Cholesterol: Statins and Beyond for the Utah Academy of Family Practice

By

Kevin J Walsh, MD
Disclosures

None
Goals of this talk

Review new guidelines
Statin intolerance/adherence options
Pharmacologic options beyond statins
Non-pharmacologic options beyond statins
When things don't seem to be working
The 2018 Cholesterol guidelines

1. In all individuals, emphasize a heart-healthy lifestyle across the life course.

2. In patients with clinical ASCVD, reduce low-density lipoprotein cholesterol (LDL-C) with high intensity statin therapy or maximally tolerated statin therapy to lower LDL-C levels by ≥50%.

3. In very high-risk ASCVD, use a LDL-C threshold of 70 mg/dL (1.8 mmol/L) to consider addition of nonstatins to statin therapy.
Definition of Very High Risk/High Risk

<table>
<thead>
<tr>
<th>Major ASCVD Events</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent ACS (within the past 12 mo)</td>
<td></td>
</tr>
<tr>
<td>History of MI (other than recent ACS event listed above)</td>
<td></td>
</tr>
<tr>
<td>History of ischemic stroke</td>
<td></td>
</tr>
<tr>
<td>Symptomatic peripheral arterial disease (history of claudication with ABI &lt;0.85, or previous revascularization or amputation (S4.1-39))</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>High-Risk Conditions</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥65 y</td>
<td></td>
</tr>
<tr>
<td>Heterozygous familial hypercholesterolemia</td>
<td></td>
</tr>
<tr>
<td>History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s)</td>
<td></td>
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<tr>
<td>Diabetes mellitus</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
</tr>
<tr>
<td>CKD (eGFR 15-59 mL/min/1.73 m²) (S4.1-15, S4.1-17)</td>
<td></td>
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<tr>
<td>Current smoking</td>
<td></td>
</tr>
<tr>
<td>Persistently elevated LDL-C (LDL-C ≥100 mg/dL [≥2.6 mmol/L]) despite maximally tolerated statin therapy and ezetimibe</td>
<td></td>
</tr>
<tr>
<td>History of congestive HF</td>
<td></td>
</tr>
</tbody>
</table>

*Very high risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions.
4. In patients with severe primary hypercholesterolemia (LDL-C level ≥190 mg/dL \([≥4.9 \text{ mmol/L}])\), without calculating 10-year ASCVD risk, begin high-intensity statin therapy without calculating 10-year ASCVD risk. If the LDL-C level remains ≥100 mg/dL \((≥2.6 \text{ mmol/L})\), add nonstatin therapy.

5. In patients 40 to 75 years of age with diabetes mellitus and LDL-C ≥70 mg/dL \((≥1.8 \text{ mmol/L})\), start moderate-intensity statin therapy without calculating 10-year ASCVD risk. If additional risk factors aim to reduce the LDL-C level by ≥50%.

Even pre-diabetes or borderline DM is at added risk
### Intensity Definitions

<table>
<thead>
<tr>
<th></th>
<th>High Intensity</th>
<th>Moderate Intensity</th>
<th>Low Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C lowering†</td>
<td>≥50%</td>
<td>30%–49%</td>
<td>&lt;30%</td>
</tr>
<tr>
<td><strong>Statins</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin (40 mg‡)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>80 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosuvastatin 20 mg (40 mg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simvastatin 10 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pravastatin 40 mg (80 mg)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Lovastatin 40 mg (80 mg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluvastatin XL 80 mg</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Fluvastatin 40 mg BID</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pitavastatin 1–4 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
New role of the Calcium Score

For any patient, if the CAC score is ≥100 Agatston units or ≥75th percentile, statin therapy is indicated
Life style-how important is it
In FH patients the risk of CVD is decreased by 33% with just life style factor control like no smoking, weight control, regular exercise, waist circumference and diet. lifestyle-related risk factors could influence the penetrance of inherited lipid disorder
### Lifestyle to reduce LDL-ECS

<table>
<thead>
<tr>
<th>Lifestyle interventions to reduce TC and LDL-C levels</th>
<th>Magnitude of the effect</th>
<th>Level of evidence</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduce dietary trans fat</td>
<td>+++</td>
<td>A</td>
<td>136, 139</td>
</tr>
<tr>
<td>Reduce dietary saturated fat</td>
<td>+++</td>
<td>A</td>
<td>136, 137</td>
</tr>
<tr>
<td>Increase dietary fibre</td>
<td>++</td>
<td>A</td>
<td>140, 141</td>
</tr>
<tr>
<td>Use functional foods enriched with phytosterols</td>
<td>++</td>
<td>A</td>
<td>142, 143</td>
</tr>
<tr>
<td>Use red yeast rice supplements</td>
<td>++</td>
<td>A</td>
<td>144–146</td>
</tr>
<tr>
<td>Reduce excessive body weight</td>
<td>++</td>
<td>A</td>
<td>147, 148</td>
</tr>
<tr>
<td>Reduce dietary cholesterol</td>
<td>+</td>
<td>B</td>
<td>149</td>
</tr>
<tr>
<td>Increase habitual physical activity</td>
<td>+</td>
<td>B</td>
<td>150</td>
</tr>
<tr>
<td>Use soy protein products</td>
<td>+/-</td>
<td>B</td>
<td>151</td>
</tr>
</tbody>
</table>
Primary Prevention

Assess ASCVD Risk in Each Age Group
Emphasize Adherence to Healthy Lifestyle

**Primary Prevention:****
- **Age 0-19 y**
  - Lifestyle to prevent or reduce ASCVD risk
  - Diagnosis of familial hypercholesterolemia

- **Age 20-39 y**
  - Estimate lifetime risk to encourage lifestyle to reduce ASCVD risk
  - Consider statin if family history of premature ASCVD and LDL-C ≥160 mg/dL (≥4.1 mmol/L)

- **Age 40-75 y and LDL-C ≥70-190 mg/dL (≥1.8-4.9 mmol/L)**
  - No risk assessment; High-intensity statin (Class I)
  - Diabetes mellitus and age 40-75 y
  - Moderate-intensity statin (Class I)

- **Age >75 y**
  - Clinical assessment, Risk discussion

**ASCVD Risk Enhancers:**
- Family history of premature ASCVD
- Persistently elevated LDL-C (≥160 mg/dL (≥4.1 mmol/L))
- Chronic kidney disease
- Metabolic syndrome
- Conditions specific to women (e.g., premenopausal, premature menopause)
- Inflammatory diseases (especially rheumatoid arthritis, psoriasis, HIV)
- Ethnicity (e.g., South Asian ancestry)

**Risk discussion: Emphasize lifestyle to reduce risk factors (Class I)**
- <5%
  - “Low Risk”

- 5% - 7.5%
  - “Borderline Risk”

- ≥7.5% - <20%
  - “Intermediate Risk”

- ≥20%
  - “High Risk”

**Risk discussion: If risk enhancers present then risk discussion regarding moderate-intensity statin therapy (Class Iib)**
- If risk estimate + risk enhancers favor statin, initiate moderate-intensity statin to reduce LDL-C by 30% - 49%

**Risk discussion:**
- If risk decision is uncertain:
  - Consider measuring CAC in selected adults:
    - CAC = 0 (lowers risk; consider no statin, unless diabetes, family history of premature CHD, or cigarette smoking are present)
    - CAC = 1-99 favors statin (especially after age 55)
    - CAC = 100+ and/or ≥75th percentile, initiate statin therapy

**Diabetes mellitus and age 40-75 y**
- Risk assessment to consider high-intensity statin (Class Iia)

**Intermountain Healthcare**
Primary Prevention

Primary Prevention:
Assess ASCVD Risk in Each Age Group
Emphasize Adherence to Healthy Lifestyle

- Age 0-19 y
  - Lifestyle to prevent or reduce ASCVD risk
  - Diagnosis of Familial Hypercholesterolemia → statin

- Age 20-39 y
  - Estimate lifetime risk to encourage lifestyle to reduce ASCVD risk
  - Consider statin if family history premature ASCVD and LDL-C ≥160 mg/dL (≥4.1 mmol/L)

- Age 40-75 y and LDL-C ≥70-<190 mg/dL (≥1.8-<4.9 mmol/L) without diabetes mellitus
  - 10-year ASCVD risk percent begins risk discussion
Primary Prevention

- **<5% “Low Risk”**
  - Risk discussion: Emphasize lifestyle to reduce risk factors (Class I)

- **5% - <7.5% “Borderline Risk”**
  - Risk discussion: If risk enhancers present then risk discussion regarding moderate-intensity statin therapy (Class IIb)

- **≥7.5% - <20% “Intermediate Risk”**
  - Risk discussion: If risk estimate + risk enhancers favor statin, initiate moderate-intensity statin to reduce LDL-C by 30% - 49% (Class I)

- **≥20% “High Risk”**
  - Risk discussion: Initiate statin to reduce LDL-C ≥50% (Class I)

If risk decision is uncertain:
Consider measuring CAC in selected adults:
- CAC = zero (lowers risk; consider no statin, unless diabetes, family history of premature CHD, or cigarette smoking are present)
- CAC = 1-99 favors statin (especially after age 55)
- CAC = 100+ and/or ≥75th percentile, initiate statin therapy

Intermountain Healthcare
Primary Prevention

Assess ASCVD Risk in Each Age Group
Emphasize Adherence to Healthy Lifestyle

- **Age 0-19 y**
  - Lifestyle to prevent or reduce ASCVD risk
  - Diagnosis of Familial Hypercholesterolemia → statin

- **Age 20-59 y**
  - Estimate lifetime risk to encourage lifestyle to reduce ASCVD risk
  - Consider statin if family history premature ASCVD and LDL-C ≥160 mg/dL (≥4.1 mmol/L)

- **Age 40-75 y and LDL-C ≥70-<190 mg/dL (≥1.8-<4.9 mmol/L)**
  - without diabetes mellitus
  - 10-year ASCVD risk percent begins risk discussions

If you’re not sure then these factors push you in favor of starting statins

**ASCVD Risk Enhancers:**
- Family history of premature ASCVD
- Persistently elevated LDL-C ≥160 mg/dL (≥4.1 mmol/L)
- Chronic kidney disease
- Metabolic syndrome
- Conditions specific to women (e.g., preeclampsia, premature menopause)
- Inflammatory diseases (especially rheumatoid arthritis, psoriasis, HIV)
- Ethnicity (e.g., South Asian ancestry)

**Lipid/Biomarkers:**
- Persistently elevated triglycerides (≥175 mg/dL, ≥2.0 mmol/L)

In selected individuals if measured:
- hs-CRP ≥2.0 mg/L
- Lp(a) levels >50 mg/dL or >125 nmol/L
- apoB ≥130 mg/dL
- Ankle-brachial index (ABI) <0.9
Risk Enhancing Factors-
Family History of premature heart disease
Metabolic syndrome
CKD
Chronic Inflammatory Diseases
Elevate triglycerides >170 (and prob >120)
Preeclampsia, premature menopause
South Asian patients
CRP> 2, Apolipoprotein B>130, ABI<0.9
Lipoprotein (a) > 50
HO Chest Radiation
Coronary Calcium score
10-year risk of fatal CVD in populations at high CVD risk

Total cardiovascular risk estimation

European Heart Journal (2011) 32, 1769–1818
MESA-Guideline groups by CAC

- **Recommend Statins**: CAC = 0: 41, CAC 1-100: 30, CAC > 100: 29
- **Consider Statins**: CAC = 0: 57, CAC 1-100: 31
- **Statins not recommended**: CAC = 0: 79, CAC 1-100: 17, CAC > 100: 4
CT-angiogram

- LAD-with dye
- Calcified plaque
- Soft lipid rich plaque
- LDL disease
Mixed Plaque with soft component (black) surrounding calcified (white) component.
Apps to help you

MESA based app to calculate your coronary artery age from the CAC score

ACC app to estimate 10 yr Risk
### Treatment Goals for Non-HDL-C, LDL-C, and Apo B in mg/dL

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Treatment Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-HDL-C</td>
</tr>
<tr>
<td>Low</td>
<td>&lt;130</td>
</tr>
<tr>
<td>Moderate</td>
<td>&lt;130</td>
</tr>
<tr>
<td>High</td>
<td>&lt;130</td>
</tr>
<tr>
<td>Very High</td>
<td>&lt;100</td>
</tr>
</tbody>
</table>
Understanding Non-HDL-C

Non-HDL-C = Total cholesterol - HDL-C
What is the Advantage of Non-HDL-C over LDL-C in Assessing ASCVD Risk?

- Non-HDL-C is more predictive of ASCVD risk in observational studies and on-Rx trials.
- When non-HDL-C and LDL-C are discordant, risk follows non-HDL-C.
- Non-HDL-C testing is universally available, requires no additional cost, and is accurate in the non-fasting state.

Prevalence of Discordance: Women’s Health Study

A. LDL-C and NHDL-C
- Discordant: 11.6%
- Concordant: 88.4%

B. LDL-C and ApoB
- Discordant: 18.9%
- Concordant: 81.1%

C. LDL-C and LDL-P
- Discordant: 24.3%
- Concordant: 75.7%
# NMR Lipoprotein

## LDL Particle Concentration

<table>
<thead>
<tr>
<th>Percentile</th>
<th>2</th>
<th>20</th>
<th>50</th>
<th>80</th>
<th>90</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LDL-P concentration</strong></td>
<td>nmol/L</td>
<td>Low</td>
<td>Moderate</td>
<td>Borderline High</td>
<td>High</td>
</tr>
<tr>
<td>&lt;700</td>
<td>&lt;1000</td>
<td>1000-1299</td>
<td>1300-1599</td>
<td>1600-2000</td>
<td>&gt;2000</td>
</tr>
</tbody>
</table>

| **LDL-C concentration** | mg/dl | Optimal | Near or above optimal | Borderline High | High | Very High |
| <70 | <100 | 100-129 | 130-159 | 160-189 | >190 |
Impact of LDL-C / LDL-P Discordance on Suspected Coronary Artery Disease: Framingham Offspring Study

- Low Risk Group
- Low LDL-P (n=284)
- High Risk Group
- High LDL-P (n=282)

Risk tracks with LDL-P
Subjects with HDL-C <40 mg/dl or TG 100-400 mg/dl had increased LDL-P, despite relatively normal LDL-C.
## Possible causes of hypertriglyceridaemia

<table>
<thead>
<tr>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic predisposition.</td>
</tr>
<tr>
<td>Obesity.</td>
</tr>
<tr>
<td>Type 2 diabetes.</td>
</tr>
<tr>
<td>Alcohol consumption.</td>
</tr>
<tr>
<td>Diet high in simple carbohydrates.</td>
</tr>
<tr>
<td>Renal disease.</td>
</tr>
<tr>
<td>Hypothyroidism.</td>
</tr>
<tr>
<td>Pregnancy (physiological triglyceride concentrations double during the third trimester).</td>
</tr>
<tr>
<td>Paraproteinaemia and autoimmune disorders such as systemic lupus erythematosus.</td>
</tr>
</tbody>
</table>

### Multiple medications including:
- Corticosteroids.
- Oestrogens, especially those taken orally.
- Tamoxifen.
- Antihypertensives: adrenergic beta-blocking agents (to a different degree), thiazides.
- Isotretinoin.
- Bile acid-binding resins.
- Ciclosporin.
- Antiretroviral regimens (protease inhibitors).
- Psychotropic medications: phenothiazines, second generation antipsychotics.
# Triglyceride Reduction=20-50% with Diet in Patients with TG 150-500 mg/dl

<table>
<thead>
<tr>
<th>Dietary Factor</th>
<th>% Change in TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss of 5-10%</td>
<td>- 20%</td>
</tr>
<tr>
<td>Mediterranean diet pattern v. low fat diet</td>
<td>- 10-15%</td>
</tr>
<tr>
<td>Fiber (total, insoluble, soluble) in individuals with T2 DM</td>
<td>- 8-13%</td>
</tr>
<tr>
<td>Reduce added sugars</td>
<td>- 5-10%</td>
</tr>
<tr>
<td>Fructose (≥100g/day)</td>
<td>+ Dose-response increase in TG</td>
</tr>
<tr>
<td>Marine-derived Omega 3 fatty acids (per gram)</td>
<td>- 5-10%</td>
</tr>
<tr>
<td>Eliminate trans fatty acids (per 1% replacement with MUFA/PUFA)</td>
<td>- 1%</td>
</tr>
<tr>
<td>Alcohol (per 1oz./day)</td>
<td>+ 5-10%</td>
</tr>
</tbody>
</table>

Adapted from Miller et al. *Circulation* 2011;123:2292-333
## Available Prescription ω-3 FA Formulations

<table>
<thead>
<tr>
<th></th>
<th>EPA+DHA EE(^1,2) (e.g. Lovaza)</th>
<th>EPA only EE(^3) (e.g. Vascepa)</th>
<th>EPA+DHA FFA(^4) (e.g. Epanova)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic available?</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Indication</strong></td>
<td>Indicated as an adjunct to diet to reduce TG levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| **Omega-3 Content** | EPA: 0.465 g  
DHA: 0.375 g  
EPA/DHA: 55%/45% |
|                  | EPA: 1 g  
EPA/DHA: 100%/0% |
|                  | EPA: 0.55 g  
DHA: 0.2 g  
EPA/DHA: 73%/27% |
| **Regimen, capsules** | 2 BID with meals or 4 QD with meals\(^2\) |
|                  | 2 BID with meals |
|                  | 2 or 4 QD, with or without meals |

1. Lovaza prescribing information  
2. Omtryg prescribing information  
3. Vascepa prescribing information  
4. Epanova prescribing information  

EE=ethyl ester, FA=fatty acid(s); FFA=free FA; EPA=Eicosapentaenoic Acid; DHA=Docosahexaenoic acid  
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EPA/DHA: 55%/45% |
|                          | EPA: 1 g  
EPA/DHA: 100%/0% |
|                          | EPA: 0.55 g  
DHA: 0.2 g  
EPA/DHA: 73%/27% |
| Regimen, capsules        | 2 BID with meals or 4 QD with meals\(^2\) |
|                          | 2 BID with meals                |
|                          | 2 or 4 QD, with or without meals |

1. Lovaza prescribing information  
2. Omtryg prescribing information  
3. Vascepa prescribing information  
4. Epanova prescribing information  
EE=ethyl ester; FA=fatty acid(s); FFA=free FA; EPA=Eicosapentaenoic Acid; DHA=Docosahexaenoic acid  
Statin Non-adherence Rates

60% of ACS admissions are non-adherent at 2 years
64% of chronic CAD are non-adherent
75% of primary prevention cases are non adherent.
In the Netherlands 53% are nonadherent at 2 years
Recurrent MI risk is 55% lower in the adherent group
Death was 25% lower in the adherent group post MI
Death in diabetics was 41% lower in the adherent group post MI
Statin discontinuation was associated with 2.86 fold increase risk of mortality
Incidence of SAMS

pooling data for 56,000 patients from 42 large randomized trials, there were no differences in reported muscle symptoms with statins compared with placebo, with 13% of participants in each group having reported muscle symptoms

Similarly, 22% of participants taking statins in the U.S. National Health and Nutrition Examination Survey reported muscle pain compared with 16.7% of non-statin users
Rhabdomyolysis

1.6 per 100,000 patients treated
Muscle tenderness
At risk for renal failure
Often times ppt by drug interactions leading to increasing statin blood levels
CK elevations occur
GAUSS-3

Inability to tolerate atorvastatin at 10mg and any other statin at any dose or, alternatively, 3 or more statins, with 1 at the lowest average daily starting dose and 2 other statins at any dose.

More than 80% of patients had a history of intolerance to 3 or more statins before entering the study.
GAUSS-3

participants, of whom >80% had experienced intolerable muscle symptoms to at least 3 different statins

Over a 12-week period, 42.6% of participants experienced intolerable muscle symptoms only when treated with atorvastatin 20 mg

Conversely, 26.5% experienced muscle symptoms with placebo and not with atorvastatin;

9.8% had symptoms on both placebo and atorvastatin,

17.3% had no symptoms with either treatment.
### Table 2. Patients Experiencing Intolerable Muscle-Related Symptoms During Phase A of GAUSS-3 Trial

<table>
<thead>
<tr>
<th>Category, No. (%)</th>
<th>Atorvastatin Followed by Placebo (n = 245)</th>
<th>Placebo Followed by Atorvastatin (n = 246)</th>
<th>All Randomized Patients (n = 491)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms with atorvastatin but not placebo</td>
<td>126 (51.4)</td>
<td>83 (33.7)</td>
<td>209 (42.6)</td>
</tr>
<tr>
<td>Symptoms with placebo but not atorvastatin</td>
<td>42 (17.1)</td>
<td>88 (35.8)</td>
<td>130 (26.5)</td>
</tr>
<tr>
<td>Symptoms with both placebo and atorvastatin</td>
<td>22 (9.0)</td>
<td>26 (10.6)</td>
<td>48 (9.8)</td>
</tr>
<tr>
<td>No symptoms with either treatment</td>
<td>47 (19.2)</td>
<td>38 (15.4)</td>
<td>85 (17.3)</td>
</tr>
<tr>
<td>Did not start period 2 treatment</td>
<td>8 (3.3)</td>
<td>11 (4.5)</td>
<td>19 (3.9)</td>
</tr>
</tbody>
</table>

Abbreviation: GAUSS-3, Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects 3.

* Nineteen patients bypassed phase A because of creatine kinase elevation ≥10× the upper limit of normal.

* Does not include 1 patient who never received study drug.
GAUSS-3 Zetia

Absolute change in LDL=31
Mean % change in mean total cholesterol 11.6%
Mean % change in nonLDL cholesterol 14.6%
Mean % change in Apo B 11.7%
21.9% had myalgias with zetia and 6.8% dcd drug
very high baseline LDL-levels, which on average exceeded 210mg/dL
# PRIMO: Risk of Muscular Symptoms with Individual Statins

<table>
<thead>
<tr>
<th>Statin</th>
<th>Dosage</th>
<th>Percentage of patients with muscular symptoms*</th>
<th>Odds Ratio† [95% CI]</th>
<th>P value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pravastatin</td>
<td>40 mg/day</td>
<td>10.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>40–80 mg/day</td>
<td>14.9%</td>
<td>1.28 [1.02–1.60]</td>
<td>0.035</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>40–80 mg/day</td>
<td>18.2%</td>
<td>1.78 [1.39–2.29]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>80 mg/day</td>
<td>5.1%</td>
<td>0.33 [0.26–0.42]</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*% values relative to the total number of patients with or without muscular symptoms.
† Odds ratios were calculated using pravastatin as the reference.
‡ P values were determined by Pearson's Chi-squared test.
Should Coenzyme Q-10 be Used to Treat Statin-induced Myopathy?

- Statins inhibit production of farnesyl pyrophosphate, an intermediary to the production of ubiquinone or coenzyme Q-10.
- Coenzyme Q-10 participates in electron transport during oxidative phosphorylation in mammalian mitochondria.
- Chronic statin therapy may reduce Co Q-10 blood levels
- The data is inconsistent in the benefits of Co Q-10 therapy to reduce myalgias.
- Most studies demonstrate no benefit to Co Q-10 therapy.
- The data is not sufficient to recommend Co Q-10 prophylactic or acute treatment for statin-induced myalgias.
In 74 men and 72 women (age 59 ± 14 years) intolerant to ≥2 statins because of myalgia, myositis, myopathy, or myonecrosis and found to have low (<32 ng/mL) serum vitamin D, we prospectively assessed whether vitamin D supplementation (vitamin D2: 50,000-100,000 units/week) to normalize serum vitamin D would allow successful rechallenge therapy with statins.
Vitamin D and statin intolerance

a prescription with the loading dose of ergocalciferol (D2) 50 000 units per week for 8 to 12 weeks and maintenance dose of cholecalciferol (D3) 800 to 1000 units per day were provided for those with vitamin D level less than 20 ng/mL and a prescription of D3 800 to 1000 units daily for those with vitamin D level in between 20 and 30 ng/mL. Vitamin D deficiency was defined as serum 25OH vitamin D level less than 30 ng/mL.
Vitamin D and statin intolerance

subjects who had vitamin D deficiency and statin intolerance were able to reinitiate and maintain statin therapy after treatment with a vitamin D supplement even if they had not achieved the desired vitamin D serum level.

Approximately 40% of the patients restarted the same statin that they could not tolerate previously, and more than half of these patients tolerated the same dosage as before.
Vitamin D in myalgias

On follow-up at median 6 months, 12 months, and 24 months on statins and vitamin D, 88%, 91%, and 95% of the previously statin-intolerant patients, respectively, were free of myalgia, myositis, myopathy, and/or myonecrosis.
Vitamin D in myalgias

On follow-up at median 6 months, 12 months, and 24 months on statins and vitamin D, 88%, 91%, and 95% of the previously statin-intolerant patients, respectively, were free of myalgia, myositis, myopathy, and/or myonecrosis.
When a patient develops myalgias/myopathy after being on statin for years ask yourself—

Was the dose recently changed?
Was a new med added?
Have they developed a Vit D deficiency, ie winter in Utah
Any new supplements? Grapefruit juice?
Drugs potentially interacting with statins metabolized by CYP3A4 loading to increased risk of myopathy and rhabdomyolysis

<table>
<thead>
<tr>
<th>Anti-infective agents</th>
<th>Calcium antagonists</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Itraconazole</td>
<td>Verapamil</td>
<td>Ciclosporin</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Diltiazem</td>
<td>Danazol</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>Amlodipine</td>
<td>Amiodarone</td>
</tr>
<tr>
<td>Erythromycin</td>
<td></td>
<td>Ranolazine</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td></td>
<td>Grapefruit juice</td>
</tr>
<tr>
<td>Telithromycin</td>
<td></td>
<td>Nefazodone</td>
</tr>
<tr>
<td>HIV protease inhibitors</td>
<td></td>
<td>Gemfibrozil</td>
</tr>
</tbody>
</table>

Adapted from Egan and Colman and Wiklund et al.
# HMG-CoA Reductase Inhibitor: Adverse Effects

## Risk factors for the development of myopathy*

<table>
<thead>
<tr>
<th>Concomitant Use of Meds</th>
<th>Other Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrate</td>
<td>Advanced age (especially &gt;80 years)</td>
</tr>
<tr>
<td>Nicotinic acid (Rarely)</td>
<td>Women &gt; Men especially at older age</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Small body frame, frailty</td>
</tr>
<tr>
<td>Antifungal azoles**</td>
<td>Multisystem disease‡</td>
</tr>
<tr>
<td>Macrolide antibiotics†</td>
<td>Multiple medications</td>
</tr>
<tr>
<td>HIV protease inhibitors</td>
<td>Perioperative period</td>
</tr>
<tr>
<td>Nefazadone</td>
<td>Alcohol abuse</td>
</tr>
<tr>
<td>Verapamil, Amiodarone</td>
<td>Grapefruit juice (&gt;1 quart/day)</td>
</tr>
</tbody>
</table>

*General term to describe diseases of muscles
**Itraconazole, Ketoconazole
†Erythromycin, Clarithromycin
‡Chronic renal insufficiency, especially from diabetes mellitus

Alternate day Statins

In a meta analysis no statistically significant difference between alternate-day and daily regimens of atorvastatin and rosuvastatin in terms of LDL-C and TG.

Fluvastatin and Pravastatin not different in LDL, TG or TC
A systematic review and meta-analysis of the therapeutic equivalence of statins

Weng TC, et al. J Clin Pharm Ther. 2010;35;139-151
Treating statin intolerance

Slowly increase the dose and follow for symptoms.

My favorite statin in the tough patients are pitavastatin, fluvastatin (lipophilic) or pravastatin, resuvostatin (hydrophilic).

Once you get to your maximal dose you can add zetia to obtain added LDL lowering.

Additional measures include niacin, phytosterols, welchol, metamucil,
Non-statin Options

Ezetimibe
Bile Acid Sequestrants
Fibrates
Niacin
Terminal Ileal Resection
Neutraceuticals-plant sterols/stanols, soluble fiber, Oatmeal, Bergamot etc
The FDA subsequently mandated that no RYR supplement sold in the United States may legally contain more than trace amounts of statins.

Traditional RRY has no statin in it and the supplements were found to have been spiked with lovastatin.
Non statin therapy by the Guidelines

Ezetimibe is the most commonly used nonstatin agent. It lowers LDL-C levels by 13% to 20% and has a low incidence of side effects.

Bile acid sequestrants reduce LDL-C levels by 15% to 30% depending on the dose.

PCSK9 inhibitors are powerful LDL-lowering drugs. They generally are well tolerated, but long-term safety remains to be proven. Cost effectiveness issues persist. Last check $1,114/mo.
What to do if you’re not at Goal?

Next most valuable-Ezetimibe
Consider fenofibrate, bile acid sequestrans, Niacin, metamucil, plant sterols,
Lastly consider soy protein, bergamot,
Repatha, Evolocumab-PCSK 9 inhibitors if known disease and you’re not even close to goal.
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Bile Acid Resins: Efficacy

- In patients with hypercholesterolemia, bile acid resins:
  - Decrease LDL-C 12%-25%
  - Increase HDL-C 4%-5%
  - Increase triglyceride levels in some patients
- Colesevelam also indicated as adjunct to diet and exercise to improve glycemic control in Type II DM

Bile Acid Resins: Adverse Effects

- Common adverse reactions reported with bile acid resins include:
  - Constipation
  - Headache
  - Abdominal discomfort, intestinal gas, indigestion
  - Diarrhea
  - Musculoskeletal pain
  - Impairment of fat soluble vitamins
**Bile Acid Sequestrants**

- Can bind other drugs and decrease absorption:
  - With colestipol and cholestyramine interacting drugs should be given 1 hr before or 4 hrs after
  - Interaction risk is less problematic with colesevelam
- Known drug interaction with colesevelam:
  - glyburide, levothyroxine, and oral contraceptives with ethinyl estradiol or norethindrone; should be dosed 4 hrs before colesevelam
Bile Acid Resins: Formulation Differences

- Tablet form (colesevelam hydrochloride, colestipol hydrochloride)
  - Colesevelam 0.625 g/tablet, 6-7 tablets/day
  - Colestipol 1.0 g/tablet, up to 16 tablets/day
- Colesevelam oral suspension- 3.75 g/day in 4-8 oz (1/2 to 1 cup) water or 1.875 grams BID with meals
- Powder form (cholestyramine) that must be mixed with water before use; 4 g/dose

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- Powder form (cholestyramine) that must be mixed with water before use; 4 g/dose
Mechanism by Which Bile Acid Sequestrants Lower LDL-C Levels

• Bile acids are delivered to the intestine through the bile
• Approximately 95% of bile acids are normally reabsorbed in the terminal ileum through intestinal bile acid transporters and subsequently returned to the liver in the process of enterohepatic recirculation
• Bile acid sequestrants (BAS) bind bile acids in the intestine and increase the excretion of bile acids in the feces
• The decrease in bile acid returned to the liver leads to upregulation of key enzymes responsible for bile acid synthesis, particularly CYP7A1
• The increase in cholesterol catabolism to bile acids results in a compensatory increase in hepatic LDL receptor activity, clearing LDL-C from the circulation
• LDL-C blood levels are reduced

LDL = low-density lipoprotein; LDL-C = LDL cholesterol.

colesevelam HCl-ezetimibe combination therapy was associated with significant reductions in mean levels of total cholesterol (27.5%), LDL-C (42.2%), and non-HDL-C (37.1%) in statin intolerant patients.
**Fibrates: Efficacy**

Baseline ↑ LDL cholesterol + ↓ triglycerides + fibrate = ↓ LDL-C

---

**Table 4. Mean Percent Change in Lipid Parameters at End of Treatment**

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Total-C</th>
<th>LDL-C</th>
<th>HDL-C</th>
<th>TG</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pooled Cohort</strong>&lt;br&gt;(n=646)</td>
<td>306.9 mg/dL</td>
<td>213.8 mg/dL</td>
<td>52.3 mg/dL</td>
<td>191.0 mg/dL</td>
</tr>
<tr>
<td>All FEN (n=361)</td>
<td>-18.7%*</td>
<td>-20.6%*</td>
<td>+11.0%*</td>
<td>-28.9%*</td>
</tr>
<tr>
<td>Placebo (n=285)</td>
<td>-0.4%</td>
<td>-2.2%</td>
<td>+0.7%</td>
<td>+7.7%</td>
</tr>
<tr>
<td><strong>Baseline</strong>&lt;br&gt;LDL-C &gt; 160 mg/dL and TG &lt; 150 mg/dL&lt;br&gt;(n=334)</td>
<td>307.7 mg/dL</td>
<td>227.7 mg/dL</td>
<td>58.1 mg/dL</td>
<td>101.7 mg/dL</td>
</tr>
<tr>
<td>All FEN (n=193)</td>
<td>-22.4%*</td>
<td>-31.4%*</td>
<td>+9.8%*</td>
<td>-23.5%*</td>
</tr>
<tr>
<td>Placebo (n=141)</td>
<td>+0.2%</td>
<td>-2.2%</td>
<td>+2.6%</td>
<td>+11.7%</td>
</tr>
<tr>
<td><strong>Baseline</strong>&lt;br&gt;LDL-C ≥ 160 mg/dL and TG ≥ 150 mg/dL&lt;br&gt;(n=242)</td>
<td>312.8 mg/dL</td>
<td>219.8 mg/dL</td>
<td>46.7 mg/dL</td>
<td>231.9 mg/dL</td>
</tr>
<tr>
<td>All FEN (n=126)</td>
<td>-16.8%*</td>
<td>-20.1%*</td>
<td>+14.6%*</td>
<td>-35.9%*</td>
</tr>
<tr>
<td>Placebo (n=116)</td>
<td>-3.0%</td>
<td>-6.6%</td>
<td>+2.3%</td>
<td>+0.9%</td>
</tr>
</tbody>
</table>

* Duration of study treatment was 3 to 6 months.

* p = < 0.05 vs. Placebo.
# Fibrates: Efficacy

Baseline ↑ triglycerides + low LDL-C + fibrate = ↑ LDL-C

Table 5. Effects of TRICOR in Patients With Hypertriglyceridemia

<table>
<thead>
<tr>
<th>Study</th>
<th>Placebo</th>
<th>TRICOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline TG levels 350 to 499 mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides</td>
<td>N Baseline (Mean)</td>
<td>Endpoint (Mean)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>28 449</td>
<td>450</td>
</tr>
<tr>
<td>VLDL Triglycerides</td>
<td>19 367</td>
<td>350</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>28 255</td>
<td>261</td>
</tr>
<tr>
<td>HDL Cholesterol</td>
<td>28 35</td>
<td>36</td>
</tr>
<tr>
<td>LDL Cholesterol</td>
<td>28 120</td>
<td>129</td>
</tr>
<tr>
<td>VLDL Cholesterol</td>
<td>27 99</td>
<td>99</td>
</tr>
<tr>
<td>Baseline TG levels 500 to 1500 mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides</td>
<td>N Baseline (Mean)</td>
<td>Endpoint (Mean)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>44 710</td>
<td>750</td>
</tr>
<tr>
<td>VLDL Triglycerides</td>
<td>29 537</td>
<td>571</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>44 272</td>
<td>271</td>
</tr>
<tr>
<td>HDL Cholesterol</td>
<td>44 27</td>
<td>28</td>
</tr>
<tr>
<td>LDL Cholesterol</td>
<td>48 100</td>
<td>90</td>
</tr>
<tr>
<td>VLDL Cholesterol</td>
<td>42 137</td>
<td>142</td>
</tr>
</tbody>
</table>

* = p < 0.05 vs. Placebo
Fibrates: Adverse Effects

- Generally well tolerated
- Gastrointestinal AE's (e.g. dyspepsia, diarrhea, etc.)
- Increase in liver transaminases
- Pre-existing gallbladder disease
- Can cause myopathy alone
- Associated with cholelithiasis
- Associated with deep vein thrombosis/emboli
- May potentiate the action of oral anticoagulants
- Potential interaction with TZDs on lowering HDL
- Contraindications: Hepatic or renal dysfunction
  - Gemfibrozil may be preferred with renal insufficiency
Niacin treatment

Niacin is especially good at increasing HDL but it also lowers LDL and Triglycerides.

No outcomes benefit data

Flushing is the major side effect and always warn people about this

Start with a low dose, eg 250 mg with food once a day and gradually increase until you get to 2000 mg. Take with food, your daily asa and it will blunt the flushing.
Niacin: Efficacy

• In patients with diabetes and mixed dyslipidemia, niacin:
  – Increases HDL-C 15%-30%
  – Decreases TG levels 15%-50%
  – Have dose-dependent effects on LDL-C (up to 40%)*
  – Decreases lipoprotein(a) levels by 25%
  – Decreases fibrinogen levels by 14%
  – Decreases Lp-PLA2 by an additional 20% when added to statin therapy

Brown BG. Am J Coll Cardiol 2007;99(supp):6:32C-34C.
Adding psyllium fiber resulted in reductions in low-density lipoprotein-cholesterol equivalent to doubling the statin dose.
Oat beta glucan

LDL-cholesterol reduction was almost double in trials that administered ≥3·0 g/d of oat β-glucan compared with those that administered <3·0 g/d.

Pooled analyses showed that oat β-glucan has a lowering effect on LDL-cholesterol, non-HDL-cholesterol and apoB.

British Journal of Nutrition (2016), 116, 1369–382
Plant Sterols/Stanols - Mechanism

- Reduce LDL-C concentration by decreasing intestinal cholesterol absorption
- Subsequently, endogenous cholesterol synthesis is increased which up-regulates LDL-C receptor expression
- Recent evidence suggests they also lower cholesterol by increasing trans-intestinal cholesterol excretion
Bergamot in statin intolerant pts

Reduced TC 21.8% with 500 mg bergamot and 29.3% with 1000 mg bergamot vs 0.1% in the placebo group.

LDL-C reduced 24.1% [500 mg/day] and 30.6% [1000 mg/day] versus 1.1% [placebo].

HDL-C increase 22.3% [500 mg/day] and 40.1% [1000 mg/day] versus 1.2% [placebo].

No SE but only 30 d fu.
Who do you consider for PCSK9 agents

Familial hypercholesterolemic pt
Rare CAD pts with persistently elevated LDL despite maximally tolerated statins, zetia and additional nonstatin agents
The Bottom Line

Make sure your patients take some dose of statin, Vit D helps with tolerance
Pay attention to triglycerides
Pre diabetes and borderline diabetes is just as bad as DM
Lifestyle factors are important- waist, pedometers, diet
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