Early high-dose Rosuvastatin for Contrast-Induced Nephropathy Prevention in Acute Coronary Syndrome

The PRATO-ACS (Protective effect of Rosuvastatin and Antiplatelet Therapy On contrast-induced acute kidney injury and myocardial damage in patients with Acute Coronary Syndrome) Study

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on behalf of the PRATO-ACS investigators
Disclosures

We have no conflicts of interest
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Trial Registration clinicaltrial.gov Identifier: NCT01185938

PRATO-ACS study
Contrast Nephropathy
Role of Statins

Anti-lipidemic and pleiotropic properties (anti-oxidant, anti-inflammatory, anti-thrombotic) may have a nephro-protective effect improving endothelial function and reducing oxidative stress.

Uncertainties include:
- type and dose
- timing
- target population

PRATO-ACS study
Study Hypothesis

On-admission high-dose statins for CI-AKI prevention in ACS patients

Does early high-dose hydrophilic statin rosvuastatin - in addition to standard preventive measures (hydration and N-acetylcysteine) - exert beneficial effects against CI-AKI in statin-naïve patients with NSTE-ACS scheduled for early invasive strategy?
Methods

Inclusion criteria

All consecutive statin-naïve NSTE-ACS patients admitted to CCU and scheduled for early invasive strategy

Study period: July 2010-August 2012
Methods

Exclusion criteria

- Emergency (within 2 hrs) angiography
- Acute renal failure or ESRF requiring dialysis
- Baseline serum creatinine ≥ 3 mg/dl
- Contraindications to statin treatment
- Contrast administration within the last 10 days
- Refusal to consent

PRATO-ACS study
Methods

Study Design

Statin-naive & Early Invasive Strategy NSTE-ACS patients

Contrast

CCI-Admission

~ 24 H

Hydration, N-Acetylcystein

Coronary Angiography ± PCI

Rosuvastatin
40 mg (LD) then 20 mg/day

Controls

R

Primary Endpoint:
↑ Cr ≥ 0.5 mg/dl or ≥ 25 % within 72 hrs of contrast exposure

Sample size: assumed 18% CI-AKI in control and 50% reduction in treatment. With a 80% statistical power and 2-sided type 1 error of 5%; 15% drop out → ~ 540 pts
Methods

Additional End-points

1. CI-AKI defined by other criteria:

\[ \uparrow \text{Cr} \geq 25\% \text{ or } \geq 0.5 \text{ mg/dl within 48 hrs} \]
\[ \uparrow \text{Cr} \geq 0.3 \text{ mg/dl within 48 hrs} \]
\[ \uparrow \text{Cr} \geq 0.5 \text{ mg/dl within 72 hrs} \]
\[ \uparrow \text{Cr} \geq 0.3 \text{ mg/dl within 72 hrs} \]
\[ \downarrow \text{eGFR} \geq 25\% \text{ within 72 hrs} \]
Methods

Additional End-points

2. CI-AKI in pre-specified subgroups

- Age < or ≥ 70 yrs
- Gender
- Diabetes mellitus
- Creatinine Clearance < / ≥ 60 ml/min
- LV-EF ≤ / > 45%
- CI-AKI Mehran risk score ≤ / > 5
- Contrast volume administered ≤ / > 140 ml
- PCI procedure
- Clinical Risk Level (at least one of the following):
  - Age ≥ 70
  - Diabetes mellitus
  - Creatinine Clearance < 60 ml/min
  - LV-EF ≤ 45%
Methods
Additional End-points

3. Adverse Clinical Events (30 days):

- Acute renal failure requiring dialysis
- Persistent renal damage*
- All-causes mortality
- Myocardial infarction
- Stroke

*↓ eGFR ≥ 25% within 1 month in CI-AKI pts
Methods

Additional Protocol Details

Antiplatelet treatment:
ASA (300 mg LD, 100 mg/day MD)
Clopidogrel (600 mg LD, 150 mg/day → discharge)

- Hydration i.v. 12 hrs pre and post contrast medium (isotonic saline 1 ml/kg/h or 0.5 ml/kg/h if LV-EF ≤ 40%)
- Oral N-Acetylcysteine 24 hrs pre and post contrast medium (2400 mg/day)
- Nonionic, dimeric iso-osmolar contrast medium (Iodixanol) & Power injector (AC/ST)

At discharge: Clopidogrel 75 mg/day, ASA 100 mg/day &

Rosuvastatin group

Discharge

Rosuvastatin
20 mg/day
(10 mg/day if CrCL < 30 ml/min)

Controls

Atorvastatin
40 mg/day
Statin-naive & Early Invasive Strategy NSTE-ACS patients

Randomized
n = 543

Rosuvastatin
n = 271

- Excluded = 19
  - no angiography = 9
  - no 72 hrs creatinine = 10

CI-AKI analysis
n = 252

Controls
n = 272

- Excluded = 20
  - no angiography = 8
  - no 72 hrs creatinine = 12

CI-AKI analysis
n = 252
## Baseline Characteristics

### Clinical and Demographic

<table>
<thead>
<tr>
<th></th>
<th>Rosuvastatin</th>
<th>Control</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>66.2 ± 12.4</td>
<td>66.1 ± 13.5</td>
<td>0.91</td>
</tr>
<tr>
<td><strong>Age ≥ 70 years.%</strong></td>
<td>46.4</td>
<td>44.8</td>
<td>0.72</td>
</tr>
<tr>
<td>Female, %</td>
<td>34</td>
<td>34</td>
<td>0.93</td>
</tr>
<tr>
<td><strong>Body Mass Index</strong></td>
<td>26.2 ± 3.7</td>
<td>26.6 ± 4.4</td>
<td>0.35</td>
</tr>
<tr>
<td><strong>Clinical presentation, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSTE-MI</td>
<td>92.4</td>
<td>92.1</td>
<td>&gt;0.90</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>7.5</td>
<td>7.9</td>
<td>&gt;0.90</td>
</tr>
<tr>
<td><strong>Risk factors, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>56.7</td>
<td>54.8</td>
<td>0.65</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>19.8</td>
<td>22.6</td>
<td>0.45</td>
</tr>
<tr>
<td>Creatinine clearance &lt; 60ml/min</td>
<td>41.7</td>
<td>41.7</td>
<td>&gt;0.90</td>
</tr>
<tr>
<td>Previous MI</td>
<td>9.5</td>
<td>5.9</td>
<td>0.13</td>
</tr>
<tr>
<td>Previous PCI or CABG</td>
<td>11.9</td>
<td>7.1</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>Baseline LV EF (%)</strong></td>
<td>50 ± 9</td>
<td>50 ± 9</td>
<td>&gt;0.90</td>
</tr>
<tr>
<td>EF ≤ 45%</td>
<td>33.3</td>
<td>33.7</td>
<td>0.93</td>
</tr>
<tr>
<td>High Clinical Risk Level, %</td>
<td>71.4</td>
<td>67.1</td>
<td>0.29</td>
</tr>
</tbody>
</table>
## Baseline Characteristics

### Biochemical

<table>
<thead>
<tr>
<th></th>
<th>Rosuvastatin</th>
<th>Control</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine (mg/dl)</td>
<td>0.95 ± 0.27</td>
<td>0.96 ± 0.28</td>
<td>0.89</td>
</tr>
<tr>
<td>Creatinine Clearance (ml/min)</td>
<td>69.9 ± 24.4</td>
<td>69.3 ± 24.9</td>
<td>0.81</td>
</tr>
<tr>
<td>Haemoglobin (mg/dl)</td>
<td>14.1 ± 1.6</td>
<td>14.1 ± 1.6</td>
<td>0.77</td>
</tr>
<tr>
<td>hs-CRP (mg/dl)</td>
<td>0.43 (0.21-1.18)</td>
<td>0.52 (0.20-1.28)</td>
<td>0.57</td>
</tr>
<tr>
<td>cTn-I (ng/ml)</td>
<td>2.3 ± 5.1</td>
<td>2.5 ± 7.0</td>
<td>0.41</td>
</tr>
<tr>
<td>CK-MB (ng/ml)</td>
<td>19.2 ± 3.5.2</td>
<td>23.1 ± 48.8</td>
<td>0.34</td>
</tr>
<tr>
<td>LDL - Cholesterol (mg/dl)</td>
<td>135.2 ± 38.6</td>
<td>135.8 ± 42.7</td>
<td>0.85</td>
</tr>
<tr>
<td>HDL - Cholesterol (mg/dl)</td>
<td>40.2 ± 13.7</td>
<td>42.3 ± 13.3</td>
<td>0.08</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>119.7 ± 62.8</td>
<td>118 ± 73</td>
<td>0.78</td>
</tr>
<tr>
<td>Glycaemia (mg/dl)</td>
<td>131.7 ± 50.1</td>
<td>137.3 ± 53.4</td>
<td>0.23</td>
</tr>
</tbody>
</table>
# Procedural data

<table>
<thead>
<tr>
<th></th>
<th>Rosuvastatin</th>
<th>Control</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Randomization-to-Contrast time (hrs)</strong></td>
<td>22.5 (14 – 43)</td>
<td>23 (15 – 45.5)</td>
<td>0.79</td>
</tr>
<tr>
<td>Multivessel disease, %</td>
<td>48.8</td>
<td>47.6</td>
<td>0.78</td>
</tr>
<tr>
<td><strong>Contrast volume (ml)</strong></td>
<td>149.7 ± 86.8</td>
<td>138.2 ± 77.8</td>
<td>0.14</td>
</tr>
<tr>
<td>Contrast volume &gt;140 ml</td>
<td>46.4</td>
<td>40.1</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>Therapeutic strategy, %</strong></td>
<td></td>
<td></td>
<td>0.70</td>
</tr>
<tr>
<td>Medical treatment</td>
<td>21.4</td>
<td>23.8</td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td>10.7</td>
<td>11.9</td>
<td></td>
</tr>
<tr>
<td>PCI</td>
<td>67.9</td>
<td>64.3</td>
<td></td>
</tr>
<tr>
<td><strong>PCI data</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multivessel PCI</td>
<td>33.9</td>
<td>28.3</td>
<td>0.21</td>
</tr>
<tr>
<td><strong>Contrast volume (ml)</strong></td>
<td>183 ± 80</td>
<td>172 ± 72</td>
<td>0.18</td>
</tr>
<tr>
<td>Contrast volume &gt;140 ml, %</td>
<td>64.9</td>
<td>59.8</td>
<td>0.20</td>
</tr>
<tr>
<td><strong>CI-AKI Mehran risk score, median (IQR)</strong></td>
<td>3 (1 – 6)</td>
<td>2 (1 – 5)</td>
<td>0.36</td>
</tr>
<tr>
<td>( \leq 5 ), %</td>
<td>74.2</td>
<td>76.6</td>
<td></td>
</tr>
<tr>
<td>( &gt;5 ), %</td>
<td>25.8</td>
<td>23.4</td>
<td></td>
</tr>
</tbody>
</table>
CI-AKI Primary Endpoint
(≥ 0.5 or ≥ 25% within 72 hrs)

\[ OR_{\text{crude}} \, (95\% \, CI): \]
\[ 0.41 \, (0.22 - 0.74) \]

\[ OR_{\text{adjusted}} \, (95\% \, CI): \]
\[ 0.38 \, (0.20 - 0.71) \]

NNT = 12

*Adjusted for: Sex, Age, Diabetes, Hypertension, LDL-cholesterol, Creatinine Clearance, LV-EF, Contrast Volume, CI-AKI Risk Score

PRATO-ACS study
Additional Endpoints:

1. Different CI-AKI criteria

<table>
<thead>
<tr>
<th>Primary End-Point</th>
<th>Odds ratio adj (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(&gt;0.5 or 25% within 72 hrs)</td>
<td>0.38 (0.20 - 0.71)</td>
</tr>
</tbody>
</table>

Different CI-AKI criteria

- >0.5 or 25% within 48 hrs: 0.48 (0.25 - 0.91)
- > 0.3 within 48 hrs: 0.35 (0.15 - 0.83)
- > 0.3 within 72 hrs: 0.36 (0.17 - 0.77)
- > 0.5 within 72 hrs: 0.43 (0.15 - 1.23)
- eGFR < 25% within 72 hrs: 0.44 (0.23 - 0.86)

Statin better: Placebo better
Additional Endpoints:

2. Pre-specified Subgroups

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Odds ratio adj (95% CI)</th>
<th>p for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>$\geq 70$, $&lt; 70$</td>
<td>0.06</td>
</tr>
<tr>
<td>Sex</td>
<td>Male, Female</td>
<td>0.50</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Yes, No</td>
<td>0.49</td>
</tr>
<tr>
<td>Baseline EF (%)</td>
<td>$\leq 45$, $&gt; 45$</td>
<td>0.88</td>
</tr>
<tr>
<td>Cr. Clearance (ml/min)</td>
<td>$\leq 60$, $&gt; 60$</td>
<td>0.79</td>
</tr>
<tr>
<td>PCI</td>
<td>Yes, No</td>
<td>0.76</td>
</tr>
<tr>
<td>Clinical High-Risk</td>
<td>Yes, No</td>
<td>0.35</td>
</tr>
<tr>
<td>Contrast Volume (ml)</td>
<td>$&gt; 140$, $\leq 140$</td>
<td>0.51</td>
</tr>
<tr>
<td>CI-AKI score</td>
<td>$\leq 5$, $&gt; 5$</td>
<td>0.52</td>
</tr>
</tbody>
</table>
Additional Endpoints:

3. Adverse Clinical Events (30 days)

- Cumulative Renal Damage: Rosuvastatin 7.9, Control 3.6, p=0.036
- Persistent Renal Damage: Rosuvastatin 4.8, Control 2, p=0.15
- Dialysis: Rosuvastatin 0.8, Control 0, p=0.50
- MI: Rosuvastatin 0.8, Control 2, p=0.45
- Stroke: Rosuvastatin 0, Control 0, p=0.90
- Death: Rosuvastatin 0.8, Control 1.2, p=0.90

PRATO-ACS study
Conclusions-1

In statin-naïve patients with NSTE-ACS scheduled for early invasive strategy on-admission high-dose rosuvastatin:

• exerts additional preventive effects against CI-AKI (w/ hydration & N-Acetylcysteine);

• is associated to better short-term clinical outcome.

PRATO-ACS study
This study suggests that in NSTE-ACS patients scheduled for early invasive strategy high-dose statins should be given *on admission* and in any case must precede the angiographic procedure in order to reduce renal complications after contrast medium administration.