Cholesterol – a biomolecule
Bad cholesterol – a strange tale
Good cholesterol - indeed

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Bad Cholesterol

- Why is cholesterol bad?
- What is the science supporting bad cholesterol?
- What are statins?
- Why is the logic flawed?
Why is Cholesterol bad?

Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on

Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)

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May 2001
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management. Each of the guideline reports—ATP I, II, and III—has a major thrust. ATP I outlined a strategy for primary prevention of coronary heart disease (CHD) in persons with high levels of low density lipoprotein (LDL) cholesterol (≥160 mg/dL) or those with borderline-high LDL cholesterol (130-159 mg/dL) and multiple (2+) risk factors. ATP II affirmed the importance of this approach and added a new feature: the intensive management of LDL cholesterol in persons with established CHD. For CHD patients, ATP II set a new, lower LDL cholesterol goal of ≤100 mg/dL. ATP III adds a call for more intensive LDL-lowering therapy in certain groups of people,

**LDL Cholesterol: The Primary Target of Therapy**

Research from experimental animals, laboratory investigations, epidemiology, and genetic forms of hypercholesterolemia indicate that elevated LDL cholesterol is a major cause of CHD. In addition, recent clinical trials robustly show that LDL-lowering therapy reduces risk for CHD. For these reasons, ATP III continues to identify elevated LDL cholesterol as the primary target of cholesterol-lowering therapy. As a result, the primary goals of therapy and the cutpoints for initiating treatment are stated in terms of LDL.
Table 1. New Features of ATP III

Focus on Multiple Risk Factors

- Raises persons with diabetes without CHD, most of whom display multiple risk factors, to the risk level of CHD risk equivalent.
- Uses Framingham projections of 10-year absolute CHD risk (i.e., the percent probability of having a CHD event in 10 years) to identify certain patients with multiple (2+) risk factors for more intensive treatment.
- Identifies persons with multiple metabolic risk factors (metabolic syndrome) as candidates for intensified therapeutic lifestyle changes.

Modifications of Lipid and Lipoprotein Classification

- Identifies LDL cholesterol <100 mg/dL as optimal.
- Raises categorical low HDL cholesterol from <35 mg/dL to <40 mg/dL because the latter is a better measure of a depressed HDL.
- Lowers the triglyceride classification cutpoints to give more attention to moderate elevations.

Support for Implementation

- Recommends a complete lipoprotein profile (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides) as the preferred initial test, rather than screening for total cholesterol and HDL alone.
- Encourages use of plant stanols/sterols and viscous (soluble) fiber as therapeutic dietary options to enhance lowering of LDL cholesterol.
- Presents strategies for promoting adherence to therapeutic lifestyle changes and drug therapies.
- Recommends treatment beyond LDL lowering for persons with triglycerides ≥200 mg/dL.
### Table 3. Major Risk Factors (Exclusive of LDL Cholesterol) That Modify LDL Goals*

- Cigarette smoking
- Hypertension (BP ≥140/90 mmHg or on antihypertensive medication)
- Low HDL cholesterol (<40 mg/dL)†
- Family history of premature CHD (CHD in male first degree relative <55 years; CHD in female first degree relative <65 years)
- Age (men ≥45 years; women ≥55 years) *

### Table 2. ATP III Classification of LDL, Total, and HDL Cholesterol (mg/dL)

<table>
<thead>
<tr>
<th>LDL Cholesterol</th>
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<th>HDL Cholesterol</th>
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<tbody>
<tr>
<td>&lt;100</td>
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<tr>
<td>100-129</td>
<td>200-239</td>
<td>40</td>
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<tr>
<td>130-159</td>
<td>≥240</td>
<td>≥40</td>
</tr>
<tr>
<td>160-189</td>
<td></td>
<td>≥60</td>
</tr>
<tr>
<td>≥190</td>
<td></td>
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Optimal
Near optimal/above optimal
Borderline high
High
Very high
Desirable
Borderline high
High
Low
High
High LDL causes heart disease

- When excluding individuals with familial hypercholesterolemia (< 0.5%) – there is no association
- 16 reports (1970-1992) – 40 citations to supportive or inconclusive trial
- 1 citation – unsupportive trial
- # of supportive and unsupportive trials were equal
High LDL causes heart disease

- In reference to the Framingham study → 1% reduction of cholesterol = 2% reduction in heart disease
- Framingham study – a 30 year study
- The Framingham study actually states that “for 1 mg/dl drop of cholesterol, there was a 11% increase in heart disease” !!!!!!!!
Let’s recall

200 milligrams per deciliter (mg/dL) (5.2 millimoles per liter, or mmol/L)
Facts about LDL and HDL

- Most of the cholesterol is carried by LDL: true
- Normal plasma levels are 175 mg/100 mL: false
- LDL receptors necessary for LDL uptake: true
- LDL receptors regulated by intracellular Chol: true
- Familial hypercholesterolemia:
  - low LDL receptors
  - high plasma Chol (>680 mg): true
- High plasma Chol increases risk of heart attack: false
- high LDL-low HDL ratio = a warning: true / false
- serum Chol $\uparrow \rightarrow$ Chol synthesis $\downarrow$: true
- statin drugs inhibit Chol synthesis: true
- Chol in HDL is the same as Chol in LDL: true
Important Facts

- LDL levels have little if any meaning!!!
- The ratio of total cholesterol to HDL cholesterol is more important than LDL cholesterol (optimal 3.5 or less than 5)
- 200 mg/dL LDL (5.2 mmol/L) and 50 mg/dL HDL (1.3 mmol/L) → ratio 4
- Triglyceride/HDL – small than 2 (ideal) above 4 too high
The Origins of a Myth

- In 1913, Nikolai Anitschkow fed rabbits purified cholesterol.
- Blood cholesterol levels exceed 1,000 mg/dl (nearly 26 mmol/L).
- He noticed the formation of “vascular lesions closely resembling those of human atherosclerosis.”
- A parallel test done on rats and dogs failed to produce lesions.
The Origins of a Myth

- Dr. Ancel Keys (1904 – 2004)
- Interest in cardiovascular disease
- Following World War II, drop in death rate from coronary artery disease (CAD) was a direct consequence of dwindling food supplies
- Minnesota starvation experiment
- Rabbit feeding studies
The Origins of a Myth

- Basic idea – correlation between dietary fat and heart disease
- 7 country study published
- Dietary fat largely animal fat
- Animal fat contains cholesterol
- Rabbit feeding study

**High cholesterol causes heart disease**
The Establishment of a Myth

Note:
1. There is not mentioning of the total cholesterol to HDL cholesterol relation
2. There is no mentioning of triglyceride to HDL relation

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Optimal
Near optimal/above optimal
Borderline high
High
Very high
Desirable
Borderline high
High
Low
High
Lowering Cholesterol

STATINS
Pharmacology of Statins

- Statins are a set of competitive inhibitors of HMG-CoA reductase.
- Statins compete with the normal substrate (mevalonate) for HMG-CoA reductase.

![Chemical structures of Crestor, Lipitor, and mevalonate]
Critical Intermediates

1. Acetate
2. Mevalonate
3. Activated isoprene
4. Squalene

1. 3 CH₃—COO⁻
2. CH₃
3. isoprene
4. CH₂=CH₂—CH₂—OH

1. Mevalonate
2. Acetyl-CoA
3. Acetoacetyl-CoA
4. β-Hydroxy-β-methylglutaryl-CoA (HMG-CoA)

1. HMG-CoA synthase
2. HMG-CoA reductase
3. NADPH + 2H⁺
On Statins
Business of Statins

Best-selling pharmaceutical in history: atorvastatin (Lipitor)

Pfizer reported sales of US $ 12.4 billion in 2008

Lipitor earned Pfizer US $ 125 billion since 1997

NECP recommends of statins as treatment of high cholesterol levels.

NCEP considers recommending a “healthy” cholesterol level (LDL) of 175 mg/dL
Business of Statins

- North America dominates the global market for statins
- EU guidelines differ from US (!!!)
- Application of US guideline to a European population resulted in recommendation of statins for nearly all men and two-thirds of women (JAMA network, 05-29-2014)
Important Facts

- Lipitor Commercial
- Exercise and diet alone are ineffective
- 36% (to 60%) reduction
Experimental Design

- Group 1 – Exercise, Diet
- Group 2 – Lipitor, Exercise, Diet
- Group 3 – Nothing
- Group 4 – Purposely elevated cholesterol
- Group 5 – Lipitor alone
Risk Reduction – Really?

- Numbers are given as relative risk reduction.
- Example: if drug X caused a 3% reduction and placebo caused a 1% reduction, the absolute difference is 2%.
- Relative risk reduction – the percentage difference between treatment and placebo.
- Take 1% (placebo) divided by 3% (treatment) multiply by 100 = 33%.
- 3% on placebo experienced heart attack while 2% on lipitor experienced a heart attack.
Number Needed to Treat (NNT)

- Lipitor – reduction heart attack
- Of 100 people, 3% on placebo experienced a heart attack, as opposed to 2% on lipitor (3 year trial, $ 150 million in tax money)
- Out of 100 people, you prevent 1/3 of a heart attack
- The remaining 99 2/3 have no benefit
Number Needed to Treat (NNT)

The Number Needed to Treat

How well do drugs work? Ads and news stories usually say that a medicine slashes the risk of, say, heart attacks by a big number, like 50%. But that often overstates the benefit, because it fails to provide the absolute risk. If only 2 people in a group of 100 are expected to have a heart attack, then a drug that cuts the rate by 50% prevents just 1 heart attack when taken by all 100 people. That’s why researchers favor using the “number needed to treat” (NNT). It shows how many people must take a drug for one person to benefit.

<table>
<thead>
<tr>
<th>Drug</th>
<th>NNT</th>
<th>Details</th>
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<tr>
<td>Antibiotic cocktail to eradicate ulcer-causing stomach bacteria (H. pylori)</td>
<td>1.1</td>
<td>to eradicate bacteria</td>
</tr>
<tr>
<td>Antibiotic cocktail to eradicate ulcer-causing stomach bacteria (H. pylori)</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Lipitor and other cholesterol-lowering statins, when used in people who have had a heart attack or have signs of heart disease</td>
<td>16-23</td>
<td>to prevent one heart attack</td>
</tr>
<tr>
<td>Lipitor and other cholesterol-lowering statins, when used in patients without heart disease, but who have risk factors like high blood pressure</td>
<td>70-250</td>
<td>to prevent one heart attack or stroke</td>
</tr>
<tr>
<td>Lipitor and other cholesterol-lowering statins, when used in patients without heart disease, but who have risk factors such as high blood pressure</td>
<td>500+</td>
<td>to prevent death or serious medical conditions</td>
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<td>Avandia, which controls blood sugar</td>
<td>1,000+</td>
<td>to prevent heart attacks, other effects of diabetes</td>
</tr>
<tr>
<td>Zetia, which lowers cholesterol</td>
<td>1,000+</td>
<td>to prevent heart disease</td>
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Data: Brandeis, Therapeutics Initiative, BusinessWeek
Number Needed to Treat (NNT)

- The better the drug, the fewer people in clinical trials to show statistical significance.
- Low NNT means a more reliable drug.
- If you put 250 people in a room and told them they would each pay $1,000 a year for a drug they would have to take every day, that many would get diarrhea and muscle, and that 249 would have no benefit? And that they could do just as well by exercising? How many would take that?
Statin – Side Effects

- Heart Failure
- Erectile dysfunction
- Memory loss and confusion
- Cancer
- Muscle fatigue/pain and damage (including the heart muscle!!)
- Digestive problems
- Rash
- Increased blood sugar (Diabetes II)
The Ugly Side of Statins. Systemic Appraisal of the Contemporary Un-Known Unknowns
Sherif Sultan$^{1,2}$#, Niamh Hynes$^{1,2}$

comprehensive review of Pubmed, EMBASE and Cochrane databases

There is a categorical lack of clinical evidence to support the use of statin therapy in primary prevention.
What is going on?
Study Flaw 1

- Anitschkow – rabbits fed cholesterol developed “arteriosclerosis”
- Rabbits are herbivores
- Cholesterol is in animal fat only
- Carnivores/omnivores (dogs/rats) do not respond with arteriosclerosis
Study Flaw 2

The 7 country study was actually a 22 country study.
Same data – different graph
Same data – different graph
Same data – different graph

Mssai
Inuit
Rendile
Tokelau
Latest WHO data

Persistent low cholesterol is strongly associated with increased mortality due to heart disease.
More Ancel Keys

- 1955: “It is concluded that in adult men the serum cholesterol level is essentially independent of the cholesterol intake over the whole range of natural human diets.

- 1997: “There’s NO connection whatsoever between cholesterol in food and cholesterol in blood. And we’ve known that all along. Cholesterol in the diet doesn’t matter at all unless you happen to be a chicken or a rabbit.”
The Farmingham Study

- 15,000 individuals, 3 generations
- Dietary cholesterol intake inconsequential for heart disease

“There is a direct association between falling cholesterol levels over the first 14 years and mortality over the following 18 years.”

In other words, as cholesterol fell death rates went up.
The Japan Study

47,000 individuals

The lipid intervention trial

"The highest death rate observed was among those with lowest cholesterol (under 160mg/dl); lowest death rate observed was with those whose cholesterol was between 200-259mg/dl"

while prevalence in women remained low (from 10.1 to 9.9%) Considerable increases in total serum cholesterol levels do not offer an explanation of the recent decline in mortality from coronary heart disease in Japan. This
The Honolulu Study

The *Honolulu Heart Program* study, with 8,000 participants, published in 2001:

“Long-term persistence of low cholesterol concentration actually increases the risk of death. Thus, the earlier the patients start to have lower cholesterol concentrations, the greater the risk of death.”

Cholesterol and all-cause mortality in elderly people from the Honolulu Heart Program: a cohort study

Prof Dr Irwin J Schatz, MD, Prof Kamal Masaki, MD, Katsuhiro Yano, MD, Randi Chen, MS, Prof Beatriz L Rodriguez, MD, Prof J David Curb, MD

Only the group with low cholesterol concentration at both examinations had a significant association with mortality (risk ratio 1.64, 95% CI 1.13–2.36).
Risk Factors for Heart Disease

- Multifactorial (genetic, lifestyle and environmental factors, diet)
- Age
- Smoking
- Poor nutrition (2% increase in energy intake from trans fatty acids increased CHD incidence by 23%)
- Infrequent exercise
- Alcohol (1 - 2 units/day reduce the risk of CHD while higher levels of consumption increase risks)
- Psychosocial wellbeing (Work stress, lack of social support, depression, anxiety and personality (particularly hostility)
- Blood pressure
- Cholesterol
- Overweight and obesity
- Diabetes