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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  Director, UCLA Barbra Streisand Women’s Heart Health Program
Novel Pharmacologic Advances for the Treatment of Hypercholesterolemia to Reduce LDL Levels in Patients Who Are Responsive and Refractory to Statin Therapy

Disclosures

• Jan Basile, MD
  – Consultant – Lilly, Medtronic
  – Speaker - Arbor

• 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

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
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 Level and Risk of Coronary Events

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

- 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

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

Statin Randomized Clinical Trials: Reduction in Major Coronary Events

<table>
<thead>
<tr>
<th>Trial</th>
<th>Primary</th>
<th>High Risk</th>
<th>Secondary</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>ALDL</td>
<td>ALDL</td>
<td>ALDL</td>
</tr>
<tr>
<td>AF/TexCAPS</td>
<td>6605</td>
<td>6605</td>
<td>6605</td>
</tr>
<tr>
<td>WOS</td>
<td>6593</td>
<td>6593</td>
<td>6593</td>
</tr>
<tr>
<td>ABCOT</td>
<td>10305</td>
<td>10305</td>
<td>10305</td>
</tr>
<tr>
<td>HP8</td>
<td>20,536</td>
<td>20,536</td>
<td>20,536</td>
</tr>
<tr>
<td>48</td>
<td>4444</td>
<td>4444</td>
<td>4444</td>
</tr>
<tr>
<td>LIPID</td>
<td>9014</td>
<td>9014</td>
<td>9014</td>
</tr>
<tr>
<td>CARE</td>
<td>4159</td>
<td>4159</td>
<td>4159</td>
</tr>
</tbody>
</table>

Reduction (%)

-38* -31* -36* -27* -36* -25* -25%

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


Effects on MAJOR VASCULAR EVENTS

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Treatment</th>
<th>Events (%)</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></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></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></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></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></td>
<td>0·79 (0·69 – 0·90)</td>
</tr>
<tr>
<td>Unspecified</td>
<td>1397 (3-3)</td>
<td>1770 (3-9)</td>
<td></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></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></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></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></td>
<td>0·83 (0·78 – 0·88)</td>
</tr>
<tr>
<td>Any stroke</td>
<td>6354 (14-1)</td>
<td>7994 (17-8)</td>
<td></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 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

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Statin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary: 7.9</td>
<td>15.5</td>
</tr>
<tr>
<td>High Risk: 10.9</td>
<td>6.8</td>
</tr>
<tr>
<td>Primary: 28.0</td>
<td>19.4</td>
</tr>
</tbody>
</table>

Patients Experiencing Major CHD Events, %

<table>
<thead>
<tr>
<th>N \ Δ LDL</th>
<th>4S¹</th>
<th>LIPID²</th>
<th>CARE³</th>
<th>HPS⁴</th>
<th>WOSCOPS⁵</th>
<th>AFCAPS/TexCAPS⁶</th>
</tr>
</thead>
<tbody>
<tr>
<td>4444</td>
<td>28.0</td>
<td>15.9</td>
<td>13.2</td>
<td>11.8</td>
<td>6.5</td>
<td>6.8</td>
</tr>
<tr>
<td>-35%</td>
<td>19.4</td>
<td>12.3</td>
<td>10.2</td>
<td>8.7</td>
<td>15.5</td>
<td>10.9</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

Residual Risk

Diabetes vs. No Diabetes


Residual Cardiovascular Risk in Major Statin Trials

Patients Experiencing Major Coronary Events, %

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

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*

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
Consider Familial Hypercholesterolemia whenever the LDL-C is $> 190$ mg/dL

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


FH: Why is it important?

![Cumulative Probability of Clinical CAD](image)

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

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

FH: Most Common Inherited Disorder

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>FH</td>
<td>2.0</td>
</tr>
<tr>
<td>Dominant otosclerosis</td>
<td>1.0</td>
</tr>
<tr>
<td>Adult PCKD</td>
<td>0.8</td>
</tr>
<tr>
<td>Sickle cell Disease</td>
<td>0.5</td>
</tr>
<tr>
<td>Multiple Exostoses</td>
<td>0.5</td>
</tr>
<tr>
<td>Huntington’s Disease</td>
<td>0.5</td>
</tr>
<tr>
<td>Fragile X</td>
<td>0.4</td>
</tr>
<tr>
<td>Neurofibromatosis</td>
<td>0.4</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Heterozygous FH is found in 1:500 patients. 4x more common for FH compared to other disorders. 5x more common for PCKD.

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

Extracellular Fluid

LDL Particle: Apo B (site where receptor binds to LDL particle)

Cell membrane

Cytosol

PCSK9


NACE – Emerging Challenges in Primary Care: 2014
Novel Pharmacologic Advances for the Treatment of Hypercholesterolemia to Reduce LDL Levels in Patients Who Are Responsive and Refractory to Statin Therapy

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


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

---

**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. **ApoB 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)

**VLDL Assembly as Target of Therapy**

[Image of liver with cholesterol, Apo B, VLDL, MTP, and triglyceride droplet]
**Mechanism of Action**

**Antisense Oligonucleotide**

- DNA
- mRNA
- Disease-Associated Protein

**Traditional Drug**

- RNaseH
- Degrades RNA
- No Translation

**No Disease-Associated Proteins Produced**


---

**Mipomersen Monotherapy: Dose Ranging Phase 2 Trials**

**ISIS 301012 Monotherapy**

**Dose-Dependent ApoB & LDL-C Reduction**

**ApoB**

**LDL-C**

**% Change at Primary Endpoint**

<table>
<thead>
<tr>
<th>Dose (mg/week)</th>
<th>ApoB</th>
<th>LDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>400</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

% Primary endpoint analysis was 14 days post last dose: Day 0-2 for 50-200 mg/week cohorts, Day 70 for 400 mg/week.

Inhibition of Microsomal Triglyceride Transfer Protein (MTP)

- MTP is an important enzyme required for lipidation of Apo B and formation of VLDL in liver and chylus in gut
- Blocking MTP reduces hepatic VLDL, LDL and Lp(a) production and intestinal chylomicron formation

Change in Lipids Using Lomitapide with no Background Therapy

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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

Frequency (%)

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

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

**Blocking PCSK9 Activity Inhibits Intracellular Degradation of LDLR**
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% LDL-C Change with twice Weekly PCSK9 inhibitor injection


**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-04900615)</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-PCS02</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 mimic; 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 Mipomersan (FDA: HoFH)</th>
<th>MTTP-Inhibitor Lomitapide (FDA: HoFH)</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 injection reactions</td>
<td>Fatty liver</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Flu-like symptoms</td>
<td></td>
</tr>
</tbody>
</table>

LDL-C Reduction: 40-70%, 25-38%, 40-55%
Lp(a) Reduction: -1-15%, -20-30%, -1-19%
Novel Pharmacologic Advances for the Treatment of Hypercholesterolemia to Reduce LDL Levels in Patients Who Are Responsive and Refractory to Statin Therapy

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

CHD in African Americans

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

*Indicates non-Hispanic.
AA=African American.

Source: NHANES 2000
Novel Pharmacologic Advances for the Treatment of Hypercholesterolemia to Reduce LDL Levels in Patients Who Are Responsive and Refractory to Statin Therapy

**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).


**Leading Causes of Death by Race**

- **White**
  - CHD: 23.1%
  - Stroke: 36.2%
  - Cancer: 40.7%

- **Black**
  - CHD: 21.6%
  - Stroke: 33.6%
  - Cancer: 44.8%

- **Hispanic**
  - CHD: 19.7%
  - Stroke: 29.6%
  - Cancer: 50.7%

- **Asian**
  - CHD: 26.4%
  - Stroke: 34.8%
  - Cancer: 38.8%

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

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

*United States: 2003*

- **Coronary Heart Disease**
  - White Females: 160.3
  - Black Females: 125.1

- **Stroke**
  - White Females: 50.5
  - Black Females: 69.1

- **Lung Cancer**
  - White Females: 42.2
  - Black Females: 39.3

- **Breast Cancer**
  - White Females: 24.6
  - Black Females: 33.8

Source: CDC/NCHS and NHLBI. * Preliminary

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**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
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

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.