Is Lower Better for LDL or is there a “Sweet Spot”

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Association Between Achieved Low-Density Lipoprotein Levels and Major Adverse Cardiac Events in Patients With Stable Ischemic Heart Disease Taking Statin Treatment

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Evidence Supporting a "Sweet Spot" for LDL-C

- This observational cohort study compares risk of MACEs among IHD patient subgroups by observed LDL-C levels after at least 1 year of statin therapy.

- 31,600 patients, aged 34 to 80 with prior history of IHD and index LDL-C after at least one year of therapy obtained from records of a major Israeli Health System.

- Based on pharmacy records, only patients with 80% compliance to their statin were included.

- Goal was to assess MACE rates for LDL-C < 70 mg/dl, vs 70 -100 mg/dl, vs 100-130 mg/dl.

MACE was lower in those with LDL-C between 70 and 100 mg/dl than those greater than 100 mg/dl.

MACE rates were no different for those who achieved LDL-C < 70 mg/dl than those who achieved LDL-C < 100 mg/dl.

Authors concluded that there is no evidence that lowering LDL-C to levels below 70 mg/dl with statin therapy offers any benefit over achieving LDL-C levels below 100 mg/dl.

Potential confounders such as duration of follow-up.
Sweet Spot or Lower is Better

- IMPROVE-IT “proves” the LDL hypothesis is now the “LDL principle!”
- Or does it?
IMProved Reduction of Outcomes: Vytorin Efficacy International Trial

A Multicenter, Double-Blind, Randomized Study to Establish the Clinical Benefit and Safety of Vytorin (Ezetimibe/Simvastatin Tablet) vs Simvastatin Monotherapy in High-Risk Subjects Presenting With Acute Coronary Syndrome
Study Design

Patients stabilized post ACS ≤ 10 days:
LDL-C 50–125*mg/dL (or 50–100**mg/dL if prior lipid-lowering Rx)

N=18,144

Standard Medical & Interventional Therapy

Simvastatin
40 mg

Ezetimibe / Simvastatin
10 / 40 mg

Follow-up Visit Day 30, every 4 months

Duration: Minimum 2 ½-year follow-up (at least 5250 events)

Primary Endpoint: CV death, MI, hospital admission for UA, coronary revascularization (≥ 30 days after randomization), or stroke

Cannon CP AHJ 2008;156:826-32; Califf RM NEJM 2009;361:712-7; Blazing MA AHJ 2014;168:205-12
### Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Simvastatin (N=9077)</th>
<th>EZ/Simva (N=9067)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>64</td>
<td>64</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>24</td>
<td>25</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td><strong>MI prior to index ACS</strong></td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td><strong>STEMI / NSTEMI / UA</strong></td>
<td>29 / 47 / 24</td>
<td>29 / 47 / 24</td>
</tr>
<tr>
<td><strong>Days post ACS to rand (IQR)</strong></td>
<td>5 (3, 8)</td>
<td>5 (3, 8)</td>
</tr>
<tr>
<td><strong>Cath / PCI for ACS event</strong></td>
<td>88 / 70</td>
<td>88 / 70</td>
</tr>
<tr>
<td><strong>Prior lipid Rx</strong></td>
<td>35</td>
<td>36</td>
</tr>
<tr>
<td><strong>LDL-C at ACS event (mg/dL, IQR)</strong></td>
<td>95 (79, 110)</td>
<td>95 (79,110)</td>
</tr>
</tbody>
</table>
LDL-C and Lipid Changes

<table>
<thead>
<tr>
<th>1 Yr Mean</th>
<th>LDL-C</th>
<th>TC</th>
<th>TG</th>
<th>HDL</th>
<th>hsCRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simva</td>
<td>69.9</td>
<td>145.1</td>
<td>137.1</td>
<td>48.1</td>
<td>3.8</td>
</tr>
<tr>
<td>EZ/Simva</td>
<td>53.2</td>
<td>125.8</td>
<td>120.4</td>
<td>48.7</td>
<td>3.3</td>
</tr>
<tr>
<td>Δ in mg/dL</td>
<td>-16.7</td>
<td>-19.3</td>
<td>-16.7</td>
<td>+0.6</td>
<td>-0.5</td>
</tr>
</tbody>
</table>

Mean LDL-C (mg/dL)

- Median Time avg
  - 69.5 vs. 53.7 mg/dL

Number at risk:
- EZ/Simva: 8990, 8889, 8230, 7701, 7264, 6864, 6583, 6256, 5354, 4508, 3484, 2608, 1078
- Simva: 9009, 8921, 8306, 7683, 7289, 6939, 6619, 6192, 5684, 5267, 4385, 3387, 2569, 2168

Primary Endpoint – ITT

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

HR 0.936 CI (0.887, 0.988)
p=0.016

Simva — 34.7%
2742 events

EZ/Simva — 32.7%
2572 events

NNT= 50

Event Rate (%)

Time since randomization (years)

7-year event rates
Primary and 3 Prespecified Secondary Endpoints - ITT
CV Death, Non-fatal MI, or Non-fatal Stroke
IMPROVE-IT vs. CTT: Ezetimibe vs. Statin Benefit
What about “treat risk, not LDL-C level” and the benefit is the same?

Heart Protection Study
Heart Protection Study (HPS)

- Double-blind trial in 22,536 patients, age 40-80 years, at increased risk of CHD death due to prior disease:
  - MI or other CHD
  - Occlusive disease of non-coronary arteries, or
  - Diabetes mellitus or treated hypertension
- Total cholesterol was >3.5 mmol/L (>135 mg/dL)
- Randomized to simvastatin 40 mg daily or placebo
- Scheduled 5 year treatment period
- Primary Endpoint: Major vascular events

HPS: Primary Endpoint Results by Group

Heart Protection Study Collaborative Group. *Lancet.*
2002;360:7-22.
HPS: Primary Endpoint Results by LDL-C

<table>
<thead>
<tr>
<th>Baseline feature</th>
<th>STATIN (10,269)</th>
<th>PLACEBO (10,267)</th>
<th>Risk ratio &amp; 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 100 (2.6 mmol/L)</td>
<td>285</td>
<td>360</td>
<td>STATIN better</td>
</tr>
<tr>
<td>100 to 129</td>
<td>670</td>
<td>881</td>
<td></td>
</tr>
<tr>
<td>≥ 130 (3.4 mmol/L)</td>
<td>1087</td>
<td>1365</td>
<td>STATIN worse</td>
</tr>
<tr>
<td>ALL PATIENTS</td>
<td>2042 (19.9%)</td>
<td>2606 (25.4%)</td>
<td></td>
</tr>
</tbody>
</table>

Het$\chi^2 = 0.8$

High potency statins seem to be more effective than low potency.

Reducing average LDL-C levels to lower levels in studies seems to linearly produce relative risk of CV events.

Prove IT and TNT trials.
PROVE IT – TIMI 22: Lipid Results

- Median starting LDL-C was 106 mg/dL
- Median treated LDL-C values were:
  - Atorvastatin 62 mg/dL
  - Pravastatin 95 mg/dL (P<0.001)
PROVE IT: Primary Endpoint


![Graph showing the comparison of Pravastatin 40 mg (26.3%) and Atorvastatin 80 mg (22.4%). The graph indicates that Atorvastatin shows a lower percentage of patients with an event over time, with RRR: 16%, ARR: 3.9%, and NNT: 26.](Image)
Treating to New Targets (TNT): Study Design

- Double-blind controlled trial in 10,001 men and women age 35-75 years
- All patients had clinically evident CHD and LDL-C <130 mg/dL while taking atorvastatin 10 mg daily
- Patients randomized to atorvastatin 80 mg or 10 mg
- Median duration was 4.9 years

- Primary end point: Time to first major CV event (CHD death, non-procedural myocardial infarction, resuscitation after cardiac arrest, or stroke)

Treating to New Targets (TNT): LDL-C Results and Primary Endpoint

Cholesterol Treatment Trialists’ (CTT) Collaboration

- Meta-analysis of large (n>1000), randomized clinical trials that were at least 2 yrs in duration
  - More vs. Less intensive statin therapy:
    - 5 trials (n=39,612), median 5 yr follow-up
  - Statin vs. control:
    - 21 trials (n=129,526), median 4.8 yr follow-up
- Average CV event risk reductions per 1.0 mmol/L LDL-C reduction at 1 year after randomization were calculated

CTT Collaboration

Yet, not all methods of LDL lowering seem to lower risk at least when added to statin!

▶ Statins plus Niacin (AIM High 12% vs 5.5% LDL reduction, HPS2 Thrive 19.9% reduction in LDL)

▶ Statins plus fibrates? (ACCORD lipid no difference in LDL between arms, borderline benefit in High TG group)

▶ Statins plus CETP inhibitors, even those that lower LDL-C substantially (ACCELERATE trial with evacetrapib, 37% drop in LDL with 130% rise in HDL with negative outcome benefit)

PCSK9 loss of function mutation lowers LDL-C 38% over lifetime

Reduces CV risk by 88%!!!

NPC1L1 heterozygote null mutation reduced LDL by 12 mg/dl and reduced lifetime event rate by 53%

The “401K” effect

Duration counts, even in statin trials.

“For this reason, reducing LDL-C with statins in trials doesn’t yield as potent a risk reduction as that seen when examining an LDL in a population”


Conclusion

- The LDL principle is “not so simple” but LDL-C remains main target for Rx.
- **High risk individuals** with established CAD seem to get benefit from high potency therapy regardless of their LDL-C at baseline and “start a statin stupid” is a reasonable approach.
- A “sweet spot” for LDL-C seems unlikely, too simple, and not helpful.
- Not all treatment methods for “getting lower” yield positive results.
- Observational data suggest lower is probably better, at least in those with established CAD, despite the design issues of available data, but prospective properly designed trials will likely not be done.
- Duration may be a critical issue for the future with a higher yield from modest LDL-C lowering starting earlier in life, before disease progresses.
Conclusion

- “Lower may often be better, but only using the correct therapy, in the patients with the correct risk profile, for the right duration, and with the control of the right additional risk factors! (eg HTN, metabolic syndrome, Lp(a), etc.)”

- Treat everyone at high risk with high potency therapy even if their LDL is not markedly elevated. If the LDL is markedly elevated, attempt to get it low, with combination therapy if necessary, with consideration of med side effects, cost, and potential risks vs benefits

- Unfortunately, Life is never simple!!

- Use clinical judgement with individual patients and “When in doubt, examine the patient!”