Chronic Kidney Disease and Contrast Nephropathy: An Overview and Considerations in the PCI patient

Roxana Mehran, MD
Associate Professor of Medicine

Columbia University Medical Center
Cardiovascular Research Foundation
### 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>Tobacco use at baseline</td>
<td>1.82</td>
<td>1.42-2.33</td>
<td>&lt;0.001</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>Smoking history</td>
<td></td>
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<td>Interaction between PTCA and insulin-treated diabetics</td>
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<td>0.87-1.25</td>
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<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>
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<td>Age, y</td>
<td>1.05</td>
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<td>Diabetes mellitus</td>
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<td>Oral hypoglycemics</td>
<td>1.63</td>
<td>1.29-2.06</td>
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<td>Insulin</td>
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Freedom from Cardiac Death for Patients with CKD* and Diabetes (DM) BARI Trial + Registry

* CKD defined as baseline Cr > 1.5 mg/dl

Major Causes of Acute Renal Failure In Cardiac Patients

1) Radiocontrast Nephropathy (RCN)

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%
  - Absolute ↑ of > 0.5 mg/dL

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.
## Contrast-induced Nephropathy: Incidence, Risk Factors

1,826 consecutive pts undergoing PCI:
- ARF w/o dialysis = 144.6/1,000 or 14.5%
- ARF with dialysis = 7.7/1,000 or 0.7%

### Predictors of ARF +D

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR</th>
<th>CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cr Clearance</td>
<td>0.83</td>
<td>0.77-0.89</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>5.47</td>
<td>1.41-21.32</td>
<td>0.01</td>
</tr>
<tr>
<td>CONTRAST dose</td>
<td>1.008</td>
<td>1.002-1.013</td>
<td>0.01</td>
</tr>
</tbody>
</table>

## Risk Factors for CIN

<table>
<thead>
<tr>
<th>Patient-related Risk Factors</th>
<th>Procedure-related Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Renal insufficiency</td>
<td>• Multiple contrast media injection within 72 hrs</td>
</tr>
<tr>
<td>• Diabetes mellitus with renal insufficiency</td>
<td>• Intra-arterial injection site</td>
</tr>
<tr>
<td>• Age</td>
<td>• High volume of contrast media</td>
</tr>
<tr>
<td>• Volume depletion</td>
<td>• High osmolality of contrast media</td>
</tr>
<tr>
<td>• Hypotension</td>
<td></td>
</tr>
<tr>
<td>• Low cardiac output</td>
<td></td>
</tr>
<tr>
<td>• Class IV CHF</td>
<td></td>
</tr>
<tr>
<td>• Other nephrotoxins</td>
<td></td>
</tr>
<tr>
<td>• Renal transplant</td>
<td></td>
</tr>
<tr>
<td>• Hypoalbuminemia (&lt;35 g/l)</td>
<td></td>
</tr>
</tbody>
</table>

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Columbia University Medical Center

Cardiovascular Research Foundation
Scheme to define CIN risk score

Risk Factors

- Hypotension: 5
- IABP: 5
- CHF: 5
- Age >75 years: 4
- Anemia: 3
- Diabetes: 3
- Contrast media volume: 1 for each 100 cc³

Integer Score

Risk Factors

- Serum creatine > 1.5mg/dl: 4
- eGFR < 60ml/min/1.73 m²: 2 for 40 – 60, 4 for 20 – 40, 6 for < 20

Calculate

Risk Score | Risk of CIN | Risk of Dialysis
---|---|---
≤ 5 | 7.5% | 0.04%
6 to 10 | 14.0% | 0.12%
11 to 16 | 26.1% | 1.09%
≥ 16 | 57.3% | 12.6%

Mehran et al. JACC 2004;44:1393-1399.
CIN risk score derived from the development dataset predicted this complication in the validation set. (Red bars = development dataset; blue bars = validation dataset.)

CIN risk score

Contrast Induced Nephropathy, %

Risk Groups:
Risk Score:

Low ≤5
Moderate 6 to 10
High 11 to 15
Very High ≥16

7.5 8.4
14.0 12.8
26.1 29.9
57.3 55.9

Mehran et al. JACC 2004;44:1393-1399.
Prognostic significance of the proposed risk score for CIN extended to prediction of 1-year mortality. (Red bars = development dataset; blue bars = validation dataset.)

Mehran et al. JACC 2004;44:1393-1399.
Risk of Contrast-induced Nephropathy in Relation to Baseline Hematocrit

<table>
<thead>
<tr>
<th>Baseline Hct</th>
<th>1st Q</th>
<th>2nd Q</th>
<th>3rd Q</th>
<th>4th Q</th>
<th>5th Q</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;36.8%</td>
<td>23.3</td>
<td>13.3</td>
<td>11.8</td>
<td>10.6</td>
<td>10.3</td>
</tr>
<tr>
<td>≥36.8% to &lt;39.9%</td>
<td>13.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥39.9% to &lt;42.3%</td>
<td>11.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥42.3% to &lt;44.8%</td>
<td>10.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥44.8%</td>
<td>10.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$X^2$ for trend $P<0.0001$

Nikolsky, Mehran, et al. KI 2005
Prognostic Impact of CKD and Contrast Induced Nephropathy
Contrast-Induced Nephropathy Predicts Mortality

- Retrospective case control study of 16,248 hospitalized inpatients who received contrast procedures
- Cases with RCN (n = 183) matched with controls (n = 174):
  - APACHE II
  - Baseline serum creatinine
- RCN defined as > 25% increase in serum cr

Odds Ratio = 5.5 (adjusted for comorbidity)

Contrast-Induced Nephropathy: In-hospital Mortality

% In-hospital Death

No ARF: 1.1%
ARF: 7.1%
ARF + Dialysis: 35.7%

P < 0.0000001

McCullough et al. Am J Med 1997; 103-375
Preventive Trials
Specific DA-1 Agonism: Fenoldopam

A New Renal and Systemic Vasodilator
The CONTRAST Trial

Algorithm

300 patients
at increased risk for contrast nephropathy undergoing PCI

↓

Hydrate

Randomize

Fenoldopam

Matching placebo

1º prior to and 12 º after cath

Primary endpoint

Worsening renal insufficiency within 12-96 hours
CONTRAST STUDY: CIN

SCr at both baseline and during the 96° post drug administration period were available and analyzed at the central lab in 283 of 315 randomized patients (90%).

Fenoldopam (n=137)  Placebo (n=146)

<table>
<thead>
<tr>
<th>SCr increase by</th>
<th>Fenoldopam</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;25%</td>
<td>33.6%</td>
<td>30.1%</td>
</tr>
<tr>
<td>&gt;0.5 mg/dl</td>
<td>28.5%</td>
<td>24.0%</td>
</tr>
</tbody>
</table>

OR [95% CI] = 1.11 [0.79, 1.57]  P=0.61

P=0.84

Mean max SCr change (mg/dl)

0.32  P=0.27

Stone GW, et al. ACC-2003
CONTRAST: 30-Day Adverse Events

30-day incidence of death, MI or dialysis:
- With CIN: 12.2%  \( p=0.02 \)
- Without CIN: 4.1%

Stone GW, et al. ACC-2003
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

<table>
<thead>
<tr>
<th>CIN (%)</th>
<th>Control (42)</th>
<th>AC (41)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>21%</td>
<td>2%</td>
</tr>
</tbody>
</table>

p = 0.01
N-acetylcysteine (NAC) and contrast-induced nephropathy: a meta-analysis of 13 randomized placebo controlled trials

- 1892 pts. undergoing coronary angiography
- All hydrated w/ IV fluids and low-osm nonionic CM
- Impaired renal function (> 1.2 mg/dL)
- Treated with NAC oral or intravenously
- CIN defined as increase in creatinine ≥0.5 mg/dL or ≥25% from baseline to 48 hrs.

- 4 of 13 trials reported statistically significant reduction in CIN after NAC
- Overall nonsignificant 32% reduction in the risk for CIN after NAC (combined RR 0.68, 95% CI 0.46-1.01)

Relative risk for developing CIN after NAC

Type of Contrast Media
Meta-analysis: High vs. Low Osm Contrast Media

- 39 Trials - 5146 patients
- CIN ≥ 0.5 mg/dl
- CIN in 7% of all patients
- CIN in 30% of CRI patients
- For CRI, NNT=8 (treat 8 to prevent 1 CIN case)
- Low osmolal group included Ioxaglate (Hexabrix); Iodixanol (Visipaque) not studied

Barrett and Carlisle  *J Am Soc Nephrol* 92;
The NEPHRIC Study

*Nephrotoxicity in High-risk Patients*

*a Double Blind Randomized Multicentre Study of Iso-osmolar and Low-osmolar Non-ionic Contrast Media*
Patients with diabetes and serum creatinine 1.5-3.5 mg/dl who underwent coronary or aortofemoral angiography

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

### Primary Endpoint – Peak Increase in Scr from Baseline to Day 3

(\(\mu\text{mol/l}\)) \(p=0.002\)

<table>
<thead>
<tr>
<th></th>
<th>Iodixanol</th>
<th>Iohexol</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n)</td>
<td>62</td>
<td>64</td>
</tr>
<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>
The ICON Trial: Protocol

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

Ioxaglate (Hexabrix)
Iodixanol (Visipaque)

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

Mehran et al. TCT 2006
## ICON: Baseline Clinical Features

<table>
<thead>
<tr>
<th>Feature</th>
<th>Pooled</th>
<th>Pooled</th>
</tr>
</thead>
<tbody>
<tr>
<td>N patients</td>
<td>145</td>
<td>31.0 %</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>45.5 %</td>
<td>74.5 %</td>
</tr>
<tr>
<td>Insulin controlled</td>
<td>15.2 %</td>
<td>25.7 %</td>
</tr>
<tr>
<td>Hypertension</td>
<td>87.6 %</td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>82.1 %</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>60.7 %</td>
<td></td>
</tr>
<tr>
<td>PVD</td>
<td>26.2 %</td>
<td></td>
</tr>
<tr>
<td>Unstable angina</td>
<td></td>
<td>2.1 %</td>
</tr>
<tr>
<td>Previous exposure to contrast</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous contrast nephropathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior CHF</td>
<td></td>
<td>25.7 %</td>
</tr>
<tr>
<td>CrCl (cc/min)</td>
<td>45 ± 17</td>
<td></td>
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</table>

CrCl (cc/min): 45 ± 17
Primary Study Endpoint
Mean Increase in Creatinine

<table>
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<tr>
<th>Ioxaglate</th>
<th>Iodixanol</th>
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<tbody>
<tr>
<td>0.35</td>
<td>0.20</td>
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P (t-test) = 0.1486
P (Wilcoxon) = 0.08
### Increase of Creatinine from Baseline

**Secondary Study End Point**

<table>
<thead>
<tr>
<th>Creatinine Level</th>
<th>Ioxaglate</th>
<th>Iodixanol</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td>( \geq 0.5 \text{ mg/dL} )</td>
<td>18.2 %</td>
<td>16.2 %</td>
<td>0.82</td>
</tr>
<tr>
<td>( \geq 1 \text{ mg/dL} )</td>
<td>4.5 %</td>
<td>1.5 %</td>
<td>0.36</td>
</tr>
<tr>
<td>( \geq 25% )</td>
<td>24.2 %</td>
<td>16.2 %</td>
<td>0.29</td>
</tr>
<tr>
<td>( \geq 25% \text{ or } \geq 0.5 \text{ mg/dL} )</td>
<td>24.2 %</td>
<td>16.2 %</td>
<td>0.29</td>
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N=74 for Ioxaglate, N=71 for Iodixanol.
Hydration
Optimal Hydration Regimen

Mueller et al.  *Arch Intern Med* 2002
Optimal Hydration

0.9 NS vs 0.45 NS

Mueller et al Arch Intern Med 2002
Prevention of CIN with Sodium Bicarbonate

Patients With Baseline Serum Creatinine 1 to 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 $\geq 25\%$ 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>
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Merten GJ et al. JAMA, 2004;291:2328-2334
**REMEDIAL trial**

- Eligible: 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
## Results – REMEDIAL trial

<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

Briguorio C. et al, Circulation 2007
A Randomized Controlled Trial for the Prevention of Contrast Induced Nephropathy with Sodium Bicarbonate in Persons Undergoing Coronary Angiography (MEENA)

Somjot S. Brar, MD
Kaiser Permanente
Los Angeles Medical Center
Study Flow

353 Patients Undergoing Coronary Angiography, GFR ≤60

Sodium Chloride

- 178 Patients
- 22 Excluded*
  - 6 Had early CABG
  - 3 Had Early PCI
  - 11 Had Incomplete Follow Up Lab Data
  - 2 Had the Coronary Angiogram Canceled

- 156 Patients

Sodium Bicarbonate

- 175 Patients
- 28 Excluded*
  - 8 Had Early CABG
  - 3 Had Early PCI
  - 16 Had Incomplete Follow Up Lab Data
  - 1 Had the Coronary Angiogram Canceled

- 147 Patients

* p=0.33

(1:1)
GFR & Creatinine Endpoints

Incidence of Contrast Induced Nephropathy (%)

**Primary Endpoint**

- GFR: $\geq 25\%$ Decrease in GFR
- Creatinine: $\geq 25\%$ Increase in Creatinine

**Secondary Endpoint**

- GFR: $\geq 25\%$ Decrease in GFR
- Creatinine: $\geq 25\%$ Increase in Creatinine

- **GFR**
  - NaCl: 13.5
  - NaHCO3: 13.6
  - $p=0.97$

- **Creatinine**
  - NaCl: 15.4
  - NaHCO3: 16.3
  - $p=0.82$

*Note: The data represents the incidence of contrast-induced nephropathy with NaCl and NaHCO3 treatments.*
Targeted Renal Delivery

- Intra-Renal Drug Delivery
- Drug to Systemic Circulation
- Renal First-Pass Drug Elimination
Benephit™ Infusion System
(FlowMedica, Inc., Fremont, CA)
FDA (510K) Cleared January 2004
Conclusions (1)

- CKD is common in patients with CAD and CAD is common in patients with CKD.
- CKD is one of the most important single independent predictors of poor outcome.
- CIN remains a frequent source of acute renal failure and is associated with increased morbidity and mortality, and higher resource utilization.
- Baseline renal insufficiency, diabetes, dehydration predispose patients to contrast induced renal failure.
- 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, abx etc)
- n-acetylcysteine
- No Role for IV Fenoldopam
- Limit contrast agent volume
- Low Osmolar better than High Osmolar
  - Within non-ionic contrast, iso-osmolar is no better than low osmolar
- Sodium bicarbonate hydration may be useful, but still need more definitive data
- Role of Cooling Therapy is being examined: COOL RCN Study
- Role of local drug delivery for prevention of CIN requires further investigation