Statin Intolerance / Statin Side Effects

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Disclosures

- None
- Talk will address off-label use of statins (alternate day dosing) and new medications (PCSK9 inhibitors) not yet FDA approved

Case

52 ♂ type 2 DM with known CVD
- MI and CABG 3 years ago
- DM2 x 8 years, HbA1c ranges 7.5-8.1%
- Nonsmoker, BP controlled

Meds:
- Insulin
- Metformin
- Gabapentin
- Lisinopril
- ASA
- "statin intolerant"

Labs
- TC 173 (4.5)
- HDL-c 28 (0.73)
- LDL-c 109 (2.8)
- TG 180 (2.0)
- HbA1c 7.7%
- TSH 1.2

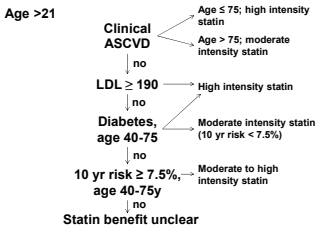
What is the most appropriate management?
A. Try another statin
B. Refer to PCSK9 research study
C. Start ezetimibe
D. Start alternate day statin therapy
E. Start statin + co-Q10

ASCVD Risk Estimator

Optimal risk factors:
- TC < 170
- HDL > 50
- sBP < 110
- No meds for HTN
- No diabetes
- No smoking

Stone et al, JACC 2014;
The risk calculator can be obtained at these sites (links to download an app):
- http://tools.cardiosource.org/ASCVD-Risk-Estimator/
- http://my.americanheart.org/professional/StatementsGuidelines/Prevention-Guidelines_UCM_457698_SubHomePage.jsp

ASCVD Statin benefit groups



Current ADA Guidelines for Lipid Lowering Therapy in Diabetes

Age	CVD or RFs	Statin Therapy intensity
<40 years	No RFs +RFs Overt CVD	None Moderate or High High
40-75 years	No RFs + RFs Overt CVD	Moderate High High
> 75 years	No RFs + RFs Overt CVD	Moderate Moderate or High High

RFs: LDL ≥ 100 mg/dl, HTN, smoking, overweight

Diabetes Care, 2015

Terminology to Describe Statin Associated Muscle Symptoms (SAMS)

Condition	Definition
Myalgia	muscle ache or weakness *without* creatine kinase (CK) elevation[1]
Myopathy	muscle symptoms *with* increased CK levels >10 x ULN[2]
Rhabdomyolysis	muscle symptoms with marked CK elevation (typically >10 x ULN) and with creatinine elevation (usually with brown urine and urinary myoglobin)[1]

1. Pasternak et al. *Circulation*. 2002;106:1024-1028.
2. Evans et al. *Drug Saf*. 2003;26:649-663.

Prevalence of SAMS

- In clinical practice 10-25% of patients report statin intolerance
  - In trials, similar reports of muscle complaints between statin and placebo groups

Factors That Increase the Risk of Statin-Induced Myopathy

Patient Characteristics
Increasing age
Female sex
Renal insufficiency
Hepatic dysfunction
Hypothyroidism
Diet (ie, grapefruit juice)
Polypharmacy

Statin Properties
High systemic exposure
Lipophilicity
High bioavailability
Limited protein binding
Potential for drug-drug interactions metabolized by CYP pathways (particularly CYP450 3A4)

Role of CYP450 3A4 in Drug Metabolism

- Responsible for converting lipophilic substrates to water-soluble products to facilitate urinary excretion
- High potential for drug-drug interactions, as approximately 50% of drugs are metabolized by this enzyme
- Hydrophilic agents do not require clinically significant metabolism through this pathway

Pharmacokinetic Profiles of Selected Lipid-Lowering Therapies

	Rosuvastatin	Pravastatin	Atorvastatin	Simvastatin	Ezetimibe
CYP450 3A4 Metabolism	No	No	Yes	Yes	No
Clinically Significant Metabolites	No	No	Yes	Yes	Yes
Plasma Clearance	Dual renal/ hepatic	Dual renal/ hepatic	Primarily hepatic	Dual renal/ hepatic	Dual renal/ hepatic
Relatively Hydrophilic	Yes	Yes	No	No	No
Hepatoselective	Yes	Yes	Yes	Yes	No
Bioavailability	20%	17%	14%	<5%	35-60%
Elimination Half-life* (hours)	19	77	14	1.9	22

High LFTs and Statins

- LFTs usually ↓ with dose reduction
- Usually no ↑ with rechallenge or alternate
- Statins do not worsen outcome in chronic ↑ LFTs from Hep B, C etc
- Statins may ↓ LFTs that are high due to fatty liver
- *If AST/ALT < 3 times ULN, ok to continue statin therapy*

ACC/AHA/NHLBI Clinical Advisory on Statins, JACC 2002

High CK and Statins

- Baseline CK not required, can be helpful
- If muscle symptoms occur, measure CK and TSH
- CK > 10 x ULN: d/c all lipid meds
- CK < 10 x ULN: measure weekly, if ↑'ing d/c meds, if ↓'ing ok to continue

ACC/AHA/NHLBI Clinical Advisory on Statins, *Circulation* 2002

Case

- Pt has history of myalgias on multiple statins, no history of ↑CK or LFTs
- Has CVD, LDL 109, HDL 28

What is the most appropriate management?
A. Try another statin
B. Refer to PCSK9 research study
C. Start ezetimibe
D. Start alternate day statin therapy
E. Start statin + co-Q10

Try another statin?

ODYSSEY ALTERNATIVE

- Pts intolerant of at least 2 different statins
- Lack of muscle symptoms in 4 wk placebo run in phase (6.9% excluded here)
- Randomly assigned to atorvastatin 20mg/d, alirocumab or ezetimibe with placebos
- 18% of alirocumab, 25% of ezetimibe, and 25% of atorvastatin pts discontinued study drug due to AEs
  - Thus many of these symptoms are <u>not</u> statin specific

Moriarty et al; presented at AHA 2014. data from my.americanheart.org accessed 3/18/2015

EAS Panel Recommendations for SAMS

- Discontinue then re-try
- Try at least 3 different statins
- Use max tolerated statin dose combined with non-statin lipid therapies

Try another statin?

- Yes, a good option
- My protocol:
  - Drug holiday with symptom diary
  - Restart same statin low dose and titrate
  - If symptoms recur, drug holiday again
  - Start alternate statin low dose and titrate

Refer to a PCSK9 research study?

ODYSSEY ALTERNATIVE

	Baseline	Alirocumab	Ezetimibe	Atorvastatin
LDL (mg/dl)	191	92	157	
Any Muscle symptoms		32.5%	41.1%	46%
Muscle symptoms leading to d/c		15.9%	20.2%	22.2%

Moriarty et al; presented at AHA 2014. data from my.americanheart.org accessed 3/18/2015

PCSK9 Inhibition

- ODYSSEY LONG TERM
  - 2341 Patients on max tolerated statins were randomized to alirocumab or placebo for 78 weeks
- OSLER-1 and OSLER-2
  - 4465 patients randomized to evolucumab or placebo in addition to standard therapy x 1 year
- Both agents ↓LDL ~60% and both studies show ↓CVD events ~50% at 12-18 months

(ACC 2015 presentations/ NEJM online first accessed 3/18/2015)

Refer to a PCSK9 research study?

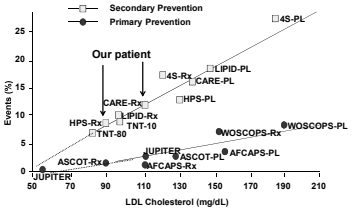
- PCSK9 inhibition is a promising option for patients truly statin intolerant (or who don't have adequate LDL lowering despite statin therapy)
- BUT long term safety still unknown, and final CVD outcomes data pending

Start Ezetimibe Monotherapy?

Ezetimibe Monotherapy

- As monotherapy expect ↓LDL ~ 18%
  - When added to statin expect ↓LDL ~ 25%
- No CVD outcomes data for ezetimibe monotherapy available

CHD Events Reduced with LDL Lowering (Statin Trial Data)



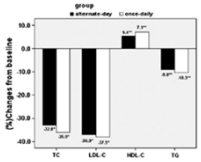
Adapted from Illingworth DR. *Med Clin North Am*. 2000;84:23-42.

Start Ezetimibe Monotherapy?

- If lowering LDL is the central mechanism for CVD benefit, we could anticipate decreased risk for recurrent CVD based on statin data
- However, will only achieve modest LDL lowering (and thus modest decrease in CVD risk)

Try Alternate Day Statin Dosing?

Alternate Day Statin Dosing



37 patients randomly assigned to rosuvastatin 10 mg daily or rosuvastatin 10 mg every other day, x 6 weeks

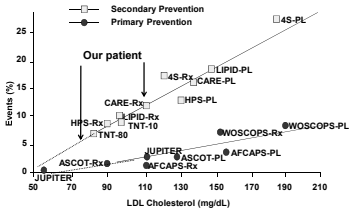
Similar results seen in a study comparing atorvastatin 10 mg daily vs 10 mg every other day; ↓LDL 38% vs 35% (Matalka, Am J Heart 2002)

Li et al, Clin Chim Acta 2012, 413:139-42

< Alternate Day Statin Dosing

- 10 patients with statin intolerance (myalgias, ↑LFTs or GI distress) were treated with rosuvastatin 5-20 mg once weekly; ↓LDL 29% at 4 months, 8 tolerated once weekly dosing (Backes et al, Am J Cardiol 2007; 100:554-5)

CHD Events Reduced with LDL Lowering (Statin Trial Data)



Adapted from Illingworth DR. *Med Clin North Am.* 2000;84:23-42.

Try Alternate Day Statin Dosing?

- *Off label use*
- No CVD outcomes data
- Would theoretically be better with atorvastatin or rosuvastatin which have relatively long half lives
- A reasonable option, may lead to greater ↓LDL and ↓CHD than ezetimibe monotherapy

Statin + CoQ10?

Statin + CoQ10

- RCT of CoQ10 in patients with confirmed statin myopathy
  - Cross-over run in on simvastatin or placebo; only subjects who had muscle pain on statin but not placebo, and no pain in washout phase were enrolled
  - Only 38.5% of pts with prior statin myalgia met this criteria
- Subjects then randomized to statin + placebo or statin + CoQ10, for 8 weeks, then 4 week washout, then other treatment for 8 weeks

Taylor et al, Atherosclerosis 2015; 238:329-35

Statin + CoQ10 Results

- Pain scores increased with statin Rx in both groups with no difference between CoQ10 or placebo
- # subjects with muscle pain was higher in CoQ10 group than placebo group (P=0.05)
- No effect of CoQ10 on lipid lowering efficacy of statin

Taylor et al, Atherosclerosis 2015; 238:329-35

Statin + Co-Q10?

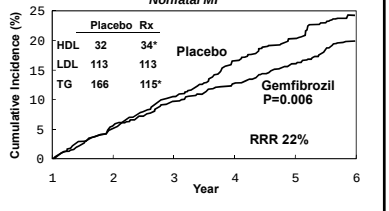
- Not likely to benefit
- Most muscle complaints on statins are not due to statins

Beyond Statins

- Ezetimibe
  - No CVD outcomes data
  - Will ↓LDL
- Fibrates
- Niacin
- Bile acid binding resins
- Fish oil
- Intensive lifestyle intervention

Fibrate Monotherapy: VA HIT

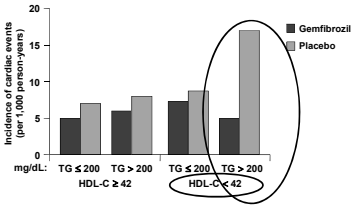
2° Prevention: ***Incidence of Death from CHD and Nonfatal MI***



* Lipid values significantly different, P<0.05

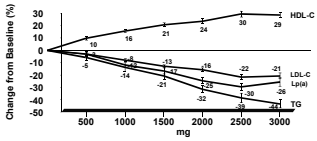
Adapted from Rubins HB et al. *N Engl J Med* 1999;341:410-418.

Fibrate Monotherapy: Helsinki Heart Study



1° Prevention; Manninen V et al. *Circulation.* 1992;85:37–45

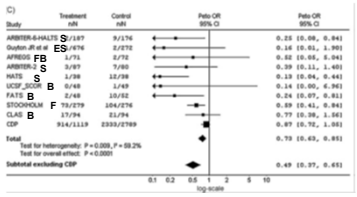
Niacin Monotherapy: Lipid Effects



Coronary Drug Project, a 2° prevention study in men, demonstrated reduction in MI and mortality with niacin monotherapy

Coronary Drug Project. *JAMA* 1975; 231:360-381. Canner PL et al. *J Am Coll Cardiol* 1986;8:1245-1255. Capuzzi DM et al. *Am J Cardiol* 1998;82:74U-81U.

Niacin: Reduction in CVD Events



S: Statin; E: ezetimibe; F: fibrate; B: bile acid resin

Meta-analysis of niacin (alone or in combination) found to significantly reduce CVD events.

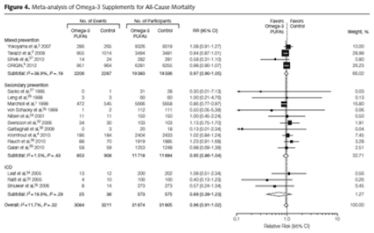
Bruckert, Atherosclerosis, 2010

Bile acid sequestrants

- **Lipid Research Clinic Coronary Primary Prevention Trial**
- **Randomized 3806 men to cholestyramine or placebo for 7.4 yrs**
- **↓LDL 20%, ↓CHD events 19%**
  - **↑violent and accidental deaths in cholestyramine group**

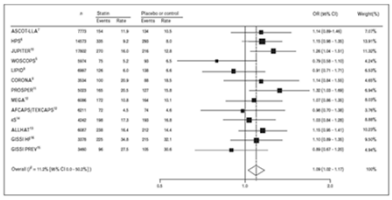
JAMA 1984; 251:351-64

Omega-3 Effect on All-Cause Mortality



Rizos et al, JAMA, 2012

BUT, Statins Increase DM



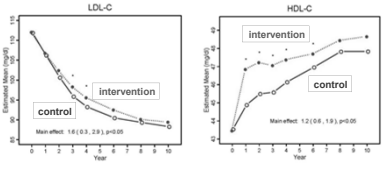
Probably dose/potency related; may be due to interference with insulin signaling; ratio is 1 new diabetic per 3 pts protected from MACE

Preiss and Sattar, Curr Opin Lipidol, 2011

Lifestyle Modification in DM

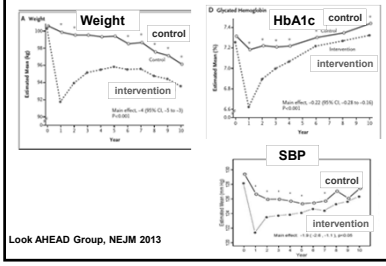
- **Look AHEAD Study: Can CV morbidity and mortality be reduced by intensive lifestyle intervention?**
- **5145 subjects with type 2 DM age 55-74**
- **intensive lifestyle changes**
  - **group and individual counseling,**
  - **low calorie diet [<30% fat, > 15% protein given by meal replacements and/or structured meal plans],**
  - **175 min activity/week**
- **vs conventional Rx (diabetes support and education)**

Look AHEAD: Lipid Effects



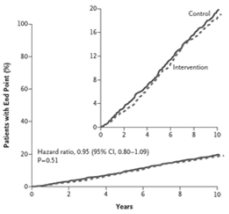
Look AHEAD Group, NEJM 2013

Look AHEAD Effects



Look AHEAD Group, NEJM 2013

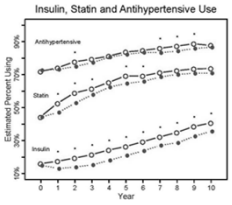
Look AHEAD: CVD events



CVD death, nonfatal MI, nonfatal stroke, hospitalization for angina

Look AHEAD Group, NEJM 2013

Look AHEAD: Confounders



Why no benefit?

LDL was only 1.6 mg/dl lower in intervention group than control group

Control group had greater use of risk reducing medical therapy

Look AHEAD Group, NEJM 2013