**Apoproteins**

- Stabilize lipoproteins ("backbone")
  - A1 --- HDL
  - B48 ---- chylo
  - B100 ---- VLDL, IDL, LDL
- Modulate enzymatic activity
  - Catalyze (CII --- LPL, A1 --- LCAT)
  - Inhibit (CIII --- LPL)
- Facilitate lipoprotein entry into cells (ligands)
  - B100 --- LDL
  - E --- chylo, VLDL & IDL, HDL?

**Plasma Lipoproteins**

- Spherical particles
- Non-polar core:
  - Cholesterol ester
  - Triglycerides
- Polar outer coat:
  - Unesterified chol
  - Phospholipids
  - Proteins (apo)

---

**Chylomicron**

- trig > 90%
- chol 1-2%
- apo < 1%

**VLDL**

- trig 60%
- chol 12%
- apo 10%
- PL 18%

**IDL**

- trig 5%
- chol 50%
- apo 25%
- PL 20%

**LDL**

- chol 20%
- apo 50%
- PL 25%
**Intrinsic Pathway**

- **Liver**
  - Bile acids
  - HMGCoAReductase
  - acetylCoA
  - chol
  - VLDL
  - IDL

**VLDL Metabolism 1**

- **Liver**
  - apo C2 (+)
  - apo C3 (-)
  - apo B
  - trig
  - IDL

**Etiology of elevated VLDL**

- **Type IV dyslipidemia**
  - **Primary (genetic)**
    - Familial Hypertriglyceridemia (FHTG)
    - Familial Combined Hyperlipidemia (FCHL)
  - **Secondary (acquired)**
    - Obesity
    - Diabetes mellitus
    - Insulin resistance syndrome
    - Chronic renal failure
    - high carbohydrate diets
    - Ethanol
    - Drugs: estrogen, beta-blockers, retinoids

**Familial Combined Hyperlipidemia**

- **Autosomal dominant**
- elevated chol and/or Tg levels
- increased CHD risk
- Family: ↑TG or ↑chol or both
  - in 50% of family members
- Many, normal sized VLDL particles
- overproduction of apo B
- elevated apo B levels

**Familial Hypertriglyceridemia**

- **Autosomal dominant**
- elevated Tg levels only
- increased CHD risk
- Family: ↑TG in 50% of family members
- Few, large sized VLDL particles
- overproduction of triglyceride
- normal apo B levels
Genetic predisposition
↑↑↑↑ insulin
↑↑↑↑ Tg
↓↓↓↓ HDL
Glucose intolerance
↑↑↑↑ CRP
Prothrombotic state
HTN
diabetes
CHD

Type III dyslipidemia
Broad-beta disease
Remnant disease

• Xanthomas:
  - palmar
  - tuberous (elbows, knees)

• Premature atherosclerosis
  - coronary (myocardial infarction, anginal syndromes)
  - cerebrovascular (carotid artery disease, CVA)
  - peripheral vascular (limb ischemia)
Hyper LDLemia

LDL metabolism within Hepatic Cells

Defective apo B100

Defective receptor activity

oxidation

Foam cell

Familial Hypercholesterolemia (FH)

- Decreased LDL-receptor
- Autosomal dominant
- Elevated LDL chol (mg/dL)
- Premature CHD
- Tendon Xanthomas
  - hands
  - elbows
  - knees
  - Achilles

<table>
<thead>
<tr>
<th></th>
<th>heterozygous</th>
<th>homozygous</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50%</td>
<td>absent</td>
</tr>
<tr>
<td></td>
<td>1:500</td>
<td>1:106</td>
</tr>
<tr>
<td></td>
<td>250-400</td>
<td>700-1000</td>
</tr>
<tr>
<td>age 35-55</td>
<td>++</td>
<td>age 15-20</td>
</tr>
<tr>
<td></td>
<td>++</td>
<td>+++</td>
</tr>
</tbody>
</table>

polygenic (common) Hypercholesterolemia

- Shiloh Shel Moshe Moniim \(\text{גכמימא}\) /\(\text{גכמימא}\)
- חומרים קלאסיים
- לא בולט בגיל צעיר
- קסנטומות
- על קסנטומות
- לעומס ארקיט\(\text{גכמימא}\) /\(\text{גכמימא}\)
- Arcus Cornea
- Xanthelasma

Arcus Cornea

Xanthelasma

Fig. 3. Gross xanthelasma which have spread around the orbit of the eye in a patient with Familial Hypercholesterolemia.

Polygenic (common) hypercholesterolemia

- שילוב של מספר פגמים
- חומרים קלאסיים
- לא בולט בגיל צעיר
- קסנטומות
- לעומס ארקיט
- Arcus Cornea
- Xanthelasma

Fig. 3. Extensive accumulation of lipids in the Achilles tendon in a patient with Familial Hypercholesterolemia.
**LDL Modifications**

- **LDL Oxidation**
  - inadequate methods to measure tissue oxidation
  - antioxidants

- **LDL size & density**
  - type A: large, buoyant
  - type B: small, dense
  - hyper TG, DM, Insulin resistance
  - familial combined hyperlipidemia
  - CHD patients

- **Lp(a)**
  - atherogenic
  - thrombogenic

---

**HDL Metabolism 1**
Reverse cholesterol transport

- Liver
- Nascent HDL
- LCAT
- HDL 3
- Unesterified cholesterol
- Esterified cholesterol

**HDL Metabolism 2**

- Liver
- Nascent HDL
- LCAT
- HDL 3
- Unesterified cholesterol

**HDL Metabolism 3**

- Liver
- Nascent HDL
- CETP
- HDL 2

**Causes of low HDL-C**

- Genetic
- Hypertriglyceridemia
- Obesity
- Diabetes mellitus
- Insulin resistance syndrome
- cigarette smoking
- Diet: high CHO, high PUFA
- Drugs
  - Anabolic steroids (testosterone, progestins)
  - beta adrenergic blockers

**Antiatherosclerotic mechanisms of HDL**

- Reverse Cholesterol Transport
  - direct (SRAP)
  - indirect (via LDL, VLDL)
- Prevents LDL Oxidation
- Prevents synthesis of prothrombotic prostaglandins
- Increases synthesis of antithrombotic prostaglandins
  - prostacycline

---
Relationship between HDL and Triglyceride-rich lipoproteins

- HDL
- Trig

Miotic distribution of the hormones

- ezetimibe
- fibrates
- niacin
- statins
- resins
- HMGCoAReductase
- acetylCoA
- chol

FHMDL-C vs LDL-C

as a predictor of CHD risk

Global risk

- Diabetes
- Heart disease
- Global risk
- Other risk factors
- Asymptomatic
Potential Mechanisms by Which Omega-3 Fatty Acids May Reduce Risk for Cardiovascular Disease

- Reduce susceptibility to ventricular arrhythmia
- Antithrombogenic
- Hypotriglyceridemic (fasting and postprandial)
- Retard growth of atherosclerotic plaque
- Reduce adhesion molecule expression
- Reduce platelet-derived growth factor
- Antiinflammatory
- Promote nitric oxide-induced endothelial relaxation
- Mildly hypotensive

Omega 3

- AHA Scientific Statement.
- Fish Consumption, Fish Oil, Omega-3 Fatty Acids, and Cardiovascular Disease.

Omega 3

AHA recommendations

<table>
<thead>
<tr>
<th>Population</th>
<th>Recommendation:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients without documented CHD</td>
<td>Eat a variety of (preferably oily) fish at least twice a week, include oils and foods rich in linolenic acid (flaxseed, canola, and soybean oils; flaxseed and walnuts)</td>
</tr>
<tr>
<td>Patients with documented CHD</td>
<td>Consume 1 g of EPA+DHA per day, preferably from oily fish. EPA+DHA supplements could be considered in consultation with the physician.</td>
</tr>
<tr>
<td>Patients needing Tg lowering</td>
<td>2-4 grams of EPA+DHA per day provided as capsules under a physician’s care</td>
</tr>
</tbody>
</table>

Side Effects

<table>
<thead>
<tr>
<th>GI Upset</th>
<th>Clinical Bleeding</th>
<th>Fishy Aftertaste</th>
<th>Worsening Glycemia*</th>
<th>Rise in LDL-C‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 1 g/d</td>
<td>Very low</td>
<td>Very low</td>
<td>Low</td>
<td>Very low</td>
</tr>
<tr>
<td>1 to 3 g/d</td>
<td>Moderate</td>
<td>Very low</td>
<td>Moderate</td>
<td>Low</td>
</tr>
<tr>
<td>&gt;3 g/d</td>
<td>Moderate</td>
<td>Low</td>
<td>Likely</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

*Usually only in patients with impaired glucose tolerance and diabetes.  
‡usually only in patients with hypertriglyceridemia.

Target endpoints

- LDLc < 100 mg/dL
- HDLc > 40 mg/dL
- Triglycerides < 200 mg/dL
Megatrials showing statin efficacy

- **Primary Prevention**
  - WOSCOP
  - ACAPS/CAPS

- **Secondary Prevention**
  - 4S
  - CARE
  - Lipid

- **Mixed**
  - APS

- **Comparative**
  - PROVE-IT, REVERSAL

- **Hypertensives**
  - ALLHAT
  - ASCOT

- **Diabetics**
  - CARDS

Mechanism of action

Acetoacetyl CoA + Acetyl CoA → 3-Hydroxy-3-methylglutaryl CoA (HMG CoA) → Mevalonic acid → Cholesterol

Regression Studies

Total Mortality

[Graph showing total mortality over years since randomization for 4S, Simvastatin, and Placebo]

The Lancet, Vol 344, November 19, 1994
**Pravastatin 40 mg**

<table>
<thead>
<tr>
<th></th>
<th>CARE</th>
<th>LIPID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type</td>
<td>2º</td>
<td>2º</td>
</tr>
<tr>
<td>Place</td>
<td>USA</td>
<td>Aust / NZ</td>
</tr>
<tr>
<td>No.</td>
<td>4159</td>
<td>9014</td>
</tr>
<tr>
<td>Ages</td>
<td>21-75</td>
<td>31-75</td>
</tr>
<tr>
<td>Sex</td>
<td>M&amp;F</td>
<td>M&amp;F</td>
</tr>
<tr>
<td>Length (y)</td>
<td>5</td>
<td>6.1</td>
</tr>
<tr>
<td>Baseline LDL</td>
<td>115-174</td>
<td>130-170</td>
</tr>
<tr>
<td></td>
<td>139</td>
<td>150</td>
</tr>
</tbody>
</table>

**Heart Protection Study (HPS)**

- Largest ever cholesterol-lowering study
- Funded by the British Medical Council & BHF
- 20,000 M&F, age 40-80
- High CHD risk – declined statins by physician
  - Below average cholesterol
  - Women
  - Age > 70
  - Non-coronary arterial disease
- Simvastatin 40 mg vs placebo
- 5.5 years
- 2 by 2 design (also randomized to antioxidants)

**HPS - results**

<table>
<thead>
<tr>
<th></th>
<th>Simvastatin</th>
<th>Placebo</th>
<th>relative reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cause mortality</td>
<td>12.9</td>
<td>14.6</td>
<td>12%</td>
</tr>
<tr>
<td>CVD death</td>
<td>7.7</td>
<td>9.2</td>
<td>17%</td>
</tr>
<tr>
<td>Major CVD events</td>
<td>19.9</td>
<td>25.4</td>
<td>22%</td>
</tr>
<tr>
<td>Non-CVD mortality</td>
<td>5.2</td>
<td>5.5</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>4.4</td>
<td>6.0</td>
<td>27%</td>
</tr>
<tr>
<td>CPK X10</td>
<td>0.1</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>ALT X3</td>
<td>0.8</td>
<td>0.6</td>
<td></td>
</tr>
</tbody>
</table>
Summary of statin benefits

- Reduce incidence by ~ 30%
- Beneficial in subgroups analyzed
- Primary & secondary prevention
- Males, females, diabetics, smokers, hypertensives
- Possible non-lipid effects
- More effective in elevated CRP
- Effect on valvular calcific disease?
- Alzheimer? Osteoporosis?
- Short and long-term safety

AVERT study
**Atorvastatin vs Revascularization**

- 18 month, multicenter
- Open label, randomized
- Stable CAD - referred for PCI

Exclusions:
- 3 vessel CAD, LM disease
- Unstable angina
- MI within previous 2 weeks
- EF < 40%

Statins vs Revascularization

- PCI
- Atorvastatin Lipitor

Statin therapy in acute coronary syndromes

- Increases patient & physician compliance
- Reduces early morbidity & mortality?

Observational studies:
- Patients discharged with statins had
  - ~ 50% less mortality over 6-12 months followup

No difference in Death Myocardial infarction

Worsening angina

With objective evidence of ischemia requiring hospitalization
**MIRACL study design**

- Prospective, randomised, multicentre, double-blind
- **3,086 patients**
- Inclusion criteria:
  - UA or non-Q-wave MI in previous 1-4 days
- 80 mg atorvastatin commenced within 24-96 h of event
- Placebo, commenced within 24-96 h of event
- Follow up for 16 weeks

**Statins in Hypertensives**

**ALLHAT**
- 33,357 pts age 50+
- HTN + 1 risk factor
- Randomized to chlorthalidone vs lisinopril vs amlopidine
- Lipid-lowering arm:
  - 19,385 pts with LDL-C 120-189 mg/dL
  - Pravastatin 40mg vs usual care
  - No difference in outcome: total or CV mortality
- **ASCOT**
  - 19,342 pts age 40-79
  - HTN + 3 risk factors
  - Randomized to beta-blocker vs amlopidine
  - Lipid-lowering arm:
    - 10,305 pts with total cholesterol < 260 mg/dL
    - Atorvastatin 10mg vs placebo
    - Stopped prematurely after 3.3 years
    - ↓ 36% events, ↓ 29% total mortality
  - p < 0.0005

**Primary efficacy measure**

Cumulative incidence (%)

- **Placebo**
- **Atorvastatin**
- 17.4% vs 14.8%
- Risk reduction = 16%
- p = 0.048

Time to first occurrence of composite endpoint of:

- Risk reduction = 16%
- p = 0.048
- 95% CI = 0.701-0.999

**CARDS Design**

- Placebo
- 2,838 patients
- Atorvastatin 10mg

**Statins in Diabetics**

- **Heart Protection Study**
- **CARD**S
  - Collaborative Atorvastatin Diabetes Study
**CARDS Patient Baseline Lipids***

<table>
<thead>
<tr>
<th></th>
<th>Placebo Median (IQR)</th>
<th>Atorvastatin Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>207</td>
<td>207</td>
</tr>
<tr>
<td>LDL-cholesterol</td>
<td>118 (100-137)</td>
<td>119 (100-138)</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>53</td>
<td>52</td>
</tr>
</tbody>
</table>

**Cumulative Hazard for Primary Endpoint**

Relative Risk Reduction 37% (95% CI: 17-52)  
P = 0.001

- Placebo: 127 events  
- Atorvastatin: 83 events

**Cumulative Hazard for Primary Endpoint**

**Cumulative Hazard for All Cause Mortality**

Relative Risk Reduction 27% (95% CI: -1-48)  
P = 0.005

- Placebo: 82 deaths  
- Atorvastatin: 61 deaths

**LDL in secondary Prevention:**

How low is low?

**Hypothesis**

40 mg Lipidal → anti-inflammatory

is not inferior to

80 mg Lipitor → Potent LDL ↓

**PROVE-IT**

Comparison of Intensive and Moderate Lipid Lowering with Statins after Acute Coronary Syndromes

Christopher P. Cannon, M.D., Eugene Braunwald, M.D., Carolyn H. McCabe, B.S., Daniel J. Rader, M.D., Jean L. Rouleau, M.D., Per-Anders Becker, M.D., Steven K. Topol, M.D., Karen A. Hill, M.A., Marc A. Helfer, M.D., Ph.D., and Allan M. Skene, Ph.D., for the Provastatin or Atorvastatin Evaluation and Infection Therapy – Thrombolysis in Myocardial Infarction 22 Investigators®
Design

- 4162 pts with Acute Coronary Syndrome
- within 10 days
  - Lipidal 40 mg vs Lipitor 80 mg
  - baseline LDLc 106 mg/dl
    - 95 vs 62
  - baseline CRP 12.3 mg/l
    - 2.1 vs 1.3

Table 3. Change in Atheroma Volume, Change in Percentage of Atheroma Volume, and Atheroma Volume in 10-mm Subsegment With the Greatest Disease Severity

<table>
<thead>
<tr>
<th></th>
<th>Pravastatin (n = 248)</th>
<th>Atorvastatin (n = 252)</th>
<th>p Value Between Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atheroma Volume, mm³</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>104.5 (154.8)</td>
<td>184.4 (115.7)</td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>166.5 (117.4 to 240.2)</td>
<td>181.3 (111.3 to 238.2)</td>
<td>.20</td>
</tr>
<tr>
<td>Follow-up</td>
<td>190.9 (122.3)</td>
<td>183.9 (108.5)</td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>186.0 (120.5 to 255.5)</td>
<td>190.9 (104.0 to 240.3)</td>
<td>.05</td>
</tr>
<tr>
<td>Normal change</td>
<td>+5.1 (1.1)</td>
<td>-0.4 (1.8)</td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>4.4 (2.1 to 6.3)</td>
<td>-2.2 (2.5 to 1.3)</td>
<td>.02</td>
</tr>
<tr>
<td>p Value compared with baseline</td>
<td>.01</td>
<td>.72</td>
<td></td>
</tr>
</tbody>
</table>

Figure 3. Kaplan-Meier Estimates of the Incidence of the Primary End Point of Death From Any Cause or a Major Cardiovascular Event. Intensive lipid lowering with the 80-mg dose of atorvastatin, as compared with pravastatin lipiddowering with the 40-mg dose of pravastatin, reduced the hazard ratio for death from any cause and major cardiovascular event by 31 percent.

Figure 2. Kaplan-Meier Estimates of the Incidence of the Primary End Point of Death From Any Cause or a Major Cardiovascular Event.
**BIP Study**
- Multicenter
- Randomized
- Double-blind
- Placebo-controlled
- Bezafibrate SR 400 mg

- Men & women
- Age 45-74
- Post MI
- Stable angina, (+) imaging
- LDL-C < 180/160 mg/dL
- HDL-C < 45 mg/dL
- Trig < 300 mg/dL

**Target endpoints**
- LDLc < 100 mg/dL
- HDLc > 40 mg/dL
- Triglycerides < 200 mg/dL

Conclusions:
- LDLc < 70 mg/dL
- At least 30-40% reduction

**Hypertriglyceridemia Intervention Study (HIT)**
- Helsinky heart Study
- Coronary Drug Project (CDP): niacin
- Stockholm Heart Study: niacin + colestipol
- Bezafibrate Intervention Study (BIP)
- Hypertriglyceridemia Intervention Study (HIT)

**BECAIT**
- Multicenter
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- Placebo-controlled
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- Age 45-74
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- Age 45-74
- Post MI
- Stable angina, (+) imaging
- LDLc < 180/160 mg/dL
- HDLc < 45 mg/dL
- Trig < 300 mg/dL
היממה الحوارית
יעילה
פשיטה
Cost-effective

חוששים לפרנסה שלכם
כקרדיולוגים
אל תדאגו
זה לא יקרה!!

 жизני
לפרנסת שלכם
METHODS
 SIMPLE
COST-EFFECTIVE