5th Asian Pacific Congress of Heart Failure
BEXCO BUSAN, Korea, April 17, 2010

Upstream atorvastatin therapy to reduce myocardial damage

Giuseppe Patti, MD, FACC, Department of Cardiovascular Sciences, Campus Bio-Medico University of Rome
Threshold of post-PCI CK-MB elevation and 1-year mortality risk (seven studies; 23,230 pts undergoing PCI)

The first ARMYDA trial has demonstrated that a 7-day pretreatment with atorvastatin (40 mg/day) is associated with 81% risk reduction of peri-procedural myocardial infarction in patients with stable angina undergoing elective PCI.
ARMDA-ACS (Atorvastatin for Reduction of MYocardial Damage during Angioplasty-Acute Coronary Syndromes) trial

Randomized, placebo-controlled, double blind, prospective trial, evaluating whether pretreatment with atorvastatin load influences outcome in patients with acute coronary syndromes undergoing early PCI

Chairman: Germano Di Sciascio

Principal investigator: Giuseppe Patti

Investigators: Vincenzo Pasceri, Giuseppe Colonna, Gennaro Sardella, Marco Miglionico, Dionigi Fischetti, Andrea D’Ambrosio, Bibi Nguyen, Antonio Montinaro, Annunziata Nusca
ARMYDA-ACS trial: Study design

580 patients excluded for:
- 451 statin therapy
- 41 emergency angiography (<48h)
- 43 ejection fraction <30%
- 30 contraindications to statins
- 15 severe renal failure

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

771 Patients
with
NSTE-ACS
sent to
early coronary
angiography
(<48 hours)

Randomization (N=191)

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

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

PCI atorvastatin
N=86

PCI placebo
N=85

Coronary
angiography

Primary end point:
30-day occurrence
of death, MI, TVR

30 days

1st blood
sample
(before PCI)

2nd and 3rd
blood samples
(8 and 24 hours
after PCI)

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

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

- Death: 5% (Atorvastatin) vs 2% (Placebo), P=0.04
- MI: 15% (Atorvastatin) vs 17% (Placebo), P=0.01
- TVR: 6% (Atorvastatin) vs 6% (Placebo)
- MACE: 17% (Atorvastatin) vs 17% (Placebo)

Composite Primary End Point (88% RRR)

Possible mechanisms of the clinical benefit:

Improvement of endothelial function and vasodilation of coronary microvessels

N=32 subjects without CAD randomized to placebo or atorvastatin (single dose of 40 mg) and undergoing at baseline and after 1 hour transthoracic doppler evaluation of LAD

Coronary flow velocity reserve
(hyperemic/basal peak diastolic velocity)

P<0.01

Hinoi T, et al. Am J Cardiol 2005
Possible mechanisms of the clinical benefit:

**Antithrombotic effects**

N=30 hypercholesterolemic pts randomized to diet or atorvastatin (10 mg/d) for 3 days

PLT CD40L expression (AU)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Atorvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>43±15</td>
<td>46±15</td>
</tr>
<tr>
<td>After</td>
<td>45±12</td>
<td>32±6</td>
</tr>
<tr>
<td>p-value</td>
<td></td>
<td>P&lt;0.01</td>
</tr>
</tbody>
</table>

Prothrombin fragment F1+2 (nM)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Atorvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>2±1</td>
<td>2±1</td>
</tr>
<tr>
<td>After</td>
<td>1.4±0.4</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td></td>
<td>P&lt;0.05</td>
</tr>
</tbody>
</table>

Possible mechanisms of the clinical benefit:

Attenuation of endothelial activation

**ARMYDA-CAMs RESULTS**

P=0.0001

P=0.0008

P=0.0001

P=0.33

ICAM-1  E-selectin  VCAM-1

Atorvastatin  Placebo

Patti G et al. J Am Coll Cardiol 2006;48:1560
Correlation between CRP levels and clinical outcome at 18 months in 73 patients undergoing PCI

P = 0.09

CRP Quartiles

MACE (%)
Possible mechanisms of the clinical benefit:

Anti-inflammatory effects

ARMYDA-ACS: Secondary end point
Post-PCI percent increase of CRP levels from baseline

P = 0.01

Atorvastatin
Placebo

High-dose atorvastatin reload pre-PCI increases circulating levels of EPCs

CD45^{dim}/CD133^{+}/CD34^{+}/KDR^{+} (%)

Atorvastatin Placebo

Patti G et al. European Society of Cardiology Congress 2009
Possible mechanisms underlying the peri-procedural protective role of statins in the setting of PCI …

- Attenuation of endothelial activation
- Improvement of endothelial function
  (by increasing NO release)

Local recruitment of inflammatory cells

Small vessel function

Reduction of procedural thrombotic activation

Effects of coronary micro-embolization

Direct myocardial protection against peri-procedural ischemia

Peri-procedural myocardial damage
It is unclear whether patients on chronic statin treatment may have a clinical benefit similar to that observed with acute administration. Indeed, in a rat model of ischemia/reperfusion, the acute protective effect of atorvastatin on myocardial injury wanes with a longer treatment, but this effect can be recaptured by a “reloading” given immediately before ischemia/reperfusion.

Mensah K et al – J Am Coll Cardiol 2005
ARMYDA-RECAPTURE (Atorvastatin for Reduction of MYocardial Damage during Angioplasty) trial

Prospective, multicenter, randomized, double blind trial investigating efficacy of atorvastatin reload in patients on chronic statin therapy undergoing PCI

Chairman: Germano Di Sciascio

Principal Investigators: Giuseppe Patti, Vincenzo Pasceri, Achille Gaspardone, Giuseppe Colonna

Investigators: Andrea D’Ambrosio, Marco Miglionico, Annunziata Nusca, Rosetta Melfi, Laura Gatto, Elisabetta Ricottini, Gianluca Pendenza, Antonio Montinaro
ARMYDA-RECAPTURE trial: Study design

793 Patients with stable angina or NSTE-ACS undergoing coronary angiography

Randomization (N=420)

737 patients excluded for:
- 243 no chronic statin therapy (31%)
- 38 emergency angiography
- 82 ejection fraction <30%
- 10 severe renal failure

68 patients excluded for indication to:
- medical therapy (N=30)
- bypass surgery (N=38)

Atorvastatin reload:
- 80 mg
- 12 hrs before angio; further 40 mg 2 hrs before
- N=210

Placebo
- 12 hrs before angio; further dose 2 hrs before
- N=210

Coronary angiography

N=352

PCI atorvastatin
- N=177

PCI placebo
- N=175

1st blood sample (before PCI)

2nd and 3rd blood samples (8 and 24 hours after PCI)

Primary end point:
- 30-day occurrence of cardiac death, MI, TVR

CK-MB, Troponin-I, HS-CRP
ARMYDA-RECAPTURE: RESULTS

Individual and Combined Outcome Measures of the Primary Endpoint at 30 days

- Cardiac death: 0.5% (Atorvastatin) vs 3.4% (Placebo), P=0.045
- MI: 8.6% (Atorvastatin) vs 9.1% (Placebo)
- TVR: 0% (Atorvastatin) vs 0% (Placebo)
- MACE (Composite Primary End Point): 3.4% (Atorvastatin) vs 3.4% (Placebo)

Composite Primary End Point (48% RRR)

ARMYDA-RECAPTURE  Secondary endpoints

MACE according to clinical presentation (stable angina or ACS)

Test for Interaction: z=2.0; P=0.022

CONCLUSIONS

- ARMYDA and ARMYDA-ACS trials indicate that a short-term, high-dose, atorvastatin pretreatment prior to PCI improves clinical outcome in pts with either stable angina and unstable angina/NSTEMI

- This benefit is mostly driven by a reduction of peri-procedural MI: 81% risk reduction in stable angina pts, NNT 8; 70% risk reduction in ACS; NNT 10

- ARMYDA-RECAPTURE trial indicates that reloading with high dose atorvastatin is associated with improved clinical outcome in patients on chronic statin therapy undergoing PCI. Acute atorvastatin bolus 80 mg + 40 mg starting 12 hrs pre-PCI confers a 48% Relative Risk Reduction of 30-day MACE at MV analysis (NNT = 17). The benefit is largely localized to patients who presented with ACS (87% Risk Reduction, NNT = 9)

- Pleiotropic effects of atorvastatin may explain such benefit

- Those findings may influence practice patterns and support the indication of a systematic “upstream” administration of high-dose atorvastatin in pts candidates to PCI, irrespective of clinical presentation and chronic statin therapy
Pleiotropic effects of statins

Statins

Target cell

PI3K

AKT

PKC

NOS

ROS

Mitochondria

Heart dilatation

Cancer

Ribosomes

Nucleus

PTEN

Myocardial protection

Preconditioning

Oxidative stress

Apoptosis
ARMYDA-RENAL Prospective Study

N=434 pts undergoing PCI on statin therapy
N= 174 statin-naive

4-yr prospective F-up

Incidence of Contrast-induced nephropathy

<table>
<thead>
<tr>
<th>Creatinine Clearance (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-PCI</td>
</tr>
<tr>
<td>Statin-treated</td>
</tr>
<tr>
<td>100</td>
</tr>
<tr>
<td>80</td>
</tr>
<tr>
<td>60</td>
</tr>
<tr>
<td>40</td>
</tr>
<tr>
<td>20</td>
</tr>
<tr>
<td>0</td>
</tr>
</tbody>
</table>

| Post-PCI                     |
| Statin-treated              |
| 100                         |
| 80                          |
| 60                          |
| 40                          |
| 20                          |
| 0                           |

P=0.0001
90% RR
3%

P=0.87
P<0.0001

Patti G et al – Am J Cardiol 2008;101:279
The Atheroma (Atorvastatin Therapy: Effects on Reduction of Macrophage Activity) Study

Ultrasmall SuperParamagnetic Iron-Oxide Enhanced Carotid MR Imaging (USPIO-RMI)

Transcranial Doppler Data Embolization Activity (1hr Monitoring)

### Meta-Analysis of Randomized Controlled Trials of Statins Versus Placebo in Patients With Heart Failure

#### CV death

<table>
<thead>
<tr>
<th>Statin</th>
<th>Placebo</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Narins (2003)</td>
<td>0</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>WINCAP (2008)</td>
<td>8</td>
<td>55</td>
<td>20</td>
</tr>
<tr>
<td>Voelckel (2009)</td>
<td>0</td>
<td>29</td>
<td>0</td>
</tr>
<tr>
<td>Yazzie (2007)</td>
<td>0</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>123</td>
<td>422</td>
<td>6.4%</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>0</td>
<td>24</td>
<td> </td>
</tr>
<tr>
<td>Heterogeneity: $I^2 = 0.00$, $H^2 = 0.59$, $df = 1, p = 0.44$, $I^2 = 0.00$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z = 0.92 (p &lt; 0.35)$</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Hospitalization for worsening HF

<table>
<thead>
<tr>
<th>Statin</th>
<th>Placebo</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Narins (2005)</td>
<td>0</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Rida M. (2009)</td>
<td>8</td>
<td>44</td>
<td>13</td>
</tr>
<tr>
<td>Voelckel (2008)</td>
<td>8</td>
<td>66</td>
<td>20</td>
</tr>
<tr>
<td>Yazzie (2008)</td>
<td>0</td>
<td>56</td>
<td>2</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>71</td>
<td>316</td>
<td>31.0%</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>28</td>
<td>00</td>
<td> </td>
</tr>
<tr>
<td>Heterogeneity: $I^2 = 0.00$, $H^2 = 0.00$, $df = 1, p = 0.70$, $I^2 = 0.00$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z = 4.75 (p &lt; 0.00001)$</td>
<td></td>
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</tr>
</tbody>
</table>

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CK-MB release after PCI: prospective follow-up on 3494 pts

P=0.009

Figure 1. CK-MB peak ratio and the adjusted probability of death after 2 years in the population as a whole. The dotted lines denote the 95% CIs.

Survival curves according to statin therapy before PCI (N=5052)
Randomized study on fluvastatin (80 mg/day, initiated after the intervention) in 1,677 patients with stable/unstable angina undergoing PCI

GRACE Registry
(N=19,537 pts with ACS; 94 hospitals)

* Significant inter-hospital variability

GRACE Study Ann Intern Med 2004;140:857
Observational, non randomized data on statin therapy and outcome after elective PCI

N=296 pts undergoing PCI

N=229 on statin therapy

N=67 statin-naive

Herrmann et al. Circulation 2002
Multicenter, randomized, placebo-controlled, double blind, prospective trial, evaluating whether 7-day pretreatment with atorvastatin influences peri-procedural outcome in patients undergoing elective PCI

Chairmen: Vincenzo Pasceri, Giuseppe Patti, Germano Di Sciascio

Investigators: Christian Pristipino, Annunziata Nusca, Andrea D’Ambrosio, Giulio Speciale, Francesco Pelliccia, Antonino Granatelli, Massimo Santini, Marco Miglionico, Giordano Dicuonzo, Addolorata Carcagni, Giuseppe Richichi
ARMYDA trial: Study design

153 patients
✓ Severe Angina, ≤ ACS
✓ Positive stress test
✓ Indication to PCI
✓ No previous statins treatment

Randomization

7 days

Atorvastatin
40 mg/ day
N=76

Placebo
N=77

PCI

30 days

Clinical Follow-up

1° Blood sample before PCI

2°-3° Blood samples 8 and 24 h post-PCI

CK MB, Tn-I, Myoglobin
Statins in patients with ACS undergoing PCI

... but patients were treated with different types of statins, variable doses and unknown duration of previous treatment.

ARMYDA trial - Secondary end point: Incidence of any post-PCI increase of CK-MB and Troponin-I above UNL

ARMYDA-ACS: Survival curves at 30 days

P = 0.01

Days after PCI

MACE-free survival (%)
ARMYDA-ACS: Secondary end point
Cardiac markers elevations

1-3 times

>3 times

P=0.002

P=0.028

Effect of a single 80 mg atorvastatin dose given within 24 hours prior to PCI

Peri-procedural MI

EFFECT OF INTENSIVE STATIN THERAPY ON CLINICAL OUTCOMES AMONG PATIENTS UNDERGOING PCI FOR ACUTE CORONARY SYNDROMES – PCI PROVE-IT

Gibson et al. J Am Coll Cardiol 2009; 54; 2290
EFFECT OF INTENSIVE STATIN THERAPY ON CLINICAL OUTCOMES AMONG PATIENTS UNDERGOING PCI FOR ACUTE CORONARY SYNDROMES

Univariate OR 0.73, p<0.001
Multivariate OR 0.74, p<0.015

Univariate OR 0.75, p<0.017
Multivariate OR 0.92, p<0.055

Gibson et al. J Am Coll Cardiol 2009; 54; 2290
Statins ... beyond lipid-lowering effect

- Decrease platelet aggregation, thrombus formation (TM, PAI, TF)
- Improve endothelial function (NO)
- Decrease adhesion molecules expression (CAMs, selectins)
- Anti-inflammatory effects (cytokines, growth-factors)
- Decrease apoptosis
- Decrease Matrix Degradation (decrease macrophages and T cells accumulation, ↓ metalloproteinases synthesis)
- Decrease adventitial neovascularization
Possible mechanisms of the clinical benefit:

Improvement of endothelial function

N=27 pts with stable angina randomized to placebo or pravastatin (single dose of 40 mg) and undergoing invasive evaluation of coronary endothelial function.

* P<0.05

Pleiotropic effects of statins – Improvement of endothelial function

Statins

Endothelial cell

Caveolin

NOS

P

AKT

NADPH oxidase

mRNA (ET-1)

mRNA (NOS)

Ribosomes

Nucleus

Mitochondria
Pleiotropic effects of statins – Anti-thrombotic effects

Statins

Monocytes/Macrophages/
Endothelial cells/Platelets/Other target cells

- Geranylgeranyl-PP

Rho

GTP

mRNA (TF)

mRNA (PAI-1)

mRNA (CD40L)

mRNA (Pro-thrombin)

mRNA (tPA)

Ribosomes

Nucleus

Mitochondria
Pleiotropic effects of statins –
Reduction of adhesion molecules expression

Statins

Monocytes/Macrophages/
Endothelial cells/Other target cells

CAM

Statins

Geranylgeranyl-PP

Rho

GTP

Nucleus

Mitochondria

Ribosomes

mRNA
Pleiotropic effects of statins –
Systemic anti-inflammatory effects

Statins
Target cell

Nucleus
Ribosomes
mRNA

Mitochondria

NFKB

NFKB

Statins
Possible mechanisms of the clinical benefit:

Direct myocardial protection

Ischemia/reperfusion on isolated perfused mouse hearts

Effect prevented by an inhibitor of PI3K

Bell RM, et al. JACC 2003
**ARMYDA-RECAPTURE: Odds Ratio for 30-day MACE**

- **ACS**: 1.8 (0.72-4.6)
- **LVEF <40%**: 2.1 (0.53-8.2)
- **IIb/IIIa inhibitors**: 3.2 (1.2-8.8)
- **Multiple stents**: 2.4 (1.1-5.4)
- **Atorvastatin reload**: 0.52 (0.20-0.82)

* P=0.041

ARMYDA-RECAPTURE: Secondary endpoints

Post-PCI increase of CRP levels from baseline

Graph showing the comparison of CRP levels between Atorvastatin and Placebo post-PCI.

- **Atorvastatin**: 2.1 ± 6.7 mg/L
- **Placebo**: 3.0 ± 9.5 mg/L

Statistical significance: P = 0.12

Chronically Acutely

Cholesterol-dependent

Plaque Volume / Lipid load

Statins

Cholesterol-independent ("Pleiotropic")

NOS3

Cardioprotection

PPARγ

RhoA

PKB/Akt

PTEN

PI3-K

Schulz R. J Am Coll Cardiol 2005
Contrast-induced nephropathy (CIN) and adverse events during follow-up after coronary angioplasty

McCullough PA, Am J Cardiol 2006
Event-free Survival according to Statin Pre-treatment and Contrast-induced Nephropathy

Group A: Statin-treated, no contrast-induced nephropathy
Group B: Statin-treated, contrast-induced nephropathy
Group C: No Statin, no contrast-induced nephropathy
Group D: No Statin, contrast-induced nephropathy

* P=0.015 vs B; P=0.001 vs C; P=0.0001 vs D
** P=0.001 vs C; P=0.018 vs B; P=0.0001 vs A

Patti G et al – Am J Cardiol 2008;101:279
## STATIN THERAPY IN CLINICAL TRIALS

### Adverse events

<table>
<thead>
<tr>
<th>STUDY</th>
<th>Follow-up</th>
<th>Patients</th>
<th>ALT/AST &gt;3 x UNL</th>
<th>CK &gt;10 x UNL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newman et al.</td>
<td>VARIABLE</td>
<td>4.798</td>
<td>26 (0.6%)</td>
<td>2 (0.06%)</td>
</tr>
<tr>
<td>PROVE-IT</td>
<td>2 YRS</td>
<td>2.099</td>
<td>69 (3.3%)</td>
<td>NA</td>
</tr>
<tr>
<td>TNT</td>
<td>4.9 YRS</td>
<td>4.995</td>
<td>60 (1.2%)</td>
<td>0</td>
</tr>
<tr>
<td>IDEAL</td>
<td>4.8 YRS</td>
<td>4.439</td>
<td>61 (1.38%)</td>
<td>0</td>
</tr>
<tr>
<td>SPARCL</td>
<td>4.9 YRS</td>
<td>2.365</td>
<td>51 (2.2%)</td>
<td>2 (0.08%)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>VARIABLE</td>
<td>18.696</td>
<td>267 (1.44)</td>
<td>4 (0.024%)</td>
</tr>
</tbody>
</table>

Waters and Ku. J Am Coll Cardiol 2009; 54; 1434
### Safety of statin therapy in clinical trials

<table>
<thead>
<tr>
<th>Source/Group</th>
<th>No. of Patients</th>
<th>AST/ALT &gt;3 × Normal</th>
<th>Myalgia or Myositis</th>
<th>Rhabdomyolysis</th>
<th>Discontinuation of Therapy</th>
<th>Severe Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Schwartz et al.</strong>&lt;sup&gt;14&lt;/sup&gt; 2001 (MIRACL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>1538</td>
<td>38 (2.5)</td>
<td>0</td>
<td>0</td>
<td>173 (1.2)</td>
<td>Hospitalization for hepatitis</td>
</tr>
<tr>
<td>Control</td>
<td>1548</td>
<td>9 (0.6)</td>
<td>0</td>
<td>0</td>
<td>169 (1.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Thompson et al.</strong>&lt;sup&gt;15&lt;/sup&gt; 2004 (PAOT)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>1710</td>
<td>7 (0.4)</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>None</td>
</tr>
<tr>
<td>Control</td>
<td>1698</td>
<td>5 (0.3)</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td><strong>Cannon et al.</strong>&lt;sup&gt;16&lt;/sup&gt; 2004 (PROVE IT-TIMI22)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>2000</td>
<td>20 (1.0)</td>
<td>0</td>
<td>0</td>
<td>20 (1.0)</td>
<td>None</td>
</tr>
<tr>
<td>Control</td>
<td>2063</td>
<td>23 (1.1)</td>
<td>56 (2.7)</td>
<td>0</td>
<td>681 (33.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Lien et al.</strong>&lt;sup&gt;17&lt;/sup&gt; 2002 (FLORIDA)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>265</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>39 (1.2)</td>
<td>None</td>
</tr>
<tr>
<td>Control</td>
<td>275</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>37 (1.5)</td>
<td></td>
</tr>
<tr>
<td><em>da Lancellotti et al.</em>&lt;sup&gt;18&lt;/sup&gt; 2004 (A to Z)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>2243</td>
<td>19 (0.8)</td>
<td>9 (0.4)</td>
<td>3 (0.1)</td>
<td>41 (1.8)</td>
<td>Rhabdomyolysis in 3 treatment group patients</td>
</tr>
<tr>
<td>Control</td>
<td>2210</td>
<td>8 (0.4)</td>
<td>1 (0.05)</td>
<td>0</td>
<td>34 (1.5)</td>
<td></td>
</tr>
<tr>
<td><strong>Den Hartog et al.</strong>&lt;sup&gt;19&lt;/sup&gt; 2001 (PAIS)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>50</td>
<td>0</td>
<td>2 (4)</td>
<td>0</td>
<td>3 (6)</td>
<td>None</td>
</tr>
<tr>
<td>Control</td>
<td>47</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Arntz et al.</strong>&lt;sup&gt;20&lt;/sup&gt; 2000 (L-CAO)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Treatment</td>
<td>70</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>22 (31.4)</td>
<td>None</td>
</tr>
<tr>
<td>Control</td>
<td>56</td>
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<td>NA</td>
<td>NA</td>
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<tr>
<td><strong>Kadowaki et al.</strong>&lt;sup&gt;21&lt;/sup&gt; 2002 (PTT)</td>
<td></td>
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<tr>
<td>Treatment</td>
<td>40</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>None</td>
</tr>
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<td>Control</td>
<td>37</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td><strong>Okazaki et al.</strong>&lt;sup&gt;22&lt;/sup&gt; 2004 (ESTABLISH)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>35</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>2 (5.7)</td>
<td>None</td>
</tr>
<tr>
<td>Control</td>
<td>35</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>1 (2.9)</td>
<td></td>
</tr>
<tr>
<td><strong>Serruy et al.</strong>&lt;sup&gt;23&lt;/sup&gt; 2002 (LIPS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Treatment</td>
<td>844</td>
<td>10 (1.2)</td>
<td>0</td>
<td>0</td>
<td>174 (20.6)</td>
<td>None</td>
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<td>Control</td>
<td>833</td>
<td>3 (0.4)</td>
<td>3 (0.4)</td>
<td>0</td>
<td>196 (23.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Kesteloot et al.</strong>&lt;sup&gt;24&lt;/sup&gt; 1997 (LAMIL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>36</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>None</td>
</tr>
<tr>
<td>Control</td>
<td>33</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td><strong>Dupuis et al.</strong>&lt;sup&gt;25&lt;/sup&gt; 2005 (RE FlE)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>30</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>None</td>
</tr>
<tr>
<td>Control</td>
<td>30</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td><strong>Caliarco et al.</strong>&lt;sup&gt;26&lt;/sup&gt;</td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>41</td>
<td>0</td>
<td>1 (2.4)</td>
<td>0</td>
<td>1 (2.4)</td>
<td>None</td>
</tr>
<tr>
<td>Control</td>
<td>40</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

CONCLUSIONS

- In patients undergoing PCI, statins could prevent perturbation of renal haemodynamics and direct damage to tubular cells associated with contrast-induced nephropathy, by attenuating the synthesis/action of various mediators (such as endothelin and angiotensin) and/or reducing inflammation and production of reactive oxygen species.

- Prevention of contrast-induced nephropathy by statins translates into a significant long-term reduction of adverse events.
ARMYDA-RECAPTURE

Conclusions

- ARMYDA-RECAPTURE indicates that reloading with high dose atorvastatin is associated with improved clinical outcome in patients on chronic statin therapy undergoing PCI.

- Acute atorvastatin bolus 80 mg + 40 mg starting 12 hrs pre-PCI confers a 48% Relative Risk Reduction of 30-day MACE at MV analysis (NNT = 17).

- The benefit is largely localized to patients who presented with ACS (87% Risk Reduction, NNT = 9).

- Rapid LDL-independent cardioprotective effects may be responsible of this phenomenon.

- These findings may support a strategy of routine reload with high dose atorvastatin early before intervention even in the background of chronic therapy.

- If confirmed by future studies, results of ARMYDA-RECAPTURE may influence practice patterns for the acute care of non ST-segment elevation ACS.
………………….. CONCLUSIONS

- Early initiation of statin therapy in medically treated pts with ACS is associated with improved clinical outcome, primarily expressed as a reduction of ischemia recurrence (even in the short-term)

- Withdraw of chronic therapy with statins in pts admitted for an acute coronary syndrome may increase the risk of CV events

- Increased protection in pts with ACS treated with high dose statins (i.e. short-term reduction of ischemia recurrence and long-term reduction of “hard” end points)

- Statins and stroke prevention in pts with ACS
Improving outcome after PCI by reducing peri-procedural MI

The ARMYDA trials

- **ARMYDA-1**
  - No statin
  - No 600 mg clop.
  - 18% Pts with CSA

- **ARMYDA-1**
  - Atorvastatin
  - No 600 mg clop.
  - 6% Pts with CSA or ACS

- **ARMYDA-2**
  - Statin
  - 600 mg clop.
  - 5% Pts with ACS

- **ARMYDA-ACS**
  - Atorvastatin
  - 600 mg clop.
  - 5% Pts with ACS
Possible mechanisms of the clinical benefit:

**Improvement of endothelial function**

N=27 pts with stable angina randomized to placebo or pravastatin (single dose of 40 mg) and undergoing invasive evaluation of coronary endothelial function.

Pleiotropic effects of statins –
Direct myocardial protection

Statins

Target cell

PPARγ

PTEN

Pl3K

PKC

Preconditioning
Oxidative stress

Heart dilatation
Cancer

Mitochondria

Ribosomes

Nucleus
Pleiotropic effects of statins – Direct myocardial protection
Possible mechanisms of the clinical benefit:

Direct myocardial protection

Ischemia/reperfusion on isolated perfused mouse hearts

Effect prevented by an inhibitor of PI3K

Bell RM, et al. JACC 2003
**Primary end point:**
Incidence of major adverse cardiac events (MACE: death, MI, TVR) from the procedure up to 30 days

MI definition:
- If normal baseline levels of CK-MB: post-procedural increase of CK-MB >2 times above UNL, according to the consensus statement of the Joint ESC/ACC Committee for the Redefinition of Myocardial Infarction for clinical trials on coronary intervention.
  - If elevated baseline levels of CK-MB: subsequent rise of >2 times in CK-MB from baseline value
  - Normal limits: CK-MB 4 ng/ml; Troponin 0.08 ng/ml; Myoglobin 80 ng/ml

**Secondary end points:**
- Any post-procedural increase of markers of myocardial injury above UNL (CK-MB, troponin-I, myoglobin)
- Post-PCI variations from baseline of CRP levels in the 2 arms
Statins in patients with ACS

Observational evidence
Statins in patients with acute MI

Retrospective analysis on 174,635 pts with acute MI of the National Registry of Myocardial Infarction 4 (NRMI 4)

* P<0.01 vs No/No pts

Fonarow GC et al. Am J Cardiol 2005
Inclusion criteria:

✓ NSTE-ACS undergoing angiography <48 hrs

Exclusion criteria:

✓ Previous or current statin therapy
✓ ACS with high risk features warranting emergency angiography
✓ LVEF <30%
✓ Contraindications to statins (liver or muscle disease)
✓ Severe renal failure (creatininine >3 mg/dl)
The Global Registry of Acute Coronary Events project

N=4,056 pts with ACS who were taking statins on hospital admission compared with N=15,481 statin-naive pts (Ann Int Med 2004)

Hospital outcomes according to statin use vs outcomes in pts never receiving statins

<table>
<thead>
<tr>
<th></th>
<th>OR for long-term statin use only</th>
<th>OR for long-term and in-hosp statin use</th>
<th>OR for in-hosp statin use only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>1.39 (0.91-2.14)</td>
<td>0.38 (0.28-0.52)</td>
<td>0.38 (0.30-0.48)</td>
</tr>
<tr>
<td>MI</td>
<td>0.69 (0.43-1.11)</td>
<td>0.74 (0.64-0.85)</td>
<td>1.07 (0.94-1.41)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.08 (0.43-2.73)</td>
<td>0.68 (0.42-1.12)</td>
<td>0.80 (0.57-1.14)</td>
</tr>
<tr>
<td>MACE</td>
<td>1.02 (0.74-1.41)</td>
<td>0.66 (0.56-0.77)</td>
<td>0.87 (0.78-0.97)</td>
</tr>
</tbody>
</table>
Observational data from N=3,653 pts discharged on statins compared with N=17,156 pts without statins on discharge (from GUSTO IIb and PURSUIT trials)

Early (<7 days) statin initiation and outcome in patients with ACS

Observational cohort from SYMPHONY and 2° SYMPHONY randomized trials (N=12,365)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>OR vs no statins</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>90-day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>1.08 (0.75-1.56)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death or MI</td>
<td>1.08 (0.91-1.29)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death or MI or recurr. isch.</td>
<td>1.15 (0.99-1.34)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>0.54 (0.74-1.41)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0.99 (0.73-1.33)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Statins in patients with ACS

Randomized studies
MRACCL trial

N=3,086 pts with ACS randomized to atorvastatin (80 mg/day) or placebo between 24 and 96 hrs after admission

End point: death, MI, resuscitated cardiac arrest, recurrent ischemia

Schwartz GG et al – JAMA 2001
Meta-analysis on 13,024 pts from 12 randomized trials comparing early (<14 days) statin therapy vs placebo or usual care in ACS pts

Briel M et al – JAMA 2006
Statins in patients with ACS

Intensive vs Moderate Statin dosing
PROVE IT - TIMI 22
Study Design

4,162 patients with an Acute Coronary Syndrome < 10 days

Double-blind

ASA + Standard Medical Therapy

Pravastatin 40 mg

Atorvastatin 80 mg

Duration: Mean 2 year follow-up (≥824 events)

Cannon et al. NEJM 2004
Kaplan-Meier estimates of the incidence of the primary end point of death/MACEs over 30 months follow-up in PROVET IT

Cannon et al. NEJM 2004
Kaplan-Meier estimates of the incidence of composite end point (death, MI or urgent revascularization) over 30 days follow-up in PROVET IT

Hazard Ratio = 0.67
p = 0.04

Pravastatin 40 mg
Atorvastatin 80 mg
CHANGES FROM (POST-ACS) BASELINE IN MEDIAN LDL-C (PROVE-IT Study)

Ray et al. Am J Cardiol 2006
REDUCTION IN MAJOR CARDIAC ENDPOINTS (PROVE IT)

Cannon et al. NEJM 2004
Cumulative incidence of hospitalization for congestive heart failure (PROVE IT – TIMI 22)

Scirica et al. JACC 2006
A to Z Trial - TIMI 21

STUDY DESIGN

Early Intensive

Simvastatin 40 mg

N = 4497

Delayed more Conservative

Placebo

Placebo

Placebo

Simvastatin 20 mg

Randomization

Mo 1

Mo 4

Mo 24

de Lemos et al. JAMA 2004
A to Z Trial Results
Primary end point: CV death, non fatal MI, ACS recurrence, stroke

HR, 0.89 (95% CI, 0.76-1.04); P = .14

de Lemos et al. JAMA 2004
CHANGES FROM (POST-ACS) BASELINE IN MEDIAN LDL-C in A to Z trial

Median LDL (mmol/L)

3.37
3.11
2.85
2.59
2.33
2.07
1.81
1.55

Month

0 1 4 8 12 16 20 24

3.2 mmol/L
1.6 mmol/L
2.1 mmol/L
1.7 mmol/L

Median LDL (mg/dL)

130
120
110
100
90
80
70
60

de Lemos et al. JAMA 2004
Meta-analysis on 27,548 pts from 4 randomized trials comparing intensive vs moderate statin dosing

**Figure 3.** Individual trials and pooled analysis showing a highly significant 16% reduction in the risk of coronary death or any cardiovascular event (myocardial infarction, stroke, hospitalization for unstable angina, or revascularization) ($p < 0.0001$). CI – confidence interval; OR – odds ratio.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Atorvastatin (N=86)</th>
<th>Placebo (N=85)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>68 (79)</td>
<td>67 (79)</td>
<td>0.88</td>
</tr>
<tr>
<td>Age (years)</td>
<td>64±11</td>
<td>67±10</td>
<td>0.06</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>25 (29)</td>
<td>28 (33)</td>
<td>0.70</td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td>63 (73)</td>
<td>63 (74)</td>
<td>0.96</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>27 (31)</td>
<td>28 (33)</td>
<td>0.96</td>
</tr>
<tr>
<td>Current smokers</td>
<td>27 (31)</td>
<td>18 (21)</td>
<td>0.18</td>
</tr>
<tr>
<td>Previous coronary intervention</td>
<td>9 (10)</td>
<td>9 (11)</td>
<td>0.82</td>
</tr>
<tr>
<td>Previous by-pass surgery</td>
<td>2 (2)</td>
<td>3 (4)</td>
<td>0.99</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>55±7</td>
<td>54±8</td>
<td>0.38</td>
</tr>
</tbody>
</table>

**Clinical pattern**

<table>
<thead>
<tr>
<th></th>
<th>Atorvastatin (N=86)</th>
<th>Placebo (N=85)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unstable angina</td>
<td>52 (60)</td>
<td>58 (68)</td>
<td>0.37</td>
</tr>
<tr>
<td>Non STEMI</td>
<td>34 (40)</td>
<td>27 (32)</td>
<td>0.37</td>
</tr>
<tr>
<td>Mean time to angiography (hours)</td>
<td>23±12</td>
<td>22±10</td>
<td>0.56</td>
</tr>
<tr>
<td>Multivessel coronary artery disease</td>
<td>29 (34)</td>
<td>39 (46)</td>
<td>0.14</td>
</tr>
</tbody>
</table>

**Therapy**

<table>
<thead>
<tr>
<th></th>
<th>Atorvastatin (N=86)</th>
<th>Placebo (N=85)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>86 (100)</td>
<td>85 (100)</td>
<td>1</td>
</tr>
<tr>
<td>Clopidogrel (600 mg load)</td>
<td>86 (100)</td>
<td>85 (100)</td>
<td>1</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>26 (30)</td>
<td>23 (27)</td>
<td>0.77</td>
</tr>
<tr>
<td>Ace-inhibitors</td>
<td>67 (78)</td>
<td>65 (76)</td>
<td>0.97</td>
</tr>
<tr>
<td>IIb-IIIa inhibitors</td>
<td>23 (27)</td>
<td>18 (21)</td>
<td>0.50</td>
</tr>
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</table>
## Procedural Features in the Atorvastatin and Placebo Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Atorvastatin (N=86)</th>
<th>Placebo (N=85)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Vessel treated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left main</td>
<td>-</td>
<td>1 (1)</td>
<td>0.97</td>
</tr>
<tr>
<td>Left anterior descending</td>
<td>51 (50)</td>
<td>54 (49)</td>
<td>0.94</td>
</tr>
<tr>
<td>Left circumflex</td>
<td>31 (30)</td>
<td>28 (25)</td>
<td>0.56</td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>20 (19)</td>
<td>26 (24)</td>
<td>0.56</td>
</tr>
<tr>
<td>Saphenous vein grafts</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>0.51</td>
</tr>
<tr>
<td>Lesion type B2/C</td>
<td>73 (85)</td>
<td>71 (84)</td>
<td>0.97</td>
</tr>
<tr>
<td>Multivessel intervention</td>
<td>17 (20)</td>
<td>25 (29)</td>
<td>0.20</td>
</tr>
<tr>
<td>Type of intervention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Balloon only</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>0.48</td>
</tr>
<tr>
<td>Stent</td>
<td>85 (99)</td>
<td>84 (99)</td>
<td>0.48</td>
</tr>
<tr>
<td>Bifurcations with kissing balloon</td>
<td>8 (9)</td>
<td>8 (9)</td>
<td>0.81</td>
</tr>
<tr>
<td>No. of stents per patient</td>
<td>1.4±0.6</td>
<td>1.5±0.9</td>
<td>0.40</td>
</tr>
<tr>
<td>Stent diameter (mm)</td>
<td>3.1±0.4</td>
<td>3.1±0.3</td>
<td>0.90</td>
</tr>
<tr>
<td>Total stent length (mm)</td>
<td>16.7±5.7</td>
<td>16.9±5.5</td>
<td>0.82</td>
</tr>
<tr>
<td>Use of drug eluting stents</td>
<td>55 (64)</td>
<td>47 (55)</td>
<td>0.32</td>
</tr>
<tr>
<td>Direct stenting</td>
<td>41 (48)</td>
<td>36 (42)</td>
<td>0.59</td>
</tr>
<tr>
<td>No. of pre-dilatations</td>
<td>2.1±1.4</td>
<td>2.2±1.7</td>
<td>0.68</td>
</tr>
<tr>
<td>Stent deployment pressure (atm)</td>
<td>11.2±4.1</td>
<td>11.6±2.7</td>
<td>0.44</td>
</tr>
<tr>
<td>Duration of stent deployment (sec)</td>
<td>16±7</td>
<td>16±5</td>
<td>1</td>
</tr>
</tbody>
</table>
Median concentrations of hs-CRP at 1 month, 4 months and at the end of study in PROVE IT-TIMI 22 and A to Z studies

Ray et al. Am J Cardiol 2006
Median concentrations of hs-CRP at 1 month, 4 months and at the end of study in PROVE IT-TIMI 22
### ARMYDA-ACS: RESULTS

Individual and Combined Outcome Measures of the Primary End Point at 30 days in the Atorvastatin and Placebo Groups

<table>
<thead>
<tr>
<th></th>
<th>Atorvastatin (N=86)</th>
<th>Placebo (N=85)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>4 (5%)</td>
<td>13 (15%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Target vessel</td>
<td>-</td>
<td>1 (2%)</td>
<td>1</td>
</tr>
<tr>
<td>revascularization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total MACE</td>
<td>4 (5%)</td>
<td>14 (17%)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Giuseppe Patti, MD, FACC
Department of Cardiovascular Sciences,
Campus Bio-Medico University of Rome
ARMYDA trial - Secondary end point: Incidence of any post-PCI increase of CK-MB and Troponin-I above UNL

Estimated cumulative 1-year incidence of death or non-fatal MI in pts with ACS vs stable angina vs without previous cardiovascular events

Ray et al. Am J Cardiol 2006
Kaplan-Meier estimates of the incidence of composite end-point (death, MI and recurrent ACS) over 30 days follow-up in the PROVET IT-TIMI22 study