td>Mean SCr change at 48-60 hrs</td>
<td>6.3%</td>
</tr>
<tr>
<td>Patients who achieved target urine output</td>
<td>21/23 (91%)</td>
</tr>
<tr>
<td>Patients with major complications possibly device or procedure related</td>
<td>2/23 (9%)</td>
</tr>
</tbody>
</table>
Prevention of CIN with Sodium Bicarbonate

Patients With Baseline Serum Creatinine >1.8 mg/dl who Underwent Contrast Exposure (Iopamidol in All)
N=137

- Sodium Chloride Hydration (154 mEq/L of Sodium Chloride)
  N=68
- Sodium Bicarbonate Hydration (154 mEq/L of Sodium Bicarbonate)
  N=69

Primary endpoint: increase in serum creatinine ≥25% within 2 days post-exposure

Merten GJ et al. JAMA, 2004;291:2328-2334
# Prevention of CIN with Sodium Bicarbonate: Results

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Sodium Chloride N=59</th>
<th>Sodium Bicarbonate N=60</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of CIN (%)</td>
<td>13.6%</td>
<td>1.7%</td>
<td>0.02</td>
</tr>
<tr>
<td>Incidence of CIN (↑SCr 0.5 mg/dL)</td>
<td>11.9%</td>
<td>1.7%</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Merten GJ et al. *JAMA*, 2004;291:2328-2334
REMEDIAL Trial

Pts with eGFR<40  
N=393

Excluded  N=42

Randomized  N=351

Saline + NAC  
N=118  
7 excluded  
111 included into analysis

Bicarbonate + NAC  
N=117  
9 excluded  
108 included into analysis

Saline+AA+NAC  
N=116  
9 excluded  
107 included into analysis

NAC = N-acetylcysteine, AA = ascorbic acid

Briguorio C. et al, Circulation 2007
## REMEDIAL Trial: Results

<table>
<thead>
<tr>
<th></th>
<th>Saline + NAC</th>
<th>Bicarbonate + NAC</th>
<th>Saline + Ascorbic Acid + NAC</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>N=111</td>
<td>N=108</td>
<td>N=107</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine increase by ≥25%</td>
<td>11 (9.9%)</td>
<td>2 (1.9%)*</td>
<td>10 (10.3%)</td>
<td>0.010</td>
</tr>
<tr>
<td>Serum creatinine increase by ≥0.5 mg/dL</td>
<td>12 (10.8%)</td>
<td>1 (0.9%)†</td>
<td>12 (11.2%)</td>
<td>0.026</td>
</tr>
<tr>
<td>eGFR decrease by ≥25%</td>
<td>10 (9.2%)</td>
<td>1 (0.9%)†</td>
<td>10 (10.3%)</td>
<td>0.018</td>
</tr>
</tbody>
</table>

*P=0.019, †P<0.01 vs. saline + NAC group

Design

- **DESIGN:** Prospective, randomized, parallel-group, single-center clinical evaluation of two hydration strategies for patients undergoing coronary angiography

- **OBJECTIVE:** To compare the incidence of CIN between periprocedural hydration with sodium bicarbonate vs. sodium chloride (0.9%, normal saline)

- **PRIMARY ENDPOINT:** Decrease in estimated GFR by \( \geq 25\% \) within 4 days of coronary angiography

353 patients enrolled between January 2006 and January 2007

- 178 patients assigned to sodium bicarbonate
  - 22 excluded
  - 156 evaluable patient

- 236 patients assigned to sodium chloride
  - 28 excluded
  - 147 evaluable patient

Hydration Protocol

- 3 mL/kg for 1 hr before the procedure
- 1.5 mL/kg during and for 4hrs post-procedure

MEENA

Meta-Analysis
Sodium Bicarbonate for the Prevention of CIN

Brar et al. cJASN 2009
Meta-Analysis

Study Flow

Dates: 1966 to 2008
Randomized Trials
Number of patients: 2,290

- 469 Citations identified
  - 168 from EMBASE
  - 261 from MEDLINE
  - 40 from Cochrane Library

- 8 Citations identified from conference proceedings

- 424 Citations excluded based on screening of titles or abstracts

- 53 Identified for further review

- 38 Citations excluded after full text review
  - Design was not correct
    - Unusual protocol
    - Difference between groups in volume administered & NAC dose

- 14 Articles included in meta-analysis (N=2,290)

Brar et al. cJASN 2009
### Forest Plot

**Summary of Published & Unpublished RCTs**

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
<th>Events, Bicarbonate</th>
<th>Events, Chloride</th>
</tr>
</thead>
<tbody>
<tr>
<td>Merten, 2004</td>
<td>0.12 (0.02, 0.55)</td>
<td>1/60</td>
<td>8/59</td>
</tr>
<tr>
<td>Saidin, 2006</td>
<td>2.17 (0.75, 6.25)</td>
<td>9/29</td>
<td>4/28</td>
</tr>
<tr>
<td>Brignon, 2007</td>
<td>0.19 (0.04, 0.82)</td>
<td>2/108</td>
<td>11/111</td>
</tr>
<tr>
<td>Chen, 2007</td>
<td>0.13 (0.02, 1.02)</td>
<td>1/55</td>
<td>7/50</td>
</tr>
<tr>
<td>Kim, 2007</td>
<td>0.98 (0.42, 2.28)</td>
<td>10/55</td>
<td>8/44</td>
</tr>
<tr>
<td>Ozcan, 2007</td>
<td>0.33 (0.11, 0.99)</td>
<td>4/88</td>
<td>12/88</td>
</tr>
<tr>
<td>Masuda, 2007</td>
<td>0.19 (0.05, 0.61)</td>
<td>2/30</td>
<td>10/29</td>
</tr>
<tr>
<td>Shaikh, 2007</td>
<td>0.75 (0.39, 1.44)</td>
<td>14/159</td>
<td>19/161</td>
</tr>
<tr>
<td>Lin, 2008</td>
<td>0.80 (0.24, 2.69)</td>
<td>4/30</td>
<td>5/30</td>
</tr>
<tr>
<td>Shavit, 2008</td>
<td>1.18 (0.30, 4.61)</td>
<td>5/51</td>
<td>3/36</td>
</tr>
<tr>
<td>Hegelin, 2008</td>
<td>1.00 (0.07, 13.64)</td>
<td>1/9</td>
<td>1/9</td>
</tr>
<tr>
<td>Brar, 2008</td>
<td>0.91 (0.56, 1.46)</td>
<td>26/158</td>
<td>30/165</td>
</tr>
<tr>
<td>Mairo, 2008</td>
<td>0.87 (0.52, 1.44)</td>
<td>25/250</td>
<td>29/252</td>
</tr>
<tr>
<td>Adolph, 2008</td>
<td>1.56 (0.27, 9.08)</td>
<td>3/71</td>
<td>2/74</td>
</tr>
</tbody>
</table>

**Heterogeneity**

\[ P = 0.02 \]
\[ I^2 = 48\% \]

**Summary:**
A summary statistic is not shown because of the significant heterogeneity that precluded pooling of these results.

*Brar et al. cJASN 2009*
Change in Renal Function

Published Randomized Trials

Δ Creatinine Sodium Bicarbonate (mg/dL)

Δ Creatinine Sodium Chloride (mg/dL)

Harm

Benefit

No effect

Improvement with Bicarb

Deterioration with Chloride

Brar et al. cJASN 2009
Meta-regression
Understanding Sources of Heterogeneity

Smaller trials show greater benefit

Trial Size

Large Trials
N=2290
12.6% vs. 10.7%
P=0.32
RR
0.85
95% CI
0.62 - 1.17

Merten Criteria
n=290

Small Trials
N=2290
13.5% vs. 6.7%
P=0.03
RR
0.50
95% CI
0.27 - 0.93

Summary: Positive effect only observed in small trials

Brar et al. cJASN 2009
Forest Plot
High Quality Studies

Quality Criteria

- Similar volume
- > 100 patients
- If NAC used, dose & route similar between groups
- No early termination

Summary: No overall benefit, but trend driven by studies with extreme treatment effects

Brar et al. cJASN 2009
N-ACETYLCYSTEINE (NAC)
CIN: Effect of n-Acetylcysteine

- Prospective, randomized
- 83 high risk patients
  - CrCl < 50 ml/min
  - Diabetes 33%
- IV CONTRAST for CT (75 ml of Low Osmolar CM)
- n-AC 600 bid x 2 days pre-
- CIN definition: creatinine increase of 0.5 mg/dl
- Hydration with 0.45% @ 1 ml/kg/h x 24 h

Tepel *NEJM* 2000

![](chart.png)
Relative Risk for Developing CIN after NAC

**Review:** Acetylcysteine and CIN  
**Comparison:** 01 NAC on CIN  
**Outcome:** 01 CIN

<table>
<thead>
<tr>
<th>Study or substury</th>
<th>NAC n/N</th>
<th>Control n/N</th>
<th>RR (Random) 95% CI</th>
<th>Risk Ratio (Random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allaqaband et al</td>
<td>8/45</td>
<td>6/40</td>
<td>1.19 (0.45, 3.12)</td>
<td></td>
</tr>
<tr>
<td>Briguori et al</td>
<td>6/92</td>
<td>10/91</td>
<td>0.59 (0.23, 1.57)</td>
<td></td>
</tr>
<tr>
<td>Diaz-Sandoval et al</td>
<td>2/25</td>
<td>13/29</td>
<td>0.18 (0.04, 0.72)</td>
<td></td>
</tr>
<tr>
<td>Durham et al</td>
<td>10/38</td>
<td>9/41</td>
<td>1.20 (0.55, 2.63)</td>
<td></td>
</tr>
<tr>
<td>Goldenberg et al</td>
<td>4/41</td>
<td>3/39</td>
<td>1.27 (0.30, 5.31)</td>
<td></td>
</tr>
<tr>
<td>Gomes et al</td>
<td>8/78</td>
<td>8/78</td>
<td>1.00 (0.40, 2.53)</td>
<td></td>
</tr>
<tr>
<td>Kay et al</td>
<td>4/102</td>
<td>12/98</td>
<td>0.32 (0.11, 0.96)</td>
<td></td>
</tr>
<tr>
<td>Nguyen-Ho et al</td>
<td>9/95</td>
<td>19/85</td>
<td>0.42 (0.20, 0.89)</td>
<td></td>
</tr>
<tr>
<td>Oldemeyer et al</td>
<td>4/49</td>
<td>3/47</td>
<td>1.28 (0.30, 5.41)</td>
<td></td>
</tr>
<tr>
<td>Pate et al</td>
<td>57/238</td>
<td>50/239</td>
<td>1.14 (0.82, 1.60)</td>
<td></td>
</tr>
<tr>
<td>RAPIDO</td>
<td>2/41</td>
<td>8/39</td>
<td>0.24 (0.05, 1.05)</td>
<td></td>
</tr>
<tr>
<td>Shyu</td>
<td>2/60</td>
<td>15/61</td>
<td>0.14 (0.03, 0.57)</td>
<td></td>
</tr>
<tr>
<td>Fung et al</td>
<td>8/46</td>
<td>6/45</td>
<td>1.30 (0.49, 3.46)</td>
<td></td>
</tr>
<tr>
<td>Total: (95% CI)</td>
<td>950</td>
<td>932</td>
<td>0.68 (0.46, 1.02)</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 124 (NAC), 162 (Control)  
Test for heterogeneity: Ch=27.54 (P=0.005), $I^2=56.4\%$  
Test for overall effect: Z=1.88 ($P=0.05$)
NEPHRIC Study: Protocol

Patients with diabetes and serum creatinine 1.5-3.5 mg/dl who underwent coronary or aortofemoral angiography

- Iso-osmolar, non-ionic Iodixanol [Visipaque]
  N=64
  Mean Contrast Volume = 163 ml
  PTCA – 17%

- Low-osmolar, non-ionic Iohexol [Omnipaque]
  N=65
  Mean Contrast Volume = 162 ml
  PTCA – 25%

- Randomized, double blind, prospective, multicenter
- Primary endpoint: peak increase in serum creatinine concentration @ 3 days after angiography

Aspelin P et al, NEJM, 2003; 348: 491-499
Primary Endpoint – Peak Increase in Scr from Baseline to Day 3

(µmol/l) \( p=0.002 \)

<table>
<thead>
<tr>
<th></th>
<th>Iodixanol (Visipaque)</th>
<th>Iohexol (Omnipaque)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>11.2 ±19.7</td>
<td>41.5 ± 68.6</td>
</tr>
<tr>
<td>Minimum</td>
<td>- 19.0</td>
<td>- 21.0</td>
</tr>
<tr>
<td>Max</td>
<td>74.0</td>
<td>331.0</td>
</tr>
</tbody>
</table>

\( n=62 \) \( n=64 \)
The ICON Trial: Protocol

Patients With Chronic Renal Insufficiency to Undergo Angiography/PCI
n=130

Ioxaglate (Hexabrix)
Low-osmolar, ionic

Iodixanol (Visipaque)
Isoosmolar, non-ionic

Primary Endpoint: Peak increase in the serum creatinine concentration between day 0 (when contrast medium was administered) and day 3

Mehran et al. JACC Int 2009
## ICON Trial: Increase of Serum Creatinine from Baseline (Secondary Study End Point)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Loxaglate (N=74)</th>
<th>Iodixanol (N=71)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 0.5 mg/dL</td>
<td>18.2 %</td>
<td>16.2 %</td>
<td>0.82</td>
</tr>
<tr>
<td>≥ 1 mg/dL</td>
<td>4.5 %</td>
<td>1.5 %</td>
<td>0.36</td>
</tr>
<tr>
<td>≥ 25%</td>
<td>24.2 %</td>
<td>16.2 %</td>
<td>0.29</td>
</tr>
<tr>
<td>≥ 25% or ≥ 0.5 mg/dL</td>
<td>24.2 %</td>
<td>16.2 %</td>
<td>0.29</td>
</tr>
</tbody>
</table>

Mehran et al. JACC Int 2009
RECOVER Trial – Renal Toxicity Evaluation and Comparison Between Visipaque and Hexabrix in Patients With Renal Insufficiency Undergoing Coronary Angiography

**Prospective, randomized trial**

- 300 patients with CrCl ≤ 60 ml/min
  - 151 pts. (140 pts. included in primary analysis) *iodixanol*
  - 149 pts. (135 pts. included in primary analysis) *ioxaglate*

**Primary endpoint – Incidence of CIN**
- Increase in SCr ≥ 25% or ≥ 0.5 mg/dl

Jo et al. JACC 2006; 48:924-30
RECOVER Trial – Incidence of CIN

<table>
<thead>
<tr>
<th></th>
<th>ioxaglate</th>
<th>iodixanol</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=300</td>
<td>7.9%</td>
<td>17.0%</td>
<td>0.021</td>
</tr>
</tbody>
</table>
**DESIGN:** Prospective, randomized, double-blind, parallel-group, multi-center clinical evaluation ipamidol-370 and iodixanol-320

**OBJECTIVE:** To compare the incidence of CIN between ipamidol-370 and iodixanol-320

**PRIMARY ENDPOINT:** Increase in SCr $\geq 0.5$ mg/dL from baseline to 45 to 120 hours after administration

482 patients enrolled between July 2005 and June 2006 in 25 clinical site in North America

14 patients withdrew consent

468 assigned to a treatment arm

230 patients assigned to Iopamidol-370

26 excluded

204 evaluable patient

236 patients assigned to Iodixanol-320

26 excluded

210 evaluable patient

Solomon, RJ et. al., Circulation 115, 3189 (2007)
CARE

- Iopamidol (n=204) vs. Iodixanol (n=210)

- p = 0.39
- p = 0.44
- p = 0.15

Incidence of CIN (%)

<table>
<thead>
<tr>
<th>Event</th>
<th>Iopamidol (%)</th>
<th>Iodixanol (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incr &gt;0.5 mg/dL in SCr</td>
<td>4.4</td>
<td>6.7</td>
</tr>
<tr>
<td>Incr &gt;25% in SCr</td>
<td>9.8</td>
<td>12.4</td>
</tr>
<tr>
<td>Decr &gt;25% in eGFR</td>
<td>5.9</td>
<td>10.0</td>
</tr>
</tbody>
</table>
Diabetic Subgroup

- Incr >0.5 mg/dL in SCr: p = 0.11
- Incr >25% in SCr: p = 0.37
- Decr >25% in eGFR: p = 0.20
Conclusions (1)

- CKD is one of the most important independent predictors of poor outcome post PCI
- CI-AKI remains a frequent source of acute renal failure and is associated with increased morbidity and mortality, and higher resource utilization
- Several factors predispose patients to CI-AKI
- Preventive measures pre procedure, as well as careful post procedure management should be routine in all patients
Conclusions (2)

- Hydration pre-PCI (12 hours recommended)
- D/C nephrotoxic drugs (NSAIDS, antibiotics, etc)
- Role of n-acetylcysteine is disputable
- Sodium bicarbonate may be useful, but need more definitive data
- Limit contrast agent volume
- Low-osmolar agents are better than high-osmolar
  - Within non-ionic contrast, the data are contradictory