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

ALAN S BROWN MD, FACC FNLA FAHA FASPC
DIRECTOR, DIVISION OF CARDIOLOGY
ADVOCATE LUTHERAN GENERAL HOSPITAL, PARK RIDGE, ILLINOIS
DIRECTOR OF CARDIOLOGY, NORTH REGION, ADVOCATE HEALTHCARE SYSTEM
Association Between Achieved Low-Density Lipoprotein Levels and Major Adverse Cardiac Events in Patients With Stable Ischemic Heart Disease Taking Statin Treatment

Morton Leibowitz, MD; Tomas Karpati, MD; Chandra J. Cohen-Stavi, MPA; Becca S. Feldman, ScD; Moshe Hoshen, PhD; Haim Bitteman, MD; Samy Suissa, PhD; Ran D. Balicer, MD, PhD

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 -100mg/dl, vs 100- 130 mg/dl.

Results

- 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

Uptitrated to Simva 80 mg if LDL-C > 79 (adapted per FDA label 2011)

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; Call{t} 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>Age (years)</td>
<td>64%</td>
<td>64%</td>
</tr>
<tr>
<td>Female</td>
<td>24%</td>
<td>25%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>27%</td>
<td>27%</td>
</tr>
<tr>
<td>MI prior to index ACS</td>
<td>21%</td>
<td>21%</td>
</tr>
<tr>
<td>STEMI / NSTEMI / UA</td>
<td>29 / 47 / 24%</td>
<td>29 / 47 / 24%</td>
</tr>
<tr>
<td>Days post ACS to rand (IQR)</td>
<td>5 (3, 8)</td>
<td>5 (3, 8)</td>
</tr>
<tr>
<td>Cath / PCI for ACS event</td>
<td>88 / 70</td>
<td>88 / 70</td>
</tr>
<tr>
<td>Prior lipid Rx</td>
<td>35%</td>
<td>36%</td>
</tr>
<tr>
<td>LDL-C at ACS event (mg/dL, IQR)</td>
<td>95 (79, 110)</td>
<td>95 (79,110)</td>
</tr>
</tbody>
</table>
LDL-C and Lipid Changes

<table>
<thead>
<tr>
<th></th>
<th>LDL-C</th>
<th>TC</th>
<th>TG</th>
<th>HDL</th>
<th>hsCRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Yr Mean</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<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 6964 6583 6256 5734 5354 4508 3484 2608 1078
Simva: 9009 8921 8306 7843 7289 6939 6807 6192 5684 5267 4395 3387 2569 1068

Time since randomization (months)
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 (%)  
0 10 20 30 40

Time since randomization (years)  
7-year event rates
Primary and 3 Prespecified Secondary Endpoints - ITT

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Ezetimibe/Simva Better</th>
<th>Simva Better</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary CVD/MI/UA/Cor Revasc/CVA</td>
<td>0.936</td>
<td></td>
<td>0.016</td>
</tr>
<tr>
<td>Secondary #1 All D/MI/UA/Cor Revasc/CVA</td>
<td>0.948</td>
<td></td>
<td>0.034</td>
</tr>
<tr>
<td>Secondary #2 CHD/MI/Urgent Cor Revasc</td>
<td>0.912</td>
<td></td>
<td>0.016</td>
</tr>
<tr>
<td>Secondary #3 CVD/MI/UA/All Revasc/CVA</td>
<td>0.945</td>
<td></td>
<td>0.035</td>
</tr>
</tbody>
</table>

UA, documented unstable angina requiring rehospitalization; Cor Revasc, coronary revascularization (≥30 days after randomization); All D, all-cause death; CHD, coronary heart disease death; All Revasc, coronary and non-coronary revascularization (≥30 days)
CV Death, Non-fatal MI, or Non-fatal Stroke

- **Simva**: 22.2%, 1704 events
- **EZ/Simva**: 20.4%, 1544 events

**HR 0.90 CI (0.84, 0.97)**

- p=0.003
- NNT= 56

*7-year event rates*
IMPROVE-IT vs. CTT: Ezetimibe vs. Statin Benefit

Proportional reduction in event rate (SE)

Reduction in LDL cholesterol (mmol/L)

CTT Collaboration.
Lancet 2005; 366:1267-78;
Sweet Spot or Lower is Better

- 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**

**SIMVASTATIN**  
(10,269)

**PLACEBO**  
(10,267)

### Rate ratio & 95% CI

**STATIN better**  
**PLACEBO better**

<table>
<thead>
<tr>
<th>Condition</th>
<th>SIMVASTATIN</th>
<th>PLACEBO</th>
<th>Rate ratio</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous MI</td>
<td>999 (23.5%)</td>
<td>1250 (29.4%)</td>
<td>0.4</td>
<td>0.2</td>
<td>0.8</td>
</tr>
<tr>
<td>Other CHD (not MI)</td>
<td>460 (18.9%)</td>
<td>591 (24.2%)</td>
<td>0.6</td>
<td>0.4</td>
<td>1.0</td>
</tr>
<tr>
<td>No prior CHD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVD</td>
<td>172 (18.7%)</td>
<td>212 (23.6%)</td>
<td>0.8</td>
<td>0.6</td>
<td>1.2</td>
</tr>
<tr>
<td>PVD</td>
<td>327 (24.7%)</td>
<td>420 (30.5%)</td>
<td>1.0</td>
<td>0.8</td>
<td>1.4</td>
</tr>
<tr>
<td>Diabetes</td>
<td>276 (13.8%)</td>
<td>367 (18.6%)</td>
<td>1.4</td>
<td>1.2</td>
<td>1.7</td>
</tr>
<tr>
<td><strong>ALL PATIENTS</strong></td>
<td>2033 (19.8%)</td>
<td>2585 (25.2%)</td>
<td>1.0</td>
<td>0.8</td>
<td>1.2</td>
</tr>
</tbody>
</table>

**HPS: Primary Endpoint Results by Group**

Heart Protection Study Collaborative Group. *Lancet*.  
2002;360:7-22.

**RRR:** 24%  
**ARR:** 5.4%  
**NNT:** 19  

**P** < 0.0001
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>
<th>STATIN better</th>
<th>STATIN worse</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100 (2.6 mmol/L)</td>
<td>285</td>
<td>360</td>
<td></td>
<td>STATIN better</td>
<td>STATIN worse</td>
</tr>
<tr>
<td>100 to 129</td>
<td>670</td>
<td>881</td>
<td></td>
<td>STATIN better</td>
<td>STATIN worse</td>
</tr>
<tr>
<td>≥ 130 (3.4 mmol/L)</td>
<td>1087</td>
<td>1365</td>
<td></td>
<td>STATIN better</td>
<td>STATIN worse</td>
</tr>
<tr>
<td>ALL PATIENTS</td>
<td>2042 (19.9%)</td>
<td>2606 (25.4%)</td>
<td></td>
<td>STATIN better</td>
<td>STATIN worse</td>
</tr>
</tbody>
</table>

Sweet Spot or Lower is Better

- 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)

- ACS response lowers LDL-C from the true baseline and 25% of patients were receiving statins before ACS event

PROVE IT: Primary Endpoint

Pravastatin 40 mg (26.3%)

Atorvastatin 80 mg (22.4%)

RRR: 16%
P = 0.005
ARR: 3.9%
NNT: 26

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

CV event reductions proportionate to LDL-C reductions, even when baseline LDL-C was <2 mmol/L (77 mg/dL)

<table>
<thead>
<tr>
<th>Further Event Reduction</th>
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<tbody>
<tr>
<td>Major Vascular Events</td>
<td>15%    (P&lt;0.001)</td>
</tr>
<tr>
<td>CHD Death or Non-Fatal MI</td>
<td>13%    (P&lt;0.001)</td>
</tr>
<tr>
<td>Coronary Revascularization</td>
<td>19%    (P&lt;0.001)</td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td>16%    (P=0.005)</td>
</tr>
</tbody>
</table>

CTT Collaboration

Proportional reduction in event rate (SE) vs. Reduction in LDL cholesterol (mmol/L)

Yet, Not all methods of LDL lowering work!?

- Statins plus Niacin
- Statins plus fibrates
- Statins plus CETP inhibitors, even those that lower LDL-C substantially
Genetic Data - DURATION COUNTS!

- PCSK9 loss of function mutation lowers LDL-C 38% over lifetime
- Reduces CV risk by 88%!!!
- The “401K” effect
- Duration counts, even in statin trials.
- For this reason, reducing LDL-C with statins 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
- A “sweet spot” seems unlikely
- Observational data suggest lower is better, at least in those with established CAD, despite the design issues of available data
- 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