بسم الله الرحمن الرحيم
The Ideal Cholesterol: is the lower is better?

By Essam Mahfouz, MD
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Cholesterol & atherogenesis

- Theoretical evidence
- Experimental evidence
- Epidemiological evidence
  - Large epidemiological trials
  - Regression trials
Lower Cholesterol Levels Associated With Lower CHD Risk

The Framingham Heart Study

CHD Incidence per 1000

≤ 204
205-234
235-264
265-294
≥ 295

Serum Cholesterol (mg/100 mL)

Relation of Serum Cholesterol to CHD Mortality

The MRFIT Study

Mortality Relative Risk

Serum Cholesterol (mg/dL)

Early High TC Levels Associated With Later CHD Events

Results After 40 Years

*1017 men, average age 22

**LDL Cholesterol**

- Remains the cornerstone of dyslipidemia therapy\(^1\)
- Strongly associated with atherosclerosis and CHD events\(^1\)
- 10% increase results in a 20% increase in CHD risk\(^1\)
- Most patients with elevated LDL untreated
  - Only 4.5 million out of 28.4 million treated\(^2,3\)

Increased Relative Risk of CHD Associated With Increasing LDL Levels

ARIC Study
Men

Adjusted for age and race
12-year follow-up
n = 5432

Relative Risk of CHD

2.35 2.85 3.35 3.85 4.35 4.85 (mmol/L)
91 110 130 149 168 188 (mg/dL)

Increased Relative Risk of CHD
Associated With Increasing LDL Levels

ARIC Study
Women

Adjusted for age and race
12-year follow-up
n = 6907

Increased Relative Risk of CHD
Associated With Increasing LDL Levels

Event Reduction in Angiographic Plaque Regression Trials

* As defined by the comparison between the change in the treated group vs the change in the control.

Clinical Events Correlate Directly With On-Treatment LDL-Cholesterol Levels

\[ y = 0.0599x - 3.3952 \]

\[ R^2 = 0.9305 \]

\[ P = 0.0019 \]

\( P = \) placebo; \( S = \) statin.

O'Keefe et al. *J Am Coll Cardiol.* 2004;43:2142
Atherosclerosis Progression Varies Directly With On-Treatment LDL Cholesterol Levels

AT = atorvastatin; CCAIT = Canadian Coronary Atherosclerosis Intervention Trial; LCAS = Lipoprotein and Coronary Atherosclerosis Study; MAAS = Multicentre Anti-Atheroma Study; MARS = Monitored Atherosclerosis Regression Study; MLD = mean lumen diameter; PLAC = Pravastatin Limitation of Atherosclerosis in the Coronary Arteries study; PR = pravastatin; REGRESS = Regression Growth Evaluation Statin Study; REVERSAL = Reversal of Atherosclerosis with Aggressive Lipid Lowering.

O'Keefe et al. J Am Coll Cardiol. 2004;43:2142
Gotto. Am J Cardiol. 2005;96(suppl):34F.
Proposed Mechanisms of Event Reduction by Lipid-Lowering Therapy

• Improved endothelium-dependent vasodilation
• Stabilization of atherosclerotic lesions
  – especially nonobstructive, vulnerable plaques
• Reduction in inflammatory stimuli
  – lipoproteins and modified lipoproteins
• Prevention, slowed progression, or regression of atherosclerotic lesions

Intermolecular Similarities And Differences Of Statins

- Intermolecular similarities
  - all statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase
  - all statins share a common dihydroxy group necessary for HMG-CoA reductase enzyme inhibition

- Intermolecular difference
  - substituents on pharmacophore moiety are responsible for pharmacokinetic and pharmacodynamic differences, which in turn affect efficacy, safety, and pleiotropic effects

Mason et al. *Am J Cardiol.* 2005;96(suppl):11F.
Chemical Structures Of Statins

Natural Or Fungal-Derived

- Lovastatin
- Simvastatin
- Pravastatin

Synthetic

- Atorvastatin
- Fluvastatin
- Cerivastatin
Vessel Wall And Endothelial Cell Membrane Changes With Atherogenesis

Mason et al. *Am J Cardiol.* 2005;96(suppl):11F.
**Metabolic Pathways Blocked By Statins**

Acetyl-CoA + Acetoacetyl-CoA

\[ \rightarrow \] HMG-CoA

Statins

Statins Block

Mevalonate

\[ \rightarrow \] Isopentanylprenyl pyrophosphate (PP)

\[ \rightarrow \] Geranyl pyrophosphate (PP)

\[ \rightarrow \] Farnesyl pyrophosphate (PP)

Squalene

\[ \rightarrow \] Cholesterol

PP = pyrophosphate.

**Slower Late Benefic**

**Related to Hepatic LDL Reduction**

**Early/Rapid and Later Benefit** (pleiotropic effect)

**Important in Vascular Cellular Responses**

\[ \rightarrow \] Geranyl geranyl pyrophosphate (PP)

Rho

\[ \rightarrow \] Translocates to the Cell Membrane

PP = pyrophosphate.

Ray and Cannon. *Am J Cardiol.* 2005;96(suppl):54F.
PLEIOTROPIC EFFECTS OF STATINS

• **Antiatherosclerotic effects on:**
  - Endothelial dysfunction
  - Inflammation (inhibition of adhesion molecules)
  - Plaque stability (inhibition of MMP)
  - LDL oxidation and density
  - SMC proliferation
  - Cholesterol esterification and accumulation

• **Antithrombotic effects on:**
  - Tissue Factor
  - Platelet aggregation
  - Blood viscosity and fibrinogen
  - Fibrinolysis

Potential Time Course of Statin Effects

- **LDL-C lowered***
- Inflammation reduced
- Vulnerable plaques stabilized
- Endothelial function restored
- Ischemic episodes reduced
- Cardiac events reduced***

* Time course established
Key Statin Trials and Spectrum of Risk

Increasing absolute CHD risk

- 4S
- LIPID
- CARE
- ASCOT-LLA
- WOSCOPS
- AFCAPS/TexCAPS
- HPS

CHD/high cholesterol
CHD/average to high cholesterol
CHD/average cholesterol
Some patients with CHD*/
average cholesterol
No MI/high cholesterol
No CHD/average cholesterol

With CHD or without CHD
With High LDL-C or with Low LDL-C

*CHD risk equivalent, e.g. diabetes.
4S Study: Provided Hard Evidence for the Use of Simvastatin 20-40mg in CHD Patients

-30 (p=0.0003)
-42 (p<0.00001)
-34 (p<0.00001)
-37 (p<0.00001)

*Primary endpoint

The survival benefits that pts allocated to simvastatin accrued during the double-blind period of 4S persisted during long-term follow-up (10.4 years)

- **All-cause Mortality**
  - Relative risk: 0.85 (95% CI: 0.74–0.97)
  - p=0.016

- **Cardiovascular Mortality**
  - Relative risk: 0.83 (95% CI: 0.71–0.98)
  - p=0.023

- **Coronary Mortality**
  - Relative risk: 0.76 (95% CI: 0.64–0.90)
  - p=0.002

- **Cancer Mortality**
  - Relative risk: 0.86 (95% CI: 0.60–1.08)
  - p=0.142

*T.E. Strandeberg et al. LANCET 2004; 364: 771–777*
Heart Protection Study

Major Vascular Events Over Time

<table>
<thead>
<tr>
<th>Year of follow-up</th>
<th>Placebo</th>
<th>Simvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>22</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>35</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>46</td>
</tr>
<tr>
<td>5</td>
<td>50</td>
<td>54</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>60</td>
</tr>
</tbody>
</table>

Risk reduction = 24% (p < 0.0001)

Benefit (mean ± SE) per 1000 patients allocated to simvastatin:
- 0 years: 5 ± 3
- 1 year: 20 ± 4
- 2 years: 35 ± 5
- 3 years: 46 ± 5
- 4 years: 54 ± 7
- 5 years: 60 ± 18

SE = standard error of the mean

Adapted from Heart Protection Study Collaborative Group Lancet 2002;360:7-22.
### Simvastatin 40mg
Vascular Events by Prior Lipid Levels

<table>
<thead>
<tr>
<th>Baseline features</th>
<th>SIMVA (10269)</th>
<th>PLACEBO (10267)</th>
<th>Risk ratio at SIMVA better</th>
<th>95% CI SIMVA worse</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL (mmol/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 3.0 (116 mg/dl)</td>
<td>602</td>
<td>761</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 3.0 &lt; 3.5</td>
<td>483</td>
<td>655</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 3.5 (135 mg/dl)</td>
<td>957</td>
<td>1190</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5.0 (193 mg/dl)</td>
<td>361</td>
<td>476</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;5.0 &lt; 6.0</td>
<td>746</td>
<td>965</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;6.0 (232 mg/dl)</td>
<td>935</td>
<td>1165</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALL PATIENTS</td>
<td>2042 (19.9%)</td>
<td>2606 (25.4%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Het $\chi^2 = 3.0$

Het $\chi^2 = 0.5$

24%SE 2.6 reduction (2P<0.00001)
Heart Protection Study
Impact of Simvastatin on Mortality

**Cause of death**
- **Vascular events**
  - Coronary
  - Other vascular
- **Nonvascular events**
- **ALL CAUSES**

**Risk ratio and 95% CI**

- **Simvastatin better**
- **Placebo better**

17% risk reduction
p<0.0001

13% risk reduction
p=0.0003

*Areas of the symbols are proportional to the amount of statistical information in each subdivision

Adapted from Heart Protection Study Collaborative Group *Lancet* 2002;360:7-22.
Impact of Simvastatin in Heart Protection Study
Major Vascular Events

Vascular event*

Major coronary event
Nonfatal MI
Coronary death

Stroke

Revascularization**

ANY MAJOR VASCULAR EVENT

Simvastatin better

Placebo better

0.4 0.6 0.8 1.0 1.2 1.4
Risk ratio and 95% CI

27% risk reduction
p<0.0001

25% risk reduction
p<0.0001

24% risk reduction
p<0.0001

24% risk reduction
p<0.0001

*Patients could be in more than one vascular event category.
**Includes coronary and noncoronary revascularizations.

Adapted from Heart Protection Study Collaborative Group *Lancet* 2002;360:7-22.
**Heart Protection Study**

**Impact of Simvastatin on Stroke**

Stroke etiology

- **All stroke**
  - Ischemic
  - Hemorrhagic
  - Unknown

**ANY MAJOR VASCULAR EVENT***

- **Simvastatin better**
- **Placebo better**

<table>
<thead>
<tr>
<th>Risk ratio and 95% CI</th>
<th>Simvastatin better</th>
<th>Placebo better</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25% risk reduction</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>24% risk reduction</td>
<td>p&lt;0.0001</td>
</tr>
</tbody>
</table>

*Major vascular events included nonfatal MI, coronary death, revascularization, and stroke.

Adapted from Heart Protection Study Collaborative Group *Lancet* 2002;360:7-22.
Impact of Simvastatin on Major Vascular Events
Patients with Diabetes

Baseline feature

<table>
<thead>
<tr>
<th>Patients with Diabetes</th>
<th>Simvastatin 40 mg better</th>
<th>Placebo better</th>
</tr>
</thead>
<tbody>
<tr>
<td>With CHD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without CHD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALL PATIENTS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With CHD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without CHD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

23% risk reduction
p<0.0001

24% risk reduction
p<0.0001

24% risk reduction
p<0.0001

25% risk reduction
p<0.0001

Consistency Across Subgroups

Adapted from Heart Protection Study Collaborative Group Lancet 2002;360:7-22; HPS Group communication.
Impact of Simvastatin on Major Vascular Events By Age and Gender

Consistency Across Subgroups

Baseline feature

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>&lt;65</th>
<th>≥65 &lt;70</th>
<th>≥70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male</td>
<td>Female</td>
<td></td>
</tr>
<tr>
<td>ALL PATIENTS</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Risk ratio and 95% CI

0.4 0.6 0.8 1.0 1.2 1.4

24% risk reduction
p<0.0001

Adapted from Heart Protection Study Collaborative Group *Lancet* 2002;360:7-22.
Post-CABG: Impact of Aggressive vs Moderate Lowering of LDL-C on Atherosclerosis

Study group characteristics

- Sample size: 1,351 (M/F)
- 1 to 11 yr post-CABG
- LDL-C 130-174 mg/dL after diet

Treatment

- Randomized, blinded to
  - lovastatin 40-80 mg + cholestyramine 8 g/day (if needed)
  - lovastatin 2.5-5 mg + cholestyramine 8 g/day (if needed)
  - aggressive LDL-C target: ≤85 mg/dL
  - moderate LDL-C target: 130-140 mg/dL

Monitoring

- Quantitative coronary angiography

**Post-CABG: End Points, Results, Conclusions**

- **Primary end point:** Mean per-patient percentage of grafts with significant progression in SVG ($\geq 0.6$ mm change)
- **Secondary end point:** New occlusions, new lesions, lumen narrowing
- **Results:**
  - aggressive treatment group: significantly less ($P<0.001$) progression, fewer new occlusions and lesions, and ↓ mean lumen diameter
  - revascularization rate ↓ 29% ($P=0.03$)
- **Conclusions:** Mean LDL-C levels of 95 mg/dL associated with greater benefit than mean LDL-C of 135 mg/dL

<table>
<thead>
<tr>
<th></th>
<th>MRE Moderate</th>
<th>MRE Aggressive</th>
<th>Difference %</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression</td>
<td>39</td>
<td>28</td>
<td>28</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>New occlusions</td>
<td>16</td>
<td>10</td>
<td>40</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>New lesions</td>
<td>21</td>
<td>10</td>
<td>52</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Mean lumen change in mm

<table>
<thead>
<tr>
<th></th>
<th>Minimum diameter</th>
<th>Mean diameter</th>
<th>Difference</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimum diameter</td>
<td>-0.38</td>
<td>-0.20</td>
<td>48</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean diameter</td>
<td>-0.34</td>
<td>-0.16</td>
<td>52</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

MRE=Mean per-patient percentage of grafts.

Post-CABG:
Event Rates by Cholesterol Group

Event=PTCA or bypass surgery

$P=0.03$.

Rationale For Statins In ACS

- Revascularization procedures do not modify underlying pathophysiology and only modestly reduce the risk of subsequent events

- Statins contribute to plaque stability and/or regression through a number of lipid-dependent and -independent (pleiotropic) mechanisms (e.g., ↓ inflammation)

- Small differences in therapeutic efficacy can result in significant differences in events

Schwartz and Olsson. Am J Cardiol. 2005;96(suppl):45F.
Role Of Statins In ACS: Non-Lipid Effects

ADP = adenosine diphosphate; CD40-L = CD40 ligand; IFN = interferon; IL = interleukin; vWF = von Willebrand factor.

Pathobiology of Lipid and non-Lipid mechanisms in ACS

Non lipid-related

- Endothelial Dysfunction/Activation
- Inflammation/Immune activation

Inhibitory

Coagulation/Platelet activation

Inhibitory

Lipid-related

- Liver
  - Hepatic cholesterol synthesis

Inhibitory

- Statins

Clinic benefit of statins
- reduced atherosclerosis progression
- reduced clinical events

Content Provided by the American College of Cardiology
# Randomized Trials Of Statins In ACS

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment</th>
<th>Duration</th>
<th>Number Of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIRACL (2001)</td>
<td>Placebo versus atorvastatin 80 mg</td>
<td>4 months</td>
<td>3086</td>
</tr>
<tr>
<td>FLORIDA (2002)</td>
<td>Placebo versus fluvastatin 80 mg</td>
<td>1 year</td>
<td>540</td>
</tr>
<tr>
<td>PROVE-IT (2004)</td>
<td>Pravastatin 40 mg versus atorvastatin 80 mg</td>
<td>2 years</td>
<td>4162</td>
</tr>
<tr>
<td>A to Z (2004)</td>
<td>Placebo for 4 months followed by simvastatin 20 mg versus simvastatin 40 mg for 1 month followed by simvastatin 80 mg</td>
<td>2 years</td>
<td>4496</td>
</tr>
<tr>
<td>PACT (2004)</td>
<td>Placebo versus pravastatin 20-40 mg</td>
<td>1 month</td>
<td>3408</td>
</tr>
<tr>
<td>PRINCESS (presented 2004)</td>
<td>Placebo versus cerivastatin 0.4 mg</td>
<td>3 months*</td>
<td>3605</td>
</tr>
</tbody>
</table>

*Study was designed with a subsequent 18-month period in which both groups were to be treated with cerivastatin 0.4-0.8 mg/dL. However, this was not accomplished due to early termination of study. Schwartz and Olsson. *Am J Cardiol.* 2005;96(suppl):45F
PROVE IT - TIMI 22: Study Design

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

Double-blind

ASA + Standard Medical Therapy

Standard Therapy (Pravastatin 40 mg)  Intensive Therapy (Atorvastatin 80 mg)

Duration: Mean 2 year follow-up (1001 events)

Primary Endpoint: Death, MI, Documented UA requiring hospitalization, revascularization (> 30 days after randomization), or Stroke

Content Provided by the American College of Cardiology
PROVE IT-TIMI 22: A Major Cardiovascular Event Or Death From Any Cause Primary End Point

Death Or Major Cardiovascular Event (%)

- Pravastatin 40 mg
- Atorvastatin 80 mg

$P = .03$

$P = .005$ Overall

PROVE IT-TIMI 22: A Major Cardiovascular Event Or Death From Any Cause At Different Censoring Times

<table>
<thead>
<tr>
<th>Censoring Time</th>
<th>Hazard Ratio (95% CI)</th>
<th>Risk Reduction (%)</th>
<th>Event Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 days</td>
<td>1.25</td>
<td>17</td>
<td>1.9</td>
</tr>
<tr>
<td>90 days</td>
<td>1.50</td>
<td>18</td>
<td>6.3</td>
</tr>
<tr>
<td>180 days</td>
<td>0.50</td>
<td>14</td>
<td>12.2</td>
</tr>
<tr>
<td>End of follow-up</td>
<td>0.75</td>
<td>16</td>
<td>22.4</td>
</tr>
</tbody>
</table>

Atorvastatin Better
Pravastatin Better

**PROVE IT-TIMI 22: CRP Levels At Enrollment And During Follow-Up**

<table>
<thead>
<tr>
<th>CRP (mg/L)</th>
<th>Baseline</th>
<th>30 Days</th>
<th>4 Months</th>
<th>End of Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>12.2</td>
<td>1.6</td>
<td>1.3</td>
<td>1.3</td>
</tr>
<tr>
<td>30 Days</td>
<td>12.2</td>
<td>1.6</td>
<td>1.3</td>
<td>1.3</td>
</tr>
<tr>
<td>4 Months</td>
<td>11.9</td>
<td>2.3</td>
<td>2.1</td>
<td>2.1</td>
</tr>
<tr>
<td>End of Study</td>
<td>11.9</td>
<td>2.3</td>
<td>2.1</td>
<td>2.1</td>
</tr>
</tbody>
</table>

* * P<.001 vs baseline.

** P<.001 vs pravastatin.

Achieved CRP With Intensive Versus Standard Statin Therapy

<table>
<thead>
<tr>
<th></th>
<th>Prava 40 (mg/L)</th>
<th>Atorva 80 (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.3</td>
<td>1.6*</td>
</tr>
<tr>
<td></td>
<td>2.1</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>2.2</td>
<td>1.4*</td>
</tr>
</tbody>
</table>

p<0.001

Death, MI or ACS Rehospitalization (Late Phase)

% of patients with death, MI or, rehospitalization for ACS

Pravastatin 40 mg

Atorvastatin 80 mg

28% RR ↓
P=0.003

Months following randomization

Ray et al. JACC 2005

Content Provided by the American College of Cardiology
Conditional Hazard Ratio of Intensive vs Standard Therapy

Primary endpoint

Year 1

HR 0.5 0.75 1.0 1.25
Intensive Therapy Better

Standard Therapy Better

p=0.07

Year 2

p=0.02

Composite endpoint

Year 1

HR 0.5 0.75 1.0 1.25
Intensive Therapy Better

Standard Therapy Better

p=0.01

Year 2

p=0.01

Ray et al. JACC 2005
Conclusions

- Benefits of intensive therapy occur within weeks, a time window consistent with the early pleiotropic effects

- Continuing high-dose statin therapy in more stable patients beyond the acute phase is associated with similar long-term benefit

  → Two “windows of cardioprotection”

- ACS patients should be started in-hospital on intensive statin therapy and should be continued long-term
AHA/CDC Panel: Recommendations for hs-CRP Laboratory Testing

- Measurements of hs-CRP:
  - Should be performed twice (2 weeks apart)
  - Results averaged, expressed as mg/L
  - Fasting or nonfasting, in metabolically stable patients
  - If level >10 mg/L, test should be repeated, patient examined for sources of infection or inflammation

- Relative risk categories for hs-CRP levels:
  - Low <1 mg/L
  - Average 1.0–3.0 mg/L
  - High >3.0 mg/L

Implications of recent statin trials on ATP III guidelines

Risk categories definitions:

- **Very high risk:**
  1. Multiple risk factors especially DM
  2. Uncontrolled risk factors
  3. Metabolic syndrome
  4. ACS

- **High risk**
  1. CAD
  2. CAD equivalent e.g. PAD, Carotid atheroma, AAA, DM, 2 Risk factors (10y risk > 20%)
Implications of recent statin trials on ATP III guidelines

- **Moderate high risk:**
  2 risk factors (10y risk 10-20%)

- **Moderate risk**
  2 risk factors (10y risk < 10%)

- **Low risk**
  0-1 risk factors

- **Change in LDL-C Galls:**
  - Very high risk LDL-C < 70mg/dl
  - High risk LDL-C < 100mg/dl
Implications of recent statin trials on ATP III guidelines

- Moderate high risk LDL-C < 130 mg/dl
- Moderate and low risk recommendations unchanged

Statin doses that can achieve 30-40% reduction in LDL-C are:

<table>
<thead>
<tr>
<th>Statin</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>10mg</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>20-40 mg</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>40mg</td>
</tr>
<tr>
<td>Pravasatin</td>
<td>40 mg</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>40-80 mg</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>5-10 mg</td>
</tr>
</tbody>
</table>
# ATP III New Galls

## TABLE 2. ATP III LDL-C Goals and Cutpoints for TLC and Drug Therapy in Different Risk Categories and Proposed Modifications Based on Recent Clinical Trial Evidence

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL-C Goal</th>
<th>Initiate TLC</th>
<th>Consider Drug Therapy**</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>High risk: CHD</em> or CHD risk equivalents†</td>
<td>&lt;100 mg/dL</td>
<td>≥100 mg/dL#</td>
<td>≥100 mg/dL†† (optional goal: &lt;70 mg/dL)††</td>
</tr>
<tr>
<td>(10-year risk &gt;20%)</td>
<td>(optional goal: &lt;70 mg/dL)††</td>
<td></td>
<td>(100 mg/dL; consider drug options)**</td>
</tr>
<tr>
<td>*Moderately high risk: 2+ risk factors‡</td>
<td>&lt;130 mg/dL¶</td>
<td>≥130 mg/dL#</td>
<td>≥130 mg/dL (100–129 mg/dL; consider drug options)‡‡</td>
</tr>
<tr>
<td>(10-year risk 10% to 20%)§§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*Moderate risk: 2+ risk factors‡ (10-year</td>
<td>&lt;130 mg/dL</td>
<td>≥130 mg/dL</td>
<td>≥160 mg/dL</td>
</tr>
<tr>
<td>risk &lt;10%)§§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*Lower risk: 0–1 risk factor§</td>
<td>&lt;160 mg/dL</td>
<td>≥160 mg/dL</td>
<td>≥190 mg/dL (160–189 mg/dL: LDL-lowering drug optional)</td>
</tr>
</tbody>
</table>
ALL of the ACS pts treated with Simvastatin 40mg achieved the new LDL treatment goal (70mg/dl) based upon the revised U.S. Guidelines (NCEP-ATPIII)

de Lemos et al. JAMA 2004;292:1307-1316
Primary Efficacy Outcome Measure: First Major Cardiovascular Event*

HR = 0.78 (95% CI 0.69, 0.89)  
P=0.0002

*CHD death, nonfatal non-proc-related 
MI, resuscitated cardiac arrest, stroke

Mean Lipid Levels During Trial

<table>
<thead>
<tr>
<th></th>
<th>TC</th>
<th>LDL</th>
<th>HDL</th>
<th>TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg</td>
<td>178</td>
<td>101</td>
<td>47</td>
<td>156</td>
</tr>
<tr>
<td>80 mg</td>
<td>150</td>
<td>77</td>
<td>47</td>
<td>132</td>
</tr>
</tbody>
</table>

IDEAL
Incremental Decrease in Endpoints through Aggressive Lipid Lowering
IDEAL Study Design...

- Multi-center (190 centers in Northern Europe) prospective, randomized, open-label blinded endpoint classification (PROBE Design)
- Patients with CHD who had experienced a MI
- Received atorvastatin 80 mg/per day or simvastatin 20 mg/per day (approximately 20% of which were increased to 40 mg/day at week 24 in patients whose total cholesterol remained greater than 190 mg/dL or whose LDL-C remained greater than 115 mg/dL).
- Median Duration: 5.5 years
- The Study was designed to have 90% power to detect an anticipate 21% relative risk reduction in primary endpoint
**IDEAL Study Objective & Endpoints...**

**Objective:**
- To determine whether an incremental decrease in the risk of CHD can be achieved by a greater decrease in LDL-C in patients with CHD who had experienced an MI

**Primary Endpoint:**
1. **Major Coronary event**: Coronary death, hospitalization for Non fatal acute MI, or Cardiac arrest with resuscitation

**Secondary Endpoints:**
1. **Major CV event**: Any primary event plus Stroke
2. **Any Coronary Heart Disease event**: Any primary event, any coronary revascularization procedure, or hospitalization for Unstable Angina.
3. **Any Cardiovascular events**: Any of the former plus hospitalization with 1ry diagnosis of CHF and PAD.
4. **Individual components of the composite endpoints**
5. **All cause Mortality**
8,888 patients with CHD who had experienced a myocardial infarction aged of 80 years or younger. The randomized patients had the following characteristics:

- Mean age: 61.7 and +/- 9.5 years
- 19.1% women (mean age 64 +/- 9.5 years)
- Mean baseline Total C: 196 mg/dL
- Mean baseline LDL-C: 122 mg/dL
- Mean baseline HDL-C: 46 mg/dL
Reductions in LDL-C by Treatment Group

Mean LDL-C at 1 Year = 102 mg/dL (2.6 mmol/L)
Mean LDL-C During Treatment = 104 mg/dL (2.7 mmol/L)

Mean LDL-C at 1 Year = 79 mg/dL (2.0 mmol/L)
Mean LDL-C During Treatment = 81 mg/dL (2.1 mmol/L)

Reductions in HDL-C by Treatment Group

Mean HDL-C at 1 Year = 47 mg/dL (1.22 mmol/L)

Mean HDL-C at 1 Year = 46 mg/dL (1.19 mmol/L)

**IDEAL: Primary outcome**

<table>
<thead>
<tr>
<th>Outcome (%)</th>
<th>Simvastatin (n=4449)</th>
<th>Atorvastatin (n=4439)</th>
<th>HR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major coronary event</td>
<td>10.4</td>
<td>9.3</td>
<td>0.89</td>
<td>0.07</td>
</tr>
<tr>
<td>CHD death</td>
<td>4.0</td>
<td>3.9</td>
<td>0.99</td>
<td>0.90</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>7.2</td>
<td>6.0</td>
<td>0.83</td>
<td>0.02</td>
</tr>
<tr>
<td>Cardiac arrest with resuscitation</td>
<td>0.2</td>
<td>0.2</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>
Cumulative Hazard of Cardiovascular Disease


Copyright restrictions may apply.
**IDEAL: Secondary outcomes**

<table>
<thead>
<tr>
<th>Outcome (%)</th>
<th>Simvastatin (n=4449)</th>
<th>Atorvastatin (n=4439)</th>
<th>HR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any CHD event</td>
<td>23.8</td>
<td>20.2</td>
<td>0.84</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>16.7</td>
<td>13.0</td>
<td>0.77</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospitalization for U/A</td>
<td>5.3</td>
<td>4.4</td>
<td>0.83</td>
<td>0.06</td>
</tr>
<tr>
<td>Fatal or nonfatal stroke</td>
<td>3.9</td>
<td>3.4</td>
<td>0.87</td>
<td>0.20</td>
</tr>
<tr>
<td>Major CV event</td>
<td>13.7</td>
<td>12.0</td>
<td>0.87</td>
<td>0.02</td>
</tr>
</tbody>
</table>
IDEAL Study: Secondary End Points

Nonfatal MI

- **Simvastatin**
- **Atorvastatin**

Cumulative Hazard (%)

<table>
<thead>
<tr>
<th>Years Since Randomization</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HR=0.83, P=0.02</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Stroke

**HR=0.87, P=0.20**

Revascularization

**HR=0.77, P<0.001**

PAD*

**HR=0.76, P=0.02**

*Newly diagnosed or requiring hospitalization.

Adapted from Pedersen TR et al. JAMA. 2005;294:2437-2445.
Other Results

- No difference in total mortality
- More nonserious adverse events resulting in drug discontinuation in the atorvastatin group and a greater proportion of patients developing liver-enzyme elevation with atorvastatin 80 mg
- Benefit of atorvastatin in line with achieved LDL cholesterol reduction
# Frequency of Adverse Events and Most Relevant Liver Enzyme Elevations

## Table 4. Frequency of Adverse Events and Most Relevant Liver Enzyme Elevations

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Simvastatin, No. (%) (n = 4449)</th>
<th>Atorvastatin, No. (%) (n = 4439)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>4202 (94.4)</td>
<td>4204 (94.7)</td>
<td>.62</td>
</tr>
<tr>
<td>Any serious adverse event</td>
<td>2108 (47.4)</td>
<td>2064 (46.5)</td>
<td>.42</td>
</tr>
<tr>
<td>Any adverse event resulting in permanent discontinuation of study drug</td>
<td>186 (4.2)</td>
<td>426 (9.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Adverse events resulting in permanent discontinuation of study drug with incidence &gt;0.5% in either treatment group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>51 (1.1)</td>
<td>97 (2.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9 (0.2)</td>
<td>38 (0.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>10 (0.2)</td>
<td>37 (0.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Nausea</td>
<td>6 (0.1)</td>
<td>22 (0.5)</td>
<td>.004</td>
</tr>
<tr>
<td>Investigator-reported myopathy</td>
<td>11 (0.25)</td>
<td>6 (0.14)</td>
<td>.33</td>
</tr>
<tr>
<td>Investigator-reported rhabdomyolysis (subset of coded myopathy)</td>
<td>3 (0.07)</td>
<td>2 (0.05)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>AST &gt;3 × ULN at 2 consecutive measurements</td>
<td>2 (0.04)</td>
<td>18 (0.41)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ALT &gt;3 × ULN at 2 consecutive measurements</td>
<td>5 (0.11)</td>
<td>43 (0.97)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Myopathy defined as CPK &gt;10 × ULN at 2 consecutive measurements with muscle symptoms</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

*Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; ULN, upper limit of normal.

*P values were calculated by 2-sided χ² test.

---

Statin Advisory: Definitions of Muscle Toxicity

- **Myopathy** — a general term referring to any disease of muscles; myopathies can be acquired or inherited and can occur at birth or later in life
- **Myalgia** — muscle ache or weakness without creatine kinase (CK) elevation
- **Myositis** — muscle symptoms with increased CK levels
- **Rhabdomyolysis** — muscle symptoms with marked CK elevation (>10x the upper limit of normal [ULN]) and creatinine elevation (usually with brown urine and urinary myoglobin)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Evaluation Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache, dyspepsia</td>
<td>Evaluate baseline symptoms, 6–8 wk after initiating therapy, then at each follow-up visit</td>
</tr>
<tr>
<td>Muscle soreness, tenderness, or pain</td>
<td>Evaluate baseline muscle symptoms and CK levels; muscle symptoms 6–12 wk after initiating therapy and at each follow-up visit; CK measurement when muscle soreness, tenderness, or pain present</td>
</tr>
<tr>
<td>ALT, AST</td>
<td>Evaluate baseline ALT/AST, 12 wk after initiating therapy, then annually or as indicated</td>
</tr>
</tbody>
</table>

ALT=alanine transferase; AST=aspartate transferase.

Statin Advisory: Clinical Precautions When Prescribing Statin Therapy

- Myopathy more likely to occur at higher doses
- Doses should not exceed those required to attain ATP III goals
- Attention should be paid to factors that may increase risk for myopathy
**Statins Advisory: Risk Factors for Statin-Associated Myopathy**

**Concomitant medications:**
- Fibrates
- Nicotinic acid (rarely)
- Cyclosporine
- Azole antifungals
  - Itraconazole, ketoconazole
- Macrolide antibiotics
  - Erythromycin, clarithromycin
- HIV protease inhibitors
- Nefazodone (antidepressant)
- Verapamil
- Amiodarone
- Large quantities of grapefruit juice (>1 qt/d)
- Alcohol abuse

**Other considerations:**
- Advanced age (especially >80 yr; women more than men)
- Small body frame, frailty
- Multisystem disease (eg, chronic renal insufficiency, especially due to diabetes)
- Multiple medications
- Perioperative periods

**Statin Advisory: Conclusions**

- Statins reduce the incidence of major coronary events, coronary procedures, and stroke in high-risk patients
- This potential is not fully realized due to underuse in clinical practice
- Statins are safe in the vast majority of patients
- Statins should be used with appropriate caution, particularly in selected patients

## Clinical Outcome Trials Testing
### Intensive Vs Standard Statin Therapy

<table>
<thead>
<tr>
<th>Trial</th>
<th>Population</th>
<th>N</th>
<th>Duration Years</th>
<th>LDL-C reduction Mg/dl</th>
<th>Risk reduction %</th>
<th>Risk reduction in CAD death or MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROVE IT-TIMI22</td>
<td>ACS</td>
<td>4162</td>
<td>2</td>
<td>33</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>A-Z</td>
<td>ACS</td>
<td>4497</td>
<td>2</td>
<td>14</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td>TNT</td>
<td>Stable CAD</td>
<td>10000</td>
<td>5</td>
<td>24</td>
<td>22</td>
<td>21</td>
</tr>
<tr>
<td>IBEAL</td>
<td>Stable CAD</td>
<td>8888</td>
<td>5</td>
<td>23</td>
<td>11</td>
<td>11</td>
</tr>
</tbody>
</table>
Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins

### Proportional effects on cause-specific mortality per mmol/L LDL cholesterol reduction

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Events (%)</th>
<th>RR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treatment</td>
<td>Control</td>
</tr>
<tr>
<td></td>
<td>(45 054)</td>
<td>(45 002)</td>
</tr>
<tr>
<td><strong>Vascular causes:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHD</td>
<td>1548 (3.4%)</td>
<td>1960 (4.4%)</td>
</tr>
<tr>
<td>Stroke</td>
<td>265 (0.6%)</td>
<td>291 (0.6%)</td>
</tr>
<tr>
<td>Other vascular</td>
<td>289 (0.6%)</td>
<td>302 (0.7%)</td>
</tr>
<tr>
<td>Any non-CHD vascular</td>
<td>554 (1.2%)</td>
<td>593 (1.3%)</td>
</tr>
<tr>
<td><strong>Any vascular</strong></td>
<td>2102 (4.7%)</td>
<td>2553 (5.7%)</td>
</tr>
<tr>
<td><strong>Non-vascular causes:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>1094 (2.4%)</td>
<td>1069 (2.4%)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>98 (0.2%)</td>
<td>125 (0.3%)</td>
</tr>
<tr>
<td>Trauma</td>
<td>51 (0.1%)</td>
<td>57 (0.1%)</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>487 (1.1%)</td>
<td>550 (1.2%)</td>
</tr>
<tr>
<td>Any non-vascular</td>
<td>1730 (3.8%)</td>
<td>1801 (4.0%)</td>
</tr>
<tr>
<td>Any death</td>
<td>3832 (8.5%)</td>
<td>4354 (9.7%)</td>
</tr>
</tbody>
</table>

Effect p < 0.0001
Proportional effects on major vascular events per mmol/L LDL cholesterol reduction

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Treatment (45 054)</th>
<th>Control (45 002)</th>
<th>RR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-fatal MI</td>
<td>2001 (4.4%)</td>
<td>2769 (6.2%)</td>
<td>0.74 (0.70–0.79)</td>
</tr>
<tr>
<td>CHD death</td>
<td>1548 (3.4%)</td>
<td>1960 (4.4%)</td>
<td>0.81 (0.75–0.87)</td>
</tr>
<tr>
<td>Any major coronary event</td>
<td>33337 (7.4%)</td>
<td>4420 (9.8%)</td>
<td>0.77 (0.74–0.80)</td>
</tr>
<tr>
<td>CABG</td>
<td>713 (1.6%)</td>
<td>1006 (2.2%)</td>
<td>0.75 (0.69–0.82)</td>
</tr>
<tr>
<td>PTCA</td>
<td>510 (1.1%)</td>
<td>658 (1.5%)</td>
<td>0.79 (0.69–0.90)</td>
</tr>
<tr>
<td>Unspecified</td>
<td>1397 (3.1%)</td>
<td>1770 (3.9%)</td>
<td>0.76 (0.69–0.84)</td>
</tr>
<tr>
<td>Any coronary revascularisation</td>
<td>2620 (5.8%)</td>
<td>3434 (7.6%)</td>
<td>0.76 (0.73–0.80)</td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>105 (0.2%)</td>
<td>99 (0.2%)</td>
<td>1.05 (0.78–1.41)</td>
</tr>
<tr>
<td>Presumed ischaemic stroke</td>
<td>1235 (2.8%)</td>
<td>1518 (3.4%)</td>
<td>0.81 (0.74–0.89)</td>
</tr>
<tr>
<td>Any stroke</td>
<td>1340 (3.0%)</td>
<td>1617 (3.7%)</td>
<td>0.83 (0.78–0.88)</td>
</tr>
<tr>
<td>Any major vascular event</td>
<td>6354 (14.1%)</td>
<td>7994 (17.8%)</td>
<td>0.79 (0.77–0.81)</td>
</tr>
</tbody>
</table>

Effect p < 0.0001
5-year absolute benefits on vascular outcomes per mmol/L LDL-C reduction in participants with and without previous MI or CHD.
Implications

The present meta-analysis indicate that the proportional reductions in the incidence of major coronary events, coronary revascularisations, and strokes were approximately related to the absolute reductions in LDL-C achieved with the statin regimens studied.
**Implications**

- The proportional reductions in such major vascular events per mmol/L LDL-C reduction were similar irrespective of the pretreatment cholesterol concentrations or other characteristics (e.g., age, sex, or pre-existing disease) of the study participants.

- Current treatment guidelines are based on lowering LDL-C to particular target levels, with somewhat lower targets for people at higher risk of coronary events.
Implications

The results of this meta-analysis suggest, however, that this strategy may not realise the full potential of such treatment.

- First, assessment of baseline risk should be based on any type of occlusive vascular event (rather than on coronary events alone), since lowering LDL cholesterol with a statin lowers the risks not just of coronary events but also of revascularisation procedures and of ischaemic strokes.

- Secondly, treatment goals for statin treatment should aim chiefly to achieve substantial absolute reductions in LDL-C (rather than to achieve particular target levels of LDL-C), since the risk reductions are proportional to the absolute LDL-C reductions.
Implications

Full compliance with available statin regimens can reduce LDL-C by at least 1.5 mmol/L in many circumstances, and hence might be expected to reduce the incidence of major vascular events by about one third. Ensuring that patients at high 5-year risk of any type of occlusive major vascular event achieve and maintain a substantial reduction in LDL-C would result in major clinical and public health benefits.
**Take Home Messages**

- Aggressive LDL-C lowering reduce CV events and NCEP 2004 Update to be fully adopted
- Physicians must follow the guidelines regarding indications and dose
- Patients already on statins must reduce their LDL-C to the new target
- The messages to the patients are:
  - For the bad cholesterol “the lower is better” for preventing MI, Stroke, need for revascularization and death
Take Home Messages

- Statins are safe overall even for patients with extremely low LDL-C levels, however side effects are more (up to 5%) but reversible
- Need to monitor their LDL-C & HDL-C
- Appropriate diet and exercise programs are essential

⚠️ Need for new therapeutic modalities “Beyond Statins”