Statin-Associated Muscle Symptoms (SAMS): Impact on Statin Therapy

European Atherosclerosis Society Consensus Panel Statement on

Assessment, Aetiology and Management

Stroes ES et al. Eur Heart J 2015 ;36:1012-1022

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REVIEW

Clinical update

Statin-associated muscle symptoms: impact on statin therapy—European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management

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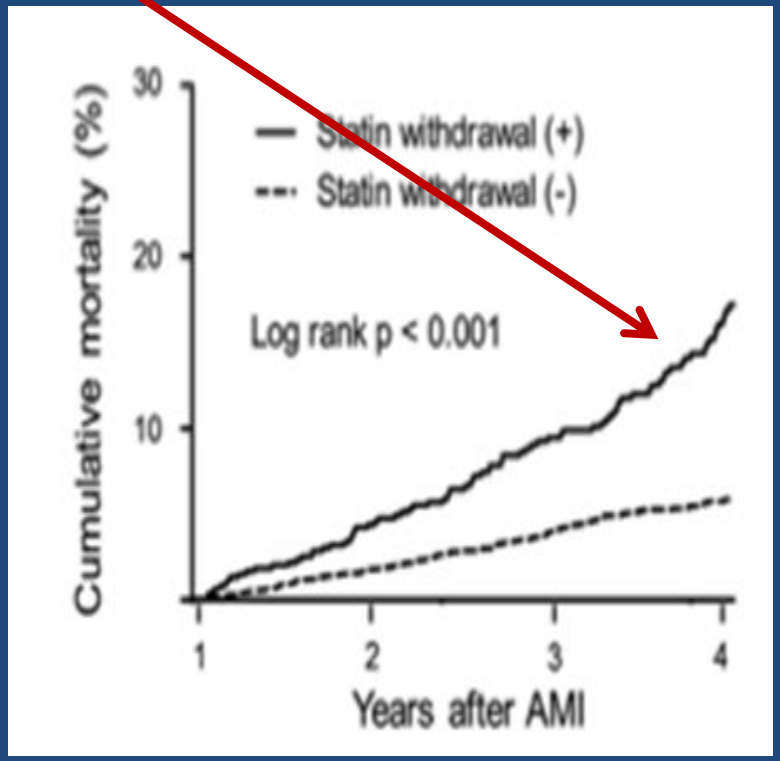
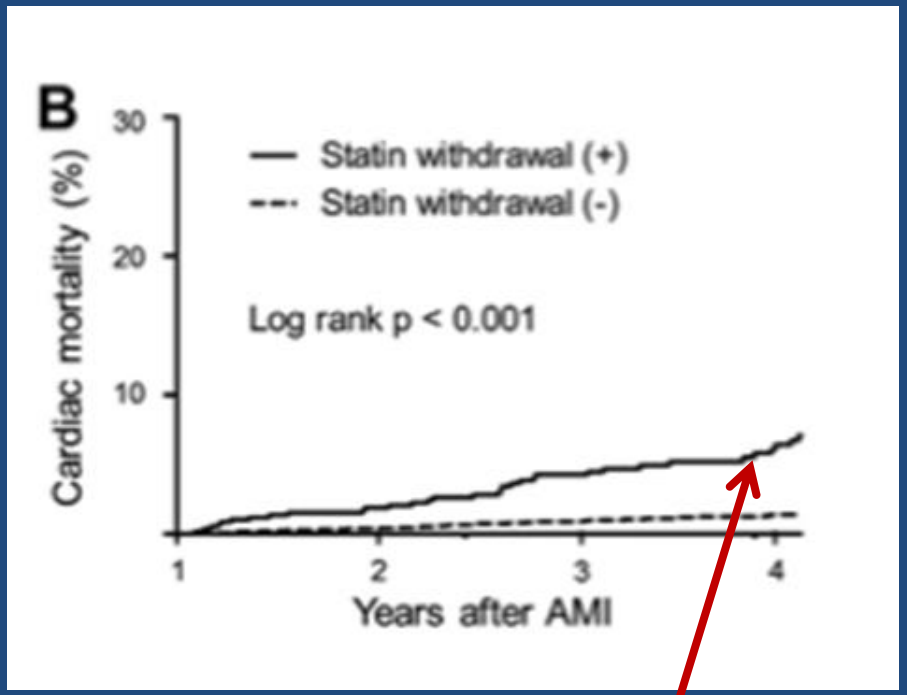
Stroes ES et al. Eur Heart J 2015 ;36:1012-1022

Statin intolerance:
A major cause of poor adherence which impacts the cardiovascular benefits of statins

Poor statin adherence increases mortality

>3-fold increase in all-cause mortality





>4-fold increase in cardiac mortality

Kim MC et al. Am J Cardiol 2015 ;115:1-7

- **Statin associated muscle symptoms (SAMS):**
  One of the main reasons for statin non-adherence or discontinuation

RCT: No difference in myalgia rates

35 trials; 74,000 patients; 17 months mean follow-up

Adverse event	Trials	Statin *	Placebo	HR	(& 95% CI)
Myalgia	21	15.4%	18.7%	0.99	(0.96-1.03)
CK elevation	16	0.9%	0.4%	1.18	(0.89-1.56)
Rhabdomyolysis	20	0.17%	0.12%	1.09	(0.65-1.83)

*Atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin, but excluding cerivastatin

Kashani A et al. Circulation 2006 ;114:2788-97

PRIMO: Observational, retrospective study

Statin	Dose (mg/d)	% with muscle symptoms	Odds ratio (95% CI)	P-value
Pravastatin	40	10.9		
Atorvastatin	40-80	14.9	1.28 [1.02–1.60]	0.035
Simvastatin	40-80	18.2	1.78 [1.39–2.29]	<0.001
Fluvastatin	80	5.1	0.33 [0.26–0.42]	<0.001

7924 patients treated with high dose statin for >3 months before the study or discontinued/modified high dose statin due to muscular side effects in last 3 months

Overall 10.5% reported muscle symptoms

Bruckert E et al. Cardiovasc Drugs Ther. 2005 ;19: 403–414

Why the discrepancy between RCT and Observational Studies?

RCT:

- **Exclusion of patients unlikely to adhere or using interacting drugs?**
- **Lack of dedicated questionnaires into muscle complaints?**

Observational studies:

- **Patients aware of muscle symptoms with statin use due to package inserts / doctors warning / media attention ?**
- ***But lack of placebo for comparison***

Newman CB, Tobet JA. JAMA 2015;313:1011-2.

Incidence of SAMS using a RCT design

Statins on Skeletal Muscle Function and Performance (STOMP)

Subjects (n=440)

- Men and women
- >20 years
- No prior statin use

Design

- Randomised, double blind
- 80 mg atorvastatin vs. placebo for 6 months

Muscle function

- Handgrip strength
- Elbow flexor/extensor
- Knee flexor/extensor

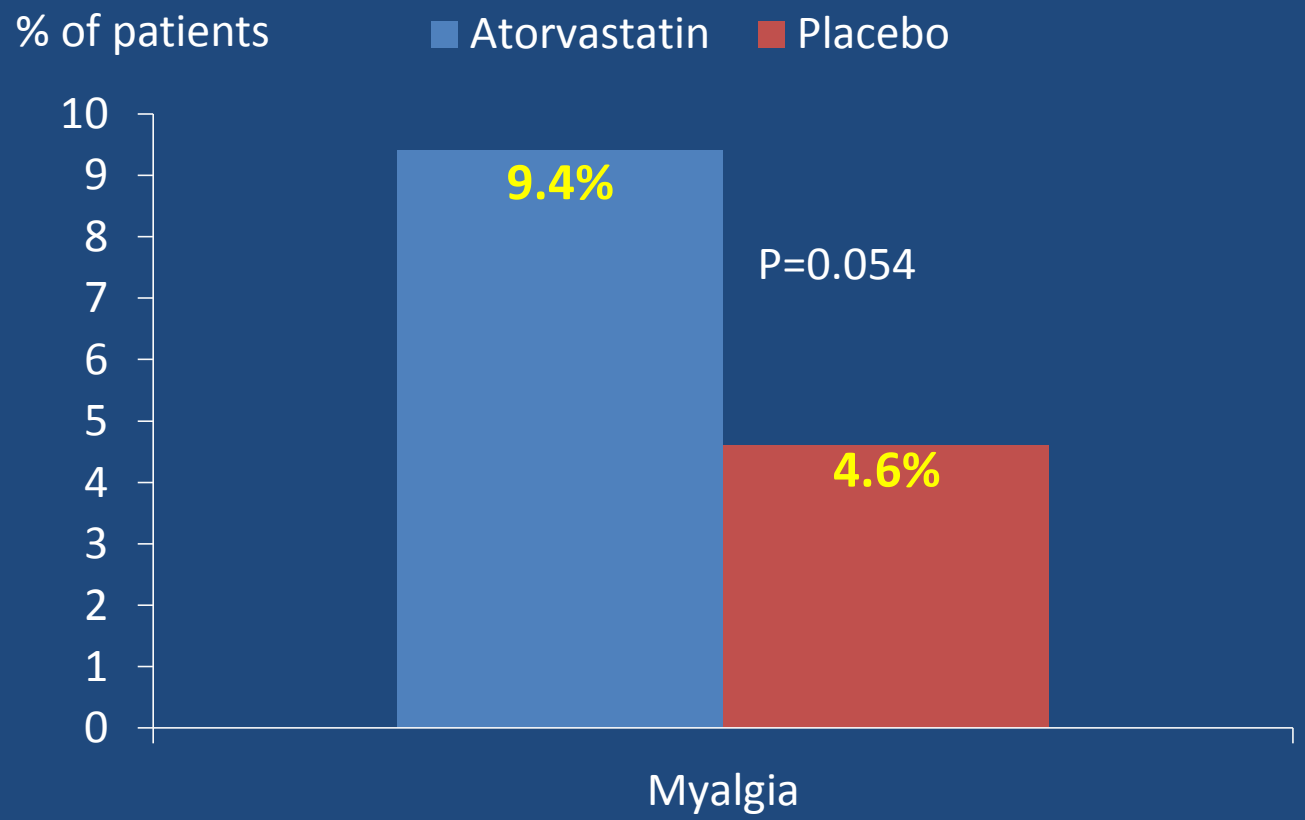
Aerobic performance (VO_2Max)

Physical activity (accelerometer)

Muscle symptoms- called twice monthly

Parker BA et al. Circulation 2013; 127:96-103

STOMP: Frequency of SAMS



Assessment made before and after atorvastatin 80 mg or placebo , administered for 6 months to 420 healthy, statin-naive subjects.

Parker BA et al. Circulation 2013; 127:96-103

How to identify SAMS

Defining SAMS

- **There is no "gold standard" diagnostic test**

Symptoms	CK	When to consider SAMS?
Muscle symptoms	Normal	Often called myalgia; may be statin-related
Muscle symptoms	> ULN and <4 x ULN >4 <10 X ULN	Consider increased exercise; may be statin-related
Muscle symptoms	>10 X ULN	Often called myositis or 'myopathy' even in the absence of a muscle biopsy; Associated with statin or underlying muscle disease
Muscle symptoms	>40 X ULN	Rhabdomyolysis
None	> ULN and <4 X ULN	May be statin related
None	>4 X ULN	Clinical significance unknown

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Assessing SAMS

- Usually symmetrical and proximal
- Affect large muscle groups (thighs, buttocks, calves and back muscles)
- Usually occur early (within 4¬6 weeks) of starting statin ; but can occur after many years of treatment.
- May occur with an increase in statin dose, initiation of an interacting drug, or increase in physical activity
- May appear more rapidly if patient is re-challenged with a statin

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Consider risk factors for SAMS

- >80 years, female, low BMI, Asian descent
- Excess physical activity
- Excess alcohol or grapefruit or cranberry juice
- Acute infection, hypothyroidism, impaired renal or hepatic function, organ transplant recipient, trauma, HIV, diabetes
- Vitamin D deficiency
- Surgery with high metabolic demands
- History of CK elevation or unexplained muscle/joint/tendon pain, or myopathy on another lipid-lowering therapy
- Inflammatory or inherited metabolic, neuromuscular/muscle disorders
- Polymorphisms in cyt P450 isoenzymes or drug transporters

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Consider factors that influence statin pharmacokinetics

- Pre-existing risk factors and co-morbidities
- High-dose statin therapy
- Polypharmacy
- Drug-drug interactions (eg gemfibrozil, macrolides, azole antifungal agents, protease inhibitors and immunosuppressive drugs, inhibitors of CYP450 isoenzymes, OATP 1B1, or P-gp)
- Pharmacogenetics

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How to manage SAMS

Step 1: Counsel for benefit/harm

Allow sufficient time to:

- Counsel the patient about the cardiovascular benefit of statins
- Re-emphasise the long-term safety and absence of 'organ damage' with statins, even when discomfort/pain is present
- Explain the high likelihood of successful re-challenge with statin

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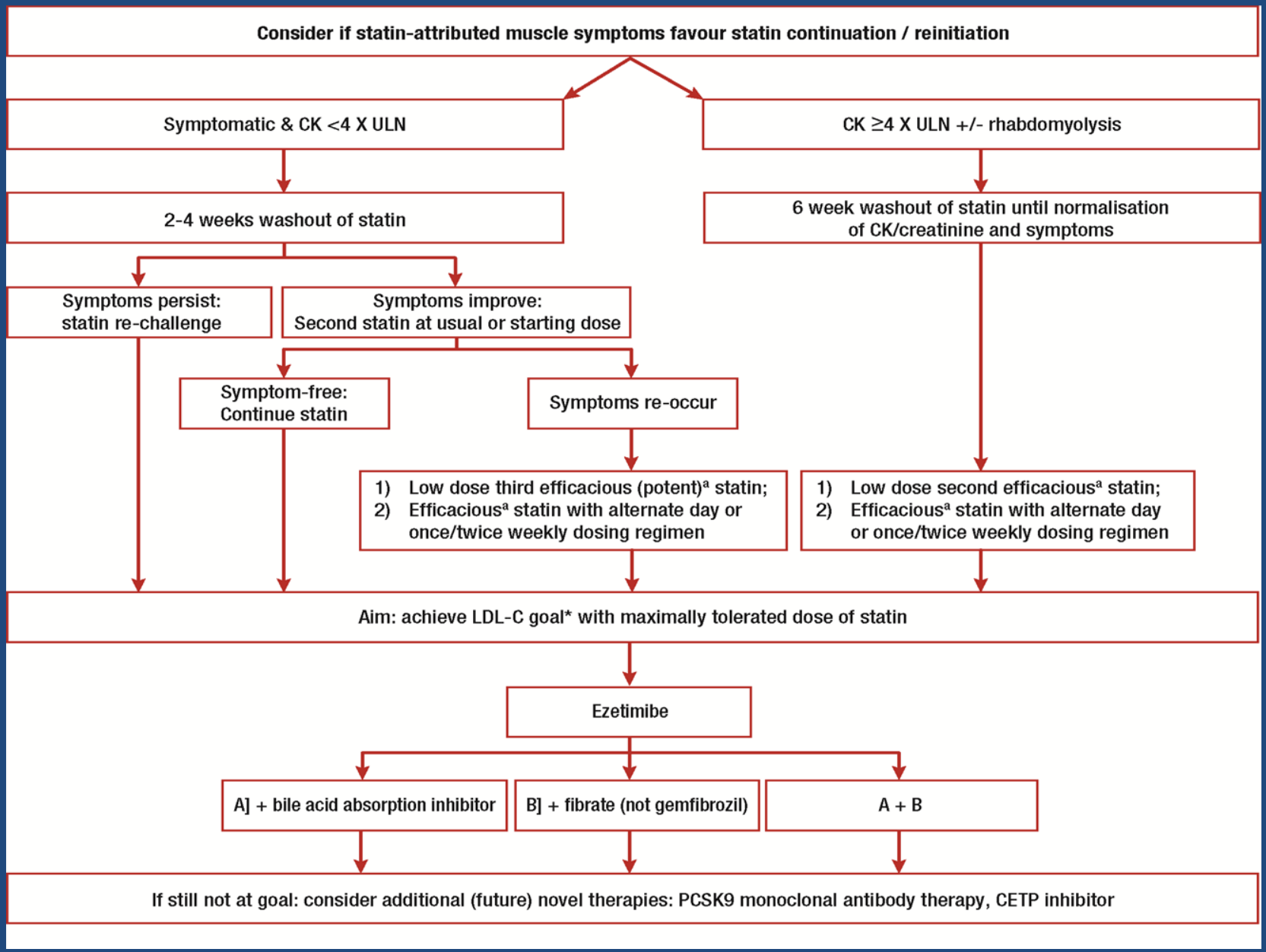
Step 2: Use a standardised approach



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Management of SAMS
Muscle symptoms and CK < 4 X ULN

CVD risk	Management strategies
Low	• Consider therapeutic lifestyle changes vs. risk of continuing statin
High	• Consider benefits of ongoing statin therapy vs. burden of muscle symptoms • Withdraw statin, followed by one or more re-challenges (after a washout) • Consider an alternative statin, a statin at lowest dose, intermittent (i.e. non-daily) dosing of a highly efficacious statin, or the use of other lipid lowering medications

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Management of SAMS
Muscle symptoms and CK > 4 X ULN

Patients at high CVD risk

CK < 10 X ULN
- Continue statin while monitoring CK

CK > 10 X ULN and no secondary cause, stop the statin

- If CK levels decrease, consider re-starting statin at a lower dose, or start a lower dose of an alternative statin. Monitor symptoms and CK
- If CK elevation persists, consider referral to a neuromuscular specialist for investigation of an underlying myopathy
- If rhabdomyolysis is suspected, do not re-start statin; refer for assessment of renal damage .

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Treatment options in SAMS

Statin

Non statin

- First choice: ezetimibe
- Bile acid sequestrants or fibrates in combination with ezetimibe

Nutraceuticals

- Viscous fibre (mainly psyllium, 10 g daily) and foods with added plant sterols/stanols

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What role for complementary therapies?

- Various complementary therapies have been suggested, including ***coenzyme Q10 (ubiquinone)***, and ***vitamin D supplements***
- None are supported by RCT evidence

- ***Red yeast rice (Monascus purpureus)*** has been shown to reduce LDL-C levels by 20-30%.
- However, in the absence of robust evidence for long-term efficacy and tolerability, and the lack of standardisation of current preparations, this is currently not recommended.
- Red yeast rice can also induce SAMS due to the statin-like content (monacolin K, similar to lovastatin)

Stroes ES et al. Eur Heart J 2015 ;36:1012-1022

Step 3: Rechallenge the patient

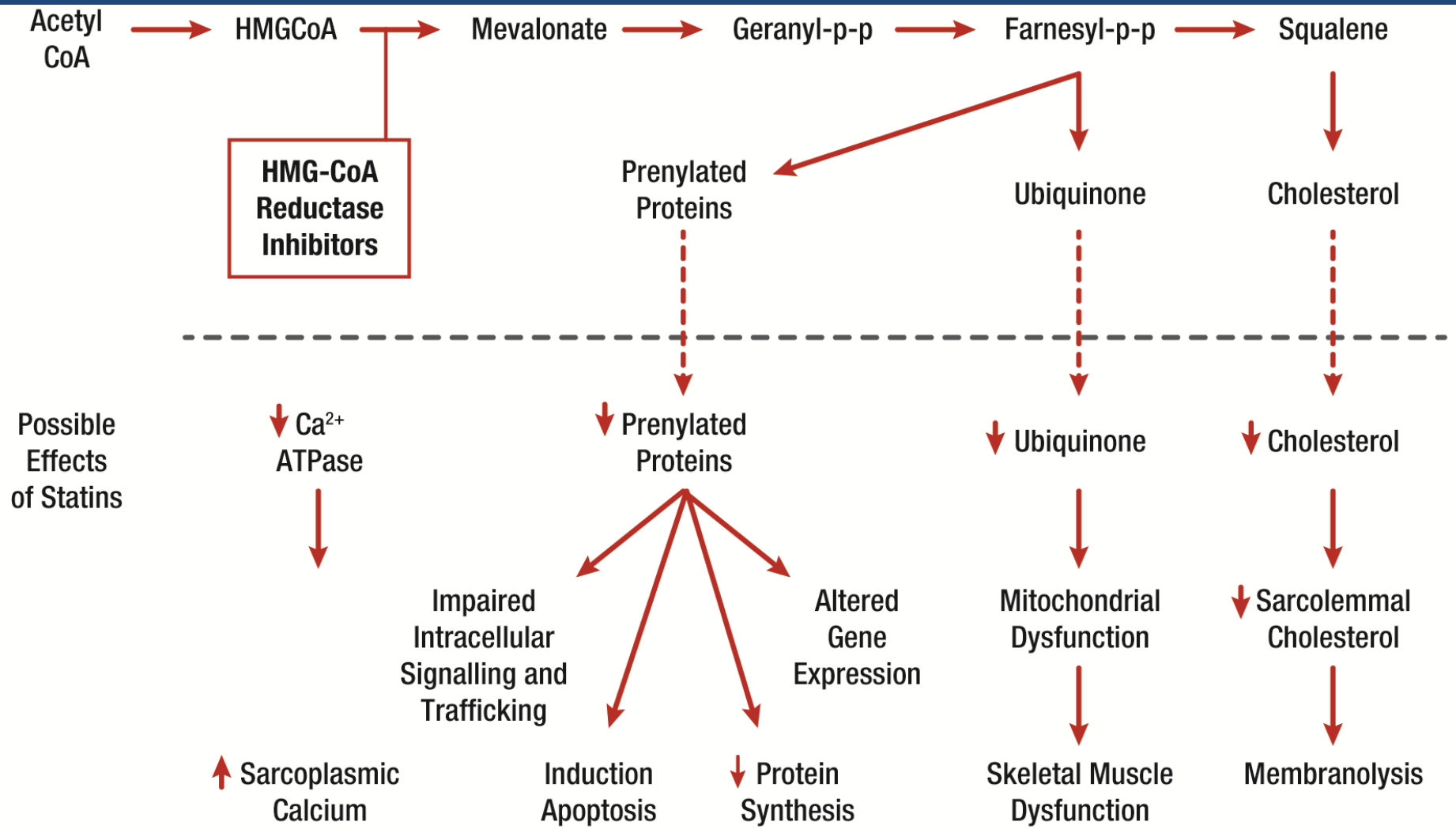
Most patients rechallenged can tolerate statins long-term

- Retrospective cohort study in 107,835 patients
- 18,778 (17.4%) patients had statin-related events. Statins were discontinued at least temporarily by 11,124 of these patients
- On re-challenge:
  - ✓ 92.2% were still on a statin >12 months later
  - ✓ 47.6% were on the same statin to which they had the statin-related adverse event

Zhang H et al. Ann Intern Med 2013;159:75-6

Pathophysiology of SAMS

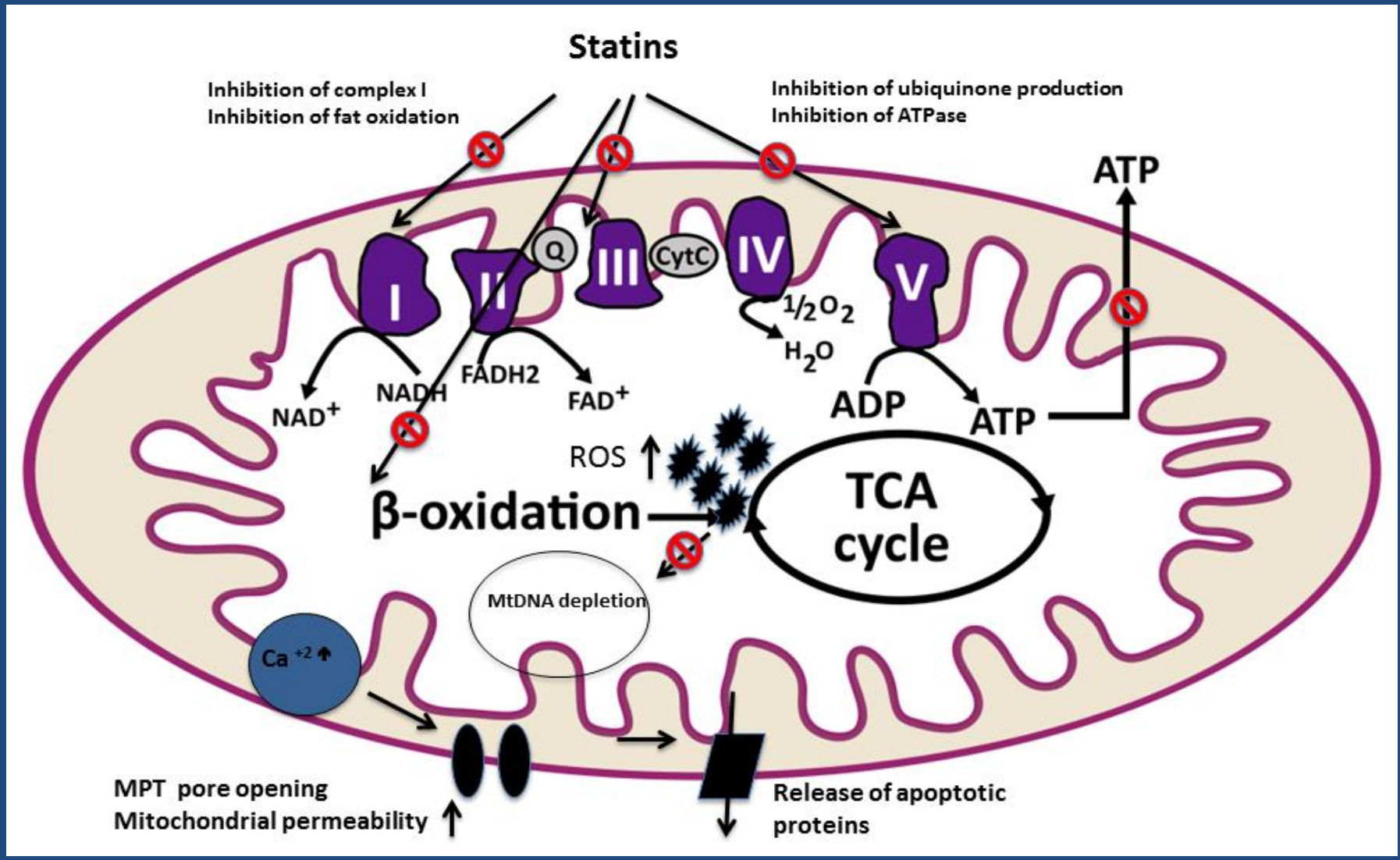
Effects potentially involved in statin-related muscle injury/symptoms



Stroes ES et al. Eur Heart J 2015 ;36:1012-1022; adapted from Needham M et al. Neuromuscul Disord. 2014;24(1):4-15

Role of mitochondrion

Possible targets of statins in the mitochondrion with deleterious effects on muscle function



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Potential mechanisms implicated in mitochondrial toxicity

Effect of statins on mitochondria

↓ubiquinone attenuates electron transfer complex I-III

↓prenylation ETC proteins

↓farnesyl/geranylgeranyl-PP leading to impaired growth / autophagy

↓membrane cholesterol affecting membrane fluidity and ion channels

calcium release from s.reticulum leading to impaired calcium signalling

Needham M et al. Neuromuscul Disord. 2014;24(1):4-15
Stroes E et al. Eur Heart J 2015 ;36:1012-1022

Summary

SAMS is a major reason for ‘referral’

- Leading to statin non-adherence / discontinuation
- Contributing to decreased CVD-benefit from statins

‘Golden’ principles in management of SAMS

- Always strive to continue ‘maximally-tolerated’ statin therapy
- Always apply repetitive de-/re-challenges