Treatment of Blood Cholesterol: New Approaches / New Agents

Laurence S. Sperling, M.D., FACC, FACP, FAHA, FASPC
Professor of Medicine (Cardiology)
Professor of Global Health
Director- Center for Heart Disease Prevention
Emory University
Immediate Past President, American Society for Preventive Cardiology
Chairman of ACC Cardiometabolic Working Group
Chairman of The U.S. National Cardiometabolic Alliance
About the Presenter

Laurence S. Sperling, MD, FACC,FACP,FAHA
Professor of Medicine
Director of The Center for Heart Disease Prevention
Emory University School of Medicine
Atlanta, GA

DISCLOSURES

No potential conflicts related to this presentation
New approaches / New Agents

• New approaches / Guidelines
• Focus on FH
• New Agents
New approaches / New Agents

- New approaches / Guidelines
- Focus on FH
- New Agents
## ATP III Update (2004)

### LDL-C Treatment Targets

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>LDL-C Goal</th>
<th>Initiate TLC</th>
<th>Consider Drug Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High risk:</strong> CHD or CHD risk equivalents (10-year risk &gt;20%)</td>
<td>&lt;100 mg/dL (optional goal: &lt;70 mg/dL)</td>
<td>≥100 mg/dL</td>
<td>≥100 mg/dL ( &lt;100 mg/dL: consider drug Rx)</td>
</tr>
<tr>
<td><strong>Moderately high risk:</strong> 2+ risk factors (10-year risk 10% to 20%)</td>
<td>&lt;130 mg/dL (optimal &lt;100 mg/dL)</td>
<td>≥130 mg/dL</td>
<td>≥130 mg/dL (100-129 mg/dL: consider Rx)</td>
</tr>
<tr>
<td><strong>Moderate risk:</strong> 2+ risk factors (risk &lt;10%)</td>
<td>&lt;130 mg/dL</td>
<td>≥130 mg/dL</td>
<td>≥160 mg/dL</td>
</tr>
<tr>
<td><strong>Lower risk:</strong> 0-1 risk factor</td>
<td>&lt;160 mg/dL</td>
<td>≥160 mg/dL</td>
<td>≥190 mg/dL</td>
</tr>
</tbody>
</table>

Nov. 13, 2013

C-DAY

Cholesterol?
Controversy?
Confusion?
Conundrum?
Courage......?
Guidelines should inform clinical judgment, but not replace it....
### What’s New in the Cholesterol Guidelines?

<table>
<thead>
<tr>
<th>1</th>
<th>Focus on ASCVD Risk Reduction: 4 statin benefit groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Based on a comprehensive set of data from RCTs that identified <strong>4 statin benefit groups</strong> which focus efforts to reduce ASCVD events in secondary and primary prevention.</td>
</tr>
<tr>
<td></td>
<td>• Identifies <strong>high-intensity and moderate-intensity statin therapy</strong> for use in secondary and primary prevention.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2</th>
<th>A New Perspective on LDL–C and/or Non-HDL–C Treatment Goals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• The Expert Panel was unable to find RCT evidence to support continued use of specific <strong>LDL–C and/or non-HDL–C treatment targets</strong>.</td>
</tr>
<tr>
<td></td>
<td>• The appropriate intensity of statin therapy should be used to reduce ASCVD risk in <strong>those most likely to benefit</strong>.</td>
</tr>
<tr>
<td></td>
<td>• <strong>Nonstatin therapies do not provide acceptable ASCVD risk reduction benefits</strong> compared to their potential for adverse effects in the routine prevention of ASCVD.</td>
</tr>
</tbody>
</table>
### Global Risk Assessment for Primary Prevention

- This guideline recommends use of the new Pooled Cohort Equations to estimate 10-year ASCVD risk in both white and black men and women.
- By more accurately identifying higher risk individuals for statin therapy, the guideline focuses statin therapy on those most likely to benefit.
- It also indicates, based on RCT data, those high-risk groups that may not benefit.
- Before initiating statin therapy, this guideline recommends a discussion by clinician and patients.

### Safety Recommendations

- This guideline used RCTs to identify important safety considerations in individuals receiving treatment of blood cholesterol to reduce ASCVD risk.
- Using RCTs to determine statin adverse effects facilitates understanding of the net benefit from statin therapy.
- Provides expert guidance on management of statin-associated adverse effects, including muscle symptoms.
## Recommendations for Secondary Prevention

### Treatment Targets

1. The panel makes no recommendations for or against specific LDL-C or non-HDL-C targets for the primary or secondary prevention of ASCVD.

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>NHLBI Grade</th>
<th>NHLBI Evidence Statements</th>
<th>ACC/AHA COR</th>
<th>ACC/AHA LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (No recommendation)</td>
<td>1-4</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

### Secondary Prevention

1. **High-intensity statin therapy** should be initiated or continued as first-line therapy in women and men ≤75 years of age who have *clinical ASCVD*[^1], unless contraindicated.

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>NHLBI Grade</th>
<th>NHLBI Evidence Statements</th>
<th>ACC/AHA COR</th>
<th>ACC/AHA LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A (Strong)</td>
<td>1, 6-8, 10-23, 26-28</td>
<td>I</td>
<td>A</td>
</tr>
</tbody>
</table>

2. In individuals with *clinical ASCVD*[^1] in whom high-intensity statin therapy would otherwise be used, when high-intensity statin therapy is contraindicated[^2] or when characteristics predisposing to statin-associated adverse effects are present, moderate-intensity statin should be used as the second option if tolerated (Table 8 for Safety of Statins, Recommendation 1).

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>NHLBI Grade</th>
<th>NHLBI Evidence Statements</th>
<th>ACC/AHA COR</th>
<th>ACC/AHA LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A (Strong)</td>
<td>13-22, 24, 27, 28</td>
<td>I</td>
<td>A</td>
</tr>
</tbody>
</table>

3. In individuals with *clinical ASCVD* >75 years of age, it is reasonable to evaluate the potential for ASCVD risk-reduction benefits and for adverse effects, drug-drug interactions and to consider patient preferences, when initiating a moderate- or high-intensity statin. It is reasonable to continue statin therapy in those who are tolerating it.

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>NHLBI Grade</th>
<th>NHLBI Evidence Statements</th>
<th>ACC/AHA COR</th>
<th>ACC/AHA LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E (Expert Opinion)</td>
<td>---</td>
<td>IIa</td>
<td>B (16.20-43)</td>
</tr>
</tbody>
</table>
Statin Therapy Recommendations - 4 Groups

Clinical ASCVD - High

LDL-C ≥ 190 - High

Diabetes (Age 40-75) - Mod (High)

Risk ASCVD ≥ 7.5% (Age 40-75) - Mod

-statin intensity
Biomarkers and Noninvasive Testing Can Inform Treatment Decision (when Uncertain Based on Risk Assessment)

1) Primary LDL-C >160 mg/dl or other genetic evidence of hyperlipidemia
2) Family history of premature ASCVD with onset <65 in a female first degree or <55 years of age in a male first degree relative
3) C-reactive protein >=2 mg/L
4) CAC score >=300 or >=75th%tile for age and sex
5) ABI <0.9 indicative of PAD
6) Elevated lifetime risk of CVD
Monitoring Statin Response and Adherence

**Figure 5. Statin Therapy: Monitoring therapeutic response and adherence**

- **Assess medication and lifestyle adherence**
  - Fasting lipid panel*

  - Anticipated therapeutic response?  
    - Yes  
      - Reinforce continued adherence  
        - Follow-up 3-12 mo  
        - Anticipated therapeutic response?  
          - Yes  
            - Reinforce improved adherence  
              - Increase statin intensity‡  
              - OR  
                - Consider addition of nonstatin drug therapy  
              - Follow-up 4-12 wk & thereafter as indicated  
          - No  
        - Reinforce medication adherence  
          - Reinforce adherence to intensive lifestyle changes  
          - Exclude secondary causes of hypercholesterolemia  
            (Table 6)  
          - Follow-up 4-12 wk

    - No  
      - Less-than-anticipated therapeutic response
        - Intolerance to recommended dose of statin therapy  
          - Yes  
            - Management of statin intolerance  
              (Table 8, Rec 8)  
          - No

  - Indicators of anticipated therapeutic response and adherence to selected statin intensity:
    - High-intensity statin therapy‡ reduces LDL–C approx. ≥50% from the untreated baseline.
    - Moderate-intensity statin therapy reduces LDL–C approx. 30% to <50% from the untreated baseline.

*Fasting lipid panel includes triglycerides, total cholesterol, HDL–C, and LDL–C.

‡Increase in statin dose or addition of a nonstatin drug to increase LDL–C reduction.
# High, Moderate and Low Intensity Statin Dosages

**Table 5. High- Moderate- and Low-Intensity Statin Therapy (Used in the RCTs reviewed by the Expert Panel)**

<table>
<thead>
<tr>
<th>High-Intensity Statin Therapy</th>
<th>Moderate-Intensity Statin Therapy</th>
<th>Low-Intensity Statin Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily dose lowers LDL–C on average, by approximately ≥50%</td>
<td>Daily dose lowers LDL–C on average, by approximately 30% to &lt;50%</td>
<td>Daily dose lowers LDL–C on average, by &lt;30%</td>
</tr>
<tr>
<td>Atorvastatin (40†)–80 mg</td>
<td>Atorvastatin 10 (20) mg</td>
<td>Simvastatin 10 mg</td>
</tr>
<tr>
<td>Rosuvastatin 20 (40) mg</td>
<td>Rosuvastatin (5) 10 mg</td>
<td>Pravastatin 10–20 mg</td>
</tr>
<tr>
<td></td>
<td>Simvastatin 20–40 mg†</td>
<td>Lovastatin 20 mg</td>
</tr>
<tr>
<td></td>
<td>Pravastatin 40 (80) mg</td>
<td>Fluvastatin 20–40 mg</td>
</tr>
<tr>
<td></td>
<td>Lovastatin 40 mg</td>
<td>Pitavastatin 1 mg</td>
</tr>
<tr>
<td></td>
<td>Fluvastatin XL 80 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluvastatin 40 mg bid</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pitavastatin 2–4 mg</td>
<td></td>
</tr>
</tbody>
</table>
New approaches / New Agents

- New approaches / Guidelines
- Focus on FH
- New Agents
Focus on
Familial Hypercholesterolemia (FH)

Hidden in plain sight............
Recommendations for Primary Prevention in Persons $\geq 21$ Years of Age with LDL-C $\geq 190$ mg/dL

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Level of Evidence</th>
<th>Level of Recommendation</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Individuals with LDL-C $\geq 190$ mg/dL or triglycerides $\geq 500$ mg/dL should be evaluated for secondary causes of hyperlipidemia (Table 6).</td>
<td>B (Moderate)</td>
<td>I†</td>
<td>B (44,45)</td>
</tr>
<tr>
<td>2. Adults $\geq 21$ years of age with primary LDL-C $\geq 190$ mg/dL should be treated with statin therapy (10-year ASCVD risk estimation is not required):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Use high-intensity statin therapy unless contraindicated.</td>
<td>B (Moderate)</td>
<td>I§</td>
<td>B</td>
</tr>
<tr>
<td>- For individuals unable to tolerate high-intensity statin therapy, use the maximum tolerated statin intensity.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. For individuals $\geq 21$ years of age with an untreated primary LDL-C $\geq 190$ mg/dL, it is reasonable to intensify statin therapy to achieve at least a 50% LDL-C reduction</td>
<td>E (Expert Opinion)</td>
<td>IIa</td>
<td>B (20.46-50)</td>
</tr>
<tr>
<td>4. For individuals $\geq 21$ years of age with an untreated primary LDL-C $\geq 190$ mg/dL, after the maximum intensity of statin therapy has been achieved, addition of a nonstatin drug may be considered to further lower LDL-C. Evaluate the potential for ASCVD risk reduction benefits, adverse effects, drug-drug interactions, and consider patient preferences.</td>
<td>E (Expert Opinion)</td>
<td>IIb</td>
<td>C (51)</td>
</tr>
</tbody>
</table>
2013 ACC/AHA Blood Cholesterol Guidelines

1. The panel could find *no data supporting the routine use of nonstatin drugs* combined with statin Rx to reduce further ASCVD events. In addition, identification of any RCTs that assessed ASCVD outcomes in statin-intolerant patients was not found.

2. Clinicians treating *high-risk pts who have a less-than-anticipated response to statins, who are unable to tolerate a less-than-recommended intensity of a statin, or who are completely statin intolerant* may consider the addition of a nonstatin therapy. High-risk individuals include those with ASCVD, those with LDL–C ≥190 mg/dL, and individuals with DM.

<table>
<thead>
<tr>
<th>Genetic Disorder</th>
<th>Gene Defect</th>
<th>Lipids Elevated</th>
<th>Genetics</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipoprotein Lipase Deficiency</td>
<td>LPL</td>
<td>Chylos</td>
<td>Auto Rec</td>
<td>1/1,000,000</td>
</tr>
<tr>
<td>Familial Hepatic Lipase Deficiency</td>
<td>LIPC</td>
<td>VLDL Remnants</td>
<td>Auto Rec</td>
<td>&lt;1/1,000,000</td>
</tr>
<tr>
<td>Familial Dysbetalipoproteinemia</td>
<td>APOE</td>
<td>Chylos Remnants</td>
<td>Auto Rec</td>
<td>1/10,000</td>
</tr>
<tr>
<td>Familial Hypercholesterolemia</td>
<td>LDLR</td>
<td>LDL</td>
<td>Auto Dom</td>
<td>1/500</td>
</tr>
<tr>
<td>Familial Defective apoB100</td>
<td>apoB-100</td>
<td>LDL</td>
<td>Auto Dom</td>
<td>&lt;1/1000</td>
</tr>
<tr>
<td>Autosomal Dominant Hypercholesterolemia</td>
<td>PCSK9</td>
<td>LDL</td>
<td>Auto Dom</td>
<td>&lt;1/1,000,000</td>
</tr>
<tr>
<td>Sitostereolemia</td>
<td>ABCG5 or ABCG8</td>
<td>LDL</td>
<td>Auto Rec</td>
<td>&lt;1/1,000,000</td>
</tr>
</tbody>
</table>
Genetics of FH

- FH1  LDL-R (short arm chromosome 19)
- FH2  defective apoB-100
- FH3  overexpression PCSK9
Familial Hypercholesterolemia.....
“Hidden in plain sight”

- Autosomal dominant inheritance- >1700 mutations of LDL receptor gene
- Heterozygotes - 2x LDL, Clinical CAD 40’s-50’s (1:500)
- Homozygotes - 4-5 fold LDL; early athero
- 20% identified.....

FH Roundtable/ Summit, March 2013
Prevalence of FH

- Homozygotes: 1: million
- Heterozygotes: 1:500
- Founder effect (can be): 1:50
  - French Canadians
  - Christian Lebanese
  - South African Afrikaners
  - Ashkenazi Jews

Willard K, NLA Lipid Spin, 2013
FH exposes people to very high cholesterol from birth, thus reaching a threshold for CHD earlier in life.

Cumulative exposure (cholesterol yrs) by age:
FH vs unaffected (healthy) individuals

Threshold for CHD: reached by age 40 for those with HeFH and age 20 for HoFH, > 70 yrs in healthy individuals

Adapted from Horton et al. J Lipid Res. 2009;50:S172-S177
Identification of FH

- Physical findings?
- Cholesterol measurement
- Family Hx

Curr Cardiol Rev. 2008;4(1)
Physical characteristics of FH

- Xanthelasma of the eyelid in hetero-FH
- Arcus corneae and xanthelasma of the eyelid in hetero-FH
- Xanthoma on extensor tendons of the hand in hetero-FH
- Achilles tendon xanthoma in hetero-FH
- X-ray measurement of Achilles tendon thickness

Under supervision of Mabuchi (Kanazawa Univ., Japan)
FH Screening

• General population
  – Family history
  – Universal cholesterol screening

• Cascade screening in affected families
  – Do you use DNA testing?
    • 80% have *LDLR* mutation
    • With rare exception you don’t manage patients differently based on mutation
Central role of the FH registry in improving outcomes

Clinician, patient entered data

Determinants of longitudinal outcomes

Gain insight into patient experiences

Encourage cascade screening
Facilitate research and clinical trials

Improve knowledge gaps

Drive regulatory changes

Facilitate FH “biobank”

Educational material
Aggregate data
New approaches / New Agents

- New approaches / Guidelines
- Focus on FH
- New Agents
Current Non-Statin Therapies

1) Ezetimibe
2) Bile Acid Resins
3) Niacin
4) Fibrates - (not pure FH ; FCH)
5) OM3’s
6) LDL apheresis

Novel / Emerging Therapies

1) Lomitapide
2) Mipomersen
3) CETP Inhibitors
4) PCSK9 Inhibitors
Emory Univ. Hospital / Clinic
FH referral center
Time averaged LDL

- LDL-C
- Diet Therapy
- Diet & Drug Therapy
- LIPOSORBER® Treatment

- Pre
- Time Average
- Post

Time
LDL Apheresis

- FDA approved
- 60-80% LDL reduction
- Largest observational study - 72% event reduction
- Small RCTs- regression
- Potential vascular benefits
  - Endothelial function
  - Reduction in inflammatory markers (CRP, VCAM, MCP-1)

CETP Inhibitors

• Evacetrapib
  – ACCELERATE………..HALTED Oct. 2015
  – 18K with high vascular risk
  – Standard care +/- Eva 130 mg

• Anacetrapib
  – REVEAL
  – > 30K with ASCVD
  – Atorva +/- Ana 100 mg

• Results expected in 2017
## New Therapies to Lower LDL-C Beyond Underlying Statin Therapy (courtesy P. Wilson)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Lomitapide</th>
<th>Mipomersen</th>
<th>PCSK9</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Delivery</strong></td>
<td>Oral (pill)</td>
<td>Injection (subq every week)</td>
<td>Injection (subq every 4 weeks)</td>
</tr>
<tr>
<td><strong>Action</strong></td>
<td>MTP inhibitor</td>
<td>Anti-sense ApoB oligonucleotide</td>
<td>Antibodies to PCSK9</td>
</tr>
<tr>
<td><strong>LDL-C Effect in statin Rx HoFH</strong></td>
<td>↓ 40-50%</td>
<td>↓ 25%</td>
<td>↓ 50%</td>
</tr>
<tr>
<td><strong>Availability</strong></td>
<td>REMS*</td>
<td>REMS*</td>
<td>In research trials</td>
</tr>
<tr>
<td><strong>Monitor</strong></td>
<td>Liver Ftn Tests</td>
<td>Liver Ftn Tests</td>
<td></td>
</tr>
<tr>
<td><strong>Concerns</strong></td>
<td>Hepatotoxicity Drug interactions</td>
<td>Hepatotoxicity Site injection rxn Flu symptoms</td>
<td>Antibody development</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>$300,000/pt/yr</td>
<td>$300,000/pt/yr</td>
<td>Not available</td>
</tr>
</tbody>
</table>

*REMS= Risk Evaluation and Mitigation Strategies*
Pro-protein convertase subtilisin-like kexin type 9 (PCSK9) - 692 amino acid protease primarily expressed in liver, intestine and kidney

Secreted PCSK9 forms a complex with the EGF-A domain of the LDLR extracellular domain (ECD), leading to endocytosis of the PCSK9-LDLR complex and subsequent degradation of the LDLR

Horton JD, Cohen JC, and Hobbs HH. J Lipid Research 2009;50:S172-177
The Role of PCSK9 in the Regulation of LDL Receptor Expression

LDL=low-density lipoprotein; LDL-R=LDL receptor; PCSK9=proprotein convertase subtilisin/kexin type 9; SREBP-2=sterol regulatory element-binding protein-2.
Currently Approved PCSK9 mAb in US

Alirocumab
- Indicated as adjunct to diet & maximally tolerated statin therapy for treatment of adults with HeFH or clinical ASCVD, who require additional lowering of LDL-C
- **Recommended starting dose:** 75 mg SC q2weeks (may increase to 150 mg SC q2weeks)

Evolocumab
- Indicated as adjunct to diet & maximally tolerated statin therapy treatment of adults with
  - HeFH, HoFH (beyond other maximal tolerated lipid therapy)
  - clinical ASCVD, who require additional lowering of LDL-C
  - 140 mg SC q2weeks or 420 mg SC once monthly (only for HoFH)
  - For HoFH, response to therapy depends on degree of LDL-receptor function
PCSK9 mAb Meta-Analysis
24 RCTs 10,159 patients; LDL-C reduction -47.5%

Cardiovascular Mortality
HR=0.45 [0.23-0.86], p=0.015

MI
HR=0.49 [0.26-0.93], p=0.030

Unstable Angina
HR=0.61 [0.06-6.14], p=0.68

Total Mortality
HR=0.50, p=0.084

CK Increase
HR=0.72, p=0.026

Serious AEs
HR=1.01, p=0.88
Cumulative Incidence of Cardiovascular Events from Evolocumab (over 52 weeks) and Alirocumab (over 78 weeks)
Wong ND, Rosenblit PD. NLA Lipid Spin 2015;13(4)

- **OSLER 1&2, 52 weeks**
  - LDL, mg/dL, Baseline\(\rightarrow\)12wk:
    - Standard-therapy: 121 \(\rightarrow\) 116
    - Evolocumab: 120 \(\rightarrow\) 48 (61% reduction)
  - LDL, mg/dL (Baseline\(\rightarrow\)24wk)
    - Placebo: 122\(\rightarrow\)119
    - Alirocumab: 123 \(\rightarrow\) 48 (62% reduction)

- **ODYSSEY, 78 weeks**
  - LDL, mg/dL (Baseline\(\rightarrow\)24wk)
    - Placebo: 122\(\rightarrow\)119
    - Alirocumab: 123 \(\rightarrow\) 48 (62% reduction)

**Cumulative Probability of Event (%)**
- Prespecified Exploratory Outcome Incidence of Adjudicated CV events
- HR 0.47 (95% CI 0.28 - 0.78) \(p = 0.003\)
- HR 0.52 (95% CI 0.31 to 0.90) \(p = 0.02\)

**PLACCB**

- 2.2
  - 31 / 1489 pts

- 0.95
  - 29 / 2976 pts

- 3.3
  - 26 / 788 pts

- 1.7
  - 27 / 1550 pts


PCSK9 mAb = Proprotein convertase subtilisin / kexin type 9 monoclonal antibody therapy
PCSK9 Inhibitors - Delivery System

- Biologics
- Store in the fridge
  - Warm to room temp
- SQ injection pens
  - Abd, thigh, arm
- A-mab
  - 75 or 150 mg q 2 wks
- E-mab
  - 140 mg q 2 wks
  - 420 mg q month
## OUTCOME STUDIES

<table>
<thead>
<tr>
<th><strong>Alirocumab</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ODYSSEY Outcomes</strong> <em>(NCT01663402)</em></td>
</tr>
<tr>
<td>Enrolling post-acute MI or hospital UA w/in 12 mon; Rx w/ atorva 40/80 mg/d, rosvu 20/40 mg/d or max tolerated; LDL &gt; 70, nonHDL &gt; 100, or apo B &gt; 80; Endpoint – time to ASCVD event; n=18,000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Bococizumab</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spire-1</strong> <em>(NCT01975376)</em></td>
</tr>
<tr>
<td>Enrolling high risk CVD event; LDL 70-100 or nonHDL 100-130; on LLRx; Randomized to Boco 150 mg SC Q2W vs placebo; n=12,000</td>
</tr>
</tbody>
</table>

| **Spire-2** *(NCT01975389)* |
| Same as above except LDL > 100 or nonHDL > 130; n=6300 |

<table>
<thead>
<tr>
<th><strong>Evolocumab</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fourier</strong> <em>(NCT01764633)</em></td>
</tr>
<tr>
<td>Enrolling MI, CVA, or PAD + RF; Rx with atorva ≥ 20 mg or equivalent; LDL &gt; 70 or nonHDL &gt; 100; Endpoint – time to 1st ASCVD event; Rx w/ 140 Q2W or 420 mg QM vs placebo; n=22,500</td>
</tr>
</tbody>
</table>

| **Glagov** *(NCT01813422)* |
| Enrolling pts with evidence for coronary stenosis; LDL > 80 or 60-80 w/ RF; Rx w/ statin, niacin or eze; Rx 420 mg SC QM for 72 mon; n=950 |

[www.clinicaltrials.gov](http://www.clinicaltrials.gov)
Discontinuation of Bococizumab (global clinical development)

- Announced by Pfizer on Nov. 1, 2016
- Including SPIRE 1 & 2
- “B-mab not likely to provide value to patients, physicians, or our shareholders”
- After completion of 6 studies observed
  - Unanticipated attenuation of LDL-C lowering over time
  - Unanticipated higher level of immunogenicity (anti-drug Abs)
  - Higher rate of injection site reactions
PCSK 9 Questions……..

1. Outcome of RCTs?
2. Cost effectiveness?
3. Widespread applicability?
4. Statin intolerant population?
5. Neurocognitive & immunologic AEs?
6. LDL-C < 30?
7. Impact of competitive market?
8. Impact on Guidelines?
9. The future….Game changer?
Summary: New approaches / New Agents

- 4 statin benefit groups (benefit > risk)
- Guidelines should inform clinical judgement, but not replace it
- Critical to identify and treat individuals with FH
  - subsequent cascade screening
- Non-statin therapies available
  - Evaluate safety, efficacy, and outcomes data
Thanks......
Targets?

“Bummer of a birthmark, Hal.”
Physicians are used to goals & targets…..

- BP
- A1C, fasting BG
- GPA
- SAT & MCAT scores
- FT % or golf handicap
LDL cholesterol and benefit in clinical trials
Is lower better?

Adapted from Rosensen RS. Exp Opin Emerg Drugs 2004;9(2):269-279
Optimal Lipid Targets for the New Era of CV Prevention

- LDL < 70 mg/dl (FOR ALL)
- Non-HDL < 90 mg/dl
- Fasting TGs < 100 mg/dl
- HDL
  - Highly Functional
  - ??? > 50 mg/dl

2013 ACC/ AHA Blood Cholesterol Guidelines

• Subgroups with class II-IV HF or HD
  – No recommendation

• Safety
  – CK not routinely measured
  – Transaminase measurements
  – Incident Diabetes (modest increased risk)

Circulation Online; Nov. 12, 2013
Pay for Performance? What should we measure?

• On treatment LDL?
• % reduction of LDL from baseline?
• Appropriate intensity of statin used?
• Meaningful discussion between clinician & patient (informed clinical decision making)………. 
The Cycle of Clinical Effectiveness

- Concept
- Clinical Trials
- Guidelines
- Performance Indicators
- NCDR Registries
- Outcomes
- QUALITY
- Performance
28-36% of Guideline-Recommended Patients Not on Statins: ACC NCDR PINNACLE Registry (Maddox et al., JACC 2014)

**FIGURE 2** Lipid-Lowering Therapies, Overall and by Patient Risk Group

Display of lipid-lowering therapies by patient risk group. Percentages total >100% due to differing contraindication number per group. Refer to the methods section for further details. ASCVD = atherosclerotic cardiovascular disease; CVD = cardiovascular disease; DM = diabetes mellitus; LDL = low-density lipoprotein.
Challenges to Utilization & Adherence of GL-Recommended Rx
Hirsh, Smilowitz, Rosenson, Fuster, Sperling. JACC 2015;66(2):184-192

Provider Behavior:
- Challenges:
  - Failure to prescribe statin
  - Failure to maximally intensify statin therapy
  - Failure to re-introduce statin
  - Time constraints
- Solutions:
  - Education
  - Clinical decision support tools (EMR prescribing alerts)
  - Adherence to Guidelines
  - Participation in Quality Improvement programs
  - Team-based approach
  - Dosing strategies for patients with presumed statin intolerance
  - Re-challenging with statin in subjects with a history of myalgia

Patient Factors:
- Challenges:
  - Demographics, socioeconomics
  - Patient education
  - Comorbid conditions
  - Depression (particularly post-ACS)
  - Cognitive impairment
  - Caregiver involvement
  - Adverse reactions & intolerance
  - Polypharmacy
  - Drug-drug interactions
  - “White coat adherence”
- Solutions:
  - Discharge counseling
  - Education
  - Smart phone reminder applications
  - Pill burden reduction with fixed-dose combination therapy (Polypill)
  - Once-daily med dosing
  - Patient outreach programs
  - Caregiver participation
  - Cardiac rehabilitation

Health System Factors:
- Challenges:
  - Limited access to medical care
  - Multiple providers
  - Copayments and insurance coverage
  - Drug costs
  - Clinical inertia
- Solutions:
  - Education / media campaign
  - Coordination of care
  - Reduce or eliminate copays
  - Pill burden reduction with fixed-dose combination therapy (Polypill)
  - Pharmacy refill tracking / reminders
  - Automated pill counts

Optimal Statin Use
Enhancing Physicians’ Use of Clinical Guidelines

• “Guideline developers should rethink their goals…”

• 5 Strategies to increase guideline adherence
  1. Use an unambiguous checklist
  2. Partner with implementation scientists & systems engineers
  3. Integrate guidelines
  4. Rely on systems & technology to ensure patients receive recommended therapies (create information ecosystems)
  5. Create transdisciplinary teams

Pronovost PJ. JAMA 2013. 28
Tale of Two Scientists
Goldstein & Brown

- Nobel Prize in Medicine & Physiology (1985)
- Discovered hepatic LDL receptor
- Demonstrated FH due to mutations in genetic coding
Supravalvular AS

- Ao Root with Ross procedure
- 21 yo F with FH
The Mona Lisa
Da Vinci’s Mona Lisa: FH?

Xanthelasma

???
Mona Lisa

- Madonna Lisa Maria di Gherardini
  - Born Florence 1479
- Married age 16
- 24 yo @ sitting for painting in 1503
- Died in 1516 @ age 37
  - Suddenly, cause unknown

Therapy for FH

• Combination Lipid Therapy
• Some homozygotes exhibit partial response to statins
• Portocaval shunting (high morbidity and mortality)
• Liver transplantation- limited applicability / high morbidity
• gene therapy has been disappointing (Nat Med. 1995;1:1148-1154)
• **Low-density lipoprotein apheresis**

FH- Summary

• FH is hidden in plain site (1:500)
  – Awareness & action
  – Cascade screening

• ACC/ AHA high risk group
  – High intensity statins ; > 50% LDL reduction

• Combination Rx

• LDL apheresis

• Novel & emerging Rxs
  – Lomitapide & mipomersen
  – CETP?? and PCSK9 inhibitors
FH is more common than many well known genetic diseases

- 1:300 – 1:500 worldwide
- 620,000 FH patients in US
- Average LDL is 220 mg/dl
- 20 fold increased risk of coronary heart disease
- Causes 20% of MIs before age 45 and 5% before age 60

Hopkins et al. J. Clinical Lipidology. 2011
Goldberg et al. J. Clinical Lipidology. 2011
Guidelines....
Understanding Opportunities for HEALTHCare

• Science: What we can do
• Guidelines: What we should do
• Registries: What we do
“Evidence-Based” Not “Evidence-Bound”

Three Key Dimensions

Scientific evidence

Patient preference

Clinical Judgment
DEFINE- Anacetrapib
(CHD or high risk on statin; LDL 81 mg/dL)

**LDL-C**

-39.8% \( (P<0.001) \)

**HDL-C**

+138.1% \( (P<0.001) \)

Anacetrapib n = 804 771 716 687 646 604 568 540
Placebo n = 803 759 741 743 735 711 691 666

Anacetrapib n = 776 757 718 687 647 607 572 543
Placebo n = 766 761 741 744 736 711 691 666

Disease Modulating Therapies

- IL-1 mab
- IL-6 mab
- TNF-alpha blockers
- Chemokine receptor 2 inhibitors
- MTX
**LDL-C and % Reduction in LDL-C Should Be Used to assess response to therapy but not as performance standards**

1. In individuals who have a less-than-anticipated therapeutic response or are intolerant of the recommended intensity of statin therapy, the following should be performed:
   - Reinforce medication adherence.
   - Reinforce adherence to intensive lifestyle changes.
   - Exclude secondary causes of hyperlipidemia.

   |   | A (Strong) | 45 | I | A |

2. It is reasonable to use the following as indicators of anticipated therapeutic response to the recommended intensity of statin therapy. Focus is on the intensity of the statin therapy. As an aid to monitoring:
   - High-intensity statin therapy generally results in an average LDL-C reduction of ≥50% from the untreated baseline;
   - Moderate-intensity statin therapy generally results in an average LDL-C reduction of 30 to <50% from the untreated baseline;
   - LDL-C levels and percent reduction are to be used only to assess response to therapy and adherence. They are not to be used as performance standards.

# Treatment-Emergent Neurocognitive Adverse Events

<table>
<thead>
<tr>
<th>Number of patients (%)</th>
<th>Alirocumab (n=1550)</th>
<th>Alirocumab with LDL-C &lt;25 mg/dL (N=575)</th>
<th>Placebo (n=788)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any neurocognitive disorder†</td>
<td>18 (1.2)</td>
<td>3 (0.5)</td>
<td>4 (0.5)</td>
</tr>
<tr>
<td>Amnesia</td>
<td>5 (0.3)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Memory impairment</td>
<td>4 (0.3)</td>
<td>0</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Confusional state</td>
<td>4 (0.3)</td>
<td>1 (0.2)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Confusion postoperative</td>
<td>1 (&lt;0.1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dementia</td>
<td>1 (&lt;0.1)</td>
<td>1 (0.2)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Disorientation</td>
<td>1 (&lt;0.1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Disturbance in attention</td>
<td>1 (&lt;0.1)</td>
<td>0</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Frontotemporal dementia</td>
<td>1 (&lt;0.1)</td>
<td>1 (0.2)</td>
<td>0</td>
</tr>
<tr>
<td>Reading disorder</td>
<td>1 (&lt;0.1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Transient global amnesia</td>
<td>1 (&lt;0.1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vascular encephalopathy</td>
<td>1 (&lt;0.1)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

†These terms were selected using custom Medical Dictionary for Regulatory Activities (MedDRA) queries that were based on five high-level group terms: deliria (including confusion); cognitive and attention disorders and disturbances; dementia and amnestic conditions; disturbances in thinking and perception; and mental impairment disorders.

New This Fall

American Society for Preventive Cardiology:  www.aspconline.org
Exclude Causes of Secondary Dyslipidemia

- Diabetes
- Hypothyroidism
- Obstructive liver disease
- Chronic renal failure
- Drugs that raise LDL cholesterol and lower HDL cholesterol (progestins, anabolic steroids, and corticosteroids)
Non-HDL- Do the Math

- Everything you need to know to calculate non-HDL you learned in 1st grade
- Think beyond LDL….
  - Non-HDL (no added expense); TC/HDL ratio
- Increasing awareness of non-HDL
  - Attainable goal
  - On all lab reports

Adapted from Ramjee V, Sperling LS, Jacobson TA. J Am Coll Cardiol 2011;58:462
What’s good about the Guidelines?

• **Simplification** of initial approach
• Goals include prevention of **stroke**
• Focus on reducing risk
  – High risk......High intensity Rx
  – Benefit > risks
• **Inclusion of FH** (LDL > 190) in high risk groups
• Emphasis on guidelines as a **starting point**
Evolution of Global Risk Assessment

NCEP ATP I
1988

Framingham
MRFIT
LRC-CPPT
Coronary Drug Project
Helsinki Heart CLAS

NCEP ATP II
1994

Angiographic trials (FATS, POSCH, SCOR, STARS, Ornish, MARS)
Meta-analyses (Holme, Rossouw)

NCEP ATP III
2001

4S
WOSCOPS
CARE
LIPID
AFCAPS/ TexCAPS

Updated NCEP ATP III
2004

HPS
PROVE-IT
ASCOT-LLA
PROSPER
ALLHAT-LLT

AHA/ACC Update 2006

Intensity of therapy adjusted to absolute risk……..

NHLBI = National Heart, Lung, and Blood Institute.
NCEP ATP = National Cholesterol Education Panel Adult Treatment Panel.
AHA = American Heart Association.
ACC = American College of Cardiology.
Calculated LDL

• Friedewald equation
  – LDL = TC – HDL – TG/5
  – Less accurate as TG’s increase
  – Less accurate at LDL < 100 mg/dl
  – TC- HDL= LDL +IDL+Lp(a) = the “non-HDL” fraction

– Frost PH Am J Cardiol 1998 26;81(4A)
– McNamara JR, et a; Clin Chem 1990;36(1)
Non-HDL-C = Total Cholesterol – HDL-C

Total Cholesterol

Apo B

VLDL

IDL

LDL

Lp(a)

HDL

Atherogenic TG-rich lipoproteins
Comparative Performance of Lipid Measures: LDL, Non-HDL and ApoB

<table>
<thead>
<tr>
<th>Performance</th>
<th>LDL-C</th>
<th>Non-HDL-C</th>
<th>ApoB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relevance to emerging population</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Assesses residual cardiometabolic risk</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Off-treatment CVD risk prediction</td>
<td>X</td>
<td>XX</td>
<td>XX</td>
</tr>
<tr>
<td>On-treatment CVD risk prediction</td>
<td>XX</td>
<td>XX</td>
<td></td>
</tr>
<tr>
<td>Subclinical CVD prediction</td>
<td>XX</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Treatment reduces risk</td>
<td>X</td>
<td>XX</td>
<td>XX</td>
</tr>
<tr>
<td>Additional risk reclassification</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ease of Use</th>
<th>LDL-C</th>
<th>Non-HDL-C</th>
<th>ApoB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Independent of prandial state</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Independent of triglyceride level</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Familiar conceptual framework</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Well-defined treatment targets</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Well-defined intervention effects</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Can safely meet recommended goals</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Practical Limitations</th>
<th>LDL-C</th>
<th>Non-HDL-C</th>
<th>ApoB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine in-hospital testing</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Additional direct cost</td>
<td></td>
<td></td>
<td>XX</td>
</tr>
<tr>
<td>Delayed time-to-result</td>
<td></td>
<td></td>
<td>XX</td>
</tr>
</tbody>
</table>

Ramjee V, Sperling LS, Jacobson TA. J Am Coll Cardiol 2011;58:462