Early and Intensive Statin Treatment in Patients with Acute Coronary Syndromes

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Most fatalities occur within the first 30 days after ACS

- Acute MI
- Unstable angina
- Stable angina
PURSUIT: Retrospective analysis shows early mortality reduction with lipid-lowering therapy

- **NSTE ACS Discharged medication**
- **Lipid-lowering agents (n=2141)**
- **No lipid-lowering agents (n=6374)**

Log rank $\chi^2=87, p<0.001$

### Rationale of Statin therapy for ACS

<table>
<thead>
<tr>
<th>Benefit</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gives constant reduction in risk</td>
<td>most effective when absolute risk is highest</td>
</tr>
<tr>
<td>Other non-lipid-lowering effects</td>
<td>eg anti-inflammatory, effects on endothelial dysfunction</td>
</tr>
<tr>
<td>May stabilize plaque</td>
<td>maximum benefit when given early</td>
</tr>
<tr>
<td>Patient already in hospital</td>
<td>patient more likely to adhere to therapy</td>
</tr>
<tr>
<td>Discharged on statin therapy</td>
<td>underscores need for continued statins</td>
</tr>
</tbody>
</table>
# Intensive versus moderate lipid lowering with statins

## Statin started within 12 days of hospital presentation

**Table III. Details of lipid reduction therapy**

<table>
<thead>
<tr>
<th>Trial name</th>
<th>Statin arm</th>
<th>Less intensive lipid reduction arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-CAD[^9])</td>
<td>Pravastatin 40mg + cholestyramine +/- nicotinic acid (if needed to achieve LDL-C &lt;130 mg/dL). Those already at goal at enrollment, were started on pravastatin 20mg</td>
<td>Usual care. Lipid reduction therapy was determined by the family physician. Only 13 patients were treated with antilipid therapy (8 patients received a statin)</td>
</tr>
<tr>
<td>PTT[^10])</td>
<td>Pravastatin 40mg</td>
<td>Placebo</td>
</tr>
<tr>
<td>FLORIDA[^11])</td>
<td>Fluvastatin 80mg (given in a divided dose)</td>
<td>Placebo</td>
</tr>
<tr>
<td>Colivicchi et al.[^12])</td>
<td>Atorvastatin 80mg</td>
<td>The goal was for all patients to have levels of LDL-C &lt;100 mg/dL. For those already at goal, no lipid-lowering therapy was given. For all others, atorvastatin or current therapy was used to achieve goal. At follow-up, 12 patients received atorvastatin (mean dose 18mg), 14 patients received simvastatin (mean dose 19mg), and 8 patients received pravastatin (mean dose 37mg)</td>
</tr>
<tr>
<td>PROVE-IT[^13])</td>
<td>Atorvastatin 80mg</td>
<td>Pravastatin 40mg</td>
</tr>
<tr>
<td>ESTABLISH[^14])</td>
<td>Atorvastatin 20mg</td>
<td>Usual care. A cholesterol absorption inhibitor was initiated for LDL-C &gt;150 mg/dL</td>
</tr>
<tr>
<td>A-to-Z[^15])</td>
<td>Simvastatin 80mg for the duration of trial, after 1 month of simvastatin 40mg</td>
<td>Simvastatin 20mg for the duration of the trial, after 4 months of placebo</td>
</tr>
</tbody>
</table>

\[^9]\) PROVE-IT study

\[^10]\) PTT study

\[^11]\) FLORIDA study

\[^12]\) Colivicchi et al. study

\[^13]\) PROVE-IT study

\[^14]\) ESTABLISH study

\[^15]\) A-to-Z study

LDL-C = low-density lipoprotein-cholesterol.
Intensive versus moderate lipid lowering with statins

Fig. 3. Odds ratio (OR) of all-cause mortality for statin therapy compared with less intensive therapy at a mean follow-up of 23 months. The results demonstrate a long-term survival benefit from initiation of statin therapy.
Time of initiation of statin therapy
Early Benefits of High dose statin in ACS

**MIRACL**
- Placebo (n=1,540)
- Atorvastatin 80mg (n=1538)

**PROVE-IT**
- Pravastatin 40mg (n=2063)
- Atorvastatin 80mg (n=2099)

The Benefit of Aggressive LDL Lowering With Atorvastatin Was Apparent Within 30 Days

Schwartz GG et al. JAMA. 2001;285:1711-1718;
Very early initiation of Statin therapy

The mortality reduction of ACS patients from 10 statin RCTs statin therapy (n=4,030) vs control group (n=4,022)

<table>
<thead>
<tr>
<th>Sub-group</th>
<th>Number of Trials</th>
<th>Statin n/N</th>
<th>Control n/N</th>
<th>Odds Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean time for initiation of statin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 day</td>
<td>4</td>
<td>32/1911</td>
<td>51/1907</td>
<td>0.63 (0.40, 0.99)</td>
<td>0.045</td>
</tr>
<tr>
<td>2 days</td>
<td>2</td>
<td>2/86</td>
<td>2/82</td>
<td>0.91 (0.13, 6.37)</td>
<td>0.925</td>
</tr>
<tr>
<td>3 days</td>
<td>1</td>
<td>32/1538</td>
<td>30/1548</td>
<td>1.08 (0.65, 1.78)</td>
<td>0.778</td>
</tr>
<tr>
<td>Overall</td>
<td>7</td>
<td>66/3535</td>
<td>83/3537</td>
<td>0.80 (0.58, 1.12)</td>
<td></td>
</tr>
</tbody>
</table>

Test of Overall Effect p=0.194
I² = 0%
Remaining issues

- What about more intensive lipid lowering?

- How early should we start statin in patients with ACS?
Relationship between LDL-C levels and CV event rate

- **Rx** - Statin therapy
- **Pl** - Placebo
- **Pra** - pravastatin
- **Atv** - atorvastatin
- **Sim** - simvastatin

**Primary Prevention**

**Secondary Prevention**

- **4S - Rx**
- **4S - PI**
- **LIPID - Rx**
- **LIPID - PI**
- **CARE - Rx**
- **CARE - PI**
- **HPS - Rx**
- **HPS - PI**
- **PROVE-IT - Pra**
- **PROVE-IT - Atv**
- **PROVE-IT - Atv80**
- **IDEAL - Sim**
- **IDEAL - Atv**
- **ASCOT - Pl**
- **MEGA - Rx**
- **MEGA - Pl**

**Event rate (%)**

**LDL-C achieved mg/dL (mmol/L)**

- **0**
- **40** (1.0)
- **60** (1.6)
- **80** (2.1)
- **100** (2.6)
- **120** (3.1)
- **140** (3.6)
- **160** (4.1)
- **180** (4.7)
- **200** (5.2)

Remaining issues

• What about more intensive lipid lowering?
  – High does of rosuvastatin

• How early should we start statin in patients with ACS?
Lipid-Modifying Efficacy and safety of Rosuvastatin versus Atorvastatin in ACS

Patients (n=825), 18–75 years with:
- Non-ST or ST segment elevation ACS receiving optimal reperfusion therapy
- Evidence of CAD
- LDL-C >70mg/dL (~1.8 mmol/L) and fasting triglycerides <500 mg/dL (~5.6 mmol/L)

**Visit:**
- Week: 1 – 2 to 3 days
- Week: 2 – 1 day
- Week: 3 – 2
- Week: 4 – 6
- Week: 5 – 12

**LUNAR Study Design**

- Rosuvastatin 20 mg (n=277)
- Rosuvastatin 40 mg (n=270)
- Atorvastatin 80 mg (n=278)

Dietary run in / eligibility
Lipids CRP Safety
Lipids Safety
Lipids CRP Safety
Lipids CRP Safety

Rosuvastatin 40 mg Reduces LDL-C more than Atorvastatin 80 mg in ACS

Results of LUNAR

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Average change in LDL-C from baseline (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosuvastatin 20 mg</td>
<td>-42.0</td>
</tr>
<tr>
<td>Rosuvastatin 40 mg</td>
<td>-46.8*</td>
</tr>
<tr>
<td>Atorvastatin 80 mg</td>
<td>-42.7</td>
</tr>
</tbody>
</table>

*p=0.0219 vs atorvastatin 80 mg

Rosuvastatin 20 and 40 mg Increases HDL-C more than Atorvastatin 80 mg in ACS

*p<0.01 vs atorvastatin 80 mg; **p<0.001 vs atorvastatin 80 mg

Comparison of serious adverse events between two statins

<table>
<thead>
<tr>
<th>Variable</th>
<th>RSV20 (n = 267)</th>
<th>RSV40 (n = 263)</th>
<th>ATV80 (n = 269)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any serious adverse event</td>
<td>28 (10.5%)</td>
<td>23 (8.7%)</td>
<td>38 (14.1%)</td>
</tr>
<tr>
<td>Serious cardiovascular adverse event</td>
<td>9 (3.4%)</td>
<td>5 (1.9%)</td>
<td>6 (2.2%)</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>4 (1.5%)</td>
<td>3 (1.1%)</td>
<td>3 (1.1%)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>5 (1.9%)</td>
<td>2 (0.8%)</td>
<td>2 (0.7%)</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>0</td>
<td>0</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>Withdrawal owing to adverse event</td>
<td>10 (3.7%)</td>
<td>16 (6.1%)</td>
<td>25 (9.3%)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>5 (1.9%)</td>
<td>6 (2.3%)</td>
<td>17 (6.3%)</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>2 (0.8%)</td>
<td>1 (0.4%)</td>
</tr>
</tbody>
</table>
Lipid-Modifying Efficacy of Rosuvastatin versus Atorvastatin in ACS

The CENTAURUS Study

Patients (n=1115)
18–75 years
N-STEMI ACS, hospitalised within 24 h of onset
PCI planned
Evidence of CAD

Placebo (n~686)
Rosuvastatin 20 mg (n=406+)
Atorvastatin 80 mg (n=423+)

Visit: 1 Day: 1–6
PCI -4
20
3 1 month
4 3 months

ACS, eligibility, randomisation, lipids, tolerability, ECG
PCI AE
Lipids Tolerability ECG
Lipids Tolerability ECG
Lipids Tolerability ECG

ACS=acute coronary syndrome; PCI=percutaneous coronary intervention; CAD=coronary artery disease; AE=adverse event; ECG=electrocardiogram
+ n=number of patients randomized and received at least one dose of study medication

Lablanche JM. Arch Cardiovasc Dis 2010;103:160-169
# Effect of Rosuvastatin and Atorvastatin on the ApoB/ApoA-I Ratio

## Results From CENTAURUS

<table>
<thead>
<tr>
<th>ApoB/ApoA-I Change (%)</th>
<th>Rosuvastatin 20 mg</th>
<th>Atorvastatin 80 mg</th>
<th>Estimated Difference Median CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>At 1 month:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>-44.4</td>
<td>-42.9</td>
<td>-2.6 [-4.5, -0.0]</td>
<td>0.02</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>-43.1 ± 16.5</td>
<td>-40.5 ± 16.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>At 3 months:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>-44.4</td>
<td>-44.4</td>
<td>0.0 [-2.5, +1.7]</td>
<td>0.87</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>-41.2 ± 20.1</td>
<td>-41.7 ± 17.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ITT=intent-to-treat; Apo=apolipoprotein
Wilcoxon rank-sum test with Hodges-Lehman estimate of median difference between late rosvastatin 20 mg and late atorvastatin 80 mg

Lablanche JM. Arch Cardiovasc Dis 2010;103:160-169
Remaining issues

• What about more intensive lipid lowering?
  – High does of rosuvastatin

• How early should we start statin in patients with ACS?
  – Preloading of statin before percutaneous coronary intervention (PCI)
Pre-medication reduces Myocardial Damages

- PCI-related myocardial injury - The most frequent complication after PCI
- Can be significantly reduced and outcome improved with appropriate pharmacological treatment before PCI
- Medication for Anti-inflammation, Anti-thrombosis prior to PCI procedure
Potential mechanisms of early & late benefit of statins in ACS & PCI

- Inhibition of thrombus signaling cascade
  - ↓ thrombus formation

- ↓ Platelet activation

- ↓ coagulation

Lipid effects:
- ↓ LDL-C
- ↓ chylomicron and VLDL remnants, IDL, LDL-C
- ↓ AT-1 receptor
- ↓ VSMC proliferation

Lumen

Macrophages

Statins*

- Restore endothelial function:
  - ↑ endothelial progenitor cells
  - ↑ NO bioactivity
  - ↓ reactive oxygen species
- ↓ macrophages
- ↓ inflammation
- ↓ immunomodulation

*Statins may differ in terms of these effects/mechanisms

Angeli F et al. Ther Advance Cardiovasc Therapeutics 2012 6(4) 163-174
The original ARMYDA trial demonstrated that 7-day pretreatment with atorvastatin (40 mg/day) confers 81% risk reduction of peri-procedural MI in patients with Stable Angina undergoing elective PCI.

**Primary end point: Incidence of MI**

P = 0.025

<table>
<thead>
<tr>
<th>Trials</th>
<th>Patients, n</th>
<th>Type of Population</th>
<th>Clinical Presentation</th>
<th>Type of Statin</th>
<th>Statin Regimen Before PCI</th>
<th>Statin Regimen After PCI</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARMYDA</td>
<td>153</td>
<td>Statin naive</td>
<td>Stable angina</td>
<td>Atorvastatin</td>
<td>7-Day pretreatment with 40 mg/d vs placebo</td>
<td>Atorvastatin 40 mg/d</td>
<td>30 d</td>
</tr>
<tr>
<td>ARMYDA-ACS</td>
<td>171</td>
<td>Statin naive</td>
<td>NSTE-ACS</td>
<td>Atorvastatin</td>
<td>80 mg 12 h before PCI + 40 mg 2 h before PCI vs placebo</td>
<td>Atorvastatin 40 mg/d</td>
<td>30 d</td>
</tr>
<tr>
<td>ARMYDA-RECAPTURE</td>
<td>383</td>
<td>Statin-treated</td>
<td>53% Stable angina; 47% NSTE-ACS</td>
<td>Atorvastatin</td>
<td>80 mg 12 h before PCI + 40 mg 2 h before PCI vs placebo</td>
<td>Atorvastatin 40 mg/d</td>
<td>30 d</td>
</tr>
<tr>
<td>Briguori et al</td>
<td>451</td>
<td>Statin naive</td>
<td>92% Stable angina/ asymptomatic; 8% unstable angina</td>
<td>Atorvastatin</td>
<td>≥3-Day pretreatment (average 17 days) vs no statin pretreatment</td>
<td>The same statin as before PCI in the statin group and atorvastatin 20 mg/d in the control group</td>
<td>30 d</td>
</tr>
<tr>
<td>NAPLES II</td>
<td>668</td>
<td>Statin naive</td>
<td>Stable angina/ asymptomatic; 2% unstable angina</td>
<td>Atorvastatin</td>
<td>80 mg &lt; 24 h before PCI vs no-statin pretreatment</td>
<td>Atorvastatin 20 mg/d</td>
<td>30 d</td>
</tr>
<tr>
<td>STATIN STEM</td>
<td>171</td>
<td>Statin naive</td>
<td>STEMI</td>
<td>Atorvastatin</td>
<td>80 mg in the emergency room vs 10 mg</td>
<td>Atorvastatin 10 mg/d</td>
<td>30 d</td>
</tr>
<tr>
<td>Yeselka et al</td>
<td>200</td>
<td>Statin naive</td>
<td>Stable angina</td>
<td>Atorvastatin</td>
<td>2-Day pretreatment with 80 mg/d vs no statin pretreatment</td>
<td>NA</td>
<td>In-hospital</td>
</tr>
<tr>
<td>Yun et al</td>
<td>445</td>
<td>Statin naive</td>
<td>NSTE-ACS</td>
<td>Rosuvastatin</td>
<td>40 mg 16 h before PCI vs no statin pretreatment</td>
<td>Rosuvastatin 10 to 40 mg/d</td>
<td>30 d</td>
</tr>
<tr>
<td>Bozbas et al</td>
<td>93</td>
<td>Statin naive</td>
<td>Stable angina</td>
<td>Pravastatin</td>
<td>7-Day pretreatment with 10 mg/d vs 40 mg/d vs no statin pretreatment</td>
<td>Pravastatin 10 to 40 mg/d</td>
<td>In-hospital</td>
</tr>
<tr>
<td>Kinoshita et al</td>
<td>42</td>
<td>Statin naive</td>
<td>Stable angina</td>
<td>Atorvastatin</td>
<td>5-20 mg/d ≥ 2 wk before PCI to reach LDL-C &lt; 70 vs &lt; 100 mg/dL</td>
<td>A to rivastatin 5 to 20 mg/d</td>
<td>6 mo</td>
</tr>
<tr>
<td>Jia et al</td>
<td>228</td>
<td>Statin naive</td>
<td>29% STEMI; 71% NSTE-ACS</td>
<td>Simvastatin</td>
<td>7-Day pretreatment with 80 mg vs 20 mg</td>
<td>Simvastatin 20 mg/d</td>
<td>In-hospital</td>
</tr>
<tr>
<td>Hara et al</td>
<td>37</td>
<td>Statin naive or statin treated</td>
<td>NSTE-ACS</td>
<td>Atorvastatin</td>
<td>20 mg 24 h before PCI vs no statin pretreatment</td>
<td>Atorvastatin 20 mg/d</td>
<td>30 d</td>
</tr>
<tr>
<td>Cay et al</td>
<td>299</td>
<td>Statin naive</td>
<td>Stable angina</td>
<td>Rosuvastatin</td>
<td>40 mg 24 h before PCI vs no statin pretreatment</td>
<td>Rosuvastatin 10 to 40 mg/d</td>
<td>In-hospital</td>
</tr>
</tbody>
</table>

13 RCT's
3,341 patients
Statin Pretreatment in PCI: Meta-analysis
Incidence of Periprocedural MI

Patti et al. Circulation 2011;123:1622-32

Periprocedural myocardial infarction (%)

<table>
<thead>
<tr>
<th></th>
<th>High-dose statin</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=946 Normal CRP</td>
<td>7.8</td>
<td>10.9</td>
</tr>
<tr>
<td>N=915 Normal CRP</td>
<td>4.3</td>
<td>7.8</td>
</tr>
<tr>
<td>N=369 High CRP</td>
<td>12.3</td>
<td>10.9</td>
</tr>
<tr>
<td>N=365 High CRP</td>
<td>4.3</td>
<td>12.3</td>
</tr>
</tbody>
</table>

31% RRR $P=0.021$
68% RRR $P<0.001$
Statin Pretreatment in PCI:
Meta-analysis MACE at 30 Days in High Dose Statin vs Control Arms

MACE: Death, MI, TVR

Patti et al. Circulation 2011;123:1622-32

OR 0.56

Log-rank $P < 0.00001$
Statin treatment and ACS patient outcome?
→ Statin loading before PCI

• High dose Statin and Caucasian patients
  • ARMYDA-ACS: Atorvastatin 80/40mg
• High dose Statin and Korean patients
ARMYDA-ACS trial: Study design

771 pts with NSTE-ACS sent to early coronary angiography (<48 hours) Jan ’05 - Dec ‘06

Randomization (N=191)

Atorvastatin 80 mg 12 hrs pre-angio; further 40 mg 2 hrs before N=96

Placebo 12 hrs pre-angio; further dose 2 hrs before N=95

Coronary angiography

PCI atorvastatin N=86

PCI placebo N=85

20 pts excluded for indication to:
- medical therapy (N=8)
- bypass surgery (N=12)

30 days

40mg atorvast

30-day death, MI, TVR

2 nd and 3 rd blood samples (8 and 24 hrs post-PCI)

1 st blood sample (pre-PCI)

580 pts excluded for:
- 451 statin therapy
- 41 emergency angiography
- 43 LVEF <30%
- 30 contraindications to statins
- 15 severe renal failure

Primary combined end point:


CK-MB, troponin-I, myoglobin, CRP
ARMYDA-ACS

Individual and Combined Outcome Measures of the Primary End Point at 30 days

<table>
<thead>
<tr>
<th>Event</th>
<th>Atorvastatin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>4/86 (5%)</td>
<td>13/85 (15%)</td>
</tr>
<tr>
<td>MI</td>
<td>4/86 (5%)</td>
<td>13/85 (15%)</td>
</tr>
<tr>
<td>TVR</td>
<td>1/85 (2%)</td>
<td>14/85 (17%)</td>
</tr>
<tr>
<td>MACE</td>
<td>4/86 (5%)</td>
<td>14/85 (17%)</td>
</tr>
</tbody>
</table>

P=0.04
P=0.01

MI definition:
If normal baseline levels of CK-MB: post-procedural increase of CK-MB >2 times above UNL,

If elevated baseline levels of CK-MB: subsequent rise of >2 times in CK-MB from baseline value

Statin treatment and ACS patient outcome?
→ Statin loading before PCI

• High dose Statin and Caucasian patients
  • ARMYDA-ACS : Atorvastatin 80/40mg
• High dose Statin and Korean patients
  • Yun KH, et al : rosuvastatin 40/10mg
Clinical effect of high loading dose of rosvuastatin before PCI for Korean ACS patients

Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Control group (n = 220)</th>
<th>Rosuvastatin group (n = 225)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63 ± 11</td>
<td>64 ± 10</td>
<td>0.635</td>
</tr>
<tr>
<td>Male (%)</td>
<td>137 (62.3)</td>
<td>136 (60.4)</td>
<td>0.692</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>121 (55.0)</td>
<td>123 (54.7)</td>
<td>0.944</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>65 (29.5)</td>
<td>75 (33.3)</td>
<td>0.390</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>80 (36.4)</td>
<td>83 (36.9)</td>
<td>0.908</td>
</tr>
<tr>
<td>Left ventricular EF (%)</td>
<td>60 ± 10</td>
<td>61 ± 11</td>
<td>0.328</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.1 ± 0.5</td>
<td>1.0 ± 0.3</td>
<td>0.121</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>202 ± 49</td>
<td>196 ± 44</td>
<td>0.165</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>174 ± 129</td>
<td>175 ± 119</td>
<td>0.943</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dl)</td>
<td>45 ± 12</td>
<td>44 ± 10</td>
<td>0.575</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dl)</td>
<td>124 ± 40</td>
<td>122 ± 38</td>
<td>0.497</td>
</tr>
<tr>
<td>Troponin T (ng/ml)</td>
<td>0.2 ± 0.6</td>
<td>0.2 ± 0.7</td>
<td>0.982</td>
</tr>
<tr>
<td>Multi-vessel disease (%)</td>
<td>118 (53.6)</td>
<td>126 (56.0)</td>
<td>0.616</td>
</tr>
<tr>
<td>ACC/AHA B2/C lesion (%)</td>
<td>165 (75.0)</td>
<td>169 (75.1)</td>
<td>0.978</td>
</tr>
<tr>
<td>Drug-eluting stent (%)</td>
<td>212 (96.4)</td>
<td>216 (96.0)</td>
<td>0.841</td>
</tr>
<tr>
<td>Stent diameter (mm)</td>
<td>3.2 ± 0.4</td>
<td>3.2 ± 0.4</td>
<td>0.060</td>
</tr>
<tr>
<td>Stent length (mm)</td>
<td>46 ± 29</td>
<td>45 ± 24</td>
<td>0.707</td>
</tr>
<tr>
<td>Stent number</td>
<td>1.7 ± 1.0</td>
<td>1.7 ± 0.8</td>
<td>0.858</td>
</tr>
<tr>
<td>Maximal pressure (atm)</td>
<td>17 ± 4</td>
<td>17 ± 3</td>
<td>0.331</td>
</tr>
<tr>
<td>Multi-vessel stenting (%)</td>
<td>70 (31.8)</td>
<td>80 (35.6)</td>
<td>0.404</td>
</tr>
<tr>
<td>Use of GPI (%)</td>
<td>18 (8.2)</td>
<td>14 (6.2)</td>
<td>0.424</td>
</tr>
<tr>
<td>Procedural complications (%)</td>
<td>28 (12.7)</td>
<td>24 (10.7)</td>
<td>0.499</td>
</tr>
<tr>
<td>Periprocedural MI (%)</td>
<td>25 (11.4)</td>
<td>13 (5.8)</td>
<td>0.035</td>
</tr>
</tbody>
</table>

## Pre- and post-PCI medication

<table>
<thead>
<tr>
<th></th>
<th>Control group (n=220)</th>
<th>Rosuvastatin group (n=225)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-PCI medication (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEI</td>
<td>83 (38)</td>
<td>87 (39)</td>
<td>0.838</td>
</tr>
<tr>
<td>ARB</td>
<td>22 (10)</td>
<td>25 (11)</td>
<td>0.703</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>83 (38)</td>
<td>96 (43)</td>
<td>0.288</td>
</tr>
<tr>
<td>Calcium antagonist</td>
<td>23 (11)</td>
<td>28 (12)</td>
<td>0.510</td>
</tr>
<tr>
<td><strong>Post-PCI medication (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>217 (98.6)</td>
<td>222 (98.2)</td>
<td>1.000</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>220 (100)</td>
<td>225 (100)</td>
<td>1.000</td>
</tr>
<tr>
<td>ACEI or ARB</td>
<td>198 (90.0)</td>
<td>204 (90.7)</td>
<td>0.812</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>168 (76.4)</td>
<td>162 (72.0)</td>
<td>0.293</td>
</tr>
<tr>
<td>Calcium antagonist</td>
<td>80 (36.4)</td>
<td>82 (36.4)</td>
<td>0.986</td>
</tr>
<tr>
<td><strong>Statin therapy (%)</strong></td>
<td></td>
<td></td>
<td>0.499</td>
</tr>
<tr>
<td>Continued rosuvastatin 10 mg</td>
<td>191 (86.8)</td>
<td>192 (85.3)</td>
<td></td>
</tr>
<tr>
<td>Discontinued</td>
<td>4 (1.8)</td>
<td>1 (0.4)</td>
<td></td>
</tr>
<tr>
<td>Dose reduction to 5 mg</td>
<td>2 (0.9)</td>
<td>1 (0.4)</td>
<td></td>
</tr>
<tr>
<td>Dose elevation to 20 mg</td>
<td>2 (0.9)</td>
<td>2 (0.9)</td>
<td></td>
</tr>
<tr>
<td>Changed to other statin</td>
<td>21 (9.5)</td>
<td>29 (12.9)</td>
<td></td>
</tr>
</tbody>
</table>

PCI: percutaneous coronary intervention; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin II receptor blocker.
Incidence of periprocedural myocardial injury

Fig. 2. Incidence of periprocedural myocardial injury, defined by post-procedural increase of creatine kinase-MB >2 times above the upper limit of normal, in the control group and high dose rosuvastatin loading group.

Fig. 3. Incidence of troponin T (TnT) elevation in control group and rosuvastatin loading group.

Yun KH et al. Int J Cardiol. 2009;137:246-51
Long term benefits of rosuvastatin loading before PCI for ACS

Change in LDL-cholesterol


<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>24h after PCI</th>
<th>1 month</th>
<th>6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>445</td>
<td>429</td>
<td>354</td>
<td>311</td>
</tr>
<tr>
<td>Control group (mg/dl)</td>
<td>123.8 ± 40.0</td>
<td>117.3 ± 32.9</td>
<td>69.6 ± 21.6</td>
<td>72.3 ± 22.5</td>
</tr>
<tr>
<td>Rosuvastatin group (mg/dl)</td>
<td>121.6 ± 38.1</td>
<td>104.8 ± 29.1</td>
<td>72.8 ± 24.3</td>
<td>73.2 ± 24.9</td>
</tr>
<tr>
<td>p value</td>
<td>0.497</td>
<td>&lt;0.001</td>
<td>0.189</td>
<td>0.705</td>
</tr>
</tbody>
</table>
**Change in high-sensitivity CRP**

![Graph showing the change in high-sensitivity CRP levels over time.](image)

### Table: CRP Levels

<table>
<thead>
<tr>
<th>Time</th>
<th>Baseline (mg/l)</th>
<th>24h after PCI (mg/l)</th>
<th>1 month (mg/l)</th>
<th>6 months (mg/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>4.9 ± 8.7</td>
<td>15.9 ± 27.7</td>
<td>1.7 ± 2.8</td>
<td>1.4 ± 2.1</td>
</tr>
<tr>
<td>Rosuvastatin group</td>
<td>4.6 ± 8.7</td>
<td>9.2 ± 12.5</td>
<td>1.9 ± 3.9</td>
<td>1.7 ± 2.1</td>
</tr>
<tr>
<td>p value</td>
<td>0.656</td>
<td>&lt;0.001</td>
<td>0.366</td>
<td>0.133</td>
</tr>
</tbody>
</table>

Statin treatment and ACS patient outcome?
→ Statin loading before PCI

• High dose Statin and Caucasian patients
• High dose Statin and Korean patients
  • Yun KH, et al : rosuvastatin 40/10mg
• High dose statin and Asian patients
  • Wang Z, et al : Rosuvastatin 20mg/10mg
Effect of Rosuvastatin loading before PCI for ACS patients

215 patients with NSTE-ACS sent to undergo early coronary angiography (<48 hours)

Randomization (N=167)

Rosuvastatin Group (20 mg Rosuvastatin 2-4 hours before angiography)

Control Group (Placebo 2-4 hours before angiography)

48 patients excluded for the following:
- 34 Statin therapy
- 11 Emergency angiography
- 3 Renal failure, severe liver disease

CAG

42 patients excluded for the following:
- 16 Medical therapy
- 22 CABG
- 4 Normal coronary artery

PCI + Rosuvastatin 10mg N=62

PCI + Control 10mg N=63

Post-PCI therapy and laboratory examination

*MI definition:*

If normal baseline levels of CK-MB: post-procedural increase of CK-MB or cTnI >3 times above UNL,

If elevated baseline levels of CK-MB: subsequent rise of >3 times in CK-MB or cTnI from baseline value

20mg loading dose of rosvastatin prior to PCI decrease the incidence of MI

Effect of Rosuvastatin – hsCRP, IL-6 level

*P <0.01 versus pre-PCI
#P <0.01 versus the rosvastatin group

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

Anna Toso, MD
on behalf of the PRATO-ACS investigators
Statin-naive & Early Invasive Strategy NSTE-ACS patients

**Methods**

**Study Design**

- CCU-Admission
- Contrast
- CI-AKI

Rosuvastatin
40 mg (LD) then 20 mg/day

Controls

**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*
Study Flow

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
CI-AKI Primary Endpoint
(≥ 0.5 or ≥ 25% within 72 hrs)

OR\textsubscript{crude} (95% CI):
0.41 (0.22 - 0.74)

OR\textsubscript{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:

3. Adverse Clinical Events (30 days)

- **Cumulative Renal Damage**
  - Rosuvastatin: 3.6
  - Control: 7.9
  - 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: 2
  - Control: 0.8
  - p = 0.45

- **Stroke**
  - Rosuvastatin: 0
  - Control: 0
  - p = 0.90

- **Death**
  - Rosuvastatin: 0.8
  - Control: 1.2
  - p = 0.90

**PRATO-ACS study**
Summary

• Early and intensive statin treatment in patients with ACS improved clinical outcomes.

• High doses of Rosuvastain were more effective than high doses of Atorvastatin in reducing LDL-C and increasing HDL-C in ACS patients.

• High dose of rosuvastatin loading before PCI significantly improved 12-month clinical outcomes in patients with ACS who underwent an early invasive strategy.

• High dose rosuvastatin loading in statin-naïve patients with NSTE-ACS scheduled for early invasive strategy exerts additional preventive effects against CIN (w/ hydration & N-Acetylcysteine).
경청해주셔서 감사합니다
Lipid Levels after ACS LUNAR study

507 patients
STEMI 212
NSTEMI 176
UA 119

Figure 1: Mean Serum LDL-C, HDL-C, and TC Levels on Days 1, 2, and 4

ACS = acute coronary syndromes; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; STEMI = ST-segment elevation myocardial infarction; TC = total cholesterol; UA = unstable angina.