LDL How Low can (should) you Go and be Safe

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Definition of Low LDL

• National Health and Nutritional Survey (NHANES) and Vanderbilt Synthetic Derivative (Vanderbilt EHR database) observed <50mg/dl as low LDL

• <50 mg/dl was <5% of all the lab values in the data set

• But with the use of high dose-high intensity statins and statin plus eztemibe and or PCSK9 Inhibitors-- values 25-40 mg/dl will become more common
Why do we need LDL.

- The role of LDL (low density lipoprotein) is to transport fats (triglycerides and cholesterol) though water inside and outside the cells. Cholesterol not water soluble so it requires a lipoprotein for transport. (1)

- Cholesterol required for cell membrane integrity and is a precursor for synthesis of Vitamin D, steroid hormones like cortisol and aldosterone and sex hormones progesterone, estrogen and testosterone. (1)

- LDL levels of 50 mg/dl do not seem to lead to problems but more data is needed to prove that levels <25 mg/dl will not be problematic (2)

2. Robinson JG et al, Effect of Evolocumab or Ezetimibe Added to Moderate or High-Intensity Statin Therapy on LDL-C Lowering in Patients with Hypercholesterolemia, The LAPLACE-2 Randomized Clinical Trial, JAMA. 2014;311(18):1870-1882
Low LDL

• Individuals with very low LDL-C concentrations are generally healthy and have low CV risk. No clear increased risk of cancer has been identified in humans with very low LDL-C,

• Data is sparse but LDL-C < 50 mg/dl does not appear to be inherently unsafe, as long as some LDL-C is still present.

• Future studies will need to shed further light on which patients might benefit from further LDL-C lowering beyond recommended levels in current guidelines as well as on possible risks.

Lower LDL better

• The COURAGE (1) study demonstrated that if you had optimal medical therapy with a goal of 80 mg/dL, you didn't require angioplasty. (stable angina)

• The IMPROVE-IT (2) trial demonstrated a significant improvement in outcomes when the LDL cholesterol was reduced to a mean of 53.7 mg/dL on a combination of statin and ezetimibe vs 69.5 mg/dL on statin alone

• IMPROVE-IT trial proved the cholesterol hypothesis: the lower, the better.

1. COURAGE Trial Research, Group Optimal Medical Therapy with or without PCI for Stable Coronary Disease, N Engl J Med 2007; 356:1503-1516
2. Bohula EA et al. Achievement of dual low-density lipoprotein cholesterol and high-sensitivity C-reactive protein targets more frequent with the addition of ezetimibe to simvastatin and associated with better outcomes in IMPROVE-IT. Circulation. 2015;132:1224–1233.
Value of lower LDL?

• Cholesterol Treatment Trialists meta-analysis demonstrated for every 38.7 mg/dl drop in LDL there was a 22% relative risk reduction across the spectrum of LDL levels. (1)

• Another meta-analysis demonstrated a linear reduction in risk down to LDL of 50 mg/dl. In this study individuals with LDL-cholesterol levels <50 mg/dl had a significantly lower risk of major cardiovascular events compared with individuals who had higher LDL-cholesterol levels, 50 to 74 mg/dL and 75 to 99 mg/dL.(2)

Genetic causes of low LDL

• 3363 black subjects examined, 2.6 percent (85) had loss of function mutations in PCSK9; these mutations were associated with a 30-40% percent reduction in mean LDL cholesterol and an 88 percent reduction in the risk of CHD

• A few cases no PCSK9 in the circulation—LDL <20 mg/dl. No comorbidities

• LDL found to be 40 to 50mg/dl at birth


15 year Follow Up
LDL Targets?

- The ACC/AHA guideline recommended a 50% reduction in baseline LDL for high risk patients using high intensity statins and no target—ADA agrees

- The National Lipid Association (NLA) maintains that targets are important. NLA targets are <70 mg/dl for high risk patients. International Athero and ACCE agree

- The IMPROVE-IT trial compared ezetimibe/simvastatin to simvastatin monotherapy achieved an average LDL-C of 54mg/dl versus 70mg/dl, and this was associated with a 6% reduction in ASCVD.

- Evidence from multiple studies supports a strong dose response relationship between LDL-C and ASCVD. The longer the exposure to high LDL the greater the chance of ASCVD. Address LDL elevations early and aggressively to reduce the incidence of ASCVD.

Bohula EA et al. Achievement of dual low-density lipoprotein cholesterol and high-sensitivity C-reactive protein targets more frequent with the addition of ezetimibe to simvastatin and associated with better outcomes in IMPROVE-IT. Circulation. 2015;132:1224–1233 .
**LDL Targets?**

- Targets for LDL (Low Density Lipoprotein) with treatment have recently been abandoned by some experts.
- Other experts believe in targets because of the residual risk that remains even after a target of <70 mg/dl is reached. In some studies residual risk can be over 50% even with LDL significantly reduced.
- Reductions down to 50 mg/dl are associated with decreased plaque progression and plaque regression.
- Newer treatment options with PCSK9 inhibitors added to statins demonstrate significant reductions in LDL to as low as 25mg/dl and are safe for at least one year.

*Shahady E, LDL How low can we Go and be Safe Consultant May 2016 in press*
Plaque regression vs plaque stabilization?

• Plaque stabilization occurs when LDL is <70mg/dl but plaque regression will not occur until LDL approaches 50mg/dl.

• The Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial (high dose vs low dose) demonstrated progression of disease in the less potent statin group who had LDL levels averaging 110 mg/dl.

• The high dose statin group experienced no significant progression of atheroma volume with an average LDL level of 79 mg/dl.

• ASTEROID Study Evaluated Effect of Rosuvastatin on Intravascular Ultrasound Derived Coronary Atheroma Burden--patients received same high dose therapy for 24 months.

• With treatment LDL cholesterol dropped to an average of 60.8 mg/dl and atheroma volume shrank by 6.8%. evidence that plasma LDL lowering below (≤40-60mg/dl) associated with reductions in cardiovascular events and reduction of atheroma.

Impact of High Triglycerides on LDL?

- High serum triglyceride levels mathematically decrease LDL levels when the LDL is measured through indirect methodology using the Friedewald formula. Common way LDL is measured on your lab reports.

- When they are measured by direct analysis through ultracentrifuge the LDL levels are more accurate.

- Friedewald formula estimates LDL levels
  - LDL=Total Cholesterol minus HDL minus Triglycerides/5.
  - An example would be Total Cholesterol (200) minus HDL (40) and Triglycerides (250) divided by 5 equals 50 so the LDL=200-40-50=110.

  - If the Triglycerides level was 100 the LDL would now be 200-40-20=140. Triglycerides/5=20. A lower triglyceride level led to a higher calculated LDL. (110 vs. 140).

Impact of PCSK9 Inhibitors

• The recent addition of PCSK9 inhibitors combined with statins to treat elevated LDL has demonstrated even more significant reductions in LDL down to 25 mg/dl.

• 1,609 patients treated with evolocumab had at least one LDL-C value < 25 mg/dl. Dosing was not modified or interrupted because of the low LDL and the patients were followed for one year.

• Serious adverse events in the evolocumab treated group were the same (2.3 to 2.9%) for LDL levels of <25 mg/dl, <40 mg/dl and >40 mg/dl. Patients will need to be followed for more a year to provide clearer evidence of safety but the initial data seems to point to safety for LDL <25 mg/dl.

Robinson J, et al. Effect of Evolocumab or Ezetimibe Added to Moderate or High-Intensity Statin Therapy on LDL-C Lowering in Patients With Hypercholesterolemia JAMA. 2014;311:1870-1882
Safety with Statins

• In patients treated with intensive lipid-lowering therapy by statins, no relationship between achieved LDL levels and the likelihood of adverse safety events.

• No increases in the rates of expected side effects such as myopathy or elevations in liver enzyme levels

• In addition to the examination of rates of anticipated side effects, there was no increase in all-cause mortality, intracranial hemorrhage, ophthalmologic side effects, or trauma/suicide with lower achieved LDL levels

Distribution of LDL levels 80 mg Atorvastatin daily for 4 months

Table 2. Major Safety and Efficacy Outcomes (Percent of Subjects)

<table>
<thead>
<tr>
<th>Safety Measure</th>
<th>Achieved LDL Cholesterol (mg/dl)</th>
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<th>p Trend</th>
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<tr>
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<td>&gt;80–100</td>
<td>&gt;60–80</td>
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<td>&lt;40</td>
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<td></td>
<td>n = 256</td>
<td>n = 576</td>
<td>n = 631</td>
<td>n = 193</td>
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**Muscle side effects**

- **Myalgia**: 6.4, 4.3, 6.2, 5.7, 0.75
- **Myositis**: 0.4, 0.6, 0.6, 0, 0.64
- **CK >3× ULN**: 2.3, 0.7, 1.9, 1.0, 0.18
- **CK >10× ULN**: 0, 0, 0.3, 0, 0.45
- **Rhabdomyolysis**: 0, 0, 0, 0, 1.0

**Liver side effects**

- **ALT >3× ULN**: 3.2, 3.0, 3.2, 2.6, 0.98
- **Study drug discontinued because of LFT**: 2.0, 2.6, 2.4, 1.6, 0.83

**Major efficacy measures**

- **Death**: 1.1, 1.4, 1.3, 0.5, 0.59
- **CHD death**: 0.5, 0.5, 0.6, 0.0, 0.06
- **Myocardial infarction**: 1.0, 0.7, 0.5, 0.6, 0.009
- **Any stroke**: 0.8, 0.9, 0.6, 1.6, 0.32

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Statin induced diabetes with low LDL

- **Risk of statin-induced diabetes is dose-dependent,** but small in magnitude and **confined to an unmasking of a strong predisposition to diabetes or accelerated diagnosis in individuals with diabetes risk factors.**

- Observational cohort study--normoglycemia patients (n = 4460; 33 % taking statins) and 4563 IFG patients (n = 1865; 41 % taking statin)

- Hazard Ratio (HR) for diabetes increased 1.19-1.24—HR for mortality decreased 0.70-0.74

- Recommendations for statin use should not be affected by concerns over an increased risk of developing diabetes, since **the benefit of reduced mortality clearly outweighs this small risk.**

*Castro MR et al Statin Use, Diabetes Incidence and Overall Mortality in Normoglycemia and Impaired Fasting Glucose Patients, J Gen Intern Med 2016 Feb 5. [Epub ahead of print]*
LDL Limbo—How low can you go

• Naturally occurring or low LDL levels with lipid lowering therapy does not seem to be associated with increased safety concerns.

• While the ACC/AHA Guidelines suggest that patients who achieve LDL-C levels <40 mg/dL lipid lowering therapy should be removed, there is no scientific basis for this recommendation.

• In a recent article in the Lancet, Paul Ridker, MD, reviews the data regarding LDL and genetics. Data support low LDL syndromes as having cardio-protective benefits.

• More recent data showing that mutations associated with the NPC1L1 receptor translate to a lifetime reduction in 12 mg/dL in LDL-C and translate to a >50 percent reduction in cardiovascular events.

• Low levels of LDL from birth seem to be desirable and safe.
Conclusions

- LDL targets are supported by many professional organizations and many clinicians.
- Some patients are hypo responders to Statins and others are hyper responders with values at all levels.
- Low LDL is not rare and will become more common with the use of new medications like PCSK9 Inhibitors.
- At the present time low LDL (25-40) does not seem to cause complications.
Questions-Comments?

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Web Sites
www.diabetesmasterclinician.org
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