"Lipid Management in 2016: Back to the Future"
Gerald E. Pytlewski, D.O.

Lipid Management in 2016: Back to the Future
Gerald Pytlewski DO, FACC
Associate Chief of Cardiology
St. Luke’s University Health Network
Diplomate: American Board of Clinical Lipidology

The Nobel Prize in Medicine 1985:
Brown MS & Goldstein JL
"for their discoveries concerning the regulation of cholesterol metabolism"

Recycling of LDLRs Enables Efficient Clearance of LDL-C Particles
LDL Particles Cause Atherosclerosis

Low Density Lipoprotein (LDL) particles are the causal agents in atherosclerosis.

The more LDL particles a person has, the higher the risk for plaque buildup that causes heart attacks, regardless of how much cholesterol those particles carry.

Fredrickson et al. NEJM 1967; 276: 148

LDL-C Goals for High-Risk Patients Have Become More Intensive Over Time

- In ATP I, high-risk patients had either definite CHD or 2 other CHD risk factors.\(^1\)
- The ATP II guidelines define high-risk patients as having either prior CHD or other atherosclerotic disease.\(^2\)
- ATP III guidelines and the 2004 update define high-risk patients as those with CHD or CHD risk equivalents.\(^3,4\)
- The information above is focused only on the LDL-C goals for high-risk patients.
The Future
(2013 and beyond)

- LDL cholesterol – Primary Target
- Non-HDL cholesterol - Co-Primary Target?
- HDL cholesterol? May depend on CTEP Inhibitor trials
- Anti-Inflammatory therapy (CRP,LpPLA2)

New Agents: PCSK9 Inhibitors > LpPLA2 Inhibitors > CETP Inhibitors.
Highlights of 2013 ACC/AHA Guidelines

- New Pooled Cohort Equations for atherosclerotic cardiovascular disease (ASCVD) risk assessment
  - Stroke now included in ASCVD risk assessment, in addition to myocardial infarction (MI)
  - Separate equations for non-white populations
- Statin therapy to lower LDL-C > 50% recommended in 4 groups:
  1. Adults with clinical ASCVD
  2. Adults with LDL-C ≥190 mg/dL
  3. Adults 40 to 75 years of age with diabetes
  4. Adults ≥7.5% estimated 10-year risk of ASCVD
- No Non-HDL, HDL-C, or advanced treatment targets

ACC/AHA Perspective on Non-Statin Lipid Drug Therapy

- Non-statins without demonstrated ASCVD risk reduction may favorably alter lipids but have an unfavorable risk/benefit ratio
  - Niacin in AIM-HIGH and HPS-2 THRIVE
  - Fibrates in ACCORD-Lipid, FIELD
  - Lack of ASCVD event end-point data on ezetimibe
  - CETP inhibitors torcetrapib and dalcetrapib
- The use of non-statin drugs should generally be avoided
- High risk: Atorvastatin 40-80 mg or Crestor 20-40 mg

Cardio monitor

- 4,676 U.S. outpatients with CVD from 250 primary care physicians and 50 cardiologists
Is High-Dose Statin Therapy the End of the Line?

The Reduction in CHD Risk is Proportional to the % LDL-C Lowering

New Approaches to LDL Reduction

What is in development?

- Cholesterol Absorption Inhibitors
- Squalene Synthase (SSI) inhibitors
- Thyroxin Receptor Agonists
- Apo B mRNA antisense drugs
- Microsomal Triglyceride Transfer Protein (MTP) inhibitors
- PCSK9 Inhibitors
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**Study Design**

Patients stabilized post ACS ≤ 10 days:
LDL-C 50–125 mg/dL (or 50–100 mg/dL if prior lipid-lowering Rx)

- **N=18,144**
  - Standard Medical & Interventional Therapy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>LDL-C Change</th>
<th>Follow-up Visit</th>
<th>Duration</th>
<th>Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simvastatin 40 mg</td>
<td></td>
<td>Follow-up Visit Day 30, every 4 months</td>
<td>Minimum 2 ½-year follow-up (at least 5250 events)</td>
<td>CV death, MI, hospital admission for UA, coronary revascularization (≥ 30 days after randomization), or stroke</td>
</tr>
<tr>
<td>Ezetimibe / Simvastatin 10 / 40 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Ezetimibe / Simvastatin 10 / 40 mg
- Uptitrated to Simva 80 mg if LDL-C > 75 (adapted per FDA label 2011)

**Primary Endpoint**

Cardiovascular death, MI, hospital admission for UA, coronary revascularization (≥ 30 days after randomization), or stroke

- HR 0.936 CI (0.887, 0.988)
- p=0.016
- NNT= 50

**LDL-C and Lipid Changes**

Median Time avg 69.5 vs. 53.7 mg/dL

**Primary Endpoint — ITT**

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
- NNT= 50

7-year event rates
Cholesterol Absorption Inhibitors

FDA panel dashed hopes for broader use of Zetia, Vytorin

Committee votes 10-5 against backing the cholesterol meds to reduce CV risks

Benefit considered too modest

New Approaches to LDL Reduction

- Cholesterol Absorption Inhibitors
- Apo B mRNA antisense drugs
- Microsomal Triglyceride Transfer Protein (MTP) inhibitors
- PCSK9 Inhibitors
Significantly Elevated LDL-C Levels in HoFH Are Typically the Result of Defective or Absent LDL Receptor Function

- Mechanisms of conventionally used cholesterol-lowering medications for patients with HoFH rely on up-regulation of the LDL receptor

For adult patients with HoFH, consider adding a treatment that works independently of the LDL receptor


Inhibition of Apo B-100 production

- Apo B-100 is an important structural and functional component of lipoproteins
- Blocking apo B-100 production blocks VLDL, LDL and Lp(a) production

Mipomersen Significantly Reduced LDL-C

Reduction in LDL-C over 28 weeks (full analysis set)

PET 5.2%

~28.0%
KYNAMRO™ (mipomersen sodium)

KYNAMRO™ is an oligonucleotide inhibitor of apolipoprotein B-100 synthesis

Lancet 2010; 375: 998-1006

Inhibition of MTP

MTP is an important enzyme required for lipidation of apo B and formation of VLDL in liver and chylomicron in gut.

Blocking MTP reduces hepatic VLDL, LDL and Lp(a) production and intestinal chylomicron formation.

Juxtapid Delivered a 50% Reduction in LDL-C in Patients Who Completed 26 Weeks of Treatment; N=23

Mean % Change in Direct LDL-C from Baseline

Juxtapid [prescribing information]. Juxtapid Pharmaceuticals; 2014.
In Summary

- Juxtapid is an oral adjunct treatment for adult patients with HoFH
- Juxtapid works independently of the LDL receptor
- As an adjunctive therapy, Juxtapid has the potential to provide additional significant reductions in LDL-C levels
- Juxtapid can cause elevations in transaminases and hepatic steatosis. Because of the risk of hepatotoxicity, Juxtapid is available only through the Juxtapid REMS Program
- Compass offers your patients education and product support throughout treatment with Juxtapid

Please see Boxed Warning on slide 4 and additional important safety information on slides 35–38. Please see accompanying full Prescribing Information.

New Approaches to LDL Reduction

- Apo B mRNA antisense drugs
- Microsomal Triglyceride Transfer Protein (MTP) inhibitors
- PCSK9 Inhibitors

PCSK9 is a Key Regulator of LDLR Recycling

- PCSK9 mediates degradation of the LDLR by interacting with the extracellular domain and targeting the receptor for degradation

Please see Boxed Warning on slide 4 and additional important safety information on slides 35–38. Please see accompanying full Prescribing Information.
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Concept of Lifetime Cumulative LDL-C Exposure and Vascular Risk

Horton et al, J Lipid Res 2003; 50: S172-S177

EDITORIAL COMMENT

PCSK9 Inhibition: The Next Statin?*

Robert A. Vogel, MD
Denver, Colorado

Changes in LDL-C from Baseline to Week 12 by Treatment Group (mITT Population) REGN 727

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Baseline LDL-C mg/dL [mmol/L]</th>
<th>% Change LDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>150.8 [3.9]</td>
<td>-10.7 (5.0)</td>
</tr>
<tr>
<td>REGN727 150 mg Q4W</td>
<td>166.7 [4.3]</td>
<td>-28.9 (5.1)*</td>
</tr>
<tr>
<td>REGN727 200 mg Q4W</td>
<td>169.8 [4.4]</td>
<td>-31.5 (4.9)*</td>
</tr>
<tr>
<td>REGN727 300 mg Q4W</td>
<td>139.6 [3.6]</td>
<td>-52.5 (5.1)*</td>
</tr>
<tr>
<td>REGN727 150 mg Q2W</td>
<td>147.2 [3.8]</td>
<td>-67.9 (4.9)*</td>
</tr>
</tbody>
</table>

*P<0.0001 for % change REGN727 vs. Placebo.

Stein EA et al. Lancet online May 26, 2012
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The Impact of Atorvastatin Dose on % LDL-C Change With SAR236553

SAR236553

50 mg Q2W 200 mg Q4W 300 mg Q4W 100 mg Q2W 150 mg Q2W

LDL-C Mean (+/- 95% CI) % Change from Baseline to Week 12

-80 -60 -40 -20 0 20 40 60 80

-100

Atorvastatin 10 mg (N=66)
Atorvastatin 20 mg (N=69)
Atorvastatin 40 mg (N=44)

McKenney et al. J Am Coll Cardiol 2012;59:2344-2353

Praluent® - alirocumab

Manufacturer: Sanofi and Regeneron Pharmaceuticals
FDA Approval Date: July 24, 2015
Praluent®- alirocumab
Summary

• Praluent® (alirocumab) is the first-in-class PCSK9 inhibitor that reduces LDL-C
• Indicated for the treatment of adults with HOFH, HEFH or clinical ASCVD, who require additional LDL-C lowering despite diet and maximally tolerated statin therapy
• Dose is 75 or 150 mg every 2 weeks given as a SC injection
• The most common AEs observed include hypersensitivity reactions
• LDL-C should be monitored within 4-8 weeks

Post-hoc Adjudicated Cardiovascular TEAEs!
Safety Analysis (at least 52 weeks for all patients in ongoing study)

Kaplan-Meier Estimates for Time to First Adjudicated Major CV Event
Safety Analysis (at least 52 weeks for all patients continuing treatment, including 807 patients who completed W78 visit)

Cox model analysis:
HR= 0.46 (95% CI 0.26 to 0.82)
Nominal p-value = <0.01

Primary endpoint for the ODYSSEY OUTCOMES trial: CHD death, Non-fatal MI, Fatal and non-fatal ischemic stroke, Unstable angina requiring hospitalisation. LLT, lipid-lowering therapy

Primary end point for the ODYSSEY OUTCOMES trial: CHD death, Non-fatal MI, Fatal and non-fatal ischemic stroke, Unstable angina requiring hospitalisation. LLT, lipid-lowering therapy

Post-hoc Adjudicated Cardiovascular TEAEs!
Safety Analysis (at least 52 weeks for all patients in ongoing study)

ODYSSEY LONG TERM Study Design

ClinicalTrials.gov identifier: NCT01507831.
Summary & Conclusion

Patients with hypercholesterolemia on a stable regimen of statin ± ezetimibe, SC AMG 145 for 12 weeks:
- Reduced LDL-C (ultracentrifugation) by up to 66% at the end of the dosing interval compared to placebo
- Reduced calculated LDL-C by up to 85% 1 week post dose
- Reduced total and non-HDL cholesterol, apo B, TC/HDL, Apo B/A1
- Well-tolerated with no dose-related increase in adverse events

PCSK9 inhibition with AMG 145 offers a new paradigm for LDL-C reduction that warrants testing in a large, phase III cardiovascular outcomes trial.

OSLER-1: Conclusions

- The OSLER-1 two year analysis evaluated evolocumab for hypercholesterolemia in the longest duration exposure to an anti-PCSK9 antibody reported to date.
- Findings from > 1700 patient-years of drug exposure suggest a highly effective, consistent, and well-tolerated therapy.
  - Evolocumab reduced LDL-C by an average of 50% beyond that achieved with optimal SOC in various hypercholesterolemic patient populations.
  - No adverse laboratory signals were observed.
  - No major increase in AEs was observed in patients who reached low or very low LDL-C levels.

Repatha™ (evolocumab) Primary Hyperlipidemia in Patients with Clinical ASCVD—Study 1 (12 Week Trial)

Effect of Repatha™ on LDL-C in Patients with Atherosclerotic CVD When Combined with Statins
- Repatha™ 140 mg every 2 weeks
- Placebo
- Atorvastatin 80 mg QD
- Rosuvastatin 40 mg QD
- Simvastatin 40 mg QD

Mean Percent Change in LDL-C from Baseline

- Placebo: -1%
- Atorvastatin: -10%
- Rosuvastatin: -15%
- Simvastatin: -20%
Phase 3 trials of euvolocumab

Repatha™ - Evolocumab
Literature Review

DESCARTES 52 week trial

- Purpose: To evaluate safety and efficacy of a 52 week treatment with evolocumab
- Design: randomized, double blind phase 3
  - 88 centers in 9 countries

Blom DJ et al. N Engl J Med: 370 (19); 1809-1819

Trial conclusion:
- Evolocumab reduced LDL-C levels by 57% as compared with placebo at 52 weeks in patients at risk for coronary diseases receiving lipid lowering therapy

Blom DJ et al. N Engl J Med: 370 (19); 1809-1819
Repatha™ - Evolocumab

Manufacturer: Amgen Inc

FDA Approval Date: August 27, 2015

Summary

- Repatha™, evolocumab, is a PCSK9 inhibitor that reduces LDL-C by increasing the number of available LDL-Rs
- Evolocumab is indicated as adjunct treatment with HeFH, HoFH or clinical atherosclerotic cardiovascular disease who require additional lowering of LDL-C
- Suggested subcutaneous dosing is 140 mg every 2 weeks or 420 mg every month
- Common adverse drug reactions include respiratory and injection-site reactions
- Suggested monitoring: LDL-C 4 to 8 weeks after starting therapy.

Fourier Study

27,500 patients with cardiovascular disease (prior MI, stroke or PAD)
Age 40 to 85 years
21 other high-risk features

Primary Endpoint: CV death, MI, hosp for UA, stroke, coronary revasc
NLA Recommendations for Patient-Centered Management of Dyslipidemia Part 2

• First US national recommendation for use of PCSK9 inhibitors as a therapeutic option for treatment of dyslipidemia

• Summary of Key Recommendations
  – Highlights the importance of managing atherogenic cholesterol
  – Reinforce importance of lifestyle changes required for cardiovascular health
  – Add non-statin lipid-lowering therapy to ongoing statin therapy for further LDL-C lowering if benefit outweighs risk

http://www.lipidjournal.com/pb/assets/raw/Health20Advance/journals/jacl/NLA_Recommendations_manuscript.pdf

NLA Recommended Potential Candidates for PCSK9 Inhibitors

<table>
<thead>
<tr>
<th>Segment</th>
<th>Specific population</th>
<th>LDL-C (mg/dL) on maximally-tolerated statin (max ezetimibe)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FH</td>
<td>HO/HE FH patients without ASCVD</td>
<td>≥ 130</td>
</tr>
<tr>
<td>ASCVD</td>
<td>ASCVD not at Goal</td>
<td>≥ 100</td>
</tr>
<tr>
<td></td>
<td>Selected ASCVD patients such as those with recurrent CV events</td>
<td>≥ 70</td>
</tr>
<tr>
<td>Statin Intolerance</td>
<td>High or very high risk patients who meet the NLA definition of statin intolerance</td>
<td>No goal mentioned</td>
</tr>
</tbody>
</table>

http://www.lipidjournal.com/pb/assets/raw/Health20Advance/journals/jacl/NLA_Recommendations_manuscript.pdf

Lower is Better, But How Low?

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Novel anti-atherosclerotic agents
Darapladib in animal models and clinical trials

STABILITY Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy
Estimated enrolment: 15,500
- Darapladib vs placebo in well treated patients with CHD plus other risk.
- 1ary endpoint: major coronary event

SOLID – TIMI52 Stabilization of plaques using darapladib.
- Incidence of major coronary events in patients with ACS
- Darapladib 160 mg vs placebo started within 30 days of index ACS event.

Should High-Density Lipoproteins Be a Target of Therapy?

- ATP III Guidelines on HDL-C: "Current documentation of risk reduction through controlled clinical trials is not sufficient to warrant setting a specific goal value for raising HDL-C" (Grundy SM et al. Circulation. 2004;110:227-239)
- Failure of ACCORD, FIELD, AIM-HIGH and the experience with CETP Inhibitors have raised doubts re: the value of raising HDL-C

Approaches for Raising HDL

What is in development?
- Cholesterol Ester Transfer Protein (CETP) inhibitors
- ER-Niacin / Laropiprant combination
- ApoA1 based strategies
- LCAT replacement strategies
- ABCA1 agonists / miR-33 inhibition
**Cholesteryl Ester Transfer Protein (CETP)**

60 Å-long tunnel filled with two hydrophobic cholesteryl esters and plugged by an amphiphilic phosphatidylcholine at each end.

The two tunnel openings are large enough to allow lipid access, which is aided by a flexible helix and possibly also by a mobile flap.

The curvature of the concave surface of CETP matches the radius of curvature of HDL particles, and potential conformational changes may occur to accommodate larger lipoprotein particles.

Qiu X et al. Nature Structural & Molecular Biol. 2007;14:106-113

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**Role of CETP in Atherosclerosis**

- Human CETP deficiency usually associated with marked ↑ in HDL-C
- CETP activity is inversely correlated with plasma HDL-C
- Decreasing CETP activity has consistently inhibited atherosclerosis in animal models


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**Elevated Triglycerides Are Associated With Increased Small, Dense LDL Particles**

- Fewer Particles
  - Apolipoprotein B
  - Correlates with:
    - TC 198 mg/dL
    - LDL-C 130 mg/dL
    - TG 50 mg/dL
    - HDL-C 50 mg/dL
    - Non-HDL-C 148 mg/dL

- More Particles
  - More apolipoprotein B
  - Correlates with:
    - TC 210 mg/dL
    - LDL-C 130 mg/dL
    - TG 250 mg/dL
    - HDL-C 30 mg/dL
    - Non-HDL-C 180 mg/dL


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**CETP Inhibitors: 3 Down, 1 Remains**

- ↑ HDL-C
- ~80%
- ~80%
- ~138%
- ~30%

<table>
<thead>
<tr>
<th>CETP</th>
<th>Dalcetrapib</th>
<th>Evacetrapib</th>
<th>Torcetrapib</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ CVD (25%)</td>
<td>but OK HDL function (off-target eff.?)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*No ↓ CVD, but OK HDL function, +/- athero?

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**REVEAL**

- 30,000 patients with occlusive arterial disease in North America, Europe and Asia
- Background LDL-lowering with atorvastatin
- Randomized to anacetrapib 100 mg vs. placebo
- Primary outcome: Coronary death, myocardial infarction or coronary revascularization

**National Lipid Association Consensus Statement on HDL**

- Although low HDL-C identifies patients at elevated risk, and much investigation suggests that HDL may play a variety of antiatherogenic roles, HDL-C is not a therapeutic target at the present time.
- Risk stratified atherogenic lipoprotein burden (low-density lipoprotein cholesterol and non-HDL-C) should remain the primary targets of therapy in patients at risk.

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POMA 108th Annual Clinical Assembly
May 4-7, 2016
Highlight of US Lipid Management Recommendations

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Association of Clinical Endocrinologists &amp; American College of Endocrinology (AACE/ACE)</td>
<td>In diabetic patients at high or very high risk for ASCVD, recommended goals are: LDL-C: &lt;70mg/dL; non-HDL-C: &lt;100mg/dL; ApoB: &lt;80mg/dL.</td>
</tr>
<tr>
<td>National Lipid Association (NLA)</td>
<td>In very high risk patient populations recommended goals are: non-HDL-C: &lt;100mg/dL; LDL-C*: &lt;70mg/dL; ApoB: &lt;80mg/dL.</td>
</tr>
<tr>
<td>American College of Cardiology &amp; American Heart Association (ACC/AHA)</td>
<td>Statin-Centric Approach with four (4) major treatment groups: Individuals with clinical ASCVD**; Individuals with LDL-C ≥190 mg/dL; Individuals with diabetes aged 40-75 years with LDL-C 70-189 mg/dL and without clinical ASCVD; Individuals age 40-75 years with LDL-C 70-189 mg/dL &amp; estimated 10-year ASCVD risk ≥7.5%.</td>
</tr>
</tbody>
</table>


The Future of Lipid Lowering Therapy

Statins +/- Ezetimibe will remain Cornerstone

• The real battle in the future will be between PCSK9-I and CETP inhibitor(s).
• MTP Inhibitors: HOFH patients
  * oral versus sc
every day versus bi-weekly or once monthly
• atherogenic lipoproteins with or without HDL increase