Lipid Management 2018: Creating Harmony in an Ever-Changing Landscape of Guidelines

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Disclosures

• **Advisory Board**: Akcea, Amgen, Sanofi/Regeneron
Objectives

• Provide overview of evidence for benefits of statin and non-statin therapies in ASCVD risk reduction
• Compare and contrast 2 major PCSK9 inhibitor CV outcomes trials
• Identify major groups of patients who have demonstrated benefit with non-statin therapies
• Discuss changes to new 2018 ACC/AHA lipid guidelines
# Lowering LDL-C Reduces ASCVD

<table>
<thead>
<tr>
<th>Study</th>
<th>Statin</th>
<th>Mean Baseline LDL-C</th>
<th>Mean LDL-C Reduction</th>
<th>% Reduction in Coronary Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Prevention</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WOSCOPS</td>
<td>Pravastatin 40mg</td>
<td>192</td>
<td>26</td>
<td>31 (P&lt;0.001)</td>
</tr>
<tr>
<td>AFCAPS/TEXCAPS</td>
<td>Lovastatin 20-40mg</td>
<td>150</td>
<td>25</td>
<td>37 (P&lt;0.001)</td>
</tr>
<tr>
<td>ASCOT</td>
<td>Atorvastatin 10mg</td>
<td>133</td>
<td>35</td>
<td>36 (P&lt;0.001)</td>
</tr>
<tr>
<td>HOPE-3</td>
<td>Rosuvastatin 10mg</td>
<td>128</td>
<td>26</td>
<td>24 (P&lt;0.002)</td>
</tr>
<tr>
<td>JUPITER</td>
<td>Rosuvastatin 20mg</td>
<td>108</td>
<td>44</td>
<td>44 (P&lt;0.000001)</td>
</tr>
<tr>
<td>Secondary Prevention</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4S</td>
<td>Simvastatin 20-40mg</td>
<td>188</td>
<td>35</td>
<td>34 (P&lt;0.0001)</td>
</tr>
<tr>
<td>CARE</td>
<td>Pravastatin 40mg</td>
<td>139</td>
<td>32</td>
<td>24 (P=0.003)</td>
</tr>
<tr>
<td>LIPID</td>
<td>Pravastatin 40mg</td>
<td>150</td>
<td>25</td>
<td>24 (P&lt;0.0001)</td>
</tr>
</tbody>
</table>

Table adapted from Maron DJ, et al. *Circulation.* 2000;101:207-213

*CTTC.* *Lancet.* 2010; 376(9753):1670-1681

Statins are the mainstay of therapy.

CTTC meta-analysis showed **20%-25%** reduction in major CV end points for every **1 mmol/liter (39 mg/dl)** reduction in LDL-C*
Major Lipid Trials: LDL-C Achieved vs Rates of Coronary Events

Evolving Evidence, Evolving Guidance

Primary End Point:
CV Death, MI, Stroke, Coronary Revasc, Unstable Angina

Hazard Ratio, 0.75
(95% CI, 0.68–0.83)

Impact of Ezetimibe in ACS

IMPROVE-IT Study

18,144 ACS patients randomized to simvastatin (40 mg QHS) or simvastatin/ezetimibe (40 mg/10 mg QHS) for 7 years

Event Rate (%)

40
30
25
20
15
10
5
0

Years

HR 0.936, P=.016

Mean LDL-C (mg/dL)

Median time average
69.5 (1.8) vs 53.7 (1.4) [mg/dL (mmol/L)]

# Key PCSK9 Inhibitor CV Outcomes Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Evolocumab (AMG 145)</th>
<th>Alirocumab (SAR236553 / REGN727)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sample size</strong></td>
<td>27,564</td>
<td>18,924</td>
</tr>
<tr>
<td><strong>Patients</strong></td>
<td>Stable ASCVD (MI, stroke, or PAD) with high-risk features</td>
<td>4-52 weeks post-ACS</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>63</td>
<td>58</td>
</tr>
<tr>
<td><strong>Statin</strong></td>
<td>Atorvastatin ≥20 mg or equivalent 69% 0.2%</td>
<td>Evidence-based medical Rx 89% 2.5%</td>
</tr>
<tr>
<td><strong>High-intensity statin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>No statin</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>LDL-C mg/dL (mmol/L): inclusion</strong></td>
<td>≥70 (≥1.8) 92 (2.4)</td>
<td>≥70 (&gt;1.8) 87 (2.3)</td>
</tr>
<tr>
<td><strong>Baseline LDL-C mg/dL (mmol/L)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PCSK9 inhibitor dosing</strong></td>
<td>Q2W or Q4W</td>
<td>Q2W</td>
</tr>
<tr>
<td><strong>Endpoint</strong></td>
<td>1*: CV death, MI, stroke, revascularization, or hospitalization for UA Key 2*: CV death, MI, or stroke</td>
<td>CHD death, MI, ischemic stroke, or hospitalization for UA</td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td>26 months</td>
<td>34 months</td>
</tr>
</tbody>
</table>

Global Enrollment

27,564 patients randomized at 1242 sites in 49 countries between 2/2013 – 6/2015
FOURIER Trial Design

27,564 high-risk, stable patients with established CV disease (prior MI, prior stroke, or symptomatic PAD)

Screening, Lipid Stabilization, and Placebo Run-in
High or moderate intensity statin therapy (± ezetimibe)

LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL

Evolocumab SC
140 mg Q2W or 420 mg QM

Placebo SC
Q2W or QM

RANDOMIZED DOUBLE BLIND

Follow-up Q 12 weeks
Median 26 mth [22,30]

Evolocumab in Stable, High-Risk ASCVD

LDL Cholesterol

Placebo

59% mean reduction (95%CI 58-60), P<0.00001

Absolute reduction: 56 mg/dl (95%CI 55-57)
(1.45 mmol/L)

Evolocumab
(median 30 mg/dl, IQR 19-46 mg/dl)
(0.78 mmol/L)

Weeks

Evolocumab in Stable, High-Risk ASCVD

**Primary Endpoint**

Hazard ratio 0.85
(95% CI, 0.79-0.92)
P < 0.0001

-15%

**Key Secondary Endpoint**

Hazard ratio 0.80
(95% CI, 0.73-0.88)
P < 0.0001

7.9%
Evolocumab in Stable, High-Risk ASCVD

Landmark Analysis

Evolocumab vs Placebo:
- 16% RRR
  - HR 0.84 (95% CI 0.74-0.96)
  - P=0.008
  - -16%

- 25% RRR
  - HR 0.75 (95% CI 0.66-0.85)
  - P<0.00001
  - -25%

ODYSSEY OUTCOMES:
18,924 patients randomized at 1315 sites in 57 countries
Nov 2, 2012 – Nov 11, 2017
ODYSSEY Outcomes: Treatment Assignment

Post-ACS patients (1 to 12 months)
Run-in period of 2 to 16 weeks on high-intensity or maximum-tolerated dose of atorvastatin or rosuvastatin
At least one lipid entry criterion met
Randomization
Alirocumab SC Q2W
Placebo SC Q2W
Follow-up: median 2.8 years
8242 (44%) patients with potential f/u ≥3 years

ODYSSEY Outcomes: A Target Range for LDL-C

We attempted to maximize the number of patients in the target range and minimize the number below target by blindly titrating alirocumab (75 or 150 mg SC Q2W) or blindly switching to placebo.

- Target range: 0.65-1.29 mmol/L
- Undesirably high baseline range

[Diagram showing the distribution of patients below target, acceptable range, and undesirably high baseline range with arrows indicating alirocumab and placebo groups.]

Randomized 18,924 patients
- Alirocumab (N=9462)
- Placebo (N=9462)

Follow-up*: median 2.8 (Q1–Q3 2.3–3.4) years
- 8242 (44%) patients with potential follow-up >3 years

1955 patients experienced a primary endpoint
- 726 patients died

- Premature treatment discontinuation
  - 1343 (14.2%)
- Blinded switch to placebo (2 consecutive LDL-C values <15 mg/dL)
  - 730 (7.7%)
- Patients lost to follow-up (vital status)
  - 14

Not applicable
- 1496 (15.8%)

LDL-C: Intent-to-Treat and On-Treatment Analyses

Graph showing LDL-C levels over time with mean LDL-C values in mg/dL and mmol/L. The graph highlights a 60% reduction in LDL-C with a mean of 39.8 mg/dL (0.97 mmol/L) at 0 months, increasing to 48.0 mg/dL (1.38 mmol/L) at 48 months. The on-treatment analysis shows a 53% reduction in LDL-C with a mean of 37.6 mg/dL (0.97 mmol/L) at 0 months, increasing to 53.3 mg/dL (1.40 mmol/L) at 48 months.

DOI: 10.1056/NEJMoa1801174
Primary Efficacy Endpoint: MACE

MACE: CHD death, non-fatal MI, ischemic stroke, or unstable angina requiring hospitalization

ARRa: 2.0%

RRR: -15%

Hazard ratio, 0.85 (95% CI, 0.78–0.93) P<0.001

No. at Risk
Placebo 9462 8805 8201 3471 629
Alirocumab 9462 8846 8345 3574 653

*Based on cumulative incidence

DOI: 10.1056/NEJMoA1801174
Evolving Evidence and Identifying the High-risk Patient

- Achieved LDL-C level
- Diabetes
- Prior MI
- MI Size and Type
- Extent of CAD
- PAD
- Lp(a)
Long-term Safety and Efficacy of Achieving Very Low Levels of LDL-C: A Prespecified Analysis of the IMPROVE-IT Trial

Long-term Safety and Efficacy of Achieving Very Low Levels of LDL-C: A Prespecified Analysis of the IMPROVE-IT Trial

<table>
<thead>
<tr>
<th>Prespecified Safety End Points</th>
<th>Achieved LDL-C Level (mg/dL) at 1 mo, No. (%) of Patients</th>
<th>P Value for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;30 (n = 971)</td>
<td>30-49 (n = 4780)</td>
</tr>
<tr>
<td>Adverse event leading to drug discontinuation</td>
<td>92 (9.5)</td>
<td>451 (9.4)</td>
</tr>
<tr>
<td>Rhabdomyolysis, myopathy, or myalgias with CK elevation &gt;5 times ULN</td>
<td>4 (0.4)</td>
<td>30 (0.6)</td>
</tr>
<tr>
<td>Rhabdomyolysis or myopathy</td>
<td>0</td>
<td>13 (0.3)</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>0</td>
<td>6 (0.1)</td>
</tr>
<tr>
<td>AST or ALT above 3 times ULN</td>
<td>21 (2.2)</td>
<td>97 (2.0)</td>
</tr>
<tr>
<td>Gall bladder adverse event</td>
<td>35 (3.6)</td>
<td>155 (3.2)</td>
</tr>
<tr>
<td>Neurocognitive adverse events</td>
<td>20 (2.1)</td>
<td>121 (2.5)</td>
</tr>
<tr>
<td>Short-term</td>
<td>12 (1.2)</td>
<td>61 (1.3)</td>
</tr>
<tr>
<td>Longer-term</td>
<td>8 (0.8)</td>
<td>60 (1.3)</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>3 (0.3)</td>
<td>41 (0.9)</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>45 (4.6)</td>
<td>200 (4.2)</td>
</tr>
<tr>
<td>Noncardiovascular death</td>
<td>56 (5.8)</td>
<td>244 (5.1)</td>
</tr>
<tr>
<td>Cancer</td>
<td>87 (9.0)</td>
<td>413 (8.6)</td>
</tr>
</tbody>
</table>

FOURIER: Efficacy and safety of very low levels of LDL-C with evolocumab

- 10% achieved LDL-C <0.5 mmol/L or 20 mg/dL
- 41% achieved LDL-C <1.3 mmol/L or 50 mg/dL

- Monotonic relationship between achieved LDL-C and CVOTs down to LDL-C <0.2 mmol/L (<10 mg/dL).
- No safety concerns with very low LDL-C levels over a median of 2.2 years.

EBBINGHAUS Study of cognitive function during treatment with evolocumab

- Subgroup of FOURIER
- 1204 patients, 19 months
- Assessed cognitive function during treatment
  - Cambridge Neuropsychological Test Automated Battery

- No significant differences

What did the RCTs demonstrate?
Identifying the high-risk patient
ASCVD Risk Reduction Is Proportional To Baseline Risk

- Reduction in ASCVD events is related to the
  - Extent of LDL-C reduction
  - Baseline level of risk
- Greatest absolute number of events avoided in pts at greatest risk

Effects of Lowering LDL-C with Statin Therapy in Patients at Variable Risk of Vascular Disease: Meta-analysis of Individual Data from 27 Randomized Trials
IMPROVE-IT: Addition of ezetimibe to moderate-intensity statin post-ACS

- Characteristics that identified patients most likely to benefit
  - History of CHF
  - HTN
  - Age >75 yrs
  - Diabetes
  - Prior stroke
  - Prior CABG
  - PAD
  - eGFR <60
  - Smoking
CV safety and efficacy of evolocumab in patients with and without diabetes: FOURIER
Efficacy and safety of alirocumab in DM: Pooled analyses from phase 3 trials

Post-randomization A1c, Fasting Glucose, and New-onset Diabetes by Baseline Glucometabolic Status

Ray KK, American Diabetes Association 2018 (Orlando, FL)
**Effect of Evolocumab by Universal MI Type**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>HR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>6.3</td>
<td>0.73</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Type 1</td>
<td>4.5</td>
<td>0.68</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Type 2</td>
<td>2.9</td>
<td>1.09</td>
<td>NS</td>
</tr>
<tr>
<td>Type 4</td>
<td>1.1</td>
<td>0.65</td>
<td>.004</td>
</tr>
</tbody>
</table>

Due to small numbers, Types 3 and 5 are not presented individually.

Effect of Evolocumab by MI Type: NSTEMI and STEMI

**NSTEMI**

- 3-Year KM Rate: 0%
- HR: 0.77 (95% CI: 0.68-0.88)
- P: <.001

**STEMI**

- 3-Year KM Rate: 0%
- HR: 0.64 (95% CI: 0.49-0.84)
- P: <.001

Clinical Benefit of Evolocumab by Extent of CAD

CV death, MI, stroke, and MALE in patient with and without PAD

Major Adverse Limb Events

Placebo  Evolocumab

No PAD
N=23,922
HR 0.81
95% CI (0.73-0.90)
P<0.001

PAD
N=3642
27% RRR
HR 0.73
(0.59-0.91)
P=0.0040

13.0%
9.5%
7.6%
6.2%

3.5% ARR
NNT(2.5y) 29
1.4% ARR
NNT(2.5y) 72
Lp(a), CV risk, and evolocumab: FOURIER

Change in Lp(a) from Baseline to Week 48 with Evolocumab

Efficacy by Baseline Lp(a)

- Median absolute change in Lp(a): -11 nmol/L
- Median % change in Lp(a): -26.9%

CV death, MI or stroke (3y KM rate, %)

- Lp(a) <= median: 7.48
- Lp(a) > median: 8.17

EAS, May 7, 2018
Lp(a) and alirocumab: ODYSSEY Outcomes

Median LDL-C and Lp(a) Change Across Lp(a) Quartiles (Alirocumab Group)

Change between baseline and Month 4; median (IQR)

<table>
<thead>
<tr>
<th>Quartile</th>
<th>LDL-C Change</th>
<th>Lp(a) Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quartile 1</td>
<td>-53.7 (-35.5,68)</td>
<td>-5.12 (-2.25,-7.86)</td>
</tr>
<tr>
<td>Quartile 2</td>
<td>-54.1 (-37.1,-71.0)</td>
<td>-9.8 (-3.18,-16.2)</td>
</tr>
<tr>
<td>Quartile 3</td>
<td>-53.3 (-36.3,-70.3)</td>
<td>-8.0 (-8.0,-34.3)</td>
</tr>
<tr>
<td>Quartile 4</td>
<td>-54.1 (-38.7,-71.0)</td>
<td>-20.2</td>
</tr>
</tbody>
</table>

Bittner VA, presented ISA, 2018. Toronto, Canada, June 12, 2018
CLINICAL PRACTICE GUIDELINES
Evolving evidence: Non-statin trials in the 2010s

2013: **No data that nonstatin therapy added to statin therapy provided incremental reduction in CHD events**

2014: IMPROVE-IT (n=18,144)

2017: FOURIER (n=27,564)

2017: SPIRE 1 and SPIRE 2 (27,438)

2017: REVEAL (n=30,624)

2018: ODYSSEY Outcomes (n=18,924)

2018: REDUCE-IT (n=8,179)

2018: **7 major trials with non-statins recently completed, enrolling 130,873 patients**
2018 ACC/AHA BLOOD CHOLESTEROL GUIDELINES

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

https://www.ahajournals.org/doi/pdf/10.1161/CIR.0000000000000624
What remains the same?

• Lifestyle as the foundation of therapy
• Therapy based on level of risk
• Statins as the mainstay of lipid-lowering for ASCVD risk reduction
• Continues to be based on intensity of statin
What remains the same?

• Response to therapy based on % LDL-C reduction
• Reiterated the importance of monitoring response to therapy
• 4 statin benefit groups
  – ASCVD
  – LDL-C >190 mg/dL
  – Diabetes
  – High-risk primary prevention
• Inadequate response to therapy should be addressed, particularly in higher risk patients

https://www.ahajournals.org/doi/pdf/10.1161/CIR.0000000000000624
What has been refined or revised?

• Role of non-statin therapies
  – New large RCTs since 2013 guidelines
  – Provides evidence-based guidance on ezetimibe, PCSK9 inhibitors (and BAS in LDL-C >190 mg/dL)

• Includes LDL-C “thresholds” for intensification of therapy
  – “In very high-risk ASCVD, use a LDL-C threshold of 70 mg/dL (1.8 mmol/L) to consider addition of non-statins to statin therapy.”
  – In agreement with the 2017 ACC Expert Consensus Decision Pathway on the role of non-statin therapies

https://www.ahajournals.org/doi/pdf/10.1161/CIR.0000000000000624
What has been refined or revised?

- Class I (LOE B-NR) that ezetimibe should be considered prior to addition of PCSK9 inhibitor

  3. In patients with clinical ASCVD who are judged to be very high risk and considered for PCSK9 inhibitor therapy, maximally tolerated LDL-C lowering therapy should include maximally tolerated statin therapy and ezetimibe (S4.1-14, S4.1-15).

- Includes value statement on PCSK9 inhibitors for ASCVD and LDL-C >190 mg/dl

  6. At mid-2018 list prices, PCSK9 inhibitors have a low cost value (> $150,000 per QALY) compared to good cost value (< $50,000 per QALY) (Section 7 provides a full discussion of the dynamic interaction of different prices and clinical benefit) (S4.1-21–S4.1-23).

https://www.ahajournals.org/doi/pdf/10.1161/CIR.0000000000000624
What has been refined or revised?

Like the 2017 ACC ECDP on non-statin therapies

ASCVD not at very high risk
“ASCVD without comorbidities”

ASCVD at very high risk
“ASCVD with comorbidities”

https://www.ahajournals.org/doi/pdf/10.1161/CIR.0000000000000624
New or expanded...

- Hypertriglyceridemia
- Chronic kidney disease
- Chronic inflammatory disorders and HIV
- Special patient populations
  - Older adults
  - Children and adolescents
  - Ethnicity (Asian Americans, Hispanic/Latino Americans, Blacks)
  - Women

https://www.ahajournals.org/doi/pdf/10.1161/CIR.0000000000000624
Summary

• Lifestyle intervention remains the foundation of ASCVD risk reduction.
• Statins are the mainstay of lipid-lowering therapy for ASCVD risk reduction.
• Evolving evidence has now defined a role for non-statin therapies in very high- and high-risk patients with inadequate lowering of LDL-C on maximally tolerated statin therapy.
• Analysis of RCTs for ezetimibe and PCSK9 inhibitors help to define those highest risk patients who are most likely to benefit from combination therapy.
Case Challenge and Discussion
Case Discussion

The patient is a 62 year old WM with a history of diabetes, symptomatic PAD, and ASCVD s/p AWMI 18 months ago. He has been on atorvastatin 80 mg since his MI, and was doing well until 6 months ago when he developed recurrent exertional CP. He has now undergone cardiac catheterization and stenting of a new LAD lesion with resolution of symptoms.
Case Discussion

At the time of intervention his lipid profile on atorva 80 mg was:

- Total Cholesterol 188 mg/dL
- LDL-C (calculated) 115 mg/dL
- HDL-C 45 mg/dL
- TG- 140 mg/dL
- 40% reduction in LDL-C from baseline
Case Discussion

• What are your recommendations for next steps in management of this patient?
  • Continue current therapy
  • Change to rosvastatin 40 mg daily
  • Add ezetimibe 10 mg daily
  • Add PCSK9 inhibitor
  • Add bile acid sequestrant
  • Other?
Case Discussion

- The patient is changed to rosuvastatin 40 mg, with the subsequent development of bilateral thigh pain and weakness approximately 10 days later. This resolves within one week of stopping medication and restarts three days after beginning the same dose of rosuvastatin.

- The patient is placed back on atorvastatin 80 mg and repeat LDL-C level at 2 months is 117 mg/dL.
Case Discussion

• What would be your next step in management of this patient?
  • Continue current therapy
  • Diagnose patient with statin intolerance and use non-statin therapy only
  • Resume treatment with atorvastatin 80 mg and add ezetimibe
  • Resume treatment with atorvastatin 80 mg and add PCSK9 inhibitor
  • Switch to simvastatin 40 mg daily and ezetimibe
  • Other?
Case Challenge

The patient is started on ezetimibe 10 mg with reduction of LDL-C to 95 mg/dL.

Evolocumab 140 mg SQ/2 weeks is started. 8 weeks later his lipid panel is

- TC 76 mg/dL
- LDL-C (calculated) 30 mg/dL
- HDL-C 40 mg/dL
- TG 30 mg/dL

The patient is concerned about his low LDL-C and asks if this is dangerous, could it cause harm and is hesitant to adhere to his current treatment.
Case Challenge

Which of the following next steps would you recommend?

• Stop ezetimibe
• Decrease evolocumab dose to every 4 weeks 140 mg sq
• Decrease atorvastatin to 20 mg/day
• No change in current treatment
• Other?
Thank you!