Lipids Case Studies

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Outline

- Secondary prevention
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  - Statin intolerance
  - Supporting medicines adherence
  - Using targets
  - Other lipid management options post CVE
- Primary Prevention
  - Case study
  - QRisk
  - Statin hesitancy
  - Learning points and resources
- Q&A

Case Study: Secondary Prevention

- Richard has stable angina and a history of angioplasty and stenting
- He is not currently treated with a statin and is picked up by UCLP secondary prevention searches as a priority one patient
- You can't see any record of a statin in his notes
- His last recorded lipids are:
  - Total cholesterol 5.4mmol/L
  - Triglycerides 1.4mmol/L
  - HDL cholesterol 0.9mmol/L
  - Non-HDL-C = 5.4-0.9 = 4.5 mmol/L

Which statin should Richard be offered?

A. Atorvastatin 80mg daily as long as you start one

B. Atorvastatin 20mg daily

C. Simvastatin 40mg daily

D. Rosuvastatin 10mg daily

E. Doesn't matter which statin,

Secondary Prevention: high intensity high dose statins

- Start atorvastatin 80mg treatment in people with CVD (or rosuvastatin 20mg)
- A lower dose of atorvastatin may be considered if any of the following apply:
  - potential drug interactions
  - renal function (eGFR <30ml/min)
  - high risk of adverse effects
  - patient preference

- Do not delay statin treatment in secondary prevention to manage modifiable risk factors

- Do not wait for blood results in ACS before starting statin treatment. Take a lipid sample on admission and at 3 months after the start of treatment

- What target are we aiming for?

What treatment target should we have for Richard?

A. Total chol < 5mmol/L
and LDL chol < 3mmol/L

B. Total Chol < 4mmol/L
and LDL Chol < 2mmol/L

C. 40% reduction in non-HDL cholesterol

D. Something else

Targets..
Do we need them?

- NICE (2014)
  - 40% reduction in non-HDL cholesterol
- JBS-3 (2013)
  - Statins are recommended as they are highly effective at reducing CVD events with evidence of benefit to LDL-c < 2mmol/L which justifies intensive non-HDL-c lowering
    - Non-HDL-c < 2.5mmol/L
- ACC / AHA / NI (2013)
  - No treatment targets
  - Recommend moderate or high intensity statin

NICE endorsed AAC pathway (2020)

- 40% reduction in non-HDL cholesterol
- If baseline non-HDL cholesterol is not available – consider a target of non HDL chol < 2.5mmol/L

Non-HDL cholesterol =

Total Cholesterol – HDL cholesterol

Improving our Patient's Health Outcomes

It's not just *IF* a patient is non-adherent, but *WHY*

Treating to target… which statin has the most cholesterol lowering effect?

A. Fluvastatin

B. Simvastatin

C. Rosuvastatin

D. Atorvastatin

E. Pravastatin

Statin hesitancy/intolerance

The HCA contacts Richard to:

- Gather information: Blood results, BP, weight, smoking status
- Promote self-management: Education on cholesterol and CVD risk
- Encourage behaviour change: Brief interventions and signposting e.g. smoking, weight, diet, exercise, alcohol

Richard explains that he did try a statin after his Percutaneous Coronary Intervention (PCI) and did not get on with it due to muscle pains so the HCA refers the patient to you….

You arrange a remote consultation with Richard

- *How would you approach the discussion with Richard regarding taking a statin?*

Discussion points

- Take a history from Richard regarding symptoms:

-course: when did statin therapy stop following PCI- when did muscle symptoms start? Was an alternative statin tried? What was original dose reduced/withheld and restarted?

-muscle symptoms: symmetrical? Certain times of day? Exercise?

-resolution on withdrawal: did symptoms stop after stopping the statin? Did you let anyone know?

-risk factors for intolerance: age (older people appear to be more vulnerable), hypothyroidism, pre-existing muscle disease, renal impairment and interacting medications. Other suspected risk factors include female gender, diabetes mellitus and Chinese (and East Asian in general) ancestry.

- Listen to his concerns and try to address them
- Explain the LDC-C/ non HDL-C reductions and his level of risk
- Explain the benefits and safety of statins
- Nocebo effect - acknowledging that for him his symptoms are real, but sharing that some studies have shown that these symptoms may not be related to statins and therapy could often be retried
- Discuss options for reducing LDL-C/ non-HDL-C:
  - Trial of an alternative statin or previous statin at a lower dose and reiterate
  - Adding ezetimibe
  - Ezetimibe monotherapy
- Referral to lipid clinic for consideration of newer therapies if targets not met

Which statin side effects are you aware of?

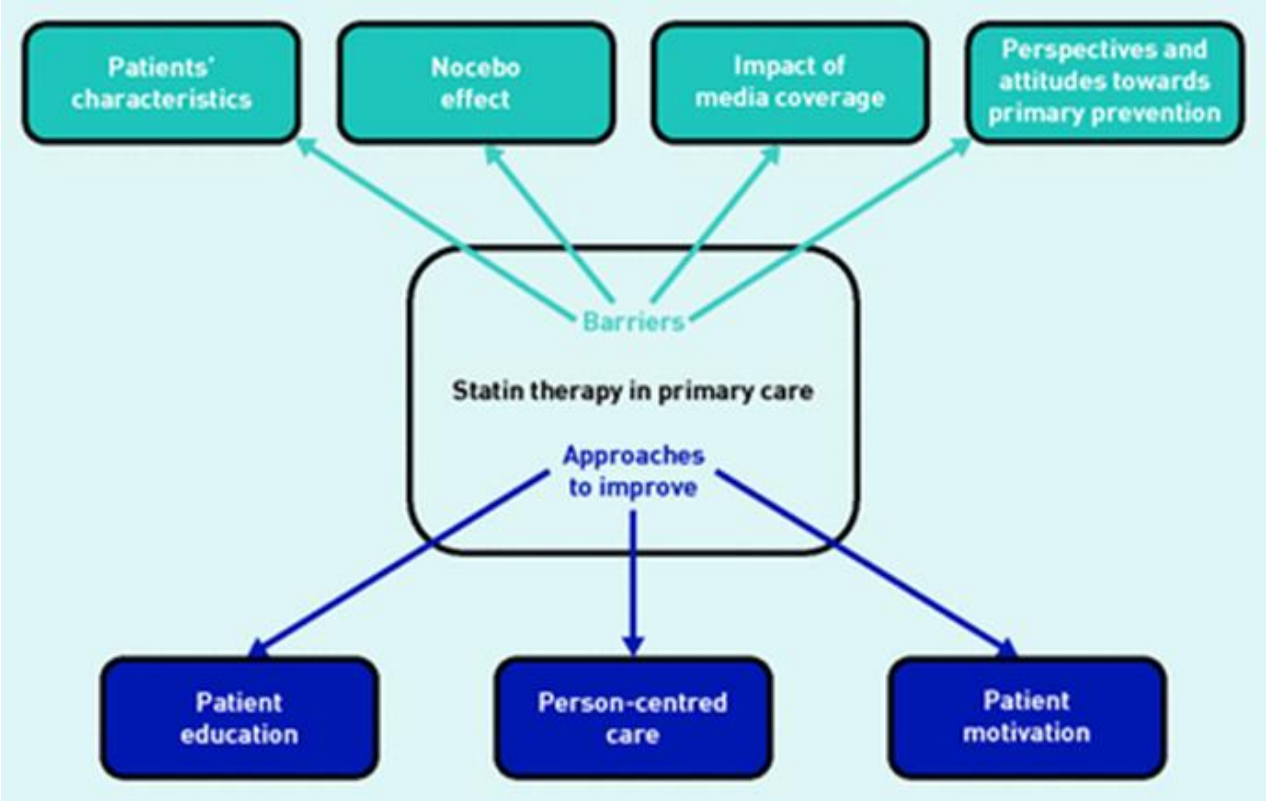
- Think about common and uncommon side effects
- Which cause the most concern for your patients?

Which statin side effects are you aware of?

- Like all medicines, statins can cause side effects. Most people tolerate them well and do not have any problems.
- Statins - Side effects - NHS (www.nhs.uk)
- Common side effects include: headache, dizziness, feeling sick, feeling unusually tired or physically weak, constipation, diarrhoea, indigestion, flatulence, muscle pain, sleep problems, low blood platelet count (1 in 100 to 1 in 10)
- Uncommon side effects include: being sick, memory problems, hair loss, pins and needles, inflammation of the liver, inflammation of the pancreas, skin problems: acne, itchy red rash, sexual problems: loss of libido or erectile dysfunction (1 in 1,000 to 1 in 100)
- Rare side effects: muscle weakness (myopathy)- check CK (1 in 10,000 to 1 in 1,000)

Adherence to statin therapy

- [Improving long-term adherence to statin therapy: a qualitative study of GPs' experiences in primary care | British Journal of General Practice (bjgp.org)]



[Use of health information technology (HIT) to improve statin adherence and low-density lipoprotein cholesterol goal attainment in high-risk patients: Proceedings from a workshop (lipid.org)]

Shared decision making concerning lifestyle and statins

Lifestyle interventions: There are many resources to support self-management eg Heart UK and British Heart Foundation, national support groups and local social prescribing options. Support the patient to review their diet, exercise, smoking cessation, alcohol intake and mental health considerations which are key to lipid management. In dietary intervention studies, CVD events were reduced by 12% over 5 years (NNT=95), and statins/lipid lowering therapies reduce CVD risk by 25% for each year of treatment per 1mmol/L LDL-C reduction -*see table below (Lancet 2016)*

Shared decision making: *Numbers needed to treat (NNT) and harm (NNH) over 5 years of daily high intensity statin therapy (Lancet 2016)*

	NNT		NNH
Primary prevention of major vascular events	20	**New cases of diabetes**	100 to 200
Secondary prevention of major vascular events	10	**Myopathy**	2,000

For 10,000 patients taking a statin for 5 years, achieving 2mmol/L LDL-C reduction: 1000 MVEs avoided (secondary prevention) and 500 MVEs avoided (primary prevention); 100 newly diagnosed diabetes, 5 cases of myopathy and 1 rhabdomyolysis, and <1 active liver disease

MVEs= major vascular events: MI, stroke, coronary revascularisation
Reference: AHA statin safety and associated adverse events, 2019

Lipid management options and LDL reduction: Consider also the evidence of a benefit for CV risk reduction with each medicine

	Approximate reduction in LDL-C				
Choice of statin or lipid lowering therapy/ daily dose	5mg	10mg	20mg	40mg	80mg
Fluvastatin			21%	27%	33%
Pravastatin		20%	24%	29%	
Simvastatin		27%	32%	37%	42%*
Atorvastatin	-	37%	43%	49%	55%
Rosuvastatin	38%	43%	48%	53% specialist initiation	-
Atorvastatin with Ezetimibe 10mg	-	52%	54%	57%	61%
Ezetimibe 10mg with Bempedoic acid 180mg	approx. 38%*				

NB. High intensity (HI) statins reduce LDL-C >40% (highlighted green) and are more effective at preventing cardiovascular events than low/medium intensity statins.

NICE recommends atorvastatin and rosuvastatin as first line HI statins.

*simvastatin 80mg is not recommended due to muscle toxicity risk

*17-18% LDL-C lowering for bempedoic acid, ezetimibe 21% approximations vary in current study data. Ref 12: C.Ballantyne et al; Eur J Prev Cardiol. 2020 Apr;27(6):593-603. doi: 10.1177/2047487319864671

Common and uncommon side effects for statins may be found here: Statins - Side effects - NHS (www.nhs.uk)

For contra-indications please refer to individual summary of product characteristics (SPC) for each medication: women of childbearing age need to ensure adequate contraception during statin treatment and for 1 month afterwards, and statins should be discontinued for 3 months before attempting to conceive

Refer to a person centred approach for addressing statin reluctance/hesitancy and potential intolerance: Statin-Intolerance-Pathway-NEW.pdf (england.nhs.uk)

Shared Decision-Making Resources

Benefits per 10,000 people taking statin for 5 years	Events avoided
Avoidance of major CVD events in patients with pre-existing CVD & a 2mmol/l reduction in LDL	1,000
Avoidance of major CVD events in patients with no pre-existing CVD & a 2mmol/l reduction in LDL	500

Adverse events per 10,000 people taking statin for 5 years	Adverse events
Myopathy	5
Haemorrhagic Strokes	5-10
Diabetes Cases	50-100

Shared decision-making resources:

- BHF information on statins
- Heart UK: Information on statins
- NICE shared decision-making guide

Collins et al 2016 Lancet Systematic Review Lancet 2016; 388: 2532–61

What % of patients complain of muscle pain on statins?

A. 3%

B. 15%

C. 34%

D. 67%

E. 87%

Muscle pain with statins

- 87% people on statins complain of muscle pain …… BUT

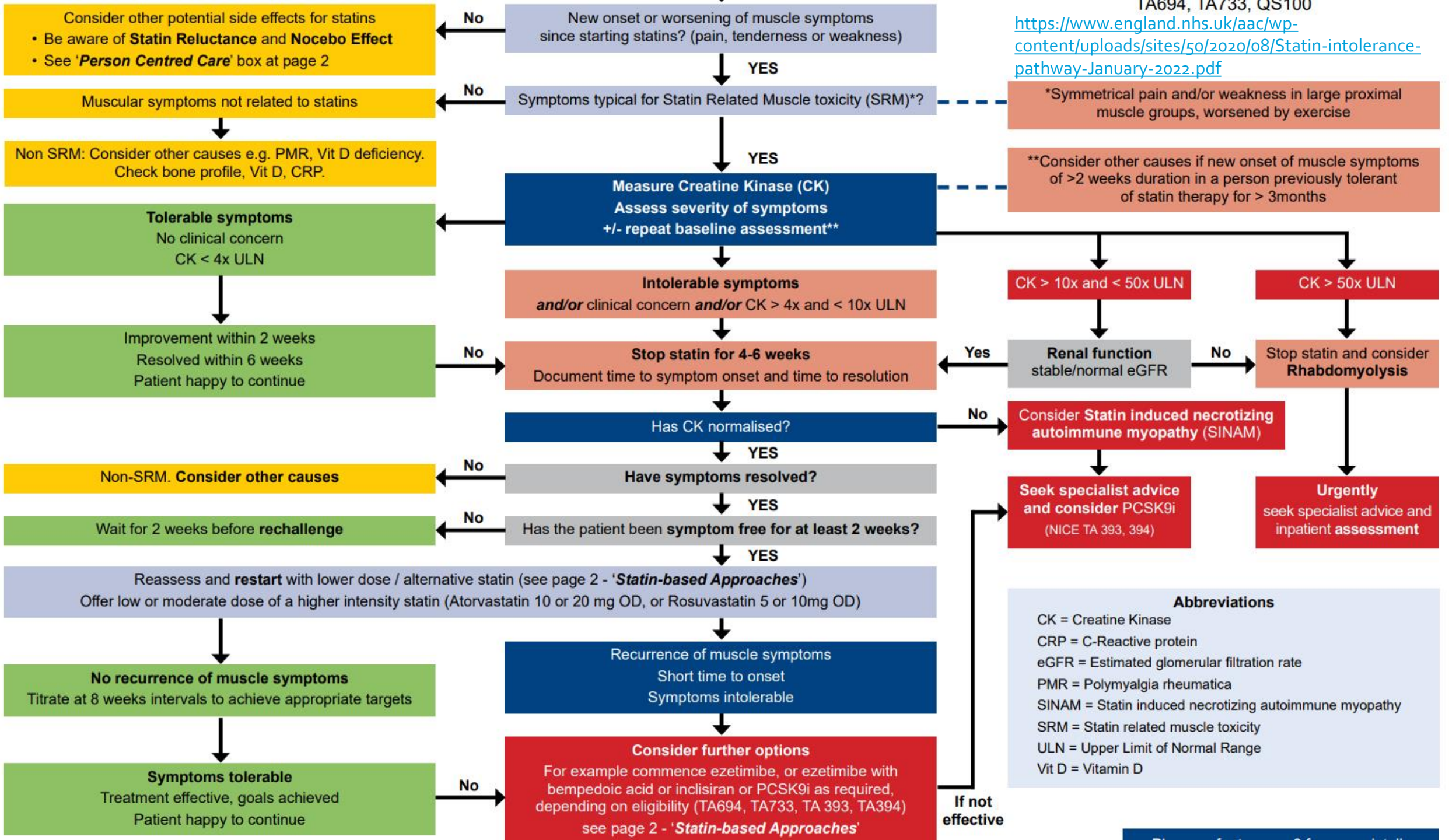
85% of people not on statins complain of muscle pain

JAMA Intern Med. 2013;173(14):1318-1326

- In n=1 trials of patients

reporting statin intolerance; muscle symptoms were no more common with statins than with placebo

JAMA. 2021;325(16):1602. doi:10.1001/jama.2021.4801


TA694, TA733, QS100
https://www.england.nhs.uk/aac/wp-content/uploads/sites/50/2020/08/Statin-intolerance-pathway-January-2022.pdf
New onset or worsening of muscle symptoms since starting statins? (pain, tenderness or weakness)
No
Consider other potential side effects for statins
• Be aware of Statin Reluctance and Nocebo Effect
• See 'Person Centred Care' box at page 2
YES
Symptoms typical for Statin Related Muscle toxicity (SRM)*?
No
Muscular symptoms not related to statins
Non SRM: Consider other causes e.g. PMR, Vit D deficiency. Check bone profile, Vit D, CRP.
*Symmetrical pain and/or weakness in large proximal muscle groups, worsened by exercise
YES
Measure Creatine Kinase (CK)
Assess severity of symptoms
+/- repeat baseline assessment**
**Consider other causes if new onset of muscle symptoms of >2 weeks duration in a person previously tolerant of statin therapy for > 3months
Tolerable symptoms
No clinical concern
CK < 4x ULN
Intolerable symptoms
and/or clinical concern and/or CK > 4x and < 10x ULN
CK > 10x and < 50x ULN
CK > 50x ULN
Improvement within 2 weeks
Resolved within 6 weeks
Patient happy to continue
No
Stop statin for 4-6 weeks
Document time to symptom onset and time to resolution
Yes
Renal function
stable/normal eGFR
No
Stop statin and consider Rhabdomyolysis
Has CK normalised?
No
Consider Statin induced necrotizing autoimmune myopathy (SINAM)
YES
Non-SRM. Consider other causes
No
Have symptoms resolved?
YES
Seek specialist advice and consider PCSK9i
(NICE TA 393, 394)
Urgently
seek specialist advice and inpatient assessment
Wait for 2 weeks before rechallenge
No
Has the patient been symptom free for at least 2 weeks?
YES
Reassess and restart with lower dose / alternative statin (see page 2 - 'Statin-based Approaches')
Offer low or moderate dose of a higher intensity statin (Atorvastatin 10 or 20 mg OD, or Rosuvastatin 5 or 10mg OD)
Recurrence of muscle symptoms
Short time to onset
Symptoms intolerable
No recurrence of muscle symptoms
Titrate at 8 weeks intervals to achieve appropriate targets
Consider further options
For example commence ezetimibe, or ezetimibe with bempedoic acid or inclisiran or PCSK9i as required, depending on eligibility (TA694, TA733, TA 393, TA394)
see page 2 - 'Statin-based Approaches'
If not effective
Symptoms tolerable
Treatment effective, goals achieved
Patient happy to continue
No
Abbreviations
CK = Creatine Kinase
CRP = C-Reactive protein
eGFR = Estimated glomerular filtration rate
PMR = Polymyalgia rheumatica
SINAM = Statin induced necrotizing autoimmune myopathy
SRM = Statin related muscle toxicity
ULN = Upper Limit of Normal Range
Vit D = Vitamin D

Classification of statin related muscle toxicity (SRM)

Alfirevic A. et. al. Clin Pharm Ther. 2014; 96:470-476

SRM	Phenotype	Incidence	Definition
SRM 0	CK elevation <4x ULN	1.5-26%	No muscle symptoms
SRM 1	Myalgia, tolerable	190/100,000 Patient-years; 0.3-33%	Muscle symptoms without CK elevation
SRM 2	Myalgia, intolerable	0.2-2/1,000	Muscle symptoms, CK <4x ULN, complete resolution on dechallenge
SRM 3	Myopathy	5/100,000 Patient-years	CK elevation >4x ULN <10x ULN ± muscle symptoms, complete resolution on dechallenge
SRM 4	Severe myopathy	0.11%	CK elevation >10x ULN <50x ULN, muscle symptoms, complete resolution on dechallenge
SRM 5	Rhabdomyolysis	0.1-8.4/100,000	CK elevation >10x ULN with evidence of renal impairment + muscle symptoms or CK >50x ULN
SRM 6	Autoimmune-mediated necrotizing myositis (SINAM)	~2/million per year	Detection of HMGCR antibodies, HMGCR expression in muscle biopsy showing autoimmune myositis, incomplete resolution on dechallenge

HMGCR = 3-hydroxy-3-methylglutaryl coenzyme A reductase ULN = upper limit of normal

- SRM is a spectrum from myalgia to severe myopathy
- SRM 0 - does not preclude statin therapy, consider reducing starting dose
- SRM 1-3 manage according to pathway
- When SRM4 is suspected, without evidence of impaired renal function, discontinue statin therapy immediately and refer for outpatient assessment. Assess and treat possible contributory factors and re-assess the need for a statin. Intensify lifestyle modifications and consider alternative lipid lowering regimens.
- If rhabdomyolysis (SRM5) is suspected, immediately stop statins, urgently refer to inpatient assessment and management including intravenous rehydration as required to preserve renal function. Do not wait for measurement of urinary myoglobin. Post recovery, manage as for SRM4.
- Statin induced necrotizing autoimmune myositis (SINAM) (SRM6) should be suspected in patients with progressive muscle weakness and ongoing CK elevation despite statin withdrawal. Requires immunosuppressive treatment and avoidance of re-exposure to statins. Re-assess the need for lipid lowering therapy - may be eligible for treatment with PCSK9 inhibitor (NICE TA 393, 394).

Person-centred approach to address statin intolerance

Initial Consultation

- Be aware of "nocebo effect"[1] and "statin reluctance"[2]
- Reinforce healthy lifestyle habits (e.g. exercise, reducing weight)
- Listen to the concerns of each patient.
- Explain LDL-C targets and strategies to lower LDL-C/non-HDL-C
- Discuss options to reduce LDL-C/ non-HDL-C with pros and cons
- Explain the benefits of statins
- Evaluate and identify any risk factors and address (e.g. drug interactions)
- Work with patients to identify and agree best options and next steps

Follow up

- Follow up on agreed plan and address any issues/concern.
- Advise patients to contact you if they experience muscle symptoms
- Ongoing patient education and regular review helps addressing concerns around medicine safety and underline the importance of adherence.

(1) **Nocebo effect** is negative expectations of the patient regarding a treatment leading to reporting more negative effects even if they are prescribed a placebo.

(2) **Statin reluctance** is an attitudinal state of aversion to taking statins (often without prior exposure).

Statin-based approaches to manage muscle symptoms

- Adopt person-centred approach as described above.
- Therapy with a lower dose statin is preferred to no statin
- Apply a repetitive "De-Challenge" - "Re-Challenge" approach to establish if symptoms are caused by a statin(s) and the best statin regimen for each patient.
- Switch to a different statin or re-challenge with the same statin using a lower dose or frequency (intermittent dosages)
- Patients who do not tolerate statins on a daily basis, alternate day or twice-weekly dosing is a good option.
- Rosuvastatin and atorvastatin have longer half-lives, permitting their use on a non-daily regime.
- Adding ezetimibe to a lower dose statin may be better tolerated with robust reduction of LDL-C / non-HDL-C.
- Once a new regime is tolerated, dose / frequency can be up-titrated slowly to achieve LDL-C / non-HDL-C goals with minimal or no muscle complaints.

It is important to note that cardiovascular benefits have not been proven for all the above approaches but any reduction of LDL-C / non-HDL-C is beneficial.

LDL-C lowering options for patients with genuine statin intolerance

- Refer to the AAC Lipid Management Algorithm. (click here)
- Consider ezetimibe, (NICE TA 385) therapy as per algorithm
- Consider ezetimibe combined with bempedoic acid (NICE TA 694) as per algorithm
- Consider inclisiran if eligible for treatment according to NICE TA 733
- Consider PCSK9i if eligible for treatment according to NICE TA 393, 394

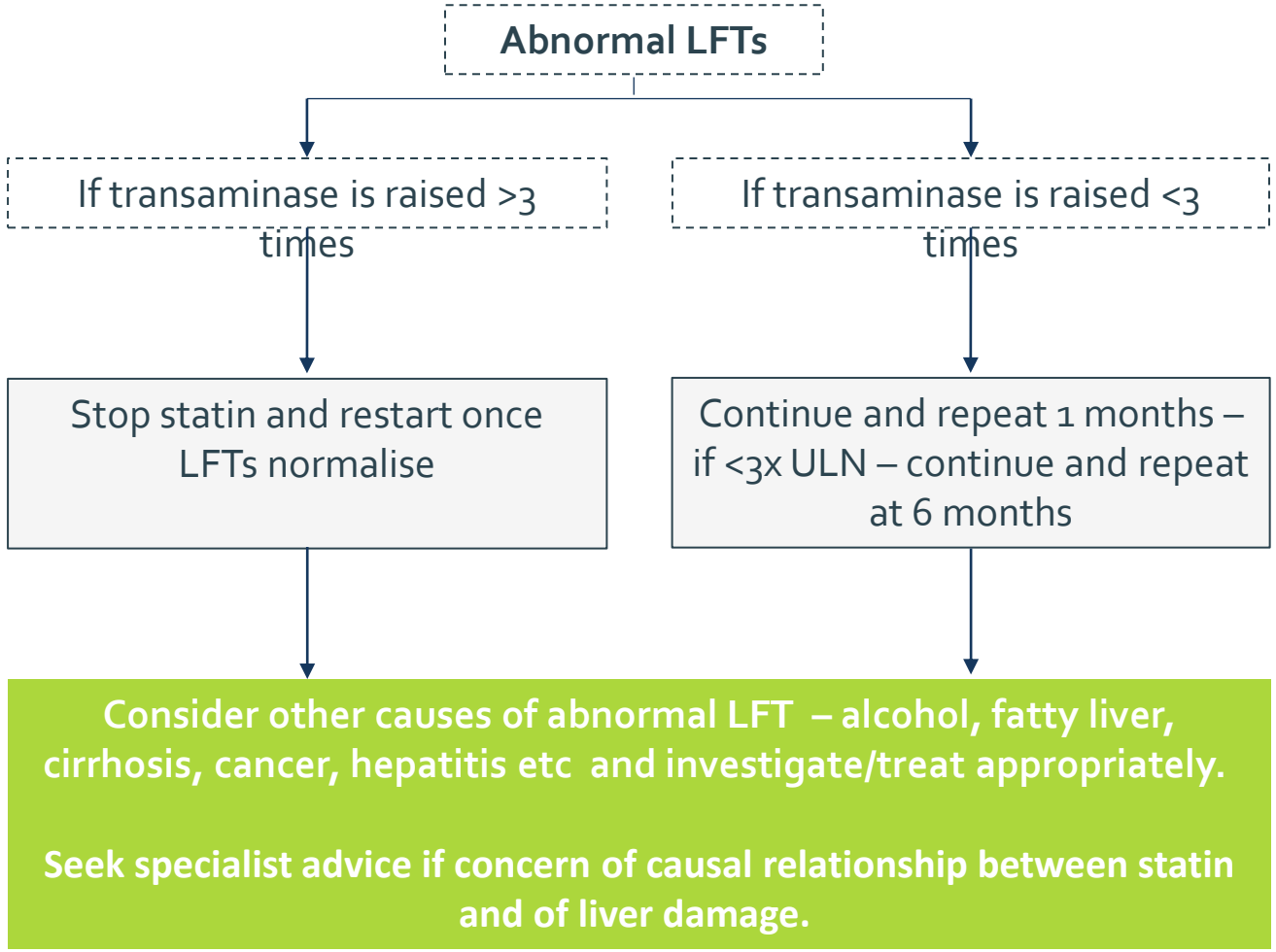
*Statin-intolerance-pathway-January-2022.pdf (england.nhs.uk)

Is the muscle pain or ache statin intolerance?

- The most common presentation of statin intolerance is **muscle aches, pains, weakness, or cramps, often called myalgias**; these can occur in up to 15% of treated patients. In most instances, the symptoms are mild and are rarely associated with muscle inflammation (myositis) and markers of muscle injury (creatine kinase)
- Statin Intolerance | Circulation (ahajournals.org)
- Factors favouring a clinical diagnosis of statin-related myopathy include:
- Symmetric, proximal large muscle pain or weakness, worsened by exercise
- Symptoms beginning 2 to 4 weeks after statin initiation
- Resolution of symptoms within 2 weeks of discontinuation
- Symptoms returning within 2 weeks after reintroducing statin
- Symptoms occurring with 2 or more different statins, at least one of which is prescribed at the lowest dosage.
- Statin intolerance and new lipid-lowering treatments | Cleveland Clinic Journal of Medicine (ccjm.org)

Liver function

PowerPhttps://s31836.pcdn.co/wp-content/uploads/Cholesterol-Framework_UCLPartners-LTCs-February-2021.pdfoint Presentation (pcdn.co)

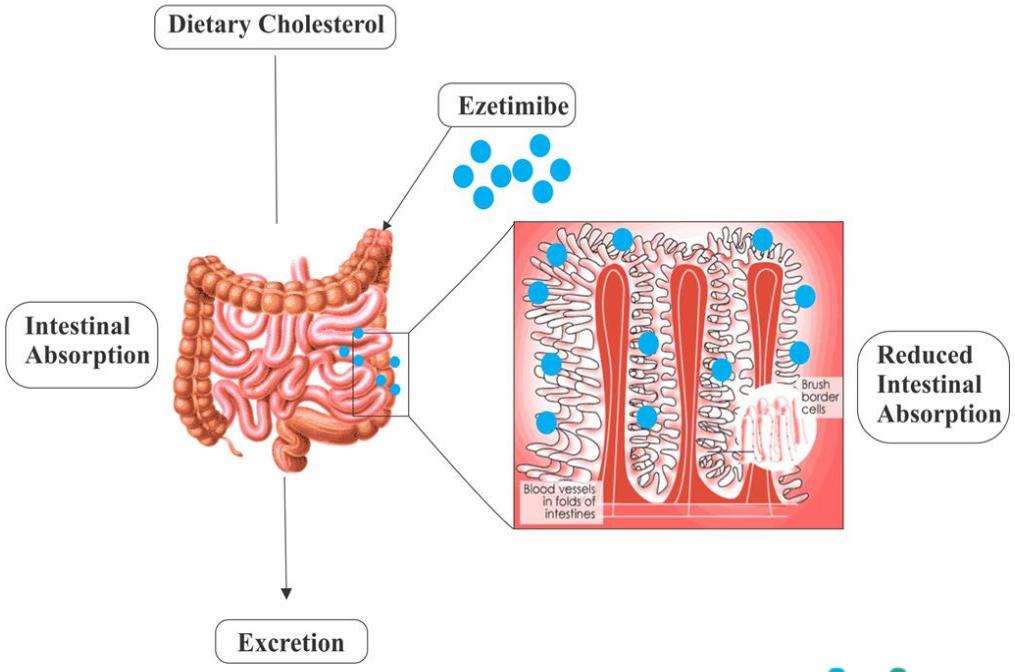


- Do not routinely exclude from statin therapy people who have liver transaminase levels that are raised but are less than 3 times the upper limit of normal.
- Most adults with fatty livers are likely to benefit from statins and this is not a contraindication.
- Check Liver function at baseline, and once between 3 months and 12 months after initiation of statin therapy.

Other options: add in ezetimibe

- Check statin adherence/intolerance/effectiveness
- Common or very common adverse effects include asthenia, diarrhoea, gastrointestinal discomfort, and gastrointestinal disorders
- IMPROVE-IT study: post ACS

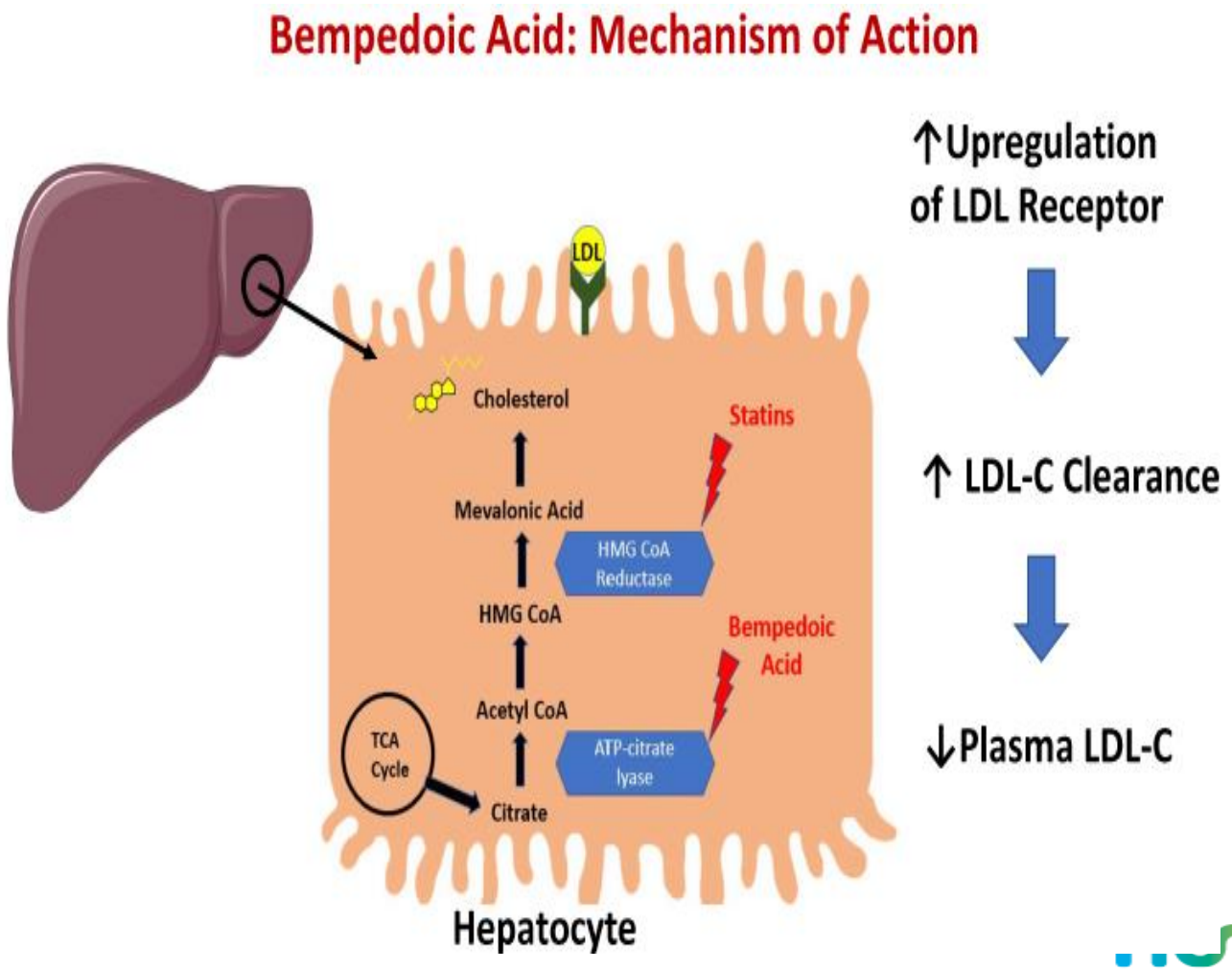
Mechanism of action	Target of action	LDL-C reduction	Even reduction
Cholesterol absorption inhibitor which targets LDL-C uptake at the jejunal enterocyte brush border.	Nieman pick C1-like 1 protein (NPC1L1P).	16–24% additional reduction on top of high dose of statins	2% absolute reduction in primary events



Akshyaya Pradhan, Monika Bhandari, Rishi Sethi, "Ezetimibe and Improving Cardiovascular Outcomes: Current Evidence and Perspectives", *Cardiology Research and Practice*, vol. 2020,

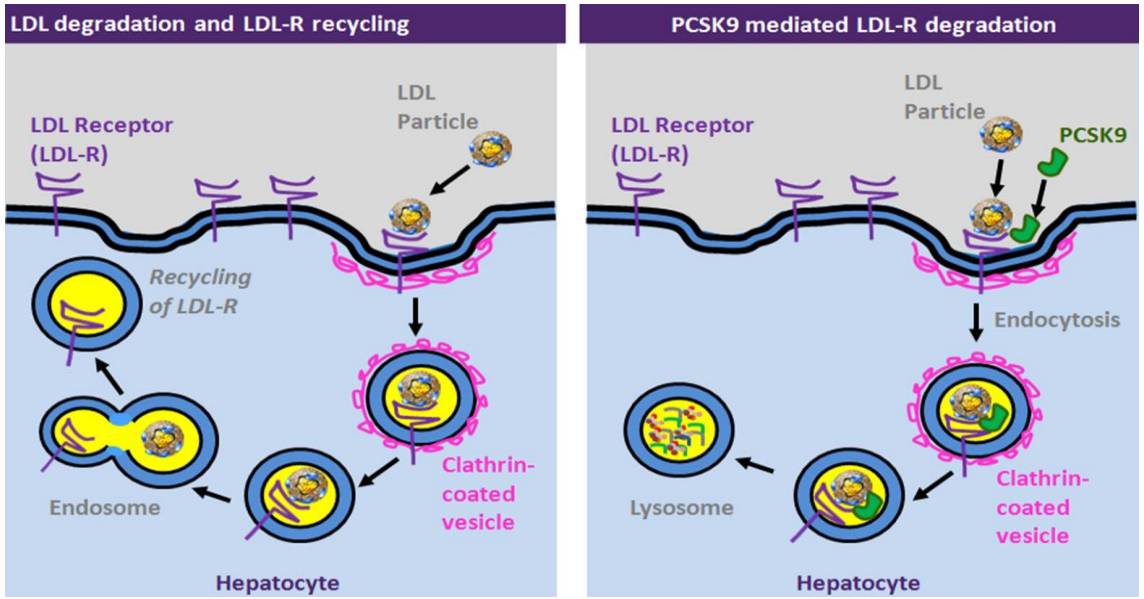
Other options: add in bempedoic acid

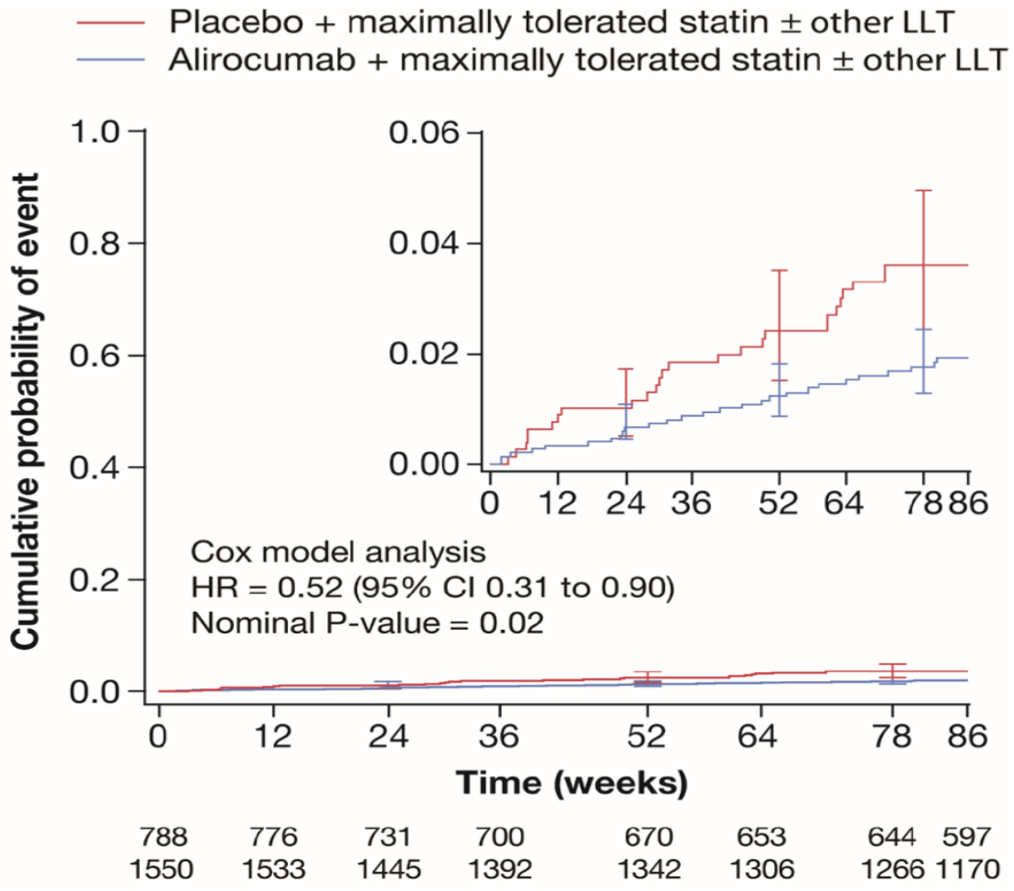
- For statin intolerance/ only able to tolerate low dose HI statin
- Add to ezetimibe therapy
- 180mg daily dose
- Combination tablet available
- Baseline checks:
- eGFR >30ml/min, LFTs, FBC- Hb
- uric acid/active gout
- Follow up checks:
- LFTs, Hb, myopathy symptoms,
- gout symptoms & hyperuricaemia
- Patient to report:
- unexplained muscle pain,
- tenderness or weakness
- CLEAR outcomes trial ongoing…



PCSK9i: place in pathways

- FH or secondary prevention (hospital only currently)
- Evolocumab or Alirocumab
- Monoclonal antibodies (mAB)
- 50-65% reduction LDL-C
- 2 weekly injections- self-injected
- Side effects: flu-like symptoms





ODYSSEY OUTCOMES: Alirocumab and CV outcomes after ACS; NEJM 2018; 379:2097-2107

Figure: Proprotein Convertase Subtilisin/Kexin type 9 inhibitors; Lambert G et al J Lipid Research 2012; 53:2515-24

Inclisiran

- A novel intracellular PCSK9 inhibitor- interferes with RNA
- Added to maximally tolerated statin and dietary measures if not achieving treatment targets in secondary prevention
- ORION-10 &11 studies: Reduces LDL-C by 50 to 52% at month 17 compared to placebo
- NICE recommends for:
  - Patients with a history of CVD eg ACS, coronary/arterial revascularisation, CHD, ischaemic stroke or PAD
  - With persistent LDL levels >2.6mmol/L despite maximum tolerated lipid-lowering therapy (HI statins and/or ezetimibe)
  - Alone or in combination with lipid lowering medication if station intolerant/contra-indicated
- SC injection twice a year
- Advantages over already licensed PCSK9 inhibitors including less frequent dosing and a benign side effect profile (injection site reactions- transient pain, erythema, rash)
- Ongoing need for data relating to cardiovascular morbidity and mortality (large-scale clinical trials of this nature in progress) and long term safety data
- Prescribing has started in some lipid clinics- some areas in consultation with specialist

EMIS/UCLP search to identify

Priority 1: CVD history:

not prescribed a statin

Review clinical information and lipid profile results- recheck lipid profile and BP measurements if not from within the last year.

Discuss with patient reason for not being prescribed a statin:

1. Non-adherence eg stopped after a period of time
2. Statin intolerance- has tried 2/3 different statins with adverse outcomes- consider alternative options/rechallenges
3. Statin hesitancy- patient is reluctant to be prescribed a statin following discussions of risk: benefit- see decision making table
4. Statin contra-indication- interacting medications, co-morbidities, frailty- document clearly decision made with patient
5. Statin refusal- despite best efforts and risk:benefit discussion

Document reason using SNOMED code and/or restart HI statin prescription- refer to community pharmacy for adherence support and schedule a follow up within 3 months.

Consider lifestyle/behavioural interventions.

Potential Outcomes:

1. Prescribe atorvastatin 80mg daily or rosuvastatin 20mg daily.: Reduce dose according to renal function/drug interactions
2. Follow statin intolerance pathway, consider ezetimibe and/or bempedoic acid as per SEL/AAC pathway
3. Refer to lipid specialist for further advice if statin intolerance
4. Schedule a follow up with practice pharmacist or community pharmacist to support adherence
5. Refer to social prescriber as indicated
6. Documentation of contra-indication and alternative management strategies considered

Priority 2: High CVD risk:

on sub-optimal intensity statin and/or

not reaching lipid management targets

Review clinical information, lipid profile and liver function test results- recheck lipid profile and BP measurements if not from within the last year:

1. Calculate up to date QRisk score- focus review on scores >20% and/or high CV risk conditions such as FH, T1DM or CKD
2. Initiate or optimise HI statin therapy
3. Add in ezetimibe and escalate therapy according to SEL pathway if non-HDL has not reduced by 40% from baseline or non-HDL >2.5 mmol/L after 3 months of maximum tolerated HI statin therapy
4. Document statin intolerance/hesitancy/contra-indications (as above)
5. Refer to lipid clinic or A&G as indicated

Potential outcomes:

1. Escalation of lipid management therapy eg. maximum tolerated HI statin dosing and/or ezetimibe
2. Review therapy in 3 months: Titrate medication to achieve 40% reduction on non-HDL-C or <2.5mmol/L
3. Review and support adherence to medication, diet and lifestyle interventions
4. Refer to lipid clinic for support if not achieving targets

Primary Prevention: Medicines Optimisation for Lipid Management

Lifestyle change and dietary measures are key to CVD event reduction together with drug therapy

In primary care check: bloods (non-fasting lipid profile: TC, TG, HDL-C, LDL-C, non-HDL-C) liver function (LFTs), HbA1c (manage/review diabetes mellitus (DM) if ≥48mmol/mol) thyroid & renal function, blood pressure (BP), weight, smoking status and calculate QRisk2 score using EMIS template (www.qrisk.org)

Please note **QRisk2 does not apply in the following conditions**: familial hypercholesterolaemia (FH), type 1 diabetes mellitus (T1DM)- *may be applied to QRisk3 calculations*, chronic kidney disease CKD (*QRisk3 has updated to eGFR <30ml/min; NICE states eGFR <60ml/min*) and/or albuminuria- **these patients are high CVD risk and require consideration for a high intensity (HI) statin**

Consider additional CVD risk factors, if present, together with with QRisk score: Severe obesity (BMI >40kg/m^2), socio-economic status, human immunodeficiency virus (HIV) treatment, severe mental illness, medications that may cause dyslipidaemia (eg. antipsychotics, corticosteroids, immunosuppressants), autoimmune disorders eg. systemic lupus erythematosus (SLE), impaired fasting glycaemia, significant hypertriglyceridaemia (*see page 9*), recent change in risk factors eg change to smoking status, BP and lipid management

Consider options with shared decision making (*see page 6*), education and lifestyle interventions to **modify CVD risk.**
For all patients consider the risk:benefit of therapy holistically: for example in patients aged ≥ 85years consider frailty, life expectancy and co-morbidities

Optimise management of BP and other co-morbidities. **Support** lifestyle interventions and medicines adherence.

If QRisk ≥10%: after addressing modifiable risk factors and following a shared decision: consider initiating or optimising statin therapy with a **moderate dose** of a **high intensity drug**: atorvastatin 20mg daily or rosuvastatin 10mg daily (*see page 6 for high intensity statin comparison table*) consider drug interactions that may affect dosing (see BNF)

After 3 months, has non-HDL cholesterol fallen by ≥ 40% from baseline?
Check adherence to medication, timing of dose, statin adverse effects/intolerance/hesitancy & diet/lifestyle interventions

Yes

No

Step 1 in primary care: Consider up-titration of statin to a maximum dose (atorvastatin 80mg or rosuvastatin 20mg to 40mg*)- *see HI statin table page 6*

Step 2 in primary care: If intolerant to higher dose of statin, consider adding ezetimibe 10mg daily (SPC- check contra-indications) to maximal tolerated statin

Step 3 in primary care with secondary care support: If intolerant to any statin, start ezetimibe 10mg daily, **and refer to lipid clinic** to consider adding bempedoic acid 180mg daily ▼ (SPC) (*see statin intolerance pathway on page 5 for further information*)

Yes

After 3 months, has non-HDL cholesterol fallen by ≥ 40% from baseline? Check adherence to medication, adverse effects/intolerance/hesitancy and lifestyle interventions

No

Review annually for adherence to medications, diet and lifestyle, check required bloods eg lipids. Refer for support as required from specialist teams.

Refer to lipid clinic (*see page 7 for SEL contact details*)

***Please note** that for rosuvastatin 40mg specialist supervision is recommended when this dose is initiated (see SPC)

Case study 2: Subita

- Subita is a 71 year old Bangladeshi woman with type 2 diabetes
- Her HbA1c is stable on metformin
- She is picked up by the UCLP primary prevention searches as a priority one patient as she is not currently on a statin
- Her cholesterol is
  - Total chol 5.4mmol/L
  - LDL chol 3.6mmol/L
  - HDL chol 0.8mmol/L
- Other considerations? Holistic approach, consider age-related aches/pains, risk:benefits, priorities for patient… Think 5 years ahead…

For lipid management, Subita should be offered?

A. Risk assessment using QRisk

B. A statin

C. Lifestyle advice

D. A statin and lifestyle advice

E. Not sure

Primary Prevention: high intensity statins

- Offer atorvastatin 20mg for the primary prevention of CVD to people with type 2 diabetes who have a 10% or greater 10-year risk of developing CVD (alternative is rosuvastatin 10mg)
- Estimate the level of risk using the QRISK2 assessment tool

ClinRisk

Welcome to the QRISK®2-2014 risk calculator: http://qrisk.org

This calculator is only valid if you do not already have a diagnosis.

Reset | Information | Publications | About | Copyright | Contact Us | Algorithm | Software

About you

Age (25-84): 71

Sex: ○ Male ◉ Female

Ethnicity: Bangladeshi

UK postcode: leave blank if unknown

Postcode:

Clinical information

Smoking status: non-smoker

Diabetes status: type 2

Angina or heart attack in a 1st degree relative < 60? ☐

Chronic kidney disease? ☐

Atrial fibrillation? ☐

On blood pressure treatment? ☐

Rheumatoid arthritis? ☐

Leave blank if unknown

Cholesterol/HDL ratio: 8.75

Systolic blood pressure (mmHg): 160

Body mass index

Height (cm):

Weight (kg):

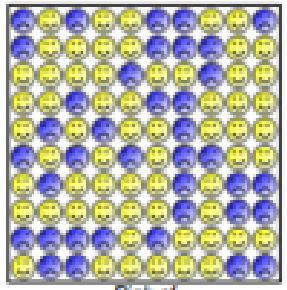
Calculate risk over 10 years. Calculate risk

Your results

Your risk of having a heart attack or stroke within the next 10 years is:

37.9%

In other words, in a crowd of 100 people with the same risk factors as you, 38 are likely to have a heart attack or st



Risk of
heart attack or stroke

Your score has been calculated using estimated data, as some information was left blank.

Your body mass index was estimated as 29.5 kg/m^2.

How does your 10-year score compare?

Your score

Your 10-year QRISK®2 score	37.9%
The score of a typical person with the same age, sex, and ethnicity*	16.8%
Relative risk**	2.3
Your QRISK® Heart Age***	> 84

* This is derived from all people of your age, sex and ethnic group, whatever their clinical information.

** Your relative risk is your risk divided by the typical person's risk.

*** Your QRISK® Heart Age is the age at which a typical person of your sex and ethnicity has your 10-year QRISK®2 score.

Subita

- Lifestyle issues addressed first
- Offer statin if QRisk remains > 10%
  - *unlikely to be achieved by lifestyle alone so don't delay!*
- Rigorous control of BP
- Retain control of blood sugar
- *Would your management change if she had CKD?*

CV Risk Assessment Recommendations

- For the primary prevention of CVD in primary care, use a systematic strategy to identify people who are likely to be at high risk
- Prioritise people for a full formal risk assessment if their estimated 10-year risk of CVD is ≥10%
- Use the QRISK2 risk assessment tool to assess CVD risk for the primary prevention of CVD in people up to and including age 84 years
  - *except type I diabetes, CKD stage 3 or more, FH or pre-existing CVD*

Subita

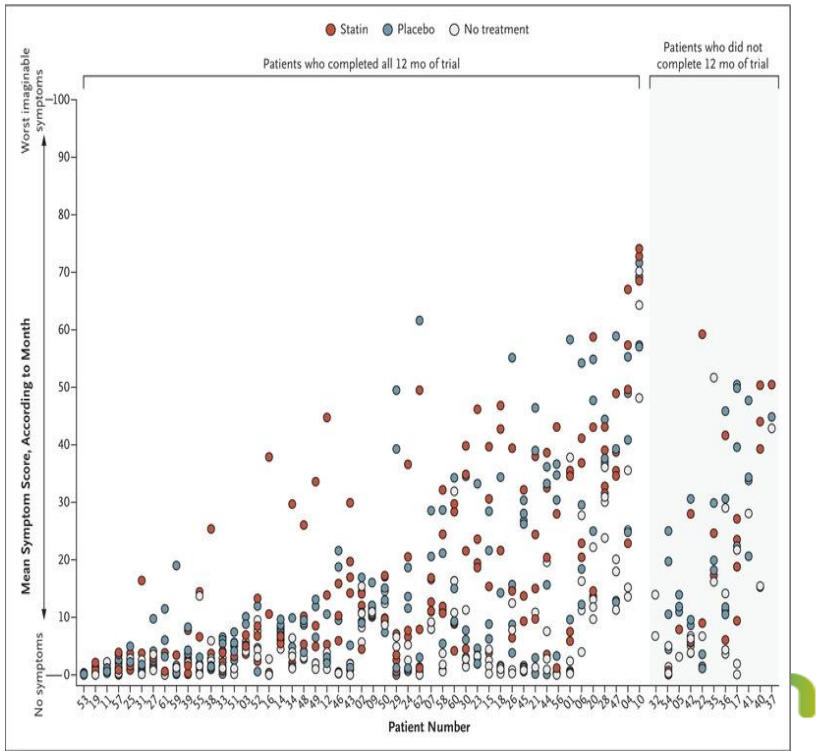
- You contact Subita by phone to offer her a statin
- She is not keen because she heard they can cause side effects
- *How would you manage the discussion?*

Shared decision making: Nocebo effect?

- Imperial college n-of-1 trial:
- Recruited patients previously discontinued statins because of side effects within 2 weeks of initiation
- Double-blind test: are symptoms induced by statin or placebo?
- 4 bottles of each: Atorvastatin 20mg or placebo or empty
- Recorded symptom intensity daily on smartphone app
- Nocebo ratio: symptom intensity induced by placebo to symptom intensity induced by statin
- 60 patients June 2016-March 2019 – 49 patients completed 12 months of study
- In patients who had discontinued statin therapy because of side effects, 90% of the symptom burden elicited by a statin challenge was also elicited by placebo

- Half the trial patients were able to successfully restart statins following the study
- >50% restarted statins once shown that symptoms not related to statin dosing
- SAMSON: self assessment method for statin side effects or nocebo

NEJM Nov 26, 2020: 383:2182-2184; FA Wood et al



Benefits per 10,000 people taking statin for 5 years	Events avoided
Avoidance of major CVD events in patients with pre-existing CVD & a 2mmol/l reduction in LDL	1,000
Avoidance of major CVD events in patients with no pre-existing CVD & a 2mmol/l reduction in LDL	500

Adverse events per 10,000 people taking statin for 5 years	Adverse events
Myopathy	5
Haemorrhagic Strokes	5-10
Diabetes Cases	50-100

Shared decision-making resources:

- BHF information on statins
- Heart UK: Information on statins
- NICE shared decision-making guide

Collins et al 2016 Lancet Systematic Review Lancet 2016; 388: 2532–61

Questions?