



Statin intolerance:

Does it exists? & How to manage?

By

Essam Mahfouz, M.D.

Professor of Cardiology, Mansoura University

CardioEgypt 2018

Agenda

- **Introduction**
- **Epidemiology**
- **Definition and classification**
- **Risk factors and mechanism**
- **Diagnosis**
- **Management**
- **Take home messages**

Introduction

- **HMGCoA reductase inhibitors or statins have revolutionized the treatment of hypercholesterolemia and the management of patients with increased cardiovascular disease (CVD) risk.**
- **Statins are well tolerated, but are associated with skeletal muscle, metabolic, neurological, and other possible side effects.**
- **Such reports are labeled as statin associated symptoms (SAS) because there is no consensus that statins are actually causative.**
- **SAS is favored over the term statin intolerance because many patients with SAS can tolerate reduced doses of these drugs.**

Epidemiology

- Statin associated muscle symptoms (SAMS), the most common statin side effect, are reported by **10% to 25%** of patients receiving statin therapy in observation studies and clinical registries while it is **5%** in clinical trials
- Cessation of statin treatment is associated with worse CV outcomes.
- A metaanalysis of 15 statin studies observed a **45%** increase in all cause mortality and a **15%** increase in CVD events in patients taking **<80%** of their prescribed statin therapy versus patients who were more adherent.

Potential adverse effects of statin

Good supportive evidence

- Myopathy
- Hepatic enzyme elevation
- Incident DM

Little or no supportive evidence

- Cancer
- Intracerebral hemorrhage
- Psychiatric illness
- Erectile dysfunction
- Cataract
- Abdominal pain
- Permanent hepatic or renal injuries

Definition & Classification

- **Statin intolerance is the inability to tolerate a dose of statin required to sufficiently reduce LDL C level and cardiovascular risk.**
- **A syndrome that has been verified, confirmed and documented that leads to suboptimal statin dosing, reductions in statin compliance, reductions in patient quality of life and function, statin cessation, and/or suboptimal LDL-C lowering.**
- **It may be:**
 - **Complete intolerance to any statin by any dose**
 - **Partial intolerance can tolerate statin in less than guideline recommended dose**

Definition & Classification

- **Myopathy any muscle symptoms related to statin**
- **Myalgia muscle pain with normal CK**
- **Myositis muscle pain with raised CK**
- **Myonecrosis**
 - **Mild > 3 ULN CK**
 - **Moderate 10-50 ULN CK**
 - **Severe > 50 ULN**
- **Rhabdomyolysis CK> 10 ULN, Myoglobinuria and + 0.5 mg creatinine above the basal**

Risk factors for statin intolerance

Patient related

- Old age > 75 y
- Female sex
- Low BMI
- Positive FH of muscle disease
- Heavy exercise
- Associated comorbidities: severe hepatic or renal disease, vitamin D def. Disorders of calcium homeostasis, surgery and major trauma & hypothyroidism

Drug related

- Dose of statin
- Type of statin
- Food interaction grape fruit, alcohol
- Drug interaction amiodarone, cyclosporine, antifungal , diltiazem

Table 15 Drugs potentially interacting with statins metabolized by CYP3A4 leading to increased risk of myopathy and rhabdomyolysis

Anti-infective agents	Calcium antagonists	Other
Itraconazole	Verapamil	Ciclosporin
Ketoconazole	Diltiazem	Danazol
Posaconazole	Amlodipine	Amiodarone
Erythromycin		Ranolazine
Clarithromycin		Grapefruit juice
Telithromycin		Nefazodone
HIV protease inhibitors		Gemfibrozil

SAMS with different statin in PRIMO study

Drug	No of patients	SAMS %
Fluvastatin 80 mg	3121	5.1
Atorvastatin 40-80 mg	1844	14.9
Pravastatin 40 mg	1901	10.9
Simvastatin 40-80 mg	1027	18.2

Mechanisms of SAMS

- Reduced sarcolemmal or T tubule cholesterol is a possible mechanism
- Reduction of coenzyme Q
- Stimulation of myocyte apoptosis
- Activating the phosphoinositide 3kinase (PI3K)/Akt pathway.
- Statins also appear to impair mitochondrial function.

Statin myalgia index score

Clinical symptoms—new or increased unexplained muscle symptoms		
Regional distribution pattern	Symmetric hip flexors/thigh aches	3
	Symmetric calf aches	2
	Symmetric upper proximal aches	2
	Nonspecific asymmetric—intermittent	1
Temporal pattern	Symptoms onset < 4 wk	3
	Symptoms onset 4 -12 wk	2
	Symptoms onset > 12 wk	1
Dechallenge	Improves on withdrawal— < 2 wk	2
	Improves on withdrawal—,2 – 4 wk	1
	Improves on withdrawal— > 4 wk	0
Challenge	Same symptoms reoccur on rechallenge— <4 wk	2
	Same symptoms reoccur on rechallenge— 4 – 12 wk	1

Probable	9-11
Possible	7-8
Unlikely	< 7

Non-invasive tests for SAMS

- Basal CK
 - Mild < 4ULN
 - Moderate 4-10 ULN
 - Severe > 10 ULN
- Post-exercise CK
- Muscle strength testing
- P 33 MRI
- Genetic testing
- Auto Antibodies to HMGcoA reductase for autoimmune statin myopathy

Clinical approach to SAMS

Rosenson, R.S. et al. J Am Coll Cardiol. 2017

CENTRAL ILLUSTRATION Clinical Approach to Patient With SAMS



Patient with suspected statin-associated muscle symptoms (SAMS)



Clinical assessment: Statin-Associated Muscle Symptom Clinical Index (SAMS-CI)

Low SAMS-CI score

High SAMS-CI score

Low SAMS-CI score

Evaluate for:

Other causes affecting musculoskeletal system
History of medication-related side effects
Depression and anxiety



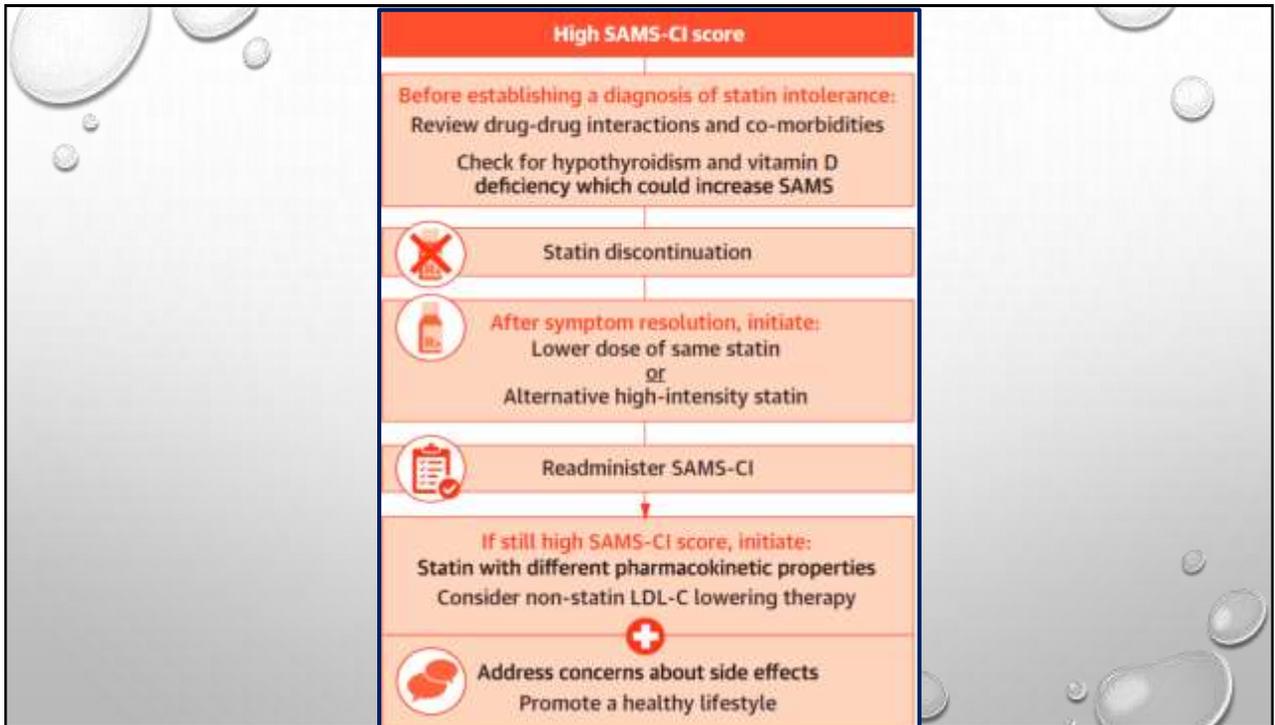
Statin discontinuation



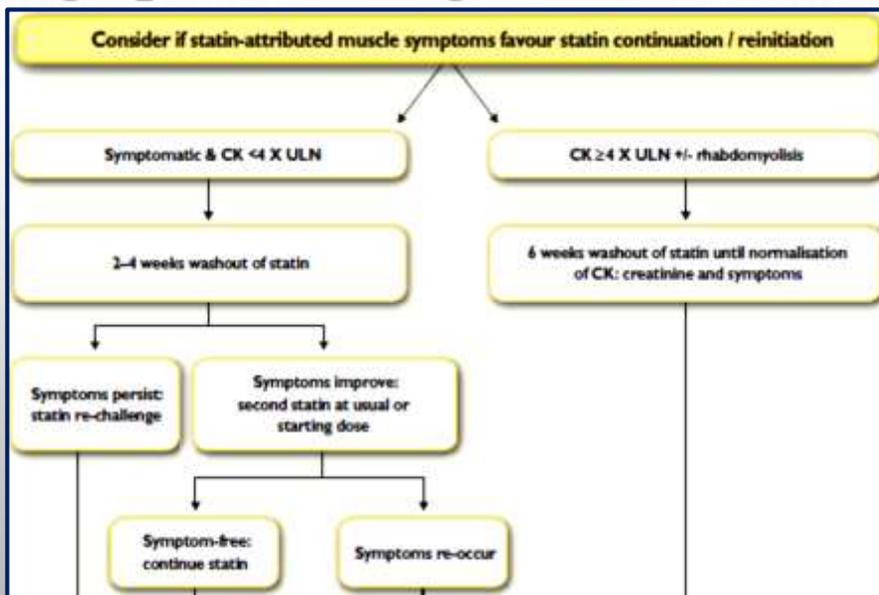
After symptom resolution, initiate:
Same dose of same statin
(low likelihood that SAMS will reoccur)
OR
Alternative high-intensity statin



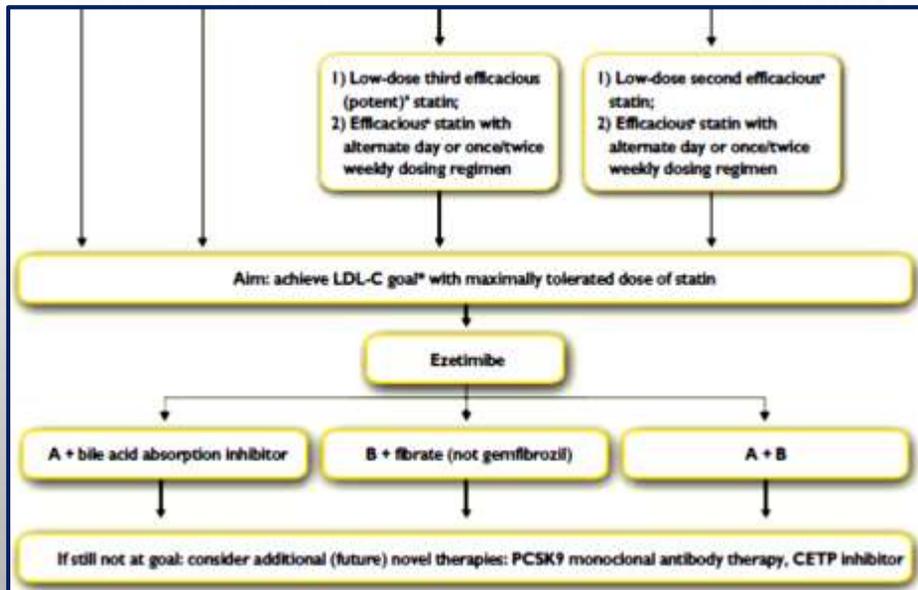
Address concerns about side effects
Promote a healthy lifestyle



Algorithm for treatment of muscular symptoms during statin treatment



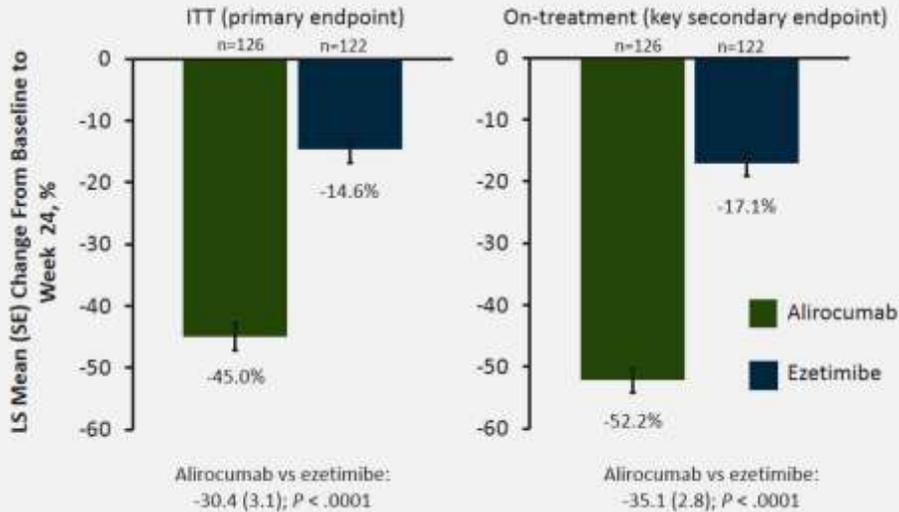
Algorithm for treatment of muscular symptoms during statin treatment



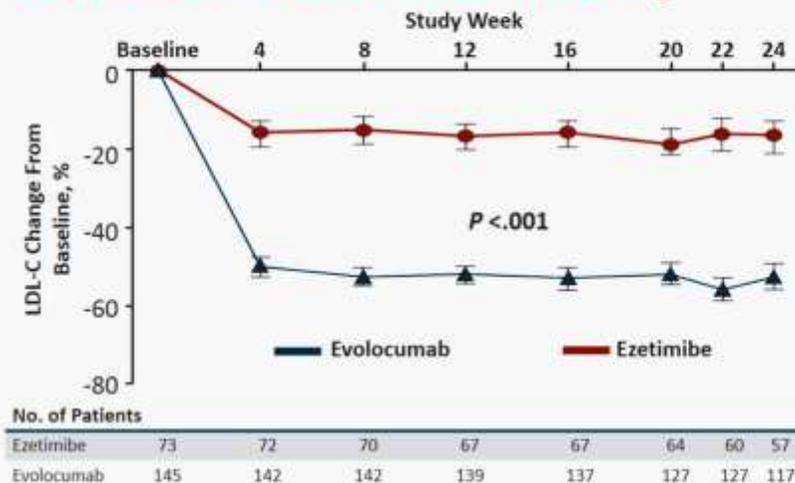
Non-statin Pharmacotherapy

- Ezetimibe
- Bile acid sequestrant
 - Colesevelam
 - Cholestyramine
 - Colestipol
- PCSK9 inhibitors
- Fibrates
- Niacin
- Bempedoic acid investigational drug

ODYSSEY ALTERNATIVE: Alirocumab in Statin Intolerance



GAUSS-3: Better LDL-C Lowering



Ezetimibe dose: 10 mg/d; evolocumab dose: 140 mg 3 × /mo (420 mg total dose/mo). GAUSS-3 indicates Goal Achievement After Utilizing an Anti-PCSK9 Antibody in Statin Intolerant Subjects 3. Error bars indicate 95% CIs.

Reproduced with permission from Nissen S, et al. *JAMA.* 2016;315:1580-1590. Copyright©(2016) American Medical Association. All rights reserved.

Nutraceuticals

- **Coenzyme Q 10**
- **Vitamin D**
- **Phytosterols**
- **Viscous fiber**
- **Red yeast rice**
- **Others: curcumin, fish oils and omega 3 FA**

Take home messages

- **Statin are a corner stone in prevention and management of ASCVD**
- **Statin associated side effects especially SAMS are an important cause for non-adherence to this important pharmacotherapy**
- **Up to 90% of patient diagnosed with SAMS can tolerate statin on stepwise approach**
- **Lower dose, alternate statin, use of long acting statin/2d or once or twice weekly can help in rechallange therapy**
- **Non statin pharmacotherapy, nutraceutical, life style modifications, and psychotherapy are helpful in overcoming this problem**

