Is it Time to Return to Cholesterol Goals for Optimal Patient Management?

CON

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• Dr. Lloyd-Jones was co-chair of the Risk Assessment Work Group and a member of the Cholesterol Guidelines Panel

Stipulations

• LDL-C/ApoB-containing particles are THE central molecule in atherogenesis
• We spent a lot of time educating people about LDL-C and that on-treatment lower LDL-C is better
• Some patients may be motivated by having a target/goal
Why not LDL Targets/Goals?

- LDL-C level has little if anything to do with response to therapy in terms of relative risk reduction
- RISK is what matters

CTT 2005: Statin vs placebo

Everyone has similar RRR benefit!

CTT 2010: Statin/More vs Control/Less
Baseline LDL Subgroups
Why not LDL Targets/Goals?

• Lack of RCT evidence to support titration of drug therapy to specific LDL–C and/or non-HDL–C goals
  – Statin trials have not directly targeted a specific goal
  – Trials have achieved certain ranges of LDL-C in their participants
  – But this is purely a function of starting LDL-C level and dose of statin, it does not suggest the “right” target level.

• What IS the right goal? Surely that is known!
  – 100 mg/dL? (ATP-III)
  – 80 mg/dL? (Canada)
  – 70 mg/dL? (Europe)
  – 55 mg/dL? (IMPROVE-IT, I guess)

• And for whom? Should it really differ for 1° and 2° prevention?
Why not LDL Targets/Goals?

- Unknown net benefit from treat-to-target strategy (as of 2013, and even now)
  - Non-statin drugs added to statin to reach goal
  - Unclear rates of additional adverse effects
  - Unknown magnitude of additional benefit, but probably small

HPS2-THRIVE (N=25,000)
ER niacin/laropiprant-simvastatin vs. simvastatin:
No ASCVD event reduction vs placebo-simvastatin

![Graph showing LDL, HDL, and TG levels](image)

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Niacin/Laropiprant-simvastatin</th>
<th>Placebo-simvastatin</th>
<th>Risk Ratio (95% CI)</th>
<th>Absolute Event Rates (per 1000)}</th>
<th>Difference (Niacin/Laropiprant-simvastatin - Placebo-simvastatin)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>245/1169 (20.9)</td>
<td>199/1169 (17.0)</td>
<td>1.18 (1.12-1.26)</td>
<td>1.04 (0.92-1.17)</td>
<td>0.08 (0.02-0.14)</td>
<td>0.001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>50/1169 (4.3)</td>
<td>42/1169 (3.6)</td>
<td>1.12 (1.00-1.28)</td>
<td>0.03 (0.00-0.07)</td>
<td>0.07 (0.01-0.13)</td>
<td>0.001</td>
</tr>
<tr>
<td>Total ischemic event</td>
<td>101/1169 (8.6)</td>
<td>73/1169 (6.3)</td>
<td>1.22 (1.10-1.36)</td>
<td>0.09 (0.02-0.16)</td>
<td>0.07 (0.01-0.13)</td>
<td>0.001</td>
</tr>
<tr>
<td>Randomized event</td>
<td>196/1169 (16.7)</td>
<td>148/1169 (12.6)</td>
<td>1.38 (1.23-1.55)</td>
<td>0.02 (0.00-0.05)</td>
<td>0.07 (0.01-0.13)</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetes mellitus — new cases</td>
<td>452/1169 (37.7)</td>
<td>377/1169 (32.2)</td>
<td>1.17 (1.12-1.23)</td>
<td>0.05 (0.02-0.08)</td>
<td>0.07 (0.01-0.13)</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetes mellitus — prevalent</td>
<td>413/1169 (35.2)</td>
<td>332/1169 (28.6)</td>
<td>1.26 (1.19-1.34)</td>
<td>0.07 (0.02-0.11)</td>
<td>0.07 (0.01-0.13)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

NEJM 2014
IMPROVE-IT (N=18,000)
LDL-C and Lipid Changes
Simva 40 vs. Simva 40/Ezetimibe 10
7 years’ F/U (!)

IMPROVE-IT (N=18,000)
Primary Endpoint
Cardiovascular Death, MI, Stroke, documented Unstable Angina
requiring rehospitalization, or coronary revascularization (>30 days)

<table>
<thead>
<tr>
<th>Eze/Simva</th>
<th>Simva</th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N=9067)</td>
<td>(N=9077)</td>
<td>32.7%</td>
<td>34.7%</td>
<td>0.94</td>
</tr>
</tbody>
</table>

Kaplan-Meier event rates to 7 years
Median follow-up 57 months
Total patient years follow-up for primary endpoint = 80,286

Why not LDL Targets/Goals?

• May result, often, in underuse of optimal statin therapy
  – 2nd prevention pt with LDL 95 on pravastatin 40 mg
  – Due to potential safety concerns, MD reduces dose of atorvastatin from 80 to 20 mg to add niacin or fibrate

• Could well result in overuse of PCSK9 inhibitors
Why not LDL Targets/Goals?

- Even the biology says high-intensity statin is the way to go, rather than LDL-C targets.

This challenges the concept of treating LDL cholesterol to threshold target levels for secondary prevention and strengthens the notion that despite achieving specific LDL cholesterol targets, many individuals harbor residual risk that is likely to be more effectively mitigated by maximally intensifying statin therapy.

So, even Steve Nissen agrees...
Why not LDL Targets/Goals?

• LDL-C degrades ability to correctly select patients for therapy
• RISK is what matters!

Accurate of Statin Assignment Using the 2013 AHA/ACC Cholesterol Guideline Versus the 2001 NCEP ATP III Guideline

• 3076 patients referred for CTA
• "The use of low-density lipoprotein targets seriously degraded the accuracy of the NCEP guideline for statin assignment."

Why not LDL Targets/Goals?

• BTW, how are you measuring LDL-C?
Agreement between Friedewald and Direct LDL-C Measurement

Why not LDL Targets/Goals?

Don’t believe me, let’s look at what the guidelines say!

Recent Guidelines and Recommendations

Opposed, with LDL Targets
- NLA (2014)
- AACE (2014)
- ADA (2014)*

In Close Agreement, without LDL Targets
- JBS3/NICE (2014)*
- KDIGO (2014)
- ADA (2015)
- VA (2015)*
- USPSTF (Now)*

* Used formal, independent systematic review and evidence synthesis to craft recommendations; limited or no RWI/COI allowed.
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Recap/Rebuttal

- LDL-C unrelated to RRR/ARR from statins – RISK is what matters
- Lack of RCT evidence to support titration of drug therapy to specific LDL-C goals
- What IS the right goal, and for whom?
- Unknown additional net benefit but probably small and may be limited by safety concerns – Lower IS better but it matters how you get there, and in whom
- May well result in underuse of optimal statin therapy
- May well result in overuse of PCSK9 inhibitors
- Use of LDL-C goals substantially degrades selection of people who will have events
- LDL-C unrelated to plaque burden RISK is what matters
- Difficulties of LDL-C measurement and targets