Statin Intolerance

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Outline
- Why are lipids important?
- Why are statins important?
- Why Don’t Patients take their statins?
  - Are statins safe?
  - Is statin intolerance real?
  - How common?
- What can you do with statin intolerant patient?
  - Meds
  - Supplements

Why are lipids important

Stamler J, et al. JAMA 1986; 256:2823

- This is a continuous, graded relationship between total and LDL-C and coronary heart disease, without clear thresholds below which CHD risk is zero.
Why are statins important

- Statins reduce cardiovascular events and total mortality in populations at even lower levels of risk than has previously been appreciated, and with an excellent margin of safety.

- Meta-analysis of 175,000 individuals
  - ~20% reduction in risk of events with each 40mg drop in LDL
  - Irrespective of age, sex, baseline LDL cholesterol, previous vascular disease, and baseline cardiovascular risk
  - 11 events prevented for 1000 treated over 5 years overall
  - NNT = 167 for lowest risk category

2013 Cochrane meta-analysis

- 18 primary prevention statin trials: 56,934 participants
- Statins significantly reduce:
  - All-cause mortality (~14%)
  - Fatal and nonfatal cardiovascular disease (~22%)
  - Coronary heart disease (~27%)
  - Stroke (~22%)
  - Coronary revascularization (~38%)

Durable Benefit

- WOSCOPS
  - Long term follow-up revealed a decrease in the combined risk of death from CHD or nonfatal MI extending 10 years after trial completion!
  - At 10-year follow-up:
    - Rate of death from CHD or nonfatal MI:
      - 11.8% in the group originally assigned to pravastatin
      - 15.5% in the group originally assigned to placebo
      - HR 0.73, 95% CI, 0.63-0.88
    - Despite the fact that both groups had nearly identical use of statins after 5 years of follow-up.

WOSCOPS Follow Up

- At 20 year follow-up, coronary heart disease mortality was reduced 27% and all-cause mortality by 13%
- No difference in safety events (cancer, etc.)
Taking a statin for that 5 year period that occurred 20 years previously provided a "persistent reduction in cardiovascular disease outcomes" over the course of those 2 decades!

- Ten years of statin treatment for 10,000 women 55yo with high cholesterol (7.5% PCE)
  - Projected to prevent 32 MIs
  - Cause 70 cases of statin-induced myopathy
  - Add 1,108 years to total life expectancy

- 2013 ACC/AHA guidelines on the treatment of cholesterol to reduce atherosclerotic risk make more patients eligible for statin therapy
  - As many as 46% of U.S. adults

- 2016 USPSTF Guidelines recommend for anyone >40yo with 1+ RFs for CAD and >7.5% risk by PCE

A lot of people should start taking statins

- Patients who would benefit from statins aren’t taking them, or aren’t taking correct dosages.
  - 1/3 of statin eligible patients are not on them
  - Fewer than half of patients with clinical CHD are being treated with high-intensity statins

The Cost of UnderTreatment

- Patients who take <80% of their statin dose have a 45% relative increase in total mortality compared with more adherent patients
  - an increase greater than that observed with poor adherence to antihypertensive drugs
Why Don’t Patients Take Their Statins?

- Some patients don’t want to
- Some patients are intolerant

The Problem

- Fewer than half of the participants noted that they stopped taking statins because of immediate adverse or side effects

Perception vs. Reality

- Most participants noted that they received or sought information on statins from sources other than their physician or pharmacist.
  - The most common sources were the experiences of family and friends, and lay sources, including the Internet and television programs.
  - Many participants also noted that they learned information on the risks of taking statins, but not information on the potential benefits of statins, from these sources.
Perception vs. Reality

- Statins are safe
  - Especially among individuals younger than 76 years.
  - This is supported by a vast body of evidence
- Statins are Effective

Reality

- The frequency of possible drug-related complications is unknown but is low and outweighed by the vascular benefits of statins therapy

The Problem

- Some patients don’t want to take statins
- Some patients are intolerant to statins

Possible statin-associated adverse effects

- Diabetes mellitus
- Hemorrhagic stroke
- Decreased cognition
- Tendon rupture
- Interstitial lung disease
- Muscle-related symptoms

Possible statin-associated adverse effects

- Low cholesterol levels in general are associated with:
  - Increased risk of DM
  - Increased risk of hemorrhagic CVA
Statin-associated muscle symptoms (SAMS)

- Most frequent statin-related symptoms.
  - Muscle symptoms with marked increases in CK levels
    - Usually defined as 10x the ULN
  - Estimated occurrence of 1 additional case per 10,000 individuals treated each year

Statins are really safe...

- A recent meta-analysis of 35 randomized controlled trials covering more than 74,000 patients identified the following rates of adverse events associated with statin use:
  - Myalgia (musculoskeletal pain/symptoms without documented CK elevations): 15.4%
  - Liver Toxicity (ALT or AST >3x ULN): 1.4%
  - Creatine kinase elevations: 0.9%
  - Myopathy/rhabdo (muscle complaints w/ CK levels ≥10x ULN): 0.2%


Patients without major increases in CK and tolerable symptoms should be reassured that statins rarely cause severe muscle injury and that the muscle symptoms usually resolve with drug cessation.

Symptoms in typical statin myalgia resolve in most patients within weeks of stopping the statin.

Rare, but important

- Statins can cause a necrotizing myopathy with antibodies against hydroxyl-methyl-glutaryl-CoA reductase.
  - Newly recognized
  - These patients present with muscle pain and weakness plus marked increases in CK levels that do not resolve with drug cessation.
  - A commercial test for the antibody is available for diagnostic purposes.
  - This condition must be recognized promptly because it can lead to persistent myopathy.

Statins causing DM?

- Statins are associated with a small but statistically significant 9% increase (OR 1.09; 95% CI, 1.02-1.17) in the incidence of diabetes according to a meta-analysis of 13 trials including 91,140 participants
  - Translates to 1 new diabetes event per 1000 person years of treatment.
  - Prevent 9 vascular events

The cardioprotective effects of statins seem to outweigh the harms.

Is statin intolerance real?
How Prevalent?

- Administrative database of Henry Ford Hospital
  - 1000 patients with Rx for statin
- Statin Intolerance was identified in 14.0%
  - Absolute intolerance in 3.1%
  - Titration intolerance in 11.8% of the patients

Observational studies

- The incidence of statin myalgia has been estimated at 10% from observational studies
- 10.5% in PRIMO study
  - Prediction of Muscular Risk in Observational Conditions
  - 7,924 patients were surveyed regarding their history of muscular symptoms while on statin therapy
  - Onset usually within 1 month of starting statin therapy.

STOMP Trial:
Effect of Statins on Skeletal Muscle Performance

- Predefined criteria for statin myalgia
  - Onset of symptoms during treatment, persistence for 2 weeks, symptom resolution within 2 weeks of treatment cessation, and symptom reappearance within 4 week of restarting treatment.
  - 9.4% of pts treated with statins and 4.6% of pts treated with placebo met the study definition of myalgia
  - Creatine kinase values were not different between the 2 groups.
  - Suggests that the true incidence of statin myalgia is approximately 5%
  - Supports the observation that approximately 10% of patients will report symptoms of myalgia.

Randomized Controlled Trials

- Rate of Statin-associated muscle symptoms as well as other side effects and adverse events have been similar between the statin and placebo groups.

Is This Really a Thing?

- PCSK9 trial examining the LDL-lowering effect of alirocumab
  - Inclusion criteria: statin intolerance of at least 2 statins
  - Pts randomized to alirocumab, ezetimibe, or atorva 20 mg
  - The rate of discontinuation due to muscle symptoms was not statistically different between the 3 medications
    - alirocumab 15.9%
    - ezetimibe 20.2%
    - atorvastatin 22.2%

- When blinded, 78% of previously intolerant participants randomized to atorvastatin were able to tolerate the medication for the duration of the 6-month trial.
GAUSS-3 Study

- Evolocumab study
- Enrolled pts with presumed statin muscle sx
- Randomized to receive either 20 mg of atorva or placebo each day for 10 weeks followed by a 2-week hiatus before crossover to the alternative treatment.


Is This Really a Thing?

- Gauss-3
- Of patients screened and enrolled who had a Hx of muscle-related adverse effects with a statin
- Only 43% reported symptoms when given a double-blinded re-challenge with atorvastatin

Nissen SE et al. JAMA 2016;315:1580-90

GAUSS-3 Study

26.5% developed muscle symptoms during placebo-only treatment


Nocebo Effect

- The inverse of the placebo effect
- It refers to adverse events, usually purely subjective, that result from expectations of harm from a drug, placebo, other therapeutic intervention or a nonmedical situation.

Nocebo Effect

- The Placebo Effect
  - Expectation of Benefit
- The Nocebo Effect
  - Expectation of Harm
Nocebo Effect

- These expectations can be driven by many factors:
  - The informed consent form in a clinical trial
  - Warnings about adverse effects communicated by clinicians when prescribing a drug
  - Information in the media about the dangers of certain treatments.

Nocebo Effect

- The best explanation for the high rate of muscle and other symptoms attributed to statins in observational studies and clinical practice
- But not in randomized controlled trials, where muscle symptoms, and rates of discontinuation due to any adverse event, are generally similar in the statin and placebo groups.

Nocebo Effect

- Statin-intolerant patients usually tolerate statins under double-blind conditions, indicating that the intolerance has little if any pharmacological basis.

- If patients are convinced that the statins are responsible, it is difficult to convince them otherwise or to ignore their symptoms.

- So, how should these symptoms be managed?
  - Educate your patient
  - Emphasize safety of meds
  - Emphasize benefit of meds
  - Make a Change

- Educate your patient
  - Emphasize safety of meds
  - Emphasize benefit of meds
  - Make a Change
The Truth About Statins

- There are 7 different statins.
- They have different chemical structures, and are handled and metabolized by the body very differently.

80-90% of people have NO side effects from statins
- 99% of people are able to find a statin that doesn’t cause them side effects.
- People may have problems with 1 or 2 or 3 of the statins, but that doesn’t mean that won’t tolerate the 4th, 5th or 6th or 7th.
- This is because the statins have different chemical structures.

Research has demonstrated that up to 90% of patients who reported SAMS were subsequently able to tolerate an alternative statin.


Statins are the most well-studied class of drugs in the history of medicine.

There have been over 200,000 patients studied in randomized, controlled clinical trials.

Statins have been on the market since 1987, when lovastatin was approved for use by the FDA.
- In that time (30 years!), there has never been any sign of an increase in cancer
- Cancer deaths decreasing
- Deaths from heart disease have gone down by 25-30% over the last 25 years, despite increases in rates of diabetes and obesity.
- The main reason for this dramatic decline in CV deaths is statin medications.

Statins are safe for your liver
- Every year, more people develop liver problems as a result of using Tylenol or supplements than statins.
- In fact, of the 1100 cases of drug-induced liver injury in the last 15 years, only 22 were attributed to statins.
- In comparison, 85 were caused by “herbal” supplements.

Statins are so safe for the liver that the FDA no longer recommends checking liver blood tests for patients who take statins.
The Truth About Statins

- Statins reduce the risk of stroke or heart attack by 50%.
- Statins have been proven to lower or at least linked to lower rates of the following problems:
  - Deaths from Heart disease: Heart Attacks
  - Death from Stroke: Strokes
  - VTE: Cancer
  - Dementia: Parkinson’s Disease
  - Death from infection: Exacerbations of MS
  - Death or Heart Attack during non-cardiac surgery

Educate Your Patients

- Patient surveys have suggested that systematic follow-up, as well as greater information about the risks and benefits of statins and the merits of alternative approaches for lowering cholesterol, could improve adherence to therapy.

Options

- Change statin
- Change (lower) dosages
- Alternative dosing regimens
- Non-statin Medications
  - Zetia
  - Bile Acid Resins
  - PCSK9 Inhibitors
  - Supplements

Change Statin

- CYP 3A4
  - Atorva
  - Simva
  - Lovra
- CYP 2C9 (minimal)
  - Fluva – No significant interactions
  - Rosuva
- No P450
  - Prava
  - Pitava

Change Statin

- “Cleanest” statins
  - Prava
  - Pitava “livalo”
Options

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Lower Dose

- Remember: The greatest percent reduction in LDL-C occurs with low-statin doses.
- Doubling dose only improves LDL by ~6%

Alternate Dose

- Once weekly dosing of Crestor is feasible and effective
  - 23% reduction in LDL-C

- Alternative dosing of Atorva
  - 10 mg qD vs. 10mg qOD vs 20mg
  - All significantly reduced LDL-C
  - No statistically significant differences existed between the three groups

Non-Statin Meds

- Zetia
- Bile Acid Resins
- PCSK9 Inhibitors

Options

- Change statin
- Low dosages
- Alternative dosing regimens
- Non-statin Medications
  - Zetia
  - Bile Acid Resins
  - PCSK9 Inhibitors
- Supplements

Non-Statin Meds

- Zetia
  - Ezetimibe + very low doses of a statin can decrease LDL-C similar to moderate- and high-dose statin
  - IMPROVE-IT
- Bile Acid Resins
- PCSK9 Inhibitors
Options

- Change statin
- Change (lower) dosages
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- Non-statin Medications
  - Zetia
  - Bile Acid Resins
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- Supplements

Coenzyme Q10

- Supplementation has not been effective in reducing symptoms in a meta-analysis of 10 studies
  - But many patients and clinicians are convinced this agent works
  - Perhaps via a placebo effect.
- Coenzyme Q10 can be tried after informing the patients that it has not been effective in clinical trials but may be useful in some patients.

Vitamin D

- Vitamin D deficiency alone can produce myopathy
- Evidence that vitamin D supplementation reduces statin-associated muscle symptoms is limited.

Red Yeast Rice Extract

- Red yeast rice and simvastatin produce similar lipid-lowering effects.
  - Meta-analysis:
    - ~16% reduction in LDL-C

So what does all this mean?
It is critically important to ensure at least some intensity of statin use by higher-risk patients.

Every patient at age 40 years or older should be considered for possible statin therapy.

Because even if you argue about an All-Cause Mortality benefit in Primary Prevention, there is no controversy that statins can reduce the large burden of disability from non-fatal stroke and coronary events.

- Educate your patients
  - About the safety and efficacy of statins
- Don’t’ give up easily
  - Try different statins and different dosing regimens
- Try Vitamin D or CoQ10
- Emphasize the need to initiate healthy behaviors