9:45 – 10:45am

Treatment of the Statin Intolerant Patient

SPEAKER
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Presenter Disclosure Information
The following relationships exist related to this presentation:
► Matthew Sorrentino, MD, FACC, FASH, has no financial relationships to disclose.

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► In accordance with pmICME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

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Treatment of the Statin Intolerant Patient

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Learning Objectives
• Determine statin intolerance through trials of different agents and/or assessment of risk for serious statin-related adverse effects
• Consider lifestyle, diet, and pharmacologic options for managing dyslipidemia in the statin intolerant patient

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Stanley: Statin Intolerance

☐ 56 y.o. man with previous anterior wall MI treated with PCI and a stent with no residual LV dysfunction
☐ Known mixed hyperlipidemia
☐ Trial of simvastatin, lovastatin and atorvastatin all caused intolerable muscle aches
☐ Lipid profile
  ■ Total cholesterol - 232
  ■ HDL-C - 34
  ■ Triglycerides - 265
  ■ LDL-C – 145
☐ Recommended treatment for lipids

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Statin Adverse Events/Treatment Options

☐ Increase in liver enzymes
  ■ Occurs in 0.5% to 2.5% of cases in dose-dependent manner
  ■ Serious liver problems are exceedingly rare
  ■ Manage by reducing statin dose or discontinue until levels return to normal
Statin Adverse Events/Treatment Options cont’d

- Myopathy: myositis and myalgias
  - Myositis (CK>10X ULN) in about 1/10,000 (possibly higher with high dose simvastatin or drug-drug interactions)
  - Myalgias 5%-10% of patients (CK usually normal)
  - Very rare cases of rhabdomyolysis
  - Reduce by
    - Cautiously using statins in patients with impaired renal function
    - Using the lowest effective dose
    - Cautious when combining statins with fibrates
    - Avoiding drug interactions
    - Intermittent dosing (2-3X/wk with high potency statin)

- Presence of muscle toxicity requires the discontinuation of the statin (CK greater than 10X ULN)

Statin Treatment Options: Myalgias

- Determine if muscle complaints are due to statin therapy
  - Muscle and joint pain history prior to prescribing statin
  - Drug free holiday with re-introduction of statin
  - Consider different statin
    - 3A4 statins – atorvastatin, simvastatin, lovastatin
    - Rosuvastatin, pravastatin pitavastatin metabolized by alternative pathways
  - Low lipophilic statins – pravastatin and rosuvastatin
  - Role of genetic testing?
    - Strong association of myopathy with the rs4363657 SNP on chromosome 12 from genomewide study (within a peptide that regulates hepatic uptake of statins)
    - Currently not cost effective to screen

Very-low Total Fat Diets

- ≤15% total calories from fat (33 g for a 2000 cal/day diet
  - Equal distribution of saturated, monounsaturated and polyunsaturated fats
  - 15% protein
  - ≥70% carbohydrates (complex carbs and whole foods, avoid simple sugars)

Lifestyle Heart Trial – 48 pts Moderate/Severe CAD

<table>
<thead>
<tr>
<th></th>
<th>Mean baseline</th>
<th>Mean 1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Experimental</td>
<td>Control</td>
</tr>
<tr>
<td>TC</td>
<td>225</td>
<td>250</td>
</tr>
<tr>
<td>LDL-C</td>
<td>144</td>
<td>166</td>
</tr>
<tr>
<td>HDL-C</td>
<td>40</td>
<td>52</td>
</tr>
<tr>
<td>Trigs</td>
<td>228</td>
<td>223</td>
</tr>
<tr>
<td>Wt (kg)</td>
<td>91</td>
<td>76</td>
</tr>
<tr>
<td>% diameter stenosis</td>
<td>40.7</td>
<td>41.3</td>
</tr>
</tbody>
</table>

Low Saturated Fat Diet (total fat 25-35% of calories)

- ATP III Therapeutic Lifestyle Change Diet
  - Reduced intake of saturated fat (<7% of calories) and cholesterol (<200 mg/d)
  - Enhance LDL-C lowering with plant stanols/stereols (2 g/d) and increased viscous (soluble) fiber (10-25 g/d)
  - Weight Reduction
  - Increased Physical Activity

Portfolio Diet Studies

- Vegetarian diet
  - 1.0 g plant sterols/1000 kcal of diet (plant sterol ester-enriched margarine)
  - 9.8 g viscous fibers/1000 kcal diet (oats, barley, psyllium, eggplant, okra)
  - 21.4 g soy protein/1000 kcal of diet (soy milk, soy meat analogs)
  - 14 g whole almonds/1000 kcal of diet
- Portfolio vs. lovastatin – 46 hyperlipidemic pts, foods provided
- Routine vs. intense portfolio – 351 hyperlipidemic pts, counseling over 6 months
**Portfolio Diet vs. Lovastatin**

<table>
<thead>
<tr>
<th></th>
<th>Control (low sat fat)</th>
<th>Portfolio</th>
<th>Control + Lovastatin 20 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C -8.0%</td>
<td>LDL-C -28.2%</td>
<td>LDL-C -30.9%</td>
<td></td>
</tr>
</tbody>
</table>


**Routine vs Intensive Dietary Portfolio: Change in LDL-C**

<table>
<thead>
<tr>
<th></th>
<th>Control (low saturated fat diet)</th>
<th>Routine Portfolio Diet (2 visits over 6 mo)</th>
<th>Intensive Portfolio Diet (7 visits over 6 mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C -3.0%</td>
<td>LDL-C -13.8%</td>
<td>LDL-C -13.1%</td>
<td></td>
</tr>
<tr>
<td>- 8 mg/dL</td>
<td>- 26 mg/dL</td>
<td>- 24 mg/dL</td>
<td></td>
</tr>
</tbody>
</table>

Jenkins DJA et al., *JAMA* 2011;306:831.

**Plant Sterols/Stanols**

- Over 40 phytosterols identified – sitosterol, campesterol, stigmasterol most common
- Stanols are saturated sterols
- 50% of cholesterol is absorbed, phytosterols and stanols are much less absorbed
- Foods enriched with plant sterol/stanol esters lowers cholesterol
  - By reducing intestinal absorption of cholesterol
  - Displaces cholesterol from micelles
  - May involve ATP-binding cassette (ABC) transport proteins


**Plant Sterols/Stanols cont’d**

- Typical diet – 150-350 mg/d of sitosterol; 15-50 mg/d stanols
- 2 gm/d phytosterols lowers LDL-C approx. 10%
- Additive to low saturated fat diet, statin therapy
- Same efficacy once a day or divided doses


**Omega-3 Fatty Acids**

- Eicosapentaenoic acid (C20:5n-3), EPA
- Docosahexaenoic acid (C22:6n-3), DHA
  - Major source is fatty fish
  - Salmon, mackerel, herring, trout
- α-linolenic acid (C18:3n-3), ALA
  - Major food sources are vegetable oils such as canola, flaxseed and soybean oil
  - Flaxseed, English walnuts, mustard oil


**GISSI-Prevenzione Trial**

- 11,324 patients (mean follow-up of 42 months)
  - Secondary prevention
- Randomized, controlled trial
  - ω-3 fatty acids (1 g of EPA/DHA per day)
  - CVD deaths reduced from 6% to 5%
  - Total mortality decreased from 10% to 8%

Lyon Diet Heart Study

- 605 participants with prior MI
  - Randomized, Single Blind Trial
  - Mean follow-up of 46 months

- Dietary Intervention Group
  - Advised to eat more fish, fruits, and vegetables
  - Use of margarine rich in ALA

- Inverse Relation Between ALA Intake and Second MI Risk
  - Primary Endpoints (Cardiac Death and Nonfatal MI) down from 4% to 1.2%
  - Secondary Endpoints decreased from 5% to 1.3%


**Fish Oils - Conclusions**

- "The first quantitative synthesis in the field showed a strong, significant effect across all major cardiovascular outcomes"
- As more randomized evidence accumulated, the effect became weaker and nonsignificant and lost its universal aspect**
- Different populations
- Lower event rates
- More optimal therapy in newer studies

**Fish Oil Supplementation Recommendations**

- Individuals at risk for CHD or known CHD
  - Two fatty fish meals per week
  - Consume 1 gram of EPA and DHA per day if do not consume fish in diet
  - Evidence more convincing for known CHD
  - Higher doses required if treating hypertriglyceridemia

**Red Yeast Rice (Monascus Purpureus, Xue Zhi Kang)**

- Yeast – grows naturally on starch
- 8 compounds (monacolins) with HMG CoA Reductase activity (lovastatin and metabolites)
- Also contains phytosterols that may add to LDL-C lowering
- If not fermented correctly – generates citrin – potentially toxic, cancer-inducing, nephrotoxic
- lowers LDL-C about 23%
Commercially Available Red Yeast Rice

- Cholestin
  - 1998 FDA: Monacolin K = lovastatin therefore regulated as a drug; banned use – has been reformulated and contains no statin
- Currently approx 30 products available
  - No cholesterol claim therefore not regulated by FDA
  - Some contain monacolins, some do not
  - Some contain citrinin
- FDA 2007 – consumers should “not buy or eat red yeast rice products...may contain an unauthorized drug that could be harmful to health”

Daily Monacolin/Lovastatin and Citrinin Red Yeast Rice

| Daily Expected Amounts of Monacolins and Citrinin for Recommended Daily Serving |
|----------------------------------|-----------------|-----------------|-----------------|-----------------|
| Red Yeast Rice Fatty Pillaging (mg) | Monacolin | Citrinin | Monacolin K | Citrinin |
| A | 20 | 21 | 1.5 | 0.8 |
| B | 30 | 32 | 3.0 | 1.5 |
| C | 40 | 42 | 4.5 | 2.3 |
| D | 50 | 52 | 6.0 | 3.1 |
| E | 60 | 62 | 7.5 | 4.0 |
| F | 70 | 72 | 9.0 | 5.0 |
| G | 80 | 82 | 10.5 | 6.0 |
| H | 90 | 92 | 12.0 | 7.0 |
| I | 100 | 102 | 13.5 | 8.0 |
| J | 110 | 112 | 15.0 | 9.0 |
| K | 120 | 122 | 16.5 | 10.0 |
| L | 130 | 132 | 18.0 | 10.0 |
| M | 140 | 142 | 19.5 | 10.0 |
| N | 150 | 152 | 21.0 | 10.0 |
| O | 160 | 162 | 22.5 | 10.0 |
| P | 170 | 172 | 24.0 | 10.0 |

Mediterranean Diet and Risk of CHD and Stroke

A. RR of CVD (combined CHD and Stroke) by quintiles of aMed
B. RR of fatal CVD (combined CHD and stroke mortality) by quintiles of aMed

Components include:
- Vegetables
- Fruits
- Nuts
- Whole grains
- Legumes
- Fish
- Ratio monounsaturated to saturated fat
- Red/processed meats
- Alcohol

Higher score = closer to Med diet

Lipid Research Clinics

The Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT)

- Multicenter, randomized, double-blind study; tested the efficacy of cholesterol lowering in reducing the risk of CHD
- 3806 asymptomatic middle-aged men with primary hypercholesterolemia [Total-C >265 mg/dL]
- Treatment group received cholestyramine resin; control group received placebo

LRC-CPPT Results

- LDL-C reduction of 12.6% with cholestyramine
- CHD death and/or Nonfatal MI
  - 19%* 24%
  - * P <0.05 vs placebo
- CHD Death
  - 19%
- Nonfatal MI

Intestinal-Acting Cholesterol-Lowering Agents

- Inhibition of bile acid re-absorption
  - Bile acid sequestrants (BAS)
    - Cholestyramine
    - Colestipol
    - Colesevelam
- Inhibition of cholesterol absorption
  - Plant stanol esters and sterol esters
  - Selective cholesterol absorption inhibitors
    - Ezetimibe
Selective Cholesterol Absorption Inhibitors: Ezetimibe

- Mechanism of action and selectivity
  - Blocks cholesterol absorption at the intestinal brush border
  - No effect on absorption of lipid-soluble vitamins
  - Lowers LDL-C approx 18% as monotherapy
- Pharmacology
  - Intestinal wall localization
  - Enterohepatic circulation
  - Minimal systemic exposure

Study of Heart and Renal Protection (SHARP): Eligibility

- History of chronic kidney disease
  - Not on dialysis: elevated creatinine on 2 occasions
    - Men: ≥1.7 mg/dL (150 µmol/L)
    - Women: ≥1.5 mg/dL (130 µmol/L)
  - On dialysis: hemodialysis or peritoneal dialysis
  - Age ≥40 years
  - No history of myocardial infarction or coronary revascularisation
  - Uncertainty: LDL-C-lowering treatment not definitely indicated or contraindicated
- Randomized to simvastatin/ezetimibe 20/10 mg vs. placebo

SHARP: Major Atherosclerotic Events

- Risk ratio 0.83 (0.74-0.94)

Features of Nicotinic Acid

- Products available (daily dose)
  - Immediate-release, 2–4 g/d
  - Sustained-release, branded 1–2 g/d
  - Sustained-release, OTC product ≤ 2 g/d
- Best agent to raise HDL-C
- Reduces coronary events (Coronary Drug Project)
- Adverse effects
  - Flushing, itching, headache
  - Hepatotoxicity, GI (sustained-release, higher doses)
  - Activation of peptic ulcer
  - Hyperglycemia and reduced insulin sensitivity
- Contraindications
  - Active liver disease or unexplained LFT elevations
  - Peptic ulcer disease

Coronary Drug Project: Mortality Reduction with Niacin in CHD Patients
Fibric Acid Derivatives

**Indications:**
- Adjunctive therapy to diet
- Hypertriglyceridemia (Type IV and V)
- Combined hyperlipidemia (Type IIb) with low HDL-C who do not respond to NA

**Mechanism of Action:**
Increases peripheral lipolysis and decreases hepatic TG production

**Efficacy:**
- Decreases TG 25%-50%
- LDL-C decreases, remains the same or increases
- Increases HDL-C 15%-25% in hypertriglyceridemia

**Side Effects:**
- GI upset (8%), cholelithiasis, myositis, abn LFTs

**Contraindications:**
- Hepatic or renal dysfunction
- Pre-existing gallbladder disease

**Intervention Trials:**
- Helsinki Heart Study, LOCAT, BECAIT, VA-HIT, BIP

Veterans Affairs HDL-C Intervention Trial (VA-HIT)

- Double-blind, randomized, placebo-controlled
- 2,531 men ≤73 yrs; treatment placebo vs. gemfibrozil 600mg bid
- Documented CHD (prior MI, revascularization, angina pectoris, or angiographic evidence of CHD)
- Lipid entry criteria
  - HDL-C ≤40mg/dL (baseline 32 ± 5)
  - LDL-C ≤140mg/dL (baseline 111 ± 23)
  - Triglycerides ≤300mg/dL (baseline 161 ± 68)
- Follow up: 5.1 years (median)

Statin Alternatives and Adjuncts

- Low saturated fat diet, increased plant stanols/sterols, fiber, nuts, fish oils, chocolate, physical activity, weight reduction
- Intestinal agents – resins, ezetimibe
- Niacin – especially with low HDL-C
- Fibrates – especially with mixed hyperlipidemia, high triglycerides and low HDL-C
- Novel LDL-C lowering agents in development

VA-HIT Trial

![VA-HIT Trial Graph](https://example.com/VA-HIT_graph.png)

Statin Alternatives and Adjuncts

Case: Statin Intolerance cont’d

- Secondary prevention – statin gives clear benefit
- Treatment trial with three statins all Cytochrome 3A4 metabolites
  - Trial of non 3A4 metabolized statin – pravastatin, rosuvastatin
  - Trial of intermittent dosing (begin low dose rosuvastatin twice a week and increase as tolerated)
- Add an intestinal agent
  - If only low intermittent dosing of a statin is tolerated, adding an intestinal agent can improve LDL-C lowering
- Encourage optimal lifestyle program

Back to Stanley

- 56 y.o. man with previous anterior wall MI treated with PCI and a stent with no residual LV dysfunction
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Clinical Pearls

- Myositis is defined as CK 10X upper limit of normal and occurs in only 0.2%-0.4% of individuals treated with statins
- Myalgias are more common and at times can be minimized with a differently metabolized statin or intermittent dosing
- 2 gm/day of phytosterols in the diet may lower LDL-C by about 10%
- High dose niacin can reduce nonfatal MI by about 26%
- Fibrates are most useful in patients with elevated triglycerides and a low HDL-C