Treating the Statin Intolerant Patient

August 14th, 2019

Rachael Wyman, MD, FACC
Cardiologist, Seattle

Melissa Hull, PharmD, CACP, CLS
Clinical Programs Coordinator

KAISER PERMANENTE®

Learning Objectives

Describe
statin
intolerance

Recognize
quality measures
impacted

Employ
strategies to
improve statin use

Outline

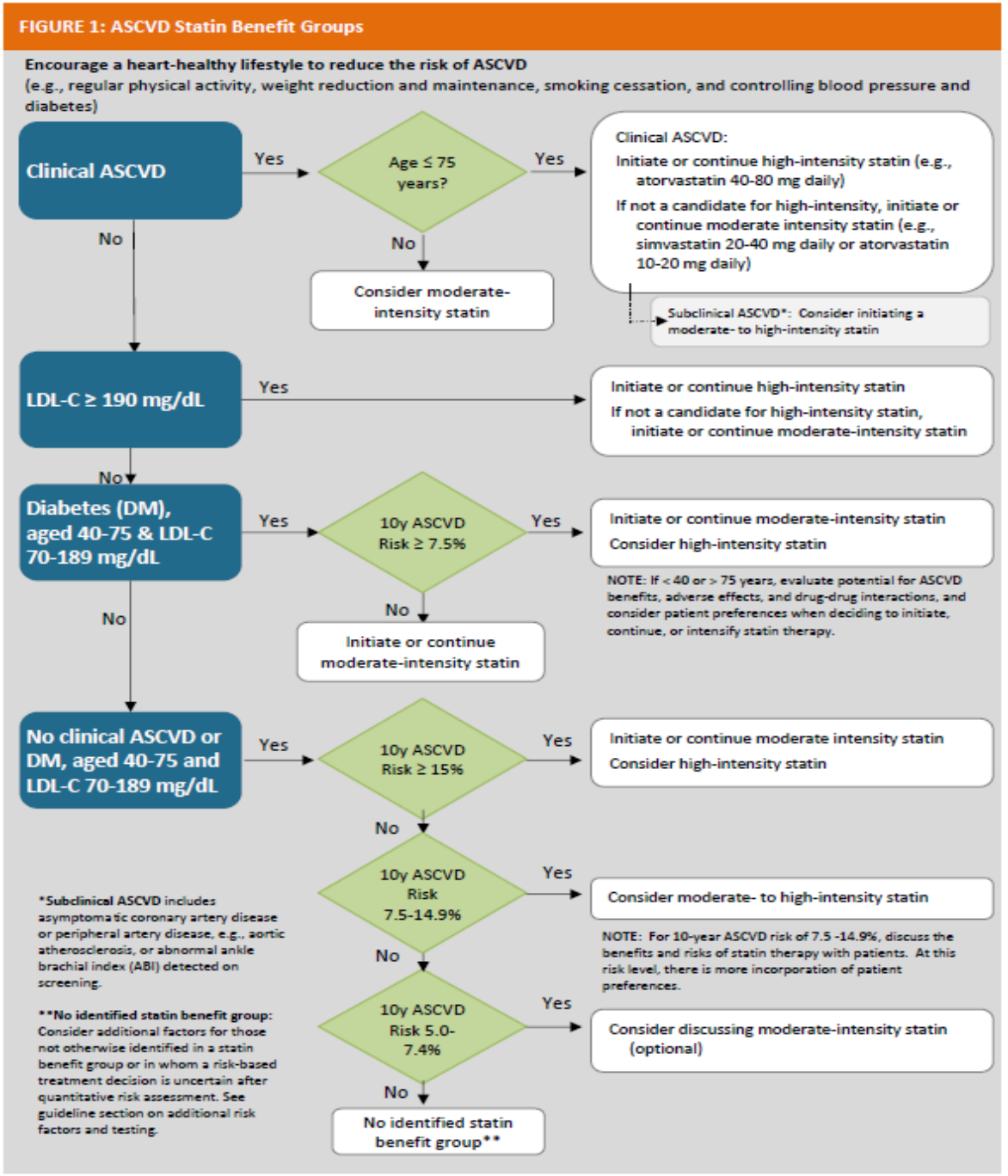
- ASCVD Guideline 2018 Update
- Quality Measures
- Statin Intolerance Defined
- ACC Online Tool
- Literature Supported Strategies
- Supplements

Patient Case: Miles

- 45 yo Caucasian male
- History of Diabetes, HTN, Obesity, Vitamin D deficiency; former smoker
- Mild to moderate pain in bilateral thighs making activity more difficult
- Current medication: metformin, lisinopril, HCTZ, simvastatin 40mg daily (new)
- BP 138/78, BMI is 32, A1c 7.2%
- Baseline Lipids (pre-statin):
  - TC 220
  - LDL 150
  - TG 160
  - HDL 38
- Cardiovascular Risk: 8.5% or 69% lifetime risk

ASCVD Guideline 2018 Update

ASCVD Statin Benefit Group



Quality Performance Measures

KPWA Data as of December 2018

	External Network Performance	Internal Care Delivery Performance	*Target*
HEDIS ASCVD: Statin (SPC)	84%	86%	*87%*
HEDIS DM: Statin (SPD)	67%	78%	*72%*
CMS DM: Statin (SUPD)	79%	89%	*83%*

2019 Target expected to jump to 89%

Strategies for Success in Internal Delivery System

Clinical Pharmacist Referral Model

- 98% of patients discharged from service with LDL < 100 mg/dL or improved from baseline
- Average LDL reduction: 61.3 mg/dL

Partnership with Clinic Quality Champ Physicians

- Physician leaders facilitating targeted outreach by providers resulted in 12% successful conversion to statin prescription

Contracted Clinic Embedded Pharmacist

- Demonstrated 40% successful conversion to statin prescription

Patient Barriers to Treatment

Misleading information

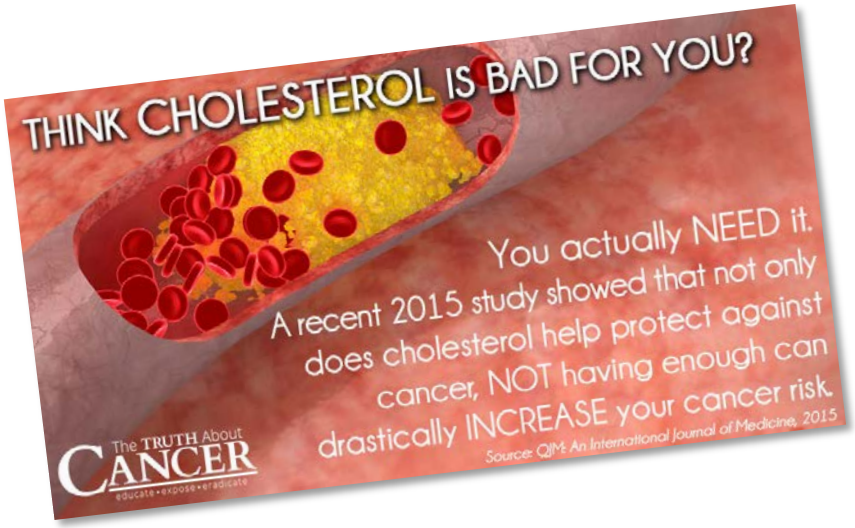
“The Diet-Heart Myth: Statins Don’t Save Lives”

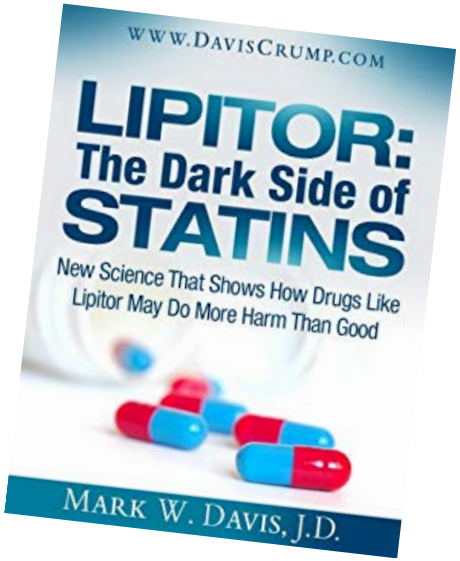
“Why People Don’t See Results Taking Statins for High Cholesterol”

“Do Guidelines Underestimate the Harms of Statins?”

“Statins, Pesticides and Wireless Radiation Affect Heart Health”

“Study Links Statins to 300+ Adverse Health Effects”

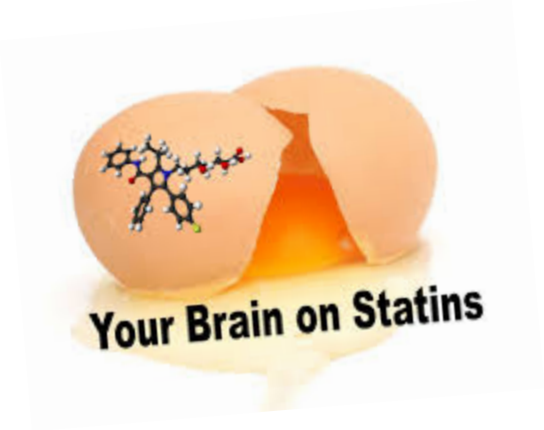


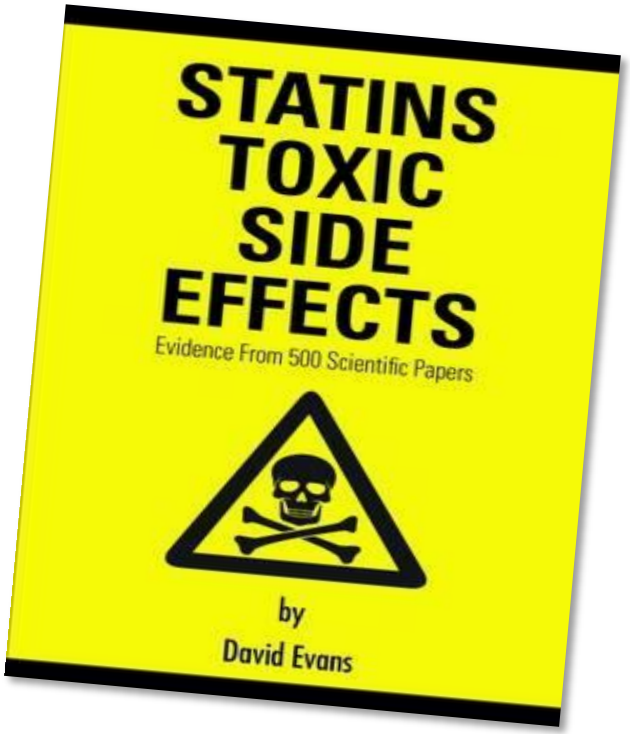


Patient Barriers to Treatment

Searchable side effects

- Muscle pain and damage
- Liver damage
- Increased blood sugar
- Neurologic side effects including memory loss and confusion





Patient Barriers to Treatment

The NO-cebo Effect

- “I’ll shall harm” vs. placebo meaning “I’ll shall please”
- Predetermined view that drug will cause harm/ill effect
- Leads to higher rates of side effects than expected
- Patient is resistant to or declines trying a statin

What is Statin Intolerance?

The National Lipid Association (Guyton 2014) defines statin treatment intolerance as:

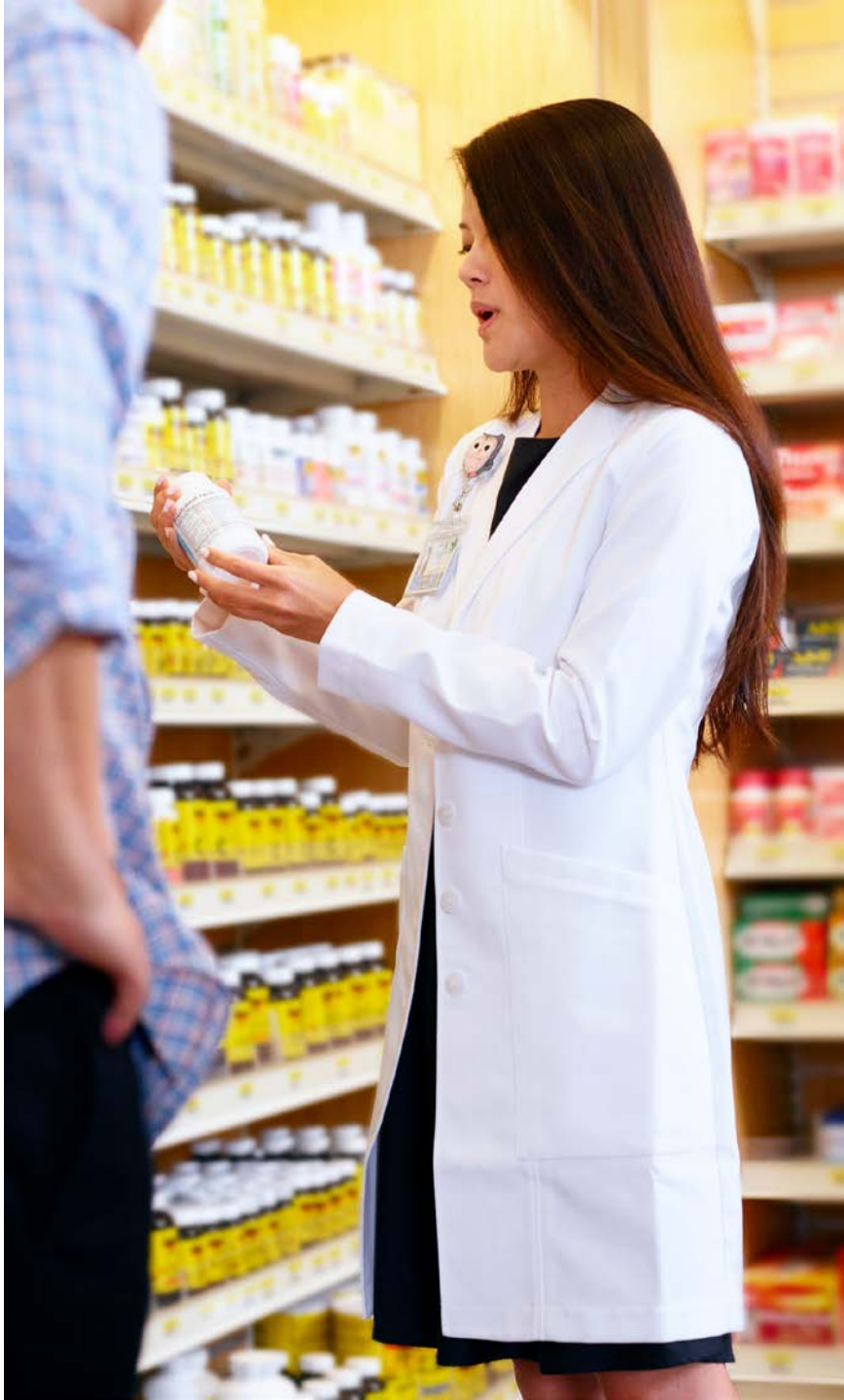
... a clinical syndrome characterized by the inability to tolerate at least 2 statins: one statin at the lowest starting daily dose AND another statin at any daily dose, due to either objectionable symptoms (real or perceived) or abnormal lab determinations, which are temporally related to statin treatment and reversible upon statin discontinuation, but reproducible by re-challenge with other known determinants being excluded (such as hypothyroidism, interacting drugs, concurrent illnesses, significant changes in physical activity or exercise, and underlying muscle disease). Specifically, the lowest starting statin daily dose, is defined as rosuvastatin 5 mg, atorvastatin 10 mg, simvastatin 10 mg, lovastatin 20 mg, pravastatin 40 mg, fluvastatin 40 mg, and pitavastatin 2 mg.

Can be partial or complete.

Muscle Aches

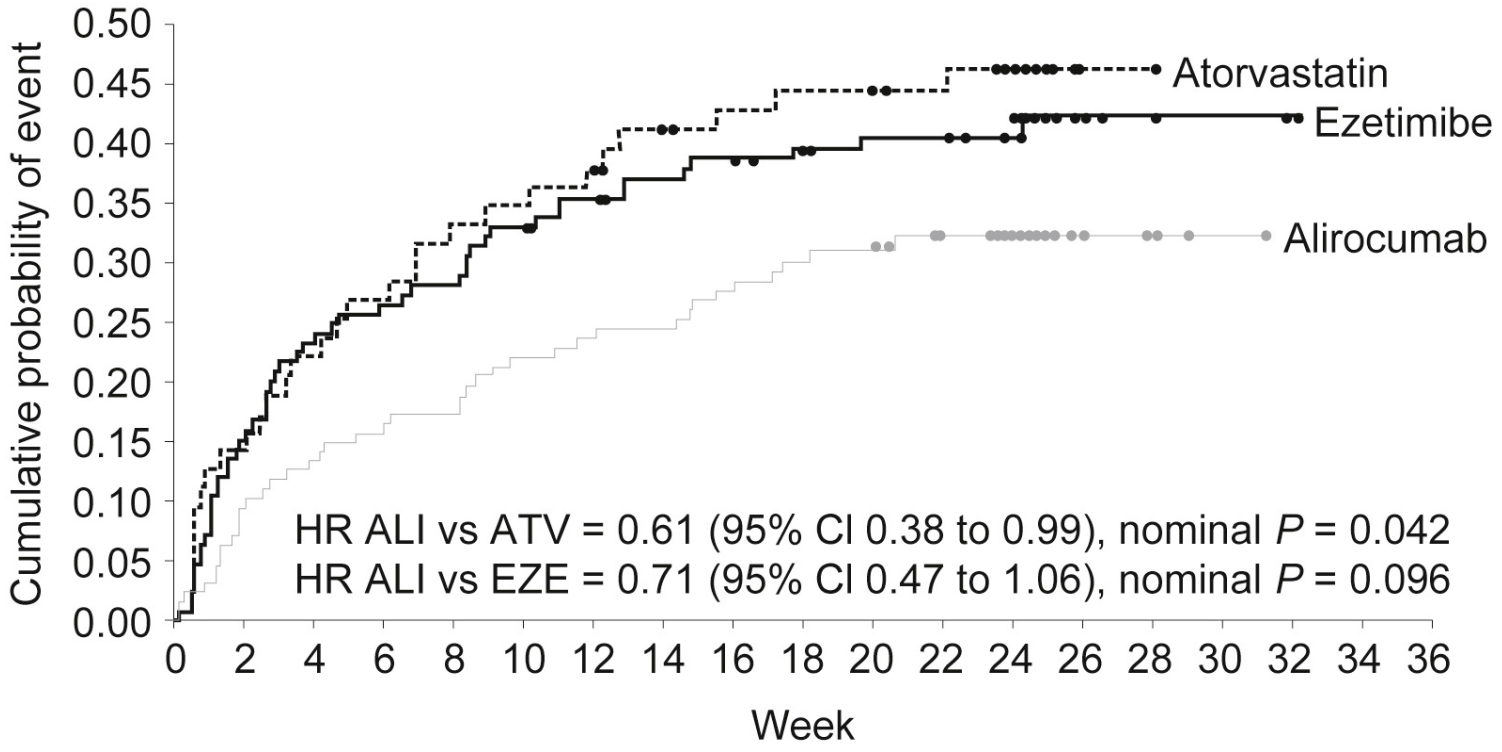
Statin Associated Muscle Symptoms (SAMS)

- Make up 72% of all statin ADEs
- Reported rate of 1.5-5% in RCTs
- 11-29% of patients per observational data



1 Hovingh GK, et. al. Atherosclerosis. 2016; 245:111-117
2 Rosenson RS, et al. J Clin Lipidol 2014;8:S58-S71
3 Bays H. AmJ Cardiol 2006;97:6C-26C

Odyssey Alternative Trial



Moriarty PM, et. al. J Clin Lipidol. 2015;9:7580769

GAUSS-3

Table 2. Patients Experiencing Intolerable Muscle-Related Symptoms During Phase A of GAUSS-3 Trial[a]

Category, No. (%)	Atorvastatin Followed by Placebo (n = 245)[b]	Placebo Followed by Atovastatin (n = 246)	All Randomized Patients (n = 491)[b]
Symptoms with atorvastatin but not placebo	126 (51.4)	83 (33.7)	209 (42.6)
Symptoms with placebo but not atorvastatin	42 (17.1)	88 (35.8)	130 (26.5)
Symptoms with both placebo and atorvastatin	22 (9.0)	26 (10.6)	48 (9.8)
No symptoms with either treatment	47 (19.2)	38 (15.4)	85 (17.3)
Did not start period 2 treatment	8 (3.3)	11 (4.5)	19 (3.9)

Abbreviation: GAUSS-3, Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects 3.

[a] Nineteen patients bypassed phase A because of creatine kinase elevation ≥10× the upper limit of normal.

[b] Does not include 1 patient who never received study drug.

Nissen SE, et. al. JAMA. 2016;315:1580-1590

Additional Adverse Drug Effects

- Cognitive effects
- Elevated blood glucose
- Ohers-insomnia, pancreatitis
- Transaminitis
  - LFTs 3XULN
  - Hepatotoxicity no different than general population
- Elevated Creatinine Kinase
  - Myositis: CK 3XULN
  - Rhabdomyolysis: CK >10,000

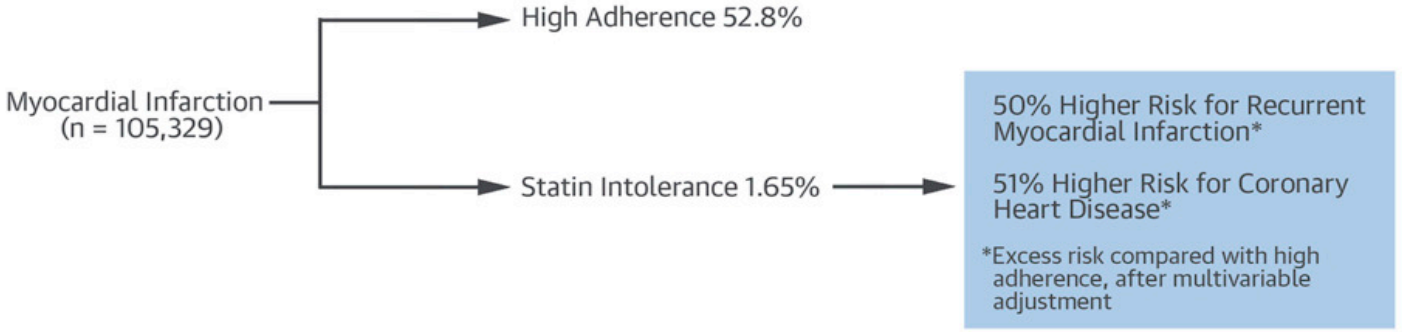
Statin Safety Task Force report 2006, 2014

Patient Case Discussion

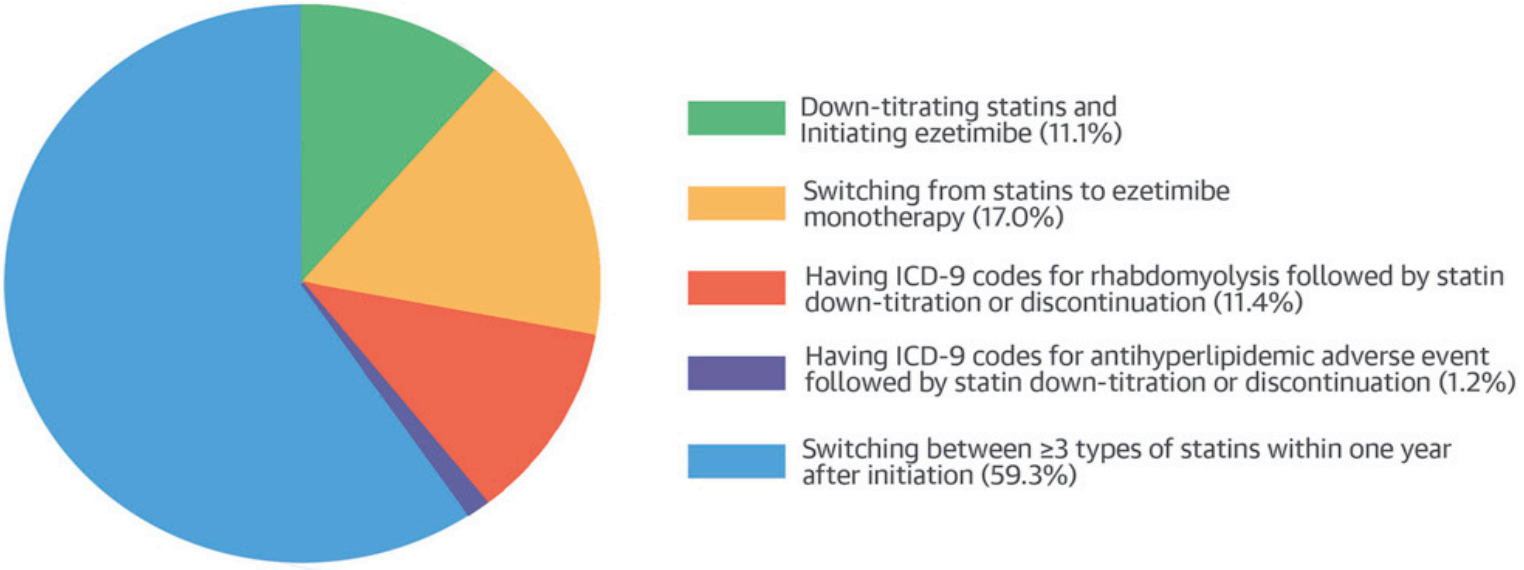
1. Is Miles at risk for statin associated myalgia?
2. What further workup would you need to determine next steps?
3. **Which next step is most appropriate?**
   - A. Tell him to tough it out. This medication will save his life!
   - B. Stop statin for 2-4 week washout and assess if symptoms resolve.
   - C. Reduce dose of simvastatin down to 20mg daily.
   - D. Change to Atorvastatin 80mg daily.

CENTRAL ILLUSTRATION: Statin Intolerance Among Medicare Beneficiaries

Excess Risk From Statin Intolerance



Reasons for Statin Intolerance



Serban, M.-C. et al. J Am Coll Cardiol. 2017;69(11):1386-95.

Strategies to Avoid Statin Side Effects

Identify those at risk for myalgia

- Multisystem disease including renal or hepatic impairment
- Unexplained elevated LFTs 3X ULN
- Age >75
- History of hemorrhagic stroke
- Prior statin intolerance or muscle disorders
- Drug Interactions
- Asian ethnicity
- Females
- Polypharmacy
- Small body frame/frail
- Athletes

Strategies to Avoid Statin Side Effects

Start with moderate intensity statin in at risk groups

MODERATE INTENSITY **Daily dose lowers** **LDL-C by approx. 30-50%**
Simvastatin 20-40 mg
Atorvastatin 10-20 mg
Lovastatin 40-80 mg
Pravastatin 40-80 mg
Rosuvastatin 5-10 mg
Fluvastatin XL 80 mg
Fluvastatin 40 mg bid
Pitavastatin 2-4 mg

2013 ACC/AHA Cholesterol Guidelines

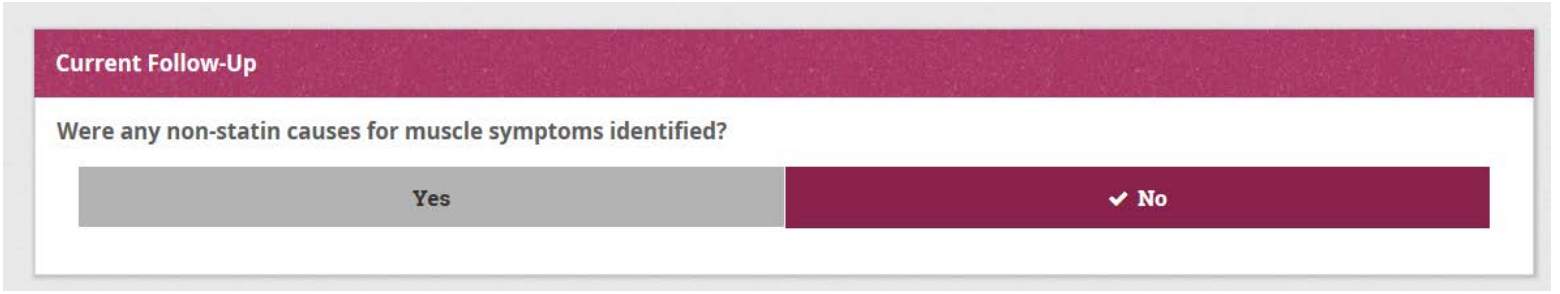
Managing SAMS

Rule out secondary causes:

- Correct hypothyroidism, vitamin D deficiency and re-challenge
- Identify if related to primary muscle disease, rheumatologic disorders, reduced renal function

Washout and Re-challenge

- Use ACC Statin Intolerance Tool: http://tools.acc.org/StatinIntolerance/#!/
- (screenshots on next page)



Recommendation

Next Steps

- Consider the pat t's ASCVD risk and cardiovascular health history, benefits of statin therapy and risk of removal, a atient preferences.

Continuing Statin Therapy

- Proceed with one of the following as appropriate:
  - A. Continue with current statin prescription
  - B. Try an alternative statin:
    - Discontinue current statin. Wait for symptoms to resolve.
    - Try patient on a low dose of an alternative statin.
    - If low dose is tolerated, gradually increase dose as toler ed.
  - If muscle symptoms have occurred on two or more statins, and symptoms outweigh risk and benefit, you may consider discussing alternate treatment methods with the patient.

Things to Consider

- Intolerance to one or more statins does not necessarily indicate intolerance to all statins.
- In addition to a variety of non-statin causes, onset of muscle symptoms in a patient who has previously tolerated statins can be caused by any number of changes in their clinical status. Continue to consider secondary causes.
- Consider characteristics of each statin such as metabolism, lipophilicity, drug interactions, etc. when prescribing. Use this app's Drug Comparison Calculator for help.

Patient Case Discussion

1. Is Miles at risk for statin associated myalgia?
   - Vit D Def
2. What further workup would you need to determine next steps?
   - LFTs, CK, Cr, Vitamin D level
3. **Which next step is most appropriate?**
   - A. Tell him to tough it out. This medication will save his life!
   - B. Stop statin for 2-4 week washout and assess if symptoms resolve.
   - C. Reduce dose of simvastatin down to 20mg daily.
   - D. Change to Atorvastatin 80mg daily.

Patient Case Discussion

Miles returns to clinic having now tried and failed simvastatin 40mg daily, and pravastatin 40mg daily. His current Vitamin D level is 15.

Which of the following would be preferred next steps?

A. Give up on statins, start ezetimibe

B. Remain off statin while correcting Vitamin D deficiency and retry statin once corrected

C. Try 3rd statin with rosuvastatin 5mg on Mon, Wed, Fri

D. Restart pravastatin 40mg daily along with CoQ10 600mg daily

Alternate Treatment Methods

- Less than daily dosing
- Supplements to aid in tolerance
  - Coenzyme Q10
  - Vitamin D
- Non-statins

Low Dose, Intermittent Atorvastatin, Rosuvastatin

- Weekly to TIW dosing achieves 21-34% reduction in LDL with 72.5 % tolerance rate[1,2,4]
- Decreased LDL at any level equates to equivalent lowering of CVD events per the Cholesterol Treatment Trialists' Collaboration[3]
- No RCT outcome trials
- Cleveland Clinic Experience -retrospective review showed trend toward mortality benefit[4]

1 Am J Cardiol 2009; 103:393-394
2 Annals of Pharmacotherapy 2008; 42(3): 341-346
3 Lancet 2010; 376 (10): 1670-1681
4 AHJ 2013;166:597-603

CoQ10 Supplementation

- Meta-analyses have not shown benefit
- RCT trial of 120 pts with prior statin myalgia
  - Double blind, crossover, simvastatin 20mg to confirm myalgia
  - 41 developed myalgia on simvastatin but not placebo
  - Randomized to simvastatin w/ CoQ10 600mg/d vs placebo
  - Serum levels rose
  - No change in myalgia
  - More patients reported pain with CoQ10 vs placebo

Only 36% of patients complaining of statin myalgia developed symptoms during the randomized, double-blind crossover of statin vs. placebo

Taylor BA et al. *Atherosclerosis*. 2015;238:329-335

Vitamin D Replacement

- Expert opinion: replace and retry statin if Vitamin D deficient
- A systematic review and 2 cohort studies suggest association between Vit D levels <30ng/ml and myalgia on statin1
- In 3 small studies, 87%, 92% and 100% of prior statin intolerant patients were able to tolerate statin after correction of vitamin D2,3,4

1 Reumatol Clin. 2016 Nov-Dec; 12(6):331-335
2 Curr Med Res Opinion 2011; 27(9):1683-90
3 Transl Res. 2009;153:11-16
4 J Pharm Pract. 2017 Oct;30(5):521-527

KP National ASCVD Guidelines

- Statin benefit groups: If unable to tolerate high-intensity statin therapy, use the maximum tolerated statin intensity.
- Use the maximum tolerated intensity of statin in individuals for whom a high- or moderate-intensity statin is recommended but not tolerated.
- In individuals at higher ASCVD risk receiving the maximum tolerated intensity of statin therapy who continue to have a less than-anticipated therapeutic response, consider adding a non-statin cholesterol-lowering drug(s) if the ASCVD risk-reduction benefits outweigh the potential for adverse effects. Higher-risk individuals include:
  - Those with clinical ASCVD ≤ 75 years of age.
  - Those with baseline LDL–C ≥ 190 mg/dL.
  - Those aged 40-75 years with diabetes mellitus.

KP National ASCVD Guidelines

- In individuals who are candidates for statin treatment but are completely statin intolerant, consider using non-statin cholesterol lowering drugs that have been shown to reduce ASCVD events in RCTs (i.e., ezetimibe) if the ASCVD risk-reduction benefits outweigh the potential for adverse effects.
- Give preference to non-statin cholesterol-lowering drugs shown to reduce ASCVD events in RCTs (i.e., ezetimibe).
- In individuals with clinical ASCVD on maximum tolerated oral lipid-lowering therapy (statin, ezetimibe, +/- bile acid sequestrant) and with persistently elevated lipids (e.g., LDL ≥ 130 mg/dL), consider discussing adding PCSK9 inhibitor with a lipid specialist (i.e., designated lipid specialist, cardiologist, or endocrinologist).

Non-Statin Therapies

- Lifestyle
  - Soluble Fiber
  - Reducing saturated and trans fats
- Ezetimibe
- Bile Acid Resins/Sequestrants
  - Cholestyramine
  - Colestipol
  - Colesevelam (Welchol)
- PCKS9 inhibitor
  - Alirocumab (Praluent)
  - Evolocumab (Repatha)

More on Lifestyle

- A healthy dietary pattern supported by all guidelines as basis for ASCVD reduction (Mediterranean, DASH)
- Portfolio diet: No statistically significant difference in LDL lowering vs lovastatin 20mg daily[1]
- Achieve 10% LDL-C reductions (when added to statin therapy)
  - Viscous or soluble fiber (nutrition sources and fiber laxatives)
    → 10-25 grams per day
  - Phytosterols (nutritional sources and supplements)
    → 2 grams per day

1 Jenkins, et al. Am J Clin Nutr. 2005 Feb;81(2):380-7

Non-Statin Medications

- Ezetimibe 10mg daily or ½ tablet or intermittent dosing for 20% LDL reduction[1,2]
- BAR per The Lipid Research Clinics Coronary Prevention Trial (LRCCPT): ~ 20% reduction in CV endpoints[3]
- For completely statin intolerant: LDL-lowering of 30% achieved with combo non statin therapy (ezetimibe, BAR, fiber, phytosterols)
- PCSK9 inhibitor in very high-risk patients[4]

1 Improve-IT: Cannon et al. NEJM 2015; 372: 2387-2397
2 Am J Cardiol 2008; 102:1205-1206
3 The Lipid Research Clinics Coronary Prevention Trial: JAMA 1984;251 (3): 351-64
4 FOURIER: Sabatine et al. NEJM; 2017: 376:1713-1722

Patient Case Discussion

Miles returns to clinic having now tried and failed simvastatin 40mg daily, and pravastatin 40mg daily. His current Vitamin D level is 15.

Which of the following would be preferred next steps?

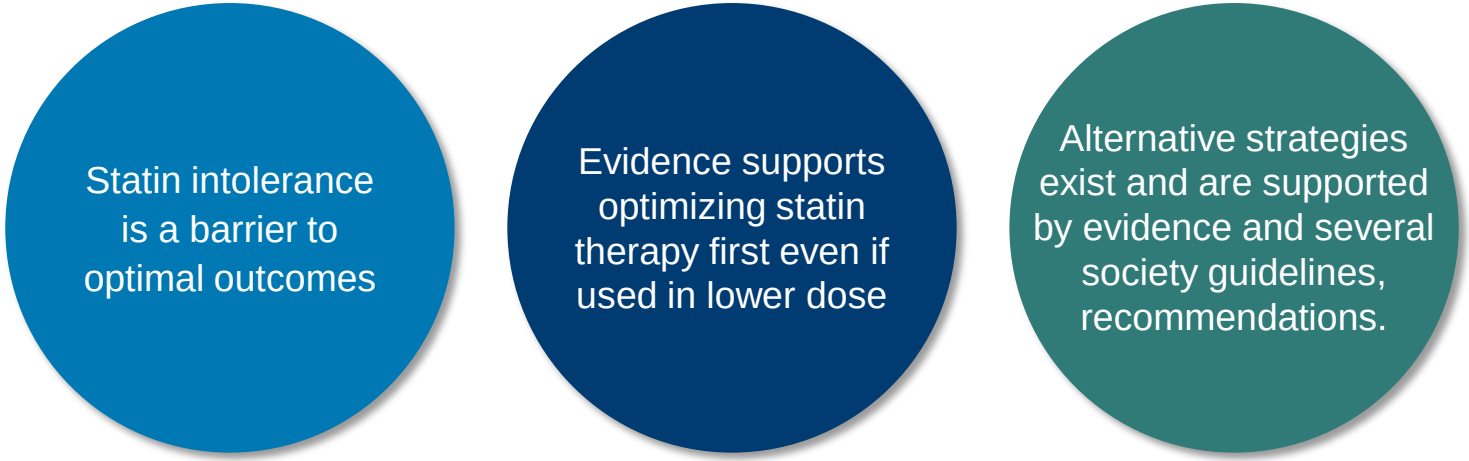
A. Give up on statins, start ezetimibe.

B. Remain off statin while correcting Vitamin D deficiency and retry statin once corrected.

C. Try 3rd statin with rosuvastatin 5mg on Mon, Wed, Fri.

D. Restart pravastatin 40mg daily along with CoQ10 600mg daily.

Summary


Statin intolerance is a barrier to optimal outcomes
Evidence supports optimizing statin therapy first even if used in lower dose
Alternative strategies exist and are supported by evidence and several society guidelines, recommendations.

Q&A

Please visit https://wa-provider.kaiserpermanente.org/provider-support/cme to register for future CMEs & visit https://wa-provider.kaiserpermanente.org/resources/education to view materials from past CMEs.