Risk of Very Low LDL-Cholesterol—Can it be too low?

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Disclosure: Advisory Boards and Speaker’s Honoraria from Amgen, MSD, Sanofi-Aventis, AstraZeneca
Preambule

• Low LDL cholesterol level is not rare and will become even more common with more widespread use of more potent hypolipidemic therapies
• Genetic causes are relative easy to identify and diagnose, even without genetic support, and may be accompanied by other problems requiring intervention
• The introduction of new drugs, such as PCSK9 inhibitors, which may lower LDL to much lower levels than usually seen, raises the question of how low we should (can) go.
Potential Clinical Correlates of Low LDL Syndrome

- Acanthocytosis with anemia
- Malabsorption of fat and fat-soluble vitamins (E and A)
- Diarrhea, steatorrhea, failure to thrive
- Elevated transaminases with hepatomegaly due to steatosis
- Neurological involvement with demyelination
- Myositis
- Retinal degeneration
Inborn Low LDL

- Familial hypobetalipoproteinemia
- Abetalipoproteinemia
- PCSK9 mutations (loss of function)
- Inherited Low LDL Syndromes
- Chylomicron Retention Disease (very rare, LDL-C about 1/3 of normal)
Acquired Low LDL Syndromes

- Anorexia
- Advanced non cholestatic liver disease
- Acute infections, neutropenia
- Cancer
- Anemias
- Hyperthyroidism
Risks of Low LDL-C Levels

Although the *risks are rare*, there is some debate whether low levels of LDL cholesterol may increase the risk of:

- Cancer
- Depression
- Anxiety
- Preterm birth and low birth weight, if cholesterol is low while pregnant
Low LDL-C and Cancer – Reverse Causation

- **No association** in the Women’s Health Initiative (16000 women) Chandler PD et al Am J Clin Nutr 2016 (Epub ahead of print)

- Blood lipids and prostate Cancer:
  - a Mendelian randomization analysis gives weak evidence that **higher LDL and TG** levels increase aggressive prostate cancer risk (Bull CJ et al Cancer Med 2016 March Epub ahead of print)

  - Risk increases with **increasing** apo B and LDL-C.


\[ \text{→ LDL-C levels are low in cancer but do not cause cancer (reverse causation)} \]
Low LDL-C and Preterm Birth/Low Birth Weight?

• High cholesterol or triglycerides ≤15 weeks were associated with a 2.8-fold (1.0-7.9) and 2.0-fold (1.0-3.9) increased risk for preterm birth <34 weeks and ≥34-<37 weeks, respectively.

• Overweight women who delivered <34 weeks had particularly elevated early pregnancy concentrations of cholesterol and low-density lipoprotein; lean women with moderate preterm birth had elevated triglycerides

High cholesterol or triglycerides (not low LDL-C) are associated with preterm birth
Low LDL-C and Anxiety/Depression

- Trait Anxiety and low LDL-C are related findings, which were independent of age, BMI, physical activity and other factors known to influence lipid levels (Suarez EC. Relations of trait depression and anxiety to low lipid and lipoprotein concentration in healthy young adult women. Psychosom Med 1999 61: 273-9)

- TC and depression were inversely related with the strongest associations in medically naïve samples (Shin JY et al. Are cholesterol and depression inversely related? A meta-analysis of the association between two cardiac risk factors Ann Behav Med 2008;36:33-43)

- No excess risk observed in those attaining LDL-C < 2.5 mmol/l with lipid-lowering therapy (Persons JE et al. Longitudinal study of low serum LDL cholesterol and depressive symptom onset in postmenopause. J Clin Psychiatry 2016; 77: 212-20)

Data indicate a relation between low LDL-C and anxiety/depression
Can LDL-C Be Too Low?

• Conditions without LDL
  – Abetalipoproteinemia
  – Homozygous hypobetalipoproteinemia

• Condition with low LDL
  – Familial heterozygous hypobetalipoproteinemia
Abetalipoproteinemia & homozygous hypobetalipoproteinemia

- Autosomal recessive, mutations in both alleles of the gene encoding Microsomal Triglyceride Transfer Protein (MTP) or both alleles of the Apo B gene itself
- Apo B-containing lipoproteins absent (Chylomicrons, VLDL, LDL)
- Neurological and ophthalmological sequelae
- Malabsorption of lipid-soluble vitamins leading to retinal degeneration, neuropathy and coagulopathy (may be prevented by low fat diet + supplementation with essential fatty acids and high doses of fat soluble vitamins
- Hepatic steatosis and AST/ALT elevations
- **No atherosclerotic cardiovascular disease**

(Lee J & Hegele RA. J Inherit Metab Dis 2015; 65: 2638-51)
Familial heterozygous hypobetalipoproteinemia – a condition with very low LDL

- Autosomal codominant
  - MTP, Apo B or PCSK9 gene mutation
- Low level of apo B-containing lipoproteins
  - LDL-C 0.5-1.3mmol/l
- No neurological or ophthalmological sequelae
- No malabsorption
- Hepatic steatosis and AST/ALT elevations
  - Cirrhosis and hepatocellular CA are rare
  - Insulin resistance
- No atherosclerotic vascular disease

Welty FK, Curr Opin Lipid 2014;25:161-168
How low should we go?

JC La Rosa et al: *Safety and effect of very low levels of low-density lipoprotein cholesterol on cardiovascular events. Am J Cardiol.* 2013 Apr 15;111:1221-9:

“Individuals with very low LDL-C concentrations are generally healthy and have low CV risk. No increased risk of cancer has been identified in humans with very low LDL-C, neither in statin-treated persons attaining a very low level of LDL-C, nor in genetically determined low levels. Data is sparse but LDL-C < 1.3mmol/l does not appear to be inherently unsafe, as long as some LDL-cholesterol is still present”.
Regardless of how low the LDL-c level is, there does not appear to be an increase in adverse events in the IMPROVE-IT study.

<table>
<thead>
<tr>
<th>LDL-c at 1 month (mmol/L)</th>
<th>Neurocognitive</th>
<th>Gall bladder</th>
<th>AST or ALT &gt;3x</th>
<th>AE → Discont</th>
<th>Myalgia with CK↑</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.79</td>
<td>P=NS</td>
<td>P=NS</td>
<td>P=NS</td>
<td>P=NS</td>
<td></td>
</tr>
<tr>
<td>0.8 -1.29</td>
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<td></td>
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<tr>
<td>1.3 – 1.79</td>
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<tr>
<td>≥ 1.8</td>
<td></td>
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</tr>
</tbody>
</table>

P=NS indicates no statistically significant difference.
Regardless of how low the LDL-c level is, the incidence of clinical safety endpoints is unchanged in the IMPROVE-IT study.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>LDL-c at 1 month (mmol/L)</th>
<th>Adj P=NS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>&lt;0.79, 0.8 -1.29, 1.3 - 1.79, ≥1.8</td>
<td>Adj P=NS</td>
</tr>
<tr>
<td>Non-CV death</td>
<td>&lt;0.79, 0.8 -1.29, 1.3 - 1.79, ≥1.8</td>
<td>Adj P=NS</td>
</tr>
<tr>
<td>CHF → hosp</td>
<td>&lt;0.79, 0.8 -1.29, 1.3 - 1.79, ≥1.8</td>
<td>Adj P=NS</td>
</tr>
<tr>
<td>Hem stroke</td>
<td>&lt;0.79, 0.8 -1.29, 1.3 - 1.79, ≥1.8</td>
<td>Adj P=NS</td>
</tr>
</tbody>
</table>
Very Low LDL-C and Risk

What about LDL-C < 0.4mmol/l as seen in trials with PCSK9 inhibitors?
# ODYSSEY Study – Treatment with Alirocumab

Treatment Emergent Adverse Events (TEAEs) in Patients with 2 Consecutive LDL-C $<0.6\text{mmol/l}$

<table>
<thead>
<tr>
<th></th>
<th>Alirocumab (N=1550)</th>
<th>Alirocumab with 2 consecutive LDL-C levels $&lt;0.6\text{mmol/l}$ (N=575)</th>
<th>Placebo (N=788)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>1255 (81.0)</td>
<td>435 (35.7)</td>
<td>650 (82.5)</td>
</tr>
<tr>
<td>Serious AE</td>
<td>290 (18.7)</td>
<td>98 (17.0)</td>
<td>154 (19.5)</td>
</tr>
<tr>
<td>AE leading to death</td>
<td>8 (0.5)</td>
<td>4 (0.7)</td>
<td>10 (1.3)</td>
</tr>
<tr>
<td>AE leading to study drug discont.</td>
<td>111 (7.2)</td>
<td>26 (4.5)</td>
<td>45 (5.8)</td>
</tr>
</tbody>
</table>

**Summary of AE – number of patients (%)**
## Treatment Emergent Adverse Effects (TEAE) at 2 Consecutive LDL-C Measurements <0.4mmol/l (52 w)

<table>
<thead>
<tr>
<th>Primary System Organ Class</th>
<th>Pooled Control (n=1894)</th>
<th>Pooled Alirocumab (n=3340)</th>
<th>Pooled Alirocumab ≥2LDL-C &lt;0.6mmol/l (n=796)</th>
<th>Pooled Alirocumab ≥2LDL-C &lt;0.4mmol/l (n=288)</th>
<th>LONG TERM Alirocumab ≥2LDL-C &lt;0.4mmol/l (n=562)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection-site reaction</td>
<td>3.9%</td>
<td>5.7%</td>
<td>3.0%</td>
<td>3.5%</td>
<td>3.6%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2.5%</td>
<td>2.8%</td>
<td>2.6%</td>
<td>2.4%</td>
<td>3.0%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1.8%</td>
<td>1.6%</td>
<td>1.8%</td>
<td>0.3%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Non-cardiac chest pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>14.9%</td>
<td>14.9%</td>
<td>10.3%</td>
<td>9.0%</td>
<td>11.2%</td>
</tr>
<tr>
<td>Metabolism &amp; Nutrition Disord.</td>
<td>6.3%</td>
<td>6.9%</td>
<td>7.0%</td>
<td>7.3%</td>
<td>8.0%</td>
</tr>
<tr>
<td>Eye Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cataract</td>
<td>3.7%</td>
<td>4.6%</td>
<td>5.3%</td>
<td>6.9%</td>
<td>6.4%</td>
</tr>
<tr>
<td></td>
<td>0.9%</td>
<td>0.8%</td>
<td>1.5%</td>
<td>2.4%</td>
<td>1.8%</td>
</tr>
<tr>
<td>Musculoskeletal &amp; connective tissue</td>
<td>25.2%</td>
<td>24.2%</td>
<td>21.1%</td>
<td>20.1%</td>
<td>22.6%</td>
</tr>
<tr>
<td>Neoplasms, benign, malign. &amp; unspec.</td>
<td>2.5%</td>
<td>2.5%</td>
<td>2.8%</td>
<td>2.4%</td>
<td>3.0%</td>
</tr>
<tr>
<td>Any Patients with Treatment Emergent pos. adj. CV Events</td>
<td>2.8%</td>
<td>3.3%</td>
<td>3.6%</td>
<td>1.7%</td>
<td>4.3%</td>
</tr>
</tbody>
</table>
## Adverse Events with Evolocumab

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Evolocumab group (%)</th>
<th>Control group (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic reactions</td>
<td>3.2</td>
<td>3.0</td>
</tr>
<tr>
<td>Neurocognitive events</td>
<td>0.6</td>
<td>0.2</td>
</tr>
<tr>
<td>Musculoskeletal events</td>
<td>14.3</td>
<td>2.8</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>5.9</td>
<td>4.8</td>
</tr>
<tr>
<td>Upper resp. tract infection</td>
<td>3.2</td>
<td>2.7</td>
</tr>
<tr>
<td>Back pain</td>
<td>3.0</td>
<td>2.7</td>
</tr>
<tr>
<td>Nausea</td>
<td>2.1</td>
<td>1.8</td>
</tr>
</tbody>
</table>

CONCLUSIONS

• Low LDL cholesterol level is not rare and will be more frequent with larger use of potent hypolipidemic drugs

• Treatment with PCSK9 inhibitors may lower LDL-C to levels <0.4mmol/l

• Treatment emergent adverse effects were not seen more frequently in patients who experienced LDL-C <0.4mmol/l in 2 consecutive measurements in a trial with alirocumab

• The only signal seen was cognitive disorders. A study (evolocumab) evaluating this endpoint is running for 4 years (Evaluating PCSK9 Binding antiBody Influence oN coGnitive HeAlth in High cardiovascUlar Risk Subjects (EBBINGHAUS). Results are expected for 2018

• The two PCSK9 inhibitors alirocumab and evolocumab seem to be equally safe even at very low levels of LDL-cholesterol
Thank you!

Welcome to the Club of Lipoproteins