First identified in the 1970s
- Mevastatin, a molecule produced by the fungus Penicillium citrinum
- Never marketed
- Mevacor® (lovastatin)
  - The first statin on the market
  - Produced by Merck in 1987
  - 1994 "4S" study
    - After 5 yrs, patients on simvastatin had a 42% less chance of dying of a heart attack.
  - Now the most commonly prescribed cholesterol-lowering medication.

Site of action: Liver
Mechanism of action:
- Reversibly inhibit HMG CoA reductase
- Preventing the liver from manufacturing cholesterol.
- Leads to upregulation of LDL receptors
- Increased uptake of VLDL, IDL, and LDL.

Pleiotropic effects:
- Reverses endothelial dysfunction
- Anti-thrombotic activity
- Anti-inflammatory/Antioxidant
- Plaque stability

Indications:
- Cerebrovascular accident; Prophylaxis
- Diabetes mellitus; Prophylaxis
- Disorder of cardiovascular system, secondary; Prophylaxis
- Primary hypercholesterolemia
- Hypertiglyceridemia
- Familial hypercholesterolemia
- ACS
- Afla prophylaxis
- Chronic Heart Failure
- Atherosclerosis
- Kidney disease
- Metabolic syndrome
- PCI

CRP predicts risk of MI and stroke in apparently healthy men

Efficacy of lovastatin in AFCAPS/TexCAPS subgroups by baseline LDL-C and hsCRP

<table>
<thead>
<tr>
<th>Study group</th>
<th>Rate of cardiovascular events</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low LDL-C/low hsCRP</td>
<td>0.025</td>
<td>0.022</td>
</tr>
<tr>
<td>Low LDL-C/high hsCRP</td>
<td>0.029</td>
<td>0.051</td>
</tr>
<tr>
<td>High LDL-C/low hsCRP</td>
<td>0.020</td>
<td>0.050</td>
</tr>
<tr>
<td>High LDL-C/high hsCRP</td>
<td>0.038</td>
<td>0.055</td>
</tr>
</tbody>
</table>

CRP=C-reactive protein; MI=myocardial infarction
*p=0.02 versus quartile 1; ***p<0.001 versus quartile 1


Median LDL-C=3.9 mmol/L (149 mg/dL). Median hsCRP=1.6 mg/L

AFCAPS/TexCAPS=Air Force/Texas Coronary Atherosclerosis Prevention Study; hsCRP=high-sensitivity C-reactive protein; LDL-C=low-density lipoprotein cholesterol; N/A=not applicable; NNT=number needed to treat to prevent one coronary event

Efficacy of lovastatin in AFCAPS/TexCAPS subgroups by baseline LDL-C and hsCRP
**JUPITER: Clinical events according to magnitude of reduction in LDL-C or hsCRP**

<table>
<thead>
<tr>
<th>Event</th>
<th>NNT for 2y</th>
<th>P &lt; 0.0001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo LDL-C achieved ≥5.7 mmol/L</td>
<td>117</td>
<td>0.0001</td>
</tr>
<tr>
<td>Placebo LDL-C achieved ≥4.7 mmol/L</td>
<td>125</td>
<td>0.0001</td>
</tr>
<tr>
<td>Placebo hsCRP achieved &lt;2 mg/L</td>
<td>135</td>
<td>0.0001</td>
</tr>
<tr>
<td>Placebo hsCRP reduction ≥50%</td>
<td>142</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

**COSMOS – study design**

<table>
<thead>
<tr>
<th>Follow-up (No.)</th>
<th>Placebo</th>
<th>Statin</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>10007</td>
<td>9298</td>
<td>1.0</td>
</tr>
<tr>
<td>1</td>
<td>971</td>
<td>8901</td>
<td>0.56 (0.46-0.68)</td>
</tr>
<tr>
<td>2</td>
<td>953</td>
<td>8901</td>
<td>0.51 (0.42-0.60)</td>
</tr>
<tr>
<td>3</td>
<td>932</td>
<td>8901</td>
<td>0.51 (0.42-0.60)</td>
</tr>
<tr>
<td>4</td>
<td>911</td>
<td>8901</td>
<td>0.51 (0.42-0.60)</td>
</tr>
</tbody>
</table>

**IVUS coronary imaging**

- Normal coronary anatomy
- Rotating transducer
**IVUS detects angiographically ‘silent’ atheroma**

IVUS (intravascular ultrasound) can detect atheroma that is not visible on standard angiography. This suggests that angiography may underestimate the true extent of atherosclerotic disease.

**Statin therapy can reduce atheroma area**

Statin therapy has been shown to reduce the area of atheroma as measured by IVUS. This is evidenced by a decrease in the area of atheroma post-treatment compared to baseline.

**COSMOS lipid profiles**

The COSMOS study looked at the effects of lipid-lowering therapy on lipid profiles. The table shows a reduction in LDL-C, HDL-C, and LDL-C/HDL-C ratio post-treatment compared to baseline.

**Reduction of Plaque Volume**

The graph shows a significant reduction in plaque volume post-treatment compared to baseline. The volumetric decrease is indicated as a percentage, with RED = 5.07% and VESSEL = 4.76%.

**COSMOS IVUS example**

An example of a COSMOS IVUS scan before and after treatment with a statin, showing reduced plaque volume and increased lumen diameter.

**Clinical Relevance of Achieved LDL and CRP After Treatment with Statin Therapy**

The figure illustrates the reduction in LDL and CRP levels after statin therapy, emphasizing the clinical relevance of achieving these targets.

---

Circulation Journal 2009; 73(11): 2110-2117

Circulation Journal: official journal of the Japanese Circulation Society

AZT-CRES 10007 Jan-2010

**Reference:**


**Reference:**


**Reference:**

[3] COSMOS lipid profiles

**Reference:**

[4] COSMOS IVUS example

**Reference:**

[5] Clinical Relevance of Achieved LDL and CRP After Treatment with Statin Therapy
**Elevated serum uric acid levels in metabolic syndrome: an active component or an innocent bystander?**

S. Tsouli et al: Metabolism 2006;55: 1293-1301

**Elevated serum uric acid levels in metabolic syndrome**

- A decrease of 43% in the cumulative incidence of venous thromboembolism
  - Rosuvastatin vs. Placebo
  - HR 0.57, 95%CI 0.37-0.86, P= 0.007

**Elevated serum uric acid levels in metabolic syndrome: an active component or an innocent bystander?**

- Analysis of total venous thromboembolism
  - Rosuvastatin
  - Placebo

- Cumulative incidence
  - Number at Risk
  - Follow-up (years)

- Rosuvastatin: 8,901
  - 8,447
  - 6,575
  - 3,927
  - 1,986
  - 1,376
  - 1,003
  - 548
  - 161
- Placebo: 8,901
  - 8,417
  - 6,574
  - 3,943
  - 2,012
  - 1,381
  - 993
  - 556
  - 182

- HR 0.57, 95%CI 0.37-0.86, P= 0.007

- 43% decrease in the cumulative incidence of venous thromboembolism

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**Effect on serum uric acid levels of drugs prescribed for indications other than treating hyperuricemia**


**ARE STATINS RENOPROTECTIVE?**

**CREATININE AND GFR CHANGES FROM BASELINE TO FINAL VISIT**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Creatinine</th>
<th>% Change</th>
<th>Change in GFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>371</td>
<td>0.8</td>
<td>-0.3</td>
<td>-0.3</td>
</tr>
<tr>
<td>Rosuvastatin 5 mg</td>
<td>297</td>
<td>1.1</td>
<td>1.6</td>
<td>1.6</td>
</tr>
<tr>
<td>Rosuvastatin 10 mg</td>
<td>255</td>
<td>1.4</td>
<td>1.3</td>
<td>1.3</td>
</tr>
<tr>
<td>Rosuvastatin 20 mg</td>
<td>303</td>
<td>1.5</td>
<td>1.3</td>
<td>1.3</td>
</tr>
<tr>
<td>Rosuvastatin 40 mg</td>
<td>284</td>
<td>1.5</td>
<td>1.3</td>
<td>1.3</td>
</tr>
<tr>
<td>Rosuvastatin 60 mg</td>
<td>261</td>
<td>1.6</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>Rosuvastatin 80 mg</td>
<td>237</td>
<td>1.6</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>Rosuvastatin 100 mg</td>
<td>303</td>
<td>1.5</td>
<td>1.3</td>
<td>1.3</td>
</tr>
<tr>
<td>Rosuvastatin 120 mg</td>
<td>284</td>
<td>1.5</td>
<td>1.3</td>
<td>1.3</td>
</tr>
<tr>
<td>Rosuvastatin 140 mg</td>
<td>261</td>
<td>1.6</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>Rosuvastatin 160 mg</td>
<td>237</td>
<td>1.6</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>Atorvastatin 10 mg</td>
<td>136</td>
<td>1.5</td>
<td>1.3</td>
<td>1.3</td>
</tr>
<tr>
<td>Atorvastatin 20 mg</td>
<td>121</td>
<td>1.6</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>Atorvastatin 40 mg</td>
<td>104</td>
<td>1.6</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>Atorvastatin 80 mg</td>
<td>94</td>
<td>1.6</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>Pravastatin 10 mg</td>
<td>34</td>
<td>1.5</td>
<td>1.3</td>
<td>1.3</td>
</tr>
<tr>
<td>Pravastatin 20 mg</td>
<td>30</td>
<td>1.6</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>Pravastatin 40 mg</td>
<td>26</td>
<td>1.6</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>Pravastatin 80 mg</td>
<td>22</td>
<td>1.6</td>
<td>1.1</td>
<td>1.1</td>
</tr>
<tr>
<td>Pravastatin 100 mg</td>
<td>18</td>
<td>1.5</td>
<td>1.3</td>
<td>1.3</td>
</tr>
</tbody>
</table>


**HEART PROTECTION STUDY: LONG-TERM STATIN THERAPY BENEFITS RENAL FUNCTION IN PRESENCE AND ABSENCE OF DIABETES**

N = 5963 diabetic patients, 14,073 non-diabetic patients

Treatment: simvastatin 40 mg or placebo, follow-up 4.6 yrs.

**GREACE: Benefit of aggressive lipid lowering vs usual care on renal function in diabetic and nondiabetic patients**

1600 Patients with CHD; target LDL-C <100 mg/dL; follow-up 48 mos

**Change in GFR (%)**

- Diabetes (n = 313)
  - Atorvastatin 10–80 mg: P < 0.001
  - Usual care: P = 0.06

- No diabetes (n = 1287)
  - Atorvastatin 10–80 mg: P < 0.001
  - Usual care: P = 0.06

*Change from baseline (at entry)*

\[ \text{GFR} = \text{mL/min/1.73 m}^2 \]

Data on file, (DA-CRS-07) AstraZeneca Pharmaceuticals LP. Wilmington, DE
GREACE-MetS: Μεταβολικό σύνδρομο & Νεφρική λειτουργία (baseline data)

<table>
<thead>
<tr>
<th>Metric</th>
<th>MetS</th>
<th>No MetS</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDRD e-GFR (ml/min/1.73 m²)</td>
<td>69.17</td>
<td>83.12</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SUA (mg/dL)</td>
<td>7.3±1.3</td>
<td>6.9±1.1</td>
<td>0.002</td>
</tr>
</tbody>
</table>

GREACE-MetS: Μεταβολικό σύνδρομο & Νεφρική λειτουργία (on treatment data)

<table>
<thead>
<tr>
<th>Metric</th>
<th>MetS (+)/statin (+)</th>
<th>MetS (+)/statin (-)</th>
<th>P value</th>
<th>MetS (-)/statin (+)</th>
<th>MetS (-)/statin (-)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDRD e-GFR (ml/min/1.73 m²)</td>
<td>72.4±10 (15%)* &amp; 64.8±18 (4.8%)*</td>
<td>68.1±17 (8.4%)* &amp; 61.1±14 (4.1%)*</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GREACE-MetS: Time course of vascular events in the two MetS groups

<table>
<thead>
<tr>
<th>Months</th>
<th>0</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
<th>36</th>
<th>42</th>
<th>48</th>
</tr>
</thead>
<tbody>
<tr>
<td>No statins</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>On statins</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

GREACE-MetS: % RRR in all vascular events in statin treated patients

<table>
<thead>
<tr>
<th>CHD all</th>
<th>CHD and MetS</th>
<th>CHD no Mets</th>
<th>p&lt;0.0001</th>
</tr>
</thead>
<tbody>
<tr>
<td>-51</td>
<td>-57</td>
<td>-41</td>
<td></td>
</tr>
<tr>
<td>-65</td>
<td>-55</td>
<td>-45</td>
<td></td>
</tr>
<tr>
<td>-35</td>
<td>-25</td>
<td>-15</td>
<td></td>
</tr>
<tr>
<td>-5</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**GREACE-MetS**: Backward stepwise logistic regression (Multivariate Cox Predictive Model) for all vascular related events in subjects with CHD and MetS on statin and CHD and MetS not on statin treatment.

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR (with every 5% increase)</td>
<td>0.82 (0.70-0.93)</td>
<td>0.001</td>
</tr>
<tr>
<td>eGFR (with every 10% increase)</td>
<td>0.73 (0.64-0.82)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>eGFR (with every 5% reduction)</td>
<td>1.16 (1.07-1.38)</td>
<td>0.003</td>
</tr>
<tr>
<td>eGFR (with every 10% reduction)</td>
<td>1.33 (1.14-1.59)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SUA (with every 5% increase)**</td>
<td>1.09 (1.03-1.18)</td>
<td>0.008</td>
</tr>
<tr>
<td>SUA (with every 5% reduction)**</td>
<td>0.85 (0.74-0.95)</td>
<td>0.002</td>
</tr>
</tbody>
</table>


**METABOLIC VS SYMBIOTIC VLDL METABOLISM**:

**STATINES VS NEPHRIC LEISURE:**

- **ΔeGFR**: 1.22ml/min/year (p=0.0002)
- **ΔeGFR** se atoma me γενετική νόσο: 0.93ml/min/year (p=0.03)
- Ομοσπονδιακή διαφορά σε άτομα με υγειακή ή διαφορική νεφροκρίσει και σεζικματαικότητα
- Μικρή μείωση της ρυθμικής (0.37g/24h)
Statins and renal function: Is the compound and dose making a difference?

H επίδραση των στατινών στη νεφρική λειτουργία πίθανα εξαρτάται από το φάρμακο, την υπολιπιδαιμική δράση και την ομάδα ασθενών

Landmesser et al.; Circulation 2005; 111: 2356-63

Do statins have a beneficial effect on the kidney?

Nature Clinical Practice Nephrology 2006;2: 666-67


Statin treatment may be beneficial to both the kidneys and the heart


Serum LDL-cholesterol - change after 4 weeks -

Ezetimibe (10 mg/d) 15.4 %
Simvastatin (10 mg/d) 15.6 %

VBWG

Statin treatment may be beneficial to both the kidneys and the heart


VBWG

Statins and renal function: Is the compound and dose making a difference?

H επίδραση των στατινών στη νεφρική λειτουργία πίθανα εξαρτάται από το φάρμακο, την υπολιπιδαιμική δράση και την ομάδα ασθενών


VBWG

Do statins have a beneficial effect on the kidney?

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Statin treatment may be beneficial to both the kidneys and the heart
Endothelial function - flow-dependent dilation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Baseline</th>
<th>4 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simvastatin (10 mg/d)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ezetimibe (10 mg/d)</td>
<td>12</td>
<td>12</td>
</tr>
</tbody>
</table>

Statin dose escalation, but not Ezetimibe improves endothelial function

Baseline    4 weeks

<table>
<thead>
<tr>
<th>Drug</th>
<th>Baseline</th>
<th>4 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ezetimibe (10 mg/d)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ezetimibe (10 mg/d)</td>
<td>12</td>
<td>12</td>
</tr>
</tbody>
</table>

P<0.01

Ezetimibe (10 mg/d)
Simvastatin (10 mg/d)

Landmesser et al.; Circulation 2005; 111: 2356–63

Proposed Vasculoprotective Effects of Statins in the Vascular Endothelium

- Reduce thrombogenicity
- Improve plaque stability
- Provide antioxidant effect
- Reduce inflammation

Statin dose escalation, but not Ezetimibe improves endothelial function

Reduction of LDL cholesterol
Change of endothelial function

Proposed Vasculoprotective Effects of Statins in the Vascular Endothelium

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Reduction of LDL cholesterol
Change of endothelial function

Landmesser et al.; Circulation 2005; 111: 2356–63

Endothelium modification in atherosclerosis

Progression of Atherosclerosis Begins With Endothelial Dysfunction

Abnormal endothelium results in:
- Vasoconstriction
- Lipid deposition and reduced clearance
- Platelet and leukocyte adhesion
- Smooth muscle cell migration and growth

High dose pravastatin (80mg) administered to hypercholesterolemic patients with chronic liver disease was safe and well tolerated.


Hepatology 2007;46: 1453-1463
Atherosclerosis Is an Inflammatory Disease

Pleiotropic effects of statins on the vessel wall

- Platelet activation
- Endothelial progenitor cells
- Endothelial function
- NO bioactivity
- Free radicals
- Endothelin
- Inflammation
- Immunomodulation
- MMPs
- LCL cholesterol
- HDL cholesterol
- Triglycerides


Macrophage
Foam cell
CRP
Monocyte
CRP

• A marker of inflammation that may be a predictor of CV events

More than a Marker: Does CRP play a direct role in Atherothrombosis?

PROVE IT: LDL-C and C-Reactive Protein Levels and Outcomes after Statin Therapy

LDL ≥70 mg/dl, CRP ≥1 mg/L 4.5
LDL <70 mg/dl, CRP ≥1 mg/L 3.1
LDL ≥70 mg/dl, CRP <1 mg/L 2.3
LDL <70 mg/dl, CRP <1 mg/L 1.9

60 % Reduction
Lipoprotein-associated phospholipase A\textsubscript{2} (Lp-PLA\textsubscript{2})

Produced by inflammatory cells

- Hydrolyzes oxidized phospholipids to generate proinflammatory molecules
  - Lyso phosphatidylcholine
  - Oxidized fatty acids

- Upregulated in atherosclerotic lesions where it co-localizes with macrophages

The role of Lp-PLA\textsubscript{2} in CHD

- Lp-PLA\textsubscript{2} is expressed in the media and intima of atherosclerotic lesions
- Co-localizes with macrophages, foam cells, and monocytes
- Produces proinflammatory molecules including lysophosphatidylcholine and oxidized fatty acids

Population studies have demonstrated a 2-fold risk increase with elevated Lp-PLA\textsubscript{2}

- Hazard ratio for coronary events
  - Packard: 1.55 (1.28-1.89)
  - Ballantyne: 1.35 (1.14-1.60)

- Hazard ratio for stroke
  - Ballantyne: 1.27 (1.01-1.59)
  - Khusiyenova: 1.21 (1.01-1.45)

- Hazard ratio for CAD
  - Blake: 1.27 (1.01-1.59)
  - Blake: 1.21 (1.01-1.45)

Statin treatment reduces Lp-PLA\textsubscript{2}

- Type IIA dyslipidemia (n = 55):
  - Baseline: 100
  - Atorvastatin 20 mg, 4 mos: 87.1
  - Plasma Lp-PLA\textsubscript{2} activity (nmol x mL\textsuperscript{-1} x min\textsuperscript{-1})

- Type IIB dyslipidemia (n = 21):
  - Baseline: 82.2
  - Atorvastatin 20 mg, 4 mos: 73.8

- *P < 0.001 vs baseline

Lp-PLA\textsubscript{2} is independent of CRP and other CAD Risk Factors

- Relative risk of CAD associated with a 1 SD increase in Lp-PLA\textsubscript{2} or CRP

- Model | RR (95% CI) | P-value
  - Unadjusted CRP | 1.55 (1.28-1.89) | <0.0001
  - Lp-PLA\textsubscript{2} | 1.35 (1.14-1.60) | 0.006

- Multivariable adjustment\* CRP | 1.27 (1.01-1.59) | 0.04
  - Lp-PLA\textsubscript{2} | 1.21 (1.01-1.45) | 0.04

\*Age, systolic BP, TC/HDL-ratio, physical activity, BMI, smoking, DM, alcohol intake, education

Oxidized LDL and thrombogenesis

- Inflamed intima
- Increased expression of ICAM-1
- Increased expression of VCAM-1
- Increased expression of P-selectin
- Increased expression of PDGF
- Increased expression of TGF-β
Superior Reductions in Oxidative Stress in Membranes With Atorvastatin vs Other Statins

In MIRACL, Atorvastatin Enhanced the Removal of Oxidized LDL-C From Vessel Wall

Atherosclerosis May Culminate in Plaque Instability, Rupture, and Thrombosis

Antithrombotic Actions of Statins

Cholesterol lowering and cardiovascular events:
Program on surgical control of the Hyperlipidemias (POSCH)
MIRACL: Atorvastatin Significantly Reduced Recurrence of Ischemic Events in Patients With ACS

Death, nonfatal acute MI, cardiac arrest with resuscitation, or recurrent symptomatic ischemia with objective evidence requiring emergency rehospitalization. Adapted from Schwartz GG et al. JAMA. 2001;285:1711-1718.

What Accounts for the Potential Vasculoprotective Effects of Atorvastatin?

Reduction of lipids

- Endothelial effects
- Anti-inflammatory effects
- Antioxidant effects
- Plaque stabilization

Inhibition of HMG-CoA Reductase May Have Beneficial Effects in Addition to LDL-C Lowering

Hypothesized
Αντιοξειδωτικές δράσεις

- Μείωση των LDL και κυρίως των μικρών πυκνών LDL
- Μείωση της δραστηριότητας της οξυγόνωσης της αίματος (Heme oxygenase)

Επιδράσεις στα ενδοθηλιακά κύτταρα

- Μείωση της παραγωγής ελεύθερων ριζών O₂ (αύξηση της δραστηριότητας της ενδοθηλιακής αιμετικής) (Heme oxygenase)
- Μείωση της σύνθεσης του NO (eNOS)
- Αύξηση της κινοτοποίησης, του πολλαπλασιασμού, της μετανάστευσης και της επιφάνειας των προδρόμων ενδοθηλιακών κυττάρων (EPC)

Αντιφλεμονώδεις δράσεις

- Μείωση της hs CRP
- Μείωση της έκρηξης του MCP-1 (monocyte chemoattractant protein)
- Μείωση της έκρηξης του CD 40 στα ενδοθηλιακά κύτταρα και τα μακροφάγα
- Μείωση της έκρηξης των CDim υποδοχών
- Μείωση της δραστηριότητας των προσεκκλησιακών μορίων των ενδοθηλιακών κυττάρων VCAM-1, ICAM-1 και E-selectin

Επίδραση στις μεταλλοπρωτεινάσεις

- Μείωση της παραγωγής των μεταλλοπρωτεινάσεων που παράγονται από τις μακροφάγη - θεραπευτική της αιμοτροπίας των ανθρώπινων πλακών

Δράσεις στα αιμοπετάλια και στη βρομβωτική διαδικασία

- Μείωση της κανάτας συσυσσώμανσης των αιμοπετάλων
- Μείωση της ανοιχτότητας του άνοιγμα της ακολουθίας των αιμοπετάλων
- Αύξηση της δραστηριότητας της eNOS (αύξηση της συσυσσώμανσης των αιμοπετάλων)
- Μείωση του ιστικού παράγοντα (TF)
- Αύξηση της έκρηξης του ενεργοποιήτη το πλασμαγόνων και κατάστασης της ανοιχτότητας της ακολουθίας των αιμοπετάλων
- Αύξηση της έκρηξης της δραστηριότητας της θρομβομοδουλώσης (αύξηση της αντικαταστηματικής δράσης της πρωτείνης G)

Δράσεις στα λεία μυικά κύτταρα

- Μείωση της μεταδιαδρομής και του πολλαπλασιασμού τους
- Αύξηση της απόσπασης των λείων μυικών κυττάρων
Growing evidence that statins have many more effects unrelated to cholesterol lowering.

Emerging evidence that statins may be useful in other disease states that may greatly impact geriatric patients.
- Osteoporosis
- Dementia
- Cancer

The most common disease of bone, affects about 10 million people in the U.S. >50 yrs old.
- As the elderly population grows, the prevalence increases.
- Characterized by reduced bone mass, microarchitectural deterioration, and increased skeletal fragility.
- Often a silent disease until there is a fracture
- 14.35% will die within 1 year of hip fracture
- Caused by an imbalance between bone formation and bone resorption.

Drugs such as bisphosphonates, estrogen, and selective estrogen receptor modulators (SERMs) are used to slow bone loss.
- Nitrogenous Bisphosphonates are the most commonly prescribed anti-osteoporotic agent.
- They don’t however increase bone formation
- Nitrogenous bisphosphonates (Boniva®, Fosamax®, Actonel®) act on bone metabolism by binding and blocking the enzyme farnesyl diphosphate synthase...

**New Statin Research**

**Osteoporosis**

**Osteoporosis**

**Mechanism of Action**

**Pathway**

FPPS happens to be downstream in the HMG-CoA reductase pathway.
- FPPS prevents the formation of two metabolites that are essential for connecting proteins to the cell membrane aka prenylation.
  - Bisphosphonates are specific to bone and inhibiting prenylation affects many proteins found in osteoclasts.
  - Statin drugs may do this, but unlike bisphosphonates, they aren’t specific to bone tissue.
  - This alone is not promising.
- Second mechanism!
  - In mice, lovastatin was shown to activate the promoter region for bone morphogenetic protein-2.
  - This protein is a growth factor that causes osteoblasts to proliferate.
  - Bone volume increased nearly 50% compared with placebo.
  - Similar effects found with fluvastatin, simvastatin, and mevastatin.
Clinical Studies

- Actual human data is mixed on whether statins reduce the incidence of fractures in humans.
- None of the studies were RCTs designed to examine the issue.

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Design</th>
<th>No. of Statin users</th>
<th>Fracture site</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meier et al(15) 2001 JAMA</td>
<td>Case-control</td>
<td>1,030</td>
<td>All</td>
<td>OR 0.55 (0.44-0.69)</td>
</tr>
<tr>
<td>Bauer et al(18) SOF and R FR30 trial</td>
<td>Cohort</td>
<td>598</td>
<td>Hip</td>
<td>OR 0.30 (0.08-1.18)</td>
</tr>
<tr>
<td>LaCroix et al(19) WHI OS</td>
<td>Case-control</td>
<td>7,847</td>
<td>Hip</td>
<td>HR 0.98 (0.60-1.62)</td>
</tr>
<tr>
<td>Reid et al(21) LIPID study</td>
<td>Randomized</td>
<td>4,512</td>
<td>All</td>
<td>HR 1.05 (0.80-1.37)</td>
</tr>
</tbody>
</table>

- Doses may need to be higher to affect bone than to lower cholesterol.

Why Inconsistent Findings?

- Non-controlled trials
  - Obesity: more likely to be on cholesterol, but less likely to have a fracture.
  - Test a specific statin

Future Study

- Prospective randomized controlled trials
  - Exclude confounding variables
- Studies looking at specific statins
  - Often grouped together
  - Pravastatin has consistently failed to demonstrate fracture protection
- Synergism between bisphosphonates and statins

Dementia

- Dementia is the decline of reasoning, memory, and cognitive functions caused by underlying medical conditions/diseases. This decline eventually impairs the ability to carry out everyday activities.
- It is estimated that more than 5 million people live with some form of dementia in the US.
- Alzheimer's is the most common age-related memory loss disease; 30-50% post 85 yrs of age.
- #1 reason for placing elderly in the nursing home
- 6th leading cause of death
- Evidence that patients using statins may have better cognitive performance compared with those not using statins.
- Some studies, high cholesterol levels appear to accelerate the formation of beta-amyloid plaques.
ApoE: Lipoprotein found on the surface of chylomicrons and IDL. Also plays a role in Alzheimer’s disease and cognition. Elevated cholesterol levels in brain neurons may alter membrane functioning and result in the cascade leading to plaque formation and AD. The E4 allele increases the risk of developing AD by 10-30% by age 75. ApoE can signal the production of amyloid-beta. ApoE4 carriers tend to have high cholesterol. Statins may reduce production of beta-amyloid protein. Statins that cross blood-brain barrier may reduce the ability of beta-amyloid to act as a seed for neurofibrillary tangle formation.

Hydrophilic vs. lipophilic

Memory loss however, is listed as a possible side effect for statins.

The second most common cause of dementia. Caused by atherosclerosis or hardening of the arteries in the brain. Partially blocking blood flow can cause an infarction. Associated with hypertension and high cholesterol. Treating these conditions can slow the progress of vascular dementia.

According to the National Cancer Institute, taking a statin may help protect you against some forms of cancer. Breast, Colorectal, Liver, Lung, Ovarian and Prostate cancer studied so far. Studies show statins may be useful in both prevention and treatment of cancer.

Myelin hypothesis

Cholesterol is essential in the formation of myelin. The more lipophilic statins are able to cross the blood-brain barrier and decrease the amount of CNS cholesterol below the critical value necessary for the formation of myelin. Inadequate myelin production results in demyelination of nerve fibers in the CNS, resulting in memory loss.

Cholesterol also seems to affect β-amyloid plaques. Better designed controlled trials are needed to validate the finding that statin therapy may be protective against cognitive decline in older patients.
Breast Cancer – Many studies demonstrated in vitro inhibition of breast cancer cell lines by statins, and synergistic effects with other agents as well. An example would be Campbell et al’s Breast cancer growth prevention by statins in Cancer Res. 2006 Sep;66(17):8707-14.

Colon Cancer – There are many reports of statins inducing apoptosis in human colon cancer cell lines and preventing its carcinogenesis. Furthermore, synergists with COX-2 inhibitors, gamma tocotrienol, chemotherapy, TRAIL, butyrate has been demonstrated in vitro and studies showing statins ability to reduce inflammation in colon tissue raises the hope that it may be useful in inflammatory bowel diseases as a chemopreventative against colon cancer.

Ovarian Cancer – There is research to establish that statins induces cell death in ovarian cancer. What is interesting is the existence of possible differential effect between lipophilic (eg simvastatin) v. hydrophilic (e.g. pravastatin) statins (Kato et al, J Cell Mol Med. 2009 May 11)

Unlike the in vitro, there is not as much clinical evidence in humans.

There was actually concern in 2000s that statin use may increase cancer - Dispelled after the analysis of large studies
- Still the possibility of carcinogenic properties
- In humans, studies use statins as either adjuvants to treat cancer or to prevent cancer.

Evidence for Risk Reduction

- Breast Cancer - In a review by Kochhar and team of 40,421 females, statin use was associated with a 31% risk reduction of breast cancer after controlling for age, smoking, alcohol use, and diabetes (J Clin Oncology 26: 73, 2008).
- In the same vein, Kwan et al. observed that breast cancer patients who took statins after diagnosis were less likely to have had recurrences than were patients who did not take statins (Breast Co-Op Treat. 2008 Jan;16(1):573-9).
- In 2008, Kumar et al. made the interesting observation that women on statins who developed breast cancer developed less aggressive cancers which are of lower grade and less invasive (Cancer Epidemiol Biomarkers Prev. 2008 May;17(5):1298-33).

Evidence for adjuvant treatment

- Enhances the cytotoxic and apoptotic effects of doxorubicin chemotherapy against human colon cancer cells and in murine tumor models (Oncol Rep. 2008 May;19(3):795-9)
- Synergizes with zoledronic acid (Zometa, a bisphosphonate) against myeloma (Anticancer Drugs. 2006 Jul;17(6):421-9)
Discussion
- A serious look should be taken at statins for primary/secondary cancer prevention.
- As long as patient has no other contraindications, it is reasonable to consider statin therapy in specific clinical trials.
- Not all statins are equal and some may work better than others.
- Although most of the available evidence suggests a possible beneficial effect of statins on cancer, further study is needed with better designed trials.

Other areas of potential
- Auto-immune conditions
- Organ transplantation
- Polycystic ovarian syndrome (PCOS)
- Arrhythmias
- Chronic obstructive pulmonary disease (COPD)
- Sepsis
- Contrast-induced nephropathy
- Cataract
- Age-related macular degeneration
- Sub-arachnoid hemorrhage
- Asthma
- Thromboembolism

Conclusion
- Statins have great untapped potential in many disease states.
- This potential should be looked at closely but also skeptically.
  - Beneficial for drug companies to add as many indications as possible.
  - Closely look at the data presented and evaluate with an open mind.
- Unfortunately with many statins coming off patent, there isn’t much incentive for companies to fund other studies.