Statins: from molecular pharmacology to controlled clinical trials

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Cardiovascular Medicine
Quillen College of Medicine

PRESSE MÉDICALE, original paper in July 1916:
Langen CD, Professor of Medicine, Weltearden University, Dutch East Indies (JAVA)

“Blood cholesterol levels in Indonesian natives are half as high as those in Europeans”

“Whether this hypocholesterolemia of Indonesians is related to nutrition or a genetic trait will require further evaluation”

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PLASMA TOTAL CHOLESTEROL IN UNACCULTURATED POPULATIONS

MEAN TC: 123 ± 10 mg/dl (n=13)
95% CONFIDENCE LIMIT 117 - 129 mg/dl
MEAN BMI: 22.5 kg/m² (n=13)
Plasma Lipids and Apolipoproteins in a Population of Orang Asli (“Aborigines”) from West Malaysia
Cadlish JK et al. Atherosclerosis 1997;129: 49-51

Lipid males >40 YO (n=45) Females >40 YO (n=23)
Total cholesterol 66 mg/dl 69 mg/dl
LDL-cholesterol 27 mg/dl 33 mg/dl
HLD-cholesterol 14 mg/dl 12 mg/dl
Triglycerides (fasting uncertain) 114 mg/dl 166 mg/dl

CORD BLOOD (NEONATAL) LIPIDS

<table>
<thead>
<tr>
<th>WT kg</th>
<th>BMI kg/m²</th>
<th>TC</th>
<th>LDL-C</th>
<th>HDL-C</th>
<th>TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>n=68</td>
<td>3.37</td>
<td>14</td>
<td>56 ± 15</td>
<td>23 ± 9</td>
</tr>
<tr>
<td>Female</td>
<td>n=37</td>
<td>3.24</td>
<td>14</td>
<td>61 ± 18</td>
<td>24 ± 10</td>
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</tbody>
</table>

DYSLIPIDEMIA-MODULATING AGENTS (%)

<table>
<thead>
<tr>
<th>LDL-C</th>
<th>TG</th>
<th>HDL-C</th>
<th>LP(a)</th>
<th>LP-PLA₂</th>
<th>CRP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LDL-C</strong></td>
<td><strong>STATIN</strong></td>
<td>20-65</td>
<td>10-35</td>
<td>5-15</td>
<td>0</td>
</tr>
<tr>
<td><strong>CEZETIMIBE</strong></td>
<td>15-20</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td><strong>RESINS</strong></td>
<td>15-30</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>TG</strong></td>
<td><strong>FIBRATES</strong></td>
<td>0-10</td>
<td>30-50</td>
<td>5-20</td>
<td>0</td>
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<tr>
<td><strong>NIACIN</strong></td>
<td>5-25</td>
<td>20-50</td>
<td>15-35</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>OMEGA-3</strong></td>
<td>0</td>
<td>35-50</td>
<td>0-5</td>
<td>0</td>
<td>0</td>
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<tr>
<td><strong>HDL</strong> AND <strong>LP(a)</strong></td>
<td><strong>AGENTS</strong></td>
<td>5-25</td>
<td>20-50</td>
<td>15-35</td>
<td>0</td>
</tr>
<tr>
<td><strong>NIACIN</strong></td>
<td>5-25</td>
<td>20-50</td>
<td>15-35</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>CETP #Anacetrapib</strong></td>
<td>40</td>
<td>140</td>
<td>10-0</td>
<td>0-10</td>
<td>0-10</td>
</tr>
</tbody>
</table>

* ) effect when TG >400
# ) NEJM 2010; 363 : 2406 - 2415

CETP Inhibition
Cholesteryl ester transfer protein (CETP) is a plasma protein that catalyzes the transfer of CE from HDL to apoB-containing lipoproteins (VLDL and LDL-C) in exchange for triglyceride

Liver Free Cholesterol (FC) in Extrahepatic Tissues
VLDL, IDL, LDL, CM
CE
LDL-R
Bile
CE
LCAT
HDL
CETP Inhibition
Changes in Cholesterol Levels and Blood Pressure during the Study Period.

Lp(a) and Cardiovascular Disease Risk

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-smokers</td>
<td>5-40 years</td>
<td>Non-smokers</td>
</tr>
<tr>
<td>Non-smokers</td>
<td>5-40 years</td>
<td>Non-smokers</td>
</tr>
<tr>
<td>Non-smokers</td>
<td>5-40 years</td>
<td>Non-smokers</td>
</tr>
<tr>
<td>Non-smokers</td>
<td>5-40 years</td>
<td>Non-smokers</td>
</tr>
</tbody>
</table>

Lp(a) borderline high (ULN) 30mg/dl (=75 nM)


AKIRA ENDO, DISCOVERER OF THE FIRST STATIN (ML-2368, 1972)

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History
1949 John Gofman links lipoproteins to heart disease
1959 HMGCoA enzyme identified (Bucher N. Fed Proc 1959;18:205)
1964 Konrad Bloch (Harvard) Nobel Prize for sterol biogenesis
1969 AKIRA ENDO, inspired by A. Fleming, postulates that fungi should produce cholesterol synthesis inhibitors
1972 Endo, after testing 6,392 fungus strains, isolates from Penicillium citrinum first statin (ML236B, mevastatin, later named Compactin®, Beecham Ltd.)
1976 Period 1972-76: disappointing animal tests by Endo
1978 Successfull clandestine human tests incite the Sankyo Co. to develop compactin as a drug
1979 Endo discovers 2nd statin (monacolin*; J Antibiotics 1979;32:852-54), later called lovastatin (Mevacor® Merck®)
1987 Merck starts international sale of lovastatin/Mevacor
1994 4S Trial: simvastatin (produced by side-chain methylation of lovastatin) reduces all-cause mortality

* Patents for Monacolin (A Endo): Feb. 1979, for Lovastatin/Mevacor (AW Albers, MERCK)
Akira Endo
(born 1933)

- Heinrich Wieland Prize 1987
- Warren Alpert Prize Harvard, 2000
- Albert Lasker Award 2008*)

*) Eighty Lasker Laureates also received Nobel Prize, incl. 28 in last 20 years

Rate-limiting Step of Cholesterol Synthesis: HMG-CoA Reductase

Inhibitors of HMG-CoA Reductase

<table>
<thead>
<tr>
<th>Agent</th>
<th>Total Mortality</th>
<th>P-Value</th>
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</thead>
<tbody>
<tr>
<td>simvastatin</td>
<td>↑ - 30%</td>
<td>&lt; 0.0003</td>
</tr>
<tr>
<td>pravastatin</td>
<td>↓ - 22%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>rosuvastatin (LDL&lt;50)</td>
<td>↓ - 12%</td>
<td>&lt; 0.0003</td>
</tr>
<tr>
<td>Niaspan® (LDL-C 40-80mg/dl)</td>
<td>no ± with simvastatin ± ezetimibe)</td>
<td></td>
</tr>
<tr>
<td>anacetrapib (produced LDL-C of no ± in CV event!) &amp; +40% in HDL-C of +140%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Statins - Molecular Basis of Clinical Trials

THE MEVALONATE PATHWAY

HMG-CoA \[\rightarrow\] HMG-CoA Reductase Inhibitors (Statins)

Geranyl-synthase Inhibitors (Amino-bisphosphonates)

Geranyl Diphosphate \[\rightarrow\] Cholesterol

Geranylgeranyldiphosphate \[\rightarrow\] GTPase Activator Protein (Rho, Cdc42, Rac)

Cavin-1 \[\rightarrow\] Rab proteins

Ubiqitination (Ubiquitin Q8)
Importance of Peptide Glycosylation

The covalent attachment of oligosaccharides to peptides is one of the major biosynthetic functions of the endoplasmic reticulum (ER)

About half of human proteins are glycosylated

Most of the membrane bound proteins produced in the ER -- including those to be transported to the Golgi apparatus, endosomes, lysosomes and plasma (surface) membranes -- are glycoproteins. Contrarily, very few proteins in the cytosol are glycosylated

A special lipid from the mevalonate (pre-sterol) pathway called DOLICHOL co-valently binds oligosaccharides to be attached to peptides in the ER membrane

Glycosylation is a protein modification that plays a major role in determining protein folding and stability

Abrogation of Insulin-like Factor-I (IGF-I) and Insulin Action by Mevalonic Acid Depletion


In human pre-adipocytes and adipocytes in culture, IGF and insulin receptors are shown to depend critically upon statin-sensitive receptor glycosylation.

Statin-induced dolichol depletion determines a retention of un-glycosylated receptors in the endoplasmic reticulum

Glycosylation inhibitors such as tunicamycin, but not farsenylation inhibitors, mimicked the statin effects

Statin Therapy in Special Populations

Diabetics

Recent retrospective analyses suggest that statins in elderly patient were mildly diabetogenic.

In Jupiter (NEJM 2008;359:21952207), physician reported DM occured in 270 treated vs. 216 placebo patients; corresponding Hgb-A1C were 5.88% vs. 5.80%, Δ = 0.08%; FBS 98mg/dl vs. 98mg/dl.

In a 13-trial (n=9,1140 patients) meta-analysis (Lancet 2010;375:735-42), new DM (FBS>7mM) was diagnosed in 4.89% statin vs. 4.5% placebo patients. But new DM had better outcome than non-DM placebo patients and there were no corrections for advanced age confounders (HT, β-block, HCT, on treatment BMI).
New Onset Diabetes in 3 Large Randomized Trials with Atorvastatin: Waters DD et al. JACC 2011 (April 5); 57:1535-1545

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>New DM</th>
<th>TNT (n=7,595)</th>
<th>IDEAL (n=7,461)</th>
<th>SPARCLE (n=3,803)</th>
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<tr>
<td></td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>FBG mg/dl</td>
<td>108</td>
<td>96</td>
<td>108</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>P&lt;0.0001</td>
<td>P&lt;0.0001</td>
<td>P&lt;0.0001</td>
<td>P&lt;0.0001</td>
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<tr>
<td>BMI kg/m²</td>
<td>30.7</td>
<td>27.8</td>
<td>28.9</td>
<td>26.8</td>
</tr>
<tr>
<td></td>
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<td>P&lt;0.0001</td>
<td>P&lt;0.0001</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>BP % pts</td>
<td>62%</td>
<td>49%</td>
<td>40%</td>
<td>29%</td>
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<tr>
<td></td>
<td>P&lt;0.0001</td>
<td>P&lt;0.0001</td>
<td>P&lt;0.0001</td>
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<tr>
<td>β-block % pts</td>
<td>60%</td>
<td>53%</td>
<td>79%</td>
<td>74%</td>
</tr>
<tr>
<td></td>
<td>P&lt;0.0001</td>
<td>P&lt;0.025</td>
<td>P&lt;0.0025</td>
<td>P&lt;0.0006</td>
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<tr>
<td>LDL-C mg/dl</td>
<td>99</td>
<td>97</td>
<td>119</td>
<td>122</td>
</tr>
<tr>
<td></td>
<td>P&lt;0.108</td>
<td>P&lt;0.031</td>
<td>P&lt;0.0041</td>
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<tr>
<td>HDL-C mg/dl</td>
<td>48</td>
<td>48</td>
<td>43</td>
<td>47</td>
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<tr>
<td></td>
<td>P&lt;0.0001</td>
<td>P&lt;0.0001</td>
<td>P&lt;0.0001</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>TG mg/dl</td>
<td>158</td>
<td>130</td>
<td>152</td>
<td>128</td>
</tr>
<tr>
<td></td>
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<td>P&lt;0.0001</td>
<td>P&lt;0.0001</td>
<td>P&lt;0.0001</td>
</tr>
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</table>

Importance of Peptide Lipidation

Isoprenylation is a posttranslational peptide modification that plays a critical role in peptide localization and function. Special transferases attach the lipophilic farnesyl or geranyl-geranyl moieties to peptides expressing a CAAX sequence (cysteine---aliphaticAA---aliphaticAA---C-terminalAA). These attachments permit the peptides to exert their functions by anchoring to intra-cellular and surface membranes, and determining intra- and inter-molecular hydrophobic interactions.

For instance, isoprenylated monomeric (Ras, Ran, Rhob, Rheb, Rac, Rab, Rap, RND) and trimeric G-proteins (α- or γ-subunits) regulate mitosis, apoptosis, cell adhesion, cell migration, inflammation (NF-κB), coagulation, and other crucial cell functions.

Thus, statins, by influencing isoprenoid availability, may exert many effects not directly related to cholesterol.

LIPIDATION

Membrane protein attachment by fatty acids (myristic, palmitic) and isoprenoids (farnesyl, geranyl-geranyl)
Statin Therapy in Special Populations

5. Heart Failure

In the CORONA trial (NEJM 2007; 357:2248-61), HF patients (n=5,011, age >60y, LVEF 0.31, CRP 3.5mg/l) randomized to 10mg rosuvastatin/24h/placebo had a 45% LDL-C↓ and 37% CRP↓, but there was no difference in the combined CV-outcome (CV death + nonfatal MI / stroke) after 33 months.

Does CORONA reflect Ras-mediated limitation of compensatory cardiac hypertrophy?
Effects of Statins on Monomeric G-protein Isoprenylation

Statins ↓ G-protein Lipidation

CTGF, Coagulation factors

Corona HF Trial

CRP

Importance of Peptide Lipidation in the Blood Coagulation Cascade


Statins can downregulate the blood coagulation cascade, mostly because of decreased tissue factor (TF) activity.

TF-initiated coagulation plays a pivotal role in fibrin-rich clot formation in both slow-flow veins and high-flow arteries (platelet-rich thrombi in athero-thrombosis).

Most of the anticoagulant effects of statins are attributable to the inhibition of isoprenylation (lipidation) of signaling proteins.

TF synthesis depends upon Rho kinase activation via geranyl-geranylation of monomeric G protein Rho.

Statin-induced decreased TF expression can be reversed supplying mevalonate.

Original Article

A Randomized Trial of Rosuvastatin in the Prevention of Venous Thromboembolism


In Jupiter, 17,802 subjects with LDL-C <130 mg/dL and CRP > 2 mg/l were randomized to 20mg rosuvastatin/day or placebo. At entry, median age was 66y, BMI 28 kg/m², LDL-C 108 mg/dl, HDL-c 49 mg/dl, and CRP 4.25 mg/l. Over a median follow-up of 1.9 y, rosuvastatin decreased total venous thromboembolism risk (VTE) by -43% (HR 0.57; P<0.009), without increased risk of bleeding.

For the prospective subgroup “provoked VTE” (trauma, surgery, cancer/chemotherapy, hospitalization-associated), risk reduction was even higher, -48% (HR 0.52).

For the subgroup total deep vein thrombosis (with or without VTE), risk reduction was -45% (HR 0.55; P <0.003)
Effects of Statins on Monomeric G-protein Isoprenylation

Ramasubbu, K. et al. J Am Coll Cardiol 2008;51:415-426

Rac1-Induced CTGF Regulates Connexin 43 and N-Cadherin Expression in AF

Adam, O. et al. J Am Coll Cardiol 2010;55:469-480 (FIG 8, p. 478)

Atrial Fibrosis: Mechanisms and Clinical Relevance in Atrial Fibrillation
Burstein B, Nattel S
JACC 2008;51:802-809 (review; 113 references)

“...This paper reviews the current understanding of how atrial fibrosis creates a substrate for atrial fibrillation”

Statin Therapy in the Prevention and Treatment of Atrial Fibrillation
Lee LY, Blaha MJ, Jones SR. J Clin Lipidol 2011;5:18-29 (Systematic Review, 81 References)

Conclusion:
“Statin therapy appears to be useful in the prevention of AF in patients with coronary artery disease and possibly congestive heart failure and in the prevention of perioperative AF in cardiac surgery.”
Prevention of Atrial Fibrillation with Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receoptor Blockers: a Meta-Analysis

Healy GS et al J Am Coll Cardiol 2005;45:1832-1839

CONCLUSION:
“ARB’s appear to be effective in the prevention of AF”

CRP-synthesis suppression by statin is mediated by reduced geranyl-geranylation of Rac-1 (Hep3B cells)


Effects of Statins on Monomeric G-protein Isoprenylation

CRP synthesis suppression by statin is mediated by reduced geranyl-geranylation of Rac-1 (Hep3B cells)

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

LDL > 70 mg/dL, CRP > 2 mg/L
LDL > 70 mg/dL, CRP < 2 mg/L
LDL < 70 mg/dL, CRP > 2 mg/L
LDL < 70 mg/dL, CRP < 1 mg/L

n = 4,164
2005;352:20-28 Ridker PM. NEJM

follow-up (years)
LDL ≤ 70 mg/dL, CRP ≤ 1 mg/L
LDL > 70 mg/dL, CRP > 2 mg/L
LDL > 70 mg/dL, CRP < 2 mg/L
LDL < 70 mg/dL, CRP > 1 mg/L

0.00 0.20 0.40 0.60 0.80 1.00
Recurrent MI or Coronary Death

2.5 2.0 1.5 1.0 0.5 0.0
Follow-Up (Years)

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Statins: Clinical Pharmacology

PREVALENCE OF STATIN THERAPY

Statins are by far the best-selling prescription drugs worldwide

Statin sales worldwide in 2009 exceeded 25 billion dollars

The best-selling statin, atorvastatin (Lipitor®), is about to become generic in November 2011

STATINS: IC50's for hrHMG-CoA, logP(log of partition coefficient), protein binding (PB), T½, and disposal

<table>
<thead>
<tr>
<th></th>
<th>PRAVA</th>
<th>FLUVA</th>
<th>SIMVA</th>
<th>ATORVA</th>
<th>ROSUVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC50nM*</td>
<td>60</td>
<td>30</td>
<td>15</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Log P</td>
<td>-0.23</td>
<td>3.24</td>
<td>4.68</td>
<td>4.06</td>
<td>0.13</td>
</tr>
<tr>
<td>PB, %</td>
<td>50</td>
<td>98</td>
<td>95</td>
<td>98</td>
<td>88</td>
</tr>
<tr>
<td>T½, h</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>14</td>
<td>20</td>
</tr>
<tr>
<td>%renal↑</td>
<td>20</td>
<td>3</td>
<td>13</td>
<td>&lt;2</td>
<td>10</td>
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<tr>
<td>Hepatic 1st Pass</td>
<td>60</td>
<td>60</td>
<td>70</td>
<td>30</td>
<td>60</td>
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* Science 2001;292:1160-1162
STATINS: METABOLISM BY P450 ENZYMES

<table>
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<tr>
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<th>SIMVA</th>
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<th>PRAVA</th>
<th>FLUVA</th>
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<tbody>
<tr>
<td></td>
<td>+</td>
<td>+</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>3A4</td>
<td>+</td>
<td>+</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>2C9</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>(+)</td>
<td>(+)</td>
</tr>
<tr>
<td>2C8</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>(+)</td>
<td>(+)</td>
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</tbody>
</table>

* Activity increased with drugs acting as substrates and/or inhibitors of 3A4:
  - Imidazole antifungals, macrolides, HIV protease inhibitors, cyclosporine, tacrolimus, sirolimus, verapamil, diltiazem, labetalol, amiodarone, SNRI’s, tricyclics, diazepam, nefazodone, cimetidine, grapefruit, docetaxel, doxorubicin, vinblastine.

STATINS: DRUG INTERACTIONS

<table>
<thead>
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<th>LOVA</th>
<th>SIMVA</th>
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<th>PRAVA</th>
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<th>ROSUVA</th>
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<tbody>
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<td>Imidazole Antifungal</td>
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<td>+</td>
<td>+</td>
<td>--</td>
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</tr>
<tr>
<td>Amiodarone</td>
<td>+</td>
<td>+</td>
<td>NR</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>NR</td>
<td>+</td>
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<tr>
<td>Macrolides</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>NR</td>
<td>+</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>HIV Protease Inhibitors</td>
<td>+</td>
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<td>+</td>
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</tr>
<tr>
<td>Warfarin</td>
<td>+</td>
<td>+</td>
<td>--</td>
<td>--</td>
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</tr>
<tr>
<td>SSRI</td>
<td>+</td>
<td>+</td>
<td>+</td>
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NR: not reported

PERCENT REDUCTION OF LDL-C BY 20mg/d STATIN

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<th>ROSUVA</th>
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<tr>
<td>-20%</td>
<td>-20%</td>
<td>-25%</td>
<td>-35%</td>
<td>-45%</td>
<td>-55%</td>
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STATIN DOSE (mg/d) TO REDUCE LDL-C BY 40-45%

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<th>ROSUVA</th>
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<th>CERIVA</th>
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<tbody>
<tr>
<td>(80)</td>
<td>(80)</td>
<td>80</td>
<td>40*</td>
<td>20</td>
<td>10</td>
<td>4</td>
<td>0.4</td>
</tr>
</tbody>
</table>

* FDA restricted simvastatin 80mg (June 8, 2011) based on the SEARCH trial, showing myopathy (rhabdomyolysis) in 52 (20%) pts. with 80mg, but only in 1 (0%) pt. with 20 mg simvastatin.

STATIN INTOLERANCE

DEFINITIONS BY NATIONAL LIPID ASSOCIATION (NLA)

1) Myalgia...............Muscle aches, CK below ULN
2) Myopathy...............Myalgia plus CK > 10x ULN
3) Rhabdomyolysis... Myopathy plus creatinine > ULN (CK often >40x >ULN)
STATIN INTOLERANCE
DEFINITIONS/GUIDELINES BY NATIONAL LIPID ASSOCIATION

1) FDA and NLA recommend AST/ALT (LFT) measurements at baseline; FDA additionally at 3 months and annually

2) LFT's elevated < 3x ULN, continue statin, if this degree of LFT's persists, consider lowering statin dose or may discontinue statin ("judgement")

3) AST/ALT attributable to obesity/DM-2 : continue statin; if active liver disease is suspected, esp. with hyperbilirubinemia: discontinue; elevated gamma glutamyl transpeptidase (γGT) as such is not a reason for statin discontinuation

4) If AST/ALT is > 3x ULN (< 3% of patients), discontinue statin

RISK FACTORS OF STATIN INTOLERANCE

- Elderly, frail patients
- Females
- Asians (Chinese)
- Renal Disease (elevated creatinine)
- Hypothyroidism
- High Statin Doses
- Glucocorticoid Therapy
- Immunosuppression, HIV
- Infection
- Postoperative
- Alcoholism
- Drugs (fibrates, P450 CYP3A4 metabolizers)
- Genetic predisposition

MANAGEMENT OF STATIN MYALGIA

If CK ↑ < 10x ULN, may continue statin, but monitor CK

If CK ↑ > 10x ULN and/or creatinine > ULN: stop statin

Monitor Transaminases (LFT’s)
  if is < 3x ULN → continue or lower dose of statin
  if > 3x ULN → stop statin

Try:

Statin dose (in mg/d: rosuvata 2.5, fluva-XL 80, pitava 1)

Vitamin D (1000 IU/d) and/or ubiquinone / CoQ10 (200mg/d)

Risk associated with statin therapy--
A systematic overview of randomized clinical trials
Kashani et al. Circulation 2006;114:2788-97

Among 74,102 subjects from 35 trials, elevations in myalgia, CK, rhabdomyolysis, or discontinuation due to any effect were not significant (cerivastatin trials excluded)

Transaminase elevations (≥ 3x ULN) ≥ 2 consecutive sampling) occurred in 0.43% of patients (RR 1.3) – but liver disease or liver failure was not significantly elevated

Routine monitoring of CK and transaminases (ALT) does not appear warranted in asymptomatic patients.
Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials
Cholesterol Treatment Trials (CTT) ; Lancet 2010;376:1670-1681

Each trial ≥ 1000 patients treated for ≥ 2 yrs; 5 trials compared high- vs. low-dosed statin, 21 trials statins vs. control (placebo).

Each 1 mMol/l LDL-C reduction lowered the risk of occlusive vascular events by about 20%, irrespective of baseline cholesterol concentration, which implies that a 2-3 mMol/l reduction would reduce risk by 40% or more.

Across the 26 trials, all-cause mortality was reduced by 10% for each 1mmol/l LDL-C reduction, largely reflecting CV death reductions.

High intensity treatment was not associated with significantly increased side effects. Also, no significant effects on cancer mortality or other non-CV mortality.

GOOD AFTERNOON

Statin Therapy : Special Populations

1. Children
2. Pregnancy
3. Obesity
4. Diabetics
5. Heart Failure
6. Kidney Disease
7. Liver Disease
8. Immunosuppression
9. Organ Transplant
10. HIV

Statin Therapy in Special Populations

1. Children
Atherosclerosis starts in infancy (Stary, PDAY, Bogalusa, etc)
Statins in high concentrations are anti-mitotic (and potentially chemotherapeutic); therefore, their use is contraindicated during pregnancy and early childhood.
LDL targets in childhood not clearly defined (suggested 75% goal <110mg/dl; <70 mg/dl is defensible). Statins are considered at age ≥10y with LDL-C ≥160 mg/dl if there are added risk factors (DM, family hist. CAD, obesity, HT, HDL-, transplant, Kawasaki, hypothyroidism, inflammat. disease (SLE), organ failures.
In homozygous familial hypercholesterolemias, maximal statin (rosuvastatin 40-80mg/24h) may reduce LDL-C by ~25% and LDL-apheresis 1x/week by ~75%
“quadrupel therapy” (statin+ezetimibe+niacin+fenofibrate) may be considered before resorting to LDL-apheresis, considered when drugs fail to reduce LDL-C below 200-300 mg/dl.
2. Pregnancy

Statins are contraindicated in women who are pregnant or might become pregnant (pregnancy category X). This recommendation is based predominantly on animal experiments. Nursing mothers should avoid statins that may be concentrated in mammalian milk.

3. Obesity

There are no specific recommendations for the pharmacotherapy of dyslipidemias in obesity.

The cannabinoid receptor type 1 antagonist rimonabant was effective in reducing appetite, promoting weight loss (abdominal fat loss), decreasing triglyceridemia (VLDL↑) and small-dense LDL fraction, and increasing HDL (HDL₂/HDL₃ ratio↑).

4. Diabetics

In ATP III (2001), DM (fasting BS >126mg/dl) is considered high risk for CAD (other high risks: symptomatic coronary or non-coronary atherosclerosis, Framingham 10-yr CHD risk>20% plus ≥2 major risk factors (ie, smoke, BP>140/90, HDL-C <40mg/dl, family history premature CHD, ie, <65y women, <55y men). Statins are used in high risk to attain LDL-C <100 (or :<70) mg/dl.

Meta-analysis (4 trials,90,000 DM-pts): each LDL-C↑ by 40mg/dl was associated with 20%↑ CV-events. Fenofibrate reduces microvascular disease, ie, retinopathy, albuminuria, amputations (Field trial).

5. Heart Failure

In the CORONA trial (NEJM 2007; 357:2248-61), HF patients (n=5,011, age >60y, LVEF 0.31, CRP 3.5mg/l) randomized to 10mg rosuvastatin/24h/placebo had a 45% LDL-C↑ and 37% CRP↑, but there was no difference in the combined CV-outcome (CV death + nonfatal MI / stroke) after 33 months.

Does CORONA reflect Ras-mediated limitation of compensatory cardiac hypertrophy?
6. Kidney Disease

Chronic kidney disease (CKD) is often associated with hypertriglyceridemia and low HDL. There may be increased VLDL synthesis. Low lipoprotein lipase results from decreased enzyme expression and high inhibition by apoCIII, whereas low HDL may reflect the pro-inflammatory state. **High CV risk is a hallmark of CKD** and aggressive therapy to LDL-C <100 mg/dl is recommended with the use of statins. Because statins are not predominantly excreted by the kidney, their dosages is reduced only at low GFRs (<15ml/min.1.73m²).

7. Liver Disease

Persistent long-term dose-dependent elevations in ALT, AST (but not γGT or bilirubin) occur in about 1% of pts. Treatment should be discontinued when elevations exceed 3x ULN. Minor elevations often return to normal during continued therapy. In large trials with high doses of atorva- (80mg) or rosuva-statin (40mg), excess liver damage in treated vs. placebo pts. has not been demonstrated. In chronic liver disease (but not in acute disease or liver failure) statin therapy is safe incl. hepatitis C, biliary cirrhosis, NASH/NAFLD, others.

8. Immunosuppression

Effects of immunosuppressants on statins are incompletely elucidated and some recommendations are not evidence-based. See below organ transplantation.

9. Organ Transplant

Dyslipidemia is common (prevalence up to 85%) among transplant patients. LDL-C and TG elevations occur usually within the first 2-3 weeks post-transplant (ie, start statin early) and plateau by 3 months, if there is not continued weight gain. Contributing to LDL-C↑ are immuno-suppressants (steroids; cyclosporine, tacrolimus, rapamycin) and diabetes, renal failure, nephrotic syndrome, hypothyroidism, male sex. Lipophilic cyclosporine carried within LDL and HDL may affect lipoprotein metabolism directly. Rapamycin inhibits lipoprotein lipase, resulting in reduced renal excretion of apoB-containing lipoproteins and high TG. CYP3A4-metabolizable statins (Lova, Simva, less Atorva) may accumulate (levels 6-20x↑) when CYP3A4 is inhibited by cyclosporine and others (increased myopathy risk).
10. HIV

Patients on protease inhibitors should preferably avoid statins metabolized by P 450 3A4 enzyme (lova, simva, atorva). Also, nonnucleoside reverse transcriptase inhibitors induce 3A4; may then require higher statin doses.

Use statins minimally metabolized by P450 2C9/2C8, ie, prava, rosuva, fluva (prava and rosuva – but less so fluva – are relatively hydrophilic).

Avoid bile acid sequestrants that may bind HIV drugs and raise triglycerides (high TG is a frequent HIV complication).

The “Residual Risk” Folly

Relation between on-treatment HDL cholesterol concentrations and subsequent cardiovascular risk in previous statin trials

<table>
<thead>
<tr>
<th>Statin</th>
<th>Relation of on-treatment HDL cholesterol to residual risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR Qa 3G 0</td>
<td>Higher HDL correlated with lower residual risk</td>
</tr>
<tr>
<td>PR EX 3H 0</td>
<td>Midrange HDL correlated with intermediate residual risk</td>
</tr>
<tr>
<td>PR R 3I 0</td>
<td>Lower HDL correlated with higher residual risk</td>
</tr>
</tbody>
</table>

984 subjects with 10 yr Framingham risk scores for CAD events (death, nonfatal MI) <10% and LDL-C 155 mg/dl, and mean CIMT 1.2 mm were randomized to 40mg rosuvatatin or placebo.

In intention-to-treat patients over a 2-y follow-up, LDL-C fell to 78 mg/dl (-49%). Concomitantly, CIMT increased by 0.0004 mm vs. 0.0088 mm in controls (P <0.001), consistent with statin-related atherosclerosis progression slowing. Incidence of myalgia in treated vs. placebo patients averaged 12.7 vs. 12.1 % (NS). Transaminases in treated patients averaged 1.4% vs. 0.0% in untreated controls.

Conclusion: Rosuvatatin slowed carotid atherosclerosis progression (CIMT thickening), but did not induce regression.

“Effect of rosuvastatin on regression of CIMT in low-risk individuals with subclinical atherosclerosis - The METEOR trial." JAMA 2007; 297: 1344-1353

349 patients (mean age 59, BMI 28 kg/m², LDL-C [mg/dl] 130, HDL-C 43, TG 152) received sequential coronary IVUS studies while on rosuvatatin therapy, 40mg/day.

After a 2y-follow-up, LDL-C declined to 61 mg/dl (53% reduction; P < 0.001). Concomitantly, IVUS indexes of atherosclerosis declined, with “total atheroma volume” exhibiting a median reduction of 6.8%.

As assessed from the pre-specified IVUS indexes, rosuvatatin, 40 mg/d, appeared to have promoted coronary atherosclerosis regression.
“Échanges cholestéroliniques et pathologie de la race”

Langen CD (Professeur à l’école de médecine à Weltereden)
(Weltereden = oldest JAVA Medical School, founded 1853)


(major finding)
“Le taux cholestérolinémique des indigènes serait inférieur à celui des Européens. En effet, la moyenne de la valeur cholestérolinique des indigènes fut trouvée à la moitié de celles des Européens.”

(concluding remarks)
“La question si l’hypocholestérolémie physiologique des indigènes aux Indes néerlandaises est due à la nutrition ou bien à une propriété de la race (devra considérer) des recherches ultérieures.”

This represents the discovery of "non-Western" low blood cholesterol, — "hypocholesterolemia of the indigenes" [natives]
Post-translational Peptide Modification

Some peptides, a striking example p53, can be modified by multiple groups at multiple sites to yield nearly endless molecular variability.

<table>
<thead>
<tr>
<th>Modifying group</th>
<th>Effect on Peptide function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphate on Ser, Thr, Tyr</td>
<td>Drives peptide assembly into larger complexes</td>
</tr>
<tr>
<td>Methyl /Acetyl on Lysine</td>
<td>Histone modification propagating chromatin silencing through cell division (epigenetic regulation)</td>
</tr>
<tr>
<td>N-acetylglycosamine on Ser, Thr</td>
<td>Enzyme activity &amp; gene expression in glucose regulation</td>
</tr>
<tr>
<td>Ubiquitin on Lys</td>
<td>Mono-ubiquitin for vesicular peptide transport</td>
</tr>
<tr>
<td>Lipoprotein_Palmitoyl on Cys</td>
<td>Poly-ubiquitination for proteasomal degradation</td>
</tr>
<tr>
<td>Myristoyl on Gly</td>
<td>Attachment to vesicular &amp; surface membranes</td>
</tr>
</tbody>
</table>

HDL-C Raising with Rosuvastatin vs. other Statins

![Graph showing HDL-C raising with Rosuvastatin vs. other Statins](image)

*P<0.002 vs rosuvastatin 10 mg; †P<0.002 vs rosuvastatin 20 mg.
†P=0.002 vs rosuvastatin 40 mg.
Blocks in the Post-Squalene Pathway may Produce Severe, often Lethal Defects

Pharmacological tools used to explore pre- and post-squalene pathways

Comparison of the interleukin (IL)-6-glycoprotein 130 (gp130)-Janus kinase (JAK)-signal transducer and activator of transcription 3 (STAT3) signal cascade in end-stage failing human hearts with the cardiac phenotype of mice harboring systemic or cardiac-restricted knockouts in this cascade

Natural Products Derived from Activated Isoprene Units

- Bile acids
- Steroid hormones
- Vitamin D
- Vitamin A
- Vitamin E
- Vitamin K
- Phytol chain of chlorophyll
- Quinone electron carriers: Coenzyme Q10, plastoquinone
- Isoprene
Antitumor effects of statins.

**Antitumor Effects of Statins**

- Inhibition of Tumor Cell Growth
  - Reduction of mitotic perturbation, cell-cycle arrest, cell death induction
  - Downregulation of glycolysis, mitochondrial dysfunction
- Repression of Tumor Metabolism
  - Reduction of proliferation of cancer cells
  - Reduction of metabolic activities
  - Inhibition of tumor growth
  - Inhibition of tumor growth factor-induced signal cell death

Apoptosis
- Induction of apoptosis
  - Activation of pro-apoptotic proteins such as Bax and Bad
  - Induction of mitochondrial pathway
  - Induction of caspase-3, -7, -8, and -9
- Induction of pyroptosis
  - Activation of pyroptosis proteins such as Gasdermin-D

Hindler K et al. The Oncologist 2006;11:306-315

Statin therapy may represent a potentially novel treatment strategy for preventing cardiac hypertrophy and for improving myocardial vascularization.

**Statin Therapy**

- Inhibition of membrane translocation of tumor suppressor p53 [16,14]
- Inhibition of neovascularization
- Improvement of cardiac peripheral vasodilatory function