Update to Lipid Management: Guidelines and Novel Drugs

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Objectives

- Discuss treatment goals recommended by the practice guidelines
- Classify patient populations that will require lipid management
- Review the pharmacology of recommended drugs
- Describe the pharmacology and indications for newly approved lipid lowering drugs
- Apply guideline recommendations to a patient case

Abbreviations

- Low-Density Lipoproteins (LDL)
- Very Low-Density Lipoproteins (VLDL)
- High-Density Lipoproteins (HDL)
- Triglycerides (TG)
- Total Cholesterol (TC)
- Atherosclerotic Cardiovascular Disease (ASCVD)
- Liver Function Tests (LFTs)
- Cardio Vascular Outcomes Trial (CVOT)
- Acute Coronary Syndromes (ACS)
The Guidelines

- 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular (ASCVD) Risk in Adults
- Blood Cholesterol Expert Panel
  - Focus was to treat blood cholesterol to reduce ASCVD risk
  - Data from randomized control trials (RCTs), and meta-analyses of RCTs
  - Addressed treatment of adults ≥21 y/o

What is ASCVD?

- Atherosclerotic Cardiovascular Disease
  - Coronary Heart Disease
  - Peripheral Artery Disease
  - Stroke
  - Acute Coronary Syndromes

Expert Panel Findings

- No evidence to support a reduction of ASCVD events using LDL or non-HDL levels as targets for treatment
- Extensive RCT data supporting the appropriate intensity of statin for reducing ASCVD risk
- Non-statin therapies (e.g. niacin) to lower non-HDL did not further reduce ASCVD outcomes
Treatment Goals

- Moving away from
  - Target to treat
  - Lowest is best

- Treat level of ASCVD risk
  - Using the maximum tolerated statin intensity

Classifying Patients

- Most likely to benefit from cholesterol treatment and 10-year ASCVD risk tool

- Statin benefitting patient groups:
  - Clinical ASCVD
  - Primary LDL-C elevations ≥190 mg/dL
  - 40-75 y/o with diabetes and LDL-C 70-189 mg/dL
  - 40-75 w/o clinical ASCVD or diabetes with LDL-C 70-189 mg/dL and an estimated 10-year ASCVD risk ≥7.5%

10-Year ASCVD Risk Calculator

- Old calculator: Framingham CHD risk score
  - Data from old trials
  - Does not include stroke as an outcome
  - Cohorts included mostly white men and women

- New calculator: Pooled Cohort Risk Assessment Equations (patients 40-75 y/o)
  - Based on pooled data from 5 large NIH-funded cohorts
  - White and black men and women
  - Includes stroke in the risk calculation
10-Year ASCVD Risk Calculator

- Can be accessed online through various web sites or through a mobile application

Where to begin?

ASCVD

LDL≥190

Diabetes

10-year risk

Statins as the mainstay drug therapy

Non-Statin Therapies

- Bile acid sequestrants, niacin, absorption inhibitors, PCSK9-inhibitors, MTP-inhibitors, and Apo-B synthesis inhibitors

- Preserved for patients
  - On high intensity statin and require additional reduction in LDL-C
  - Familial Hypercholesterolemia
Statins

- MOA: HMG-Coenzyme A Reductase Inhibitors

- Order of potency: "Peter, Rose, And Sam Love Pringle Flavors"
  - Pitavastatin, Rosuvastatin, Atorvastatin, Simvastatin, Lovastatin, Pravastatin, Fluvastatin

- Adverse Effects: myalgia, arthralgia, nausea, diarrhea, increase in LFTs, rhabdomyolysis, and diabetes

Statins

- High-Intensity: reduction in LDL-C by approximately ≥50%

- Moderate-Intensity: reduction in LDL-C by 30% to <50%

- Low-Intensity: Reduction in LDL-C by <30%
Statins

- High- and moderate-intensity statins reduce ASCVD events in high risk primary and all secondary prevention patients

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<th>Moderate</th>
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Lifestyle Modifications

- Emphasized in guideline as the foundation for ASCVD risk reduction
  - Adhering to a heart healthy diet that is low in sodium and fats
  - Regular exercise habits
  - Maintaining a healthy weight
  - Avoidance of all tobacco products

Initiating therapy

- Primary prophylaxis
  - High-intensity:
    - ≥21 y/o with LDL≥190
    - 40-75 y/o with Diabetes
    - 40-75 y/o and 10-year risk ≥7.5%
  - Moderate Intensity:
    - ASCVD risk 5% to <7.5%
    - If intolerant to high-intensity
  - Low Intensity:
    - If intolerant to moderate intensity
Initiating therapy

- Secondary prophylaxis
  - High-intensity: ≤75 y/o
  - Moderate-intensity: >75 y/o
    - If intolerant to high-intensity
  - Low-intensity:
    - If intolerant to moderate intensity

Initiating Therapy

- Patients at risk for statin adverse effects:
  - Multiple or serious comorbidities (e.g. impaired renal or hepatic function)
  - History of previous statin intolerance or muscle disorder
  - Elevations in ALT >3 times the ULN
  - Concomitant use of drugs affecting statin metabolism
  - Age >75 years
Initiating Therapy

- Monitoring:
  - Baseline LFTs on all patients and during statin therapy in patients with hepatic symptoms
  - Baseline CK only in patients with increased risk for muscle events and during statin therapy in patients experiencing muscle symptoms
  - New-onset diabetes mellitus

Familial Hypercholesterolemia

- Autosomal dominant genetic disorder of chromosome #19
  - Mutated LDL receptor (95% of FH cases)
  - Mutated apolipoprotein B (Apo B-100)
  - Mutated proprotein convertase subtilisin/kexin type 9 (PCSK9) (<1% FH)
- Significant elevations in LDL and TC
- High risk for ASCVD event early in life
- 620,000 cases in the U.S. (Underdiagnosed and undertreated)
Familial Hypercholesterolemia (FH)

- Two types:
  - Heterozygous FH (HeFH)
    - Most common; 1 in every 200 individuals
    - Present with LDL-C ~220 mg/dL
    - Average time to first ASCVD event is 40-50 years for men and women respectively
  - Homozygous FH (HoFH)
    - Affects ~1 in every 160,000-300,000 individuals
    - Severe elevations in LDL-C ~650-1000 mg/dL
    - Average time to first ASCVD event is 20 years

- Up to 50% increase in risk for CHD
- LDL-C ≥190 mg/dL and/or non-HDL-C ≥220 mg/dL
- National Lipid Association (NLA) recommends screening all first-degree relatives (50% probability)
Familial Hypercholesterolemia (FH)

- Physical Manifestations: tendon xanthomas, arcus cornea (<45 y/o), tuberous xanthomas, and/or xanthelasma

FH Treatment

- High-intensity statin first-line therapy
  - LDL-C ≥190 mg/dL
  - Goal LDL-C reduction by ≥50%
  - Upregulates LDL-receptors on hepatocyte surface
  - Larger reductions in CHD risk compared to patients w/o FH
  - HoFH usually refractory to statin effects

Vermissen J, et al., Efficacy of statins in familial hypercholesterolemia: a long term cohort study

- Cohort study, mean follow-up of 8.5 years
- 2,146 FH patients without CHD
- Outcome measured: risk of CHD in treated and untreated (delay in statin initiation) FH patients
- Conclusions: FH patients using statins had risk of CHD reduced to that of the general population
FH Treatment
- FH patients may need additional agents to reduce LDL-C levels
- Initiation of non-statin therapies in patients on maximum statin intensity or statin intolerant
- Ezetimibe, niacin, and bile acid sequestrants
- Novel drugs
  - HeFH: Juxtapid® (lomitapide)
  - HoFH: Kynamro® ( mipomersen), Praluent® (alirocumab) and Repatha® (evolocumab)

Ezetimibe (Zetia®)
- MOA: inhibition of cholesterol absorption in small intestines
- ADEs: upper respiratory tract infection, diarrhea, arthralgia, sinusitis, and extremity pain
- Studied in HeFH and HoFH
- Further reduction in LDL-C levels by up to 25%
- Generally safe and well tolerated

Ezetimibe (Zetia®)
- Dosed daily without regards to meal
- Zetia® (ezetimibe)
  - 10mg tablets
- Vytorin® (ezetimibe/simvastatin)
  - 10/10mg tablets
  - 10/20mg tablets
  - 10/40mg tablets
Ezetimibe (Zetia®)
- IMPROVE-IT trial
  - Statistically lower CV events with ezetimibe/statin combinations vs. statin alone in patients with ACS
  - Ezetimibe/statin resulted in up to 70% LDL-C reduction in patients with HeFH
- Gagne C, et al.
  - Ezetimibe/statin resulted in an additional 20.5% LDL-C reduction in HoFH patients

Ezetimibe (Zetia®)

Niacin (nicotinic acid)
- Regular release
  - Niacor® 100mg TID, titrated to 3g divided in 2 to 3 doses daily
- Sustained (controlled) release
  - Slo-Niacin® 250-750mg daily
  - Several over the counter brands exist
- Extended release
  - Niaspan® 500mg daily, titrated over 4-8 weeks to 2g daily
Niacin (nicotinic acid)

- **MOA:** Not fully understood
  - Increase NAD+ and NADH: coenzymes for lipid metabolism
  - Increase lipoprotein lipase activity and HDL
  - Reduces TC, Apo B, TG, VLDL, and LDL
  - LDL-C reduction by ~17% when added to statin therapy
- **ADEs:** flushing, diarrhea, nausea, vomiting, cough, and pruritus
  - Flushing may be pretreated with ASA
    - Up to 325mg taken 30 minutes prior to dose

Bile Acid Sequestrants

- Cholestyramine, colestipol, colesevelam
- **MOA:** binds to bile acids in the intestines, forming an insoluble complex and increases excretion
- **ADEs:** constipation, abdominal pain, flatulence, nausea, vomiting, diarrhea, eructation, and anorexia
- **Drug-drug interactions**
  - Administer at least 2 hours before or 4 hours after administration of other drugs

Bile Acid Sequestrants

- Colesevelam is preferred agent in practice
  - Less GI side effects and most tolerable
  - Effective at lower doses
  - Studied in FH patients
- Added to statin/ezetimibe regimen in FH patients requiring additional reduction in LDL
  - Additional reduction in LDL-C by ~12%
- Products contain phenylalanine, take caution in PKU patients
Bile Acid Sequestrants

- Colesevelam (Welchol®) 625mg tablets or 3.75g powder packets
  - 3.75g Daily or 1.875g BID
- Cholestyramine (Questran®) 4g powder packets
  - 4g daily or BID
  - Titrated over to 8-16g divided in 1-2 doses
- Colestipol (Colestid®) 5g granules or 2g tablets
  - 5-30g daily or in divided doses
  - 2-16g daily or in divided doses

Newly Approved Novelty Drugs

- Praluent alirocumab
- Repatha evolocumab
- Juxtapid® (lomitapide)

Juxtapid®(lomitapide)

- FDA approved December 2012
  - Indicated for HoFH as an adjunct to lifestyle modification and other lipid-lowering treatments
- MOA: selective microsomal triglyceride protein (MTP) inhibitor
  - MTP is a lipid transfer protein found in hepatocytes and enterocytes involved in assembly of Apo B-containing proteins
- ADEs: diarrhea, nausea, vomiting, dyspepsia, and abdominal pain
Juxtapid® (lomitapide)
- Black box warning: can cause elevations in transaminases and hepatic steatosis
- Certified physicians and pharmacies participating in Juxtapid REMS program
- Dosage:
  - 5, 10, 20, 30, 40, and 60 mg capsules
  - Initiate at 5mg daily, titrate in 2 weeks then monthly to a maximum tolerated dose of 60mg daily

Juxtapid® (lomitapide)
- Measure LFTs prior to initiation and during dose titrations
  - Dose adjustment or discontinue needed if ALT/AST elevations ≥3 times ULN
- RCTs compared of ezetimibe and atorvastatin and in combination with Juxtapid
  - More significant LDL-C reduction than monotherapy
  - Average reduction of LDL-C by ~50% when combined with other lipid-lowering agents.

Juxtapid® (lomitapide)
- Diagram showing mechanism of action of lomitapide in Endocytosis and Hepatocytology.
Kynamro® (mipomersen)

- FDA approved January 2013
  - As an adjunct to lipid lowering medications and diet to reduce LDL-C, Apo B, TC, and non-HDL-C in patients with HoFH
- MOA: antisense oligonucleotide Apo-B synthesis inhibitor
  - Binds to mRNA coding region for Apo-B inhibiting translation
  - Selective for hepatocytes
- ADEs: injection site reactions, flu-like symptoms, nausea, headache, and elevated serum transaminases

Kynamro® (mipomersen)

- Dose: 200mg subcutaneously weekly
- Black box warning: can cause elevations in transaminases and hepatic steatosis
  - Certified physicians and pharmacies participating in Kynamro REMS program
- Reduces Apo-B, VLDL, LDL-C, and TC
- Measure LFTs prior to initiation and during dose titrations
  - Dose adjustment or discontinue needed if ALT/AST elevations ≥3 times ULN
Kynamro® (mipomersen)
- Effect on LDL-C seen by week 5 and maximum reductions by week 21
- Studied in HoFH, HeFH, and patients with severe hypercholesterolemia
- Stein E, et al.
  - Randomized, double-blind, placebo-controlled trial
  - 124 HeHF patients with CAD on maximum statin therapy
  - Statistically significant reductions in LDL-C by an additional 28% compared to placebo

Raal F, et al.
- Randomized, double-blind, placebo-controlled, phase III study
- 45 HoFH patients ≥12 years old already receiving lipid-lowering drugs
- Mean percentage change in LDL-C was significantly greater with mipomersen than placebo
- Additional reduction in LDL-C by ~25%

PCSK9 Inhibitors
- Proprotein convertase subtilisin/kexin type-9
  - Enzyme involved in breaking down LDL receptors on hepatocyte membranes
- PCSK9 inhibition results in an upregulation of LDL receptors that bind and internalize serum LDL-C
- Drugs: Praluent® (alirocumab) and Repatha® (evolocumab)
- Monoclonal antibodies selective for PCSK9
- Not evaluated for CV outcomes
PCSK9 Inhibitors

FDC approved in July 2015
- As an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with
  - HeFH
  - Clinical ASCVD and require additional reduction in LDL-C
- ADEs: nasopharyngitis, injection site reactions, and influenza

Praluent® (alirocumab)
- Single-dose pre-filled syringe
  - 75mg/mL or 150mg/mL
- Initiate dose at 75mg subcutaneously once every 2 weeks
  - If LDL-C response is inadequate, may increase dose in 1-2 months to 150mg subcutaneously every 2 weeks
- If a dose is missed, instruct the patient to administer the injection within 7 days
  - If it is more than 7 days, instruct the patient to wait for their next scheduled dose
Repatha® (evolocumab)

- FDA approved in August 2015
  - As an adjunct to diet and maximally tolerated statin for the treatment of adults with
    - HeFH
    - HoFH
    - Clinical ASCVD and require additional reduction in LDL-C
  - ADEs: nasopharyngitis, upper respiratory tract infection, influenza, and injection site reactions

Repatha® (evolocumab)

- Dosing:
  - HeFH or hyperlipidemia with CVD:
    - 140mg subcutaneously every 2 weeks or
    - 420mg once monthly (3 Repatha injections consecutively within 30 min)
  - HoFH:
    - 420mg once monthly
  - Phase II and III trials compared monotherapy with Repatha to placebo and to ezetimibe
    - LDL-C reduction up to 57% compared to placebo
    - Up to 37% compared to ezetimibe

Future CVOTs

- ODYSSEY Outcomes Trial:
  - Alirocumab's effects on CVD outcomes in patients with ACS
  - 18,000 patients enrolled
  - 1,613 events ~8.9%
  - Completion in December 2017
- FOURIER Trial:
  - Evolocumab's effects on CVD outcomes
  - 27,000 patients enrolled
  - 1,630 events ~6.0%
  - Completion in October 2017
Pipeline Novelty Drugs

- Bococizumab injection
  - PCSK9 inhibitor in phase III trials
  - FDA approval expected in 2017 (FH and non-FH)
  - SPIRE1&2: CVOT with 26,000 subjects and 1,352 events ~5.2%
- anti-PCSK9 vaccine by Pfizer
  - Given annually "Cholesterol Shot"
  - Phase-I animal studies show LDL-C effects lasting up to 10 months
- Small molecule PCSK9 inhibitors for oral administration
  - Pfizer and Betagenon
  - Entering Phase-I trials

Patient Case

- Patient LG is a 59 year old white female with a PMHx of HTN on lisinopril/HCTZ at home. No significant SHx or FHx documented. Her lipid panel and vitals is as follows:
  - TC=209
  - HDL=27
  - LDL=128
  - TG=202
  - BP: 135/80 mmHg
  - T=98.4 °F
  - HR=89 BPM

Patient Case

- Adult ≥21 y/o
- ASCVD
- LDL ≥190
- Diabetes 40-75 y/o
- 10-Year ASCVD Risk 5% to <7.5%
- 10-Year ASCVD Risk ≥7.5%
Patient Case

  - 10-year ASCVD risk: 7.7%

- What is the treatment of choice for LG?
  - High-intensity statin in addition to lifestyle modifications

Summary

- Guidelines identify 4 patient groups most likely to benefit from statin therapy
- FH is a genetic disorder that is underdiagnosed and undertreated
- FH patients require additional therapies to reduce their LDL-C levels
- MTP inhibitors, Apo-B synthesis inhibitors, and PCSK9 inhibitors are all novelty drugs approved for treating FH patients
Questions?

References