High intensity statin therapy in DM + ASCVD and Managing statin intolerance

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Disclosures

Objectives

- Evidence for statins in DM + ASCVD
- Statin intolerance
    - Who discontinues and why?
    - Definition of intolerance
    - Prevalence: RCT vs. observational data
    - Algorithms + case-based management

Placebo-controlled statin trials in ASCVD with DM

Trial & date	Intervention	Population	DM sample	Outcomes
4S 1994	Simvastatin 20-40mg vs. placebo	4,444	483 (11%)	Mortality ↔ MACE ↓55%
CARE 1996	Pravastatin 40mg vs. placebo	4,159	586 (14%)	MACE ↔ Fatal or non-fatal CHD ↓25%
LIPID 1998	Pravastatin 40mg vs. placebo	9,014	1,077 (12%)	MACE ↔ CVE ↓21%
HPS 2002	Simvastatin 40mg vs. usual care	20,536	3,051 (15%)	↓27% CHD death, non-fatal MI ↓24% stroke (6-↓39%, P=0.01) ↓22% MACE (13-30%, P<0.0001)
SPARCL 2006	Atorvastatin 80mg vs. placebo	4,731	798 (17%)	MACE ↓ 51% No difference in stroke.

Haffner SM Arch Intern Med 1999; Goldberg RB Circulation 1998; LIPID NEJM 1998; HPS Lancer 2003; Callahan A AMA Neuro 2011

Placebo-controlled statin trials in DM with ASCVD

Groups	Events (%) Treatment	Control	RR (CI)	Test for heterogenity or trend
Type of diabetes:				
Type 1 diabetes	147 (20·5%)	196 (26·2%)	0·79 (0·62–1·01)	χ^2_1=0·0; p=1·0
Type 2 diabetes	1318 (15·2%)	1586 (18·5%)	0·79 (0·72–0·87)	
Sex:				
Men	1082 (17·2%)	1332 (21·4%)	0·78 (0·71–0·86)	
Women	383 (12·4%)	450 (14·6%)	0·81 (0·67–0·97)	χ^2_1=0·1; p=0·7
Age (years):				
≤65	701 (13·1%)	898 (17·1%)	0·77 (0·68–0·87)	
>65	764 (18·9%)	884 (21·8%)	0·81 (0·71–0·92)	χ^2_1=0·5; p=0·5
Currently treated hypertension:				
Yes	1030 (16·3%)	1196 (19·1%)	0·82 (0·74–0·91)	
No	435 (14·2%)	586 (19·3%)	0·73 (0·63–0·85)	χ^2_1=2·7; p=0·1
Body-mass index:				
<25·0	276 (15·7%)	362 (20·4%)	0·78 (0·64–0·95)	
≥25·0–<30·0	639 (15·9%)	774 (19·8%)	0·77 (0·68–0·88)	χ^2_1=0·5; p=0·5
≥30·0	532 (15·1%)	628 (17·6%)	0·82 (0·71–0·95)	
Systolic blood pressure (mm Hg):				
<160	993 (15·0%)	1276 (19·1%)	0·76 (0·69–0·85)	
≥160	472 (17·1%)	505 (19·2%)	0·83 (0·71–0·96)	χ^2_1=1·3; p=0·3
Diastolic blood pressure (mm Hg):				
≤90	1176 (16·5%)	1417 (19·8%)	0·81 (0·73–0·89)	
>90	288 (12·9%)	364 (17·1%)	0·73 (0·61–0·87)	χ^2_1=1·7; p=0·2
Smoking status:				
Current smokers	266 (17·5%)	347 (22·5%)	0·78 (0·64–0·96)	
Non-smokers	1199 (15·2%)	1435 (18·5%)	0·79 (0·72–0·87)	χ^2_1=0·0; p=0·9
Estimated GFR (mL/min/1·73m²):				
<60	415 (20·6%)	477 (24·0%)	0·83 (0·71–0·97)	
≥60–<90	816 (15·5%)	961 (18·4%)	0·81 (0·72–0·91)	χ^2_1=2·9; p=0·09
≥90	194 (12·5%)	286 (18·7%)	0·65 (0·50–0·84)	
Predicted risk of major vascular event (per year):				
<4·5%	474 (8·4%)	631 (11·2%)	0·74 (0·64–0·85)	
≥4·5–<8·0%	472 (23·2%)	540 (27·3%)	0·80 (0·66–0·96)	
≥8·0%	519 (30·5%)	611 (35·8%)	0·82 (0·70–0·95)	χ^2_1=1·8; p=0·2
All diabetes	**1465 (15·6%)**	**1782 (19·2%)**	**0·79 (0·74–0·84)**	

Global test for heterogeneity within subtotals: χ^2_{13}=13·9: p=0·4

RR (99% CI)

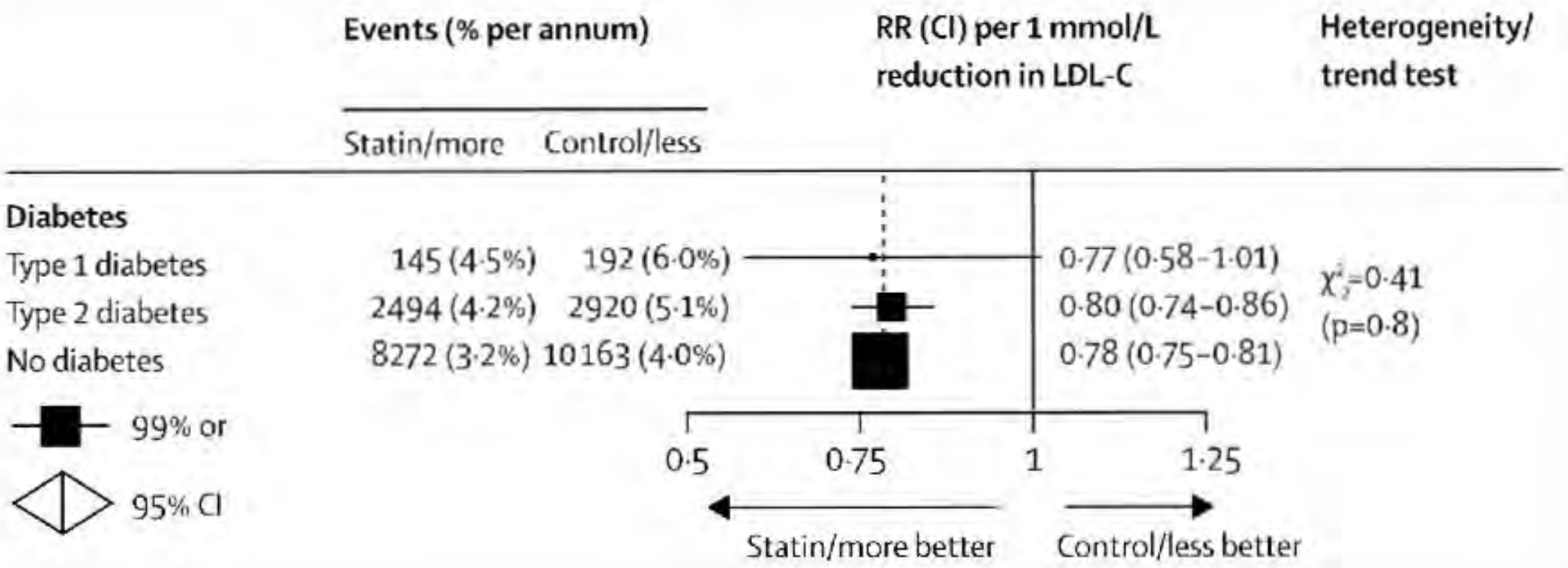
RR (95% CI)

0·5 Treatment better 1·0 1·5 Control better

CTT Lancet 2008

COORDINATE-Diabetes

High intensity trials in DM with ASCVD



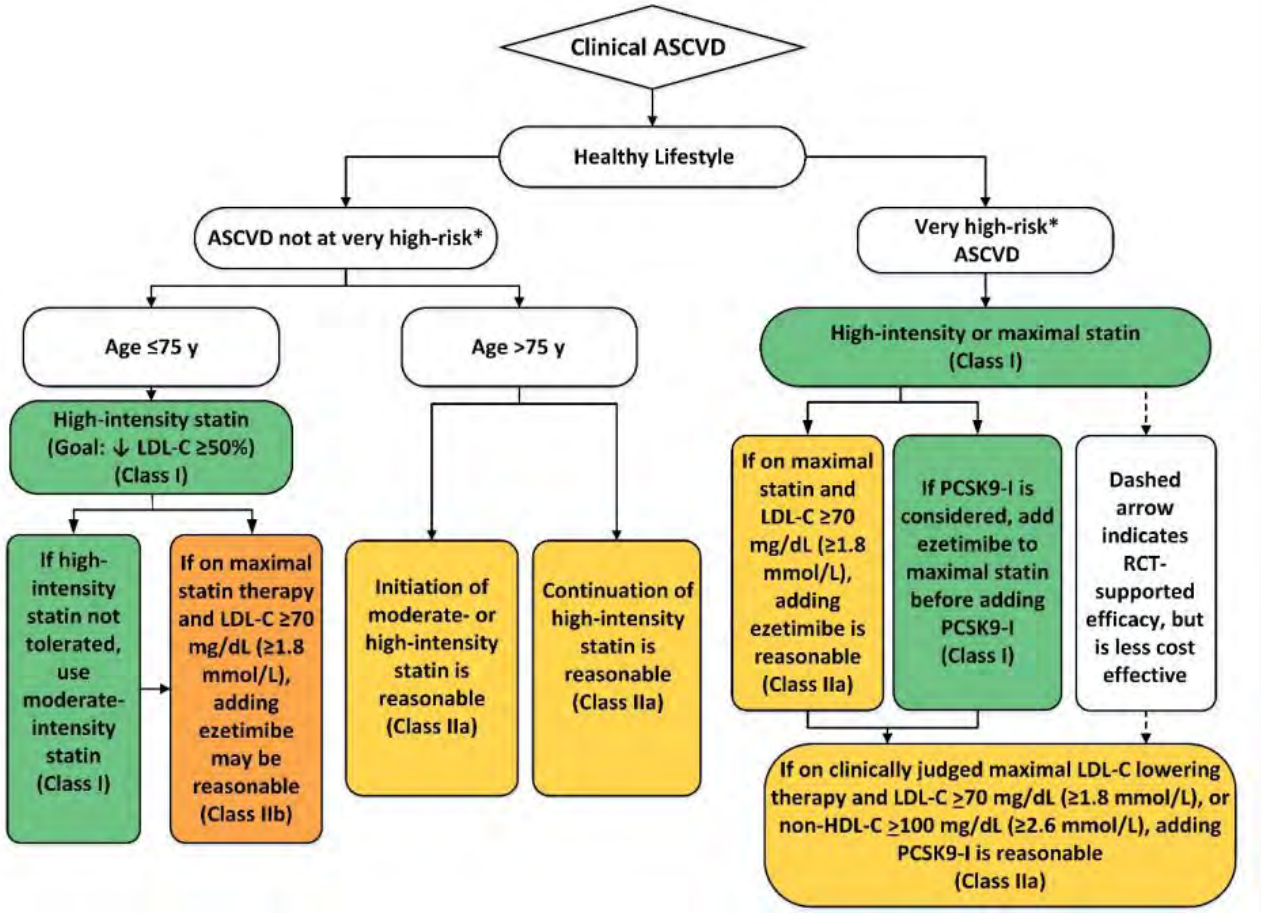
CTT Lancet 2010

Statin intensity

	High intensity	Moderate Intensity	Low Intensity
LDL-C lowering	≥50%	30-49%	<30%
Statins	Atorvastatin 40-80mg Rosuvastatin 20-40mg	Atorvastatin 10-20mg Rosuvastatin 5-10mg Simvastain 20-40mg	Simvastatin 10mg
		Pravastatin 40-80mg Lovastatin 40-80mg Fluvastatin XL 80mg Pitavastatin 1-4mg	Pravastatin 10-20mg Lovastatin 20mg Fluvastatin 20-40mg

Grundy et al JACC 2018

Statin guidelines: ACC



Major ASCVD Events
Recent ACS (within the past 12 mo)
History of MI (other than recent ACS event listed above)
History of ischemic stroke
Symptomatic peripheral arterial disease (history of claudication with ABI <0.85, or previous revascularization or amputation (S4.1-39))
High-Risk Conditions
Age ≥65 y
Heterozygous familial hypercholesterolemia
History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s)
Diabetes mellitus
Hypertension
CKD (eGFR 15-59 mL/min/1.73 m^2) (S4.1-15, S4.1-17)
Current smoking
Persistently elevated LDL-C (LDL-C ≥100 mg/dL [≥2.6 mmol/L]) despite maximally tolerated statin therapy and ezetimibe
History of congestive HF

Grundy et al JACC 2018

Statins in key subgroups

Subgroup	Considerations
Elderly	No specific hazard in trials including >65, >75, >80yos (PROSPER, CORONA) Higher levels of comorbidity and polypharmacy increase risk of AE
Prior ICH	Limited data. Potential signal in those with prior history of ICH. Risk/benefit assessment of further ICH vs. MACCE
Chronic Kidney disease	Safe for CKD 2 through 4 (SHARP, UK-HARP), and dialysis. No convincing benefit in dialysis (4D, AURORA)
Liver disease	Contraindicated in 'active liver disease'. However treatment when ALT/AST up to 3 x ULN does not lead to deterioration No evidence of harm (+/- possible benefit) in biopsy proven NAFLD or HBV/HCV No data in decompensated or cirrhotic liver disease

Kjekshus J *NEJM* 2007; Shepher J *Lancet* 2002; Baigent C *Lancet* 2011; Flint AC *JAMA Neurol.* 2014; Goldstein LB *Neurology* 2008; Tonelli *Circulation* 2004; Baigent C *Am J Kidney Dis* 2005; Chalasani N *Gastroenterology* 2004; Vuppalanchi R *Am J Med Sci* 2005; Tikkanen MJ *Int J Cardiol.* 2013; Fellstrom BC *NEJM* 2009

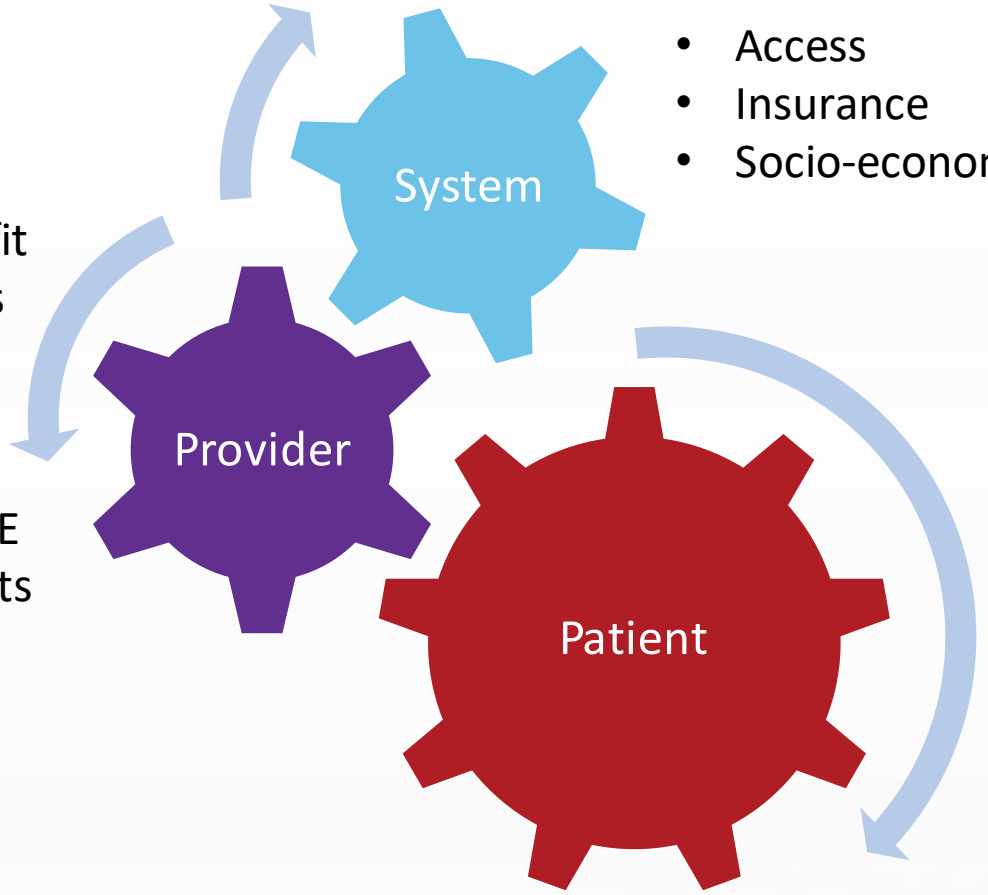
Statin non-persistence

- In real-world practice, persistence with statins after 3 years:
    - <30% in primary prevention
    - <45% in secondary prevention
- Non-persistence is associated with poor outcomes
    - After adjustment for ‘healthy behavior’
- Non-persistence is **more** than intolerance

Banach M *Int J Cardiol.* 2016; Jackevicius CA *JAMA* 2002; Rodriguez F *JAMA Cardiology* 2019

Reasons for discontinuation: more than intolerance

- Inadequate knowledge of benefit
- Preconceived beliefs about risks
  - dementia, ICH, liver failure
- Inertia from prior rare 'events'
- Unwillingness to re-challenge
- Lack of time to elucidate ADR/AE and temporal sequence of events

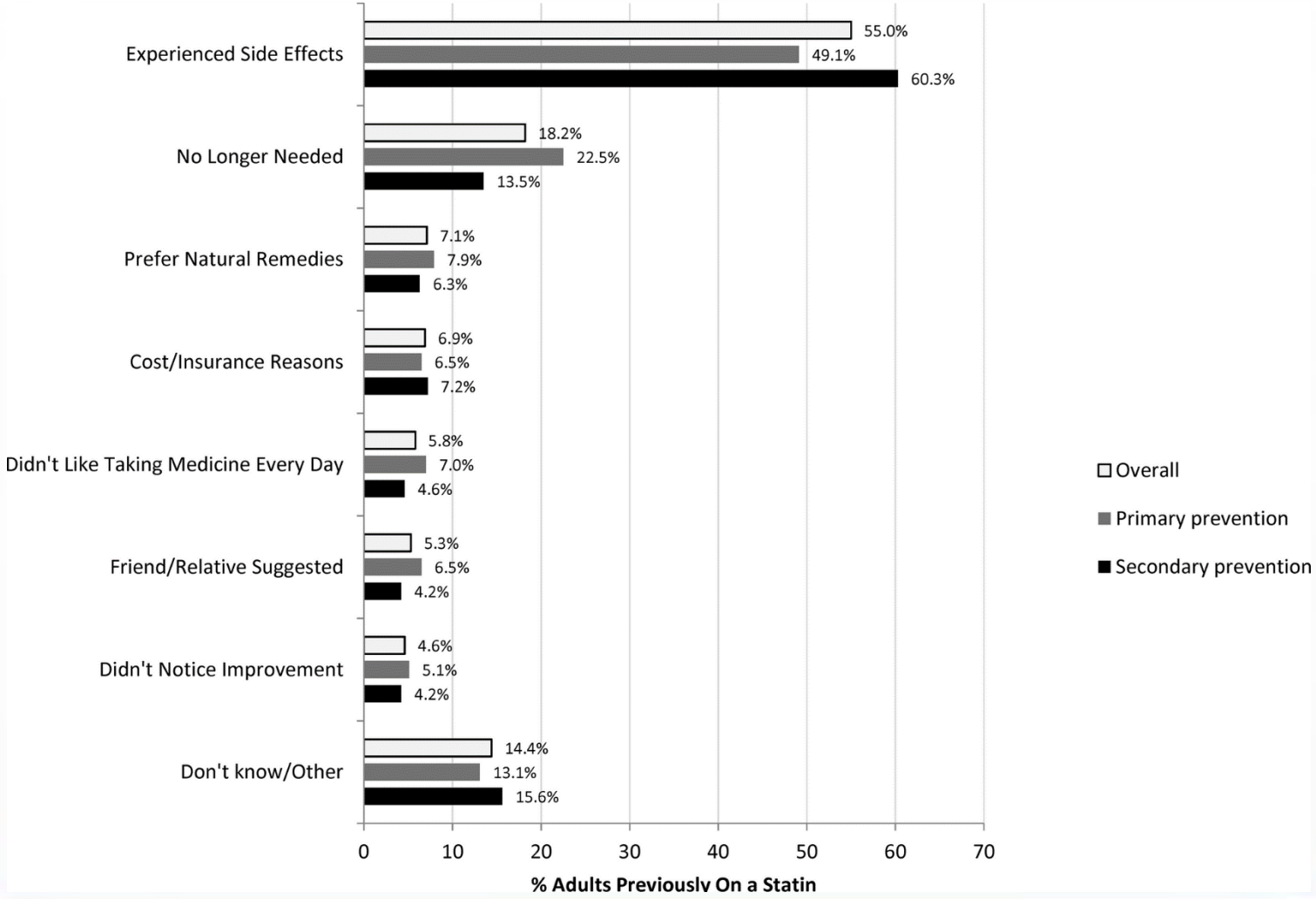


- Access
- Insurance
- Socio-economic status

- Incomplete understanding of benefits
- Fear of side effects (media, others)
- Misattribution of ADRs
- True adverse events
- Unwillingness to re-challenge
- (Affordability)

Bradley CK JAHA 2019; Nanna MG JAMA Cardiol 2019; Spence JD JAHA 2016

From PALM, in those that discontinued statins…



Bradley et al. *JAHA* 2019

COORDINATE-Diabetes

Statin intolerance: definition

An inability to tolerate the dose of a statin required to sufficiently reduce a person's LDL cholesterol and/or cardiovascular risk due to significant adverse effects, including abnormally elevated markers of either liver or muscle function.

Fitchett DH *Circulation* 2015

Statin intolerance: extent of problem

- Most RWD suggest between 10-40% have symptoms that lead to cessation
- SAMS are the most common reported AE – the cause in up to 50%
- RCT data suggest minimal absolute difference in SAMS
    - Significant nocebo effect

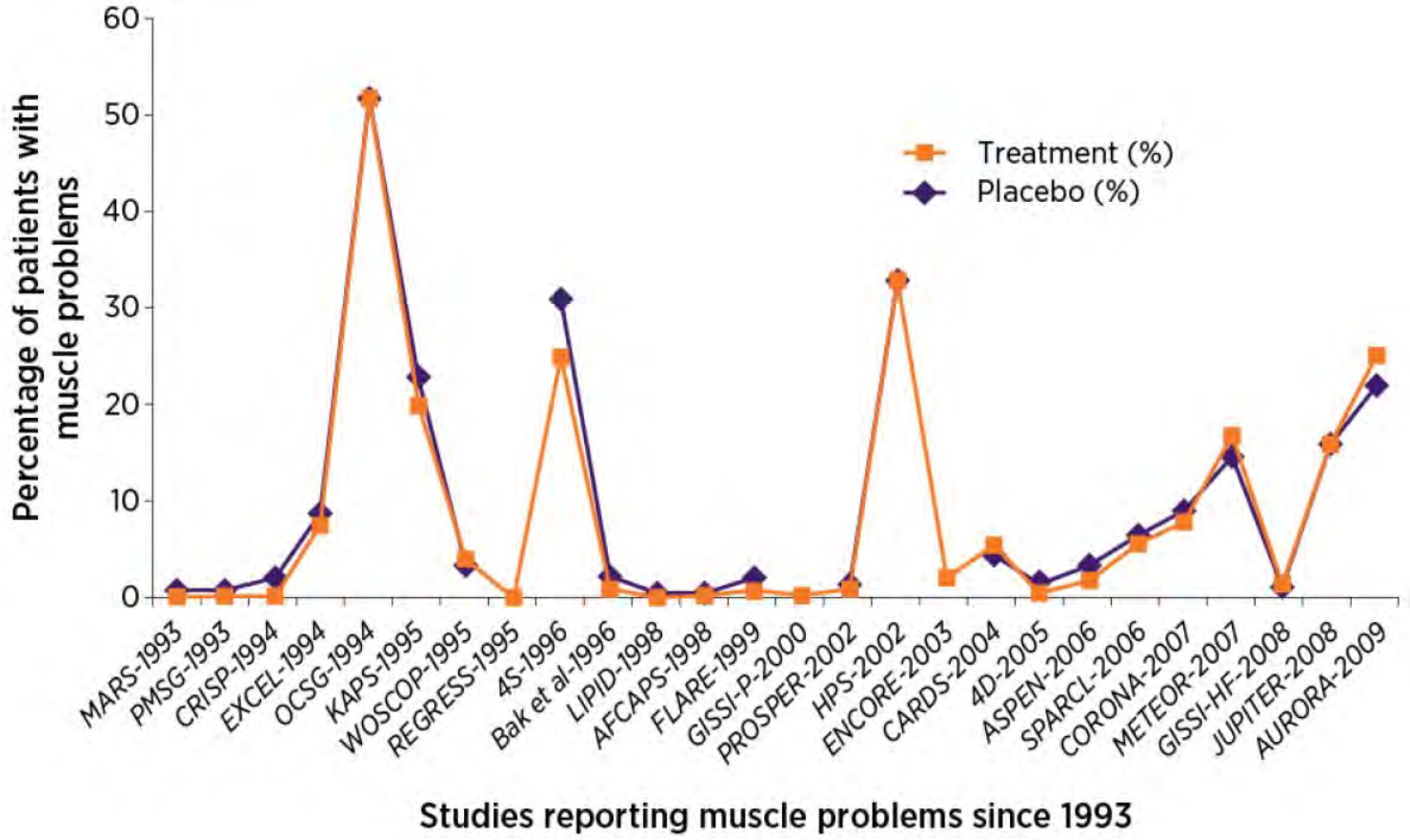
Zhang et al. *Ann Intern Med* 2013; Cohen JD *J Clin Lipidol*. 2012

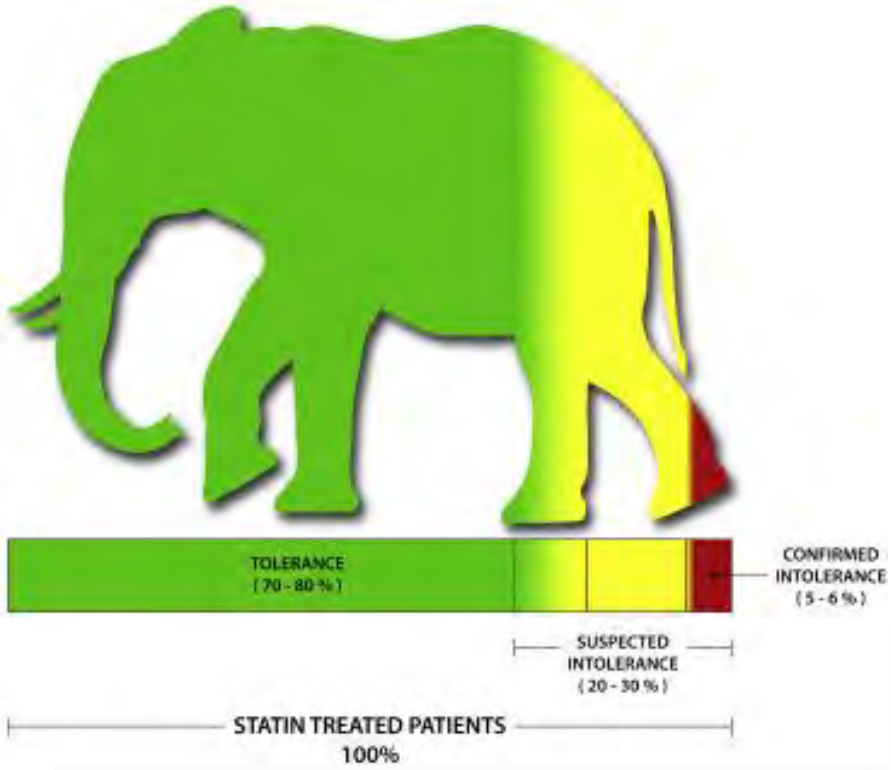
Muscle Adverse Event Terminology

Adverse Event Term	Definition
Statin-associated muscle symptoms (SAMS)	Muscle symptoms reported during statin therapy but not necessarily caused by the statin
Myalgia	Muscle pain or aches, no CK rise
Myopathy/myositis	Unexplained muscle pain or weakness accompanied by CK concentration > 10 x ULN
Rhabdomyolysis	Severe form of myopathy, CK typically > 40 x ULN, which can cause myoglobinuria and acute renal failure

Newman CB et al. *Arterioscler Thromb Vasc Biol* 2019

SAMS in RCTs: elephant in the room





Ganga HV et al. *Am Heart J.* 2014; Mancini G *Can J Cardiol* 2016

GAUSS-3

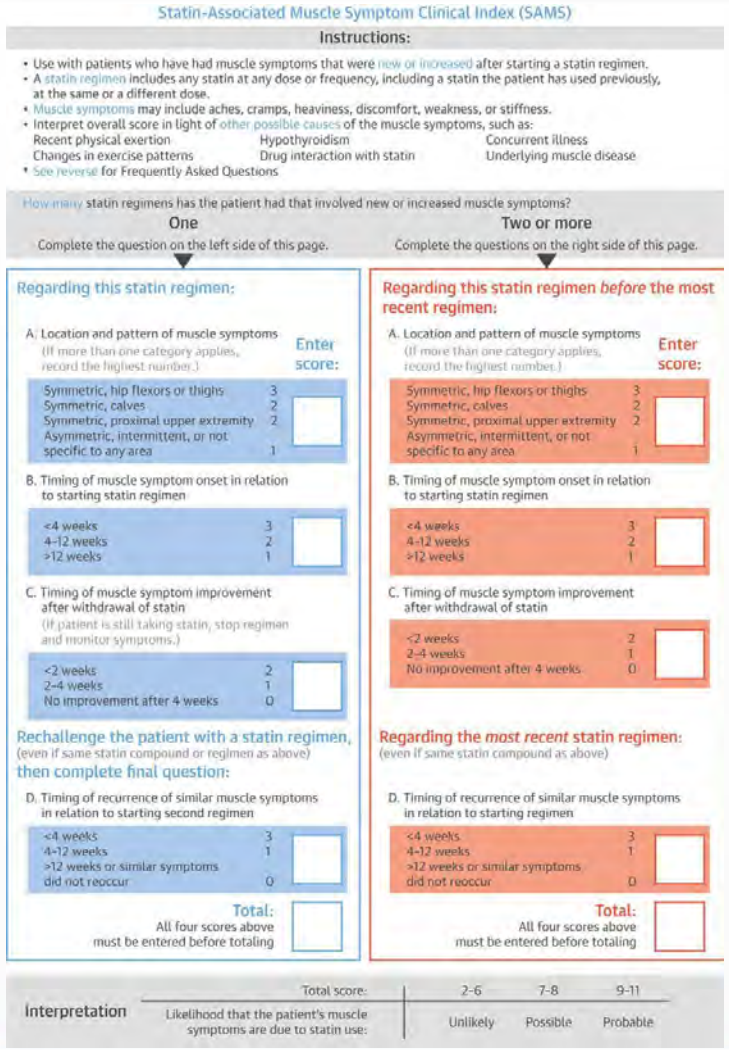
- Placebo/statin double-blind crossover design to document SAMS
- Over 12 week period, intolerable SAMS experienced by those on:
  - Statin only: 42.6%
  - Placebo only: 26.5%
  - Both: 9.8%
- On re-challenge, 16% greater intolerance to statin than placebo
- Only 17.3% had no symptoms with either

Even after careful documentation of intolerance to 3 different statins,

***on re-challenge only 1 in 8 have intolerable SAMS** that can be ascribed to statin*

Nissen SJ et al. *JAMA* 2016

Many approaches to a patient with SAMS



Statin-Associated Muscle Symptom Clinical Index (SAMS)

Instructions:

- Use with patients who have had muscle symptoms that were new or increased after starting a statin regimen.
- A statin regimen includes any statin at any dose or frequency, including a statin the patient has used previously, at the same or a different dose.
- Muscle symptoms may include aches, cramps, heaviness, discomfort, weakness, or stiffness.
- Interpret overall score in light of other possible causes of the muscle symptoms, such as:
  Recent physical exertion; Hypothyroidism; Concurrent illness
  Changes in exercise patterns; Drug interaction with statin; Underlying muscle disease
- See reverse for Frequently Asked Questions

How many statin regimens has the patient had that involved new or increased muscle symptoms?

One — Complete the question on the left side of this page.

Two or more — Complete the questions on the right side of this page.

Regarding this statin regimen:

A. Location and pattern of muscle symptoms (If more than one category applies, record the highest number.) — Enter score:

Symmetric, hip flexors or thighs	3
Symmetric, calves	2
Symmetric, proximal upper extremity	2
Asymmetric, intermittent, or not specific to any area	1

B. Timing of muscle symptom onset in relation to starting statin regimen

<4 weeks	3
4–12 weeks	2
>12 weeks	1

C. Timing of muscle symptom improvement after withdrawal of statin (If patient is still taking statin, stop regimen and monitor symptoms.)

<2 weeks	2
2–4 weeks	1
No improvement after 4 weeks	0

Rechallenge the patient with a statin regimen, (even if same statin compound or regimen as above) then complete final question:

D. Timing of recurrence of similar muscle symptoms in relation to starting second regimen

<4 weeks	3
4–12 weeks	1
>12 weeks or similar symptoms did not reoccur	0

Total: All four scores above must be entered before totaling

Regarding this statin regimen *before* the most recent regimen:

A. Location and pattern of muscle symptoms (If more than one category applies, record the highest number.) — Enter score:

Symmetric, hip flexors or thighs	3
Symmetric, calves	2
Symmetric, proximal upper extremity	2
Asymmetric, intermittent, or not specific to any area	1

B. Timing of muscle symptom onset in relation to starting statin regimen

<4 weeks	3
4–12 weeks	2
>12 weeks	1

C. Timing of muscle symptom improvement after withdrawal of statin

<2 weeks	2
2–4 weeks	1
No improvement after 4 weeks	0

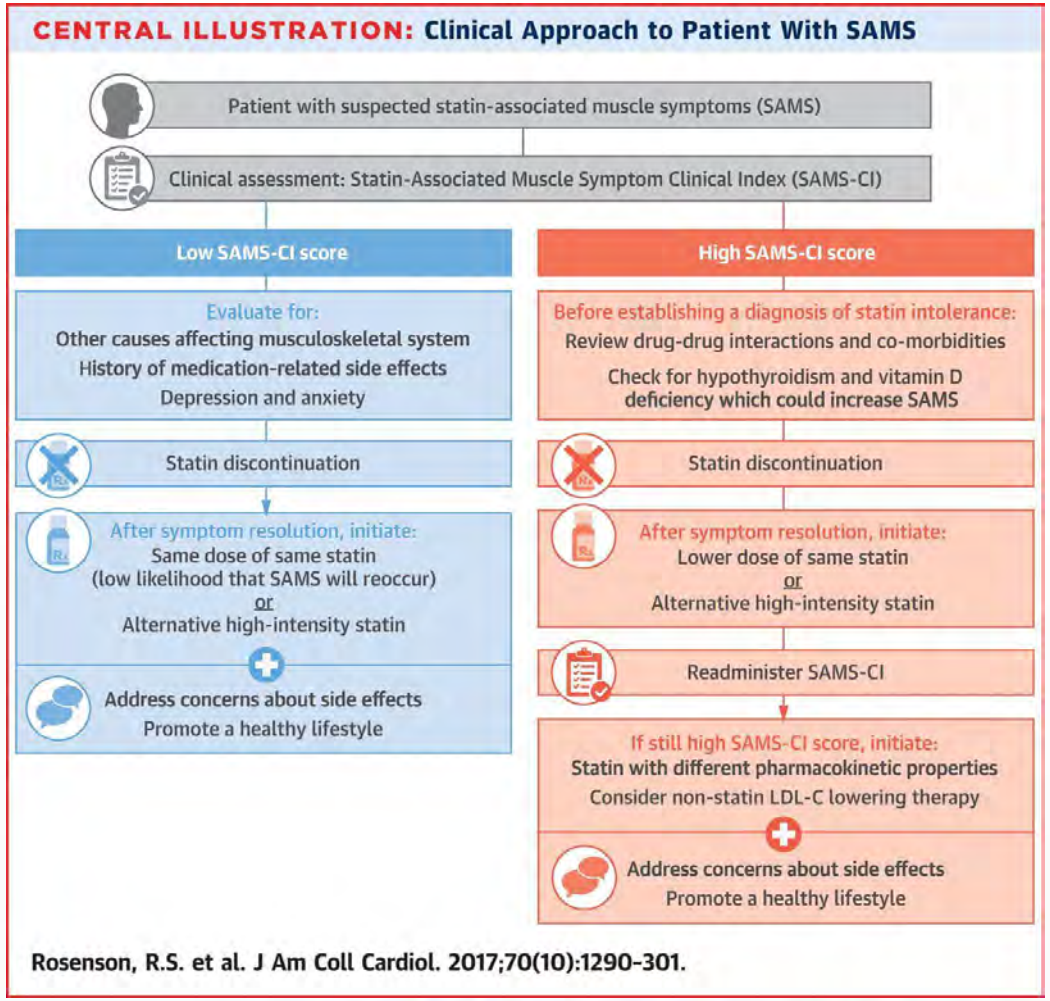
Regarding the *most recent* statin regimen: (even if same statin compound as above)

D. Timing of recurrence of similar muscle symptoms in relation to starting regimen

<4 weeks	3
4–12 weeks	1
>12 weeks or similar symptoms did not reoccur	0

Total: All four scores above must be entered before totaling

Interpretation	Total score:	2-6	7-8	9-11
	Likelihood that the patient's muscle symptoms are due to statin use:	Unlikely	Possible	Probable



COORDINATE-Diabetes

Rosensen RS *JACC* 2017

Approaching a previously 'intolerant' patient

- Take time to counsel on individualized net clinical benefit.
- Demonstrate a systemic approach to excluding a physiological/pathological contribution:
    - exclude vitamin D deficiency, hypothyroidism, check baseline LFTs/CK
- Reiterate that each statin is (subtly) different
- Offer a second opinion from a lipidologist
- Reiterate the safety of re-challenge and likelihood of success (75%)

Banach M *Arch Med Sci* 2015

Commencing a re-challenge in an 'intolerant' patient

- Must allow at least a 2-week washout
- After establishing temporal association with a particular statin:
    - Switch from lipophilic agents (simvastatin, lovastatin, atorvastatin) to rosuvastatin/pravastatin (rosuvastatin preferred)
- Start at the lowest dose and frequency – alternate daily or weekly to start (Ruisinger et al)
- Consider asking patient to keep a log-book of symptoms to discern temporal association

Ruisinger JF *Am J Cardiol* 2009

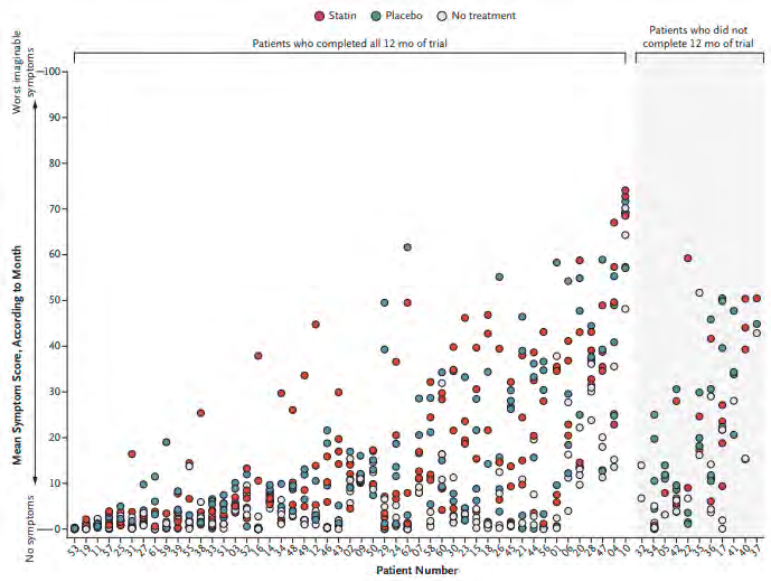
Value of n-of-1 trials

- In clinical care, determining links between symptoms and statins is difficult.
  - Blinded n-of-1 trials help to uncouple symptoms and exposure

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

N-of-1 Trial of a Statin, Placebo, or No Treatment to Assess Side Effects



RESEARCH

OPEN ACCESS

Check for updates

Statin treatment and muscle symptoms: series of randomised, placebo controlled n-of-1 trials

Emily Herrett,[1] Elizabeth Williamson,[2] Kieran Brack,[3] Danielle Beaumont,[3] Alexander Perkins,[2] Andrew Thayne,[3] Haleema Shakur-Still,[3] Ian Roberts,[3] Danielle Prowse,[3] Ben Goldacre,[4] Tjeerd van Staa,[5] Thomas M MacDonald,[6] Jane Armitage,[7] Jon Wimborne,[8] Paula Melrose,[8] Jayshireen Singh,[9] Lucy Brooks,[10] Michael Moore,[11] Maurice Hoffman,[12] Liam Smeeth,[1] on behalf of the StatinWISE Trial Group

Table 2 | Estimated effects for secondary outcomes comparing statin with placebo periods (from participant questionnaire; n=152)

	No (%) of participants		Odds ratio (99% CI)
	Statin periods	Placebo periods	
Muscle symptoms	248/397 (62.5)	239/388 (61.6)	1.11 (0.62 to 1.99)
Muscle symptoms, not attributed to other causes	216/397 (54.4)	200/388 (51.6)	1.22 (0.77 to 1.94)

Participants contributed multiple periods to these summaries and so the odds ratio cannot be directly calculated from these fractions. Odds ratios above 1 indicate higher odds on statins.

COORDINATE-Diabetes

Wood F et al. *N Engl J Med* 2020; Herrett E et al. *BMJ* 2001

Role of complementary therapies

- No convincing evidence for CoQ10 (Class III, Level B)
- No convincing evidence for Vitamin D supplementation, particularly in context of normal vitamin D levels
- Either or both could be considered in the context of SAMS (data free)

Mancini GB *Can J Cardiol* 2013

Case 1: Barbara

68-year-old woman

PMHx: T2DM, hypercholesterolemia, hypertension, IHD (NSTEMI 2012)

Medications: metformin 1gm BID, lisinopril/HCT 20/12.5mg daily, empagliflozin 10mg; simvastatin 40 mg daily; clopidogrel 75mg daily

Laboratory evaluation: LDL: 130 mg/dL

History: Started an exercise program 3 months ago. Developed bilateral calf pain. Cut back on the exercise to be 'modest' but calf pain persisted.

Ceased simvastatin, symptoms improved after 3 weeks.

Resumed simvastatin, symptoms returned in 1 week.

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History: Started an exercise program 3 months ago. Developed bilateral calf pain. Cut back on the exercise to be 'modest' but calf pain persisted.
Ceased simvastatin, symptoms improved after 3 weeks.
Resumed simvastatin, symptoms returned in 1 week.

SAMS risk factors: female, >65yo, lipophilic statin, associated with exercise

PLAN: Change to non-lipophilic agent such as rosuvastatin. Start at 5mg. Up-titrate to 20mg.

Consider vitamin D levels, exclude hypothyroidism.

Case 2: Jon

55-year-old man

PMHx: T2DM, hypercholesterolemia, IHD (STEMI 2017), cigarette smoking, obese

Medications: metformin 1gm BID, perindopril 8mg daily, empagliflozin 10mg; atorvastatin 40 mg daily, aspirin 81mg daily, ticagrelor 90mg BID

Laboratory evaluation: LDL: 140 mg/dL; AST 103 + ALT 144

History: Routine health check up. No myalgia.

Further history reveals 6 x beers most days.

Case 2: Jon

55-year-old man
PMHx: T2DM, hypercholesterolemia, IHD (STEMI 2017), cigarette smoking
Medications: metformin 1gm BID, perindopril 8mg daily, empagliflozin 10mg; atorvastatin 40 mg daily, aspirin 81mg daily, ticagrelor 90mg BID
Laboratory evaluation: LDL: 140 mg/dL; AST 103 + ALT 144
History: Routine health check up. No myalgia.
Further history reveals 6 x beers most days.

LFTs 2-3 x ULN - ?alcohol ?NAFLD ?statin

PLAN: Continue statin. Counsel RE: EtOH and weight.

Ongoing elevation – consider other etiologies

Case 3: Lauren

44-year-old woman

PMHx: T2DM, hypercholesterolemia, IHD (NSTEMI 2016), CKD (GFR 31)

Medications: metformin, liraglutide, ramipril, clopidogrel.

Laboratory evaluation: LDL: 150 mg/dL

History: Has tried 'every statin'. Muscle aches on 'all of them'. Unclear whether CK performed on any occasion but definitely no history of rhabdomyolysis.

Case 3: Lauren

44-year-old woman

PMHx: T2DM, hypercholesterolemia, IHD (NSTEMI 2016), CKD (GFR 31)

Medications: metformin, liraglutide, ramipril, clopidogrel.

Laboratory evaluation: LDL: 150 mg/dL

History: Has tried 'every statin'. Muscle aches on 'all of them'. Unclear whether CK performed on any occasion but definitely no history of rhabdomyolysis. Can't remember all statins but last one was lovastatin.

High risk patient, LDL not to target. Likely to need significant effort to consider re-challenge.

PLAN: Assess willingness to re-challenge, consider rosuvastatin low dose, low frequency.

Consider TFTs, vitamin D and baseline CK +/- CoQ10

Summary

- Non-persistence is associated with poor outcomes
- SAMS is a common clinical entity affecting non-persistence
- Carefully controlled RCTs suggest absolute statin-related effect ~ 5%
- Re-challenge associated with 75% success (depending on measure)
- An intentional, deliberate and careful approach is required in patients who are considered ‘statin intolerant’
- Blinded n-of-1 trials difficult to implement but may be of benefit in select individuals