North Central London

Lipid Management: Medicines Optimisation Pathways

Developed by NCL Joint Formulary Committee & UCL Partners

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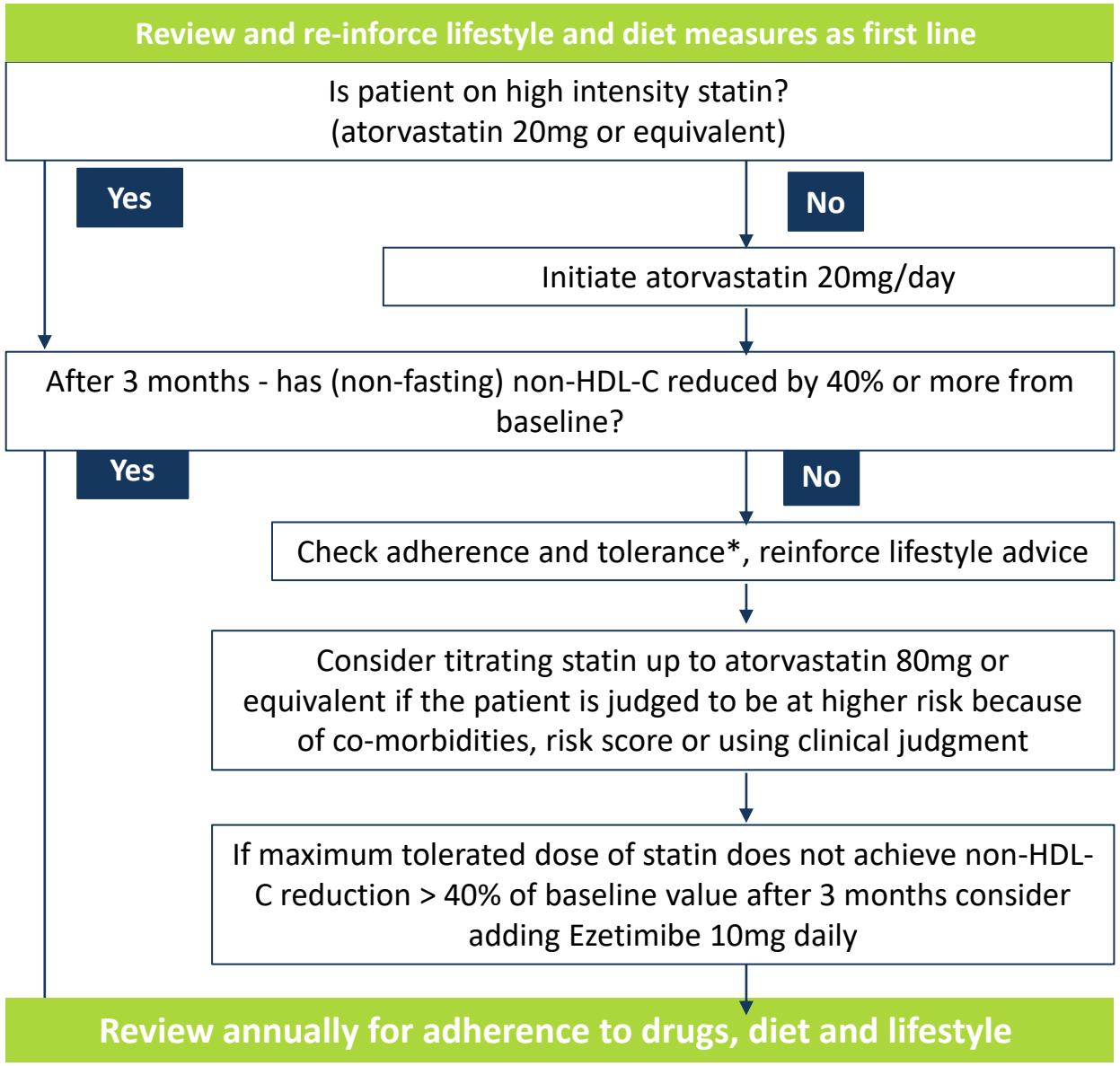

Optimal High Intensity statin for Primary Prevention (High intensity statins are substantially more effective at preventing cardiovascular events than low/medium intensity statins)	
Atorvastatin	20mg
Rosuvastatin	10mg

* If statin not tolerated, follow statin intolerance pathway and consider ezetimibe 10mg daily +/- bempedoic acid 180mg daily

Further information on management for patients with chronic kidney disease (CKD) is available in the NHS AAC lipid management guidance

Optimisation Pathway for Secondary Prevention

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Is patient on high dose, high intensity statin*?
(atorvastatin 80mg or equivalent)

No → **Initiate / increase to high dose high intensity statin** ** and reinforce lifestyle and diet measures

Yes

Is (non-fasting) non-HDL-C reduced by 40% or more from baseline at 3 months? ***
(if baseline non-HDL not available, consider intensification of therapy if non-HDL-C > 2.5mmol/L)

No

Yes

Check adherence to statin and lifestyle measures. Consider adding ezetimibe 10mg daily
If statin not tolerated, follow statin intolerance pathway and consider ezetimibe 10mg daily +/- bempedoic acid 180mg daily ****.

Is non-HDL-C reduced by 40% or more from baseline after 3 further months? ***
(if baseline non-HDL not available, consider intensification of therapy if non-HDL-C > 2.5mmol/L)

No

Yes

Consider injectable therapies
Arrange fasting blood test to assess eligibility:
- **Inclisiran** - if fasting LDL-C ≥ 2.6mmol/L despite maximum tolerated lipid lowering therapy **OR**
- **Refer for PCSK9i (Evolocumab and Alirocumab)** if fasting LDL-C > 4mmol/L (or > 3.5mmol/L if recurrent events)

Review annually for adherence to drugs and support for diet and lifestyle measures

Optimal High Intensity Statin for secondary prevention (High intensity statins are substantially more effective at preventing cardiovascular events than low/medium intensity statins)	
Atorvastatin	80mg
Rosuvastatin	20mg

* Dose may be limited if:
- eGFR<30ml/min – see product license or NHS AAC lipid management guidance
- Drug interactions
- Intolerance
- Older age / frailty

See product license or NHS AAC lipid management guidance for further information

** See statin intensity table

*** Current NICE Guidance recommends a 40% reduction in non- HDL cholesterol

**** Measure uric acid and renal function

Statin Intensity Table – NICE recommends Atorvastatin and Rosuvastatin as First Line

Approximate Reduction in LDL-C					
Statin dose mg/day	5	10	20	40	80
Pravastatin		20%	24%	29%	
Simvastatin		27%	32%	37%	42%
Atorvastatin		37%	43%	49%	55%
Rosuvastatin	38%	43%	48%	53%	
Atorvastatin + Ezetimibe 10mg		52%	54%	57%	61%

Low/moderate intensity statins will produce an LDL-C reduction of 20-30%

Medium intensity statins will produce an LDL-C reduction of 31-40%

High intensity statins will produce an LDL-C reduction above 40%

Simvastatin 80mg is not recommended due to risk of muscle toxicity

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

Statin Intolerance Pathway

Important considerations

- Most adverse events attributed to statins are no more common than placebo*
- Consider food and drug interactions which may be contributing to adverse effects – see SPC *
- Stopping statin therapy is associated with an increased risk of major CV events. It is important not to label patients as 'statin intolerant' without structured assessment
- If a person is not able to tolerate a high-intensity statin, aim to treat with the maximum tolerated dose
- A statin at any dose reduces CVD risk – consider annual review for patients not taking statins to review cardiovascular risk and interventions

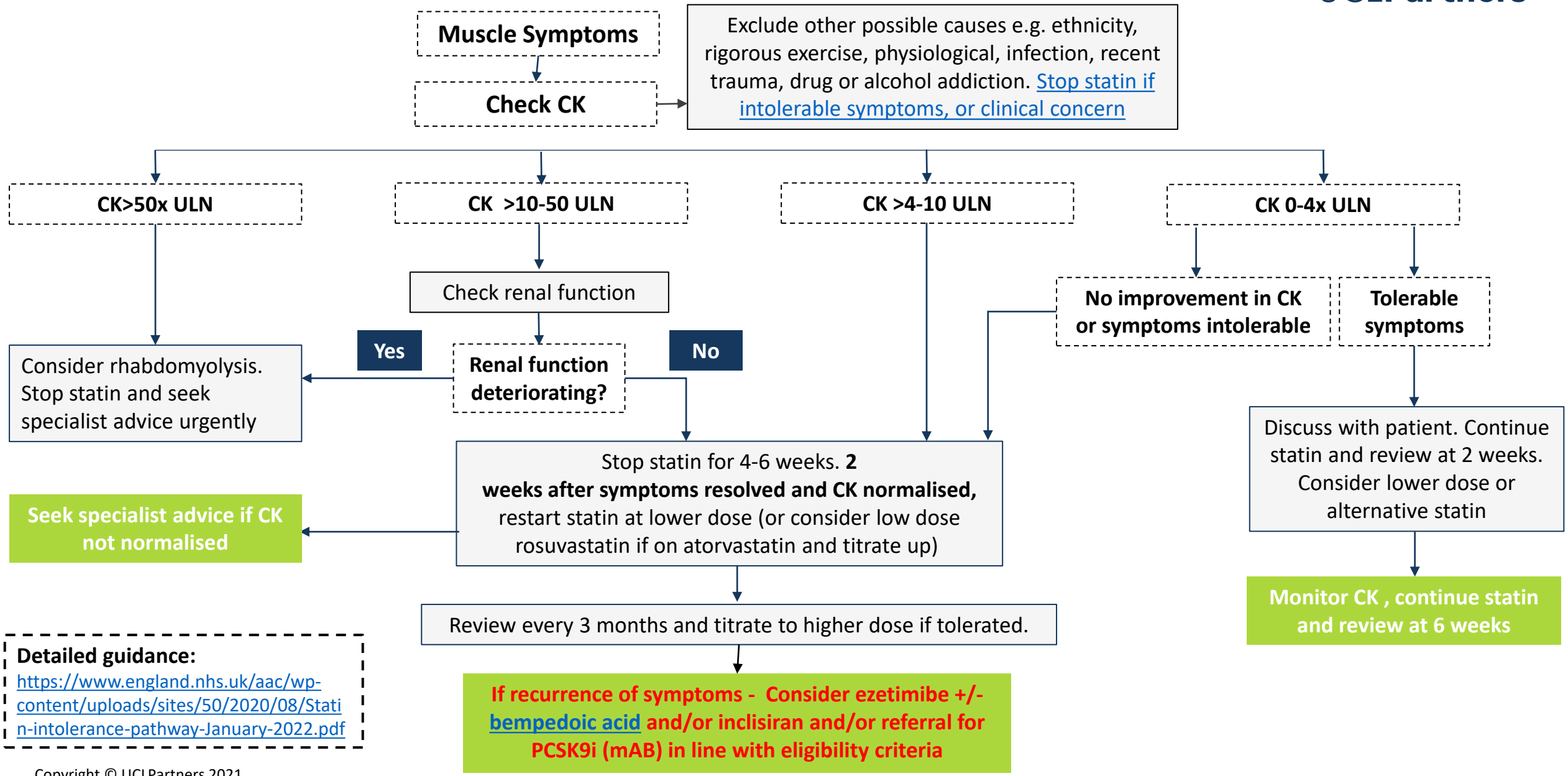
*(*Collins et al systematic review, Lancet 2016)*

A structured approach to reported adverse effects of statins

1. Stop for 4-6 weeks.
2. If symptoms persist, they are unlikely to be due to statin
3. Restart and consider lower initial dose
4. If symptoms recur, consider trial with alternative statin
5. If symptoms persist, consider ezetimibe
6. Add in bempedoic acid if required for further lipid lowering as per NICE guidance

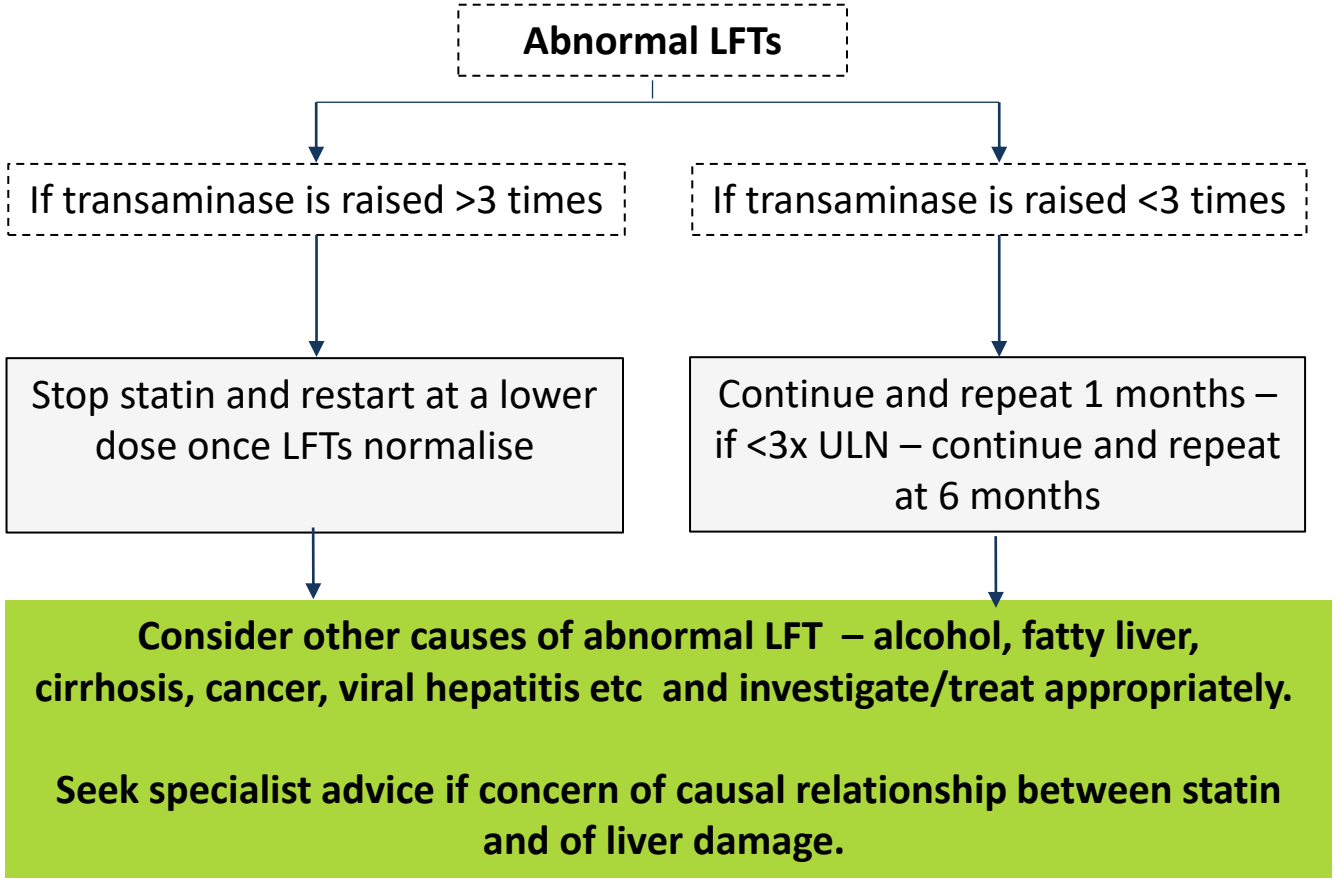
Atorvastatin SmPC:
https://www.medicines.org.uk/emc/product/5274/smpc#gref
Rosuvastatin SmPC:
https://www.medicines.org.uk/emc/product/4366/smpc#gref

Muscle Symptoms Pathway



Detailed guidance:
https://www.england.nhs.uk/aac/wp-content/uploads/sites/50/2020/08/Statin-intolerance-pathway-January-2022.pdf

Abnormal Liver Function Test (Transaminitis) Pathway



- 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, at 3 months and 12 months after initiation of statin therapy.

Lipid Clinic Contact Details

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Links to Related Guidance

Familial hypercholesterolaemia: https://www.nice.org.uk/guidance/cg71

Hypertriglycerdiaemia guidance: https://www.ncl-mon.nhs.uk/wp-content/uploads/Guidelines/2_Guidance_for_the_management_of_hypertriglyceridaemia.pdf

NHS AAC National Guidance for Lipid Management for Primary and Secondary Prevention of CVD: https://www.england.nhs.uk/aac/wp-content/uploads/sites/50/2020/04/Summary-of-national-guidance-for-lipid-management-for-primary-and-secondary-prevention-of-cardiovascular-disea.pdf

Summary of Lipid Lowering Therapies

Drug class	NICE approved Indication	Administration	LDL-lowering efficacy	CV outcomes evidence	Safety data
Statins	Primary prevention, Secondary prevention, Familial hypercholesterolaemia (FH)	Oral tablet given once daily	High intensity statins can lower LDL-C by 40% -55% (depending on agent and dose)[1]	Multiple outcome studies confirming CV outcomes benefit across a wide range of patient cohorts. For every 10,000 people treated for 5 years: - In secondary prevention (established CVD): 1,000 heart attacks, strokes or deaths avoided - NNT over 5 years = 10 - In primary prevention: 500 heart attacks, strokes or deaths avoided[7] - NNT over 5 years = 20	Long term safety data has been well established over 30 years For every 10,000 people treated for 5 years: - 5 cases of myopathy - 5-10 haemorrhagic strokes - 50-100 new cases of diabetes [7]
Ezetimibe	Primary prevention, Secondary prevention and FH where statins are contraindicated, not tolerated or ineffective	Oral tablet given once daily	An additional LDL-C reduction of 24% in combination with statins[2]	Two CV outcomes studies in secondary prevention on top of statins – demonstrating NNTs between 42-50 for preventing major cardiovascular event over 3.5-7 years. [8,9] For every 10,000 people with CVD treated for 5 years: - Approximately 200 major CV events avoided	Long term safety data has been well-established over 15 years
PCSK9i (Alirocumab/ Evolocumab)	Secondary prevention and FH in patients who meet eligibility criteria	Self-administered S/C injection every two weeks	An additional LDL-C reduction of approximately 50% (range 25-70%) alone or in combination with statins or ezetimibe. [3,4]	Two CV outcomes studies in secondary prevention on top of statins [10,11] For every 10,000 people treated for 2 years - Approximately 150 major CV events avoided - NNT over 2 years = 65[12]	Safety data has been established over 5 years
Bempedoic acid	For use where statins are not tolerated in combination with ezetimibe, if ezetimibe alone does not control LDL-C well enough	Oral tablet given once daily	An additional LDL-C reduction of approximately 28% (range 22-33%) when combined with ezetimibe[5]	No CV outcomes data. On-going studies due to report in 2022.	Short term safety data from trials of up to 2 years.
Inclisiran	Secondary prevention in patients who meet eligibility criteria	S/C injection administered by a healthcare professional every six months, once stabilised	An additional LDL-C reduction of approximately 50% (range 48-52%) alone or in combination with statins or ezetimibe[6]	No CV outcomes data. On-going studies due to report in 2026.	Short term safety data from trials of up to 2 years.

References:

1. NICE CG181 2014 https://www.nice.org.uk/guidance/cg181/chapter/1-recommendations; 2. NICE TA385 2016 https://www.nice.org.uk/guidance/ta385; 3. NICE TA393 2016. https://www.nice.org.uk/guidance/ta394 4. NICE TA394 2016. https://www.nice.org.uk/guidance/ta394 5. NICE TA694 2021. https://www.nice.org.uk/guidance/ta694 6. NICE TA733 2021. https://www.nice.org.uk/guidance/ta733. 7. Collins et al. 2016. Lancet 2016; 388: 2532–61. 8. Cannon CP et al. 2015. N Engl J Med 2015; 372:2387-2397; 9. Anyanwu P et al. 2020. N Engl J Med 2020; 382:9-19; 10. Sabatine et al. 2017: N Engl J Med 2017; 376:1713-1722; 11. Schwarz GG et al. 2018. N Engl J Med 2018; 379:2097-2107; Can Fam Physician. 2018 Sep; 64(9): 669.

Inclisiran for secondary prevention

- Inclisiran is indicated only for patients:
  - With established CVD
  - On optimal oral lipid lowering therapy including high intensity statins where tolerated
  - Where LDL-C remains ≥ 2.6mmol/L
- Inclisiran lowers LDL-C by approx. 50%, but there are currently no long term CVD outcome data or safety data and this should be taken into account when making a shared decision with the patient about appropriate treatment choices
- Inclisiran is administered at a dose of 284mg by subcutaneous injection
- It should be given at month 0 (initiation), month 3, month 9 and then every 6 months thereafter.
  - If a planned dose is missed by more than 3 months, a new dosing schedule should be started – inclisiran should be administered initially, again at 3 months, followed by every 6 months.
  - It should be administered by a healthcare professional into the abdomen; alternative injection sites include the upper arm or thigh.
- The only adverse reactions associated with inclisiran reported to date are injection site reactions (8.2%)
- More information on inclisiran can be found at: https://www.medicines.org.uk/emc/product/12039/smpc#gref

Bempedoic acid for use in statin intolerance

- Bempedoic acid with ezetimibe is recommended as an option for treating primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia as an adjunct to diet in adults. It is recommended only if:
  - statins are contraindicated or not tolerated and
  - ezetimibe alone does not control low-density lipoprotein cholesterol well enough
- Bempedoic acid lowers LDL-C by an additional 28% (range 22-33%) when combined with ezetimibe. There are currently no long term CVD outcome data or safety data and this should be taken into account when making a shared decision with the patient about appropriate treatment choices
- The recommended dose of bempedoic acid is one film-coated tablet of 180 mg taken once daily
- Bempedoic acid with ezetimibe can be prescribed as separate tablets or a fixed-dose combination
- Bempedoic acid was associated with a slightly increased risk of tendon rupture, involving the biceps tendon, rotator cuff, or Achilles tendon. Other more commonly reported adverse events in clinical trials were upper respiratory tract infection, back pain, abdominal pain or discomfort, bronchitis, pain in extremity, anaemia, and elevated liver enzymes
- More information on bempedoic acid can be found at: https://www.medicines.org.uk/emc/product/11743/smpc#gref