# Beyond the Statin: Additional Medications for Lipid Management

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# Disclosures

- I have no relevant financial relationships or affiliations with commercial interests to disclose

# Objectives

- Recognize those with Familial Hypercholesterolemia that have early indication for medication
- Discuss alternative therapies in those who are intolerant to statin but at high CV risk
- Understand indications for PCSK9-inhibitors, Ezetimibe, Niacin

# Current Guidelines

- Focus on the 4 major benefit groups
  - Those with clinical ASCVD
  - Those with LDL ≥ 190 mg/dl (4.9 mmol/L)
  - Those with diabetes aged 40-75 and LDL ≥ 70 mg/dl (1.8 mmol/L)
  - Those with LDL ≥ 70 mg/dl (1.8 mmol/L) AND 10-yr risk ≥ 7.5%
- Use LDL levels to guide additional therapy with non-statin meds (addition of ezetimibe or PCSK9 inhibitors)

# Consider Other Risk Enhancing Factors

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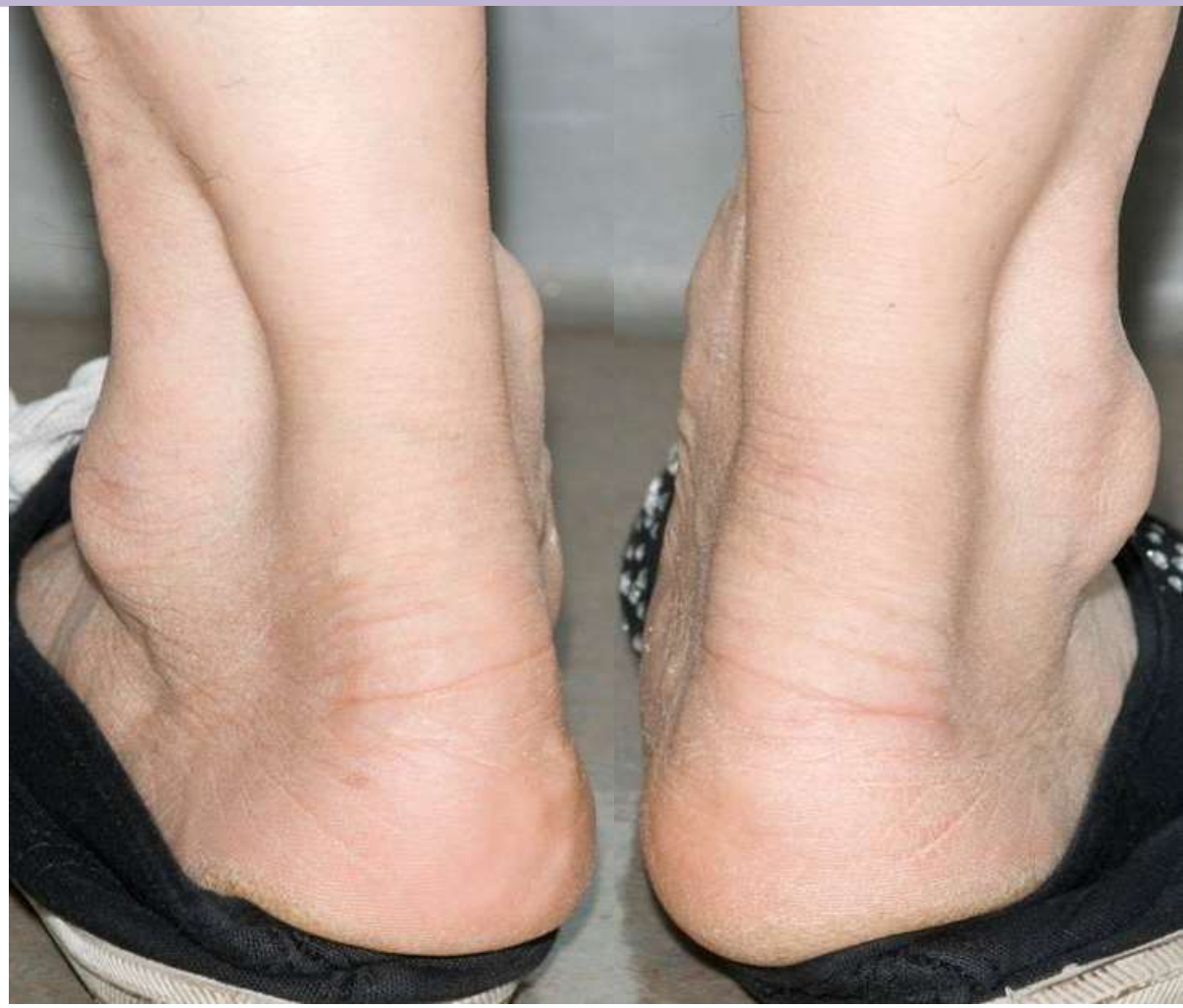
- Family history
- Metabolic syndrome
- CKD
- History of pre-eclampsia or premature menopause (age < 40)
- Chronic inflammatory disorders (eg. RA, psoriasis, chronic HIV)
- High risk ethnicity (eg South Asian ancestry)
- TG > 175 mg/dl (2.0 mmol/L)
- hsCRP > 2.0 mg/L (19 nmol/L) (if measured)
- Lp(a) > 50 mg/dl (125 nmol/L)
- Reduced ankle-brachial index

# 2018 Guidelines

- Emphasis on healthy lifestyle over the lifespan
- Use of maximally tolerated doses of statins
  - The lower the LDL the greater the risk reduction
- *Treatment of severe hyperlipidemia at any age*
  - *LDL > 190 mg/dl (>4.9 mmol/L)*
- Use of non-statin medications in addition for patients at very high risk
  - Multiple ASCVD events or 1 major ASCVD event + high risk conditions
  - *Add a 2nd medication if LDL > 70 mg/dl (1.8 mmol/L)*
  - Use ezetimibe, (or PCSK9-inhibitors if needed)

# Familial Hypercholesterolemia: Homozygotes

- LDL ↑ 6-8 fold; TC >1000, HDL low
- Manifest CAD by age 10
- Treatment:
  - LDL apheresis
  - Liver transplantation
  - Gene therapy



Palpable widening of Achilles tendon >

# Familial Hypercholesterolemia: Heterozygotes

- LDL ↑ 2-3 fold, normal HDL, TG
- Causes 4% of premature CAD
- LDL elevated from birth
- *Treat if LDL>190, at <u>any</u> age*
  - *Statins, ezetimibe, PCSK9 inhibitors*
- If untreated CAD manifests at (men):
  - 5% by age 30
  - 20% by 40
  - 50% by 50

*And screen their family members, including children*

But what if my patient can’t (or won’t) take a statin?

# Statin Intolerance

- Statin use: 25% of US adults > 40 yrs
- Statin discontinuance (in “real world”): ~10%

<u>Statin adverse effects</u>

- Serious muscle injury, including rhabdo: <0.1%
- Serious hepatotoxicity: ~ 0.001%
- Statin induced diabetes: ~ 0.2% per year of treatment

*Why the discrepancy? Why do so many patients discontinue statins when adverse rates are so low?*

# The Power of Thought

## Placebo Effect

- Benefit derived from belief that a therapy is active (when it is not)

## Nocebo Effect

- Harm derived from belief that a therapy is harmful (when it is not)

*…and don't overlook healthcare system contributions*

*Mistrust*

*Costs*

*Insurance changes*

*Provider handoffs*

# Approach to Statin Intolerance

- First, maximize control of other ASCVD risk factors
  - Smoking, BP, diabetes, etc

- Take a drug holiday then restart same statin
  - Many myalgias are due to other causes, symptom diary off then on statin can demonstrate that
- Try another statin (try at least 3)
  - Start low, and titrate
- Try alternate day statin*



* Off label use

# Approach to Statin Intolerance when Statins not an Option

- Use other lipid lowering agents and/or other medications that decrease CV risk
  - Ezetimibe
  - PCSK9-inhibitors
  - Bempedoic acid
  - Bile acid binding resins
  - Niacin
  - Non lipid lowering drugs with CV benefits (BP, diabetes drugs)

# Beyond Statins

- Consider non-statin medications when statins can't or won't be used
- Add non-statin medications for patients at very high risk
  - Multiple ASCVD events or 1 major ASCVD event + high risk conditions
  - *Add a 2nd medication if LDL > 70 mg/dl (1.8 mmol/L)*
  - Use ezetimibe, (or PCSK9-inhibitors if needed*)



**** The guidelines are based on cost-effectiveness considerations***

# Approach

- Start or add* a non-statin drug with CVD benefits
  - Ezetimibe
  - Bile acid resins
  - PCSK9 inhibitor
  - Bempedoic acid
  - Niacin
  - Icosapent ethyl

- **Inhibits intestinal cholesterol absorption**
- **↓LDL 18% as monotherapy**
- **With monotherapy MSK complaints very rare**
- **↓CV events with ezetimibe + statin vs statin alone**

**Add a non-statin drug when LDL >70 mg/dl on max tolerated statin*



Cannon et al; NEJM 2015

# Approach

- Start or add* a non-statin drug with CVD benefits
  - Ezetimibe
  - Bile acid resins
  - PCSK9 inhibitor
  - Bempedoic acid
  - Niacin
  - Icosapent ethyl

- **Facilitate cholesterol excretion thru GI tract**
- **↓LDL 10-30%**
- **However, use limited due to frequent GI complaints (30-50%)**
- **Contra-indicated if TG > 400 mg/dl**
- **No RCT evidence of ↓CV events**

**Add a non-statin drug when LDL >70 mg/dl on max tolerated statin*

# Approach

- Start or add* a non-statin drug with CVD benefits
  - Ezetimibe
  - Bile acid resins
  - PCSK9 inhibitor
  - Bempedoic acid
  - Niacin
  - Icosapent ethyl

- Increases LDL uptake by increasing LDL-receptors
- ↓LDL 50-60%
- However, MSK complaints ~5-20% in real world experience, typically in patients with history of statin intolerance
- ↓CV events with PCSK9i + statin vs statin alone

**Add a non-statin drug when LDL >70 mg/dl on max tolerated statin*



FOURIER Trial; NEJM 2017
ODYSSEY Trial; NEJM 2018

# Approach

- Start or add* a non-statin drug with CVD benefits
  - Ezetimibe
  - Bile acid resins
  - PCSK9 inhibitor
  - Bempedoic acid
  - Niacin
  - Icosapent ethyl

- **Inhibits cholesterol synthesis**
- **↓LDL 30%**
- **However, MSK complaints ~7% in studies, ~35% in real world report**
- **CV outcomes studies underway**

**Add a non-statin drug when LDL >70 mg/dl on max tolerated statin*

# Approach

- Start or add* a non-statin drug with CVD benefits
  - Ezetimibe
  - Bile acid resins
  - PCSK9 inhibitor
  - Bempedoic acid
  - Niacin**
  - Icosapent ethyl

- Decreases VLDL synthesis leading to lower LDL and lower TG
- ↓LDL up to 40% (↓TG ~ 30%)
- However, use limited by GI intolerance, flushing, glucose intolerance, other
- ** minimal evidence of further benefit when added to statin

**Add a non-statin drug when LDL >70 mg/dl on max tolerated statin*



HPS2-THRIVE trial; NEJM 2014

# Approach

- Start or add* a non-statin drug with CVD benefits
  - Ezetimibe
  - Bile acid resins
  - PCSK9 inhibitor
  - Bempedoic acid
  - Niacin**
  - Icosapent ethyl

- **A highly purified EPA**
- **Lowers TG~ 30%**
- **May have anti-inflammatory, anti-oxidative benefits**
- **↓CV events with IPE + statin vs statin alone**

**Add a non-statin drug when LDL >70 mg/dl on max tolerated statin*



REDUCE-IT trial; NEJM 2019

# Alternative Approach

- Start or add diabetes drugs with CVD benefits*
  - –GLP-1 analogs
  - –SGLT2 inhibitors
  - –Pioglitazone

# Encourage Compliance

Medications that aren't taken don't work


**"You haven't been taking your cholesterol medication, have you Mr. Grosshart?"**