Navigating the Challenging Issues in Lipid Management

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Challenging Issues in the Management of Hyperlipidemia

- Managing hypercholesterolemia in the statin-intolerant patient.
- Appropriate use of PCSK9 inhibitors
- Treatment of hypertriglyceridemia

Elevated Lipids Have the Greatest Impact on MI Risk

Challenging Issues in the Management of Hyperlipidemia

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Managing Hypercholesterolemia in the Statin-Intolerant Patient

Statin-Related Side Effects

• Myalgia
• Hepatic transaminase elevation (HTE)
• Myositis (myalgia accompanied by a CPK level > 3x ULN)
• Sleep disturbances
• GI symptoms

What is Statin Intolerance?

• A clinical syndrome characterized by the inability to tolerate at least 2 statins:
  – One statin at the lowest starting dose AND
  – Another statin at any dose causing either objectional symptoms or abnormal lab results, which are reversible with statin discontinuation
• Lowest starting daily doses:
  – rosuvastatin 10 mg
  – atorvastatin 10 mg
  – simvastatin 20 mg
  – pravastatin 20 mg
  – lovastatin 20 mg
  – fluvastatin 20 mg
  – pitavastatin 2 mg

Drug Interactions Involving Cytochrome P450 Isoenzymes

Liver

CYP450 Isoenzymes

Inhibitors

Substrates

Extrahepatic metabolism

Liver

Rosuvastatin (90%)

Pravastatin & Pitavastatin

Atorvastatin

Simvastatin

Lovastatin

Vytorin

Rosuvastatin (90%), Pravastatin & Pitavastatin

Fluvastatin

Calcium channel blockers

Cyclosporine

Losartan

Ivermectin

Grapefruit

Azole antifungals

Macrolide Antibiotics

Methotrexate

Protease inhibitors

Cimetidine

Fluoxetine HCL (Prozac)

Fluvoxamine (Luvox)

Carnitine

Theophylline

Nagelride

Ergot

Sulfonylureas

Repaglinide (Prandin)

Amiodarone

Cimetidine

Carvedilol

Thiazolidinediones

Gemfibrozil

Ketoconazole

Nateglinide (Starlix)

Fenofibrate

Recommendations for the Approach to the Statin-Intolerant Patient (Myalgia)

• If a patient is taking a lipid-soluble statin (lovastatin, atorvastatin, simvastatin) consider switching to a water-soluble statin (rosuvastatin, pravastatin, pitavastatin)

• Consider fluvastatin ER (80 mg, QHS) as a “last resort effort”
  – time-released statin
  – little to no systemic exposure of active drug

Recommendations for the Approach to the Statin-Intolerant Patient (Myalgia) contd.

• Assess TSH and vitamin D levels.
• Skeletal muscle weakness and cramping are well-known symptoms of subclinical hypothyroidism and vitamin D insufficiency.
• Subclinical hypothyroidism has an estimated prevalence of 3.8% in the general population without known thyroid disease.
• Vitamin D insufficiency has an estimated prevalence of 42% in the general population.

Holick, MF. NEJM, 2007; 266-281.
Karmisholt, J. et al. Thyroid, 2008; 18: 303-308
Forrest, KY, & Starkweather. Nutr Res, 2011; 31: 48-54
Correction of Metabolic Abnormalities Increases Statin Utilization

- 102 hyperlipidemic patients were referred to our lipid clinic over a 16-month period because of perceived statin intolerance (myalgia)
- 55 of these patients were found to have either subclinical hypothyroidism or vitamin D insufficiency
- Correction of these metabolic abnormalities allowed 40 patients (70%) to tolerate a statin ± ezetimibe


Recommendations for the Approach to the Statin-Intolerant Patient (Myalgia) contd.

- Consider alternative therapies:
  - BAS
  - ezetimibe
  - nutritional supplements (plant stanols, psyllium)
  - No red yeast rice
- Variable statin dosing (QOD, 2x/week, etc.)
  - Only for statins with long half-lives (atorvastatin, rosuvastatin, pitavastatin)
- PCSK9 inhibitors

PCSK9 Inhibitors
(proprotein convertase subtilisin/kexin type 9 inhibitors)
**PCSK9 Inhibitors**

- PCSK9 is an enzyme secreted predominantly by the liver.
- PCSK9 regulates plasma LDL levels by facilitating the degradation of hepatic LDL receptors.
- PCSK9 inhibitors are monoclonal antibodies that bind to plasma PCSK9 preventing interaction with hepatic LDL receptors.

**LDLRs Are Recycled After Delivery of LDL to Endosomes for Degradation**

**PCSK9 Promotes the Degradation of LDLRs via the Lysosome Thereby Increasing Plasma LDL-C Levels**

Monoclonal Antibody Binding to PCSK9 Prevents Degradation of the LDLR

Original Indications for PCSK9 Inhibitors

- PCSK9 inhibitors are indicated as adjunct to diet and maximally tolerated statin therapy (or intolerance) for the treatment of adults with:
  - Heterozygous Familial Hypercholesterolemia
  - Homozygous Familial Hypercholesterolemia (only evolocumab)
  - Clinical ASCVD, who are not at goal and require additional LDL-C lowering.
Patients with clinical ASCVD are divided into high-risk and very high-risk categories:

**High Risk**
- ACS (within 12 months)
- MI
- Ischemic stroke
- Symptomatic PAD

**Very High Risk**
- 2 or more of the high-risk ASCVD manifestations
- 1 high-risk ASCVD manifestation with:
  - HTN
  - DM
  - Age > 65
  - Coronary revascularization
  - Current smoking
  - Ht. FH
  - CKD
  - Ischemic CHF

Grundy, SM, et al. AHA Scientific Sessions 2018; Nov. 10-12, 2018; Chicago, IL.

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**2018 Guideline on the Management of Blood Cholesterol: PCSK9 Inhibitors**

- Recommendations for PCSK9 inhibitor use take into consideration their high cost.
- High-risk ASCVD patients: Use maximally tolerated statin ± ezetimibe to reduce LDL-C by ≥ 50%.
- Very high-risk ASCVD patients: Use an LDL-C threshold of 70 mg/dL to consider addition of non-statin to statin therapy.
  - LDL-C within 15% of 70 mg/dL: ezetimibe
  - LDL-C greater than 15% of 70 mg/dL: PCSK9 inhibitor

Grundy, SM, et al. AHA Scientific Sessions 2018; Nov. 10-12, 2018; Chicago, IL.

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**2018 Guideline on the Management of Blood Cholesterol: PCSK9 Inhibitors contd.**

- Heterozygous familial hypercholesterolemia patients without clinical ASCVD: Should the LDL-C level with a statin +/- ezetimibe remain ≥ 100 mg/dL, add a PCSK9 inhibitor
- Risk of an MI in individuals whose cause of hypercholesterolemia is heterozygous Familial Hypercholesterolemia is 22 times higher than average.
- The risk of an MI in individuals with other causes of hypercholesterolemia (e.g., Polygenic Hypercholesterolemia, secondary hypercholesterolemia) is 6 times higher than average.

Judicious Approach for Prescribing PCSK9 Inhibitors

• 180 patients were referred to our lipid clinic over a 16-month period specifically for initiation of a PCSK9 inhibitor
• 124 of these patients claimed statin-intolerance and 56 were not at their LDL-C goal on maximally tolerated statin +/- ezetimibe
• 102 (57%) did not qualify for a PCSK9 inhibitor because they did not meet the established indications of clinical ASCVD or het FH
• 78 patients met the established indications, were given a PCSK9 inhibitor prescription, and all received insurance approval within 3 weeks


Recommendations for PCSK9 Inhibitor Utilization

• Emphasis on the use of PCSK9 inhibitors for patients who will most benefit:
  – ASCVD (very high risk) not at goal on maximally tolerated oral therapy
  – Het FH
• Prescribe only to patients meeting the established indications
• Thoroughly evaluate patients experiencing statin intolerance before prescribing a PCSK9 inhibitor or other non-statin therapies

Evaluation and Treatment of Hypertriglyceridemia
Elevated Plasma Triglyceride

• The relation between hypertriglyceridemia and ASCVD is complex because the hypertriglyceridemic state is heterogeneous with respect to the underlying cause.
• The underlying causes of hypertriglyceridemia can generate various triglyceride-rich lipoproteins that differ based on size, number and composition, and therefore, have different atherogenic potential.

Causes of Hypertriglyceridemia

<table>
<thead>
<tr>
<th>SECONDARY CAUSES</th>
<th>PRIMARY CAUSES</th>
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</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>Familial combined hyperlipidemia</td>
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<tr>
<td>Insulin resistance (type 2 diabetes)</td>
<td>Sporadic hypertriglyceridemia</td>
</tr>
<tr>
<td>Insulin deficiency (type 1 diabetes)</td>
<td>Familial hypertriglyceridemia</td>
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<tr>
<td>Renal insufficiency</td>
<td>Lipoprotein lipase deficiency</td>
</tr>
<tr>
<td>High saturated/trans fat diet</td>
<td>Apo C-2 deficiency</td>
</tr>
<tr>
<td>High refined carbohydrate diet</td>
<td>Familial mixed hypertriglyceridemia</td>
</tr>
<tr>
<td>Excess alcohol ingestion</td>
<td>Dysbetalipoproteinemia</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>Protease inhibitors</td>
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<tr>
<td>HCTZ</td>
<td></td>
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<td>Statins</td>
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Reduction of CV Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT)

- 8179 patients with established ASCVD, one additional risk factor, a fasting TG level of 150-499 mg/dL, and an LDL-C level of 41-100 mg/dL, and on a stable dose of a statin for 4 weeks.

**Primary Endpoint**
- CV deaths
- NSTEMI
- Non-fatal stroke
- Coronary revascularization
- UA

**Median F.U.: 4.9 Y**

Icosapent Ethyl
2 gms, bid
(n = 4089)

Placebo
Mineral oil
(n = 4090)

Bhatt, D. et al. NEJM 2019; 380: 11-22

**REDUCE-IT (Results)**

- A primary endpoint event occurred in 17.2% of patients in the icosapent ethyl group compared to 22.0% of the patients in the placebo group (HR, 0.75; 95% CI 0.68-0.83; p < 0.001).
- The absolute between-group difference was 4.8%
- The number needed to treat to avoid one primary endpoint event was 21 over a median follow-up of 4.9 years

**REDUCE-IT (triglyceride reduction)**

- The attainment of TG levels of ≥ 150 mg/dL or < 150 mg/dL after one year had no influence on the efficacy of icosapent ethyl as compared to placebo with respect to the primary or secondary endpoints
- Responsible mechanisms: ?
  - Antiplatelet effect
  - Plaque stabilization
  - Anti-inflammatory effect

Bhatt, D. et al. NEJM 2019; 380: 11-22
Elevated Plasma Triglyceride and Atherogenic Potential

- The link between hypertriglyceridemia and elevated risk of ASCVD is through the metabolism of triglyceride-rich lipoproteins adversely altering the composition and metabolism of LDL and HDL particles, which enhances atherogenic potential.

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Triglyceride Level Influences LDL-C and HDL-C Concentration

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Plasma LDL-C Level Inadequately Predicts LDL Concentration (i.e., ASCVD Risk) in Hypertriglyceridemia

- A more accurate way to determine LDL concentration in hypertriglyceridemic subjects (≥200 mg/dL) is to assess apo B-100 concentration (non-HDL-C level can also be used since it is surrogate measure of the apo B-100 level)
- A recent ADA/ACC consensus statement suggests measuring and treating apo B-100 rather than the LDL-C in patients with elevated triglycerides

<table>
<thead>
<tr>
<th>LDL-C Goal</th>
<th>Apo B-100 Goal</th>
<th>Non-HDL-C Goal</th>
</tr>
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<tbody>
<tr>
<td>&lt; 130 mg/dL</td>
<td>&lt; 100 mg/dL</td>
<td>&lt; 160 mg/dL</td>
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<tr>
<td>&lt; 100 mg/dL</td>
<td>&lt; 90 mg/dL</td>
<td>&lt; 130 mg/dL</td>
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<tr>
<td>&lt; 70 mg/dL</td>
<td>&lt; 80 mg/dL</td>
<td>&lt; 100 mg/dL</td>
</tr>
</tbody>
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Brunzell JD et al, Diabetes Care 2009;31:811-822
Brunzell JD et al, JACC 2008;51:1512-1524
Treatment of Very High Triglycerides (≥ 500mg/dL)

- Lower triglycerides to prevent pancreatitis (fibrate, nicotinic acid or omega-3-FAs)
- Evaluate and attempt to correct any secondary causes
- If TGs are > 1000 mg/dL, reduce caloric intake from fat to < 10% of calories. Also,
  - Restrict refined carbohydrates
  - Reduce or eliminate alcohol intake
- When triglycerides are less than 400 mg/dL, turn to LDL (i.e., apo B)-lowering therapy

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