The New Cholesterol Guidelines: Has the World turned Upside Down?

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What’s Wrong with ATP-III?

- **Secondary Prevention**
  - Residual risk on statin treatment is substantial (70-75% of coronary events still occur).

- **Primary Prevention**
  - Most people are not treated until after their first MI.
  - Women are undertreated

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Cholesterol Treatment Trialists
Lancet November 9, 2010

Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 17,000 participants in 26 randomised trials

Summary

Methods: We analyzed individual patient data from randomised trials involving at least 10,000 participants and at least 5 years' follow-up. Relevant outcomes of interest were major coronary events (death from coronary heart disease, non-fatal myocardial infarction, or non-fatal stroke) occurring during follow-up. For each type of trial, we calculated the relative risk reduction and the average absolute risk reduction, and the number needed to treat to prevent one event was calculated. At 1 year after randomization.
“No Limit”
CTT Meta-analysis

• 1 mM ↓ LDL → 24% ↓ major vascular events
• 2 mM ↓ LDL → 42% ↓ major vascular events
• 3 mM ↓ LDL → 56% ↓ major vascular events

Implications for Guidelines

• Think risk, not LDL
• How much LDL is lowered is more important than what target is reached.

A Serious Flaw:

Secondary prevention only works if you survive your first myocardial infarction
The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials

Cholesterol Treatment Trialists Collaboration (CTT)

Summary

Background
Statins reduce LDL cholesterol and prevent vascular events, but their net effects in people at low risk of vascular events remain uncertain.

Methods
This meta-analysis included individual participant data from 27 trials of statin versus control (n=34,567; mean LDL cholesterol difference -0.8 mmol/L; mean follow-up 5.5 years) and the trials of statin versus no statin (n=24,603; difference -0.5 mmol/L; 5.1 years). Major vascular events were major coronary events (ischaemic non-fatal myocardial infarction or coronary death), stroke, or coronary revascularisations. Participants were separated into the categories of baseline 5-year major vascular event risk on control therapy (low risk: <10%, medium risk: 10% to <20%, high risk: ≥20%); in each, the mean LDL cholesterol reduction was estimated.

Findings
Reduction of LDL cholesterol with a statin reduced the risk of major vascular events (RR 0.79; 95%CI 0.77-0.81; per 1.0 mmol/L reduction), largely irrespective of age, sex, baseline LDL cholesterol or previous vascular disease, and of vascular and all-cause mortality. The proportional reduction in major vascular events was similar in the two lowest risk categories as in the higher risk category (RR per 1.0 mmol/L reduction from lowest to highest risk: 0.82 [95%CI 0.75-0.88], 0.89 [95%CI 0.80-0.98]).
CTT 5-10% Group: Benefit

For each 1 mM LDL reduction:
- 34% ↓ major vascular events
- 17% ↓ total mortality

All Groups: Risk

- For each 1 mM LDL reduction:
  - 0.5 excess cases myopathy / 1,000 pts / 5 years (NNH = 2000)
  - 0.5 excess hemorrhagic strokes / 1,000 pts / 5 years (NNH = 2000)
- Low dose statin: 6 excess diabetes cases / 1,000 pts / 5 years (NNH = 167)
- High dose statin: 16 excess diabetes cases / 1,000 pts / 5 years (NNH = 63)

Benefit/Risk

[Graph showing Benefit/Risk assessment for different doses of statin]
CTT <5% Group: Benefit (MEGA, JUPITER, AFCAPS)

For each 1 mM LDL reduction:
• 39% ↓ major vascular events
• No ↓ total mortality

Benefit/Risk

Implications for Guidelines
• Statin therapy clearly benefits patients with 10-year risk below 10%.
Guideline Development: Ground Rules

- Randomized Controlled Trials only
- Allowed 3 Critical Questions (CQ)

Critical Questions (“CQ”)

"If I ran the zoo . . ."

Critical Questions  (F. Zieve, 2014)

CQ1: Does the evidence support that cholesterol plays a critical role in the development of atherosclerosis?
Critical Questions (F. Zieve, 2014)

**CQ1:** Does the evidence support that cholesterol plays a critical role in the development of atherosclerosis?

**CQ2:** Do therapies that lower LDL-C reduce clinical coronary heart disease events?

**POSCH Trial**

838 men and women with past MI (Baseline LDL 166)

Partial ileal Bypass  
Control

Mean f/u 9.7 years

Buchwald et al NEJM 323:946 (1990)
POSCH: Cholesterol

POSCH: CHD Death or MI

Critical Questions (F. Zieve, 2014)

**CQ1:** Does the evidence support that cholesterol plays a critical role in the development of atherosclerosis?

**CQ2:** Do therapies that lower LDL-C reduce clinical coronary heart disease events?

**CQ3:** Does greater reduction in LDL-C lead to greater event reduction?
Critical Questions ("CQ")
(ACC/AHA TFOPG, 2013)

**CQ1:** What is the evidence for LDL-C and non-HDL-C goals for the secondary prevention of ASCVD?

**CQ2:** What is the evidence for LDL-C and non-HDL-C goals for the primary prevention of ASCVD?

**CQ3:** For primary and secondary prevention, what is the impact on lipid levels, effectiveness and safety of specific cholesterol-modifying drugs used for lipid management in general and in specific subgroups?

A Kinder, Gentler Guideline

"This guideline should not be used as a performance standard."

"This guideline is intended as a basis for a conversation between doctor and patient."
What's New in the Guideline?

1. No LDL-C or non-HDL-C targets
2. Four statin benefit groups
3. Global Risk Assessment for primary prevention

4 Major Statin Benefit Groups

• Clinical ASCVD
• Primary untreated LDL-C > 190 mg/dl
• Diabetes, age 40-75
• Estimated 10-year ASCVD risk ≥ 7.5%

Important Definitions (1)

" Moderate-Intensity Statin Therapy"
- Lower LDL by approximately 30-50%
(Praza 40, Simva 20-40, Atorva 10-20)

"High-Intensity Statin Therapy"
- Lower LDL by "approximately ≥ 50%"
(Atorva 80, Rosuva 40)
Important Definitions (2)

“Clinical ASCVD” (automatic statin)
ACS, MI, stable or unstable angina, arterial revascularization (coronary or other), stroke, TIA, PAD

“Hard ASCVD” (risk calculation)
CHD death, nonfatal MI, fatal or nonfatal stroke
Global 10-year ASCVD Risk

60yo white male with diabetes  
Cholesterol 170  
HDL-C 50  
Syst BP 110 on no meds  
Nonsmoker  
10.8%

Global 10-year ASCVD Risk

50yo white male with diabetes  
Cholesterol 190  
HDL-C 40  
Syst BP 120 on HCTZ 12.5 mg  
Nonsmoker  
8.0%
5% - 7.5% Risk: Factors favoring Treatment

1. Primary LDL>160 or other evidence of genetic hyperlpidemias
2. Family Hx premature ASCVD (<55M, <65F)
3. CRP>2 mg/l (>0.2 mg/dl)
4. CAC – Agatston score ≥300 or ≥75th percentile for age, sex, ethnicity
5. ABI<0.9
6. ↑ lifetime risk of ASCVD

![Diagram](image)

**HPS2-THRIVE Primary Endpoint:** Major Vascular Events

Risk ratio 0.96 (95% CI 0.90 – 1.03)
Logrank P=0.29
HPS2-THRIVE:
Baseline Lipids on Statin +/- Ezetimibe

Total Cholesterol 128
LDL-C (calc) 59
HDL-C 44
Triglycerides* 125

*64% fasted > 8 hrs

Goals of Therapy
("the more things change . . .")

Old Goal New Goal
LDL < 70  ➔  > 50% LDL reduction
LDL < 100  ➔  30 – 50% LDL reduction

図3 脂質低下療法による治療後の
LDL-C値(A)およびLDL-C変化率(B)と
最小血管径縮小の進行率

CCTT: Coronary Care Treatment Trial
CCTT: Canadian Intervention Trial
FATS: Familial Atherosclerosis Treatment Study
LCAS: Lipoprotein and Coronary Atherosclerosis Study
MAAS: Multicentre Anti-Atherome Study
MARS: Monitored Atherosclerosis Regression Study
PLAC1: Pravastatin Limitation of Atherosclerosis in the Coronary Arteries
REGRESS: Regression Growth Evaluation Statin Study

The Baseline Problem

- Clinical ASCVD
- Familial Dyslipidemia
- Diabetes + RF

Default = 80mg Atorvastatin

Check the LDL level!!

Global Risk Assessment

CV Death
Myocardial Infarction
Stroke

Global Risk Assessment
10-year Risk

Sex
Age
Race
Total Cholesterol
HDL-C
Systolic BP
Treatment for Hypertension
Diabetes
Smoking
### Global Risk Assessment

#### 10-year Risk

<table>
<thead>
<tr>
<th>60yo white male</th>
<th>FRS 16%</th>
<th>Global Risk 12%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol 200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL 40</td>
<td></td>
<td></td>
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<tr>
<td>Syst BP 130 on Rx</td>
<td></td>
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</tr>
<tr>
<td>Nondiabetic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsmoker</td>
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</tbody>
</table>

### Global Risk Assessment

#### Lifetime Risk

- Estimates lifetime risk for a 50yo with your risk profile
- Only 5 possible values for each gender

### Lifetime Risk Calculation

<table>
<thead>
<tr>
<th>55yo White male</th>
<th>55yo White male</th>
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</thead>
<tbody>
<tr>
<td>Chol 179</td>
<td>Chol 180</td>
</tr>
<tr>
<td>HDL 50</td>
<td>HDL 50</td>
</tr>
<tr>
<td>Syst BP 140</td>
<td>Syst BP 140</td>
</tr>
<tr>
<td>Nondiabetic</td>
<td>Nondiabetic</td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>Nonsmoker</td>
</tr>
<tr>
<td>10-year Risk 3.8%</td>
<td>10-year Risk 3.8%</td>
</tr>
<tr>
<td>Lifetime Risk 5%</td>
<td>Lifetime Risk 5%</td>
</tr>
<tr>
<td>10-year Risk 3.8%</td>
<td>10-year Risk 3.8%</td>
</tr>
<tr>
<td>Lifetime Risk 36%</td>
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</tr>
</tbody>
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Summary

**High Risk:** Treat more vigorously → High Dose Statin ($\geq 50\% \downarrow$ LDL)

**Moderate Risk:** Treat more people → Moderate Dose Statin ($30-50\% \downarrow$ LDL)