PHARMACOLOGIC TREATMENT OF DRUG RESISTANT HYPERCHOLESTEROLEMIA
MAYO CLINIC PHARMACY GRAND ROUNDS

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Mayo Clinic Health System – Mankato
LEARNING OBJECTIVES

Describe guideline recommended treatment to reduce LDL-C

Evaluate landmark clinical trials of novel therapeutic agents indicated for treatment resistant hypercholesterolemia

Develop a pharmacologic care plan for a patient with treatment resistant hypercholesterolemia
ABBREVIATIONS

- **ABI**: Ankle Brachial Index
- **ACS**: Acute Coronary Syndrome
- **ALT**: Alanine Transaminase
- **apoB**: Apolipoprotein B
- **ASCVD**: Atherosclerotic Cardiovascular Disease
- **AST**: Aspartate Transaminase
- **CHD**: Coronary Heart Disease
- **CKD**: Chronic Kidney Disease
- **CPK**: Creatine Phosphokinase
- **CVD**: Cardiovascular Disease
- **DM**: Diabetes Mellitus
- **eGFR**: Estimated Glomerular Filtration Rate
- **FH**: Familial Hypercholesterolemia
- **HDL**: High Density Lipoprotein
- **HeFH**: Heterozygous Familial Hypercholesterolemia
- **HIV**: Human Immunodeficiency Virus
- **hsCRP**: High Sensitivity C-Reactive Protein
- **HTN**: Hypertension
- **LDL-C**: Low Density Lipoprotein Cholesterol
- **Lp(a)**: Lipoprotein (a)
- **MI**: Myocardial Infarction
- **PCI**: Percutaneous Coronary Intervention
- **PCSK9**: Proprotein Convertase Subtilisin/Kexin Type 9
- **RA**: Rheumatoid Arthritis
- **TC**: Total Cholesterol
- **TG**: Triglycerides
- **VLDL**: Very Low-Density Lipoprotein
- **VLDL-C**: Very Low-Density Lipoprotein Cholesterol
- **VLDL-C**: Very Low-Density Lipoprotein Cholesterol
EPIDEMIOLOGY

Elevated cholesterol increases the risk for heart disease, the leading cause of death and the 5th leading cause of stroke.

Nearly 12% of adults 20 years and older had a TC > 240 mg/dL between 2015 and 2018.

Average serum cholesterol is 191 mg/dL for adults 20 years and older.

17% had HDL below 40 mg/dL.


Adapted from Journal of Lipids, 2021, 1-5. https://doi.org/10.1155/2021/9883352
### CVD DUE TO HIGH CHOLESTEROL LEVELS

- Raised LDL-C
- Dysfunctional vascular endothelium becomes occupied
- Engulfment of LDL-C by macrophages and additional recruitment
- Foam cells form
- Secretion of additional inflammatory cytokines and oxidative stress
- Vascular smooth muscle expansion and plaque formation
- Arterial diameter decreased and plaque rupture
- Thrombotic and ischemic outcomes

Adapted from Journal of Lipids, 2021, 1–5
PATIENT CASE

MK is a 64-year-old male who presents to the clinic for an MTM visit and cholesterol management for his hypercholesterolemia.

• PMH:
  • Obesity
  • HTN
  • 20-pack year smoker
  • BMI 34 kg/m²

• Labs:
  • SCr 0.95 mg/dL
  • CrCl 89.6 mL/min
  • BP 139/82
  • All other labs WNL

• Family History
  • Premature ASCVD

• Lipid Panel
  • TC: 269 mg/dL
  • TG: 154 mg/dL
  • HDL: 35 mg/dL
  • LDL: 203 mg/dL

• Medications
  • Aspirin 81 mg daily
  • Lisinopril 20 mg daily
  • Metoprolol XL 50 mg daily
QUESTION #1

Which of the following is an appropriate guideline-recommended treatment for this patient’s hypercholesterolemia?

a) Atorvastatin 20 mg PO daily + lifestyle interventions
b) Simvastatin 40 mg PO daily
c) Ezetimibe 10 mg PO daily
d) Rosuvastatin 40 mg PO daily + lifestyle interventions
INITIAL TREATMENT OF
HYPERCHOLESTEROLEMIA
LIFESTYLE MANAGEMENT/NON-PHARMACOLOGIC
2018 AHA/ACC GUIDELINES ON MANAGEMENT OF BLOOD CHOLESTEROL

• Healthy diet
  • Vegetables
  • Fruits
  • Whole grains
  • Legumes
  • Healthy protein sources
    • Low fat dairy products
    • Low fat poultry
    • Nuts
  • Non-tropical vegetable oils
  • Limit intake of sweets and sugar sweetened beverages
  • Limit intake of red meat

• Exercise
  • 3-4 sessions/week
  • At least 40 minutes
  • Aerobic exercise
  • Involving moderate to vigorous intensity activity

• Metabolic Syndrome
  • Increase risk of ASCVD
  • DM
  • All-cause death
# Medication Overview

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism of Action</th>
<th>Adverse Effects</th>
<th>Monitoring</th>
<th>Place in Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td>Competitive inhibitors of HMG CoA reductase the rate limiting step in cholesterol synthesis</td>
<td>Hepatic injury, muscle related side effects, GI side effects, and headache</td>
<td>Creatinine kinase, liver enzymes (AST and ALT), total bilirubin, and alkaline phosphatase</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; Line</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>Inhibits absorption of cholesterol in the small intestine</td>
<td>Generally well tolerated, hepatic injury, and muscle related side effects</td>
<td>Signs and symptoms of myopathy, lipid panel, CPK, AST, and ALT</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; Line as Add On Therapy</td>
</tr>
<tr>
<td>Bile Acid Sequestrants</td>
<td>Decrease absorption and increase fecal loss of bile salt bound LDL</td>
<td>Often limited by GI side effects such as nausea, bloating, cramping and constipation</td>
<td>Lipid panel and TG</td>
<td>Add On Therapy</td>
</tr>
<tr>
<td>Fibrates</td>
<td>Activate peroxisome proliferator activated receptor alfa (PPARα), resulting in elimination of TG, LDL, and synthesis of apoAI, apoAIII, and HDL</td>
<td>Muscle and GI side effects</td>
<td>Signs and symptoms of myopathy, lipid panel, ALT, and AST</td>
<td>Add On Therapy</td>
</tr>
</tbody>
</table>
## PATIENT BENEFIT GROUPS

### 2018 AHA/ACC GUIDELINES ON MANAGEMENT OF BLOOD CHOLESTEROL

<table>
<thead>
<tr>
<th>Benefit Group</th>
<th>Patient Criteria</th>
<th>LDL Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe Hypercholesterolemia – LDL-C ≥ 190 mg/dL</td>
<td>20-75 years of age with LDL-C ≥ 190 mg/dL</td>
<td>Reduction of LDL-C by ≥ 50%</td>
</tr>
<tr>
<td>Adults with Diabetes Mellitus</td>
<td>40-75 years of age with DM and LDL-C between 70-189 mg/dL</td>
<td>Reduction of LDL-C by ≥ 50%</td>
</tr>
<tr>
<td>Primary Prevention</td>
<td>40-75 years of age with LDL-C levels 70-189 mg/dL</td>
<td>10-year ASCVD risk ≥ 20%: reduction of LDL-C by ≥ 50% OR 10-year ASCVD risk 7.5%-19.9% with risk enhancing factors: reduction of LDL-C of at least 30-49%</td>
</tr>
<tr>
<td>Secondary Prevention</td>
<td>Clinical ASCVD</td>
<td>Reduction of LDL-C by ≥ 50%</td>
</tr>
</tbody>
</table>
## STATIN INTENSITIES

<table>
<thead>
<tr>
<th>Lowering effect</th>
<th>High</th>
<th>Moderate 30%-49%</th>
<th>Low &lt;30%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin 40-80 mg Rosuvastatin 20-40 mg</td>
<td>Atorvastatin 10-20 mg Rosuvastatin 5-10 mg Simvastatin 20-40 mg Pravastatin 40-80 mg Lovastatin 40-80 mg Fluvastatin XL 80 mg Fluvastatin 40 mg BID Pitavastatin 1-4 mg</td>
<td>Simvastatin 10 mg Pravastatin 10-20 mg Lovastatin 20 mg Fluvastatin 20-40 mg</td>
<td></td>
</tr>
</tbody>
</table>
DEFINING ASCVD RISK

- 10-year ASCVD risk
  - Age 40-79 or lifetime risk for age 20-59
- Low Risk: <5%
- Borderline Risk: 5%-7.4%
- Intermediate Risk: 7.5%-19.9%
- High Risk: ≥20%

- American College of Cardiology
  - Website to calculate risk
  - Phone app

<table>
<thead>
<tr>
<th>Clinical ASCVD</th>
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</thead>
<tbody>
<tr>
<td>Acute Coronary Syndrome (ACS)</td>
</tr>
<tr>
<td>History of MI</td>
</tr>
<tr>
<td>Stable or Unstable Angina or</td>
</tr>
<tr>
<td>Coronary Other Arterial</td>
</tr>
<tr>
<td>Revascularization</td>
</tr>
<tr>
<td>Stroke</td>
</tr>
<tr>
<td>Transient Ischemic Attack (TIA)</td>
</tr>
<tr>
<td>Peripheral Arterial Disease</td>
</tr>
<tr>
<td>(PAD) Including Aortic Aneurysm</td>
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</tbody>
</table>

SEVERE HYPERCHOLESTEROLEMIA
2018 AHA/ACC GUIDELINES ON MANAGEMENT OF BLOOD CHOLESTEROL

**LDL-C ≥ 190 mg/dL**

- **Goal**: Reduction of LDL-C by ≥ 50%
- Maximum tolerated statin
- Not at goal and LDL-C remains ≥ 100 mg/dL
  - Add on ezetimibe
- Not at goal and with fasting TG 300 mg/dL or lower on statin and ezetimibe
  - Addition of a bile acid sequestrant may be considered
- Heterozygous FH and LDL-C remains ≥ 100 mg/dL on statin and ezetimibe
  - Add on PCSK9 inhibitor
- LDL-C of 220 mg/dL or > and on statin and ezetimibe
  - Add on PCSK9 inhibitor

*Circulation. 2019;139:e1082–e1143*
**Diabetes Mellitus**

**Goal:** Reduction of LDL-C by ≥ 50%
- DM regardless of ASCVD risk
  - Moderate intensity statin
- DM with LDL-C between 70-189 mg/dL
  - Assess 10-year risk of first ASCVD event
- Multiple risk factors
  - High intensity statin
- 10-year ASCVD risk of 20% or > and on statin
  - Add on ezetimibe
- Adults 20-39 years old with risk enhancers
  - May be reasonable to initiate statin

**Diabetes Specific Risk Enhancers**
- ≥ 10 years DMT2 or ≥ 20 years DMT1
- Albuminuria ≥ 30 mcg of albumin/mg creatinine
- eGFR <60 mL/min/1.73m²
- Retinopathy
- Neuropathy
- ABI <0.9
PRIMARY PREVENTION
2018 AHA/ACC GUIDELINES ON MANAGEMENT OF BLOOD CHOLESTEROL

• Goals:
  • ASCVD risk ≥ 7.5% - <20% (intermediate): reduce LDL-C by 30-49%
  • ASCVD risk ≥ 20% (high risk): reduce LDL-C by ≥ 50%

- Low risk – ASCVD risk <5%
  • Lifestyle interventions
- Intermediate risk + risk enhancers
  • Moderate intensity statin
- High risk
  • High intensity statin

40-75 years of age with LDL-C level of 70 – 189 mg/dL without DM

<table>
<thead>
<tr>
<th>ASCVD Risk Enhancers</th>
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</thead>
<tbody>
<tr>
<td>Family history of premature ASCVD</td>
</tr>
<tr>
<td>Persistently elevated LDL-C ≥ 160 mg/dL</td>
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<tr>
<td>Chronic Kidney Disease</td>
</tr>
<tr>
<td>Metabolic Syndrome</td>
</tr>
<tr>
<td>Women specific conditions (preeclampsia or</td>
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<tr>
<td>premature menopause)</td>
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<tr>
<td>Inflammatory diseases (RA, psoriasis, HIV)</td>
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<tr>
<td>Ethnicity (ex: South Asian ancestry)</td>
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<tr>
<td>Persistently elevated TG ≥ 175 mg/dL</td>
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<tr>
<td>Hs-CRP ≥ 2 mg/dL</td>
</tr>
<tr>
<td>Lp(a) ≥ 50 mg/dL or &gt; 125 nmol/L</td>
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<tr>
<td>apoB ≥ 130 mg/dL</td>
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<tr>
<td>ABI &lt; 0.9</td>
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Circulation. 2019;139:e1082–e1143
FAMILIAL HYPERCHOLESTEROLEMIA

- FH: autosomal dominant condition
  - Heterozygous: 1 normal allele and 1 mutated allele
  - Homozygous: 2 mutated alleles

- Gene mutations:
  - LD-LR Mutation
    - Most predominant (88%)
    - Accumulation of LDL-C in blood
  - ApoB Dysfunction
    - Less binding, accumulation of LDL-C in the blood
  - PCSK9 Increased Function
    - No LDLR recycling, accumulation of LDL-C in the blood

Optimized statin, ezetimibe, PCSK9 inhibitor

SECONDARY PREVENTION
2018 AHA/ACC GUIDELINES ON MANAGEMENT OF BLOOD CHOLESTEROL

Clinical ASCVD

**Goal**: Reduction of LDL-C by ≥ 50%
- ASCVD not very high risk or very high risk ASCVD
- High intensity statin
  - Intolerable – moderate intensity statin
- Not at goal or LDL-C ≥ 70 mg/dL
  - Add on ezetimibe
  - Add on PCSK9 inhibitor - if cost/benefit is favorable
- >75 years with ASCVD
  - Moderate or high intensity statin

### Clinical ASCVD

<table>
<thead>
<tr>
<th>ASCVD Category</th>
<th>Treatment Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Coronary Syndrome (ACS)</td>
<td>High intensity statin</td>
</tr>
<tr>
<td>History of MI</td>
<td>Moderate intensity statin if intolerable</td>
</tr>
<tr>
<td>Stable or Unstable Angina or Coronary Other Arterial Revascularization</td>
<td>Add on ezetimibe</td>
</tr>
<tr>
<td>Stroke</td>
<td>Add on PCSK9 inhibitor - if cost/benefit is favorable</td>
</tr>
<tr>
<td>Transient Ischemic Attack (TIA)</td>
<td>Add on PCSK9 inhibitor - if cost/benefit is favorable</td>
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<tr>
<td>Peripheral Arterial Disease (PAD) Including Aortic Aneurysm</td>
<td>Add on PCSK9 inhibitor - if cost/benefit is favorable</td>
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*Circulation. 2019;139:e1082–e1143*
## SECONDARY PREVENTION

### 2018 AHA/ACC GUIDELINES ON MANAGEMENT OF BLOOD CHOLESTEROL

<table>
<thead>
<tr>
<th>High-Risk Conditions</th>
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</thead>
<tbody>
<tr>
<td>≥ 64 years old</td>
</tr>
<tr>
<td>Heterozygous FH</td>
</tr>
<tr>
<td>History of prior coronary artery bypass surgery or PCI outside of the major ASCVD event</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>CKD (eGFR 15-59 mL/min/1.73m²)</td>
</tr>
<tr>
<td>Current Smoking</td>
</tr>
<tr>
<td>Persistantly elevated LDL-C ≥ 100 mg/dL despite maximally tolerated statin therapy and ezetimibe</td>
</tr>
<tr>
<td>History of congestive HF</td>
</tr>
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<thead>
<tr>
<th>Major ASCVD Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent ACS within past 12 months</td>
</tr>
<tr>
<td>History of MI (other than recent ACS listed above)</td>
</tr>
<tr>
<td>History of ischemia stroke</td>
</tr>
<tr>
<td>Symptomatic PAD</td>
</tr>
</tbody>
</table>
SECONDARY PREVENTION

2022 ACC EXPERT CONSENSUS DECISION PATHWAY ON THE ROLE OF NONSTATIN THERAPIES

In what patient populations should newer non-statin therapies be considered?

In what situations should newer non-statin therapies be considered?

Which therapies should be considered and in what order to maximize patient benefit and preference?
SECONDARY PREVENTION
2022 ACC EXPERT CONSENSUS DECISION PATHWAY ON THE ROLE OF NONSTATIN THERAPIES

• Very high risk clinical ASCVD on statin therapy for secondary prevention

• New goal: reduction of LDL-C by ≥ 50% and LDL-C of <55 mg/dL on maximally tolerated statin
  • Increase to high intensity statin if not already on one
  • Still not at goal
    1. Consider ezetimibe and/or PCSK9 inhibitor (evolocumab or alirocumab)
      1. PCSK9 monoclonal antibodies are the initial non-statin agent in addition to other agents as needed for desired LDL-C reduction
    2. Consider inclisiran or bempedoic acid
TREATMENT RESISTANT HYPERCHOLESTEROLEMIA

• Additional therapy may be needed to further reduce LDL
  • In a retrospective analysis of 186,670 patients who had clinical ASCVD with LDL >70 mg/dL
    • 21% of those with ASCVD who increased statin therapy reached goal of LDL ≤ 70 mg/dL
    • 23% of those with ASCVD who added ezetimibe to statin regimen reached goal of LDL ≤ 70 mg/dL

Therapeutics and clinical risk management, 14, 2425–2435. https://doi.org/10.2147/TCRM.S180783
TREATMENT RESISTANT HYPERCHOLESTEROLEMIA
LANDMARK TRIALS
PCSK9 INHIBITORS AND INCLISIRAN
EVOLOCUMAB AND CLINICAL OUTCOMES IN PATIENTS WITH CARDIOVASCULAR DISEASE
SABATINE ET AL., 2017. (FOURIER TRIAL)

• **Study Design**
  - Randomized, multinational, double blind, placebo controlled
  - n = 27,564 patients

• **Patients**
  - 40-85 years old with ASCVD
  - LDL-C ≥ 70 mg/dL or non-HDL-C ≥ 100 mg/dL
  - Optimized lipid lowering regimen (median baseline LDL – 92 mg/dL)
  - 69.3% on high intensity statin
  - 30.4% on moderate intensity statin
  - 5.2% also taking ezetimibe
EVOLOCUMAB AND CLINICAL OUTCOMES IN PATIENTS WITH CARDIOVASCULAR DISEASE
SABATINE ET AL. 2017. (FOURIER TRIAL)

Interventions

- Evolocumab 140 mg SQ every 2 weeks or Evolocumab 420 mg SQ monthly (n = 13,784 patients)
- Placebo (n = 13,780 patients)

Outcomes (2.2 years)

- Primary: composite of CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization
- Secondary: composite of CV death, MI, or stroke
**EVOLOCUMAB AND CLINICAL OUTCOMES IN PATIENTS WITH CARDIOVASCULAR DISEASE**

SABATINE ET AL. 2017. (FOURIER TRIAL)

<table>
<thead>
<tr>
<th>LDL-C Outcomes</th>
<th>Evolocumab (n=13,784)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% reduction at 48 weeks</td>
<td>59% reduction (95% CI, 58-60)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Mean absolute reduction</td>
<td>56 mg/dL (95% CI, 55-57)</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

**LDL-C Reduced to**

<table>
<thead>
<tr>
<th>LDL-C Reduced to</th>
<th>Evolocumab (n=13,784)</th>
<th>Placebo (n=13,780)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤70 mg/dL</td>
<td>87%</td>
<td>18%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≤40 mg/dL</td>
<td>67%</td>
<td>0.5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≤25 mg/dL</td>
<td>42%</td>
<td>&lt;0.1%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*N Engl J Med. 2017;376(18):1713-1722*
EVOLOCUMAB AND CLINICAL OUTCOMES IN PATIENTS WITH CARDIOVASCULAR DISEASE
SABATINE ET AL. 2017. (FOURIER TRIAL)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Placebo (n=13,780)</th>
<th>Evolocumab (n=13,784)</th>
<th>HR (95% CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>1,344 (11.2%)</td>
<td>1,563 (9.8%)</td>
<td>0.85 (0.79-0.92)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Secondary</td>
<td>1,013 (7.4%)</td>
<td>816 (5.9%)</td>
<td>0.80 (0.73-0.88)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

QUESTION #2

• Based on the FOURIER trial, evolocumab 140 mg SQ every 2 weeks or evolocumab 420 mg SQ monthly was associated with a mean absolute reduction in LDL of approximately what percent?
  a) 30%
  b) 60%
  c) 40%
  d) 70%
ALIROCUMAB AND CARDIOVASCULAR OUTCOMES AFTER ACUTE CORONARY SYNDROME
SCHWARTZ ET AL., 2018. (ODYSSEY OUTCOMES)

• Study Design
  • Randomized, multicenter, double blind, placebo controlled
  • n = 18,924 patients

• Patients
  • 40 ≥ years old - hospitalized with acute coronary syndrome in prior 1-12 months
  • LDL ≥ 70 mg/dL, non-HDL ≥ 100 mg/dL or apoB ≥ 80 mg/dL
  • High intensity or maximally tolerated statin
  • 83.0% with MI
  • 6.8% with unstable angina
  • 88.8% receiving high intensity statin

ALIROCUMAB AND CARDIOVASCULAR OUTCOMES AFTER ACUTE CORONARY SYNDROME
SCHWARTZ ET AL., 2018. (ODYSSEY OUTCOMES)

Interventions
- Alirocumab 75 mg SQ every 2 weeks (n = 9,462)
- Placebo (n = 9,462)

Outcomes (2.8 years)
- Primary: composite of death from CHD, non-fatal MI, fatal or non-fatal ischemic stroke, or unstable angina requiring hospitalization

Outcomes (2.8 years)
- Secondary: any CHD event, major CHD event, any cardiovascular event, a composite of death from any cause, ischemia driven coronary revascularization procedure, and hospitalization for CHF
### ALIROCUMAB AND CARDIOVASCULAR OUTCOMES AFTER ACUTE CORONARY SYNDROME

**SCHWARTZ ET AL., 2018. (ODYSSEY OUTCOMES)**

<table>
<thead>
<tr>
<th>LDL-C Outcomes Intention to treat</th>
<th>Alirocumab (n= 9,462)</th>
<th>Placebo (n= 9,462)</th>
<th>Percent Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (mean)</td>
<td>92 mg/dL</td>
<td>92 mg/dL</td>
<td>0%</td>
</tr>
<tr>
<td>4 months</td>
<td>40 mg/dL</td>
<td>93 mg/dL</td>
<td>57%</td>
</tr>
<tr>
<td>12 months</td>
<td>48 mg/dL</td>
<td>96 mg/dL</td>
<td>50%</td>
</tr>
<tr>
<td>48 months</td>
<td>66 mg/dL</td>
<td>103 mg/dL</td>
<td>36%</td>
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ALIROCUMAB AND CARDIOVASCULAR OUTCOMES AFTER ACUTE CORONARY SYNDROME
SCHWARTZ ET AL., 2018. (ODYSSEY OUTCOMES)

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<th>Placebo (n= 9,462)</th>
<th>HR (95% CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>903 (9.5%)</td>
<td>1,052 (11.1%)</td>
<td>0.85 (0.78-0.93)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Alirocumab (n= 9,462)</th>
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<th>HR (95% CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any CHD event</td>
<td>1,199 (12.7%)</td>
<td>1,349 (14.3%)</td>
<td>0.88 (0.81-0.95)</td>
<td>0.001</td>
</tr>
<tr>
<td>Major CHD event</td>
<td>793 (8.4%)</td>
<td>899 (9.5%)</td>
<td>0.88 (0.80-0.96)</td>
<td>0.006</td>
</tr>
<tr>
<td>Any cardiovascular event</td>
<td>1,301 (13.7%)</td>
<td>1,474 (15.5%)</td>
<td>0.87 (0.81-0.94)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Composite of death from any cause, non-fatal MI, or non-fatal ischemic stroke</td>
<td>973 (10.3%)</td>
<td>1,126 (11.9%)</td>
<td>0.86 (0.79-0.93)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death from CHD</td>
<td>205 (2.2%)</td>
<td>222 (2.3%)</td>
<td>0.92 (0.76-1.11)</td>
<td>0.38</td>
</tr>
</tbody>
</table>

TWO PHASE 3 TRIALS OF INCLISIRAN IN PATIENTS WITH ELEVATED LDL CHOLESTEROL
RAY ET AL., 2020 (ORION-10)

• Study Design
  • Randomized, double blind, placebo controlled, phase 3 trial
  • n = 1,561 patients

• Patients
  • ASCVD
  • LDL ≥ 70 mg/dL at screening
  • Stable doses of lipid lowering therapies for 30 days before screening in 89.2%
  • 68% receiving high intensity statin
  • 9.9% using ezetimibe alone or in combination with statin
  • Baseline LDL-C of 104.7 mg/dL
TWO PHASE 3 TRIALS OF INCLISIRAN IN PATIENTS WITH ELEVATED LDL CHOLESTEROL
RAY ET AL., 2020 (ORION-10)

Interventions
- Inclisiran 284 mg SQ day 1, day 90, day 270, and day 450 (n= 781)
- Placebo (n= 780)

Outcomes (18 months)
- Primary: placebo corrected percentage change in LDL-C from baseline to day 510 and time adjusted percentage change in LDL-C from baseline after day 90 and up to day 540

Outcomes (18 months)
- Secondary: absolute change in LDL-C from baseline to day 510, time adjusted absolute change in LDL-C from baseline after day 90 and up to day 540 and the percent change from baseline to day 510 in levels of PCSK9, TC, apoB, and non-HDL-C

**TWO PHASE 3 TRIALS OF INCLISIRAN IN PATIENTS WITH ELEVATED LDL CHOLESTEROL**

RAY ET AL., 2020 (ORION-10)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Inclisiran (n= 781)</th>
<th>Placebo (n= 780)</th>
<th>Difference</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary – placebo corrected</td>
<td>-51.3%</td>
<td>1%</td>
<td>-52.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Primary – time corrected</td>
<td>-51.3%</td>
<td>2.5%</td>
<td>-53.8%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Secondary – absolute change</td>
<td>-56.2 mg/dL</td>
<td>-2.1 mg/dL</td>
<td>-54.1 mg/dL</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Secondary – time adjusted</td>
<td>-53.7 mg/dL</td>
<td>-0.4 mg/dL</td>
<td>-53.3 mg/dL</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Secondary – percent change serum PCSK9</td>
<td>-69.8%</td>
<td>13.5%</td>
<td>-83.3%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
TWO PHASE 3 TRIALS OF INCLISIRAN IN PATIENTS WITH ELEVATED LDL CHOLESTEROL
RAY ET AL., 2020 (ORION-11)

• **Study Design**
  • Randomized, double blind, placebo controlled, phase 3 trial
  • n = 1,617 patients

• **Patients**
  • ASCVD or an ASCVD risk equivalent
    • DMT2, FH, 10-yr risk or CV event ≥ 20%
    • LDL ≥ 100 mg/dL
  • LDL ≥ 70 mg/dL at screening
  • Stable doses of lipid lowering therapies for 30 days before screening in 94.7%
  • 203 patients (12.6%) in the risk equivalent category
    • 132 (65%) diabetes
    • 30 (14.8%) HeFH
    • 41 (20.2%) 10-yr risk or CV event ≥ 20%
  • 78.6% receiving high intensity statin
  • 7.1% using ezetimibe alone or in combination with statin
  • Baseline LDL-C of 105.5 mg/dL
TWO PHASE 3 TRIALS OF INCLISIRAN IN PATIENTS WITH ELEVATED LDL CHOLESTEROL
RAY ET AL., 2020 (ORION-11)

**Interventions**

- Inclisiran 284 mg SQ day 1, day 90, day 270, and day 450 (n= 810)
- Placebo (n= 807)

**Outcomes (18 months)**

- Primary: placebo corrected percentage change in LDL-C from baseline to day 510 and time adjusted percentage change in LDL-C from baseline after day 90 and up to day 540

**Outcomes (18 months)**

- Secondary: absolute change in LDL-C from baseline to day 510, the time adjusted absolute change in LDL-C from baseline after day 90 up to day 540 and the percent change from baseline to day 510 in levels of PCSK9, TC, apoB, and non-HDL-C

*N Engl J Med 2020; 382:1507-1519*
TWO PHASE 3 TRIALS OF INCLISIRAN IN PATIENTS WITH ELEVATED LDL CHOLESTEROL
RAY ET AL., 2020 (ORION-11)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Inclisiran (n= 810)</th>
<th>Placebo (n= 807)</th>
<th>Difference</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary – placebo corrected</td>
<td>-45.8%</td>
<td>4%</td>
<td>-49.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Primary – time corrected</td>
<td>-45.8%</td>
<td>3.4%</td>
<td>-49.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Secondary – absolute change</td>
<td>-50.9 mg/dL</td>
<td>1 mg/dL</td>
<td>-51.9 mg/dL</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Secondary – time adjusted absolute change</td>
<td>-48.6 mg/dL</td>
<td>0.3 mg/dL</td>
<td>-48.9 mg/dL</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Secondary – percent change serum PCSK9</td>
<td>-63.6%</td>
<td>15.6%</td>
<td>-79.3%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
MK came back to the clinic 12 weeks after being started on rosuvastatin. His lipid panel was still elevated, and ezetimibe 10 mg daily was added. MK presents back to the clinic today, 3 months later, for check up on his hypercholesterolemia. The patient’s lipids are still elevated as shown below. The patient expressed that he is willing to add additional medication to continue to lower his lipids but would like a medication with the least number of injections.

- **PMH:**
  - Obesity
  - HTN
  - MI 1 year ago
  - 20-pack year smoker
  - BMI 34 kg/m²

- **Labs:**
  - SCr 1.0 mg/dL
  - CrCl 88 mL/min
  - BP 133/81
  - All other labs WNL

- **Family History**
  - Premature ASCVD

- **Lipid Panel**
  - TC: 240 mg/dL
  - TG: 127 mg/dL
  - HDL: 41 mg/dL
  - LDL: 174 mg/dL

- **Medications**
  - Aspirin 81 mg PO daily
  - Lisinopril 20 mg PO daily
  - Metoprolol XL 50 mg PO daily
  - Rosuvastatin 40 mg PO daily
  - Ezetimibe 10 mg once PO daily
QUESTION #3

• Based on the patient case, which of the following would be the most appropriate option to add on to MK’s hypercholesterolemia regimen to lower LDL?
  a) Evolocumab 140 mg SQ every 2 weeks
  b) Alirocumab 75 mg SQ every 2 weeks
  c) Inclisiran 284 mg SQ initially, then again at 3 months, and then every 6 months thereafter
  d) Fenofibrate 54 mg PO daily
**PCSK9 INHIBITORS – EVOLOCUMAB**

**Mechanism of Action**
- IgG2 monoclonal antibody that inhibits the binding of proprotein convertase subtilisin kexin type 9 (PCSK9) to LDL receptor increasing the number of LDL receptors to clear LDL

**Dosing**
- 140 mg SQ every 2 weeks
- 420 mg SQ once a month
- 420 mg SQ every 2 weeks

**Adverse Effects**
- Injection site reactions, nasopharyngitis, upper respiratory tract infections, influenza, back pain, hypersensitivity reactions, and diabetes mellitus

**Monitoring**
- Lipid panel and hypersensitivity reactions

**Pricing (per mL)**
- 140 mg/mL: $311.89
- 420 mg/3.5 mL: $193.07

### Mechanism of Action

- IgG1 monoclonal antibody that inhibits the binding of proprotein convertase subtilisin kexin type 9 (PCSK9) to LDL receptor increasing the number of LDL receptors to clear LDL.

### Dosing

- 75 mg SQ every 2 weeks
- 150 mg SQ every 2 weeks
- 300 mg SQ every 4 weeks

### Adverse Effects

- Injection site reactions, nasopharyngitis, influenza, upper respiratory tract infections, diarrhea, bronchitis, and myalgia

### Monitoring

- Lipid panel and hypersensitivity reactions

### Pricing (per mL)

- 75 mg/mL: $270
- 150 mg/mL: $286.45

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**INCLISIRAN**

**Mechanism of Action**
- Double stranded small interfering RNA that in hepatocytes utilizes the RNA interference mechanism and directs catalytic breakdown of mRNA for PCSK9

**Dosing**
- 284 mg SQ initially, then again at 3 months, and then every 6 months
- Administered by a health care professional

**Adverse Effects**
- Injection site reactions, arthralgia, urinary tract infection, diarrhea, bronchitis, extremity pain, and dyspnea

**Monitoring**
- Lipid Panel

**Pricing (per mL)**
- 284 mg/1.5 mL: $2,600
TAKE AWAY CLINICAL PEARLS

- **Evolocumab**
  - PCSK9 inhibitor
  - 140 mg SQ every 2 weeks

- **Alirocumab**
  - PCSK9 inhibitor
  - 75 mg SQ every 2 weeks

- **Inclisiran**
  - siRNA agent
  - 284 mg SQ initially, at 3 months, and then every 6 months
TAKE AWAYS

• The ACC/AHA guidelines divide patients into four main patient management groups to control hypercholesterolemia
  • Severe hypercholesterolemia
  • Diabetes Mellitus
  • Primary Prevention
  • Secondary Prevention

• Statins are first line medications to reduce LDL
  • There may be situations where additional LDL lowering medications are necessary for drug resistant hypercholesterolemia

• Landmark clinical trials
  • FOURIER: PCSK9 inhibitor – evolocumab
  • ODYSSEY OUTCOMES: PCSK9 inhibitor – alirocumab
  • ORION-10 and ORION-11: siRNA antilipemic – inclisiran
QUESTIONS & DISCUSSION