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, epidem./obs. data, genetic, metabolic studies: focus on ↓LDL-C

2002 NCEP ATP III

RCTs only! Only statins have the convincing evidence

2013 ACC/AHA
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 ≥ 190 mg/dl</th>
<th>DM, LDL-C 70-189 mg/dl, age 40-75</th>
<th>Primary prev. (10-yr risk ≥ 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

2015 NLA Part 1/2

2013 ACC/AHA

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]

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**NLA Part 1 / Part 2 (2015)**

On-Treatment LDL Cholesterol vs. events
- Reduce LDL-C or non-HDL-C by ~40 mg/dl
- Lower (RRR) ASCVD by ~20%

**5-yr ASCVD event rate (%)** vs. **LDL Cholesterol (mg/dl)**

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

**Statin Benefit Groups**

- **Clinical ASCVD**
  - LDL-C < 190 mg/dl
- **DM, LDL-C 70-189 mg/dl, age 40-75**
- **Primary prev. (10-yr risk ≥ 7.5%)**

**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

Kelly M. Bartsch, PharmD, BCPS, CLS
Specialty Practice Pharmacist - Ambulatory Care
The Ohio State University Wexner Medical Center

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

Statins – Potency + Lipophilicity

**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

  24% additional LDL-C reduction

- Primary end point composite: cardiovascular death, nonfatal MI, UA requiring hospitalization, coronary revascularization (≥ 30 d after randomization), nonfatal CVA


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**IMPROVE-IT**

- Outcomes from non-statin driven LDL-C reduction

  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

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**Drug information:**

**Graphic original**

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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 $\geq$ 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 unstable angina, or cor. revascularization</td>
<td>CHD death, non-fatal MI, fatal or non-fatal ischemic stroke, or UA requiring hospitalization</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)

Kazi et al. JAMA 2016
Aviles et al JAMA Cardiol 2017
Fonarow et al. JAMA Cardiol 2017
Bhatt et al. 2018 Unpublished
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Recent History of Preventative Cardiology

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

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

- Assess ASCVD risk in each age group
- Emphasize adherence to healthy lifestyle


Principles of the guideline

- Consider ASCVD risk “enhancers” when making treatment decisions

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 (IIa)
Lifestyle, reduce risk factors (I)

Low risk

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)

Yes

Very high risk?

No

- 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

• 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?

Yes

No

• High (or if >75 yrs, moderate or high [IIa]) 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**

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- 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

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Graphic original.
**SGLT2 inhibitors**

- **Therapeutic glycosuria**
  
  ![Diagram showing mechanism of SGLT2 inhibitors]

- **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

- Insulin: neutral effect
  - Insulin glargine
  - Insulin degludec

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

- GLP-1 receptor agonists: mixed
  - Lixisenatide (ELIXA) ±
  - Exenatide (EXSCEL) ±
  - Linagliptide (LEADER) + [HR 0.87]
  - Semaglutide (SUSTAIN-6) + [HR 0.74]

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

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

\[
\begin{array}{c}
\text{EPA} \\
\text{OM-3 FA} \\
\text{DHA}
\end{array}
\]


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

- Do they reduce serum triglycerides?  
  - Yes
- Do they change outcomes?

\[
\begin{array}{|c|c|}
\hline
\text{Parameter} & \text{Approximate effect of }\omega-3\text{-PUFA treatment} \\
\hline
\text{Non-HDL-C} & \downarrow 5\text{-}14\% \\
\text{Triglycerides} & \downarrow 19\text{-}44\% \\
\text{HDL-C} & \pm \\
\text{LDL-C} & \downarrow 6\%\text{-}\uparrow 25\% \\
\hline
\end{array}
\]

**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><strong>Meta-analysis of 10 trials</strong>&lt;br&gt;Aung et al. <em>JAMA Cardiol</em> 2018&lt;br&gt;(n=77,917) prior CHD, CVA, or high ASCVD risk</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><strong>GISSI-Prevenzione</strong>&lt;br&gt;investigators <em>Lancet</em> 1999;&lt;br&gt;(n=11,324) with recent MI (2x2 design also with vit. E)</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><strong>JELIS</strong>&lt;br&gt;Yokogawa et al. <em>Lancet</em> 2007&lt;br&gt;(n=18,645) unselected hypercholesterolemic (Total-C &gt; 252 mg/dl) Japanese patients</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>

**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>

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</td>
</tr>
<tr>
<td>79 RCTs, (n=112,059)</td>
<td></td>
<td>Plant-based (ALA): ↓21% arrhythmias</td>
</tr>
<tr>
<td>GISSI-HF (n=6,975) with HF</td>
<td>1 g/d mixed</td>
<td>No difference in atrial fibrillation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓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</th>
<th>Dose</th>
<th>Labeled Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Icosapent ethyl</td>
<td>Vascepa®</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®</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®</td>
<td>2-4 g qd +/- food</td>
<td>Significant hypertriglyceridemia (&gt;500 mg/dl) as adjunct to diet and exercise</td>
</tr>
<tr>
<td></td>
<td>Mostly EPA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


- **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>250 “omega-3”</td>
<td>360 mg EPA</td>
<td>300 mg DHA</td>
</tr>
</tbody>
</table>

|                     | 150 mg EPA | 100 mg DHA | 360 mg EPA | 300 mg DHA |


"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

Highlights

<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>5-10%</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, SREBP1, 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/d</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

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