Early Statin Therapy in Acute Coronary Syndrome

The Faster, The Better!

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Angioplasty Summit 2005
Causes of Death Worldwide, 2001

Death / Millions

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>8.0</td>
<td>8.6</td>
</tr>
<tr>
<td>B</td>
<td>4.0</td>
<td>3.2</td>
</tr>
<tr>
<td>C</td>
<td>3.4</td>
<td>1.7</td>
</tr>
<tr>
<td>D</td>
<td>1.8</td>
<td>1.7</td>
</tr>
<tr>
<td>E</td>
<td>1.5</td>
<td>1.3</td>
</tr>
<tr>
<td>F</td>
<td>0.4</td>
<td>0.5</td>
</tr>
</tbody>
</table>

A: Cardiovascular disease
B: Cancer
C: Accidents
D: Respiratory disease
E: HIV/AIDS
F: Diabetes

(2001, WHO)
Drug-Eluting Stents

![Diagram showing the effect of Drug-Eluting Stents on restenosis rate compared to Balloon, BMS, and DES.]
Atherosclerosis is a diffuse process.

Lack of luminal obstruction does not mean a lack of atherosclerosis.
Prevention of acute coronary events must be the primary goal.

50% of patients with CAD presented with AMI or SCD.
Statin Therapy in CAD

Time from Index Coronary Events (months)

Stable CAD
- 4S (n=4444)
- HPS (n=20536)
- CARE (n=4159)
- LIPID (n=9014)

Acute Coronary Syndromes
- MIRACL (n=3086)
- PROVE-IT (n=4162)
- A-to-Z (n=4497)
Recurrent Events after ACS

AMI (n=1829)

UA (n=563)

Days after presentation

Number of events
Multiple Plaque Rupture

Incidence (%)

- IRA/ target lesion: 66%
- Non-IRA/ non-target lesion: 27% *
- Multiple plaque ruptures: 5% *

AMI (n=122)
SAP (n=113)

* p<0.01

AMI Data
Circulation 2004:110:92
Statin Therapy in ACS

• Are statins beneficial early post ACS?

• Does the degree of LDL lowering matter?
Risk reduction in patients with an ACS treated with lipid-lowering therapy.

Early benefit (in-hospital)
- Mayo Clinic
- PRISM trial

Late benefit (16 wk to 1y)
- Swedish Study
- Mayo Clinic
- PURSUIT/Gusto IIB
- In TIME II
  - prior lipid treatment
  - no prior lipid treatment
- OPUS/TIMI 16
- SYMPHONY

*Eur Heart J 2004:6:A32*
MIRACL: Reductions in Recurrent Ischemic Events

Atorvastatin 80 mg/d over 16 weeks in ACS patients (n=3086)

<table>
<thead>
<tr>
<th>Number at Risk</th>
<th>Time since randomization (weeks)</th>
<th>Cumulative incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>0</td>
<td>17.4%</td>
</tr>
<tr>
<td>Placebo</td>
<td>14.8%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>17.4%</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>17.4%</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>17.4%</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>17.4%</td>
</tr>
</tbody>
</table>

death, resuscitated cardiac arrest, nonfatal MI, or recurrent angina

Pravastatin can be safely administered within 24h of the onset of symptoms of an ACS, with a favorable but not significant trend in outcome at 30 days compared with placebo.
PROVE-IT

4,162 Patients With an ACS <10 Days, TC<240mg/dl

ASA + Standard Medical Therapy

- “Standard Therapy”
  - Pravastatin 40mg

- “Intensive Therapy”
  - Atorvastatin 80mg

2x2 Factorial: Gatifloxacin vs. Placebo

Duration: Mean 2-Year Follow-up (>925 Events)

Primary Endpoint: Death, MI, Documented UA Requiring Hospitalization, Revascularization (>30 Days After Randomization)
Among patients who have recently had an ACS, an intensive lipid-lowering statin regimen provides greater protection against death or major cardiovascular events than does a standard regimen.

- N=4,162 ACS (early invasive-3/4; multiple medications)

16% reduction:
death/MI/uAP/revascularization

p=0.005

PROVE-IT

% Patients with Event*
A to Z in Patients With ACS

- No early divergence in even rates
- A favorable trend toward reduction of MACE.

STEMI 40%, NSTEMI 60%
TC ≤ 250 mg/dl

Simvastatin 20mg
16.7%

Simvastatin 80mg
14.4%

dead, MI, readm & stroke: 11%↓, p=0.14
CHF: 28%↓, p=0.04
CV death: 25%↓, p=0.05

JAMA 2004:292:1307
# Intensive Statin Therapy in ACS

<table>
<thead>
<tr>
<th></th>
<th>A to Z</th>
<th>MIRAACL</th>
<th>PROVE-IT</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Patients</td>
<td>4,497</td>
<td>3,086</td>
<td>4,162</td>
</tr>
<tr>
<td>Δ LDL-C, mg/dl</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early</td>
<td>62</td>
<td>63</td>
<td>33</td>
</tr>
<tr>
<td>Late</td>
<td>15</td>
<td>NA</td>
<td>28</td>
</tr>
<tr>
<td>Δ CRP, %</td>
<td>17</td>
<td>34</td>
<td>39</td>
</tr>
<tr>
<td>Event reduction, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early</td>
<td>0</td>
<td>16</td>
<td>18</td>
</tr>
<tr>
<td>Late</td>
<td>11</td>
<td>NA</td>
<td>16</td>
</tr>
<tr>
<td>Myopathetic event*</td>
<td>9(0.4%)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*CK higher than 10 times the upper limit of normal
In-Hospital Initiation of Lipid-Lowering Therapy After Coronary Intervention as a Predictor of Long-term Utilization

The initiation of lipid-lowering therapy in the inpatient setting increases the rate of its subsequent use, making this an important method of ensuring appropriate secondary prevention.

Retrospective analysis (PCI patients)

- Inpatient (n=175)
- Outpatient (n=1951)

<table>
<thead>
<tr>
<th>Time After Discharge</th>
<th>Inpatient (%)</th>
<th>Outpatient (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 d</td>
<td>81</td>
<td>13</td>
</tr>
<tr>
<td>6 mo</td>
<td>77</td>
<td>25</td>
</tr>
</tbody>
</table>

Arch Intern Med 2003; 163: 2576
Summary

• Early initiation of statin therapy is safe and may have a benefit in the reduction of ischemic events in ACS patients.

• Early statin therapy should be considered in all patients admitted with ACS.
Intensive inhibition of HMG-CoA reductase

HMG-CoA reductase is an ubiquitous enzyme which is present in vascular and inflammatory cells as well as in hepatocytes.

Isoprenoids bind a number of G-proteins such as Rho and Ras by prenylation. Rho activates a number of nuclear TF such as NFkB.
High-Dose Atorvastatin in the MIRACL Study

Compared with placebo, atorvastatin significantly reduced CRP and SAA at 16 weeks follow-up.

High-dose atorvastatin potentiated the resolution of inflammation after ACS, reinforce the concept of early lipid lowering soon after ACS.
The impact of aggressive therapy with atorvastatin (LDL goal of <100 mg/dL) vs moderate therapy (usual care with various statins) on plaque volume and content using ICUS.
Landmark Clinical Trials: Statins as a class reduce mortality and morbidity.

PROVE-IT and REVERSAL: LDL-C reduction alone does not explain all of the differences in efficacy.

Statin Difference
Are they all the same?
Early Benefits of Atorvastatin in ACS

- Placebo (n=1,540)
- Atorvastatin 80mg (n=1538)
- Pravastatin 40mg (n=2063)
- Atorvastatin 80mg (n=2099)

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

Time Since Randomization (Months)
Early Benefits Not Seen With Pravastatin or Simvastatin in Secondary Prevention

CARE

LIPID

HPS

Pravastatin

Placebo

Pravastatin

Placebo

Simvastatin

Placebo

Time (years)

Time (years)

Time (years)

p=0.002

p=0.001

p=0.014

0 1 2 3 4 5

0 1 2 3 4 5

0 1 2 3 4 5
Patients who have low CRP levels after statin therapy have better clinical outcomes than those with higher CRP levels, regardless of the resultant level of LDL cholesterol.

PROVE-IT: CRP Analysis

Patients who have low CRP levels after statin therapy have better clinical outcomes than those with higher CRP levels, regardless of the resultant level of LDL cholesterol.
Probability to Get in the Best Group: 4-Fold Difference!

PROVE-IT: CRP Analysis

- Pravastatin
- Atorvastatin

<table>
<thead>
<tr>
<th>LDL</th>
<th>CRP</th>
<th>Pravastatin</th>
<th>Atorvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;70</td>
<td>&gt;2</td>
<td>45</td>
<td>20</td>
</tr>
<tr>
<td>&gt;70</td>
<td>&lt;2</td>
<td>35</td>
<td>15</td>
</tr>
<tr>
<td>&lt;70</td>
<td>&gt;2</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>&lt;70</td>
<td>&lt;2</td>
<td>15</td>
<td>5</td>
</tr>
</tbody>
</table>
The progression rate at any level of LDL-C reduction was lower with atorvastatin compared with pravastatin.
## Statin Differences

- **Head-to-head comparison**

There is no doubt that all statins have had an immense impact on the way we manage patients with CAD.

Recent clinical data suggest that they are not equally effective for all patient subsets.
Conclusions

- Overall, statin therapy should be initiated in the setting of ACS, regardless of plasma lipid values.

- The results of recent clinical trials herald the beginning of a new era of intensive statin therapy.