**LDL and the Benefits of Statin Therapy**

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**ACC/AHA did not recommend a target-based approach. Right?**

P 2899 “The Expert Panel was unable to find any RCTs that evaluated titration of all individuals in a treatment group to specific LDL-C targets <100 mg/dl or <70 mg/dl, nor were any RCTs comparing 2 LDL-C treatment targets identified. No statin RCTs reporting on-treatment non-HDL-C levels were identified.”

P 2901 “The Expert Panel did not find evidence to support titrating cholesterol-lowering drug therapy to achieve optimal LDL-C or non-HDL-C levels because the clinical trials were essentially fixed-dose trials.”

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**The Truth and nothing but the Truth ...**

ACC/AHA GUIDELINES
What did ACC/AHA actually recommend re Targets?

Table 4 Recommendations for Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults p 2900

“Recommendations: Treatment Targets
1. The Expert Panel makes no recommendation for or against specific LDL-C or non-HDL-C targets for the primary or secondary prevention of ASCVD.
   ACC/AHA LOE –”

But is that what ACC/AHA recommended?

Summary of Key Recommendations for the Treatment of Blood Cholesterol to reduce ASCVD risk in Adults

Table 3 Recommendations
• 2 c Achieve at least a 50% decrease in LDL-C
• C 1 Assess adherence, response to therapy, and adverse clinical effects within 4-12 weeks following statin initiation or changes in therapy.
  — Anticipated therapeutic response ≥ 50% reduction in baseline LDL-C for high intensity statins and 30% to 50% for moderate intensity statins ...
• E. Less than anticipated response iii) Increase statin intensity, or if on maximally-tolerated statin intensity, consider addition of nonstatin therapy in selected high-risk individuals.”

This is a Target Strategy except the Target is per cent reduction in LDL-C not absolute level

ACC/AHA GUIDELINES
The Two Core Papers

• The Causal Exposure Paradigm vs the Risk Factor Paradigm
  BMJ. 2014;348:g3047

The Risk Benefit Guidelines Model

• All Guidelines state that the decision to lower LDL should primarily be based on risk.
• Based on the HPS and the CTT meta-analysis, all Guidelines state that the benefit of statins is related to risk not to the level of LDL.
• The maximal dose of statins is the preferred dose as more has been shown to better than less.
The Evidence Pillars of the Risk Model

I. The Heart Protection Study

- Benefit of statin therapy are constant and independent of the level of LDL and related to the baseline risk.
- Benefits the same above and below LDL C 80 mg/dl

II. Cholesterol Treatment Trialists

- The relative benefit of statins is constant. Lowering LDL C by 1 mmol/L (40 mg/dl) reduces risk by 20%.

HPS: details about the 80 mg/dl finding

- HPS reported that the reduction in clinical events was the ‘same order of magnitude’ in those with an initial LDL-C <80 mg/dl as in those with an LDL-C above this level. (data was not shown)
- However, in HPS, LDL-C was determined by direct measurement and the values obtained by the method that was used are approximately 20 mg/dl lower than the average values calculated by the Friedewald equation.
- Therefore, HPS direct 80 mg/dl = Friedewald 100 mg/dl.

How much Gold is there in the Golden Rule of the CTT?

- CTT reported that reduction of LDL-C by 1 mmol/L (38.5 mg/dl) resulted in an approximately 20% reduction in the event rate and this rate of reduction was the same as any given baseline level of LDL-C.
- This has been interpreted as the benefit of statin therapy is determined by the baseline risk and not by the baseline level of LDL-C.
Therefore, CTT & HPS may have demonstrated that the relative benefit of LDL lowering by 1 mmol/L is constant. However, if the relative benefit is constant, this means that the absolute benefit is not constant. If so, the absolute possible benefit depends on the starting level of LDL: the higher the baseline level of LDL, the greater the possible benefit.

Furthermore it is the relative decrease in LDL produced by a statin that is constant not the decrease.

<table>
<thead>
<tr>
<th>Statin</th>
<th>5</th>
<th>10</th>
<th>20</th>
<th>40</th>
<th>80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simvastatin</td>
<td>23%</td>
<td>27%</td>
<td>32%</td>
<td>37%</td>
<td>42%</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>31%</td>
<td>37%</td>
<td>43%</td>
<td>49%</td>
<td>55%</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>38%</td>
<td>43%</td>
<td>48%</td>
<td>53%</td>
<td>58%</td>
</tr>
</tbody>
</table>

The higher the baseline level the greater the drop. The greater the drop, the greater the clinical benefit. Therefore, the higher the baseline level, the greater the potential benefit.
Yet another limitation to the ACC/AHA Regimen-Based Approach

- There is no RCT evidence that A80>A40 or even >A20. That is, there is no RCT evidence that high dose statin > moderate dose statin
- Side effects of statins: myalgia, diabetes, renal failure are related to dose.
- Adherence related to side effects.
- Some statin is infinitely better than no statin particularly since approximately ¾ of the benefit is with the lowest dose.

JUPITER: Change in LDL C with rosuvastatin 20 mg

And finally this …

Benefit is not always related to risk

- Hemodialysis
- Heart Failure

There are triggers of cardiovascular events that are sensitive to statin therapy and there are triggers that are not.
The LDL Benefit Model

- Risk is the consequence of the intramural arterial disease produced by LDL and the other causal factors of atherosclerosis.
- LDL injures the wall over time.
- Benefit from LDL lowering therapy relates to the absolute level of LDL and the absolute lowering of LDL.
- ApoB is the best marker of LDL.

Heart Protection Study: Baseline LDL C and Outcome

<table>
<thead>
<tr>
<th>LDL C mmol/L</th>
<th>Placebo (% Events)</th>
<th>Simvastatin (% Events)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3.0</td>
<td>22.2</td>
<td>17.7</td>
</tr>
<tr>
<td>≥3.0-&lt;3.5</td>
<td>25.7</td>
<td>19.0</td>
</tr>
<tr>
<td>≥3.5</td>
<td>27.2</td>
<td>22.2</td>
</tr>
</tbody>
</table>

Evidence the level of LDL does matter

Risk decrease by baseline LDL-C level for trials from Cholesterol Treatment Trialists meta-analysis (CTT 2010 Lancet 2010; 376: 1670–81).
RCT evidence statin benefit relates to LDL

- JUPITER on-Rx risk substantially less once on-Rx LDL-C <70 mg/dl (Mora et al JACC 2012; 307: 1302)
- TNT once pre-Rx factors taken into account, post-Rx LDL-C not predictive of future events (Mora et al Circulation 2012;125:1979)
- CARE & LIPID: the higher the baseline LDL-C, the higher the event rate (Sacks et al Circulation 2000;102:1893)

IMPROVE-IT demonstrates that if there is not much LDL to begin with, there is not much benefit to further lowering of LDL.

“In IMPROVE-IT, at seven years, 32.7 percent of patients taking ezetimibe experienced a primary endpoint event compared to 34.7 percent of patients taking simvastatin alone (hazard ratio of 0.936, p=0.016). Based on the LDL-C range compared in the study’s treatment arms (at one year, a mean LDL-C of 53 mg/dL versus 70 mg/dL, respectively), the 6.4 percent relative risk reduction observed in the ezetimibe arm in IMPROVE-IT was consistent with the treatment effect that had been projected based on prior studies of statins.”

"Given that a multitude of observational studies have demonstrated that cardiovascular risk is exponentially related to the level of LDL in patients with and without symptomatic disease, why would anyone think outcome in statin therapy is unrelated to baseline LDL?"
Where there really no Target Trials as ACC-AHA state?

Actually, 6 trials (AFCAPS/TexCAPS, MEGA, TNT, PROVE-IT, GREACE, Post-CABG) state they were target trials— that is, regimens were selected to produce a prespecified level of LDL-C.

If we choose to have a target, which target should we choose?

Risk vs Benefit

Risk Pre Rx

Risk Post Rx

Benefit

ApoB level (standard deviations above mean)

ApoB (mg/dl) 85 112 139
Benefit as HR per SD decrease in marker

<table>
<thead>
<tr>
<th>Marker</th>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL C</td>
<td>1.24 (1.18-1.31)</td>
</tr>
<tr>
<td>Non-HDL C</td>
<td>1.24 (1.18-1.31)</td>
</tr>
<tr>
<td>apoB</td>
<td>1.31 (1.22-1.40)</td>
</tr>
</tbody>
</table>

Relations of change in plasma levels of LDL-C, non-HDL-C and apoB with risk reduction from statin therapy: a meta-analysis of randomized trials.

Further evidence the risk attributable to LDL depends on the mass of LDL

<table>
<thead>
<tr>
<th>Marker</th>
<th>HR Pre Rx*</th>
<th>HR Post Rx**</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td>1.25 (1.18-1.33)</td>
<td>1.13 (1.10-1.17)</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>1.34 (1.24-1.44)</td>
<td>1.16 (1.12-1.19)</td>
</tr>
<tr>
<td>apoB</td>
<td>1.43 (1.35-1.50)</td>
<td>1.14 (1.11-1.18)</td>
</tr>
</tbody>
</table>

*Sniderman et al Circ Qual Care Outcomes;
** Boekholdt et al JAMA

ApoB Phenotypes
How should we chose targets levels?

- Guidelines choices
- Levels in Successful RCTs
- Equivalent Population Percentile
On Rx Population Percentiles in the 6 statin RCTs with LDL C<80 mg/dl

<table>
<thead>
<tr>
<th></th>
<th>LDL C</th>
<th>Non-HDL C</th>
<th>apoB</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNT</td>
<td>12</td>
<td>14</td>
<td>66</td>
</tr>
<tr>
<td>IDEAL</td>
<td>15</td>
<td>15</td>
<td>41</td>
</tr>
<tr>
<td>JUPITER</td>
<td>3</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>CARDS</td>
<td>11</td>
<td>14</td>
<td>35</td>
</tr>
<tr>
<td>HPS</td>
<td>15</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>PROVE-IT</td>
<td>5</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Mean PP</td>
<td>14</td>
<td>16</td>
<td>34</td>
</tr>
<tr>
<td>Concn</td>
<td>71</td>
<td>104</td>
<td>80</td>
</tr>
</tbody>
</table>

Cumulative Distribution LDL C, non-HDL-C and apoB NHANES 2006

Equivalent Target Levels

<table>
<thead>
<tr>
<th></th>
<th>LDL C mg/dl</th>
<th>Non-HDL C mg/dl</th>
<th>apoB mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Risk</td>
<td>100</td>
<td>130</td>
<td>75</td>
</tr>
<tr>
<td>Very High Risk</td>
<td>70</td>
<td>100</td>
<td>65</td>
</tr>
</tbody>
</table>