2017 Update in Internal Medicine: Clinical Dyslipidemia Update

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10/19/17
Disclosures

• Regeneron Pharmaceuticals
  – Consultant in 2016-2017 (not currently active)
  – Industry sponsored research
Objectives

• The ACC/AHA cholesterol guidelines - moving beyond 2013

• High cholesterol – moving beyond statins

• High TAG / Low HDL-C – moving beyond LDL-C targets
Residual ASCVD Risk

Statin Effects on CV Event Reduction and Residual Risk

- Residual Cardiovascular Risk ~70%

Challenges and Unmet Needs

HIGH CHOLESTEROL: MAPPING UNMET NEED

108m
Americans have high cholesterol

66m
are diagnosed*

41m
are treated*

31m
have controlled cholesterol with treatment

10m
have uncontrolled cholesterol despite treatment

Prevalence
Diagnosed
Treated
Controlled

*Diagnosis defined as over diagnosed
*Treatment defined as over treated

Source: HIS Global Insight analysis based on National Health and Nutrition Examination Survey

Opportunities to Control High Cholesterol

Increase Adherence
Taking medicines more consistently can help some reach their goal

Modify Prescribed Treatments
Combining treatments or changing dosage can lower cholesterol levels for some

Improve Diet and Exercise
Implementing lifestyle changes can reduce cholesterol levels for many

New Medicines Could Help Those With...

Statin Intolerance: Deeper treatment to stay healthy because of side effects or potential for adverse events.
Inadequate Statin Response: An uncommon genetic condition called familial hypercholesterolemia.

HIS Global insight analysis / NHANES. http://www.fromhopetocures.org/infographic/high-cholesterol-mapping-unmet-need
2013 AHA/ACC Guidelines: Overview

- Paradigm shift; simplified *population*-focused approach
- Focus on ↓ ASCVD risk by improving evidence-based use of statins
  - Based exclusively on evidence from RCTs (up to 2013)
    - “Intensities” rather than “targets”
- Non statin therapy not extensively addressed (lack of RCT evidence)

### 2013 AHA/ACC Guidelines: Statin benefit groups

<table>
<thead>
<tr>
<th>Patient Subgroups for Which the Benefits of Statins Outweigh the Risks</th>
<th>Patient Group</th>
<th>Recommended Intensity of Statin Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><em><em>Clinical ASCVD</em> (secondary prevention)</em>*</td>
<td>Age ≤ 75 years with no statin-related safety concerns †</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Age &gt; 75 years or with statin-related safety concerns</td>
<td>Moderate</td>
</tr>
<tr>
<td><strong>LDL ≥ 190 mg/dL without clinical ASCVD</strong></td>
<td>Ages ≥ 21 years</td>
<td>High</td>
</tr>
<tr>
<td><strong>Diabetic patients without clinical ASCVD, ages 40-75 years, with LDL 70-189 mg/dL</strong></td>
<td>10-year ASCVD risk &lt; 7.5% ‡</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>10-year ASCVD risk ≥ 7.5%</td>
<td>High</td>
</tr>
<tr>
<td><strong>Non-diabetic patients without clinical ASCVD, ages 40-75 years, with LDL 70-189 mg/dL</strong></td>
<td>10-year ASCVD risk ≥ 7.5%</td>
<td>Moderate-to-high</td>
</tr>
</tbody>
</table>

* defined as acute coronary syndromes, history of myocardial infarction, stable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease of atherosclerotic origin.
† characteristics that may predispose patients to statin adverse effects include (but are not limited to): multiple or serious comorbidities, including impaired renal or hepatic function; history of previous statin intolerance or muscle disorders; unexplained ALT elevations ≥ 3 times upper limit of normal; patient characteristics or concomitant use of drugs affecting statin metabolism; age > 75 years.
# TABLE 1

## Statin therapy: Intensity and indications

<table>
<thead>
<tr>
<th>Approximate amount of LDL-C lowering</th>
<th>High intensity</th>
<th>Moderate intensity</th>
<th>Low intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 50%</td>
<td>30%–49%</td>
<td>&lt; 30%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Indications</strong></th>
<th><strong>High intensity</strong></th>
<th><strong>Moderate intensity</strong></th>
<th><strong>Low intensity</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical ASCVD, age &lt; 75</td>
<td>LDL-C ≥ 190 mg/dL</td>
<td>LDL-C ≥ 190 mg/dL (if unable to tolerate high-intensity statin)</td>
<td>None</td>
</tr>
<tr>
<td>Diabetes, age 40–75 with LDL-C 70–189 mg/dL and 10-year ASCVD risk ≥ 7.5%</td>
<td>Diabetes, age 40–75 with LDL-C 70–189 mg/dL and 10-year ASCVD risk ≤ 7.5%</td>
<td>No diabetes, age 40–75, with LDL-C 70–189 mg/dL and 10-year ASCVD risk ≥ 7.5%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Examples</strong></th>
<th><strong>High intensity</strong></th>
<th><strong>Moderate intensity</strong></th>
<th><strong>Low intensity</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin 40–80 mg</td>
<td>Rosuvastatin 20–40 mg</td>
<td>Atorvastatin 10–20 mg</td>
<td>Simvastatin 10 mg</td>
</tr>
<tr>
<td>Pravastatin 10–20 mg</td>
<td>Rosuvastatin 5–10 mg</td>
<td>Simvastatin 20–40 mg</td>
<td>Pravastatin 10–20 mg</td>
</tr>
<tr>
<td>Fluvastatin 40 mg</td>
<td>Pravastatin 40–80 mg</td>
<td>Fluvastatin 40 mg</td>
<td>Lovastatin 20 mg</td>
</tr>
<tr>
<td>Lovastatin 40 mg</td>
<td>Fluvastatin XL 80 mg</td>
<td>Lovastatin 40 mg</td>
<td>Fluvastatin 20–40 mg</td>
</tr>
<tr>
<td>Pitavastatin 2–4 mg</td>
<td>Fluvastatin 40 mg twice a day</td>
<td>Pitavastatin 2–4 mg</td>
<td>Pitavastatin 1 mg</td>
</tr>
</tbody>
</table>

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*Clinicians should decide between moderate- and high-intensity statin therapy for this group.

LDL-C = low-density lipoprotein cholesterol; ASCVD = atherosclerotic cardiovascular disease
Summary of current pharmacological lipid therapies

Other guidelines and recommendations since 2013


Comparison of ACC versus NLA guidelines
Fire & Forget (FF) vs Treat to Target (TT) vs Lower is Better

**Fire and Forget**
- Simpler
- Good for population health

**BUT**
- Over treat in 1° prevention
- Under treat in 2° prevention

**Treat to Target / Lower is better**

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Beyond statins: Ezetimibe

June 2015: IMPROVE-IT

- RCT n=18,144 with ASCVD (2° prevention)
- Ezetimibe + statin vs statin alone (moderate dose simvastatin)
- ↓ LDL-C by 24% or 69.5→53.7 mg/dL
- 1° Composite (CV death, ASCVD event, CVA) ↓ 6% RR / 2% AR (6y)
- 2° Composite endpoints ↓ ~5-9%
- ↓ MI (13%), CVA (14-21%), revasc (19%)
- No ↓ overall CV death

Beyond statins: Fibrates and Niacin

• Fibrates
  – 2014: ACCORD-LIPID showed that adding fenofibrate to a statin in 2DM subjects at high risk for ASCVD did not improve ASCVD outcomes (possible benefit in males ↑TG/↓HDL-C subgroup)

• Niacin
  – 2014: AIM-HIGH showed that adding niacin to a statin in subjects with ASCVD did not improve ASCVD outcomes
  – 2014: HPS2-THRIVE showed that adding niacin/liropiprant to a statin in subjects with ASCVD did not improve ASCVD outcomes

The Race for PCSK9 Inhibition

Praluent (alirocumab) 07/24/15
Repatha (evolocumab) 08/27/15
PCSK9 inhibition increases LDL-R recycling

Overview of phase III clinical trials for PCSK9i


* 2016 Bococizumab removed from market
Efficacy of PCSK9 mAb Inhibitors: LDL-C

≥50-60% ↓ in LDL-C independent of
- Treatment (+/- statin, +/- ezetemibe)
- Statin dose (low, high)
- Diagnosis (+/- FH, +/- ASCVD)
- Clinical/demographic features (age, sex, DM, BMI, risk level)
- Comorbid disease (hepatic or renal)
- Other drugs
- Time (sustained effect)
- Also ↑ HDL, ↓ TAG, ↓ Lp(a)

Descartes Study (Evolocumab)

Efficacy of PCSK9 mAb Inhibitors: LDL-C

Efficacy and Safety of Alirocumab in Reducing Lipids and Cardiovascular Events

Jennifer G. Robinson, M.D., M.P.H., Michel Far nier, M.D., Ph.D., Michael Kempf, M.D., Jean Bergeron, M.D., Geral d Luc, M.D., Mauricio Averna, M.D., Erik S. Stroes, M.D., Ph.D., Gisle Langset, M.D., Frederick J. Raal, M.D., Ph.D., Mahfouz El Shahawy, M.D., Michael J. Koren, M.D., Norman E. Lepor, M.D., Christelle Lorenzato, M.Sc., Robert Pardy, M.D., Umesh Chaudhari, M.D., and John J.P. Kastelein, M.D., Ph.D., for the ODYSSEY LONG TERM Investigators.

Efficacy and Safety of Evolocumab in Reducing Lipids and Cardiovascular Events


Efficacy of PCSK9 mAb Inhibitors: MACE

**FIGURE 1** Cardiovascular Events in Long-Term PCSK9 Trials

<table>
<thead>
<tr>
<th>Event Rate (%)</th>
<th>HR 0.52 [0.31, 0.90]</th>
<th>HR 0.47 [0.28, 0.78]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3.3</td>
<td>2.2</td>
</tr>
<tr>
<td>Placebo</td>
<td>26/788</td>
<td>31/1,489</td>
</tr>
<tr>
<td>Alirocumub</td>
<td>27/1,550</td>
<td>29/2,976</td>
</tr>
</tbody>
</table>


# Efficacy of PCSK9 mAb Inhibitors: MACE

<table>
<thead>
<tr>
<th></th>
<th>Dec 2017</th>
<th>May 2017</th>
<th>March 2017</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trial Name</strong></td>
<td>Alirocumab</td>
<td>Evolocumab</td>
<td>Bococizumab</td>
</tr>
<tr>
<td><strong>ODYSSEY® Outcomes</strong></td>
<td>(Secondary prevention)</td>
<td>(Secondary prevention)</td>
<td>(Secondary prevention)</td>
</tr>
<tr>
<td><strong>No of patients</strong></td>
<td>18000</td>
<td>22500</td>
<td>12000</td>
</tr>
<tr>
<td><strong>Dosage</strong></td>
<td>sc, Q2W</td>
<td>sc, Q2W or Q4W</td>
<td>sc, Q2W</td>
</tr>
<tr>
<td><strong>Start date</strong></td>
<td>October 2012</td>
<td>January 2013</td>
<td>October 2013</td>
</tr>
<tr>
<td><strong>Expected end date</strong></td>
<td>March 2018</td>
<td>February 2018</td>
<td>August 2017</td>
</tr>
<tr>
<td><strong>Primary endpoint</strong></td>
<td>CHD death</td>
<td>CV death</td>
<td>CV death</td>
</tr>
<tr>
<td></td>
<td>Nonfatal MI</td>
<td>MI</td>
<td>Nonfatal MI</td>
</tr>
<tr>
<td></td>
<td>Fatal and nonfatal ischemic stroke</td>
<td>Stroke</td>
<td>Nonfatal stroke</td>
</tr>
<tr>
<td></td>
<td>High-risk UA requiring hospitalization</td>
<td>Hospitalization for UA</td>
<td>Hospitalization for UA needing urgent revascularization</td>
</tr>
<tr>
<td><strong>Duration</strong></td>
<td>Up to month 64</td>
<td>Up to 5 years</td>
<td>Up to month 60</td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td>Patients 4 to 52 weeks after ACS</td>
<td>History of clinically evident CVD: MI, stroke or symptomatic PAD and ≥1 major RF or ≥2 minor RFs</td>
<td>High-risk patients</td>
</tr>
<tr>
<td></td>
<td>• LDL-C ≥70 (1.8 mmol/L) (on atorvastatin 40–80 mg or rosvastatin 20–40 mg)</td>
<td>• LDL-C ≥70 (1.8 mmol/L) or • Non–HDL-C ≥100 (2.6 mmol/L) (on atorvastatin 20 to 80 mg or equivalent)</td>
<td>• LDL-C ≥100 (2.6 mmol/L) or • Non–HDL-C &gt;100 (2.6 mmol/L) and &lt;130 (3.4 mmol/L) and receiving background LLT</td>
</tr>
</tbody>
</table>

## Efficacy of PCSK9 mAb Inhibitors: MACE in SPIRE-1/2

<table>
<thead>
<tr>
<th></th>
<th>SPIRE 1</th>
<th>SPIRE 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of Patients</strong></td>
<td>17,000</td>
<td>9,000</td>
</tr>
<tr>
<td><strong>Inclusion criteria</strong></td>
<td>Age ≥18 and high risk of CV event Must be on background lipid lowering therapy</td>
<td></td>
</tr>
</tbody>
</table>
| **Exclusion criteria**        | ● Planned coronary revascularization  
                                 ● NYHA functional class IV CHF or LVEF <25%  
                                 ● Creatinine clearance < 30 ml/min/1.73m²  
                                 ● Prior hemorrhagic stroke |
| **Entry lipid values**        | LDL-C ≥70 to <100 mg/dL                        |
| **Treatment**                 | Bococizumab 150 mg Q2W SC vs. Placebo SC |
| **Primary Endpoint**          | 4-way composite endpoint of: CV death / non-fatal MI / non-fatal stroke / hospitalization for unstable angina needing urgent revascularization |
| **Secondary Endpoints**       | Composite endpoint of CV death, non-fatal MI, and non-fatal stroke  
                                 Composite endpoint of all-cause death, non fatal MI, and non-fatal stroke  
                                 Hospitalization for unstable angina needing urgent revascularization |

Efficacy of PCSK9 mAb Inhibitors: MACE in SPIRE-1/2

- **1:** LDL 92 → 38/57 mg/dL (↓43%) x 7m;
- **2:** LDL 133 → 58/89 mg/dL (↓61%) x 12m

- **1:** ↓ Nonfatal CVA 48%
- **2:**
  - 1° Composite (CV death, MI, CVA, USA revasc) ↓ 21%
  - 2° Composite (CV death, MI, CVA) ↓ 26%
  - ↓ MI (26%), CVA (54%)
  - No ↓ overall CV death (very low rate)

- ↑ benefit with ↓ LDL-C and ↑ time
- Side effects: Many, anti-Rx antibodies

Efficacy of PCSK9 mAb Inhibitors: MACE in FOURIER

Efficacy of PCSK9 mAb Inhibitors: MACE in FOURIER

- Mean LDL 92→30mg/dL = ↓59%; 2y
- 1° Composite (CV death, MI, CVA, hosp USA, revasc) ↓ ~15%
- 2° Composite (CV death, MI, CVA) ↓ ~20%
- ↓ MI (27%), CVA (21%), revasc (22%)
- No ↓ overall CV death (very low rate)
- NNT 74 over 2y
- ↑ benefit with ↓ LDL-C and ↑ time
- Side effects: injection site rx (2%)

Safety of PCSK9 mAb Inhibitors

Association of PCSK9 inhibitors c/w placebo with incidence of any adverse events

Guidelines and recommendations since 2013


### 2016 ACC Expert Consensus Decision Pathway

**Table 2. Patient-Level Approach to Use of Specific Nonstatin Therapies in Addition to Optimized Statin.**

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Secondary prevention</strong>: clinical ASCVD without comorbidities</td>
<td><strong>Primary prevention</strong>: baseline LDL-C ≥ 190 mg/dL</td>
<td><strong>Primary prevention</strong>: 40-75 years without clinical ASCVD but with diabetes, and baseline LDL-C 70-189 mg/dL</td>
<td><strong>Primary Prevention</strong>: 40-75 years without clinical ASCVD or diabetes, with 10-yr risk ≥ 7.5% and baseline LDL-C 70-189 mg/dL</td>
</tr>
<tr>
<td>First line if &lt;50% LDL-C reduction or LDL-C ≥ 100 mg/dL</td>
<td>First line if &lt;50% LDL-C reduction or LDL-C ≥ 100 mg/dL</td>
<td>First line if &lt;50% LDL-C reduction or LDL-C ≥ 100 mg/dL or non-HDL-C ≥ 130 mg/dL</td>
<td>First-line if &lt; 50% LDL-C reduction or LDL-C ≥ 100 mg/dL AND 10-year ASCVD risk ≥ 20%, baseline LDL ≥ 160 mg/dL, poorly controlled other ASCVD risk factors, family history of premature ASCVD, elevated Lp(a), evidence of subclinical atherosclerosis (eg, coronary artery calcification), elevated hs-CRP, chronic kidney disease, HIV, or other chronic inflammatory disorders</td>
</tr>
<tr>
<td>Second line if ezetimibe intolerant and triglycerides &lt;300 mg/dL</td>
<td>Second line if ezetimibe intolerant and triglycerides &lt;300 mg/dL</td>
<td>Second line if ezetimibe intolerant and triglycerides &lt;300 mg/dL</td>
<td>Second-line if ezetimibe intolerant and triglycerides &lt;300 mg/dL</td>
</tr>
<tr>
<td><strong>Secondary prevention</strong>: clinical ASCVD with comorbidities</td>
<td><strong>Secondary prevention</strong>: clinical ASCVD and baseline LDL-C ≥ 190 mg/dL (not a result of secondary causes)</td>
<td><strong>Secondary prevention</strong>: clinical ASCVD and baseline LDL-C ≥ 190 mg/dL (not a result of secondary causes)</td>
<td><strong>Secondary prevention</strong>: clinical ASCVD and baseline LDL-C ≥ 190 mg/dL (not a result of secondary causes)</td>
</tr>
<tr>
<td>First line if &lt;50% LDL-C reduction or LDL-C ≥ 70 mg/dL</td>
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</tr>
</tbody>
</table>

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2016/2017 ACC Expert Consensus Decision Pathway

Table 2. Patient-Level Approach to Use of Specific Nonstatin Therapies in Addition to Optimized Statin.10

<table>
<thead>
<tr>
<th>Table 2: Patient-Level Approach to Use of Specific Nonstatin Therapies in Addition to Optimized Statin.10</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ezetimibe</strong></td>
</tr>
<tr>
<td>Secondary prevention: clinical ASCVD without comorbidities</td>
</tr>
<tr>
<td>Secondary prevention: clinical ASCVD with comorbidities*</td>
</tr>
<tr>
<td>Secondary prevention: clinical ASCVD and baseline LDL-C ≥190mg/dL (not a result of secondary causes)</td>
</tr>
<tr>
<td><strong>Group 1</strong></td>
</tr>
<tr>
<td>Primary prevention: baseline LDL-C ≥190mg/dL</td>
</tr>
<tr>
<td><strong>Group 4</strong></td>
</tr>
<tr>
<td>Primary Prevention: 40-75 years without clinical ASCVD or diabetes, with 10-yr risk ≥7.5% and baseline LDL-C 70-189 mg/dL</td>
</tr>
</tbody>
</table>

*↓50% or LDL-C ≥70 or non-HDL-C ≥100mg/dL
¥ LDL-C ≥100 or non-HDL-C ≥130mg/dL

2016/2017 ACC Expert Consensus Decision Pathway

2016 ECDP
• Included new RCTs with ezetimibe, niacin, and niacin/laropiprant
• Specific situations (i.e. statin intolerance, suboptimal response)
• Consideration of “Thresholds” in select high risk groups
• Defined high risk (and further stratified groups by risk)
• Included some specific populations (i.e. CHF, HD, pregnancy)

2017 ECDP
• Included new RCTs with the PCSK9 inhibitors
• Consideration of “Thresholds” in all groups
• Added additional risk factors for consideration as high risk
• Downgraded BAS

2016/2017 ACC Expert Consensus Decision Pathway

2016 ECDP
Consider **thresholds** of
• % decrease in LDL-C in statin benefit groups
• absolute LDL-C level
  – clinical ASCVD
  – baseline LDL-C $\geq 190$ mg/dL
  – primary prevention
• absolute LDL-C and/or non-HDL-C
  – DM ± clinical ASCVD

2017 ECDP
Consider **thresholds** of
• % decrease in LDL-C, absolute LDL-C level, or non-HDL-C levels for patients in each of the 4 statin benefit groups.

2016/2017 ACC Expert Consensus Decision Pathway

**2016 ECDP**

≥21y +ASCVD +Statin +LDL-C 70-189

- *Without* comorbidities
  - ≥50% reduction in LDL-C
  - LDL-C <100 mg/dL
- *With* comorbidities / high risk
  - ≥50% reduction in LDL-C
  - LDL-C <70 mg/dL


**2017 ECDP**

≥21y +ASCVD +Statin +LDL-C 70-189

- *All*
  - ≥50% reduction in LDL-C
  - LDL-C <70 mg/dL
  - Non-HDL-C <100 mg/dL

2016/2017 ACC Expert Consensus Decision Pathway

2016 ECDP
≥21y +ASCVD +Statin +LDL-C 70-189
• With comorbidities / high risk and greater than threshold
  – Consider ezetimibe first, then BAS second (if TAG<300), then PCSK9i third

2017 ECDP
≥21y +ASCVD +Statin +LDL-C 70-189
• With comorbidities / high risk and greater than threshold
  – Consider ezetimibe or PCSK9i
  – Ezetimibe if need <25% ↓ in LDL-C and increased risk
  – PCSK9i if >25% ↓ in LDL-C and increased risk, other issues related to cost and administration

2016/2017 ACC Expert Consensus Decision Pathway

2016 ECDP

≥21y + ASCVD + Statin + LDL-C 70-189

• Increased risk if
  – DM, ASCVD event <3m, ASCVD while on statin, poorly controlled ASCVD risk factors, increased Lp(a), CKD, baseline LDL-C ≥190 not due to secondary causes

2017 ECDP

≥21y + ASCVD + Statin + LDL-C 70-189

• Increased risk if
  – Same as 2016 plus age ≥65y, prior MI or non-hemorrhagic CVA, smoking, PAD with prior MI/CVA, h/o coronary revasc, CAD ≥40% stenosis in ≥2 lg vessels, HDL-C <40 M / 50 F, hsCRP>2 mg/L, or MetS
2016/2017 ACC Expert Consensus Decision Pathway

Maximally tolerated guideline-recommended statin
Optimized lifestyle intervention
Assessment of adherence and tolerance

Monitor LDL-C Response

YES

Met LDL-C Threshold

NO

*↓50% or LDL-C ≥70 or non-HDL-C ≥100mg/dL

↓50% or LDL-C ≥100 or non-HDL-C ≥130mg/dL or high risk markers

Group 1

2° prevention
ASCVD +Low risk
No comorbidities

Ezetimibe 1st
PCSK9i 2nd

Group 2

2° prevention
ASCVD +High risk
+comorbidities or
Baseline LDL-C>190

Ezetimibe or PCSK9i

Group 3

1° prevention
Baseline LDL-C≥190

DM

Group 4

1° prevention
ASCVD risk ≥7.5%

Ezetimibe

Cost effectiveness of PCSK9 inhibitors

• Current cost: ~14,500/y
• 2016 (Pre FOURIER):
  – ↓ $4536-5400/y ICER of $100,000/QALY
  – ↓ $2200/y to avoid exceeding growth targets for US health care costs
• 2017 (Post FOURIER):
  – ↓ $4215/y ICER of $100,000/QALY

PCSK9i Approval Algorithm

Clinical ASCVD
1. ACS or history of myocardial infarction
2. Unstable or stable angina
3. Stroke or TIA (presumed to be atherosclerotic)
4. Coronary revascularization (PCI, CABG, stent)
5. Peripheral arterial disease or revascularization

Heterozygous FH
1. LDL-C ≥190 mg/dl (LDL-C ≥160 mg/dl for <20 years) AND any of the following:
2. First-degree relative with premature coronary artery disease
3. First-degree relative with FH-range LDL-C
4. Positive genetic testing (LDL-receptor, apoB or PCSK9)

Emerging targets for lipid-lowering therapy

Beyond Statins and LDL-C: CETP Inhibitors

• CETP inhibitors ↑HDL-C
  – 2007 ILLUMINATE showed that adding torcetrapib to a statin in subjects with ASCVD worsened ASCVD outcomes
  – 2012 dal-OUTCOMES study showed that adding dalcetrapib to a statin in subjects with ASCVD did not improve ASCVD outcomes

Beyond Statins and LDL-C: CETP Inhibitors

Sep 2017: HPS3/TIMI55-REVEAL
- RCT n=30,449 with ASCVD (2° prevention)
- Anacetrapib + statin vs statin alone
- ↓ LDL-C by 41% (61→38 mg/dL)
- ↓ non-HDL-C by 18% (92→79 mg/dL)
- ↑ HDL-C by 104% (40→85 mg/dL)
- ↓ ApoB, Lp(a), TAG
- 1° 1st major coronary event = Composite (CV death, MI, revasc) ↓ 9% RR / 3% AR (4.1y)
- ↓ MI (11%), revasc (10%)
- No ↓ overall CV death

ASCVD is complex, multifactorial disease: what is the next step to solving the puzzle?

Questions
Additional information
## PCSCK9 mAb inhibition: indications

### Alirocumab (Praluent) - Sanofi
- As an adjunct to diet and maximally tolerated statin in
  - Adults with HeFH
  - Clinical ASCVD who require additional LDL-C lowering
- “Not approved for general use in statin intolerant patients”

### Evolocumab (Repatha) - Amgen
- As an adjunct to diet and maximally tolerated statin in
  - Adults with HeFH or HoFH
  - Clinical ASCVD who require additional LDL-C lowering
- “Includes patients who have been optimized on statins, or cannot tolerate any statin type or dose”

[https://www.praluenthcp.com/](https://www.praluenthcp.com/)

[https://www.repathahcp.com/about-repatha/](https://www.repathahcp.com/about-repatha/)
PCSCK9 mAb inhibition: Adverse events

Alirocumab (Praluent) - Sanofi

• Most common:
  – Nasopharyngitis, injection site reactions, influenza

• Most serious:
  – Hypersensitivity reaction

• Most likely to lead to discontinuation:
  – Allergic reaction, ↑LFTs

• Other:
  – Neurocognitive complaints

Evolocumab (Repatha) - Amgen

• Most common:
  – Nasopharyngitis, URI, influenza, back pain, injection site reactions

• Most serious:
  – Hypersensitivity reaction

• Most likely to lead to discontinuation of therapy:
  – Myalgia

• Other:
  – Neurocognitive, myalgia, arthralgia

PCSCK9 mAb inhibition: Dosing

Alirocumab (Praluent) - Sanofi

- 75 or 150 mg SQ q 2w
  - Prefilled syringe or pen
  - 4°C until 30min before use
- No dose adjustment for
  - hepatic failure, renal failure, age
- No known drug interactions
- Not studied in pregnancy

Evolocumab (Repatha) - Amgen

- 140 mg SQ q 2w
  - Prefilled syringe or pen
  - RT for up to 30d
- No dose adjustment for
  - hepatic failure, renal failure, age
- No known drug interactions
- Not studied in pregnancy

https://www.praluenthcp.com/  
https://www.repathahcp.com/about-repatha/
PCSCK9 mAb inhibition: How to prescribe

Alirocumab (Praluent) - Sanofi
- Very expensive (Retail ~14K/year)
- Prior authorization required
  - Support service
- Patient copay card
  - $0/6m and $10 after that
- Patient bridge program
  - 90d supply pending appeal
- Patient assistance program
  - Free for 12m, renewable
- Self-injection training

Evolocumab (Repatha) - Amgen
- Very expensive (Retail ~14k/year
- Prior authorization required
  - Support service
- Patient copay card
  - $5 up to annual max
- Other financial assistance on case by case basis
- Self-injection training

https://www.praluenthcp.com/
https://www.repathahcp.com/about-repatha/
FH: Clinical manifestations

- Hypecholesterolemia
- Increased risk of ASCVD
- Xanthelasma
- Corneal arcus
- Tendon xanthoma or thickening
- Tuberous xanthoma
Diagnosis of familial hypercholesterolemia

Diagnostic Criteria

- DLCN – Dutch Lipid Clinic Network
- Simon Broome Register
- MedPed/WHO criteria
- In Epicare: .EndoLipidFH

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**Box 1 | FH diagnosis (DLCN diagnostic criteria)****

- >8 points: definite FH diagnosis
- 6–8 points: probable FH diagnosis
- 3–5 points: possible FH diagnosis
- <3 points: unlikely FH diagnosis

Abbreviations: DLCN, Dutch Lipid Clinic Network; FH, familial hypercholesterolaemia.

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**Table 1 | DLCN diagnostic criteria for FH****

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history</td>
<td></td>
</tr>
<tr>
<td>First-degree relative with known premature (men: &lt;55 years; women: &lt;60 years) coronary and vascular disease, or first-degree relative with known LDL-C level above the 95th percentile by age, gender for country</td>
<td>1</td>
</tr>
<tr>
<td>First-degree relative with tendonous xanthoma and/or arcus cornealis, or children aged less than 18 years with LDL-C level above the 95th percentile by age, gender for country</td>
<td>2</td>
</tr>
<tr>
<td>Clinical history</td>
<td></td>
</tr>
<tr>
<td>Patient with premature (men: &lt;55 years; women: &lt;60 years) coronary artery disease</td>
<td>2</td>
</tr>
<tr>
<td>Patient with premature (men: &lt;55 years; women: &lt;60 years) cerebrovascular or peripheral vascular disease</td>
<td>1</td>
</tr>
<tr>
<td>Physical examination</td>
<td></td>
</tr>
<tr>
<td>Tendonous xanthoma</td>
<td>6</td>
</tr>
<tr>
<td>Arcus cornealis prior to age 45 years</td>
<td>4</td>
</tr>
<tr>
<td>LDL-C levels</td>
<td></td>
</tr>
<tr>
<td>LDL-C ≥8.5 mmol/l (~330 mg/dl)</td>
<td>8</td>
</tr>
<tr>
<td>LDL-C 6.5–8.4 mmol/l (~250–329 mg/dl)</td>
<td>5</td>
</tr>
<tr>
<td>LDL-C 5.0–6.4 mmol/l (~190–249 mg/dl)</td>
<td>3</td>
</tr>
<tr>
<td>LDL-C 4.0–4.9 mmol/l (~155–189 mg/dl)</td>
<td>1</td>
</tr>
<tr>
<td>DNA analysis</td>
<td></td>
</tr>
<tr>
<td>Causative mutation in the LDLR, ApoB or PCSK9 gene</td>
<td>8</td>
</tr>
</tbody>
</table>

Abbreviations: DLCN, Dutch Lipid Clinic Network; FH, familial hypercholesterolemia; LDL-C, LDL-cholesterol.

Genetic testing for familial hypercholesterolemia

• In Epic: .ENDOLIPIDFHGENETEST
• Molecular Genetics and Diagnostics at Magee Womens Hospital (412864-6140)
• Dx: Familial hypercholesterolemia
• Testing: Send out to Gene Dx in Maryland
• Codes: CPT Code for FH: 81401, 81405, 81406 (panel: ApoB, LDLR, LDLAP1, PCSK9)
• Need to call insurance company with the above information to determine coverage
Registry

Please refer patients with the following to our registry:

- Severe hypertriglyceridemia (TAG>1000), PLUS
- History of TG-associated pancreatitis (not due to other factors, i.e. alcohol, gallstones, etc).

Contact kershawe@pitt.edu
Or
Pitt+me (https://pittplusme.org/)