Novel Pharmacologic Advances for the Treatment of Hypercholesterolemia to Reduce LDL Levels in Patients Who are Responsive and Refractory to Statin Therapy

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- **Jan Basile, MD**
  - Consultant - Amgen, Arbor, Eli-Lilly, Forest Labs, Janssen, Lundbeck, Medtronic, Novartis
  - Grant/Research support - The National Heart, Lung, and Blood Institute (Sprint)
  - Speakers Bureau - Arbor, Janssen

- **Keith C. Ferdinand, MD, FACC, FAHA**
  - Consultant - Boehringer Ingelheim, Sanofi, Amgen, Eli Lilly
  - Speaker/Consultant - Astra Zeneca

- **Karol E. Watson, MD, PhD, FACC**
  - Clinical Trials Adjudication Committee – Merck and Company
  - Research grants – NHLBI and NIDDK

- **Elizabeth Ofili, MD, MPH, FACC**
  - Grant/Research support - National Institute of Health
  - Consultant/Advisory Board – Bristol-Myers Squibb, Novartis, Arbor, Eli-Lilly, Merck & Co., Janssen Research and Development

Learning Objectives

- Understand the concept of residual cardiovascular risk despite statin therapy
- Recognize patient populations who may need alternate or additional treatment in conjunction with statin therapy
- Define the role of novel therapies to lower LDL cholesterol
- Identify minority populations that would benefit from lipid lowering therapy
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

In randomized, controlled trials of statins vs. placebo, statins have consistently shown cardiovascular risk reduction of approximately:

1. 50%
2. 25%
3. 10%
4. Unsure

Pre-test ARS Question 3

Which of the following patients would be expected to respond less well to statins:

1. A patient with a PCSK9 gain of function mutation
2. A patient with a PCSK9 loss of function mutation
3. A patient with apo E2 genotype
4. Unsure
Pre-test ARS Question 4

*Which of the following classes of medications would NOT provide additional LDL-C lowering when added to statin therapy*

1. MTP inhibitors
2. PCSK9 inhibitors
3. Apo B antisense oligonucleotides
4. Thrombin inhibitors
5. Unsure

Pre-test ARS Question 5

*Which of the following statements is TRUE*

1. Hispanic Americans have the highest coronary heart disease rates in the US
2. Heart disease is the leading cause of death for African American women, but breast cancer is the leading cause of death for White women
3. The leading cause of death among Asian Americans is cardiovascular disease
4. Hispanic Americans have higher coronary heart disease mortality rates than African Americans
Novel Pharmacologic Advances for the Treatment of Hypercholesterolemia to Reduce LDL Levels in Patients Who Are Responsive and Refractory to Statin Therapy

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


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

<table>
<thead>
<tr>
<th>Year</th>
<th>Goal:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988 ATP I</td>
<td>&lt;150 mg/dL</td>
</tr>
<tr>
<td>1993 ATP II</td>
<td>&lt;100 mg/dL</td>
</tr>
<tr>
<td>2001 ATP III</td>
<td>&lt;100 mg/dL</td>
</tr>
<tr>
<td>2004 ATP III Update</td>
<td>&lt;100 mg/dL</td>
</tr>
<tr>
<td>2006 2nd AHA/ACC</td>
<td>Very-high-risk pts: &lt;70 mg/dL</td>
</tr>
<tr>
<td>2010 ADA</td>
<td>Overt CVD: &lt;70 mg/dL</td>
</tr>
</tbody>
</table>

Definition of high-risk or highest-risk patients:
- ATP I: definite CHD or 2 other CHD risk factors
- ATP II: prior CHD or other atherosclerotic disease
- ATP III and the 2004 update: CHD or CHD risk equivalents
- Very-high-risk pts: multiple major risk factors (especially diabetes), severe and poorly controlled risk factors (eg, cigarette smoking), multiple components of the metabolic syndrome (especially TG ≥ 200 mg/dL + non-HDL-C ≥ 130 mg/dL with HDL-C < 40 mg/dL), and recent acute coronary syndromes.

**Novel Pharmacologic Advances for the Treatment of Hypercholesterolemia to Reduce LDL Levels in Patients Who Are Responsive and Refractory to Statin Therapy**

- 92% of patients with AMI have LDL < 160 mg/dL
- 77% of patients with AMI have LDL < 130 mg/dL
- 49% of patients with AMI have LDL < 100 mg/dL

**LDL Level and Risk of Coronary Events**

Log-Linear Relationship Between LDL-C Levels and Relative Risk for CHD


**Statin Randomized Clinical Trials: Reduction in Major Coronary Events**

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>ALDL Reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF/TexCAPS</td>
<td>6605</td>
<td>-27%</td>
</tr>
<tr>
<td>WOS</td>
<td>6595</td>
<td>-26%</td>
</tr>
<tr>
<td>ASCOT</td>
<td>10305</td>
<td>-26%</td>
</tr>
<tr>
<td>HP8</td>
<td>20,536</td>
<td>-29%</td>
</tr>
<tr>
<td>CARE</td>
<td>4159</td>
<td>-26%</td>
</tr>
</tbody>
</table>

Reduction (%): 
- Primary: -38*, -31*, -36*, -27*, -38* 
- High Risk: -38* 
- Secondary: -25*, -25*

*P<0.001; †P=0.0005; ‡P<0.0001; §P=0.002.

Novel Pharmacologic Advances for the Treatment of Hypercholesterolemia to Reduce LDL Levels in Patients Who Are Responsive and Refractory to Statin Therapy

2013 ACC/AHA Expert Panel
Recommendation 2:
Use Statins in these 4 Groups
- Clinical ASCVD (Atherosclerotic cardiovascular disease)*
- LDL-C $\geq 190$ mg/dL, Age $\geq 21$ years
- Primary prevention – Diabetes: Age 40-75 years, LDL-C 70-189 mg/dL
- Primary prevention - No Diabetes**: $\geq 7.5\%$ 10-year ASCVD risk***, Age 40-75 years, LDL-C 70-189 mg/dL

* Acute Coronary Syndrome, Hx of MI, stable or unstable angina, coronary or other arterial vascularization, stroke, TIA, or atherosclerotic PAD
** Requires risk discussion with clinician before use of statin therapy
*** Statin therapy ay be considered if risk decision is uncertain after use of ASCVD risk calculator


Effects on MAJOR VASCULAR EVENTS

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Events (%)</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>$\downarrow$</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>$\downarrow$</td>
<td>0·81 (0·75 – 0·87)</td>
</tr>
<tr>
<td>Any major coronary event</td>
<td>3337 (7·4)</td>
<td>4420 (9·8)</td>
<td>$\downarrow$</td>
<td>0·77 (0·74 – 0·80)</td>
</tr>
<tr>
<td>CABG</td>
<td>713 (3·3)</td>
<td>1006 (4·7)</td>
<td>$\downarrow$</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>$\downarrow$</td>
<td>0·79 (0·69 – 0·90)</td>
</tr>
<tr>
<td>Unspecified</td>
<td>1397 (3·1)</td>
<td>1770 (3·9)</td>
<td>$\downarrow$</td>
<td>0·76 (0·69 – 0·84)</td>
</tr>
<tr>
<td>Any coronary revascularisation</td>
<td>2620 (5·8)</td>
<td>3434 (7·6)</td>
<td>$\downarrow$</td>
<td>0·76 (0·73 – 0·80)</td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>105 (0·2)</td>
<td>99 (0·2)</td>
<td>$\downarrow$</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>$\downarrow$</td>
<td>0·81 (0·74 – 0·89)</td>
</tr>
<tr>
<td>Any stroke</td>
<td>1340 (3·0)</td>
<td>1617 (3·7)</td>
<td>$\downarrow$</td>
<td>0·83 (0·78 – 0·88)</td>
</tr>
<tr>
<td>Any major vascular event</td>
<td>6354 (14·1)</td>
<td>7994 (17·8)</td>
<td>$\downarrow$</td>
<td>0·79 (0·77 – 0·81)</td>
</tr>
</tbody>
</table>

CTT. Lancet 2008 371: 117-125
Novel Pharmacologic Advances for the Treatment of Hypercholesterolemia to Reduce LDL Levels in Patients Who Are Responsive and Refractory to Statin Therapy

Meta-Analysis: 90,056 Individuals in 14 Randomized Clinical Trials of Statins
423,000 Patient Years of Follow-up

Per a 39 mg/dL (1 mmol) absolute reduction in LDL with Statin Rx

- 23% reduction in major cardiac events
- 20% reduction in CHD mortality
- 22% reduction in ischemic strokes
- Benefit entirely in proportion to LDL reduction
- No influence of baseline LDL on level of benefit
- No effect of sex, age, or other risk factors on benefit
- Similar relative risk reduction in all subgroups
- No increase in non-cardiovascular mortality

CTT Lancet 2005;366:1266-1278

2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

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Novel Pharmacologic Advances for the Treatment of Hypercholesterolemia to Reduce LDL Levels in Patients Who Are Responsive and Refractory to Statin Therapy

Residual CVD Risk in Statin Treated Patients

CHD Events Occur in Patients Treated with Statins

Patient Experiencing Major CHD Events, %

<table>
<thead>
<tr>
<th>N</th>
<th>Δ LDL</th>
<th>4S%</th>
<th>LIPID%</th>
<th>CARE%</th>
<th>HPS%</th>
<th>WOSCOPS%</th>
<th>AFCAPS/TexCAPS%</th>
</tr>
</thead>
<tbody>
<tr>
<td>4444</td>
<td>-35%</td>
<td>28.0</td>
<td>19.4</td>
<td>15.9</td>
<td>13.2</td>
<td>11.8</td>
<td>7.9</td>
</tr>
<tr>
<td>9014</td>
<td>-25%</td>
<td>12.3</td>
<td>10.2</td>
<td>8.7</td>
<td>15.5</td>
<td>10.9</td>
<td>6.8</td>
</tr>
<tr>
<td>4159</td>
<td>-28%</td>
<td>13.2</td>
<td>10.2</td>
<td>8.7</td>
<td>15.5</td>
<td>10.9</td>
<td>6.8</td>
</tr>
</tbody>
</table>

Novel Pharmacologic Advances for the Treatment of Hypercholesterolemia to Reduce LDL Levels in Patients Who Are Responsive and Refractory to Statin Therapy

**Residual CVD Risk is Particularly High in Statin Treated Patients with Diabetes**

Meta-Analysis of CHD Patients in 14 Statin Trials

- CVD Risk Higher Than Patients With No Diabetes on Placebo
- Control Treatment

**Residual Cardiovascular Risk in Major Statin Trials**

- Patients Experiencing Major Coronary Events, %
- ΔLDL

<table>
<thead>
<tr>
<th>ΔLDL</th>
<th>N</th>
<th>Secondary</th>
<th>High Risk</th>
<th>Primary</th>
</tr>
</thead>
<tbody>
<tr>
<td>-36%</td>
<td>4444</td>
<td>-25%</td>
<td>-29%</td>
<td>-26%</td>
</tr>
<tr>
<td>-25%</td>
<td>9014</td>
<td>-28%</td>
<td>-26%</td>
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</tr>
<tr>
<td>-29%</td>
<td>4159</td>
<td>-29%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


*Residual CVD Risk is Particularly High in Statin Treated Patients with Diabetes*


*Nonfatal MI, CHD death, stroke, or coronary revascularization
*Event rate per 1 mmol/L (39 mg/dL) reduction in LDL-C

Residual Cardiovascular Risk in Major Statin Trials

Even in well treated patients, on maximum statin dose, up to 75% of patients will still have another cardiovascular event. This is termed “residual risk”

Potential reasons for residual risk

- Non lipid factors driving risk
- Non LDL-C lipid particles driving risk
- Suboptimal LDL-C lowering with statins
  - Inherent limit to LDL-C reduction with statins
  - Possible statin intolerance
  - Inter-individual variability in statin response
Inter-individual variability in response to statins

Subjects participating in clinical trials of statin therapy, display impressive average reductions in LDL-C. An individual patient's response to statin therapy, however, can be very variable. The graph below shows dramatic interindividual variability in response to Atorvastatin 10 mg daily. This has also been observed with other statins.

CLINICAL PEARL # 2

Even though statins are robust LDL-C lowering drugs, there is significant inter-patient variability in statin response.
Genetic Factors Affect Statin responses

Serum PCSK9 levels distinguish individuals who do not respond as well to high-dose statin therapy

*Journal of Lipids* Volume 2014 (2014), Article ID 140723, 3 pages

Patients with the apoE2 allele have greater lipid reductions with statin treatment

*Human Genomics* 2004, 1:111-125

Statin Intolerance

- An estimated 5–20% cannot tolerate statin treatment
- Statin intolerance (most commonly muscle pain, aching, and weakness) commonly leads to discontinuation
- Intolerance may be the result of perception or expectation
- Most statin-intolerant patients can be successfully re-challenged
- There is a subset of patients who are truly statin intolerant

**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.

- Total cholesterol: 489 mg/dL
  - HDL-C: 39 mg/dL
  - LDL-C: 377 mg/dL
  - Triglycerides: 367 mg/dL
- Fasting Blood Sugar: 176 mg/dl
- Creatinine: 0.9 mg/dl

---

**CLINICAL PEARL # 3**

Consider Familial Hypercholesterolemia whenever the LDL-C is $\geq$ 190 mg/dL
Novel Pharmacologic Advances for the Treatment of Hypercholesterolemia to Reduce LDL Levels in Patients Who Are Responsive and Refractory to Statin Therapy

LDL-C Levels Vary With Genetic Variants in Cholesterol Metabolism

FHBL = familial hypobetalipoproteinemia; PCSK9 = proprotein convertase subtilisin/kexin type 9; LOF = loss of function; FCH = familial combined hyperlipidemia; FH = familial hypercholesterolemia


Familial Hypercholesterolemia (FH)

- Inheritable, autosomal dominant disorder
- Due to mutations that result in decreased clearance of LDL particles from plasma
  - Usually LDL receptor gene
  - Other mutations include Apo B and PCSK9 genes
- Clinical manifestations include
  - Severe hypercholesterolemia due to accumulation of plasma LDL
  - May be accompanied by cholesterol deposition in tendons and skin (xanthomas) and in the eyes
  - Evidence of CVD early in life

Novel Pharmacologic Advances for the Treatment of Hypercholesterolemia to Reduce LDL Levels in Patients Who Are Responsive and Refractory to Statin Therapy

**FH: Why is it important?**

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

**FH: Most Common Inherited Disorder**

Heterozygous FH is found in 1:500 patients

- 4x more common
- 5x more common

PCKD = polycystic kidney disease.

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

The 4 Statin Benefit Groups

- Clinical ASCVD*
  - LDL-C ≥190 mg/dL, Age ≥21 years
- Primary prevention – Diabetes: Age 40-75 years, LDL-C 70-189 mg/dL
- Primary prevention - No Diabetes†: ≥7.5%‡ 10-year ASCVD risk, Age 40-75 years, LDL-C 70-189 mg/dL

*Atherosclerotic cardiovascular disease
†Requires risk discussion between clinician and patient before statin initiation
‡Statin therapy may be considered if risk decision is uncertain after use of ASCVD risk calculator
Novel Pharmacologic Advances for the Treatment of Hypercholesterolemia to Reduce LDL Levels in Patients Who Are Responsive and Refractory to Statin Therapy

**New 2013 ACC/AHA Statin-Based Guideline to Reduce Heart-Attack Risk**


**4 Patient categories**

<table>
<thead>
<tr>
<th>Clinical ASCVD</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>75 or younger</td>
<td>High-intensity statin Daily dose lowers LDL by &gt;50%</td>
</tr>
<tr>
<td>Older than 75</td>
<td>Moderate-intensity statin Daily dose lowers LDL by 30% to 49%</td>
</tr>
<tr>
<td>With an LDL cholesterol level of &gt;190 mg/dL; &gt; 21 years old</td>
<td>High-intensity statin</td>
</tr>
<tr>
<td>With a 7.5% or more risk of heart attack in the next 10 years*</td>
<td></td>
</tr>
<tr>
<td>With type 1 or 2 diabetes between 40 and 75 years old w/o ASCVD and an LDL-C 70-189 mg/dL</td>
<td>Moderate-intensity statin</td>
</tr>
<tr>
<td>W/O ASCVD or AOMC; 40 to 75 years old w/o ASCVD and an LDL-C 70-189 mg/dL</td>
<td>Moderate-to-high intensity statin</td>
</tr>
</tbody>
</table>

*Risk determined by a new calculation that accounts for age, gender, race, Total and HDL-C, SBP, Rx for BP, smoking and Diabetes status

**High, Moderate, and Low-intensity Statin Therapy Used in Clinical Trials**

<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 &gt;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 approximately &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>Fluvastatin 80** mg</td>
<td>Fluvastatin 20**-40** mg</td>
</tr>
<tr>
<td></td>
<td>Fluvastatin 40 mg BID*</td>
<td>Pitavastatin 1** mg</td>
</tr>
<tr>
<td></td>
<td>Pitavastatin 2-4** mg</td>
<td></td>
</tr>
</tbody>
</table>

*Statins demonstrated reduction in major CVD events

**FDA approved doses not tested in clinical trials**

*Statins demonstrated reduction in major CVD events

**FDA approved doses not tested in clinical trials**

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### 2015—Recommendations for Statin Treatment In People with Diabetes

<table>
<thead>
<tr>
<th>Age</th>
<th>Risk factors</th>
<th>Recommended statin dose*</th>
<th>Monitoring w lipid panel</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 40 years</td>
<td>None</td>
<td>None</td>
<td>Annually or as needed to monitor adherence</td>
</tr>
<tr>
<td></td>
<td>CVD risk factor(s)**</td>
<td>Mod or High</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Overt CVD***</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>40–75 years</td>
<td>None</td>
<td>High</td>
<td>As needed to monitor adherence</td>
</tr>
<tr>
<td></td>
<td>CVD risk factors</td>
<td>Mod</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Overt CVD</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>&gt; 75 years</td>
<td>None</td>
<td>Mod</td>
<td>As needed to monitor adherence</td>
</tr>
<tr>
<td></td>
<td>CVD risk factors</td>
<td>Mod or High</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Overt CVD</td>
<td>High</td>
<td></td>
</tr>
</tbody>
</table>

* In addition to lifestyle therapy.
** CVD risk factors include LDL cholesterol >100 mg/dL (2.6 mmol/L), high blood pressure, smoking, and overweight and obesity.
*** Overt CVD includes those with previous cardiovascular events or acute coronary syndromes

Adapted from Table 8.1—Standards of Medical Care in Diabetes. Diabetes Care January 2015;38:S49-S57.

---

**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: 323 mg/dL
  - HDL-C: 39 mg/dL
  - LDL-C: 238 mg/dL
  - Triglycerides: 220 mg/dL
- Fasting Blood Sugar: 136 mg/dl
- Creatinine: 0.9 mg/dl

What should we do?

**CLINICAL PEARL # 4**

Addition of nonstatin cholesterol-lowering drug(s) may be considered if the ASCVD risk-reduction benefits outweigh the potential for adverse effects.
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**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

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
Novel Pharmacologic Advances for the Treatment of Hypercholesterolemia to Reduce LDL Levels in Patients Who Are Responsive and Refractory to Statin Therapy

**IMPROVE-IT**

Presented by Dr. Christopher Cannon at AHA 2014

<table>
<thead>
<tr>
<th>Primary endpoint:</th>
<th>p = 0.016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ezetimibe/simvastatin (n = 9,067)</td>
<td>32.7</td>
</tr>
<tr>
<td>Simvastatin (n = 9,077)</td>
<td>34.7</td>
</tr>
</tbody>
</table>

Cannon CP. IMPROVE IT Trial, AHA Scientific Sessions 2014; November 15-19, 2014, Chicago Il. Late breaking Clinical Trials 02.

**IMProved Reduction of Outcomes:**
**Vytorin Efficacy International Trial**

**IMPROVE-IT**

- Re-affirms the LDL hypothesis
- Lower LDL-C is Better (achieved mean LDL-C was 70 mg/dL vs 54 mg/dL at 1 year)
- Hs-CRP was 0.5 lower with combination Rx
- ITT [intention-to-treat] patients followed for 7 years all did better (pre-specified endpoint)
- All safety endpoints for cancer, myopathy, and liver side effects were met (not different from statin-alone Rx)
Effects of Drug Classes on Serum Lipids

<table>
<thead>
<tr>
<th>Drug class</th>
<th>LDL</th>
<th>HDL</th>
<th>TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resins</td>
<td>↓15-30%</td>
<td>↑3-5%</td>
<td>no Δ or ↑</td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>↓5-25%</td>
<td>↑15-35%</td>
<td>↓20-50%</td>
</tr>
<tr>
<td>Fibrates</td>
<td>↓5-20%</td>
<td>↑10-20%</td>
<td>↓20-50%</td>
</tr>
<tr>
<td>Statins</td>
<td>↓18-55%</td>
<td>↑5-15%</td>
<td>↓7-30%</td>
</tr>
<tr>
<td>Cholesterol Absorption Inhibitors</td>
<td>↓18-21%</td>
<td>↑~2%</td>
<td>~ ↓11%</td>
</tr>
</tbody>
</table>


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
New drugs for treatment of hypercholesterolemia

Novel Targets for Lipid Management

Drugs that block Lipoprotein Assembly

1. Apo B Antisense (Mipomersen)
   trade name KYNAMRO

2. MTP Inhibition (Lomitapide)
   trade name JUXTAPID
   Both drugs are only available under a REMS program
   (Risk Evaluation & Mitigation Strategies)

Investigational drugs that Increase Lipoprotein Clearance

1. PCSK9 Inhibitors (At least 8 in development)
Mipomersen, an apolipoprotein B synthesis inhibitor, lowers low-density lipoprotein cholesterol in high-risk statin-intolerant patients: a randomized, double-blind, placebo-controlled trial

Maartje E. Visser¹, Gilbert Wagener², Brenda F. Baker³, Richard S. Geary³, Joanne M. Donovan², Ulrich H.W. Beuers⁴, Aart J. Nederveen⁵, Joanne Verheij⁶, Mieke D. Trip¹, Dick C.G. Basart³, John J.P. Kastelein¹, and Erik S.G. Stroes⁷

Mechanism of Action
Antisense Oligonucleotide

DNA = deoxyribonucleic acid
mRNA = messenger ribonucleic acid.
Mipomersen Monotherapy: Dose Ranging Phase 2 Trials

ISIS 301012 Monotherapy
Dose-Dependent ApoB & LDL-C Reduction

Effect on Mipomersen on Apolipoprotein B-100

Mipomersen: Summary of Clinical Experience

• Mipomersen produced reductions in all apo B-containing atherogenic lipids when added to maximally tolerated lipid lowering therapy and diet
  – Average LDL-C reduction >100 mg/dL in severe FH populations
  – Increase or no change (+2 to +15%) in HDL
• Consistent across all patient populations studied including statin intolerant FH or non-FH
• Frequently observed on-treatment adverse events were mild to moderate responses at injection site and flu-like symptoms
• Overall safety and tolerability database suitable for treatment in the target patient population

Inhibition of Microsomal Triglyceride Transfer Protein (MTP)

• MTP is an important enzyme required for lipidation of Apo B and formation of VLDL in the liver and chylomicrons in the gut
• Blocking MTP reduces hepatic VLDL, LDL and Lp(a) production and intestinal chylomicron formation
Novel Pharmacologic Advances for the Treatment of Hypercholesterolemia to Reduce LDL Levels in Patients Who Are Responsive and Refractory to Statin Therapy

Change in Lipids Using Lomitapide with no Background Therapy

- Treatment with the MTP inhibitor lomitapide is highly efficacious in lowering LDL-C in HoFH in concomitant therapy
- Treatment with the MTP inhibitor lomitapide is generally well tolerated in HoFH in the presence of low fat diet and titration scheme
- Hepatic fat content at week 26 is increased as compared to baseline
- Hepatic fat content at week 56 and 78 is either stabilized or decreased as compared to week 26


Novel Pharmacologic Advances for the Treatment of Hypercholesterolemia to Reduce LDL Levels in Patients Who Are Responsive and Refractory to Statin Therapy

**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

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**Inherited Syndromes of Extremes of LDL-C: Story of PCSK9**

Novel Pharmacologic Advances for the Treatment of Hypercholesterolemia to Reduce LDL Levels in Patients Who Are Responsive and Refractory to Statin Therapy

**PCSK9 LOF Mutations Are Associated With Decreased Plasma LDL-C Concentrations**

81% of PCSK9<sup>Y142X</sup> and PCSK9<sup>C679X</sup> subjects had mean plasma LDL-C below 50th percentile

Moderate mean plasma LDL-C lowering effect in PCSK9<sup>R46L</sup> allele carriers


**PCSK9 Regulates LDLR Turnover Through Increased Intracellular Degradation**

PCSK9, LDLR, ARH, Fusion, Degradation, Vesicle, Endosome, Lysosome
Novel Pharmacologic Advances for the Treatment of Hypercholesterolemia to Reduce LDL Levels in Patients Who Are Responsive and Refractory to Statin Therapy

**Blocking PCSK9 Activity Inhibits Intracellular Degradation of LDLR**

![Diagram showing the inhibition of LDLR degradation](image1)

**% LDL-C Change with Twice Monthly PCSK9 inhibitor injection**

![Graph showing LDL-C change with PCSK9 inhibitor injection](image2)

Novel Pharmacologic Advances for the Treatment of Hypercholesterolemia to Reduce LDL Levels in Patients Who Are Responsive and Refractory to Statin Therapy

**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

![Graph showing LDL-C levels over time](Image)

**Post Hoc Analysis:**

**Major Adverse CV Events**
- Alirocumab = 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

**Primary Endpoint at 24 weeks % change in LDL-C**

- **Placebo**: 780, 794, 747, 746, 706, 694, 674, 659, 652
- **Alirocumab**: 1330, 1473, 1540, 1622, 1394, 1359, 1349, 1324, 1309

**Figure 2. Robinson JG et al. N Engl J Med 2015. DOI: 10.1056/NEJMoa1501031**

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**ODYSSEY Long-Term**

*Time to First Adjudicated Major CV Event*

<table>
<thead>
<tr>
<th>Achieved LDL-C over time</th>
<th>Baseline</th>
<th>24 weeks</th>
<th>52 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Placebo, mg/dL</strong></td>
<td>122.7</td>
<td>118.9 (+0.8%)</td>
<td>123.0 (+4.4%)</td>
</tr>
<tr>
<td><strong>Alirocumab, mg/dL</strong></td>
<td>121.9</td>
<td>48.3 (-61.0%)</td>
<td>53.1 (-56.8%)</td>
</tr>
<tr>
<td><strong>Difference, %</strong></td>
<td></td>
<td>-81.9</td>
<td>-61.3</td>
</tr>
</tbody>
</table>

**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 40 weeks of f/up (nominal p=0.02)**

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*Primary end point: CHD death, nonfatal MI, fatal and nonfatal ischemic stroke, unstable angina requiring hospitalization.*

Novel Pharmacologic Advances for the Treatment of Hypercholesterolemia to Reduce LDL Levels in Patients Who Are Responsive and Refractory to Statin Therapy

**OSLER 1 & 2 Studies**

Long Term Extension Studies Use of Evolocumab Or Standard Therapy

(Standard therapy in some cases included statin or ezetimibe)

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Baseline</th>
<th>Week 4</th>
<th>Week 12</th>
<th>Week 24</th>
<th>Week 36</th>
<th>Week 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard therapy</td>
<td>1489</td>
<td>1486</td>
<td>1481</td>
<td>1473</td>
<td>1467</td>
<td>1463</td>
</tr>
<tr>
<td>Evolocumab</td>
<td>2976</td>
<td>2970</td>
<td>2962</td>
<td>2949</td>
<td>2938</td>
<td>2930</td>
</tr>
</tbody>
</table>

- Absolute reduction (mg/dL)
  - Standard therapy: 60.4
  - Evolocumab: 68.3

- Percentage reduction
  - Standard therapy: 45.3
  - Evolocumab: 58.8

- P-value
  - Standard therapy: <0.001
  - Evolocumab: <0.001

Adverse Event rates similar in both groups except for neurocognitive 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-value: 0.003

Novel Pharmacologic Advances for the Treatment of Hypercholesterolemia to Reduce LDL Levels in Patients Who Are Responsive and Refractory to Statin Therapy

**PCSK9-Directed Therapies in Development**

<table>
<thead>
<tr>
<th>Company</th>
<th>Drug (Alternate Name)</th>
<th>Agent</th>
<th>Indication</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sanofi/Regeneron</td>
<td>SAR236553/REGN727</td>
<td>Human monoclonal antibody</td>
<td>Hypercholesterolemia</td>
<td>2</td>
</tr>
<tr>
<td>Amgen</td>
<td>AMG-145</td>
<td>Human monoclonal antibody</td>
<td>Hypercholesterolemia</td>
<td>2</td>
</tr>
<tr>
<td>Novartis</td>
<td>LGT-209</td>
<td>Monoclonal antibody</td>
<td>Hypercholesterolemia</td>
<td>2</td>
</tr>
<tr>
<td>Pfizer/Rinat</td>
<td>RN316 (PF-04950615)</td>
<td>Monoclonal antibody</td>
<td>Hypercholesterolemia</td>
<td>2</td>
</tr>
<tr>
<td>Genentech</td>
<td>MPSK3169A, RG7652</td>
<td>Monoclonal antibody</td>
<td>Hypercholesterolemia</td>
<td>2</td>
</tr>
<tr>
<td>Alnylam Pharmaceuticals</td>
<td>ALN-PCS502</td>
<td>siRNA oligonucleotide</td>
<td>Hypercholesterolemia</td>
<td>1</td>
</tr>
<tr>
<td>Adnexus Therapeutics/Bristol-Myers Squibb</td>
<td>BMS-962476</td>
<td>Fusion protein using Adnectin technology</td>
<td>Cardiovascular disease</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Idera Pharmaceuticals</td>
<td>TBD</td>
<td>Antisense oligonucleotide</td>
<td>Hypercholesterolemia</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Serometrix</td>
<td>SX-PCK9</td>
<td>Small peptide mimetic; LDLR antagonist</td>
<td>Hypercholesterolemia</td>
<td>Preclinical</td>
</tr>
<tr>
<td>Shifa Biomedical Corp.</td>
<td>TBD</td>
<td>Small molecule PCSK9 modulator</td>
<td>Metabolic disorders</td>
<td>Preclinical</td>
</tr>
</tbody>
</table>


**PCSK9 Monoclonal Antibodies Have Been Studied in…**

- **Monotherapy**
- **Add on to Statin +/- Ezetimibe**
- **Statin Intolerance**
- **Familial Heterozygote Hypercholesterolemia**
### Novel LDL-Lowering Approaches

<table>
<thead>
<tr>
<th></th>
<th>PCSK9-AB (Trials)</th>
<th>ASO-ApoB (Trials)</th>
<th>MTTP-inhibitor (Trials)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C Reduction</td>
<td>40-70%</td>
<td>25-38%</td>
<td>40-55%</td>
</tr>
<tr>
<td>Lp(a) Reduction</td>
<td>-1-15%</td>
<td>-20-30%</td>
<td>-1-19%</td>
</tr>
<tr>
<td>GI Side Effects</td>
<td>None</td>
<td>Mild</td>
<td>Moderate-to-severe</td>
</tr>
<tr>
<td>Transaminitis</td>
<td>None/little</td>
<td>Mild</td>
<td>Moderate-to-severe</td>
</tr>
<tr>
<td>Compliance</td>
<td>Good</td>
<td>80-90%</td>
<td>80-90%</td>
</tr>
<tr>
<td>Long Term Safety</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Quality of Life</td>
<td>Acceptable</td>
<td>Fatty liver</td>
<td>Fatty liver</td>
</tr>
</tbody>
</table>

**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.
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CHD in African Americans

CHD death rates per 100,000 persons among African Americans and Whites

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).

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**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.
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

Age-Adjusted Death Rates for Coronary Heart Disease, Stroke, and Lung & Breast Cancer for White and Black Females

United States: 2003*

<table>
<thead>
<tr>
<th>Condition</th>
<th>White Females</th>
<th>Black Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary Heart Disease</td>
<td>125.1</td>
<td>160.3</td>
</tr>
<tr>
<td>Stroke</td>
<td>50.5</td>
<td>69.1</td>
</tr>
<tr>
<td>Lung Cancer</td>
<td>42.2</td>
<td>39.3</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>24.6</td>
<td>33.8</td>
</tr>
</tbody>
</table>

Source: CDC/NCHS and NHLBI. * Preliminary
African Americans and CAD

• Highest overall CAD mortality in the US, particularly among young adults

• Major CAD risk factors include hypertension, left ventricular hypertrophy, diabetes mellitus, cigarette smoking, obesity, physical inactivity

• High mortality rates subsequent to hypertension and diabetes

• African American women are at particularly high risk

CAD = coronary artery disease. NCEP ATP III. Circulation 2002; 106:3143-3421

Racial/Ethnic Differences in Cardiovascular Disease

• Ethnic Variations

• Potential reasons for disparities
  – Biology of atherosclerosis
  – Risk factor burden
  – Suboptimal care

• Implications for therapy
  – Preventive medications have the potential to be even more beneficial in higher risk populations
Take Home Points

• Despite improvements in cardiovascular care, coronary heart disease (CHD) rates remain unacceptably high

• In patients treated with statins, residual cardiovascular risk remains

• 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
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Post-test ARS Question 1

*In randomized, controlled trials of statins vs. placebo, statins have consistently shown cardiovascular risk reduction of approximately:* 

1. 50%
2. 25%
3. 10%
4. Unsure

Post-test ARS Question 2

*Which of the following patients would be expected to respond less well to statins:* 

1. A patient with a PCSK9 gain of function mutation
2. A patient with a PCSK9 loss of function mutation
3. A patient with apo E2 genotype
4. Unsure
Novel Pharmacologic Advances for the Treatment of Hypercholesterolemia to Reduce LDL Levels in Patients Who Are Responsive and Refractory to Statin Therapy

Post-test ARS Question 3

Which of the following classes of medications would NOT provide additional LDL-C lowering when added to statin therapy

1. MTP inhibitors
2. PCSK9 inhibitors
3. Apo B antisense oligonucleotides
4. Thrombin inhibitors
5. Unsure

Post-test ARS Question 4

Which of the following statements is TRUE

1. Hispanic Americans have the highest coronary heart disease rates in the US
2. Heart disease is the leading cause of death for African American women, but breast cancer is the leading cause of death for White women
3. The leading cause of death among Asian Americans is cardiovascular disease
4. Hispanic Americans have higher coronary heart disease mortality rates than African Americans
Post-test ARS Question 5

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 6

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.