Preventive Cardiology
Beyond Statins for Cardiovascular Risk Reduction

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Introduction

• Objectives
  1. Identify clinical scenarios in which statins and/or non-statin lipid lowering treatments are indicated
  2. Describe the mechanism of action of and indications for PCSK9 inhibitors, SGLT2 inhibitors, and high dose omega-3-polyunsaturated fatty acids

• No competing interests/financial relationships to disclose
• I will discuss what is currently off-label use of icosapent ethyl (Vascepa®)
• Branded Rx/OTC products shown: not an endorsement
Outline

• Recent history of and important concepts in clinical lipidology
• New ACC/AHA Blood Cholesterol guidelines: goals are back
• PCSK9 inhibition: when and how?
• SGLT2 inhibition: inducing glycosuria improves outcomes
• Marine omega-3 polyunsaturated fatty acids: fishy or not?
• Other “nutraceuticals”: is there a role?

Recent History of Preventive Cardiology

Use what you got: RCTs, epidemiological data, genetic, metabolic studies: focus on LDL-C

RCTs only! Only statins have the convincing evidence
2013 ACC/AHA Guidelines

Step 1: Decide whether there is an indication for a statin
Next steps: unclear

- Is there a goal LDL-C to achieve?
- What is the role of non-statins?
- The LDL “hypothesis”: to what extent does non-statin LDL-C lowering reduce risk?

Statin Benefit Groups

<table>
<thead>
<tr>
<th>Clinical ASCVD</th>
<th>LDL-C ( \geq 190 ) mg/dl</th>
<th>DM, LDL-C 70-189 mg/dl, age 40-75</th>
<th>Primary prev. (10-yr risk ( \geq 7.5%))</th>
</tr>
</thead>
</table>

All roads lead to STATIN


Recent History of Preventive Cardiology

Meanwhile, the National Lipid Assn. continues a risk factor and LDL-C or non-HDL-C lowering approach

Major ASCVD risk factors (HALFS)
- HTN
- Age (M≥45, F≥55 y)
- Low HDL
- FmHx early CHD (M<55, F<65)
- Smoking

Risk Category | Non-HDL-C goal | LDL-C goal
--- | --- | ---
Low | < 130 mg/dl | < 100
Moderate | < 130 | < 100
High | < 130 | < 100
Very High | < 100 | < 70

ASCVD, or [Diabetes mellitus + end organ damage]

We live in an LDL-C paradigm. Why?

<table>
<thead>
<tr>
<th>Diagnosis ↓ Lipids (mg/dl)</th>
<th>Normal</th>
<th>Familial Hyperchol.</th>
<th>Metabolic Syndrome / DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total-C</td>
<td>158</td>
<td>342</td>
<td>318</td>
</tr>
<tr>
<td>HDL-C</td>
<td>59</td>
<td>49</td>
<td>23</td>
</tr>
<tr>
<td>LDL-C</td>
<td>88</td>
<td>280</td>
<td>?</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>53</td>
<td>67</td>
<td>1,621</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>99</td>
<td>293</td>
<td>295</td>
</tr>
</tbody>
</table>

LDL-C vs. Non-HDL-C

- We live in an LDL-C paradigm. Why?

<table>
<thead>
<tr>
<th>LDL-C</th>
<th>Non-HDL-C</th>
<th>N (MACE)</th>
<th>N (Total)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 100 mg/dl</td>
<td>≥ 130 mg/dl</td>
<td>1,877</td>
<td>10,419</td>
<td>1.21 (1.13-1.29)</td>
</tr>
<tr>
<td>≥ 100 mg/dl</td>
<td>&lt; 130 mg/dl</td>
<td>467</td>
<td>2,873</td>
<td>1.02 (0.92-1.12)</td>
</tr>
<tr>
<td>&lt; 100 mg/dl</td>
<td>≥ 130 mg/dl</td>
<td>283</td>
<td>1,435</td>
<td>1.32 (1.17-1.50)</td>
</tr>
<tr>
<td>&lt; 100 mg/dl</td>
<td>&lt; 130 mg/dl</td>
<td>2,760</td>
<td>23,426</td>
<td>1.00 (Reference)</td>
</tr>
</tbody>
</table>

- Statin-treated patients who reached goals of LDL-C, non-HDL-C, both, or neither
- When discordant, non-HDL-C predicts major CV events better than LDL-C
- HRs adjusted for sex, age, smoking, DM, SBP, and trial


2016-2017 ACC Expert Consensus

- Role of non-statin therapies for LDL-C lowering in management of ASCVD risk

Step 1: Decide whether there is an indication for a statin
Step 2: Consider non-statin therapies
Step 3: Recognize non-statin indications

- Consider adherence, statin tolerance, control of risk factors
- Consider percentage LDL-C & non-HDL-C reduction and level achieved
- Consider ezetimibe, bile acid sequestrants, PCSK9i

**Preventive Cardiology**

**Beyond Statins for Cardiovascular Risk Reduction**

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Specialty Practice Pharmacist - Ambulatory Care  
The Ohio State University Wexner Medical Center

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**Statins**

- **Dosing + Effects:**
  - Potency varies by statin and dose
    - High intensity: >50% ↓ LDL-C
    - May also decrease TRG and HDL
  - PO formulations
  - Once daily administration*
  - Newer agents can be taken at any time of day

- **Pleiotropic effects**
- **Adverse Effects:**
  - Myalgias, GI upset
- **Drug interactions**
  - Exception: fluvastatin

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*exception: fluvastatin

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[Image of a flowchart showing the metabolic pathway from citrate to cholesterol, with STATINS highlighted.]

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### Ezetimibe

**Mechanism**
- Blocks NPC1L1
- Inhibits enteric cholesterol absorption
- (Statins increase chol. absorption)

**Dosing & effect**
- 10 mg PO daily
- Expect 15-25% ↓LDL-C

Ezetimibe

- Adverse effects
  - Respiratory tract symptoms (4% vs. 2% placebo)
  - Transaminase elevations with statins (1-2%)
  - GI symptoms comparable to placebo

Dosing & effect


IMPROVE-IT

- Outcomes from non-statin driven LDL-C reduction

- 18,144 patients with acute coronary syndrome
- LDL-C at baseline: 50 to 125 mg/dl
- Randomization: simvastatin 40 mg + [ezetimibe 10 mg OR placebo]
**IMPROVE-IT**

- Outcomes from non-statin driven LDL-C reduction

**Primary end point composite:** cardiovascular death, nonfatal MI, UA requiring hospitalization, coronary revascularization ($\geq 30$ d after randomization), nonfatal CVA

24% additional LDL-C reduction


Median follow up 6 years

Outcome: HR 0.936 (95% CI 0.89-0.99)

PCSK9 inhibitors

Mechanism, dosing, and adverse effects

- **Mechanism**
  - Human IgG1/2 mAb that inhibits proprotein convertase subtilisin/kexin type 9 binding to LDLR
  - $T_{1/2}$ 17-20 days (alirocumab) or 11-17 (evolocumab) days

Dosing & effect

- **Alirocumab**: 75-150 mg SQ q2wk, OR 300 mg SQ q4wk
- **Evolocumab**: 140 mg SQ q2wk or 420 mg SQ q4wk
- Expect 50-70% additional ↓LDL-C

Graphic original
PCSK9 inhibitors

Mechanism, dosing, and adverse effects

- Adverse effects
  - Injection site reactions (7% vs. 5% placebo)
  - Nasopharyngitis, flu-like reaction, myalgias, new onset DM similar to placebo
  - Antibody formation
  - Rare serious allergic reactions

FOURIER: Outcomes from non-statin driven LDL-C reduction

- Enrollment: 27,564 patients with ASCVD, LDL-C ≥ 70 mg/dl receiving statin therapy
- Treatment: evolocumab 140 mg q2wk or 420 mg q4wk vs. placebo
- Outcome: [CV death, MI, CVA, hospitalization for UA, coronary revascularization]
- Follow up: median 2.2 years

PCSK9 inhibitors

FOURIER: Outcomes from non-statin driven LDL-C reduction

- Outcome: [CV death, MI, CVA, hospitalization for UA, cor. revasc.]
- Follow up: median 2.2 years


PCSK9 inhibitors

FOURIER: Outcomes from non-statin driven LDL-C reduction

- Adverse events: no significant difference (incl. new DM, neurocognitive events) except injection site reactions (2.1% vs. 1.6% placebo)

PCSK9 inhibitors

ODYSSEY OUTCOMES: Outcomes from non-statin driven LDL-C reduction

- Enrollment: 18,924 patients with acute coronary syndrome
- Uncontrolled cholesterol: LDL-C ≥ 70 or non-HDL-C ≥ 100 mg/dl on high-intensity or maximum-tolerated statin


HR 0.85 (95% CI 0.78-0.93, P<0.001)

PCSK9 inhibitors

ODYSSEY OUTCOMES: Outcomes from non-statin driven LDL-C reduction

- Treatment: alirocumab vs. placebo (targeted LDL-C 25 to 50 mg/dl)
- Outcome: [CHD death, nonfatal MI, ischemic CVA, UA req. hospitalization]
- Follow-up median 2.8 years


HR 0.85 (95% CI 0.78-0.93, P<0.001)
PCSK9 inhibitors

Outcomes from non-statin driven LDL-C reduction

<table>
<thead>
<tr>
<th></th>
<th>FOURIER</th>
<th>ODYSSEY OUTCOMES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint</td>
<td>CV death, MI, stroke, hospitalization for</td>
<td>CHD death, non-fatal MI,</td>
</tr>
<tr>
<td>(composite)</td>
<td>unstable angina, or cor. revascularization</td>
<td>fatal or non-fatal ischemic stroke, or UA</td>
</tr>
<tr>
<td>Treatment vs. placebo</td>
<td>9.8% vs. 11.3%</td>
<td>9.5% vs. 11.1%</td>
</tr>
<tr>
<td>Median follow up</td>
<td>2.2 years</td>
<td>2.8 years</td>
</tr>
<tr>
<td>HR</td>
<td>0.85</td>
<td>0.85</td>
</tr>
<tr>
<td>NNT</td>
<td>67</td>
<td>64</td>
</tr>
</tbody>
</table>

PCSK9 inhibitors: what about cost?

SUGGESTED COST-EFFECTIVE ANNUAL PRICE ($100,000-150,000 PER QALY)

- Approx. US Price (mid-2018)
- Approx. Canadian Price (USD)
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Recent History of Preventative Cardiology

2013 ACC/AHA
2015 NLA Part 1/2
2017 Expert Consensus
2018 ACC/AHA

LDL-C or non-HDL-C goals are optional. Non-statins are included again.

 Aren't we due for a "fully updated" guideline?!


**Statin Benefit Groups**

<table>
<thead>
<tr>
<th>Clinical ASCVD</th>
<th>LDL-C ≥ 190 mg/dl (&quot;severe primary&quot;)</th>
<th>Diabetes mellitus, LDL-C 70-189 mg/dl, age 40-75</th>
<th>Others: assess risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>No risk assessment: high-intensity statin</td>
<td>Moderate intensity statin</td>
<td>Risk assessment to consider high intensity statin</td>
<td></td>
</tr>
</tbody>
</table>

Guideline on the Management of Blood Cholesterol

• Principles of the guideline
  — Assess ASCVD risk in each age group
  — Emphasize adherence to healthy lifestyle

At all levels:
provide a “risk discussion” as it relates to the management plan

**Intermediate risk**
If risk & enhancers favor statin, initiate moderate intensity statin to lower LDL-C by 30-49% (I)

**High risk**
Initiate high-intensity statin to reduce LDL-C by ≥ 50% (I)

**Borderline risk**
Risk “enhancers” guide moderate intensity statin (IIb)

- If risk decision is uncertain consider measuring CAC
  - CAC 0 and no DM, smoking, FmHx: consider no statin
  - CAC 1-99 (esp. ≥ 55yrs): statin
  - CAC ≥ 100 (75th%)iile: statin

**Low risk**
- Lifestyle, reduce risk factors (I)


**Clinical ASCVD**
- Multiple major ASCVD events (recent ACS, h/o MI, h/o CVA, PAD), OR
- Major ASCVD event + multiple high-risk conditions (age≥65, FH, h/o PCI/CABG, DM, HTN, CKD, smoking, persistently elevated LDL≥100, h/o CHF)

**Very high risk?**
- High-intensity/maximal statin (I)
- If LDL-C ≥ 70 mg/dl, adding ezetimibe is reasonable (IIa)
- If on maximal LDL-C lowering therapy and LDL-C remains ≥ 70 (non-HDL-C ≥ 100) mg/dl, adding PCSK9 inhibitor is reasonable (IIa)

2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA
Guideline on the Management of Blood Cholesterol

Clinical ASCVD

Yes

Very high risk?

• Multiple major ASCVD events (recent ACS, h/o MI, h/o CVA, PAD), OR
• Major ASCVD event + multiple high-risk conditions (age≥65, FH, h/o PCI/CABG, DM, HTN, CKD, smoking, persistently elevated LDL≥100, h/o CHF)

No

• High (or if >75 yrs, moderate or high [IIa]) intensity statin (I), or if not tolerated, moderate intensity statin

If LDL-C ≥ 70 mg/dl, ezetimibe is reasonable


Outline

• Recent history of and important concepts in clinical lipidology
• New ACC/AHA Blood Cholesterol guidelines: goals are back
• PCSK9 inhibition: when and how?
• SGLT2 inhibition: inducing glycosuria improves outcomes
• Marine omega-3 polyunsaturated fatty acids: fishy or not?
• Other “nutraceuticals”: is there a role?
Metabolic syndrome and diabetes mellitus

- Metabolic syndrome: co-occurrence of cardiovascular risk factors
- Share mechanisms of type 2 diabetes mellitus


• Graphic original.
• Hormone sensitive lipase (HSL) mobilizes stored fat, breaking down TGs, freeing FAs
• More energy in bloodstream
• HSL is inhibited by insulin
  • Lipoprotein lipase (LPL) cleaves TGs into free fatty acids (FFAs)
  • “Clears” TG-rich particles from the circulation
  • Less energy in bloodstream
  • LPL is activated by insulin

• Hepatic VLDL production also occurs when increased circulating energy stores are needed
• VLDL production is inhibited by insulin

*Graphic original.
• VLDL can transfer its TG content to LDL
• TG-rich LDL is preferentially converted to small, dense LDL which is particularly atherogenic

• After VLDL and chylomicrons (CM) donate their lipid contents to end-tissues, they become VLDL or CM remnants
• Remnants are particularly atherogenic
Normal state
- Circulating VLDLs and CMs are kept to a minimum
- Energy is “cleared appropriately” from the bloodstream for utilization or storage

Diabetic dyslipidemia
- Increased serum triglycerides
- Decreased HDL-C
- Predominance of small dense LDL particles and VLDL/CM remnants

- Graphic original.
SGLT2 inhibitors

- **Therapeutic glycosuria**

  - [Diagram showing glucose reabsorption in proximal convoluted tubule with SGLT2 inhibitors increasing glucose excretion]

Class currently includes canagliflozin, dapagliflozin, and empagliflozin

- **Mechanism**
  - Prevent reabsorption of glucose by the kidneys
  - Net decrease in blood sugar

- **Dosing & effect**
  - Oral agents with daily dosing
  - A1c lowering of 0.5-0.8%

- **Adverse effects**
  - Hypotension
  - Urinary tract infections
  - Ketoacidosis
  - AKI

**SGLT2 inhibitors**

- **Therapeutic glycosuria**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Approximate effect of SGLT2 inhibitor treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight</td>
<td>↓ 4 kg</td>
</tr>
<tr>
<td>Visceral adipose tissue mass</td>
<td>↓ 8%</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>↓ 4%</td>
</tr>
<tr>
<td>HDL-C</td>
<td>↑ 6%</td>
</tr>
<tr>
<td>LDL-C</td>
<td>↑ 2%</td>
</tr>
</tbody>
</table>


**Summary of CV benefit/harm of diabetic drugs**

- **SGLT2 inhibitors:** positive
  - Empagliflozin (EMPA-REG OUTCOME) [HR 0.86]
  - Canagliflozin (CANVAS) [HR 0.86]

- **GLP-1 receptor agonists:** mixed
  - Lixisenatide (ELIXA) ±
  - Exenatide (EXSCEL) ±
  - Liraglutide (LEADER) + [HR 0.97]
  - Semaglutide (SUSTAIN-6) + [HR 0.74]

- **DPP4 inhibitors:** neutral effect
  - Sitagliptin (TECOS)
  - Alogliptin (EXAMINE)
  - Saxagliptin (SAVOR-TIMI 53)

- **Insulins:** neutral effect

*Agent (STUDY example) [HR for generally primary endpoint of MACE, p<0.05]*

Cefalu WT et al. *Diab Care* 2018;41:14-31.

See Dr. Joshua Joseph’s MedNet21 webcast for more information
Outline

- Recent history of and important concepts in clinical lipidology
- New ACC/AHA Blood Cholesterol guidelines: goals are back
- PCSK9 inhibition: when and how?
- SGLT2 inhibition: inducing glycosuria improves outcomes
- Marine omega-3 polyunsaturated fatty acids: fishy or not?
- Other “nutraceuticals”: is there a role?

Recall: regulation of VLDL synthesis is under the control of insulin
- Also: ω-3-polyunsaturated fatty acids (ω-3-PUFAs) inhibit VLDL lipidation and TG production

- Graphic original.
Omega-3 Fatty Acids

• Mechanism of action – not well elucidated
  • Proposed: increased beta oxidation, inhibition of acyl-CoA, decreased hepatic production of VLDL, increased LPL activity

• Dosing & effect
  • For TG >500: dosed at 2g twice daily
  • Primary effect is to lower TG
    • DHA component can increase LDL

• Adverse effects
  • Prolongation of bleeding time
  • Fishy aftertaste or belching
  • Nausea

\[\text{ω-3-poly-unsaturated fatty acids}\]

• Do they reduce serum triglycerides?
  • Yes

• Do they change outcomes?

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Approximate effect of ω-3-PUFA treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-HDL-C</td>
<td>↓5-14%</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>↓19-44%</td>
</tr>
<tr>
<td>HDL-C</td>
<td>±</td>
</tr>
<tr>
<td>LDL-C</td>
<td>↓6%-↑25%</td>
</tr>
</tbody>
</table>

**ω-3-poly-unsaturated fatty acids**

**Does treatment change outcomes?**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Endpoints / Mean Follow-up</th>
<th>Daily dose</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meta-analysis of 10 trials Aung et al. <em>JAMA Cardiol</em> 2018 <em>(n=77,917) prior CHD, CVA, or high ASCVD risk</em></td>
<td>Any CHD (fatal/nonfatal) or major vascular events 4.4 years</td>
<td>Generally 1 g EPA/DHA</td>
<td>No effect</td>
</tr>
<tr>
<td>GISSI-Prevenzione investigators. <em>Lancet</em> 1999; <em>(n=11,324) with recent MI (2x2 design also with vt. E)</em></td>
<td>Death, non-fatal MI, CVA 3.5 years</td>
<td>1 g EPA/DHA vs. Placebo</td>
<td>Benefit Composite RRR 10% Death RRR 14%</td>
</tr>
<tr>
<td>JELIS Yokogama et al. <em>Lancet</em> 2007 <em>(n=18,645) unselected hypercholesterolemic (Total-C &gt; 252 mg/dl) Japanese patients</em></td>
<td>Any CHD event (CHD death, SCD, fatal/nonfatal MI, UA, PCI, CABG) 4.6 years</td>
<td>Statin + [1.8 g EPA-only or placebo]</td>
<td>Benefit Composite RRR 19% No difference in LDL</td>
</tr>
</tbody>
</table>

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**REDUCE-IT**

- **Enrollment**: 8,179 patients with hypertriglyceridemia (135-499 mg/dl) and “controlled” LDL (41-100 mg/dl).
- **Patients** were (mean) 64 yrs, 71% male, BMI 30.8, most on statins
- **Endpoint**: [CV death, nonfatal MI, nonfatal CVA, coronary revascularization or UA]
- **Treatment**: icosapent ethyl (EPA only) 4 g/day (2 g bid with food) vs. placebo (mineral oil)
- **Follow-up**: 4.9 yrs.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment (EPA)</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides</td>
<td>↓18.3% (-39 mg/dl)</td>
<td>↑12.2% (+4.5 mg/dl)</td>
</tr>
<tr>
<td>LDL-C</td>
<td>↓13.1% (+2.0 mg/dl)</td>
<td>↑10.2% (+7.0 mg/dl)</td>
</tr>
</tbody>
</table>

[HR 0.75 NNT 21 (RRR 20% for CV death)]

REDUCE-IT

What’s the catch?

- Any adverse effects?
  - No difference in bleeding, including hemorrhagic stroke
  - Hospitalization for atrial fibrillation or flutter was 3.1% in EPA group vs. 2.1% placebo (p=0.0004).
- Is it just the triglyceride lowering?
  - ACCORD-Lipid: fenofibrate lowers TG but no change in outcome
  - AIM-HIGH, HPS2-THRIVE: niacin lowers TG but no change in outcome
- Will REDUCE-IT change practice?

ω-3-poly-unsaturated fatty acids

- Antiarrhythmic or not?

<table>
<thead>
<tr>
<th>Trial</th>
<th>Dose</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>REDUCE-IT 2019</td>
<td>4 g/d EPA only</td>
<td>↑47% excess atrial fib/flutter</td>
</tr>
<tr>
<td>Cochrane Review 2018</td>
<td>Varies (0.5 to &gt;5 g/d)</td>
<td>Marine: No difference arrhythmia Plant-based (ALA): ↓21% arrhythmias</td>
</tr>
<tr>
<td>79 RCTs, (n=112,059)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GISSI-HF (n=6,975) with HF</td>
<td>1 g/d mixed</td>
<td>No difference in atrial fibrillation ↓9% mortality; ↓8% HF admissions</td>
</tr>
</tbody>
</table>

- Animal studies suggest DHA may have antiarrhythmic properties in AF

**ω-3-poly-unsaturated fatty acids**

- **Current Rx products and labeling**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Trade Name Composition</th>
<th>Dose</th>
<th>Labeled Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Icosapent ethyl</td>
<td>Vascopa®</td>
<td>2 g bid with food</td>
<td>• Significant hypertriglyceridemia (&gt;500 mg/dL) as adjunct to diet and exercise</td>
</tr>
<tr>
<td>ω-3 acid ethyl esters</td>
<td>Lovaza® 65% EPA / 45% DHA</td>
<td>4 g qd or 2 g bid +/- food</td>
<td>• Significant hypertriglyceridemia (&gt;500 mg/dL) as adjunct to diet and exercise</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• For use as adjunct to simvastatin for hyper-TG</td>
</tr>
<tr>
<td>ω-3 carboxylic acids</td>
<td>Epanova® Mostly EPA</td>
<td>2-4 g qd +/- food</td>
<td>• Significant hypertriglyceridemia (&gt;500 mg/dL) as adjunct to diet and exercise</td>
</tr>
</tbody>
</table>


**ω-3-poly-unsaturated fatty acids**

- **Should I just buy OTC fish oil at the drug store?**

<table>
<thead>
<tr>
<th>How to get 2 g EPA</th>
<th>Vascepa</th>
<th>Lovaza</th>
<th>Viva Naturals</th>
<th>Kirkland</th>
<th>Nature Made</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>700 mg EPA</td>
<td>240 mg DHA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>250 “omega-3”</td>
<td>360 mg EPA</td>
<td>300 mg DHA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>?150 mg EPA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>?100 mg DHA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
“Nutraceuticals”

“Doc, is it OK if I take...?”

- “Certain nutraceuticals...alone or in combination with each other, as well as ezetimibe, might be considered as an alternative or add-on therapy to statins, although there is still insufficient evidence available with respect to long-term safety and effectiveness ....”


“Nutraceuticals” and lifestyle changes

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Mechanism of action</th>
<th>Dose</th>
<th>Expected Δ LDL-C (relative)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased physical activity</td>
<td>Multifactorial</td>
<td>200-300 min/week</td>
<td>↓~5%</td>
</tr>
<tr>
<td>Loss of body weight</td>
<td>Multifactorial</td>
<td>↓5% body weight</td>
<td>↓3-5%</td>
</tr>
<tr>
<td>Diet low in saturated and trans fats</td>
<td>↓LDL-C production</td>
<td></td>
<td>↓5-10%</td>
</tr>
<tr>
<td>Viscous fiber</td>
<td>Bile acid sequestration, ↑satiety</td>
<td>5-10 g/day</td>
<td>↓5-20%</td>
</tr>
<tr>
<td>Plant sterols/stanols</td>
<td>Competitive inhibition of cholesterol absorption</td>
<td>2 g/day</td>
<td>↓~10%</td>
</tr>
</tbody>
</table>

“Nutraceuticals” and lifestyle changes

**Highlights**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of action</th>
<th>Dose</th>
<th>Δ LDL-C (absolute)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berberine</td>
<td>Has PCSK9 inhibitory properties, increases LDLR expression and decreases intestinal chol. absorption</td>
<td>300 mg/day</td>
<td>25 mg/dl</td>
</tr>
<tr>
<td>Artichoke</td>
<td>Luteolin interacts with HMG-CoA reductase, SREBPs, ACAT</td>
<td>500-2,700 mg/d</td>
<td>15 mg/dl</td>
</tr>
<tr>
<td>Garlic</td>
<td>Inhibition of HMG-CoA reductase</td>
<td>5-6 g/d</td>
<td>9 mg/dl</td>
</tr>
<tr>
<td>Green tea</td>
<td>Inhibition of inducible NO synthase, inhibition of HMG-CoA reductase</td>
<td>170-1,200 mg/d</td>
<td>7 mg/dl</td>
</tr>
</tbody>
</table>


**A Case Study**

34 year-old man with family history of heart disease is interested in lowering his cholesterol “naturally” (despite low 10-year est. ASCVD risk).
**Take Home Points**

- Recent history of and important concepts in clinical lipidology
  - Please consider non-HDL-C as well as LDL-C lowering, especially in hypertriglyceridemics
- New ACC/AHA Blood Cholesterol guidelines
  - Goal atherogenic cholesterol levels are both motivating and evidence based
- PCSK9 inhibition: when and how?
  - FH or ASCVD and LDL-C > 70 or non-HDL-C > 100 mg/dl

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**Take Home Points**

- SGLT2 inhibition: inducing glycosuria improves outcomes
  - Discuss ASCVD benefits of DM drugs with PCP, endocrine
- Marine omega-3 polyunsaturated fatty acids and other “nutraceuticals”
  - May have a role, consider in statin intolerance/refusal