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James de Lemos, MD
Michael J. Bloch, MD, FACP, FASH, FNLA, FSVM

April 10, 2015

Lipid Guidelines
Where do we stand?

ATP III Update 2004:
LDL-C Goals and Cut-points for Therapy in Different Risk Categories

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL-C Goal</th>
<th>Initiate TLC</th>
<th>Consider Drug Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very High risk: ACS or CHD w/ DM, mult CRF</td>
<td>&lt;70 mg/dL</td>
<td>≥70 mg/dL</td>
<td>≥70 mg/dL</td>
</tr>
<tr>
<td>High risk: CHD or CHD risk equivalents (10-year risk &gt;20%)</td>
<td>&lt;100 mg/dL  (optional goal: &lt;70 mg/dL)</td>
<td>≥100 mg/dL</td>
<td>≥100 mg/dL (consider drug Rx)</td>
</tr>
<tr>
<td>If LDL &lt;100 mg/dL</td>
<td>≥100 mg/dL</td>
<td>≥130 mg/dL</td>
<td>&gt;130 mg/dL (100-129 mg/dL: consider drug Rx)</td>
</tr>
<tr>
<td>Moderately high risk: 2+ risk factors (10-year risk 10% to 20%)</td>
<td>&lt;130 mg/dL  (optional goal: &lt;100 mg/dL)</td>
<td>≥130 mg/dL</td>
<td>&gt;130 mg/dL (consider drug Rx)</td>
</tr>
<tr>
<td>Moderate risk: 2+ risk factors (risk &lt;10%)</td>
<td>&lt;130 mg/dL</td>
<td>≥160 mg/dL</td>
<td>&gt;160 mg/dL</td>
</tr>
<tr>
<td>Lower risk: 0-1 risk factor</td>
<td>&lt;160 mg/dL</td>
<td>≥190 mg/dL</td>
<td>&gt;190 mg/dL</td>
</tr>
</tbody>
</table>

2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation, American Pharmacists Association, American Society for Preventive Cardiology, Association of Black Cardiologists, Preventive Cardiovascular Nurses Association, and Women Heart: The National Coalition for Women with Heart Disease

Four Statin Benefit Groups

- Clinical ASCVD “secondary prevention”
- LDL-C $\geq$ 190 mg/dL without secondary cause (e.g. hi saturated/trans fats, drugs)
- Primary prevention – with Diabetes
  Age 40-75 years – LDL-C 70-189 mg/dL
- Primary prevention – without diabetes
  Age 40-75 years – LDL-C 70-189 mg/dL, estimated ASCVD risk $\geq$ 7.5%

New Risk Calculator on Line

Individuals in the fourth group can be identified by using the new Pooled Cohort Equations for ASCVD Risk Prediction, developed by the Risk Assessment Work Group.


Why Not Continue to Treat to Target?

1) Current RCT data do not indicate what the target should be
2) Unknown magnitude of additional ASCVD risk reduction with one target compared to another
3) Unknown rate of additional adverse effects from multi-drug therapy used to achieve a specific goal
4) Therefore, unknown net benefit from treat-to-target approach

2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

Excerpts from Table 2  What’s New in the Guideline?

- Global Risk Assessment for Primary Prevention - This guideline recommends use of the new Pooled Cohort Equations to estimate 10-year ASCVD risk in both white and black men and women
- New Risk Calculator on Line
- A New Perspective on LDL-C and/or Non–HDL-C Treatment Goals: The Expert Panel was unable to find RCT evidence to support continued use of specific LDL-C or non–HDL-C treatment targets.

- Non-statin therapies, as compared with statin therapy, do not provide acceptable ASCVD risk-reduction benefits relative to their potential for adverse effects in the routine prevention of ASCVD.
2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults
Excerpts from Table 2  What’s New in the Guideline?

Future updates will build on this foundation to provide expert guidance on the management of complex lipid disorders and incorporate refinements in risk stratification based on critical review of emerging data.


2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults
Excerpts from Table 2  What’s New in the Guideline?

RCTs comparing alternative treatment strategies are needed in order to inform future evidence-based guidelines for the optimum ASCVD risk-reduction approach.


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Cardiology Service Chief,
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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

Background: Cholesterol Lowering

➢ Lowering LDL cholesterol (LDL-C) has been a mainstay of cardiovascular prevention
➢ Evidence mostly from statin trials which show reduction in morbidity and mortality
  – High-dose statins further reduce non-fatal CV events
➢ To date, no lipid-modifying therapy added to statins has been demonstrated to provide a clinical benefit
  – Fibrates, niacin, CETP inhibitors
➢ Recent ACC/AHA Guidelines have emphasized use of statin therapy
➢ Despite current therapies, patients remain at high risk

Ezetimibe: Background

➢ Ezetimibe inhibits Niemann-Pick C1-like 1 (NPC1L1) protein
  – located primarily on the epithelial brush border of the GI tract
  – resulting in reduced cholesterol absorption
➢ When added to statin, produces ~20% further reduction in LDL-C
➢ Two recent human genetic analyses have correlated polymorphisms in NPC1L1 with lower levels of LDL-C and lower risk of CV events*

*MiGenes Consortium Investigators 2014; online Nov 12; Ference BA et al AHA 2014
**Goals**

**IMPROVE-IT:** First large trial evaluating clinical efficacy of combination EZ/Simva vs. simvastatin (i.e., the addition of ezetimibe to statin therapy):

- Does lowering LDL-C with the non-statin agent ezetimibe reduce cardiac events?
- "(Even) Lower (Even) Better?" (estimated mean LDL-C ~50 vs. 65mg/dL)
- Safety of ezetimibe

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**Study Design**

Patients stabilized post ACS ≤10 days:

- LDL-C 50–75 mg/dL (≥50–100 mg/dL if prior lipid-lowering Rx)
- Follow-up Visit Day 30, every 4 months

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

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**Primary and 3 Prespecified Secondary Endpoints — ITT**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>HR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause death</td>
<td>0.99</td>
<td>0.782</td>
</tr>
<tr>
<td>CVD</td>
<td>1.00</td>
<td>0.997</td>
</tr>
<tr>
<td>CHD</td>
<td>0.96</td>
<td>0.499</td>
</tr>
<tr>
<td>MI</td>
<td>0.87</td>
<td>0.002</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.86</td>
<td>0.052</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>0.79</td>
<td>0.008</td>
</tr>
<tr>
<td>UA</td>
<td>0.95</td>
<td>0.107</td>
</tr>
<tr>
<td>CVD/MI/stroke</td>
<td>1.06</td>
<td>0.618</td>
</tr>
</tbody>
</table>

**Effect of censoring duration on OT**

Increasing censoring cut off from +30 d to +6mo or +12mo increases the number of events in OT

Results in progressive increase in treatment effect

- 30 d. - 7.6%
- 6 mo. - 7.8%
- 12 mo. - 8.1%

<table>
<thead>
<tr>
<th>Censor</th>
<th>Simvastatin (n = 8855)</th>
<th>Simvastatin/EZ (n = 8851)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Off drug</td>
<td>Events(KM)</td>
<td>Events(KM)</td>
</tr>
<tr>
<td>+30 d.</td>
<td>2072 32.4%</td>
<td>1932 29.8%</td>
</tr>
<tr>
<td>+6 mo.</td>
<td>2526 33.3%</td>
<td>2093 30.9%</td>
</tr>
<tr>
<td>+12 mo.</td>
<td>2331 33.8%</td>
<td>2156 30.9%</td>
</tr>
</tbody>
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**Individual Cardiovascular Endpoints and CVD/MI/Stroke**

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<thead>
<tr>
<th>Endpoint</th>
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<tr>
<td>Primary</td>
<td>34.7</td>
<td>0.016</td>
</tr>
<tr>
<td>Secondary #1</td>
<td>40.3</td>
<td>0.034</td>
</tr>
<tr>
<td>Secondary #2</td>
<td>18.9</td>
<td>0.016</td>
</tr>
<tr>
<td>Secondary #3</td>
<td>36.2</td>
<td>0.005</td>
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**Primary and 3 Prespecified Secondary Endpoints ITT & OT**

<table>
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<tr>
<th>Endpoint</th>
<th>Simva* EZ/Simva* p-value</th>
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<tr>
<td>Primary</td>
<td>34.7 32.7 0.016</td>
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<td>36.2 34.5 0.005</td>
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**Notes:**

1. All-cause death, major coronary event, or stroke post randomization
2. CVD death, non-fatal MI, or urgent CABG or PCI (≥30 days) after randomization
3. CV death, non-fatal MI, documented UA requiring rehospitalization, all revascularization (≥30 days) after randomization, or non-fatal stroke

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**Study Design**

Patients stabilized post ACS ≤10 days:

- LDL-C 50–75 mg/dL (≥50–100 mg/dL if prior lipid-lowering Rx)

Follow-up Visit Day 30, every 4 months

Duration: Minimum 2.5-year follow-up (at least 5250 events)

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

Comparative analyses:

- Log-rank test
- Cox proportional hazards models

**Results:**

Simva* EZ/Simva* p-value

- Primary 34.7 32.7 0.016
- CVD/MI/UA/Cor Revasc/CVA 40.3 38.7 0.034
- Secondary #1 18.9 17.5 0.016
- CHD/MI/Urgent Cor Revasc/CVA 36.2 34.5 0.005

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**Simvastatin vs. Simvastatin/EZ**

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<tr>
<td>Primary ITT</td>
<td>0.97</td>
<td>0.782</td>
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<tr>
<td>Secondary #1</td>
<td>0.98</td>
<td>0.499</td>
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<td>0.052</td>
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**ITT= Intention to Treat**

**OT=On-treatment**

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)
## Safety — ITT

<table>
<thead>
<tr>
<th>Event</th>
<th>Simva n=9077</th>
<th>EZ/Simva n=9067</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT and/or AST ≥ 3x ULN</td>
<td>2.3%</td>
<td>2.5%</td>
<td>0.48</td>
</tr>
<tr>
<td>Cholecystectomy</td>
<td>1.5%</td>
<td>1.5%</td>
<td>0.96</td>
</tr>
<tr>
<td>Gallbladder-related AEs</td>
<td>3.5%</td>
<td>3.1%</td>
<td>0.10</td>
</tr>
<tr>
<td>Rhabdomyolysis*</td>
<td>0.2%</td>
<td>0.1%</td>
<td>0.37</td>
</tr>
<tr>
<td>Myopathy*</td>
<td>0.1%</td>
<td>0.2%</td>
<td>0.32</td>
</tr>
<tr>
<td>Rhabdo, myopathy, myalgia with CK elevation*</td>
<td>0.6%</td>
<td>0.6%</td>
<td>0.64</td>
</tr>
<tr>
<td>Cancer* 7-yr KM (%)</td>
<td>10.2%</td>
<td>10.2%</td>
<td>0.57</td>
</tr>
</tbody>
</table>

* Adjudicated by Clinical Events Committee

% = n/N for the trial duration

## Conclusions

**IMPROVE-IT:** First trial demonstrating incremental clinical benefit when adding a non-statin agent (ezetimibe) to statin therapy:

- **YES:** Non-statin lowering LDL-C with ezetimibe reduces cardiovascular events
- **YES:** Even Lower is Even Better (achieved mean LDL-C 53 vs. 70 mg/dL at 1 year)
- **YES:** Confirms ezetimibe safety profile

Reaffirms the LDL hypothesis, that reducing LDL-C prevents cardiovascular events

Results could be considered for future guidelines

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## Low LDL, Primary Prevention and Current Options for Management

**Michael J Bloch, MD, FACP, FASH, FNLA, FSVM**

Associate Professor, University of Nevada School of Medicine
Medical Director, Vascular Care, Renown Institute for Heart and Vascular Health
Reno, NV

- LDL remains a central factor in ASCVD
- Patients with lifetime Low LDL are at low risk for ASCVD but Low LDL-c can associate with metabolic syndrome and increased ASCVD risk
- Rx benefit hinges on risk and timing & different recommendations exist for risk assessment
- Additional markers of Cholesterol related risk such as Non-HDL-C and Apolipoprotein B/LDL-P may better represent ASCVD risk in some populations
- Alternative LDL lowering therapies may represent an additional option to ASCVD risk reduction