My Patient with CAD: Where Should His LDL-C Be?

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Disclosures

Honoraria / Research

Abbott, Aegerion, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, GlaxoSmithKline, Lilly, Merck, Miraculins, Novartis, Pfizer, Roche, sanofi, Servier, Valeant

Co-author: 2015/16 CCS lipid guidelines
February, 2016

58 year old man with DM and HT experiences an ACS

- troponin positive (NSTE MI)
- 2-vessel diffuse CAD with mild LV dysfunction
- Receives 3 drug-eluting stents
- LDL (treatment naïve) 3.8 mmol/L
What should his LDL-C target be?

1. < 2.0
2. < 1.8
3. < 1.5
4. > 50% reduction from baseline
5. As low as can be safely achieved
Overview

- Defining high risk
- Latest evidence
- Guidelines
Treatment based on risk

High risk patients

- Adjusted FRS ≥ 20%
- Clinical atherosclerosis
- Most diabetics
  - (1) >15y duration + age > 30y
  - (2) Age > 40y
  - (3) Microvascular disease
- High risk hypertension
- Abdominal aortic aneurysm
- Chronic renal disease

Health behaviour modifications
Treatment of modifiable CVD risk factors

Clinical judgement
Patient education/discussion

Statin therapy

Strong Recommendation, High-Quality Evidence
## CHARISMA Event Rates: With or Without CVD

<table>
<thead>
<tr>
<th>Endpoint – N (%)</th>
<th>Multiple Risk Factor Population</th>
<th>Pts with Qualifying CV Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo + ASA (n=1625)</td>
<td>Placebo + ASA (n=7801)</td>
</tr>
<tr>
<td>Primary Efficacy Endpoint</td>
<td>89 (5.5)</td>
<td>480 (7.9)</td>
</tr>
<tr>
<td>All Cause Mortality</td>
<td>62 (3.8)</td>
<td>306 (5.0)</td>
</tr>
<tr>
<td>Cardiovascular Mortality</td>
<td>36 (2.2)</td>
<td>191 (3.1)</td>
</tr>
<tr>
<td>Myocardial Infarction (nonfatal)</td>
<td>26 (1.6)</td>
<td>127 (2.1)</td>
</tr>
<tr>
<td>Ischemic Stroke (nonfatal)</td>
<td>23 (1.4)</td>
<td>140 (2.3)</td>
</tr>
</tbody>
</table>

Comparative impact of ischemic event timing on 4-year event rates

*All event rates adjusted for age and gender.
Is CKD 1-4 a CHD risk equivalent?

Alberta Kidney Disease Network
Tonelli et al. Lancet 2012

N=1,268,029
ESRD excluded

AMI per 1000 pt-y

- MI
- Diabetes
- GFR<60
- None

GFR<45 + Upr

No MI
No MI & no diabetes
Sub-Group Analysis  
Primary Endpoint

<table>
<thead>
<tr>
<th>Sub-Group</th>
<th>Placebo 2-year KM Rate (%)</th>
<th>Saxagliptin 2-year KM Rate (%)</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 75 years</td>
<td>6.6</td>
<td>6.9</td>
<td>1.01</td>
</tr>
<tr>
<td>≥ 75 years</td>
<td>11.3</td>
<td>10.0</td>
<td>0.96</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7.8</td>
<td>8.1</td>
<td>1.01</td>
</tr>
<tr>
<td>Female</td>
<td>6.0</td>
<td>5.7</td>
<td>0.97</td>
</tr>
<tr>
<td><strong>Atherosclerosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Established</td>
<td>8.5</td>
<td>8.4</td>
<td>0.96</td>
</tr>
<tr>
<td>Multiple Risk Factors</td>
<td>2.6</td>
<td>3.6</td>
<td>1.34</td>
</tr>
<tr>
<td><strong>Estimated GFR</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;50</td>
<td>6.3</td>
<td>6.6</td>
<td>1.01</td>
</tr>
<tr>
<td>30-50</td>
<td>11.5</td>
<td>11.0</td>
<td>1.02</td>
</tr>
<tr>
<td>&lt;30</td>
<td>17.2</td>
<td>14.7</td>
<td>0.83</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>7.2</td>
<td>7.3</td>
<td>1.00 (0.89-1.12)</td>
</tr>
</tbody>
</table>

*p > 0.05 for all interactions between treatment and subgroups*
Treatment based on risk

- Adjusted FRS $\geq 20%$
- Clinical atherosclerosis
- Most diabetics:
  1. $\geq 15$y duration + age $\geq 30y$
  2. Age $\geq 40y$
  3. Microvascular disease
- High risk hypertension
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High risk patients

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Strong Recommendation, High-Quality Evidence
• Defining high risk

• Latest evidence

• Guidelines
CTT Meta-analysis of 26 Trials by Baseline LDL-C

<table>
<thead>
<tr>
<th>Baseline LDL-C</th>
<th>Statin/Higher</th>
<th>Control/Lower</th>
<th>RR (CI) per mmol/L reduction in LDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>All trials combined*</td>
<td>10,973 (3.2%)</td>
<td>13,350 (4.0%)</td>
<td>0.78 (0.76–0.80)</td>
</tr>
<tr>
<td>&lt; 2 mmol/L</td>
<td>910 (4.1%)</td>
<td>1,012 (4.6%)</td>
<td>0.78 (0.61–0.99)</td>
</tr>
<tr>
<td>≥ 2 – &lt; 2.5 mmol/L</td>
<td>1,528 (3.6%)</td>
<td>1,729 (4.2%)</td>
<td>0.77 (0.67–0.89)</td>
</tr>
<tr>
<td>≥ 2.5 – &lt; 3.0 mmol/L</td>
<td>1,866 (3.3%)</td>
<td>2,225 (4.0%)</td>
<td>0.77 (0.70–0.85)</td>
</tr>
<tr>
<td>≥ 3.0 – &lt; 3.5 mmol/L</td>
<td>2,007 (3.2%)</td>
<td>2,454 (4.0%)</td>
<td>0.76 (0.70–0.82)</td>
</tr>
<tr>
<td>≥ 3.5 mmol/L</td>
<td>4,508 (3.0%)</td>
<td>5,736 (3.9%)</td>
<td>0.80 (0.76–0.83)</td>
</tr>
</tbody>
</table>

*CTT analysis included 169,138 subjects from 26 randomized trials evaluating standard statin therapy vs controls (usual care/no treatment/placebo) and more-intensive vs less-intensive statin therapy. Patient populations among the studies varied. More versus less intensive statin trials included patients with ACS or stable coronary disease. Statin vs control included primary prevention trials and trials of patients with pre-existing CHD, diabetes, hypertension, coronary disease, or heart failure, or patients on hemodialysis.1,2

CTT = Cholesterol Treatment Trialists; RR = response rate; CI = confidence interval; ACS = acute coronary syndrome.
Lessons from the CTTC meta-analysis

- Statins lower risk to the same relative degree independent of baseline risk and baseline LDL-C
- The absolute risk benefit with statins is greatest in the highest risk patients
- High intensity vs. lower intensity statin therapy further lowers risk
- No RCT has tested a specific strategy of dosing statin to achieve a pre-specified LDL-C target
- However, evidence suggests that treatment at lower and lower levels, leading to lower and lower achieved LDL-C levels, supports a "lower is better" philosophy

Log linear relationship between LDL-C and CHD risk

LDL-Cholesterol (mmol/L)
CVD risk based upon genetic vs. pharmacologic LDL-C “lowering”

Mean attained LDL-C on statin therapy and risk of secondary events

Meta-analysis of 8 statin trials (n=38,153)
- >40% did not reach LDL-C target (<1.8 mmol/L) on high dose statin

Patients stabilized post ACS ≤ 10 days: LDL-C 1.3 – 3.2 mmol/L (or 1.3 – 2.6 mmol/L if prior lipid-lowering Rx)

Standard Medical & Interventional Therapy

N=18,144

Simvastatin 40 mg*  Uptitrated to 80 mg if LDL-C >2.0 mmol/L

Ezetimibe / Simvastatin 10 / 40 mg*

Duration: Minimum 2 ½-year follow-up (5314 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
LDL-C and Lipid Changes

Median time avg
69.5 vs. 53.7 mg/dL
1.8 vs. 1.3 mmol/L

Primary Endpoint — ITT (2014)

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

7-year event rates

in the chronic phase of their disease. Second, we used 40 mg and 80 mg of simvastatin as background statin therapy (categorized as “moderate” and “intensive” statin therapy, respectively) with an upper limit for LDL cholesterol level at study entry to ensure that this statin regimen would be likely to reduce LDL cholesterol levels to less than 70 mg per deciliter (on average), as recommended at the time of patient enrollment in the trial.\textsuperscript{20,21} Although we studied only this regimen, current data indicate that the same relationship between reduction in LDL cholesterol levels and clinical benefit is seen across different statins and statin doses.\textsuperscript{4} It is possible, as others have suggested,\textsuperscript{41} that greater benefits from ezetimibe might have been seen if baseline LDL cholesterol levels had been higher. Finally, 42% of the pa-

\textbf{The magnitude of CV event reduction afforded by the addition of ezetimibe was consistent with that seen in previous statin trials for a similar reduction in LDL–C.}
LDL-C at 1 month and Risk of the Primary Efficacy Endpoint

<50 vs. ≥50 mg/dL
Adj* HR 0.90 (0.85-0.96) P=0.002

*Model covariates: Age, BMI, Sex, Race, Region, Hx diabetes, Current smoker, Hx hypertension, Hx MI, Hx PCI.
Overview

- Defining high risk
- Latest evidence
- Guidelines
ACC/AHA Guidelines: Four major statin benefit groups were identified for whom risk reduction clearly outweighs the risk of adverse events

- Clinical ASCVD
- Primary elevations of LDL–C >190 mg/dL (5 mmol/l)
- Diabetes 40 to 75 years with LDL–C 70 to 189 mg/dL (1.8-5.0) and without clinical ASCVD
- Without clinical ASCVD or diabetes with LDL–C 70 to 189 mg/dL (1.8-5.0) and estimated 10-year ASCVD risk >7.5%.

- Use moderate or high intensity statin therapy depending upon risk level
- Aim for 50% reduction in LDL, statin monotherapy only*
  - *No treatment target*
- New risk calculator
Is High-Dose Statin Therapy the End of the Line?
Proof That Lower Is Better — LDL Cholesterol and IMPROVE-IT

John A. Jarcho, M.D., and John F. Keaney, Jr., M.D.

Overall, IMPROVE-IT provides us with important information on the value of lowering LDL cholesterol levels, regardless of the agent used. These data help emphasize the primacy of LDL cholesterol lowering as a strategy to prevent coronary heart disease. Perhaps the LDL hypothesis should now be considered the “LDL principle.”
The results of IMPROVE-IT also imply that other interventions to reduce LDL cholesterol levels may prove to be beneficial. In this regard, the recent development of PCSK9 inhibitors is of note. These agents reduce LDL-receptor degradation, thereby enhancing LDL clearance from the circulation, and they have been shown to reduce LDL cholesterol levels by as much as 60%. Definitive clinical outcomes trials with these agents are ongoing.
CCS recommendations – high risk patients

- We suggest a target LDL-C \( \leq 2.0 \text{ mmol/L} \) or \( \geq 50\% \) reduction of LDL-C for individuals in whom treatment is initiated.

- To achieve these targets, we recommend the use of maximally tolerated statin therapy.

- There may be additional benefit to lowering LDL-C further in patients with high-risk CAD*.

* Based upon IMPROVE-IT
Ezetimibe

- Ezetimibe is recommended as second-line therapy to lower LDL-C in patients with ASCVD if targets are not reached on maximally tolerated statin therapy.

(Strong recommendation, high quality evidence)
58 year old man with DM and HT experiences an ACS

• troponin positive (NSTEMI)

• 2-vessel diffuse CAD with mild LV dysfunction

• Receives 3 drug-eluting stents

• LDL (treatment naïve) 3.8 mmol/L

• Atorvastatin 80 mg → LDL 1.9 mmol/L

• Consider adding ezetimibe
1. The risk associated with established atherosclerosis and prior events greatly exceeds that of other high risk primary prevention groups.

2. Mendelian randomization studies suggest that we may be underestimating the benefits of LDL lowering over time, and that non-statin drugs may be beneficial.

3. IMPROVE-IT teaches us 2 important lessons in high-risk CAD patients:
   a) Lowering LDL-C below current targets is beneficial
   b) Benefits can be had by lowering LDL-C with drugs other than statins

4. In high risk CAD patients, LDL should be consistently lowered to < 2.0 mmol/L, and likely even further, using optimally tolerated statin therapy +/- ezetimibe.
What should his LDL-C target be?

1. < 2.0
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4. > 50% reduction from baseline
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