ALL CLOGGED UP: DYSLIPIDEMIAS

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NO DISCLOSURES

OBJECTIVES:
• Compare and contrast the different types of dyslipidemias
• Summarize current lipid management guidelines
• Examine specific pharmacologic and non-pharmacologic strategies for the treatment of patients with various dyslipidemias

DYSLIPIDEMIA: DEFINITION
• American College of Cardiology
• American Heart Association
• National Heart, Lung, and Blood Institute
• “a disorder of lipoprotein metabolism, including lipoprotein overproduction or deficiency. Dyslipidemias may be manifested by elevation of the total cholesterol, the “bad” low density lipoprotein (LDL), and the triglyceride concentrations, AND a decrease in the “good” high-density lipoprotein (HDL) concentrations”
• Adult Treatment Panel IV

HYPERLIPIDEMIA: EXCESSIVE AMOUNTS OF LIPIDS IN CIRCULATION
• First thought to be related to atherosclerosis when found in ASHD plaques in 1930’s
• Initial recognition that Hyperlipidemia was a risk factor for CAD began with the Framingham Study in 1979.

TYPES OF DYSLIPIDEMIAS
• Primary Hyperlipidemia: are all genetically predisposed including:
• Familial Hyperlipidemia: is caused by a mutations of the LDL receptor gene that prevents the binding and internalization of LDL.
• PH is an autosomal co-dominant disorder whereby homozygotes have severe hyperlipidemia
• Characterized by elevated LDL, normal triglycerides and PH of premature CAD
• Tendon Xanthomas (thickening and irregularity of Achilles tendon) and/or of digit extensor tendons of the metacarpophalangeal joints is diagnostic of FH
Classification of hyperlipidemia

1. Primary (familial, hereditary) hyperlipidemia: is genetically determined.

<table>
<thead>
<tr>
<th>Type</th>
<th>Increased Lipoproteins</th>
<th>Synonyms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>Chylomicrons</td>
<td>Familial hypercholesterolemia</td>
</tr>
<tr>
<td>IIa</td>
<td>VLDL and LDL</td>
<td>Familial hypercholesterolemia</td>
</tr>
<tr>
<td>IIIa</td>
<td>LDL</td>
<td>Familial hypertriglyceridemia</td>
</tr>
<tr>
<td>IVa</td>
<td>LDL</td>
<td>Familial mixed hyperlipidemia</td>
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<tr>
<td>Va</td>
<td>VLDL and chylomicrons</td>
<td>Familial mixed hyperlipidemia</td>
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</tbody>
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2. Secondary (acquired) hyperlipidemia:
1. Hypercholesterolemia: hypothyroidism, nephrotic syndrome, and drugs.

Players in hyperlipidemia: Not just cholesterol anymore

- Lipids include: Cholesterol and Triglycerides
- Cholesterol exists within the circulation from 2 sources: Diet and Liver production. They are insoluble in plasma so they are carried in a variety of Lipoproteins, classified by size and composition.
- Lipoproteins can be derived from both exogenous and endogenous pathways.

Lipoproteins: Large plasma proteins composed of some form of lipid (fat)

- Transport Cholesterol, Triglycerides and phospholipids in the Blood
- Classified based on their density, composition, and electrophoretic mobility

<table>
<thead>
<tr>
<th>Classification</th>
<th>Lipid Component</th>
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<tbody>
<tr>
<td>Chylomicrons</td>
<td>Triglyceride</td>
</tr>
<tr>
<td>VLDL</td>
<td>Triglyceride</td>
</tr>
<tr>
<td>IDL (Intermediate)</td>
<td>Triglyceride &amp; Cholesterol</td>
</tr>
<tr>
<td>LDL</td>
<td>Cholesterol</td>
</tr>
<tr>
<td>HDL</td>
<td>Phospholipid</td>
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Types of dyslipidemias: Secondary hyperlipidemia

- Abnormal lipid pathology due to some other cause
- Diabetes Mellitus
- Obesity
- Hypothyroidism
- Cushing’s Syndrome
- Alcohol Use
- Nephrotic Syndrome
- Uremia
- Liver Disease
- Drug Therapy (Steroids, Estrogen, Beta Blockers, Thiazides)
**LIPID PARTICLE COMPOSITION**

![Lipoprotein Composition Chart]

**EXTERNAL PATHWAY OF LIPID METABOLISM**

- Exogenous pathway for lipid metabolism: Dietary cholesterol and fatty acids are absorbed. Triglycerides are formed in the intestinal cell from free fatty acids and glycerol and cholesterol is esterified. Triglycerides and cholesterol combine to form chylomicron.

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**ENDOGENOUS PATHWAY OF LIPID METABOLISM**

- Endogenous metabolism begins with the liver synthesizing VLDL particles containing Apo B-100 and Cholesteryl esters to form mature VLDL particles. Once released, the VLDL is cleaved (via lipoprotein lipase) into smaller VLDL remnants (IDL) and sub particles that are reabsorbed by the liver or form HDL particles.

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**OTHER INFLAMMATORY MARKERS: APOLIPOPROTEIN B**

Apolipoprotein B is the primary apolipoprotein of chylomicrons, VLDL, LDL, and IDL particles. Specific apolipoproteins function in the regulation of lipoprotein metabolism through their involvement in the transport and redistribution of lipids among various cells and tissues, through their role as cofactors for enzymes of lipid metabolism. ApoB is responsible for LDL "latching onto" blood vessels.
OTHER VASCULAR INFLAMMATORY MARKERS: LP (A)

- Lipoprotein (a): a small particle lipoprotein seen in premature CAD with no risk factors.
- Binds with other Apo B containing lipoproteins
- Enhances LDL entry and accumulation
- Potentiates LDL oxidation
- Digested by Macrophages to produce foam cells
- Stimulates smooth muscle cell proliferation
- Binds Fibrin, platelets to endothelial cells
- Competes with plasminogen for tPA, inhibiting formation of plasmin (thrombolytic)
- Treatment: Niacin

OTHER VASCULAR INFLAMMATORY MARKERS: C REACTIVE PROTEIN

- C-Reactive Protein: is one of a group of proteins called acute phase reactants that go up in response to inflammation. C-reactive protein (CRP) is produced by the liver. The levels of acute phase reactants increase in response to certain inflammatory proteins called cytokines. These proteins are produced by white blood cells during inflammation and contribute to the genesis and rupture of atherosomatous plaque.
WHAT WAS NEW IN 2013?

• 1. Identification of 4 major statin benefit groups
• 2. Shift away from general treatment to targeted approach
• 3. Definition of Statin intensity identified
• 4. New global risk assessment tool introduced for primary prevention (http://my.americanheart.org/cvriskcalculator)
• 5. Addition of non-statin drug therapies to further decrease ASCVD

GROUP 1
PATIENTS WITH CLINICAL ASCVD

• Guideline Direction: High intensity statin therapy should be initiated or continued as first-line therapy in women and men ≤75 years of age who have clinical ASCVD, unless contraindicated.

*ACC/AHA Guideline 2013/p 22/secondary prevention #1

GROUP 2
PATIENTS WITH PRIMARY ELEVATIONS OF LDL-C ≥190 MG/DL (≥4.9 MMOL/L)

• Guideline Direction: Adults ≥21 years of age with primary LDL-C ≥190 mg/dl (≥4.9 mmol/L) should be treated with statin therapy (10-year ASCVD risk estimation is not required). Use high-intensity statin therapy unless contraindicated.

*ACC/AHA Guideline 2013/p 22/primary prevention ≥21/#2

GROUP 3
PATIENTS WITH DIABETES AGED 40-75 YEARS WITH LDL 70-189 MG/DL (1.8-4.9 MMOL/L) AND WITHOUT CLINICAL ASCVD

• Guideline Direction: Moderate-intensity statin therapy should be initiated or continued for adults 40 to 75 years of age with diabetes mellitus. High-intensity statin therapy is reasonable for adults 40 to 75 years of age with diabetes mellitus with a ≥7.5% estimated 10-year ASCVD risk unless contraindicated.

*ACC/AHA Guideline 2013/p 23/primary prevention with diabetes/#1,2
GROUP 4
PATIENTS WITHOUT CLINICAL ASCVD OR DIABETES WITH LDL-C 70 TO 189 MG/DL (1.8 TO 4.9 MMOL/L) AND ESTIMATED 10-YEAR ASCVD RISK ≥7.5%

*Guideline Direction: “Adults 40 to 75 years of age with LDL-C 70 to 189 mg/dL (1.8 to 4.9 mmol/L), without clinical ASCVD or diabetes and an estimated 10-year ASCVD risk ≥7.5% should be treated with moderate-to-high-intensity statin therapy.”

ACC/AHA Guideline 2013/p 23, Primary Prevention w/o Diabetes/#2

RISK ASSESSMENT TOOLS

- [https://professional.heart.org/professional/GuidelinesStatements/PreventionGuidelines/UCM_457498ASCVD-Risk-Calculator.jsp](https://professional.heart.org/professional/GuidelinesStatements/PreventionGuidelines/UCM_457498ASCVD-Risk-Calculator.jsp)
- [http://www.reynoldsriskscore.org](http://www.reynoldsriskscore.org)


DISCREPANCIES IN THE GUIDELINES

- 2013 American Diabetic Association Guidelines
- 2013 American Association of Clinical Endocrinologist Guidelines
- 2013 International Atherosclerosis Society
- 2014 U.S. Department of Veterans Administration Dept. of Defense Practice Guidelines
- 2016 Canadian Cardiology Society Guidelines
- 2016 European Society of Cardiology/European Atherosclerosis Society
- 2016 US Preventive Services Task Force Use of Statin Recommendations

GUIDELINE DISCREPANCIES

- Different CV Risk Estimators: Some used ethnicity, presence of HTN or DM2. Some used different endpoints (primary and secondary)
  - Pooled Cohort Risk Equations
  - Framingham Risk Score
  - Systemic Coronary Risk Evaluation
- No use of Secondary Diagnostics i.e. Coronary Artery Calcium Scores: What and How to weigh that data with the numbers, Treatment?
- No consensus on treating Moderate Risk Patients; Most agreed on Lifestyle management but then what?
- No consensus on what to do with special populations i.e. solid organ transplants, rheumatic and inflammatory diseases with high potential for drug-drug interactions.


OTHER PROBLEMS WITH 2013 GUIDELINES

- New global risk calculator was used that was pooled cohort equations to develop an estimated 10 year ASCVD risk for AA/Caucasian males/females
- Not evidenced based * Poor attempts at external validation
- No other ethnicity included * No rationale for use of 7.5% as cut off
- No consideration of the inflammatory markers i.e. CRP, Lp (a), Apo B, LpPLA2


A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines


Journal of the American College of Cardiology(2018), doi: https://doi.org/10.1016/j.jacc.2018.11.003

2018 GUIDELINE HIGHLIGHTS

1) Emphasize a heart healthy life style for ALL individuals


MANAGEMENT OF HYPER/DYSLIPIDEMIAS : LIFESTYLE CHANGES

- Optimize Weight Control: BMI < 25
- Optimize BP Control
- Exercise 30-45 min daily x 5 days weekly
- Follow Low Fat, Low Carb Diet (Mediterranean or Dash Diet)
- Stop Smoking
- Sleep 6-9 hours every 24
- Engage in Socialization but Minimize Alcohol

According to the Dietary Guidelines for AmericansExternal, moderate alcohol consumption is defined as having up to 1 drink per day for women and up to 2 drinks per day for men.

2018 GUIDELINE HIGHLIGHTS

2) In patients with ASCVD (including CVA, TIA, CAD, ACS, PVD, AAA) reduce LDL-C with high intensity OR maximally tolerated statins to decrease ASCVD. This could include low risk with elevated coronary artery calcium scores (CAC)
3) In patients with very high-risk ASCVD, with LDL-C > 70, on maximally tolerated statins, consider adding Ezetimide, then PCSK9 inhibitors

Heterozygous Familial Hypercholesterolemia (HeFH)

High Risk Conditions (DM, HN, CKD with GFR15-59 ml/min/1.2 cm2, Smoking and LDL > 100)
2018 GUIDELINE HIGHLIGHTS

4) In patients 40-75 yo with severe primary hypercholesterolemia (LDL-C > 190) begin high intensity statin therapy. If LDL-C remain > 100 mg/dl add Ezetimibe. If LDL continues to be high on statin + ezetimibe, consider adding PCSK9 inhibitor.

5) In patients 40-76 yo with DM and LDL-C > 70 mg/dl, begin moderate-intensity statins.

6) In patients 40-75 yo evaluated for ASCVD, providers should have a risk reductions discussion with their patients before beginning a statin. This should include smoking cessation, BP control, HgA1C and calculated 10 year ASCVD risk assessment.

7) In patients 40-75 yo w/o DM and with LDL-C >70 mg/dl and 10 yrs. ASCVD risk is > 7.5%, start a moderate intensity statin if a discussion of treatment options favors statin therapy to lower LDL-C by > 30%. If risk status is uncertain, consider using CAC to improve specificity. If 10 yrs. risk is > 20%, reduce LDL-C by 50%.

9) In patients 40-75 yo w/o DM and LDL-C are >70 mg/dl and 10 yrs. ASCVD risk is >7.5-19.9 % AND statin therapy is uncertain, consider measuring CAC. If CAC is 1-99, favor statin therapy. If CAC > 100, statin is indicated unless other risk reductions can be achieved.
CAC MEASUREMENTS: WHEN IS IT APPROPRIATE?

• For patients who are reluctant to initiate statin therapy and want to understand their risk
• For patients concerned about restarting a statin after discontinuing due to statin-related symptoms
• Men (55-80 yo) or Women (60-80 yo) with low burden of risk factors who question benefit of statin
• Adults (40-55 yo) with Pooled Cohort Equation 10 year risk 5-7.5% with CV risk factors, but borderline LDL levels

CORONARY ARTERY CALCIFICATION SCORING

• Coronary calcium score 0: No identifiable plaque. Risk of coronary artery disease very low (<5%)
• Coronary calcium score 1-10: Mild identifiable plaque. Risk of coronary artery disease low (<10%)
• Coronary calcium score 11-100: Definite, at least mild atherosclerotic plaque. Mild coronary narrowing likely
• Coronary calcium score 101-400: Definite, at least moderate atherosclerotic plaque. Mild coronary artery disease highly likely. Significant narrowing possible
• Coronary calcium score > 400: Extensive atherosclerotic plaque. High likelihood of at least one significant coronary narrowing.

2018 GUIDELINE HIGHLIGHTS

• B) In patients 40-75 yo w/o DM and a 10 year risk of 5-19%, risk enhancing factors favor initiation of statin therapy. Risk enhancing factors include:
  • FH of premature ASCVD
  • Persistent LDL-C levels > 160
  • Metabolic Syndrome
  • HDL Precededsipla or Early Menopause
  • Chronic Inflammatory Disorders
  • Elevated Triglycerides > 170 mg/dl
  • Elevated Apolipoprotein B > 130 mg/dl
  • Elevated CPR > 2.0 mg/L
  • ABI < 0.9
  • Radiation Therapy for L Breast CA whereby coronary arteries are affected

2018 GUIDELINE HIGHLIGHTS

• 10) Assess adherence and percentage responses to LDL-C lowering medications and lifestyle changes with repeat Lipid measurements 4-12 weeks after statin initiation or dose adjustments, repeating every 3 -12 months

LIPID MANAGEMENT: STATINS

• MOA: Competitively inhibit hydroxymethylglutaryl (HMG) CoA reductase, which is an enzyme that aids in cholesterol biosynthesis
• Most statins can lower LDL production within the liver due to LDL receptor turnover allowing increased rate of LDL receptor cycling
• Statins may raise HDL, from 5-10% (Simvastatin & Rosuvastatin)
• Statins may decrease triglycerides 10-33% (Simvastatin & Rosuvastatin)

STATINS: MECHANISM OF ACTION

• Within the first enzymatic steps in cholesterolic synthesis (HMG-CoA) Reductase
• Production of this enzyme and of the LDL receptors is regulated by the amount of free cholesterol within the hepatocytes
• MOA: Within the hepatocytes, HMG-CoA reductase is inhibited, leading to decreased cholesterol production and increased LDL receptor expression.
• Hypolipidemic effect: Increased LDL receptors pull more cholesterol out of the plasma
STATIN EFFECTIVENESS

ADVERSE EFFECTS OF STATINS

- Myopathy and muscle injury occurs because CoQ10 enzymes are inhibited within the liver (CoQ10 is needed for creation of ATP for cellular energy)
- Elevated Liver Enzymes should be monitored to prevent Liver Failure
- GI Upset
- Hyperglycemia (led to more Dx of Diabetics at higher doses)
- Increased Warfarin levels (bleeding complications)
- Cataracts (in animal toxicity)
- Memory Loss & Confusion (led to decreased dosages and package warnings in 2012)


LIPID MANAGEMENT: EZETIMIBE

- MOA: Blocks absorption of lipids in the small intestine
- When goals are not met in very high-risk patients, when LDL-C levels > 70 g/dl (or patients who are intolerant of statins), it is reasonable to add ezetimibe to max tolerated statins
- IMPROVE-IT trial (Simvastatin & Ezetimibe)
- Ezetimibe can lower LDL-C by additional 20-30%
- Dosing: 10 mg daily w/wo food

- Side Effects:
  - Headache
  - Dizziness
  - Diarrhea
  - Sore throat
  - Runny nose
  - Swelling
  - Joint pain
  - Breeding

- hives, rash
- swelling
- hoarseness
- dyspnea
- fatigue
- lack of energy
- bruising

**Ezetimibe Plus Statin**

**MOA:** Ezetimibe competitively inhibits the action of the protein convertase subtilisin/kexin type 9 (PCSK9) enzyme. This prevents its ability to take cholesterol from the liver, which helps to reduce cholesterol levels in the blood.

**PCSK9 Inhibitors: Fourier Trial**

- **Benefits:**
  - LDL-C reduction by 70% or 60% with statins
  - Decreased lipoprotein (a) levels
  - A decrease in percent atheroma volume
  - Up to 30% reduction in MACE (major acute coronary events)

- **Dosing:**
  - (Alirocumab) PRALUENT 75 mg and/or 150 mg every 2 weeks or once-monthly (Q4W) 300 mg
  - (Evolocumab) REPATHA 140 mg q 2 weeks or 420 mg monthly

- **Side Effects:**
  - Severe rash
  - Swollen face

- **No Renal or Hepatic Concerns**

- **Other Benefits:**
  - Since Statins may actually increase PCSK9, adding the inhibitor can make Statins more effective

- **Very Expensive**
  - Requires Specialty Pharmacy
  - Should check LDL-C levels every 4-8 weeks after initiation or dosing changes

**Management for Hypertriglyceridemia:**

**ICOSAPENT ETHYL (VASCEPA)**

- **Indication:** Adjunct to diet to decrease triglyceride levels > 500 mg/dl

- **Benefits of EPA:**
  - Decreases inflammation
  - Decreases hs-CRP
  - Interferes with LDL transport into the intima layer of arteries

- **In patients with hepatic impairment, monitor ALT and AST levels periodically during therapy**

- **Use with caution in patients with known hypersensitivity to fish and/or shellfish**

- **The most common reported adverse reaction (incidence >2% and greater than placebo) was arthralgia (2.3% VASCEPA, 1.0% placebo)**

- **Patients receiving treatment with VASCEPA and other drugs affecting coagulation (e.g., anti-platelet agents) should be monitored periodically**

**Lipid Management: PCSK9 Inhibitors**

- **MOA:** Protein convertase subtilisin/kexin type 9 is a gene-encoded enzyme, produced in the liver, that binds to LDL receptors and prevents the transport of LDL particles back into the liver for breakdown.

- **PCSK9 Inhibitors:** Block the enzyme PCSK9 to allow for uptake of the LDL particles

- **Drugs:** Alirocumab (Praluent) and Evolocumab (Repatha) are monoclonal antibodies that bind free plasma PCSK9

**Reduce-It Trial Endpoints**

**Primary Outcomes**

**Secondary Endpoints**

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**Reduce-IT Trial Endpoints**

**Primary Outcomes**

**Secondary Endpoints**
ICOSAPENT ETHYL (VASCEPA)

- The REDUCE-IT trial in 8,179 adult patients at low-density lipoprotein cholesterol (LDL-C) goal, with established cardiovascular disease (CVD) or at high risk for CVD, and hypertriglyceridemia (fasting triglycerides (TG) ≥133 and <500 mg/dL).
- The benefits of VASCEPA were seen on a background of predominantly (93.2%) moderate- to high-intensity statin use and median baseline LDL-C levels of 73.0 mg/dL.
- 86.9% of patients were exposed for ≥ 12 months.

- Primary Endpoint: The risk for the primary composite endpoint (5-point MACE: time to first occurrence of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization; p=0.001): 24.8% RRR
- Secondary Endpoint: The key secondary composite endpoint (3-point MACE: time to first occurrence of cardiovascular death, myocardial infarction, or stroke; p=0.001): 26% RRR
- The decrease in TG at month 12 was 19.7 mg/dl

DYSLIPIDEMIA IN CHILDREN & ADOLESCENTS

- 2018 Recommendations:
  - In children and adolescents with obesity of lipid abnormalities, lifestyle counseling is first-line therapy
  - In children and adolescents ≥10 year of age with LDL-C > 190mg/dL or 160 mg/dL with clinical presentation of FH and DO NOT respond to 3-6 months of lifestyle modifications, it’s reasonable to start statin therapy
  - In children of lipid abnormalities, lifestyle counseling is first-line therapy
  - In children with FH of early CVD and significant hyperlipidemia, check Lipid profile as early as 2 years old
  - In children & adolescents with moderate or severe hyperlipidemia, screen all family members for familial hyperlipidemia

QUESTIONS?

THANK YOU!

REFERENCES

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