What Is Happening With The AHA Cholesterol Guidelines: Should we Measure Serum Cholesterol? How Low Should The LDL Be Pushed To and Can It Get There?

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No conflicts of interest pertinent to this talk

Who Needs Statins?

New Cholesterol Guidelines Based on High Quality Evidence from RCTs

Table 5. High-Moderate and Low-Intensity Statin Therapy (Used in the RCTs) reviewed by the Expert Panel

Pros

Cons

Lesser evidence not considered
- Observational studies
- Preclinical studies
- Angiographic studies
Limited generalizability for understudied (<40, >75 yrs) and subgroups (women, minorities)
Secondary Prevention: Heart Protection Study (HPS)

- 20,536 patients with CHD
- Simvastatin (40 mg qd) vs placebo
- ↓ Total mortality by simvastatin
  ↓ Total CHD, total stroke, revascularization


<table>
<thead>
<tr>
<th>Baseline LDL-C (mg/dL)</th>
<th>Statin (n=10,269)</th>
<th>Placebo (n=10,267)</th>
<th>Event Rate Ratio (95% CI)</th>
<th>Statin Better</th>
<th>Statin Worse</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100</td>
<td>282 (16%)</td>
<td>358 (21%)</td>
<td>0.76 (0.72–0.81)</td>
<td>P&lt;0.0001</td>
<td></td>
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<tr>
<td>100–129</td>
<td>668 (19%)</td>
<td>873 (25%)</td>
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<tr>
<td>≥130</td>
<td>1083 (22%)</td>
<td>1356 (27%)</td>
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<tr>
<td>Dropout</td>
<td>597 (11%)</td>
<td>764 (14%)</td>
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Lipid Lowering Intensity: PROVE-IT TIMI 22

4,162 patients with ACS; Atorvastatin 80 mg qd vs Pravastatin 40mg
The median LDL cholesterol level achieved during treatment was 95 mg/dl in the pravastatin group and 62 mg/dl in the atorvastatin group (P<0.001)


Primary Prevention: Justification for the Use of Statins in Prevention (JUPITER)

17,802 men (>50 yrs) and women (>60) with LDL-C <130 mg/dL and hs-CRP >2 mg/L randomized to rosuvastatin (20 mg) or placebo

Rosuvastatin
Placibo

44% RRR
P=0.00001, NNT=25

Statin benefits those with mean age of 66 and elevated hsCRP


Niacin in addition to Statin Therapy Does Not Lower Cardiovascular Events

AIM-High

3414 Stable CVD patients on statin +/- niacin: TG/HDL/LDL = 163/35/74 mg/dL

HPS-2: THRIVE

25,673 SIHD on simvastatin +/- ezetimibe: TC/TG/HDL/LDL = 128/125/44/63 mg/dL

In response to these and other studies, the Cholesterol Guidelines in 2013 suggested:
- Statins reduce cardiovascular events regardless of baseline LDL-C
- Higher intensity statins are better
- Non-statin cholesterol lowering on top of statin therapy does NOT further reduce cardiovascular events
**IMPROVE-IT: Primary Endpoint**

Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke

- Simva — 34.7%
- EZ/Simva — 32.7%

HR 0.936 CI (0.887, 0.988)

p=0.016

NNT= 50

**PCSK9 Inhibitors**

**Case Reports of Patients Double Loss-of-Function PCSK9 Mutations**

- 32 year-old woman had no measurable PCSK9 and a LDL-C of 14.
- 21 year-old AA woman had no measurable PCSK9 and a LDL-C of 15.
- 49 year-old French male had no detectable PCSK9 and a LDL-C of 16.

**Open-Label Study of Long-Term Evaluation against LDL Cholesterol (OSLER)**

4465 patients were randomly assigned in a 2:1 ratio to receive either evolocumab plus standard therapy or standard therapy alone. Patients were followed for a median of 11.1 mo.

61% reduction in LDL-C

Absolute reduction 73 (71-76) mg/dl

HR 0.42

95% CI 0.28-0.76

p=0.003

**Conclusions**

- Statins reduce cardiovascular events regardless of baseline LDL-C
- Higher intensity is better
- Non-statin cholesterol lowering (e.g. niacin) on top of statin therapy does NOT further reduce cardiovascular events
- Non-statin cholesterol lowering (e.g. ezetimibe) on top of statin therapy does further reduce cardiovascular events
- PCSK9 inhibitors have a profound effect on LDL-C and other lipoproteins and may further lower CV events
- Reaffirmation of the LDL hypothesis —lower is better
- Future guidelines will likely be modified

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**Thank You**