Cholesterol
Past, Present and Future

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Disclosures
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No Relations with Industry
cho·les·ter·ol
kəˈlestəˌrôl,kəˈlestəˌrōl/

from Greek *kholē* ‘bile’ + *stereos* ‘stiff’

noun: **cholesterol**; plural noun: **cholesterols**

1. a compound of the sterol type found in most body tissues, including the blood and the nerves. Cholesterol and its derivatives are important constituents of cell membranes and precursors of other steroid compounds, but high concentrations in the blood (mainly derived from animal fats in the diet) are thought to promote atherosclerosis.
Cholesterol
Chemical Structure
Outline

• Physical Examination
• Measurement
• Lipid Determinants
• Atherosclerotic Disease
• Treatment
Physical examination

Xanthelasma
Xanthomas
Arcus corneae
Xanthelasma
Achilles Tendon Xanthomas
Hand Extensor Tendon Xanthomas
Arcus Corneae
Serum Cholesterol and CHD Death
MRFIT Screenees

Cholesterol Quintile (mg/dL)

<table>
<thead>
<tr>
<th>Referent</th>
<th>1.29</th>
<th>1.73</th>
<th>2.21</th>
<th>3.42</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;182</td>
<td>182-202</td>
<td>203-220</td>
<td>221-244</td>
<td>&gt;244</td>
</tr>
</tbody>
</table>

Relative Risk

Cholesterol Quintile (mg/dL)
25 Year CHD Mortality in 12,467 Men age 40-59 yr
7 Countries Study

CHD Mortality (%) vs. Cholesterol (mg/dl)

- N Europe
- S Europe (coastal)
- United States
- Serbia
- S Europe (inland)
- Japan

Verschuren JAMA 1995; 275: 131
Mean Serum Cholesterol in Adults 1980-2000

Ueshima Circulation 2008;118: 2702
Lipoprotein Cholesterol Measurements

• Early Measurements
• Svedberg Fractions
• NHLBI / Lipid Research Clinics
• HDL-C determinations
• Apoproteins
  ApoA, ApoB, etc
  Lipoprotein (a)
  Particle quantification
LDL Molecule

- Phospholipid
- Unesterified cholesterol
- Cholesteryl ester

Polar surface
Apolar core
Apolipoprotein B

LDL Molecule
Lipoprotein Fractions
Lab Measurements

Plasma Density
1.006
(ApoB)

1.063
(ApoA)

VLDL
LDL
IDL
HDL*

Bottom*
Fraction (ApoB)

Total*

\[ \text{LDL}_{\text{Friedewald}} = \text{Total} - \text{HDL} - \left( \frac{\text{Trig}}{5} \right) \] (mg/dl)


## Typical Plasma Concentrations

### Lipoprotein Cholesterol Particles

**US Adults**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td>130 to 140</td>
<td>130 to 140</td>
</tr>
<tr>
<td>HDL-C</td>
<td>40 to 50</td>
<td>50 to 60</td>
</tr>
<tr>
<td>VLDL-C</td>
<td>Less than 20</td>
<td>Less than 20</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>200 to 210</td>
<td>200 to 210</td>
</tr>
<tr>
<td>Total Triglycerides</td>
<td>Less than 100</td>
<td>Less than 100</td>
</tr>
</tbody>
</table>
Serum Lipoprotein Size and Density

Density (g/ml)

Diameter (Angstroms)

Chylomicrons
Chylomicron Remnants
VLDL
IDL
LDL
HDL-1
HDL-2
HDL-3
Nascent HDL

60 100 140 200 280 400 600 800 1000
Cholesterol
Apolipoprotein B-100
Apolipoprotein (a)
Phospholipid
Determinants of Lipid Levels

Diet
Alcohol
Other lifestyle effects
Trends over time
## Determinants of LDL-C

<table>
<thead>
<tr>
<th>Lower</th>
<th>Higher</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low dietary saturated fat</td>
<td>High dietary saturated fat</td>
</tr>
<tr>
<td>Less dietary cholesterol</td>
<td>More dietary cholesterol</td>
</tr>
<tr>
<td>Higher intake of poly fat</td>
<td>Lower intake of poly fat</td>
</tr>
<tr>
<td>Estrogens</td>
<td>No estrogens</td>
</tr>
</tbody>
</table>
Hegsted-Keys and Lipid Change According to Dietary Intake

Keys Equation
\[ \Delta \text{Total-C} = 2.74 \cdot (\Delta \text{Sat}) - 1.31 \cdot (\Delta \text{Poly}) + 1.5 \cdot (C_2^{1/2} - C_1^{1/2}) \]

Hegsted Equations:
\[ \Delta \text{Total-C} = 2.10 \cdot (\Delta \text{Sat}) - 1.16 \cdot (\Delta \text{Poly}) + 0.067 \cdot (\Delta C) \]
\[ \Delta \text{Total-C} = 2.16 \cdot (\Delta \text{Sat}) - 1.65 \cdot (\Delta \text{Poly}) + 0.176 \cdot (\Delta C) \]
\[ \Delta \text{LDL-C} = 1.74 \cdot (\Delta \text{Sat}) - 0.77 \cdot (\Delta \text{Poly}) + 0.044 \cdot (\Delta C) \]
The Traditional Healthy Vegetarian Diet Pyramid

Daily Beverage Recommendations:
- 6 Glasses of Water

WEEKLY
- Egg Whites, Soy Milk, Dairy

DAILY
- Nuts & Seeds
- Plant Oils

AT EVERY MEAL
- Whole Grains
- Fruits & Vegetables
- Legumes & Beans

Daily Physical Activity

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US Food Pyramid

TOTAL US POPULATION, AGES 4 AND UP

Adapted from National Livestock and Meat Board and MRCA Information Services
Nutrient Intake in Various Diets

- **Atkins**: Sat Fat: 25%, Mono/Poly/Trans Fat: 35%, Protein: 22%, Carbo: 18%
- **Reaven**: Sat Fat: 7%, Mono/Poly/Trans Fat: 33%, Protein: 15%, Carbo: 45%
- **WHI Initial**: Sat Fat: 13%, Mono/Poly/Trans Fat: 25%, Protein: 16%, Carbo: 46%
- **WHI Interv**: Sat Fat: 10%, Mono/Poly/Trans Fat: 18%, Protein: 18%, Carbo: 54%
- **WHI Compare**: Sat Fat: 12%, Mono/Poly/Trans Fat: 25%, Protein: 17%, Carbo: 46%
- **ATP III**: Sat Fat: 7%, Mono/Poly/Trans Fat: 18-23%, Protein: 15%, Carbo: 50-60%
- **The Zone**: Sat Fat: 6%, Mono/Poly/Trans Fat: 24%, Protein: 30%, Carbo: 40%
- **Dash**: Sat Fat: 6%, Mono/Poly/Trans Fat: 21%, Protein: 18%, Carbo: 55%
- **Connor**: Sat Fat: 5%, Mono/Poly/Trans Fat: 25%, Protein: 15%, Carbo: 65%
- **Ornish**: Sat Fat: 3%, Mono/Poly/Trans Fat: 7%, Protein: 18%, Carbo: 72%

Per cent
## Determinants of HDL-C

<table>
<thead>
<tr>
<th>Lower</th>
<th>Higher</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Androgens, Progestins</td>
<td>Estrogen</td>
</tr>
<tr>
<td>Obese</td>
<td>Thin</td>
</tr>
<tr>
<td>Cigarettes</td>
<td>No cigarettes</td>
</tr>
<tr>
<td>No alcohol intake</td>
<td>Alcohol intake</td>
</tr>
<tr>
<td>No exercise</td>
<td>Exercise</td>
</tr>
<tr>
<td>Low sat’ d fat intake</td>
<td>More sat’ d fat intake</td>
</tr>
<tr>
<td>Genetic</td>
<td>Genetic</td>
</tr>
</tbody>
</table>
Diabetes and Lipid Extremes
Framingham Offspring
Men

HDL-C<35  Total-C 240+  LDL-C 160+  Trig 250+  HDL-C<35
Per cent
p<0.001  p<0.001

Non-Diabetic  Diabetic

Siegel Metabolism 1996; 96: 1267
Diabetes and Lipid Extremes
Framingham Offspring
Women

Siegel Metabolism 1996; 96: 1267
Development of Atherosclerosis

- Normal artery
- Early atheroma
  - 'Stabilized' plaque
    - Small lipid pool
    - Thick fibrous cap
    - Preserved lumen
- 'Vulnerable' plaque
  - Thin fibrous cap
  - Large lipid pool
  - Many inflammatory cells
- Thrombosis of a ruptured plaque
  - Fibrous cap
- Healed ruptured plaque
  - Narrow lumen
  - Fibrous intima
- Right coronary artery
- Left coronary arteries
- Acute myocardial infarction
12 Year Incidence of Myocardial Infarction
Framingham Cohort

Men

Rate per 100/12 years

HDL-C (mg/dl)

12 to 36
37 to 44
45 to 52
53 to 129

116-192
193-215
216-244
245-376

Cholesterol (mg/dl)

Abbott Arteriosclerosis 1988; 8: 207
Lifetime Risk of CHD
By Total Cholesterol Category
Framingham Men and Women

Incidence (per cent)

Age (y)

Cholesterol (mg/dL)

Men

Women

After Lloyd-Jones Arch Intern Med 2003; 163:1966
HMG-CoA Reductase Inhibitor Evidence: Primary Prevention and LDL-C on Therapy

AFCAPS= Air Force/Texas Coronary Atherosclerosis Prevention Study, ASCOT= Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm, LDL-C=Low density lipoprotein cholesterol, WOSCOPS= West of Scotland Coronary Prevention Study

## CTT Meta-Analysis 2010: ↓1 mmol/L LDLc and Mortality

<table>
<thead>
<tr>
<th>Vascular causes of death</th>
<th>Events (% per annum)</th>
<th>RR (CI) per 1 mmol/L reduction in LDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>Statin/more: 1887 (0.5%)</td>
<td>Control/less: 2281 (0.6%)</td>
</tr>
<tr>
<td>Other cardiac</td>
<td>Statin/more: 1446 (0.4%)</td>
<td>Control/less: 1603 (0.4%)</td>
</tr>
<tr>
<td>All cardiac</td>
<td>Statin/more: 3333 (0.9%)</td>
<td>Control/less: 3884 (1.1%)</td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>Statin/more: 153 (0.0%)</td>
<td>Control/less: 139 (0.0%)</td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>Statin/more: 102 (0.0%)</td>
<td>Control/less: 89 (0.0%)</td>
</tr>
<tr>
<td>Unknown stroke</td>
<td>Statin/more: 228 (0.1%)</td>
<td>Control/less: 273 (0.1%)</td>
</tr>
<tr>
<td>Stroke</td>
<td>Statin/more: 483 (0.1%)</td>
<td>Control/less: 501 (0.1%)</td>
</tr>
<tr>
<td>Other vascular</td>
<td>Statin/more: 404 (0.1%)</td>
<td>Control/less: 409 (0.1%)</td>
</tr>
<tr>
<td>Any vascular</td>
<td>Statin/more: 4220 (1.2%)</td>
<td>Control/less: 4794 (1.3%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Non-vascular causes of death</th>
<th>Events (% per annum)</th>
<th>RR (CI) per 1 mmol/L reduction in LDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>Statin/more: 1781 (0.5%)</td>
<td>Control/less: 1798 (0.5%)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Statin/more: 224 (0.1%)</td>
<td>Control/less: 237 (0.1%)</td>
</tr>
<tr>
<td>Trauma</td>
<td>Statin/more: 127 (0.0%)</td>
<td>Control/less: 127 (0.0%)</td>
</tr>
<tr>
<td>Other non-vascular</td>
<td>Statin/more: 811 (0.2%)</td>
<td>Control/less: 832 (0.2%)</td>
</tr>
<tr>
<td>Any non-vascular</td>
<td>Statin/more: 2943 (0.8%)</td>
<td>Control/less: 2994 (0.8%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>Statin/more: 479 (0.1%)</td>
<td>Control/less: 539 (0.1%)</td>
</tr>
<tr>
<td>Any death</td>
<td>Statin/more: 7642 (2.1%)</td>
<td>Control/less: 8327 (2.3%)</td>
</tr>
</tbody>
</table>
Familial Hypercholesterolemia
(LDLR, APOB, PCSK9)

Clinical
- Tendon xanthomas, arcus corneae
- Premature atherosclerosis including aortic root

Laboratory
- Increased LDL cholesterol

Genetics
- >1700 mutations of LDL receptor gene
- LDLR more frequent in S. Africa, Christian Lebanese and French Canadians
- Gene dose effects
- Molecular diagnosis of skin fibroblasts possible

Therapy
- Statins, cholesterol absorption inhibitors
- Liver transplantation
- LDL apheresis in pediatric homozygotes
LDL-C Lowering Therapy

Diet

Medications generally available
  Bile Acid Resins
  Niacin
  Statins
  Cholesterol absorption inhibitors

Newer treatments
  Apheresis
  Newer medications
Lipoprotein B Molecular Biology

MTP inhibitor (Lomitapide)

Apo Antisense Oligonucleotide (Mipomersen)

PCSK9 Inhibition

HMGCoA red. inhibitor (statins)
Cholesterol in the Future?

Lower blood levels with medications
Pharmacogenomics potential
Early awareness of high risk persons
Laboratory screening
Genetic screening
Public Health inducements
Healthy foods
Healthier “environment”