The first step in assessing the need for lipid lowering therapy is to outline the underlying condition to be treated. The ‘Lipid Patient’ falls within one of five disorders: 1. Hypercholesterolemia (↑ LDL-C, >160 mg/dL); 2. Hypertriglyceridemia (↑ TG) with expected associated reductions in HDL-C, >150 or >200 mg/dL; 3. Combined hyperlipidemia (↑ LDL-C & ↑TG); 4. ↓ HDL-C, <40 or <50 mg/dL; and 5. ↑ Lipoprotein (a), >30 mg/dL. The first step is to evaluate the patient for acquired cause of dyslipidemia including lifestyle issues (diet, sedentary behavior, tobacco, alcohol), medications (steroids, diuretics, β-blockers, cis retinoic acid, protease inhibitors, etc.).

The next step is to turn to the 2013 ACC/AHA Cholesterol Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Disease (ASCVD) Risk in Adults1. Included in this Guideline is reference to the 2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk2. Whether or not the patient meets criteria for statin therapy a heart healthy lifestyle is indicated. When the LDL-C is felt to be insufficiently lowered on a statin, there are other LDL-C lowering drugs from which to choose. Based on the IMPROVE-IT trial, ezetimibe + simvastatin was successful at reducing ASCVD events with levels achieved of 53 vs. 69 mg/dL with simvastatin alone3. Other LDL-C lowering therapies include bile acid sequestrants (5-35% as tolerated), fenofibrate (up to 25% ↓ when TG are normal), niacin (0-25% ↓) and most recently the PCSK9 inhibitors, alirocumab and evolocumab, with reductions from 45-60%4. PCSK9 inhibitors are indicated as adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (FH) or clinical atherosclerotic cardiovascular disease who require additional lowering of LDL-C. Evolocumab alone has an indication for homozygous FH as does LDL apheresis, lomitapide and mipomersen.

Hypertriglyceridemia may be the most difficult lipid disorder to evaluate and treat. Clinical trials have been fewer, less well designed and most fibrate trials support interventions only after post hoc analyses in patients with fasting TG ≥200≤500 mg/dL before treatment. The VA-HIT study is the only exception wherein gemfibrozil vs. placebo was given to men only with established coronary heart disease and an HDL-C <40 mg/dL5. High dose omega-3 fatty acids are approved only for patients with fasting TG ≥500 mg/dL, but the JELIS Study does provide some hint of benefit when added to a low potency statin6. Studies are now existent to discern additional value of omega-3 fatty acids in patients with fasting TG ≥200≤500 mg/dL. Severe hypertriglyceridemia (TG >1000 mg/dL) requires extreme dietary fat restriction as initial therapy. At present, drug treatment of patients with low levels of HDL-C is not indicated, after multiple trials have failed7. The benefit of isolated reductions in lipoprotein (a) remains unproven but an anti-sense compound is in Phase 2 trials at present.

References:
“Lipids Beyond Statins”
63rd Annual Advanced ADA Postgraduate Course
San Francisco, March 5, 2016

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University of Colorado Anschutz Medical Campus
Director, Lipid Clinic UCH

Duality of Interests

- Consultant/Advisory Boards
  - ISIS Pharmaceuticals
  - Janssen
  - Regeneron/Sanofi

- Medical Education
  - Cardiometabolic Health Congress
  - Medscape
  - Medical Education Resources
  - VOX Media

The Generic Lipoprotein

Lipoprotein Classes

- Chylomicrons
- Remnants
- VLDL
- IDL
- LDL
- HDL1
- HDL2
- HDL3

Diameter (nm)
Density (g/ml)

The Lipid Patient
Five Groups

- ↑ LDL cholesterol
- ↑ TG (↓ HDL cholesterol)

- ↑ LDL cholesterol + ↑ TG
- ↓ HDL cholesterol
- ↑ Lipoprotein (a)
Assessing Acquired Causes of Dyslipidemia

- Lifestyle
  - Diet, inactivity, alcohol, tobacco
- Medications
  - Steroids, diuretics, β-blockers, PIs, cis-RA
- Insulin resistance, metabolic syndrome
- Thyroid disease
- Liver disease
- Kidney disease
  - Proteinuria
  - ↓ GFR

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

4 Statin Benefit Groups

1. Secondary Prevention
   - LDL-C ≥ 190 mg/dL

2. Diabetes
   - 40 to 75 yrs
   - LDL-C 70-189 mg/dl

3. LDL-C ≥ 190 mg/dL
   - Rx: Optimal benefit with high intensity fixed-dose statins → lower LDL-C ≥ 50%
   - Use moderate intensity if age >75 or can’t tolerate high intensity

4. Primary Prevention
   - 40 to 75 yrs
   - LDL-C 70-189 mg/dl
   - ASCVD Risk ≥ 7.5%
   - Rx: Moderate intensity or high intensity fixed dose statin

Statin Rx not automatic, requires clinician-patient discussion

Intensity of Statin Therapy

<table>
<thead>
<tr>
<th>Statin</th>
<th>Moderate-Intensity Therapy</th>
<th>Low-Intensity Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin 10-20 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosuvastatin 10-20 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pravastatin 40 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluvastatin 40 mg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Statin Rx not automatic, requires clinician-patient discussion

*Don’t forget the 6% rule!
Now, beyond statins!

Maintain an Overall Healthy Diet!

Nutrition Lifestyle Recommendations: Lipids and BP

- **Dietary patterns emphasis-based:**
  - DASH and Mediterranean-style eating plans
- Fruits, vegetables, and whole grains
- 30 – 35% fat intake
  - <5% saturated fats, no trans fats
- Low sodium (<2400 mg/day)
- Cut out processed or pre-prepared food
- Healthy eating for a lifetime

Reviewed studies were heterogeneous and lacked the methodologic rigor to draw any conclusions regarding the effects of dietary cholesterol on CVD risk. Carefully adjusted and well-conducted cohort studies would be useful to identify the relative effects of dietary cholesterol on CVD risk.
Physical Activity Guidelines: Lipids and BP

- Advise adults to engage in aerobic physical activity
  - 3 to 4 sessions a week
  - lasting on average 40 min per session
  - involving moderate-to-vigorous intensity physical activity.

IMPROVE-IT: Primary Endpoint — ITT
Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke

Positive Impact of LDL-C Lowering with Statins Extends to Non-Statin Agents

CHD Event Rates in Secondary Prevention and ACS Trials

But the need for additional cholesterol lowering remains for some patients!

Patient Populations with an Unmet Need for Additional LDL-C Lowering

- Genetic disorder
- High risk of early CHD
- HeFH prevalence 1:200 to 1:250
- Untreated LDL-C of 200-400 mg/dL

- Previous MI / stroke / CVD or multiple CV risk factors incl. T2DM
- Difficult to achieve LDL-C goals, despite current therapies

- 20% with CHD not at goal (<100 mg/dL)
- 59% at very high CV risk not at goal (<70 mg/dL)

- 79% with HeFH not at goal (<100 mg/dL)

- 10-15% on high-intensity statins show intolerance
- Many discontinue due to muscle pain and/or weakness

Nearly all patients who need considerable LDL-C reductions will not reach goal
Cell Biology of LDL and the LDL Receptor

PCSK9 is proproteinc substrate convertase subtilisin/kexin type 9 (PCSK9)

PCSK9-Mediated Degradation of the LDL Receptor

How Statins Affect PCSK9-Mediated Degradation of the LDL Receptor

How PCSK9 Monoclonal Antibodies Restore LDL Receptor Function

Effect of Human Mutations in PCSK9 on Plasma LDL-C

Efficacy and Safety of Evolocumab in Reducing Lipids and Cardiovascular Events:
OSLER-1 & OSLER-2

- This study examined the effect of evolocumab in patients with high CVD risk.
- 4465 patients who had completed 1 of 12 phase 2 or 3 studies ("parent trials") of evolocumab were randomly assigned in a 2:1 ratio to receive either evolocumab (140 mg every 2 weeks or 420 mg monthly) plus standard therapy or standard therapy.
- Primary outcome was the incidence of adverse events.
- The secondary endpoint was % change in the LDL-C.

Sabatine MS et al, NEJM 372:1500, 2015

OSLER-1 & OSLER-2: Cumulative Incidence of CVD Events

![Graph showing cumulative incidence of CVD events](image)

Sabatine MS et al, NEJM 372:1500, 2015

ODYSSEY ALTERNATIVE:
Efficacy and Safety of Alirocumab vs. Ezetimibe, in Patients with Statin Intolerance Defined by Placebo Run-in and Statin Rechallenge Arm

Patrick M. Moriarty, Paul D. Thompson, Christopher P. Cannon, John R. Guyton, Jean Bergeron, Franklin J. Zieve, Eric Bruckert, Terry A. Jacobson, Marie T. Baccara-Dinet, Jian Zhao, Yuning Du, Robert Poud, Daniel Gíl

1Department of Internal Medicine, Division of Clinical Pharmacology, University of Kansas Medical Center, Kansas City, KS, USA; 2Harvard Hospital, Hartford, CT, USA; 3Harvard Clinical Research Institute, Boston, MA, USA; 4Duke University Medical Center, Durham, NC, USA; 5Clinique des Maladies cardio-vasculaires et des Maladies des Quilles, Québec, Canada; 6McGill University Health Centre, Montreal, QC, Canada; 7University Hospital, Richmond, VA, USA; 8Hospital des Pitié-Salpêtrière, Paris, France; 9University of Miami, Miami, FL, USA; 10Sanofi, Tarrytown, NY, USA; 11Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA

ODYSSEY ALTERNATIVE Study Design

![Diagram of study design](image)

J. Clin Lipidol. 8:554, 2014

Alirocumab Significantly Reduced LDL-C from Baseline to Week 24 vs. Ezetimibe

![Graph showing % change from baseline to Week 24 in LDL-C](image)

% change from baseline to Week 24 in LDL-C

- ITT (primary endpoint)
  - Alirocumab: -41.5% (95% CI: -54.6 to -28.4, P<0.0001)
  - Ezetimibe: -25.2% (95% CI: -33.7 to -16.7, P=0.0001)

On-treatment (key secondary endpoint)

- Alirocumab: -45.5% (95% CI: -54.0 to -36.9, P<0.0001)
- Ezetimibe: -35.4% (95% CI: -44.0 to -26.8, P<0.0001)

13% of 108 patients who received at least one rechallenge after Week 12 had dose increases.

Sabatine MS et al, NEJM 372:1500, 2015

J. Clin Lipidol. 8:554, 2014

NEJM 372:1500, 2015

Sabatine MS et al, NEJM 372:1500, 2015
Fewer Skeletal Muscle AEs with Alirocumab than with Atorvastatin

Kaplan-Meier estimates for time to first skeletal muscle event†

Cox model analysis:
- HR ALI vs ATV = 0.61 (95% CI: 0.38 to 0.99), nominal P = 0.042
- HR ALI vs EZE = 0.71 (95% CI: 0.47 to 1.06), nominal P = 0.096

Ezetimibe
- HR ALI vs EZE = 0.71 (95% CI: 0.47 to 1.06), nominal P = 0.096

Evolocumab FDA Approved August 27, 2015

“Repatha (evolocumab) is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of low density lipoprotein cholesterol (LDL-C). Repatha is indicated as an adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) for the treatment of patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C.”

PCSK9 Phase 3 Trials for CVD Events Reduction (Statin Treated)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Drug</th>
<th>LDL-C Criterion</th>
<th>Sample Size</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOURIER</td>
<td>Evolocumab</td>
<td>≥ 70 mg/dL</td>
<td>27,500</td>
<td>Jan 2018</td>
</tr>
<tr>
<td>ODYSSEY Outcomes</td>
<td>Alirocumab</td>
<td>≥ 70 mg/dL</td>
<td>18,000</td>
<td>Jan 2018</td>
</tr>
<tr>
<td>SPIRE-1</td>
<td>Bococizumab</td>
<td>≥ 70 mg/dL</td>
<td>17,000</td>
<td>June 2018</td>
</tr>
<tr>
<td>SPIRE-2</td>
<td>Bococizumab</td>
<td>≥ 100 mg/dL</td>
<td>9,000</td>
<td>Jan 2018</td>
</tr>
</tbody>
</table>

There are two other relatively new FDA-approved drugs for ‘homozygous FH’ –

Lomitapide and mipomersen
**Comparison of Approved Aggressive Therapies for FH**

<table>
<thead>
<tr>
<th>Apheresis</th>
<th>Mipomersen</th>
<th>Lomitapide</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C Reduction</td>
<td>~70-80%</td>
<td>~25-38% (higher in women)</td>
</tr>
<tr>
<td>Lp(a) Reduction</td>
<td>~70-80%</td>
<td>~20-30%</td>
</tr>
<tr>
<td>Short Term Safety</td>
<td>Good</td>
<td>Hepatic Fat (5%)</td>
</tr>
<tr>
<td>Compliance</td>
<td>Good</td>
<td>90%</td>
</tr>
<tr>
<td>Long Term Safety</td>
<td>~40 yrs</td>
<td>Unknown</td>
</tr>
<tr>
<td>Availability</td>
<td>Limited</td>
<td>Yes</td>
</tr>
</tbody>
</table>
| Cost | +++ | +++ | ++++
| Cardiac Benefit | Yes | Unknown | Unknown |
| Quality of Life | Yes, for most | Unknown | Unknown |

**What about hypertriglyceridemia?**

**Range of Triglyceride Lowering with Drugs**

- Fibrates 20-45%
- Nicotinic acid 10-30%
- Omega-3 fatty acids 15-35%
- Statins 0-35%
  - Low end – minimal or no effect
  - High end – mod to high dose

**Hypertriglyceridemia - the Most Difficult Lipid Disorder to Evaluate and Treat**

- The genetic disorders are not monogenic.
  - Rare deficiencies - LPL, apo CII, GPIHDLBP1
- The acquired disorders are almost infinite.
- Is it the TG-rich particles that confer risk for ASCVD and/or the company they keep?
- The clinical trials with fibrates to ↓ TG have suffered:
  - design
  - number of trials
  - results are hypothesis-generating at best

**VLDL Defined by Apolipoprotein Content**

![VLDL Diagram]

**Antisense Inhibition of Apolipoprotein C-III in Patients with Hypertriglyceridemia**

**June 18, 2014**
Fibrate Monotherapy Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year Reported</th>
<th>Drug</th>
<th>LDL Risk Reduction (primary endpoint)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary Drug Project (CDP)</td>
<td>1975</td>
<td>Clofibrate</td>
<td>9% (NS)</td>
</tr>
<tr>
<td>World Health Organization</td>
<td>1978</td>
<td>Clofibrate</td>
<td>20% (p&lt;0.05)</td>
</tr>
<tr>
<td>Helsinki Heart Study (HHS)</td>
<td>1987</td>
<td>Gemfibrozil</td>
<td>34% (p&lt;0.02)</td>
</tr>
<tr>
<td>VA-HDL Intervention Trial (VA-HIT)</td>
<td>1999</td>
<td>Gemfibrozil</td>
<td>22% (p&lt;0.001)</td>
</tr>
<tr>
<td>Befoxibrate Infarction Prevention (BIP)</td>
<td>2000</td>
<td>Befoxibrate</td>
<td>7.3% (p&lt;0.26)</td>
</tr>
<tr>
<td>Fenofibrate Diabetes (FIDIO)</td>
<td>2005</td>
<td>Fenofibrate</td>
<td>11% (p&lt;0.15)</td>
</tr>
</tbody>
</table>

So Let’s See What We Can Conclude Here

- Fibrates do not reduce CHD events in high risk patient groups
- The impact of hypertriglyceridemia on CHD outcomes remains unclear
  - Post-hoc analysis indicates that high risk patients with TG>200 mg/dl may be more likely to benefit.
  - The amount of TG lowering may not predict benefit, but VLDL-C may be better.

Fibrates, TG Lowering and MACE

Fibrates do not reduce CHD events in high risk patient groups
- The impact of hypertriglyceridemia on CHD outcomes remains unclear
  - Post-hoc analysis indicates that high risk patients with TG>200 mg/dl may be more likely to benefit.
  - The amount of TG lowering may not predict benefit, but VLDL-C may be better.
- Do you treat patients with fibrates who are not hypertriglyceridemic?
- The optimal trial awaits us! – VAFIT?
JELIS Study: Major Coronary Events

Several CVD outcome trials using omega-3 fatty acids in patients with triglycerides of 200-500 mg/dL have been initiated: Strength (EPA + DHA) and REDUCE-IT (EPA)

Effects of Drugs on HDL-C Levels

- Niacin 15-35%
- Fibrates 5-15%
- Statins 5-10%
- Resins 5-10%
- Estrogens – p.o. 10-15%
- PCSK9 inhibitors 5-10%
- CETP inhibitors 25-60%
  - Torcetrapib - ↑ mortality; abandoned
  - Dalcetrapib (JTT-705): Phase 3 trial stopped
  - Anacetrapib (MK-0859): Phase 3 trial ongoing
  - Evacetrapib (Lilly): Phase 3 stopped
What about the HDL trials?

HDL and Atherosclerosis
- Anti-oxidant
- Anti-inflammatory
- Anti-thrombotic
  - ↑ prostacyclin
- Promotes vascular reactivity
  - ↑ NOS
- Decreases myeloproliferative cell development
- Reverse cholesterol transport

Definitive HDL Cholesterol Outcome Studies
- AIM-HIGH
  - Purpose: This study intended to examine the CVD risk reduction of participants with CHD and low HDL-C and high TGs who were taking extended release niacin plus statins or statins alone to determine the effect of these medications on inflammation in atherosclerotic plaques.
  - N = 3414 enrolled
  - LDL-C was targeted to low levels in both groups
  - On May 26, 2011 AIM-HIGH was stopped 18 months early!

AIM HIGH: Niacin + Statin Fails to Reduce CVD Events

Definitive HDL Cholesterol Outcome Studies
- HPS2-Thrive
  - Purpose - The primary aim is to assess the effects of raising HDL-C with extended release niacin/laropiprant vs. matching placebo on the risk of MI or coronary death, stroke, or the need for revascularization in people with a history of circulatory problems.
  - Trial stopped on Dec 20, 2012 because of futility

HPS2 Thrive and CVD Risk: Another Niacin Failure

The HPS2-THRIVE Collaborative Group, NEJM 371:203, 2014
HPS2 Thrive and CVD Risk: Niacin/Laropiprant Adverse Effects

- Gastrointestinal
- Musculoskeletal
- Skin-related
- Infection
- Bleeding
- New-onset T2DM
- In T2DM – ↑ glycemia

All p<0.001 vs. placebo

The evidence is now overwhelming that low levels of HDL-C do not cause CHD!

CETP Inhibitors Markedly Increase HDL-C Levels

Dal-OUTCOMES: Incidence of the Primary Efficacy End Point

Cholesterol Efflux Capacity Beyond HDL Cholesterol Levels in Coronary Artery Disease (CAD)
HDL Cholesterol Efflux Capacity and Incident CVD Events: Dallas Heart Study
(n = 2924 without CVD)

Rohatgi A et al, NEJM 371:2383, 2014

HDL Cholesterol Efflux Capacity and Incident ASCVD Events: Dallas Heart Study
(n = 2924 without CVD)

Rohatgi A et al, NEJM 371:2383, 2014

HDL Cholesterol Efflux Capacity and Incident CVD Events: Dallas Heart Study
(n = 2924 without CVD)

Rohatgi A et al, NEJM 371:2383, 2014

Lipoprotein (a) - a potential link between atherothrombosis and atherosclerosis?

- Present at very low to very high levels - (<0.1 → >250 mg/dL)
- Concentration is strongly influenced by hereditary

Antisense therapy targeting apolipoprotein(a): a randomised, double-blind, placebo-controlled phase 1 study

Lipid Rx and ↓ CVD Events: 2016

- Statins: Yes
- Ezetimibe: Yes
- Cholestyramine: Yes
- PCSK9 inhibitors: Likely
- Fibrates: ±
- Omega-3 fatty acids: ±
- Niacin: No
- CETP inhibitors: No, ?

Thank You!