Clinical Updates for Nurse Practitioners and Physician Assistants: 2015

Lipid Management and Cardiovascular Risk Reduction: The Evolving Treatment Paradigm
Faculty

• **Elizabeth Ofili, MD, MPH, FACC**
  Professor of Medicine (Cardiology), Senior Associate Dean, Clinical Research Director, Clinical Research Center, Morehouse School of Medicine
  Founder and Chairman of the Board, AccuHealth Technologies, Inc., Atlanta, GA

• **Anekwe Onwuanyi, MD**
  Professor of Medicine, Chief of Cardiology, Morehouse School of Medicine
  Medical Director, Heart Failure Program, Grady Health System, Atlanta, GA

• **Laurence O. Watkins, MD, MPH, FACC**
  Director, Healthy Heart Center
  Port St. Lucie, FL
Disclosures

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• Anekwe Onwuanyi, MD has no relationships to disclose.

• Laurence O. Watkins, MD, MPH, FACC serves as a speaker/teacher for Arbor Pharmaceuticals and on the advisory committee for Boston Scientific.
Educational Objectives

1. Discuss the benefits of LDL-C lowering with pharmacologic therapies that improve cardiovascular outcomes
2. Recognize and understand the role of alternative or additional therapies in conjunction with statins
3. Recognize the strengths and limitations of the 2013 ACC/AHA cholesterol guidelines and how to optimally implement the recommendations
4. Recognize the potential role of emerging pharmacologic therapies to further lower LDL-C in those at high risk for cardiovascular disease
5. Recognize and develop appropriate treatment strategies for special populations (women, elderly, ethnic minorities) that would benefit from lipid lowering therapy
PRE-TEST QUESTIONS
Pre-test ARS Question 1

On a scale of 1 to 5, please rate how confident you would be in treating Hypercholesterolemia in patients that are not achieving optimal goals or are refractory to statin therapy?

1. Not at all confident
2. Slightly confident
3. Moderately confident
4. Pretty much confident
5. Very confident
Pre-test ARS Question 2

MR, a 61-year-old male with an LDL-C of 130 mg/dL and diabetes has an ASCVD risk of 6.6% based on the new risk-calculator. What therapy should MR be started on according to the ACC/AHA 2013 guidelines?

1. High-intensity statin
2. Moderate-intensity statin
3. Low-intensity statin
4. Non-statin therapy
5. None of the above
SJ, a 62 year old BF is hospitalized in the Coronary care unit following a non-ST segment MI and stent placement in a 95% right coronary lesion. Her admission lipids are LDL-C=90 mg/dl, HDL=35 mg/dL, triglycerides=160 mg/dl.
In addition to being placed on a statin, which of the following treatments has been shown to reduce her risk of cardiovascular events.

1. Niacin
2. Fenofibrate
3. Cholestyramine
4. Ezetimibe
5. None of the above
Pre-test ARS Question 4

Which of the following is NOT one of the 4 statin benefit groups according to the 2013 ACC/AHA Cholesterol Guideline to Reduce Atherosclerotic CV Disease?

1. A patient with clinical ASCVD
2. A patient with an LDL-C > 190 mg/dL
3. A patient 56 years of age with diabetes and an LDL-C of 118 mg/dL
4. A patient 67 years of age without diabetes or ASCVD with an LDL-C of 125 mg/dL and an estimated 10-year ASCVD risk of 7.5% or greater.
5. A patient 28 years of age with an LDL-C of 145 mg/DL
Pre-test ARS Question 5

Results to date with PCSK9 antibody use have demonstrated what effect?

1. Comparable lowering of LDL-C to high-intensity statins
2. Significant reductions of LDL-C levels on top of statin therapy
3. Regression of atherosclerotic disease as measured by carotid intimal medial thickness studies
4. Hepatic fibrosis at the phase 3 doses studied
5. None of the above
Pre-test ARS Question 6

According to the 2013 ACC AHA Cholesterol guidelines, which of the following is recommended therapy for a 78 year old male who suffers an NSTEMI?

1. High intensity statin therapy
2. High intensity statin therapy plus Ezetimibe
3. Moderate Intensity statin therapy
4. Moderate Intensity statin therapy plus ezetimibe
5. Ezetimibe alone
Burden of Atherosclerotic Cardiovascular Disease

- Annual rates in US
  - Myocardial infarction – 1.1 million
  - Strokes - 795,000
  - CVD Mortality – 1,344,185 (every 30 seconds a death)
  - Cardiac catheterization – 1.0 million
  - Percutaneous revascularization – 492,000
  - Surgical revascularization – 291,000

- Annual cost – >$315 billion

AHA/ACC Cholesterol Treatment Guidelines


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AHA = American Heart Association; ACC = American College of Cardiology.
### Effects on MAJOR VASCULAR EVENTS

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Treatment</th>
<th>Control</th>
<th>Rate Ratio (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-fatal MI</td>
<td>2001 (4·4)</td>
<td>2769 (6·2)</td>
<td>0·74 (0·70 – 0·79)</td>
</tr>
<tr>
<td>CHD death</td>
<td>1548 (3·4)</td>
<td>1960 (4·4)</td>
<td>0·81 (0·75 – 0·87)</td>
</tr>
<tr>
<td><strong>Any major coronary event</strong></td>
<td>3337 (7·4)</td>
<td>4420 (9·8)</td>
<td><strong>0·77 (0·74 – 0·80)</strong></td>
</tr>
<tr>
<td>CABG</td>
<td>713 (3·3)</td>
<td>1006 (4·7)</td>
<td>0·75 (0·69 – 0·82)</td>
</tr>
<tr>
<td>PTCA</td>
<td>510 (2·4)</td>
<td>658 (3·1)</td>
<td>0·79 (0·69 – 0·90)</td>
</tr>
<tr>
<td>Unspecified</td>
<td>1397 (3·1)</td>
<td>1770</td>
<td>0·76 (0·69 – 0·84)</td>
</tr>
<tr>
<td><strong>Any coronary revascularisation</strong></td>
<td>2620 (5·8)</td>
<td>3434 (7·6)</td>
<td><strong>0·76 (0·73 – 0·80)</strong></td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>105 (0·2)</td>
<td>99 (0·2)</td>
<td>1·05 (0·78 – 1·41)</td>
</tr>
<tr>
<td>Presumed ischaemic stroke</td>
<td>1235 (2·8)</td>
<td>1518 (3·4)</td>
<td>0·81 (0·74 – 0·89)</td>
</tr>
<tr>
<td><strong>Any stroke</strong></td>
<td>1340 (3·0)</td>
<td>1617 (3·7)</td>
<td><strong>0·83 (0·78 – 0·88)</strong></td>
</tr>
<tr>
<td><strong>Any major vascular event</strong></td>
<td>6354 (14·1)</td>
<td>7994 (17·8)</td>
<td><strong>0·79 (0·77 – 0·81)</strong></td>
</tr>
</tbody>
</table>

![Diagram showing rate ratios for various endpoints](image-url)

CTT. Lancet 2008 371: 117-125
Similar Benefits on Vascular Events Regardless of Baseline LDL-C, More vs Less, or Statin vs No Statin

<table>
<thead>
<tr>
<th>Baseline LDL-C (mg/dL)</th>
<th>Events (% per annum)</th>
<th>RR (CI) per 1 mmol/L reduction in LDL-C</th>
<th>Trend test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Statin/more</td>
<td>Control/less</td>
<td></td>
</tr>
<tr>
<td>More vs less statin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 80</td>
<td>704 (4.6%)</td>
<td>795 (5.2%)</td>
<td>0.71 (0.52–0.98)</td>
</tr>
<tr>
<td>80 - &lt; 100</td>
<td>1189 (4.2%)</td>
<td>1317 (4.8%)</td>
<td>0.77 (0.64–0.94)</td>
</tr>
<tr>
<td>100 - &lt; 120</td>
<td>1065 (4.5%)</td>
<td>1203 (5.0%)</td>
<td>0.81 (0.67–0.97)</td>
</tr>
<tr>
<td>120 - &lt; 140</td>
<td>517 (4.5%)</td>
<td>633 (5.8%)</td>
<td>0.61 (0.46–0.81)</td>
</tr>
<tr>
<td>&gt; 140</td>
<td>303 (5.7%)</td>
<td>398 (7.8%)</td>
<td>0.64 (0.47–0.86)</td>
</tr>
<tr>
<td>Total</td>
<td>3837 (4.5%)</td>
<td>4416 (5.3%)</td>
<td>0.72 (0.66–0.78)</td>
</tr>
<tr>
<td>Statin vs control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 80</td>
<td>206 (2.9%)</td>
<td>217 (3.2%)</td>
<td>0.87 (0.60–1.28)</td>
</tr>
<tr>
<td>80 - &lt; 100</td>
<td>339 (2.4%)</td>
<td>412 (2.9%)</td>
<td>0.77 (0.62–0.97)</td>
</tr>
<tr>
<td>100 - &lt; 120</td>
<td>801 (2.5%)</td>
<td>1022 (3.2%)</td>
<td>0.76 (0.67–0.86)</td>
</tr>
<tr>
<td>120 - &lt; 140</td>
<td>1490 (2.9%)</td>
<td>1821 (3.6%)</td>
<td>0.77 (0.71–0.84)</td>
</tr>
<tr>
<td>&gt; 140</td>
<td>4205 (2.9%)</td>
<td>5338 (3.7%)</td>
<td>0.80 (0.77–0.84)</td>
</tr>
<tr>
<td>Total</td>
<td>7136 (2.8%)</td>
<td>8934 (3.6%)</td>
<td>0.79 (0.77–0.81)</td>
</tr>
</tbody>
</table>

LDL-C values converted to non-SI units, and rounded to nearest 20 mg/dL. Adapted from Lancet. 2010 Nov 13;376(9753):1670-81.
ASCVD Statin Benefit Groups

Heart healthy lifestyle habits are the foundation of ASCVD prevention. In individuals not receiving cholesterol-lowering drug therapy, recalculate estimated 10-y ASCVD risk every 4-6 y in individuals aged 40-75 y without clinical ASCVD or diabetes and with LDL-C ≥190 mg/dL.

- Adults age >71 y and a candidate for statin therapy
- Yes

Clinical ASCVD

- Yes
- No

LDL-C ≥190 mg/dL

- Yes
- No

Diabetes Type 1 or 2

- Yes
- No

Age <75 y

- Yes
- No

High-intensity statin (Moderate-intensity statin if not candidate for high-intensity statin)

Age ≥75 y OR if not candidate for high-intensity statin

Moderate-intensity statin

Definitions of High- and Moderate-Intensity Statin Therapy (See Table 5)

- High Daily dose lowers LDL-C by approx. >50%
- Moderate Daily dose lowers LDL-C by approx. 30% to <50%

High-intensity statin (Moderate-intensity statin if not candidate for high-intensity statin)

Moderate-intensity statin

Estimated 10-y ASCVD risk ≥7.5%

- Yes
- No

High-intensity statin

Moderate-to-high intensity statin

≥7.5% estimated 10-y ASCVD risk and age 40-75 y

ASCVD prevention benefit of statin therapy may be less clear in other groups.

In selected individuals, consider additional factors influencing ASCVD risk and potential ASCVD risk benefits and adverse effects, drug-drug interactions, and patient preferences for statin treatment.
ASCVD Statin Benefit Groups

Adults >20 years of age and a candidate for statin therapy

- Clinical ASCVD and Age <75
  - NO

- LDL-C > 190 mg/dL
  - NO

- Diabetes type 1 or 2 and age 40-75
  - NO

Estimate 10-year ASCVD RISK

- >7.5 % 10-year ASCVD risk and age 40 to 75
  - YES

  High-intensity statin (Moderate intensity if not a candidate for high-intensity) Grade A

Measure risk factors every 4-6 years and recalculate 10-year ASCVD risk in those without ASCVD, diabetes, and with LDL-C <190 mg/dL
Nonadherence to Statin Treatment begins early

Adherence continues to drop over time, particularly when treating the asymptomatic patient

Adapted from cohort study using linked population-based administration data from Ontario, Canada (N=85,020). Jackevicius et al.

Adapted from cohort study using linked population-based administration data from Ontario, Canada (N=85,020). Jackevicius et al.

Patients Non-adherent to Statin Therapy Are Twice as Likely to Experience Subsequent MI

Adherence defined as fill frequency ≥80% (n=661).
Nonadherence defined as fill frequency ≤60% (n=395).

High Risk Patients with the Greatest Unmet Needs

- Statin-resistant patients
- Statin-intolerant patients
- Familial hypercholesterolemia (FH)
- Low HDL patients
Inter-individual Variability in Response to Statins

The graph below shows dramatic interindividual variability in response to Atorvastatin 10 mg daily. This has also been observed with other statins.
CLINICAL PEARL # 1

Even though statins are robust LDL-C lowering drugs, there is significant inter-patient variability in statin response.
Poor response to statins linked to CAD progression

- Data from 7 prospective trials was obtained (647 patients)
  - One-fifth of the patients were statin hyporesponders.
- Except for LDL-C, risk factors did not differ between groups.
- Even after adjustment, hypo-responders showed greater progression in percent atheroma volume than responders.

<table>
<thead>
<tr>
<th>Table 1. Changes in Atheroma Burden From Baseline to Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td>Percent Atheroma Volume&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Remodeling Index, mm&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lumen Volume, mm&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Substantial Regression</td>
</tr>
<tr>
<td>Substantial Progression</td>
</tr>
</tbody>
</table>

<sup>a</sup> Adjusted for differences in clinical characteristics and baseline atheroma burden, type and dose of statin, and trial.
High Risk Patients with the Greatest Unmet Needs

- Statin-resistant patients
- Statin-intolerant patients
- Familial hypercholesterolemia (FH)
- Low HDL patients

Statin Intolerance

• An estimated 5–20% cannot tolerate statin treatment
• Statin intolerance (most commonly muscle pain, aching, and weakness) commonly leads to discontinuation
• Most statin-intolerant patients can be successfully re-challenged
  • Intolerance may be the result of perception or expectation
  • Muscle adverse events without significant elevation of creatine kinase levels are unlikely to be related to statin
• There is a subset of patients who are truly statin intolerant

77 year old woman 2 years S/P NSTEMI who complains of muscle aches

- 77 yo female
- very functional
- Normal BP; glucose; nonsmoker
- Suffered NSTEMI 2 years ago and begun on multiple medications, including a statin
- Has tried several statins at several doses over the past 2 years but she states “I ache all over”
Which of the following strategies is least likely to decrease her muscular side effects from statins?

1. Adding Coenzyme Q 10
2. Decreasing the statin dose
3. Switching to nighttime dosing
4. Switching to alternate day dosing
5. Substituting red yeast rice
# Statin Muscle Adverse Effects

<table>
<thead>
<tr>
<th>Muscle AE</th>
<th>Incidence above placebo (per 100,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myalgias</td>
<td>1,500 to 10,000</td>
</tr>
<tr>
<td>Myopathy (Sx + CK)</td>
<td>5</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>1.6</td>
</tr>
</tbody>
</table>

Adapted from Law M, Rudnicka AR. *Am J Cardiol.* 2006;97:52C-60C
# Factors That Increase the Risk of Statin-Induced Myopathy

## Patient Characteristics
- Increasing age
- Female sex
- Renal insufficiency
- Hepatic dysfunction
- Hypothyroidism
- Diet or Meds
- Polypharmacy

## Statin Properties
- High systemic exposure
- Increased dose
- High bioavailability
- Limited protein binding
- Potential for drug-drug interactions metabolized by CYP pathways (particularly CYP450 3A4)

Adapted from Rosenson RS. *Am J Med.* 2004;116:408-416
Management of Muscle Symptoms on Statin Therapy (con’t)

- If unexplained severe muscle symptoms or fatigue develop during statin therapy:
  - promptly discontinue the statin
  - address possibility of rhabdomyolysis with:
    - CK
    - Creatinine
    - urine analysis for myoglobinuria
Management of Muscle Symptoms on Statin Therapy (con’t)

If mild-to-moderate muscle symptoms develop during statin therapy:

- Discontinue the statin until the Sx are evaluated
- Evaluate the patient for other conditions* that might increase the risk for muscle symptoms
- If after 2 months without statin Rx, muscle Sx or elevated CK levels do not resolve completely, consider other causes of muscle symptoms

*Hypothyroidism, reduced renal or hepatic function, rheumatologic disorders such as polymyalgia rheumatica, steroid myopathy, Vitamin D deficiency or primary muscle diseases
77 year old woman 2 years S/P NSTEMI who complains of muscle aches

- Statin held until symptoms disappeared
- Re-challenged with very low dose rosuvastatin every other day
- Able to tolerate new statin regimen

NOTE: No outcome studies have evaluated this dosing scheme
Many patients labelled as statin intolerance can be re-challenged with a statin; however, there is a real subgroup of patients who are truly statin intolerant.
No significant past medical history

Family history: Mother has hypertension but is otherwise well. She has no siblings and never knew her father.

- Total cholesterol
  - HDL-C 489 mg/dL
  - LDL-C 39 mg/dL
  - Triglycerides 377 mg/dL
- Fasting Blood Sugar 367 mg/dL
- Creatinine 176 mg/dl
What is the most likely cause for her hypercholesterolemia?

1. Poor diet
2. Diabetes
3. Obesity
4. Hypothyroidism
5. Familial Hypercholesterolemia
High Risk Patients with the Greatest Unmet Needs

- Statin-resistant patients
- Statin-intolerant patients
- Familial hypercholesterolemia (FH)
- Low HDL patients

FH: Most Common Inherited Disorder

Relative rate

FH: Most Common Inherited Disorder

PCKD = polycystic kidney disease.

CLINICAL PEARL # 3

Heterozygous FH occurs in about 1:500 patients
Familial Hypercholesterolemia (FH)

- Heritable, autosomal dominant disorder
- Due to mutations that cause decreased clearance of LDL
  - Usually LDL receptor gene\(^1,2\)
  - Other mutations include Apo B and PCSK9 genes
- Clinical manifestations include\(^1\)
  - Severe hypercholesterolemia
  - CVD early in life Men: 42–46 yrs; Women: 50–52 yrs
- FH is underdiagnosed and undertreated
  - > 600,000 people in the US with FH
    - But only 10% diagnosed
- FH is difficult to treat
  - High potency statin is often not enough

CLINICAL PEARL # 4

Consider Familial Hypercholesterolemia whenever the LDL-C is $\geq 190$ mg / dL
FH: Why is it important?

Cumulative Probability of Clinical CAD

- Non-FH Women
- Non-FH Men
- FH Women
- FH Men

The Phenotype of FH May Reflect LDL-R, Apo B, or PCSK9 Mutations

- LDLR gene codes for the LDL Receptor, which clears LDL particles from the circulation by binding to surface Apo B
- PCSK9 induces degradation of LDLR
- FH may be caused by mutations in Apo B, LDL-R, or PCSK9

**Extracellular Fluid**

- LDL Particle
- Apo B (site where receptor binds to LDL particle)
- Cell membrane
- Cytosol
- PCSK9
- LDL receptor


44 year old woman with recent NSTEMI

No significant past medical history
Family history: Mother has hypertension but is otherwise well. She has no siblings and never knew her father.

Atorvastatin 80 mg po qd started
44 year old woman s/p NSTEMI

3 months later...Follow-up laboratory tests

- Total cholesterol
  - HDL-C 323 mg/dL
  - LDL-C 39 mg/dL
  - Triglycerides 238 mg/dL
- Fasting Blood Sugar 220 mg/dL
- Creatinine 136 mg/dl

What should we do?
According to the 2013 ACC-AHA Cholesterol guidelines, which of the following statements is true?

1. A non-statin agent must be added to her regimen
2. Advanced lipid testing should be performed
3. An LDL goal of < 70 mg/dL is optimal
4. An LDL goal of < 100 mg/dL is optimal
5. Her current treatment is consistent with these guidelines
ASCVD Statin Benefit Groups

Adults >20 years of age and a candidate for statin therapy

Clinical ASCVD and Age ≤75
  YES
  High-intensity statin (Moderate intensity if not a candidate for high-intensity) Grade A

LDL–C >190 mg/dL
  YES
  High-intensity statin (Moderate intensity if not a candidate for high-intensity) Grade B

Diabetes type 1 or 2 and age 40-75
  YES
  Moderate intensity statin Grade A
  High intensity statin Grade E, Expert

>7.5 % 10-year ASCVD risk and age 40 to 75
  YES
  Moderate- to high-intensity statin Grade A

Estimate 10-year ASCVD RISK

Measure risk factors every 4-6 years and recalculate 10-year ASCVD risk in those without ASCVD, diabetes, and with LDL-C <190 mg/dl
## Intensity of Statin Therapy

<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><strong>Atorvastatin (40†)-80 mg</strong>&lt;br&gt;<strong>Rosuvasatin 20 (40) mg</strong></td>
<td><strong>Atorvastatin 10 (20) mg</strong>&lt;br&gt;<strong>Rosuvastatin (5) 10 mg</strong>&lt;br&gt;<strong>Simvastatin 20-40 mg‡</strong>&lt;br&gt;<strong>Pravstatin 40 (80) mg</strong>&lt;br&gt;<strong>Lovastatin 40 mg</strong>&lt;br&gt;<strong>Fluvastatin XL 80 mg</strong>&lt;br&gt;<strong>Fluvastatin 40 mg bid</strong>&lt;br&gt;<strong>Pitavastatin 2-4 mg</strong></td>
<td><strong>Simvastatin 10 mg</strong>&lt;br&gt;<strong>Pravastatin 10-20 mg</strong>&lt;br&gt;<strong>Lovastatin 20 mg</strong>&lt;br&gt;<strong>Fluvastatin 20-40 mg</strong>&lt;br&gt;<strong>Pitavastatin 1 mg</strong></td>
</tr>
</tbody>
</table>

Drugs/doses highlighted in yellow have demonstrated reduction in major CVD events in clinical trials.
Insufficient Response to Statin Therapy

• Use the maximum tolerated intensity of statin
• Consider addition of a nonstatin cholesterol-lowering drug(s)
  • If a less-than-anticipated therapeutic response
  • Only if ASCVD risk-reduction benefits outweigh the potential for adverse effects in higher-risk persons:
    • Clinical ASCVD <75 years of age
    • Baseline LDL-C ≥190 mg/dL
    • Diabetes mellitus 40 to 75 years of age
• Nonstatin cholesterol-lowering drugs shown to reduce ASCVD events in RCTs are preferred

IMPROVE-IT Study Design

Patients < 10 days post ACS LDL < 125mg/dL
(or ≤ 100mg/dL if prior LLT)

N=18,144

ASA + Standard Medical Therapy

Simvastatin 40 mg

Eze/Simva 10/40 mg

Uptitrated to Simva 80 mg if LDL >79
(adapted per FDA label 2011)

Duration: Minimum 2 1/2 year follow-up (5250 events)

Primary Endpoint: CV Death, MI, Hospital Admission for UA, revascularization (> 30 days after randomization), or Stroke

Cannon CP AHJ 2008;156:826-32
Primary endpoint:
- CV death
- MI
- UA
- coronary revascularization
- Stroke
- moderate-severe bleeding

Presented by Dr. Christopher Cannon at AHA 2014

p = 0.016

Ezetimibe/simvastatin (n = 9,067)
Simvastatin (n = 9,077)
IMPROVE-IT LDL-C levels

Median 69 mg/dl

Median 54 mg/dl

LDL < 70 mg/dL

Presented by Dr. Christopher Cannon at AHA 2014
44 year old woman s/p NSTEMI

We decided to add ezetimibe

3 months later...Follow-up laboratory tests

- Total cholesterol 261 mg/dL
  - HDL-C 39 mg/dL
  - LDL-C 178 mg/dL
  - Triglycerides 220 mg/dL
- Fasting Blood Sugar 176 mg/dl
- Creatinine 0.9 mg/dl
Addition of non-statin cholesterol-lowering drug(s) may be considered if the ASCVD risk-reduction benefits outweigh the potential for adverse effects.
New drugs for treatment of hypercholesterolemia
PCSK9

- A secreted protein which targets the LDL receptor for degradation
- Up-regulated by statin therapy
- Gain of function mutations cause high LDL-C
- Loss of function mutations cause low LDL-C
- Inhibition lowers LDL-C levels
Inherited Syndromes of Extremes of LDL-C: Story of PCSK9

Gain of function mutations in PCSK9

Loss of function mutations in PCSK9

Frequency (%)

LDL-C

Helen Hobbs et al.
PCSK9 Loss Of Function Mutations Are Associated With Decreased Plasma LDL-C Concentrations

81% of PCSK9\textsuperscript{Y142X} and PCSK9\textsuperscript{C679X} subjects had mean plasma LDL-C below 50th percentile

Moderate mean plasma LDL-C lowering effect in PCSK9\textsuperscript{R46L} allele carriers

PCSK9 Regulates LDLR Turnover Through Increased Intracellular Degradation

PCSK9

LDLR (hepatic)

ARH

Endocytosis

Fusion

Vesicle

Fusion

Endosome

Fusion

Degradation

Lysosome

Secretion
Blocking PCSK9 Activity Inhibits Intracellular Degradation of LDLR
% LDL-C Change with Once Every 2 Week PCSK9 Inhibitor On Top of Statin-based Rx

ODYSSEY LONG TERM Trial
2341 Patients with LDL-C at least 70 mg/dl Despite Maximum Tolerated Statin W or W/O other Lipid-Lowering Drugs Randomized to Alirocumab or Placebo

Post Hoc Analysis:
Major Adverse CV Events
Alorocumab = 1.7%
Placebo = 3.3%
(HR, 0.52, p=0.02)

Alirocumab group had mostly increased risk of
- injection site reaction (5.9 vs 4.2%)
- Myalgias (5.4 vs 2.9%)
- Neurocognitive events (1.2 vs 0.5%)
- Ophthalmologic events (2.9 vs 1.9%)

-LFT’s and CPK no different between groups

• Figure 2. Robinson JG et al N Engl J Med 2015;372:1489-99
In a post-Hoc safety analysis, the rate of major adverse CV events* was 48% lower among alirocumab patients than among those receiving placebo during 80 weeks of f/up (nominal p=0.02).

*Primary end point: CHD death, nonfatal MI, fatal and nonfatal ischemic stroke, unstable angina requiring hospitalization.
OSLER 1 & 2 Studies
Long Term Extension Studies Use of Evolocumab Or Standard Therapy
(Standard therapy in some cases included statin or ezetimibe)

Adverse Event rates similar in both groups except for neuro-cognitive complaints which were more frequent with evolocumab

OSLER 1 & 2 Studies
Effect on CV Events
(Pre-specified Exploratory Analysis)

Hazard ratio, 0.47 (95% CI, 0.28–0.78)
P=0.003

Cumulative Incidence (%)

Days since Randomization

No. at Risk
Standard therapy 1489 1486 1481 1473 1467 1463 1458 1454 1447 1438 1428 1361 407
Evolocumab 2976 2970 2962 2949 2938 2930 2920 2910 2901 2885 2871 2778 843

PCSK9 Monoclonal Antibodies Have Been Studied in…

• Monotherapy
• Add on to Statin +/- Ezetimibe
• Statin Intolerance
• Familial Heterozygote Hypercholesterolemia
### PCSK9 Inhibitors Furthest along in Development

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Description</th>
<th>Clinical Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alirocumab</td>
<td>Fully human IgG1 mAb</td>
<td>3*</td>
</tr>
<tr>
<td>Evolocumab</td>
<td>Fully human IgG1 mAb</td>
<td>3*</td>
</tr>
<tr>
<td>Bococizumab</td>
<td>Humanized IgG1 mAb</td>
<td>3</td>
</tr>
</tbody>
</table>

* application for approval already submitted to FDA
Heterozygous Familial Hypercholesterolemia
Frequency: 1/500

USA: 600,000 patients

FINAL OPTION - LDL apheresis
↓ LDL 75-80% acutely (50% over 2-week average)

FDA APPROVAL (HELP, LIPOSORBER)

- LDL > 200 mg/dL (with CHD)
- LDL > 300 mg/dL (no CHD)
Future Updates to the Blood Cholesterol Guideline

- This is a comprehensive guideline for the evidence-based treatment of blood cholesterol to reduce ASCVD risk
- These guidelines represent a change from previous guidelines that aligns recommendations closely to the evidence
- For primary prevention, they are “patient-centered”
- Guidelines will change in the future as high-quality data will improve future cholesterol treatment guidelines

Percentage of the Population by Race/Ethnicity: 2000 and 2025

*Indicates non-Hispanic.
AA=African American.
Striking Differences in CVD Mortality Rates by Race/Ethnicity

<table>
<thead>
<tr>
<th>Race/Ethnicity</th>
<th>CHD</th>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Hispanic Black</td>
<td>186.8</td>
<td>81.6</td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td>182.8</td>
<td>60.3</td>
</tr>
<tr>
<td>Hispanic</td>
<td>124.2</td>
<td>40.0</td>
</tr>
<tr>
<td>Native American</td>
<td>112.7</td>
<td>39.2</td>
</tr>
<tr>
<td>Asian</td>
<td>100.1</td>
<td>54.6</td>
</tr>
</tbody>
</table>

Data are expressed as mortality per 100,000 population and are based on rates age-adjusted to the 2000 standard; they are from the National Center for Health Statistics (personal communication, August 2000).

In which racial-ethnic group is cardiovascular disease the leading cause of death?

1. Hispanic Americans
2. South Asians
3. African Americans
4. White Americans
5. All of the above
Leading Causes of Death by Race

White
- CVD: 36.2%
- Cancer: 23.1%

Black
- CVD: 33.6%
- Cancer: 21.6%

Hispanic
- CVD: 29.6%
- Cancer: 19.7%

Asian
- CVD: 34.8%
- Cancer: 26.4%

CLINICAL PEARL # 5

Cardiovascular disease is the leading cause of death in all racial/ethnic groups in the United States.
CHD Death Rates Among African Americans and Whites

US Adults ≥20 Years Cholesterol Checked, Aware, Receiving Cholesterol-Lowering Medication

<table>
<thead>
<tr>
<th></th>
<th>Checked, %</th>
<th>Aware, %</th>
<th>Treated, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>White</strong></td>
<td>72.4 (2.4)</td>
<td>36.3 (1.8)</td>
<td>12.1 (1.2)</td>
</tr>
<tr>
<td><strong>Black</strong></td>
<td>63.5 (2.7)</td>
<td>30.9 (2.1)</td>
<td>10.9 (1.2)</td>
</tr>
<tr>
<td><strong>Mexican-American</strong></td>
<td>53.1 (2.9)</td>
<td>23.3 (1.9)</td>
<td>6.9 (1.1)</td>
</tr>
</tbody>
</table>

Ford, E.S. et al Circulation 2003; 107: 2185-2189
Heart Disease & Stroke Mortality Disparities

- Black men & women much more likely to die of heart disease & stroke vs. whites
- CHD & stroke not only leading U.S. causes of death, but also account for largest proportion of inequality in life expectancy between whites and blacks
- Despite existence of low-cost, highly effective preventive treatment

Despite less than optimal treatment, identification of known CV risk increases chance of treatment for dyslipidemia.

Optimal levels rarely attained in African-American adults under treatment with prescribed medication.
Statin Therapy Background

• Few statin clinical trials involve non-whites

• Possible variability exists in statin drug response among various races, with slightly diminished response in blacks

• African-Americans under represented in statin efficacy and outcome clinical trials
CHD as Cause of Death in Asians

*CHD is the leading cause of death

Vietnamese
Korean
Chinese*
Japanese*
Samoan*
Filipino*
Guamanian*
Hawaiian*
Asian Indian*

Percent of Deaths

National Vital Statistics System, CDC, NCHS
South Asians and CAD

- Rapidly growing segment of US population
- Elevated CAD incidence in young adults
- High CAD risk vs. whites, with equivalent risk factors
  - higher prevalence insulin resistance, metabolic syndrome/DM
  - elevated CRP
  - lipoprotein (a) levels

Racial and Ethnic Groups

- Cardiovascular disease is the leading cause of death for African Americans, Latinos, Asian Americans, Pacific Islanders, and American Indians.

- African American women are at the highest risk for death from heart disease among all racial, ethnic, and gender groups.

Source: American Heart Association
Take Home Points

• Despite improvements in cardiovascular care, coronary heart disease (CHD) rates remain unacceptably high.
• Response to statins is variable and influenced by many factors including genetic factors.
• New therapies are emerging for treatment of dyslipidemia.
• Patient populations at highest CHD risk may potentially benefit greatly from such therapies.
• Cardiovascular disease is the leading cause of death for all races.
Post-test ARS Question 1

MR, a 61-year-old male with an LDL-C of 130 mg/dL and diabetes has an ASCVD risk of 6.6% based on the new risk-calculator. What therapy should MR be started on according to the ACC/AHA 2013 guidelines?

1. High-intensity statin
2. Moderate-intensity statin
3. Low-intensity statin
4. Non-statin therapy
5. None of the above
SJ, a 62 year old BF is hospitalized in the Coronary care unit following a non-ST segment MI and stent placement in a 95% right coronary lesion. Her admission lipids are LDL-C=90 mg/dl, HDL=35 mg/dL, triglycerides=160 mg/dl.
Post-test ARS Question 2

In addition to being placed on a statin, which of the following treatments has been shown to reduce her risk of cardiovascular events.

1. Niacin
2. Fenofibrate
3. Cholestyramine
4. Ezetimibe
5. None of the above
Post-test ARS Question 3

Which of the following is NOT one of the 4 statin benefit groups according to the 2013 ACC/AHA Cholesterol Guideline to Reduce Atherosclerotic CV Disease?

1. A patient with clinical ASCVD
2. A patient with an LDL-C > 190 mg/dL
3. A patient 56 years of age with diabetes and an LDL-C of 118 mg/dL
4. A patient 67 years of age without diabetes or ASCVD with an LDL-C of 125 mg/dL and an estimated 10-year ASCVD risk of 7.5% or greater.
5. A patient 28 years of age with an LDL-C of 145 mg/DL
Post-test ARS Question 4

Results to date with PCSK9 antibody use have demonstrated what effect?

1. Comparable lowering of LDL-C to high-intensity statins
2. Significant reductions of LDL-C levels on top of statin therapy
3. Regression of atherosclerotic disease as measured by carotid intimal medial thickness studies
4. Hepatic fibrosis at the phase 3 doses studied
5. None of the above
Post-test ARS Question 5

According to the 2013 ACC AHA Cholesterol guidelines, which of the following is recommended therapy for a 78 year old male who suffers an NSTEMI?

1. High intensity statin therapy
2. High intensity statin therapy plus Ezetimibe
3. Moderate Intensity statin therapy
4. Moderate Intensity statin therapy plus ezetimibe
5. Ezetimibe alone
Post-test ARS Question 6

On a scale of 1 to 5, please rate how confident you would be in treating Hypercholesterolemia in patients that are not achieving optimal goals or are refractory to statin therapy?

1. Not at all confident
2. Slightly confident
3. Moderately confident
4. Pretty much confident
5. Very confident
Post-test ARS Question 7

Which of the statements below describes your approach to treating Hypercholesterolemia?

1. I do not treat Hypercholesterolemia, nor do I plan to this year.
2. I did not treat Hypercholesterolemia, but as a result of attending this course I’m thinking of doing this now.
3. I do treat Hypercholesterolemia and this course helped me change my methods.
4. I do treat Hypercholesterolemia and this course confirmed that I don’t need to change my methods.