Cholesterol and Events

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Risk Prediction

- Higher Risk: >15%
- High: >2%
- Intermediate: 0.5-2.0%
- Low: <0.5%

Braunwald E. JACC Suppl 2006
Relation of LDL to Event Rate

y = 0.1629x - 4.6776
R² = 0.9029
p < 0.0001
Meta-analysis: 90,056 Individuals in 14 Randomized Clinical Trials of Statins

423,000 Patient Years of Follow-up

Per a 39 mg/dL absolute reduction in LDL

- 23% reduction in major cardiac events
- 20% reduction in CHD mortality
- 22% reduction in ischemic strokes
- Benefit entirely in proportion to LDL reduction
- No influence of baseline LDL on level of benefit
- No effect of gender, age, or other risk factors on benefit
- Similar relative risk reduction in primary and secondary prevention
- No increase in cancer or non-cardiovascular deaths

CTT Lancet 2005;366:1266-1278
Statin Plus PCSK-9 Inhibition: MACE

Hazard ratio, 0.47 (95% CI, 0.28–0.78)
P=0.003

Sabatine et al; NEJM, 2017
Association between low density lipoprotein and all cause and cause specific mortality in Denmark: prospective cohort study
Relation of LDL to Event Rate

![Graph showing the relation between LDL cholesterol (mg/dL) and CHD events (%)](image)

\[ y = 0.0599x - 3.3952 \]

\[ R^2 = 0.9305 \]

\[ p=0.0019 \]
Pros and Cons of LDL Targets

• **Cons**
  - Statin therapy may be inadvertently held
  - Additional ineffective therapy may be administered

• **Pros**
  - LDL targets shown to be of value in high risk groups
  - LDL targets used in landmark trials
  - Additional therapies shown to be effective
  - Atherogenic lipidemia may alter drug regimen
    - High triglyceride and low HDL
  - Statin side effects are dose related

*Potential role for combined Guideline and LDL targets*
<table>
<thead>
<tr>
<th>Event*</th>
<th>80-100</th>
<th>60-80</th>
<th>40-60</th>
<th>&lt;40</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myositis or Myalgia (AE)</td>
<td>1.6</td>
<td>3.1</td>
<td>3.2</td>
<td>2.8</td>
<td>NS</td>
</tr>
<tr>
<td>CK &gt; 3x ULN</td>
<td>2.3</td>
<td>0.7</td>
<td>1.9</td>
<td>1.0</td>
<td>NS</td>
</tr>
<tr>
<td>CK &gt; 10x ULN</td>
<td>0.3</td>
<td>0</td>
<td>0.3</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>ALT &gt; 3X ULN</td>
<td>3.1</td>
<td>3.0</td>
<td>3.2</td>
<td>3.6</td>
<td>NS</td>
</tr>
</tbody>
</table>

Primary Prevention: Assess ASCVD Risk in Each Age Group
Emphasize Adherence to Healthy Lifestyle

- Age 0-19 y
  - Lifestyle to prevent or reduce ASCVD risk
  - Diagnosis of Familial Hypercholesterolemia → statin

- Age 20-39 y
  - Estimate lifetime risk to encourage lifestyle to reduce ASCVD risk
  - Consider statin if family history, premature ASCVD, and LDL-C ≥160 mg/dL (4.1 mmol/L)

- Age 40-75 y
  - LDL-C ≥70-130 mg/dL (1.8-3.4 mmol/L)
    - Without diabetes mellitus, 10-year ASCVD risk percent begins risk discussion

- Diabetes mellitus and age 40-75 y
  - Moderate-intensity statin (Class I)

- Diabetes mellitus and age 40-75 y
  - Risk assessment to consider high-intensity statin (Class IIa)

- Age >75 y
  - Clinical assessment, Risk discussion

ASCVD Risk Enhancers:
- Family history of premature ASCVD
- Persistently elevated LDL-C ≥160 mg/dL (≥4.1 mmol/L)
- Chronic kidney disease
- Metabolic syndrome
- Conditions specific to women (e.g., preeclampsia, premature menopause)
- Inflammatory diseases (especially rheumatoid arthritis, psoriasis, HIV)
- Ethnicity (e.g., South Asian ancestry)

Lipid/Biomarkers:
- Persistently elevated triglycerides (≥175 mg/dL, ≥2.0 mmol/L)

In selected individuals if measured:
- hs-CRP ≥2.0 mg/L
- Lp(a) levels >50 mg/dL or >125 nmol/L
- apoB ≥130 mg/dL
- Ankle-brachial index (ABI) <0.9

- <5% “Low Risk”
  - Risk discussion: Emphasize lifestyle to reduce risk factors (Class I)

- 5% - <7.5% “Borderline Risk”
  - Risk discussion: If risk enhancers present then risk discussion regarding moderate-intensity statin therapy (Class IIb)

- ≥7.5% - <20% “Intermediate Risk”
  - Risk discussion: If risk estimate + risk enhancers favor statin, initiate moderate-intensity statin to reduce LDL-C by 30% - 49% (Class I)

- ≥20% “High Risk”
  - Risk discussion: Initiate statin to reduce LDL-C ≥50% (Class I)

If risk decision is uncertain:
Consider measuring CAC in selected adults:
- CAC = 0 (lowers risk; consider no statin, unless diabetes, family history of premature CHD, or cigarette smoking are present)
- CAC = 1-99 favors statin (especially after age 55)
- CAC = 100+ and/or ≥75th percentile, initiate statin therapy
Comparative Cholesterol Levels

- Hunter-Gatherer Humans:
  - Hadza
  - Inuit
  - Hmong
  - Pygmy
  - San

- Wild Primates:
  - Baboon
  - Howler monkey
  - Night monkey

- Wild Mammals:
  - Horse
  - Bear
  - Peccary
  - Black rhinoceros
  - African elephant

- Modern Humans:
  - Adult American

Mean Total Cholesterol (mg/dL)
Cholesterol Controversy: Final Thoughts

• Many positive aspects of new Guidelines
  • Emphasis on statins, evidence base, greater coverage

• Questions exist regarding risk calculator
  • Compromise may be 10% ten year risk

• Role of LDL targets continues to be debated
  • Trial data support relation of risk to LDL level
  • New agents will further reduce LDL (pcsk9 inhibitors)

• Management must begin with lifestyle measures

• Ultimate decisions require physician/patient discourse