Statin intolerance
23-07-16

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Definition
Clinical cases
Management options
Definition of Statin Intolerance
The occurrence of
(1) Adverse symptoms perceived by the patient to be unacceptable,
and/or
(2) Laboratory abnormalities suggesting undue risk, which are attributed to statin therapy

and lead to its discontinuation.
Reasons for Intolerance

- Muscle complaints - Most cases
- Increased liver or muscle enzymes
- Various neurological symptoms
- Other problems - less frequent.
In most cases, decisions pertaining to statin intolerance are patient decisions.
Identify true cases of statin intolerance
Clinical case 1

- 58 yrs old Indian male
- Referred to lipid clinic
- Hyperlipidaemia since 2012
- Raised CK(807) on Simvastatin 40 mg od
- Raised CK on Rosuvastatin 5 mg EON
- Myalgia and raised CK on Atorvastatin
- All these medicines have been stopped
Clinical case 1-ct

- Asymptomatic. Direct questioning → on and off aches
- Engages in strenuous regular exercise routine (Run 5km Sat/Sun)
- p/h nil
- F/h-Father CV death at the age of 65
- O/E Wt-80 kg BMI 25.9 BP-150/91
- Lipid-T C-5.83 LDL-C-4.1 HDL C-1.34 TG-0.81
- CK 483(<200)(Has not had Statins for 2 months)
The health technology assessment in the United Kingdom has identified a cardiovascular disease event of 20% in 10 years as the threshold for treatment, of which most are non-fatal events.
## Clinical case 1-ct

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Clinical case 1-ct

- Thyroid function -normal
- Vitamin D levels-normal
- Calcium –Normal

- Likely cause of raised CK?
- Further Management?
Clinical case 1-ct

- Explain CVS risks
- Discussed about restarting statins
- Atorvastatin 10 mg on
29-02-16 on Atorvastatin 10 mg od for 4 months
CK-180
TC-4.08 TG-0.92 HDL-1.41 LDL-C 2.66
Learning points

- Mildly raised CK levels are usually not clinically significant.
- Raised CK Level may not be caused by statins.
Clinical case -2

- 50ys old Malay male
- Type 2 DM(7ys) and Hyperlipidaemia/Fatty liver
- Non smoker, No ETOH
- F/H- One brother died of? heart failure at the age of 62
- Previous Simvastatin 20 mg on 2010-2013-Stopped due to transaminitis
- Changed to Rosuvastatin 04/2013 ↔2014/01 stopped because of myalgia
- Also tried Ezetimibe and cholestyramine-could not tolerate
- No lipid lowering meds since 08/2015
Clinical case 2 ct

- Wt-84.4
- BMI-28.5
- B P-132/83
- Lipid profile:
  - TC-7.31
  - HDL-C-1.11
  - LDL-C-5.55
  - TG-2.24
# Clinical case 2 ct

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<th>17 Jul 14 08:26</th>
<th>02 Oct 14 08:03</th>
<th>13 Jan 15 10:17</th>
<th>13 Jan 15 10:28</th>
<th>05 May 15 09:30</th>
<th>25 Aug 15 08:24</th>
<th>15 Dec 15 08:15</th>
<th>15 Mar 16 08:55</th>
<th>19 May 16 08:31</th>
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<td>Gamma Glutamyl Transpeptidase</td>
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## Clinical case 2 ct

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Clinical case -2 ct
10 yr cvs risk for cvs events-JBS3 RISK CALC

On average, expect to survive to age 66 without a heart attack or stroke

Interventions

Future smoking category
No

Systolic Blood Pressure
132 → 132

Total Cholesterol
7.3 → 7.3

HDL Cholesterol
1.1 → 1.1

NonHDL Cholesterol: 6.2
BMI: 28.5

Your risk of a heart attack or stroke in the next 10 years is 30%
assuming you don’t die of anything else
<table>
<thead>
<tr>
<th>ESC/EAS</th>
<th>ACC/AHA</th>
<th>Population specific guidelines</th>
</tr>
</thead>
</table>
| **Diabetes** | • Goals for very high risk DM: LDL-C < 1.8 mmol/l or ↓ ≥ 50% if baseline LDL-C 1.8-3.5 mmol/l  
• Lipid lowering Rx for all DM pts > 40 yrs old  
• PCSK9I lower LDL-C in T2 DM (emerging evidence) | 1ry prevention  
• 40-75 yrs moderate intensity statins  
• 40-75 yrs with 10yr risk ≥ 7.5% - high intensity statins | ADA:  
• Goal: > 30% ↓ in LDL-C  
• Mod to high intensity statins  
• Consider EZE for pts with recent ACS and LDL-V > 1.3 or cannot tolerate high intensity statins  
• Consider PCSK9I for high risk DM (requiring greater LDL-C ↓ or intolerant to statins  
• Statin + fibrate / niacin not recommended |
Profound CVS benefits of statins
Statin treatment remains the mainstay of lipid lowering RX for most of the patients
The patient’s subjective assessment of perceived risks and inconveniences

Vs.

Benefits of therapy
Agreed to try Atorvastatin 10 mg on
High risk patients for CV disease Statins remains the choice to lower LDL levels
Assess the risk and benefit of statin treatment
Every effort to use statins
In practice important components

- Acceptability of symptoms,
- Attributability to statin therapy
- The degree of intolerance
SAM

Statin Associated Muscle Symptoms
The clinical presentation of muscle symptom is highly heterogeneous.

- Could be pain, aching, stiffness, tenderness or cramp.
- Attributed by the patient to statin use.
- Usually symmetrical but may be localized.
- Can be accompanied by muscle weakness.
Diagnosis - A definitive diagnosis of SAMS is difficult because symptoms are subjective and there is no ‘gold standard’ diagnostic test.
Statins inhibit the conversion of HMG-CoA to mevalonic acid, which is an important early step in cholesterol synthesis.

**Cause-proposed mechanisms**

- Reduction in ubiquinone (coenzyme Q10 - CoQ10) in skeletal muscle may contribute to statin-induced muscle injury.
- Increased levels of plant sterols in skeletal muscle in patients treated with high-dose - contribute to the muscle toxicity of statins
- Statins increase the expression of mitochondrial Carnitine acylcarnitine translocase and this effect may contribute to the alteration in FAO
- Atrogin-1, a muscle-specific ubiquitin protein ligase, may play an important role in statin toxicity. Lovastatin induces expression of atrogin-1 in humans with statin myopathy.
What laboratory tests help to confirm a diagnosis of statin intolerance?
There is no test that typically confirms a diagnosis of statin intolerance.

Obtaining adequate baseline information on current muscle and other symptoms before a patient begins a statin is important, as symptoms are often erroneously attributed to the statin when they were actually present beforehand.
Assessment

- Muscle symptoms (pain, weakness, cramps)
- Subdivided by the presence or absence of CK elevation
- Muscle group involved
- Symmetrical or not
- Interval between symptoms and statin introduction (symptom usually within 4-6 weeks)
- Recent dose changes
- Recent new medicines
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<th>Causal relation of symptoms to statin therapy</th>
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<tbody>
<tr>
<td>Likely</td>
<td>Likely</td>
<td></td>
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<tr>
<td>Unlikely</td>
<td>Likely</td>
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<table>
<thead>
<tr>
<th>Regional distribution</th>
<th>Symmetrical Widespread or large muscle gp involvement</th>
<th>Asymmetrical, unilateral Small isolated regions</th>
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</thead>
<tbody>
<tr>
<td>Characteristics of the complaint</td>
<td>Muscle pain, tenderness cramps, stiffness Weakness or heaviness during exertion</td>
<td>Shooting pain Muscle tingling or twitching</td>
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<tr>
<td>Temporal association to statin Rx</td>
<td>Symptoms appear within 3 weeks of starting statin</td>
<td>Symptoms appear &gt;12 weeks of starting statin</td>
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<tr>
<td>Dechallenge/Rechallenge testing</td>
<td>Symptoms improve within 4 weeks upon discontinuation of statin Symptoms reoccur within 4 w after re-administration of statin</td>
<td>Late or no improvement of symptoms upon discontinuation of statin Late or no reoccurrence after re-administration of statin</td>
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Assessment ct

If a patient complains of muscle symptoms,

- Evaluate risk factors which can predispose to SAM
- Exclude secondary causes (especially hypothyroidism and other common myopathies such as polymyalgia rheumatica, or increased physical activity)
- Review the indication for statin use.
Referral from poly clinic Dec 2014
56 yrs old female
Hypercholesterolemia since 08/2014
TC-12.24 HDL-C-1.04 TG-2.46 LDL-C-10.10
Non smoker
No F H of DM, premature vascular disease
Started Atorvastatin 20 mg on
CK 791,1116→Atorvastatin discontinued in 09/2014
Clinical case-3 ct

- On direct questioning
- Cold intolerance for months, easily getting tired, no recent weight gain, bowels open once in 2-3 days
- BMI-25 Wt-61.3 kg B P-100/60
- Lipid profile-TC-12.51  LDL-C11.14  TG-2.37 HDL-C-1.18
Clinical case-3 ct

- TFT=T4-2.7 TSH>100
- Δ-Hypothyroid
- Started on Thyroxine 25 mcg od and increase to 75 mcg
- Later Atorvastatin added 09/2015
- Results 02/2016

- Statin can be added once CK normalise or high risk patient Thyroxin and statin can be continued.
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<th>Clinical case 3 ct</th>
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<td><strong>Creatine Kinase</strong></td>
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<td>CKMB-Mass</td>
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<td>Troponin T, High Sensitive</td>
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<td>ECG Software Interpretation</td>
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Learning points

- Get baseline information before starting statins
- Patients on statin, hyperCKaemia → exclude other causes
- Remember conditions associated with Statin intolerance or high risk patients to SAM
Factors Associated with increased risk of Statin Intolerance

- H/o muscle symptoms with other lipid lowering treatment
- H/o unexplained muscular symptoms
- H/o unexplained CK elevation
- F/h of SAM
- Strenuous Exercise
- Hypothyroidism/Subclinical Hypothyroidism
- Vitamin D deficiency
- Drug interactions (Gemfibrozil, Macrolides, Azole anti-fungals, Verapamil, Amiadorone, Protease inhibitors, Cyclosporine)
- Advanced age
- Female gender
- Low BMI
- Alcohol abuse
Clinical case-4

- 60 yrs old male
- Hyperlipidaemia
- F/H of hyperlipidaemia and IHD
- Non smoker
- IHD PCI 2012
- Type 2 DM 2012
- Raised CK levels but minimal muscle symptoms while on Statins
- Managed with low dose statins-08/2012 to 09/2014
  Atorvastatin10 mg on ,then stopped
Clinical case-4 ct

- Asymptomatic
- Does minimal exercises
- BMI-25.2
- Lipid profile-TC-5.45 LDL-C-4.15 HDL-1.13 TG-1.62
- Renal Panel, TFT, LFT-Normal
- Aspirin, Atenolol
Clinical case-4 ct

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<tr>
<td>06/15</td>
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Clinical case-4 ct

- What is the cause of raised CK?
- How do you manage his dyslipidaemia?
Clinical case-4 ct

- Cause of raised CK-
  - Unlikely statins
  - Look for other cause
- Management of dyslipidaemia
- Could be re-challenged with statins while monitoring CK
Learning Points

- Persistently raised CK after stooping Statins unlikely related to statins
Common causes of Raised CK

- Hypothyroidism
- Alcoholism
- Excessive exercise,
- Intramuscular injections
- Multisystem disease
- Intake of other drugs
- Various Myopathies
SAM and CK levels
CK Levels

- CK is not a diagnostic tool.
- Changes in CK levels can occur daily.
- It is not recommended to routinely monitor CK. (CK elevations during statin therapy is uncommon)
- Even if an asymptomatic elevation of CK is detected, the clinical significance is unclear.
- The incidence of rhabdomyolysis in association with statin therapy is ~1 in 100 000 per year (Ck>x40)
<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Biomarker</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle symptoms</td>
<td>Normal CK</td>
<td>Often called ‘myalgia’. May be related to statin therapy. Causality is uncertain in view of the lack of evidence of an excess of muscle symptoms in blinded randomized trials comparing statin with placebo.</td>
</tr>
<tr>
<td>Muscle symptoms</td>
<td>CK &gt; ULN &lt;4 × ULN</td>
<td>Minor elevations of CK in the context of muscle symptoms are commonly due to increased exercise or physical activity, but also may be statin-related; this may indicate an increased risk for more severe, underlying muscle problems.</td>
</tr>
<tr>
<td>Muscle symptoms</td>
<td>CK &gt; 4 &lt; 10 × ULN</td>
<td></td>
</tr>
<tr>
<td>Muscle symptoms</td>
<td>CK &gt; 10 × ULN</td>
<td>Often called myositis or ‘myopathy’ by regulatory agencies and other groups (even in the absence of a muscle biopsy or clinically demonstrated muscle weakness). Blinded trials of statin vs. placebo show an excess with usual statin doses of about 1 per 10 000 per year. Pain is typically generalized and proximal and there may be muscle tenderness and weakness. May be associated with underlying muscle disease.</td>
</tr>
<tr>
<td>Muscle symptoms</td>
<td>CK &gt; 40 × ULN</td>
<td>Also referred to as rhabdomyolysis when associated with renal impairment and/or myoglobinuria.</td>
</tr>
<tr>
<td>None</td>
<td>CK &gt; ULN &lt;4 × ULN</td>
<td>Raised CK found incidentally, may be related to statin therapy. Consider checking thyroid function or may be exercise-related.</td>
</tr>
<tr>
<td>None</td>
<td>CK &gt; 4 × ULN</td>
<td>Small excess of asymptomatic rises in CK have been observed in randomized blinded trials in which CK has been measured regularly. Needs repeating but if persistent, then clinical significance is unclear.</td>
</tr>
</tbody>
</table>
Clinical case 5

72 years old lady was brought by her daughter to your clinic due to severe lethargy and body aches a week after her discharge from the hospital for chest infection.

She was not her usual energetic and chirpy self at this consultation, as compared to her regular visits for hypertension, hyperlipidaemia and gout.

Medication list revealed that she was currently on clarithromycin, colchicine and lovastatin.
The CYP450 system is responsible for the microsomal metabolism of statins. The CYP3A4 isoenzyme is responsible for the metabolism of lovastatin, simvastatin and atorvastatin.

Macrolide antibiotics (e.g. erythromycin, clarithromycin) cause competitive inhibition at the enzymatic level, resulting in higher serum levels of statins.
Colchicine and statins are both well known to cause myopathy. This interaction is more common in the elderly and those with renal insufficiency. Co-administration of both drugs may exacerbate the myotoxic effect. Colchicine is excreted by the hepatobiliary and renal systems. The liver is dependent on the availability of the CYP3A4 isoenzyme when it demethylates colchicine before excretion. Statins metabolised by the CYP3A4 pathway compete with colchicine for the CYP3A4 isoenzyme, which may result in higher serum concentrations of colchicine and statins, leading to a higher risk of myopathy.
Table II. Inhibitors and inducers of cytochrome P450 enzymatic pathway [adapted from Bellosta et al, 2004].

<table>
<thead>
<tr>
<th>CYP substrates (statins)</th>
<th>Inhibitors/substrates</th>
<th>Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP3A4</td>
<td>Ketoconazole, itraconazole, fluconazole, erythromycin, clarithromycin, tricyclic antidepressants, nefazodone, venlafaxine, fluvoxamine, fluoxetine, setraline, cyclosporine A, tacrolimus, mibefradil, diltiazem, verapamil, protease inhibitors, midazolam, corticosteroids, grapefruit juice, tamoxifen, amiodarone, warfarin</td>
<td>Phenytoin, phenobarbital, barbiturates, rifampicin, dexamethasone, cyclophosphamide, carbamazepine, omeprazole, pioglitazone</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>Ketoconazole, fluconazole, sulfinpyrazone, warfarin, protease inhibitors</td>
<td>Rifampicin, phenobarbital, phenytoin</td>
</tr>
<tr>
<td>(fluvastatin, rosvastatin)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Learning points

- There should be appropriate awareness of and attention to the potential for myopathy or rhabdomyolysis with statin therapy, as well as their interactions with other drugs.
Management of true SAM Cases
If the decision is made that statin treatment is needed

- Explain the benefit vs inconveniences
- If statin intolerance appears unlikely → RX with the same, or alternative, statin
- If the diagnosis is likely SAM → Re-challenge with another statin
- If fails try another statin
Patient with muscle complaints on his/her first statin

Discontinue statin
Discuss with the patient the issue of statin muscle side effects and explain the need for trying another statin(s)

- symptoms resolve

Try another statin at the lowest starting dose

- symptoms reappear
- symptoms persist

Search for potential provoking factors and correct as appropriate
Perform de-challenge/re-challenge testing

- symptoms reappear

Try another statin at the lowest starting dose, including re-challenge testing if appropriate
this step may be repeated in case of intolerance

- symptoms reappear

Try very low doses of statin using non-daily dosing, preferably atorvastatin or rosuvastatin
this step may be repeated in case of intolerance

- symptoms reappear

Initiate non-statin therapy

- no symptoms

Search for other causes of the symptoms and treat accordingly
Continue with therapy or gradually increase the doses, if appropriate, to achieve the highest tolerable dose

- no symptoms

Continue with therapy or gradually increase the doses, if appropriate, to achieve the highest tolerable dose

- no symptoms

Gradually increase the doses to achieve the highest tolerable dose
Add non-statin therapy if indicated
Patients with muscle symptoms with CK <4× upper limit of normal

- **For patients at low CVD risk**
  - Reassess the need for a statin
  - Therapeutic lifestyle changes, (cessation of cigarette smoking, blood pressure control, and adoption of a Mediterranean style diet) should be balanced against the risk of continuing statin therapy.

- **Those patients at high CVD risk, including those with CVD or diabetes mellitus**
  - Assess the benefits of ongoing statin therapy against the burden of muscle symptoms.
  - Withdrawal of statin therapy followed by one or more re-challenges (after a washout)

- **Additional approaches include**
  - the use of an alternative statin
  - a statin at lowest dose
  - intermittent (i.e. non-daily) dosing
  - other lipid lowering medications
Patients with muscle symptoms and elevated CK levels (>4× upper limit of normal)

Patients at low CVD risk who have symptoms with CK >4× ULN
- Stop the statin
- Reassess the need for statin
- If considered important → a lower dose of an alternative statin (monitor CK)

For patients at high CVD risk with muscle symptoms and a CK of >4× ULN (but <10× ULN)
- Continue Statin therapy (monitoring CK)
- Stop the statin (at least temporarily) if the levels exceed 10× ULN.
- If CK levels decrease after stopping the statin, restart at a lower dose of different statin (Monitor CK)
- If, CK elevation persists, there may be an underlying myopathy (e.g. hypothyroidism or a metabolic muscle disorder), and referral to a neurologist
In patients with a CK >10× ULN for which no secondary cause (e.g. exercise)

- Stop Statin therapy (potential risk of rhabdomyolysis)
- If the CK level subsequently returns to normal, → re-challenge with a lower dose of an alternative statin, monitor symptoms and CK
- If rhabdomyolysis is suspected→ do not start statin
- If indicated, non-statin LDL-C lowering agents
A large number of subjects with statin intolerance can tolerate the re-challenge with a statin therapy (reported adverse events might have other causes than statin therapy or that they could be related to a specific statin and not to the entire class.)

Statins can be

- **Reintroduced at a lower dose**; (the incidence of muscle adverse effects is increased with high-dose statins)
- **Use of a different statin**; one possibility is to change statin on the basis of its **lipophilic degree**, or on the basis of its **metabolic route** (for example, switching from a CYP450-dependent to a CYP450-independent statin)
<table>
<thead>
<tr>
<th>Statins</th>
<th>Major metabolic pathway</th>
<th>Effect on P-glicoprotein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipophilic statins</td>
<td>Lovastatin  CYP3A4</td>
<td>Inhibitor</td>
</tr>
<tr>
<td></td>
<td>Simvastatin  CYP3A4</td>
<td>Inhibitor</td>
</tr>
<tr>
<td></td>
<td>Fluvastatin  CYP2C9</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Atorvastatin CYP3A4</td>
<td>Inhibitor</td>
</tr>
<tr>
<td></td>
<td>Pitavastatin (CYP2C9)</td>
<td>Inhibitor</td>
</tr>
<tr>
<td>Hydrophilic statins</td>
<td>Pravastatin Sulfation</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Rosuvastatin CYP2C9, CYP2C19</td>
<td>–</td>
</tr>
</tbody>
</table>
Statin re-challenge

- Lower dose of a more potent statin; Rosuvastatin 5 or 10 mg
- Non-everyday statin administration.

**Rosuvastatin**
- because of its long half-life (19 h)
- its lipid-lowering potency;
- minimally metabolized by the CYP450 system and thus is potentially less likely to be involved in the interaction with other drugs.
  - Dose-2.5–20 mg once a week
  - was able to reduce significantly total cholesterol and LDL-C with a high tolerability
  - No data re: cardiovascular risk reduction
  - Every other day
  - Atorvastatin non daily dosing(half life 14 hrs) 10 mg twice a week significantly reduced LDL-C levels with a good tolerability
Once a week high-dose
- Rosuvastatin (80 mg)
- Produced lipid changes comparable to those obtained with atorvastatin 10 mg daily
- Increased the tolerability of the therapy among subjects previously intolerant to a statin

Long-term studies are required to establish whether these alternative regimens may have cardiovascular effects similar to those obtained with daily therapies but with reduced adverse side effects
70 years old lady
Type 1 DM for 51 years
Stable IHD
Treated hypothyroidism
Hypertension
Hyperlipidaemia since 2005
Simvastatin → Rash with real irritation like feeling on the back
Atorvastatin → swollen eyes
Rosuvastatin → Severe Right leg pain 1 day after
All improved after stopping respective drug
Clinical case 6 ct

- Has been on Ezetimibe 10 mg od
- Rising LDL-C since 02/16
- A1C-7.5%  LDL-C-4.81

- What options we have?
If LDL-C remains above target despite maximally tolerated statin dosage, in patients at high CVD risk →

Consider the use of ezetimibe as first choice,

Followed by bile acid sequestrants or fibrates in combination with ezetimibe
Consider if statin-attributed muscle symptoms favour statin continuation / reinitiation

- Symptomatic & CK < 4 X ULN
  - 2–4 weeks washout of statin
    - Symptoms persist: statin re-challenge
      - Symptoms improve: Second statin at usual or starting dose
        - Symptom-free: Continue statin
        - Symptoms re-occur
          1) Low dose third efficacious (potent) statin;
          2) Efficacious statin with alternate day or once/twice weekly dosing regimen

- CK ≥ 4 X ULN +/- rhabdomyolysis
  - 6 week washout of statin until normalisation of CK/creatinine and symptoms

Aim: achieve LDL-C goal* with maximally tolerated dose of statin

- Ezetimibe
  - A + bile acid absorption inhibitor
  - B + fibrate (not gemfibrozil)
  - A + B

If still not at goal: consider additional (future) novel therapies: PCSK9 monoclonal antibody therapy, CETP inhibitor

Key:
CETP = cholesteryl ester transfer protein; CK = creatine kinase; LDL-C = low-density lipoprotein cholesterol;
PCSK9 = Proprotein convertase subtilisin/kexin type 9; ULN = upper limit of the normal range;

* efficacious statin such as atorvastatin or rosuvastatin
* Reiner Z et al. (2011)
Ezetimibe

- Reduces LDL-C by 15–20%
- Easy to take with few side effects
- Well tolerated
- In patients with SAMS, the combination of ezetimibe plus fluvastatin XL reduced LDL-C by 46% and was as well tolerated as ezetimibe alone.
- The evidence of cardiovascular benefit is limited to one trial that demonstrated a modest 6% reduction of cardiovascular event
Bile acid sequestrants

- Can reduce LDL-C levels by 15–25% depending on the type and dose used,
- Improve glycaemia in patients with diabetes.
- **Colesevelam** is easier to take and better tolerated than earlier formulations.
- The combination of a bile acid sequestrant and ezetimibe can reduce LDL-C by ~30–35%.
- They have been proven to reduce cardiovascular events.
- Resins are safe, but poorly tolerated, due to G I side effects.
Fibrates

- Primarily used to lower triglycerides and increase high-density cholesterol; they also decrease LDL-C levels, but to a lesser extent.
- The effect on LDL-C is more pronounced in patients with hypertriglyceridemia.
- Accordingly, the reduction of cardiovascular risk with fibrates is only 10% in unselected patient population, but is substantially greater (≈30%) in patients with hypertriglyceridemia.
- Caution must be exercised when combining fibrates with statins, as the combination may increase the risk of myalgia.
Fenofibrate

- Can lower LDL-C by 15–20% in patients with high baseline levels who do not have concomitant hypertriglyceridaemia.
- This fibrate is easy to take, and has shown an excellent safety record in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) and Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trials.
- Additional CVD benefit has not been demonstrated.
- Serum creatinine was reversibly increased during treatment.
- Unlike gemfibrozil, there is no increased risk of rhabdomyolysis when Fenofibrate is added to a statin.
Niacin is similar to fibrates relative to its effect on blood lipids, but its use in clinical practice has dropped substantially after two clinical-endpoint trials failed to demonstrate cardiovascular benefits of niacin therapy.

Niacin also lowers LDL-C levels by 15–20%.

Recent large RCTs showed a significant excess of adverse effects and no significant CVD benefit when added to background statin treatment.
Evolocumab, Alirocumab, and Bococizumab.
Studies have consistently shown large LDL-C reductions of 50–60% in a variety of patient groups,
Meta-analyses of phase 2 and 3 trials → >50 % reduction of cardiovascular events with evolocumab and alirocumab.
Statin intolerance is one of the approved indications for use of PCSK9 inhibitors.
PCS\textsuperscript{9} Monoclonal antibodies

- Very low rate of muscle symptoms
- S C Injections
- The tolerability has been very good,
- Few injection site reactions
- No significant liver function abnormalities
- No significant CK elevations. (In clinical trials including over 6000 patients treated for 3 to 12 months)
- Four large CVD outcomes trials are ongoing and initial results are anticipated in 2017.
Nutraceuticals

- Consumption of viscous fibre (mainly psyllium, 10 g daily)
- Foods with added plant sterols or stanols (2 g daily) has also been shown to reduce LDL-C by 7% and 10%, respectively.
- The Portfolio diet, incorporating plant sterols, soya protein, viscous fibres, and nuts, has the potential to reduce LDL-C levels by 20–25%.
- Trade names-Benecol
Complementary therapies

- Ubiquinone (coenzyme Q10 [CoQ10]) and vitamin D supplementation
  - A double-blind RCT and a meta-analysis, failed to substantiate that CoQ10, even at high doses, reduced symptoms in patients with SAMS.
  - Evidence for the effectiveness of vitamin D is also controversial, although many patients with SAMS are found to have low blood levels of vitamin D.
  - Hence, supplementation with either CoQ10 or vitamin D to treat or prevent SAMS generally not recommended.
Red yeast rice (*Monascus purpureus*)

- Fermented product
- Has been shown to reduce LDL-C levels by 20–30% in short-term RCTs.
- This effect is partly due to the presence of monacolin K, a product similar to lovastatin that inhibits hepatic cholesterol synthesis, as well as plant sterols that reduce cholesterol absorption.
- Recent data suggest that red yeast rice is an effective, well-tolerated

**Number of outstanding issues**

- Lack of robust evidence that red yeast rice is efficacious and tolerated in the long term
- Lack of standardization with variable drug bioavailability in different preparations
- Possible toxic effects due to contaminants.
- Red yeast rice may also elicit SAMS because of the statin-like content.

- Long-term studies are needed
- Hypocol and Chenol
Clinical case 7

- 49 years old Indian male
- Type 2 DM (suboptimal control) since 2000
- Fatty liver
- Dyslipidaemia
- SAM and ↑ CK with statins
- Gout
08/2012  LDL-C 3.42  CK-341 cramps while on Rosuvastatin 5 mg on
Patient decided to stop statins
Has been on Hypoccol 600 mg bd(Red yeast Rice)
04/2016
TC-3.86  LDL-C-2.30  HDL-C-1.22  TG 1.08
Statins and LFT
Baseline ALT and AST measurements are recommended.

There is no need for ongoing monitoring of liver enzymes unless warranted.

ALT and AST will often increase transiently and harmlessly during the first few weeks of statin therapy.

Other factors like ethanol intake can affect LFT monitoring.
FDA → despite a rising use of statins as a class since the late 1990s, there has not been a detectable increase in the annual rates of fatal or severe liver injury cases possibly or probably causally associated with statin use.
(1) Irreversible liver damage resulting from statins is exceptionally rare and is likely idiosyncratic in nature

(2) No data exist to show that routine periodic monitoring of liver biochemistries is effective in identifying the very rare individual who may develop significant liver injury from ongoing statin therapy.
Clinical case

- 50ys old male
- Type 2 DM(7ys) and Hyperlipidaemia
- LFT
## Clinical case

<table>
<thead>
<tr>
<th>Liver Function ---</th>
<th>4Apr14 08:34</th>
<th>17Jul14 08:26</th>
<th>02Oct14 08:03</th>
<th>13Jan15 10:17</th>
<th>13Jan15 10:28</th>
<th>05May15 09:30</th>
<th>25Aug15 08:24</th>
<th>15Dec15 08:15</th>
<th>15Mar16 08:55</th>
<th>19May16 08:31</th>
<th>11Jul16 08:43</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alanine Aminotransferase</td>
<td>61↑75↑58↑99↑148↑69↑80↑90↑54</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspartate Aminotransferase</td>
<td>35↑35↑33↑49↑94↑43↑51↑41↑32</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gamma Glutamyl Transpeptidase</td>
<td>97↑</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>119↑142↑101↑</td>
</tr>
<tr>
<td>Total Protein, Serum</td>
<td>83</td>
<td>76</td>
<td>82</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>42</td>
<td>42</td>
<td>44</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Globulin</td>
<td></td>
<td>42</td>
<td>35</td>
<td>38</td>
<td>41</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Albumin:Globulin Ratio</td>
<td>0.99</td>
<td>1.20</td>
<td>1.18</td>
<td>1.05</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Bilirubin, Total</td>
<td>16</td>
<td></td>
<td>17</td>
<td>15</td>
<td>14</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Alkaline Phosphatase</td>
<td>63</td>
<td>70</td>
<td>69</td>
<td>64</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
What is the likely cause of abnormal LFT?
Will you consider Statins in this patient?
Liver and statins facts

- Statins are safe to use in patients with non alcoholic fatty liver disease.
- Statins have drug interactions with medications used to treat infections (hepatitis B, C, etc.) that require change in statin, change in statin dosing, or change in antiviral regimen dosing.
- Statins can be used in liver transplant recipients and in patients with A I Hepatitis.
Statin intolerance can be due to various causes commonest due to SAM

Identification of true cases of SAM is important and the diagnosis is clinical.

Management of SAM is essentially common sense approach considering CVS risk as well as symptoms

Statin remains the mainstay of treatment of hypercholesterolemia and every effort should be made to continue statins.
Summary continue

- Serious side effects due to statin Rx are rare but in relevant cases CK monitoring is recommended.
- Non statin RX, nutritional supplements and complementary therapies are available to try in cases where statin therapy failed.
- Newer non statin therapies like PCSK 9 monoclonal antibodies are very promising.
Thank You