DERBYSHIRE JOINT AREA PRESCRIBING COMMITTEE (JAPC)

ADULT LIPID MODIFICATION THERAPY IN NON-FAMILIAL HYPERLIPIDAEMIA

See Lipid management for primary & secondary prevention of CVD summary flowcharts (p.2&3)

Key message

- Practices should prioritise secondary prevention patients and those primary prevention patients at higher risk.
- Offer atorvastatin 80mg for secondary prevention (except CKD- starting dose 20mg, titrating up according to response)
- Use QRISK3 assessment tool to estimate 10 year CVD risk (see note 1 on p.3)
  - For primary prevention of CVD in people aged between 25-84 years (unless CKD or other high-risk group – see primary prevention algorithm)
  - In people with type 2 diabetes
- For primary prevention of CVD, it is recommended to use a systematic strategy (e.g., the NHS Health Check programme) to identify people at high risk (estimated CVD risk of 10% or more over 10 years). In those at high risk optimise other modifiable risk factors and if appropriate refer for support to make lifestyle changes, before offering statin treatment.
- Check full lipid profile (total cholesterol (TC), HDL-cholesterol, non-HDL-cholesterol and triglyceride) before starting lipid modification therapy. A fasting sample is not required. A single cholesterol level measurement could be +/- 14% of the person's true value.
- Measure total cholesterol, HDL-cholesterol and non-HDL-cholesterol in all people who have been started on a high intensity statin treatment at 2 to 3 months and aim for greater than 40% reduction in non-HDL-cholesterol for primary prevention. For secondary prevention aim for non-HDL ≤2.6 mmol/L or LDL ≤2.0 mmol/L.
- In patients who fail to achieve target lipid reduction, check adherence, timing of dose, diet and lifestyle measures, and consider increasing dose of atorvastatin if <80mg and patient at high risk. (Agree the use of higher doses with a renal specialist if eGFR<30 ml/min/1.73m^2). Consider switching to rosuvastatin in patients who fail to achieve target lipid reduction on atorvastatin. Take into account person's preferences, presence of co-morbidities, polypharmacy, frailty and life expectancy when escalating treatment for people on statin therapy.
- In patients not able to tolerate high intensity statin (atorvastatin 20mg) aim to treat with maximum tolerated dose. Consider a temporary stop, reduce dose, or changing to a lower intensity statin. See Appendix 1 for more detail.
- Bempedoic acid with ezetimibe (NICE TA694) is a treatment option if statins are contraindicated or not tolerated, and ezetimibe alone does not control LDL-c well enough. Monitor LFT at baseline, 3 &12 months.
- Inclisiran is recommended (NICE TA733) as an option for treating primary hypercholesterolaemia or mixed dyslipidaemia if there is a history of cardiovascular events and LDL-c persistently ≥2.6mmol/l despite maximum tolerated lipid lowering therapy. Locally this is classified RED- specialist only.
- NICE have produced a series of patient decision aids (PDAs) to enable patients to assess the risks and benefits of commencing statins.
- This guidance does not include the management of familial hypercholesterolaemia (FH). The Derbyshire guidance on FH can be found here.

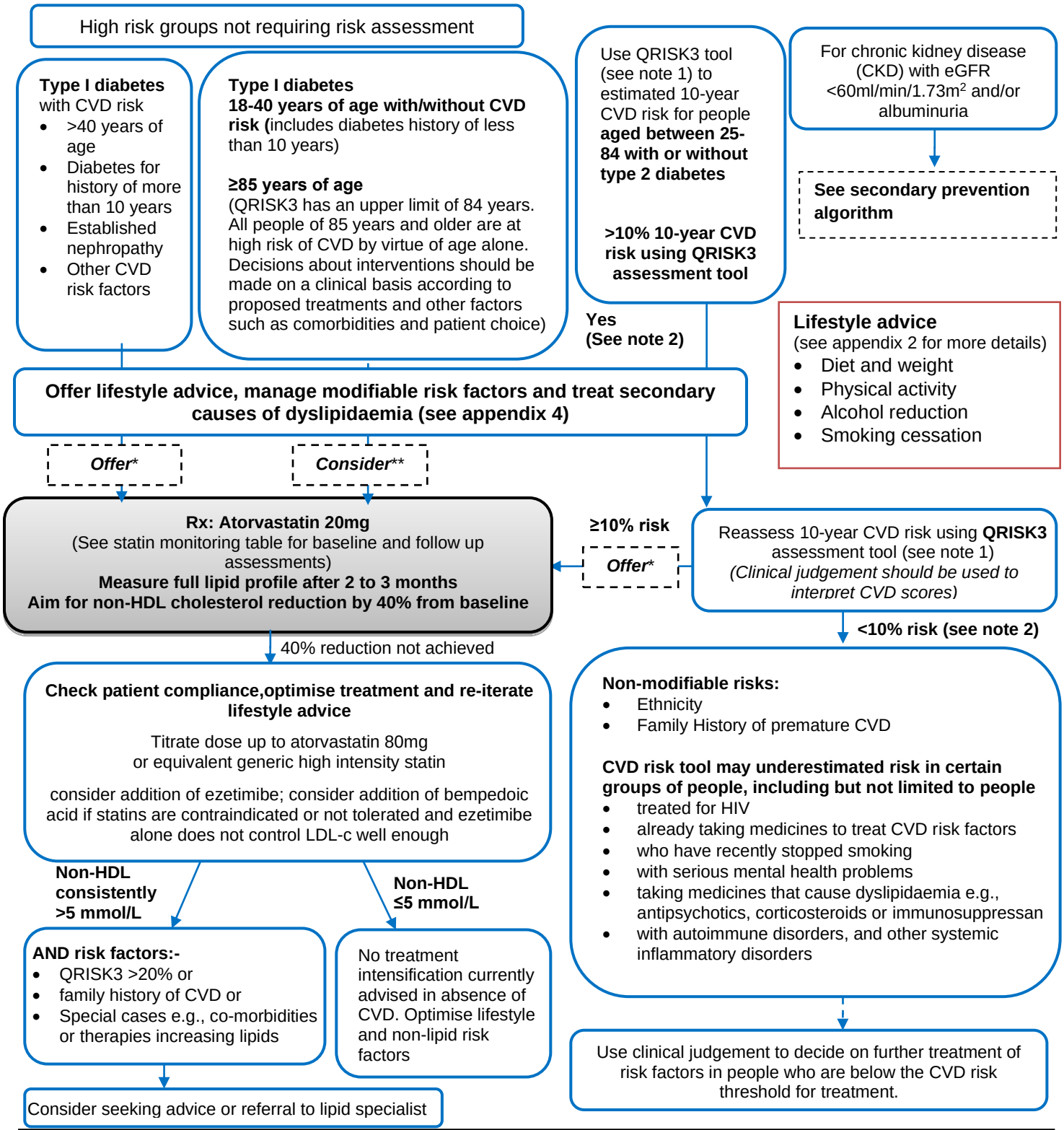
Lipid management for primary and secondary prevention of CVD- Summary

The recommended management of primary and secondary prevention are presented in the following algorithms.

Check full lipid profile (total cholesterol (TC), HDL-cholesterol, non-HDL-cholesterol and triglyceride) before starting lipid modification therapy. A fasting sample is not required. For patients with total cholesterol >7.5mmol/L or triglycerides >10mmol/L- consider familial hypercholesterolaemia (see statin monitoring table).

Primary Prevention for new patients without CKD (and non-FH)

Patients >40 years of age need assessing their CVD risk – review estimated CVD risk on an on-going basis.



NICE definition
*__Offer__ as an intervention which will do more good than harm and be cost effective
**__Consider__ as an intervention which will do more good than harm for most patients and be cost effective, but other options may be similarly cost effective.

Note 1- QRISK 3

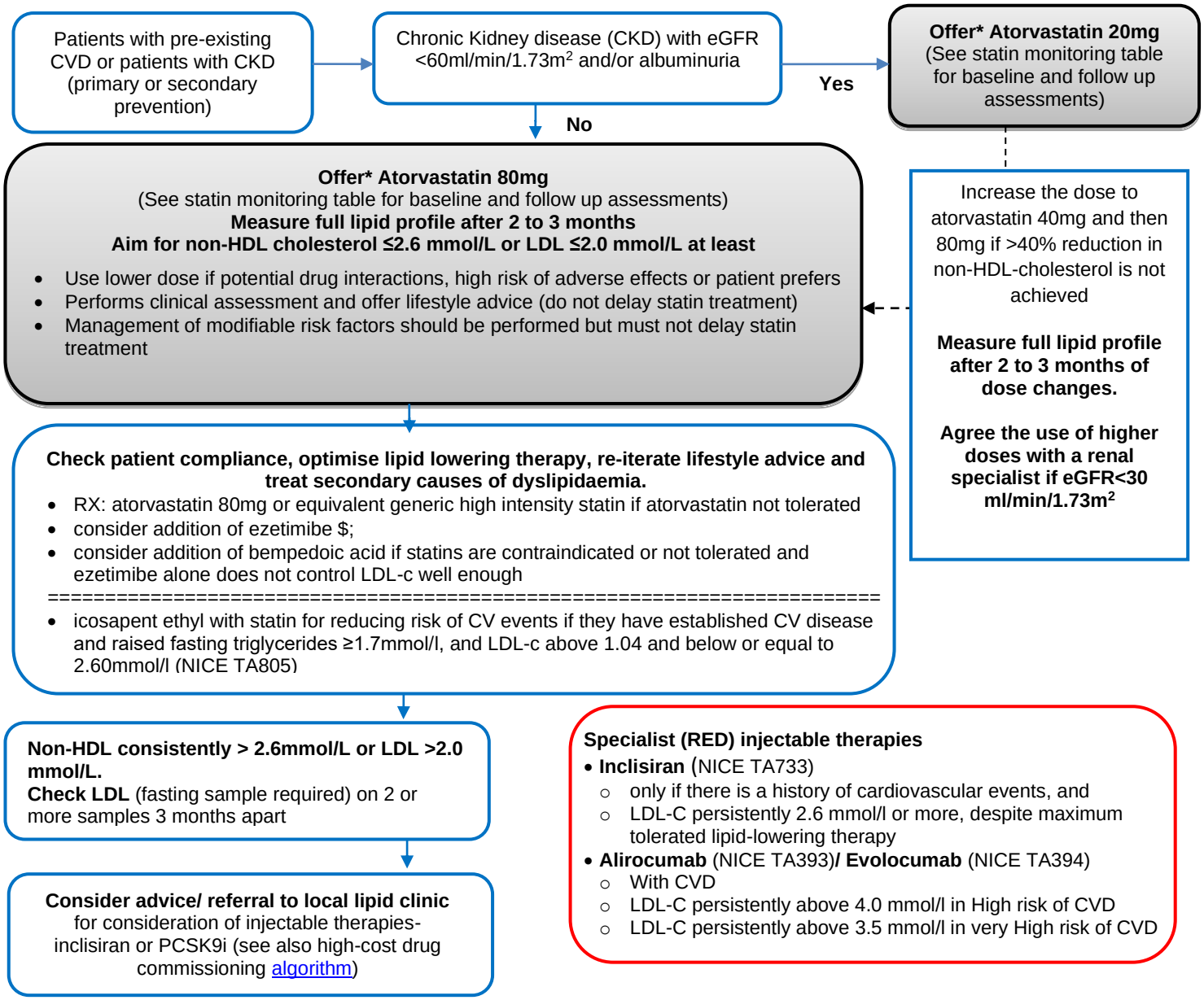
Until electronic clinical systems in which QRISK2 is embedded are updated with QRISK3, it may be necessary to use QRISK2. Use QRISK 3 (online if necessary) when assessing risk for

- people taking corticosteroids or atypical antipsychotics or
- people with systemic lupus erythematosus, migraine, severe mental illness or erectile dysfunction

Consider using a lifetime risk tool such as QRISK3-lifetime to inform discussions on CVD risk and to motivate lifestyle changes, particularly for people with a 10-year QRISK3 score less than 10%, and people under 40 who have CVD risk factors.

Note 2- NICE CG181 (updated May 2023) recommends- Do not rule out treatment with atorvastatin 20 mg for the primary prevention of CVD just because the person's 10-year QRISK3 score is less than 10% if they have an informed preference for taking a statin or there is concern that risk may be underestimated.

Secondary prevention or patients with CKD



$ NICE recommends consider ezetimibe in addition to the maximum tolerated intensity and dose of statin to reduce CVD risk further even if the lipid target for secondary prevention of CVD is met. However, trade-off between further reducing risk and increasing medication (reducing adherence) should be carefully considered. All treatment decisions should be discussed with the person as part of informed and shared decision making.

Summary of statin prescribing

OFFER	USUAL STARTING DOSE***
>10% 10-year CVD risk (see note 2 above)	Atorvastatin 20mg
Type 2 diabetes (>10% CVD risk)	Atorvastatin 20mg
Type 1 diabetes (>40 years of age; or >10 year duration; or nephropathy; or other CVD risks)	Atorvastatin 20mg
CKD (Do not use a risk assessment tool in people with an eGFR less than 60 ml/min/1.73 m2 and/or albuminuria. These people are at increased risk of CVD.)	Atorvastatin 20mg
CVD without CKD	Atorvastatin 80mg
CONSIDER	
People >85 years	Atorvastatin 20mg
People 18-40 years with type 1 diabetes, (including <10-year duration)	Atorvastatin 20mg

***** *Consider titrating the dose up, if >40% reduction in non-HDL cholesterol is not achieved*.

Intolerance to statins (see also appendix 1- myalgia)

- Advise people who are being offered a statin that the risk of muscle pain, tenderness or weakness associated with statin use is small and the rate of severe muscle adverse effects (rhabdomyolysis) because of statins is extremely low.
- Use maximum tolerated dose to treat patients. Advise patients that any statin at any dose reduces CVD risk.
- If patients report adverse effects with high intensity statins discuss the following strategies:
  - Stop statin and try again when symptoms have resolved to check if symptoms are related to the statin.
  - Reduce the dose within the same intensity group.
  - Change statin to a lower intensity group (e.g., simvastatin or pravastatin)
  - Consider alternative or additional lipid lowering therapies as per NICE technology appraisals (including ezetimibe monotherapy, ezetimibe/bempedoic combination therapy) or refer to lipid specialists for injectable therapies (where eligible).

Seek specialist advice regarding other options for treating patients at high risk of CVD (such as those with chronic kidney disease, type 1 diabetes, type 2 diabetes, or genetic dyslipidaemias) and those with CVD who are intolerant to trials of generic statins.

Statin monitoring and follow-up

Baseline monitoring

Baseline monitoring	Action
Full lipid profile (FLP) • Total cholesterol (TC) • HDL-C • non-HDL-C • triglyceride (Fasting sample not required)	**See also Derbyshire share care pathology Dyslipidaemia and JAPC FH guidance)** **Total cholesterol (TC) concentration** • **>9.0mmol/L or non-HDL-C >7.5mmol/L** → arrange for specialist assessment (even in absence of 1st degree FH premature CHD*) • **> 7.5mmol/L + FH premature CHD*** → suspect familial hypercholesterolaemia and investigate as per NICE CG71. **Triglyceride** • **>20mmol/L** → **urgent** referal to specialist (Not due to excess alcohol or poor glycaemic control). Risk of acute pancreatitis • **Triglyceride 10-20mmol/L** →repeat with fasting test between 5-14 days later and review for 2nd causes of hyperlipidaemia. If triglyceride remains > 10mmol/L → seek specialist advice. Risk of acute pancreatitis **Triglyceride 4.5-9.9mmol/L** → risk assessment tool may underestimate CVD risk; therefore, patients should not be risk scored until review. Optimise other risk factors. *Premature coronary heart disease is defined as an event before 60 years in an index individual or first-degree relative
Creatinine Kinase (CK) Measure before starting statin if persistent generalised unexplained muscle pain	• **>5 x ULN** → re-measure at 5-7days. If still 5xULN → DO NOT start statin • **<5 x ULN** → start statin at a lower dose Do Not measure CK level in asymptomatic people who are being treated with a statin.

Liver transaminases enzymes (Alanine aminotransferase or aspartate aminotransferase)	• **<3x ULN → start statin**

Other baseline monitoring:	
HbA1c	Do not stop statin because of raised blood glucose or HbA1c
Renal function and eGFR	
Thyroid Stimulating Hormone (TSH) in people with symptoms of under/ over active thyroid	
Alcohol consumption, smoking status, BP, BMI	
Advise women to stop taking statin if pregnancy is a possibility or 3 months before attempting to conceive.	
Dose titration monitoring	
NICE recommends measuring liver transaminase and full lipid profile at: Baseline 2 to 3 months after starting lipid lowering therapy 2 to 3 months after changing lipid lowering therapy (including dose changes and/or commencement of alternative lipid lowering therapy) 12 months for liver transaminase, but not again unless clinically indicated. 12 months and annually thereafter for full lipid profile. After initiating treatment with a statin, creatine kinase only needs to be checked again if definite unexplained muscle symptoms are reported (as per above)	

Follow up

Follow-up of people commenced on statin treatment	Target
Measure full lipid profile at 2 to 3 months after starting or changing lipid lowering therapy (Measure TC, HDL-C and non-HDL-C for all patients started on high intensity statins, ezetimibe or bempedoic acid)	• Aim >40% reduction in non-HDL-C • If <40% reduction in non-HDL-C → check adherence, timing of dose, diet and lifestyle • If >40% reduction still not achieved, consider increasing the dose if patient on <80mg atorvastatin and patient is at high risk of CVD due to comorbidities or risk score or use clinical judgement**.** (Seek specialist advice if eGFR <30ml/min/1.73m^2)
Review patients taking statins annually Offer an annual full lipid profile to inform discussions about secondary prevention of CVD. Consider an annual full lipid profile to inform discussions about primary prevention of CVD.	• Discuss adherence to drugs, lifestyle modification • Consider measuring non-HDL-C (fasting sample not required) to inform discussion • Discuss with people who are stable on a low- or medium-intensity statin the likely benefits and potential risks of changing to a high-intensity statin when they have a medication review and agree with the person whether a change is needed.
Measure liver transaminases enzymes at 2 to 3 months after starting or changing lipid lowering therapy & at 12 months (alanine aminotransferase or aspartate aminotransferase)	but not again after 12 months, unless clinically indicated i.e., >3xULN
Muscle pain	Advice patients to seek medical advice if they develop muscle symptoms whilst on a statin If people report muscle pain, tenderness or weakness while taking a statin and have a CK <5 times the ULN, reassure them that their symptoms are unlikely to be due to the statin.

Drug treatments

Statins

- The decision to start statins should be made after an informed discussion between the clinicians and the person about the risks and benefits of statin treatment, taking into account factors such as potential benefits from lifestyle modifications, the presence of any comorbidities, whether they are on multiple medications, whether they are frail and their life expectancy.
- NICE has grouped the statins into three intensity categories according to the percentage reduction in LDL-cholesterol. See appendix 3
- Rosuvastatin may be considered after treatment with other first-line statins. See appendix 1.

Fibrates, bile acid sequestrants and omega-3 fatty acid compounds

Do not routinely offer fibrates, bile acid sequestrants and omega-3 fatty acid compounds, alone or in combination with a statin, for the prevention of CVD in any of the following:

- Primary or secondary prevention
- CKD
- Type 1 or type 2 diabetes

Omega-3 fatty acid compound is **GREY** after consultant lipid specialist recommendation in patients with severe hypertriglyceridaemia (triglycerides >10mmol/L) after a trial of statin ± fibrates.
Omega-3-acid ethyl ester medicines may be initiated by lipid specialists after screening for AF and risk vs benefit discussion on a case-by-case basis following the MHRA drug safety alert.

MHRA alert on omega-3-acid ethyl ester medicines including Omacor/Teromeg 1000mg capsules: dose-dependent increased risk of atrial fibrillation (AF) in patients with established cardiovascular diseases or cardiovascular risk factors. Permanent discontinuation is recommended if patients develop AF whilst taking these medicines for treatment of hypertriglyceridemia. Report all suspected adverse effects associated with omega-3-acid ethyl ester medicines via Yellow Card. Advise all patients taking these medications to seek medical attention if they develop symptoms of AF.

Nicotinic acid is now obsolete and should not be used.

Ezetimibe (JAPC classification **GREEN** as per NICE TA385 and NICE NG238)
For treating primary heterozygous-familial hypercholesterolaemia (see FH guidance) and non-familial hypercholesterolaemia.

- Monotherapy as a treatment option if statin contraindicated or not tolerated. (See appendix 1)
- In combination with a statin when lipid levels are not adequately controlled, when changing from the initial statin (atorvastatin) is being considered or further reduction in CVD risk is required for secondary prevention patients.

Bempedoic Acid (JAPC classification **GREY** as per NICE TA694)
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 with ezetimibe can be used as separate tablets or a fixed-dose combination. Bempedoic acid can cause hepatic enzyme changes/ hyperuricaemia- Manufacturer advises discontinue treatment if transaminase levels at least 3 times the upper limit of normal and persist; or in hyperuricaemia accompanied with symptoms of gout. Monitor LFT at baseline and at 3 &12 months.

Icosapent ethyl (JAPC classification **GREY** as per NICE TA 805)
Icosapent ethyl with statin is recommended as an option *for reducing the risk of cardiovascular events* in adults if they have

- Established cardiovascular disease (secondary prevention), **and**
- Raised fasting triglycerides (1.7mmol/l or above), **and**
- LDL-C above 1.04mmol/l and below or equal to 2.60mmol/l

Note contains gelatin and soya lecithin (not for people with soya or peanut allergy)

Inclisiran (JAPC classification **RED** as per NICE TA733)
Inclisiran 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 there is a history of any of the following cardiovascular events:

- acute coronary syndrome (such as myocardial infarction or unstable angina needing hospitalisation)
- coronary or other arterial revascularisation procedures
- coronary heart disease
- ischaemic stroke or
- peripheral arterial disease, ***and***

Low-density lipoprotein cholesterol (**LDL-C**) concentrations are persistently **2.6 mmol/l or more**, despite maximum tolerated lipid-lowering therapy, that is maximum tolerated statins with or without other lipid-lowering therapies or, other lipid-lowering therapies when statins are not tolerated or are contraindicated.

Inclisiran is recommended only in research for treating primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia in adults who have no history of cardiovascular events. This research is in the form of a clinical trial currently in development.

PCSK9 inhibitors- alirocumab and evolocumab (JAPC classification **RED**)
NICE TA393 and TA394 recommends alirocumab and evolocumab as an option for treating primary hypercholesterolaemia or mixed dyslipidaemia in selected patients after statin/ ezetimibe treatment have been optimised.

They are only recommended by lipid specialist and are supplied through hospital via homecare; GPs may be asked to prescribe statin in conjunction. Ensure the patients treatment is optimised before considering referral to lipid specialist for consideration of PCSK9 inhibitors.

Low-density lipoprotein cholesterol concentrations above which alirocumab/ evolocumab are recommended (as per NICE TA393 & TA394)

	Without CVD	**With CVD**	
		High risk of CVD [1]	**Very high risk of CVD [2]**
Primary non-familial hypercholesterolaemia or mixed dyslipidaemia	Not recommended at any LDL-C concentration	Recommended only if LDL-C concentration is persistently above 4.0 mmol/l	Recommended only if LDL-C concentration is persistently above 3.5 mmol/l
[1]High risk of cardiovascular disease is defined as a history of any of the following: acute coronary syndrome (such as myocardial infarction or unstable angina requiring hospitalisation), coronary or other arterial revascularisation procedures, chronic heart disease, ischaemic stroke, peripheral arterial disease. [2]Very high risk of cardiovascular disease is defined as recurrent cardiovascular events or cardiovascular events in more than 1 vascular bed (that is, polyvascular disease). Abbreviations: CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol.			

Reference

1. NICE TA 385 Ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia (February 2016)
2. NICE CG 181 Cardiovascular disease: risk assessment and reduction, including lipid modification (September 2016)
3. NICE TA 393/394 Alirocumab/Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia (June 2016)
4. NICE TA 694 Bempedoic acid with ezetimibe for treating primary hypercholesterolaemia or mixed dyslipidaemia (April 2021).
5. Cannon CP, Blazing MA, Giugliano RP et al. Ezetimibe added to statin therapy after acute coronary syndromes (IMPROVE-IT). N Engl J Med 2015; 372:2387-2397.
6. Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. BMJ 2003; 326: 1423.

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Reviewed (2022) in consultation with Dr. Stanworth, Prof Reynolds UHDB.

Document update	Date updated

Appendix 1 Myalgia while taking statins- *Supporting information for clinicians*
see also NHSE/AAC statin intolerance pathway

1. Myalgia with statins is common, affecting 5-10% of patients in clinical trials of statins. Myalgia refers to muscle pain without an increase in creatinine kinase.
2. Assess severity of symptoms. Some patients may develop mild myalgia with statins but are willing to continue treatment because of the substantial cardiovascular benefits they attain.
3. Explore other causes of the myalgia, such as viral illness or hypothyroidism.
4. Check for any medications (including grapefruit juice) that might have interacted with the statin.
5. Check serum creatine kinase concentration and thyroid function. A clinically significant raised creatine kinase is defined as a concentration above 10 times the upper limit of normal and is a risk factor for rhabdomyolysis, which is a medical emergency. The statin should be stopped immediately. Modestly raised creatine kinase concentrations (under five times the upper limit of normal) are common and may be related to exercise. A creatine kinase concentration below this level is rarely clinically significant. NICE CG181 recommends re-measure after 7 days if CK >5X upper limit and stopping statin if CK still >5x upper limit.
6. If creatine kinase is not significantly raised, discuss a re-challenge with a statin at a lower dose.
7. For true intolerance try an alternative statin. e.g., simvastatin 10mg, pravastatin 10mg (titrating up to 40mg), or rosuvastatin 5mg.
8. If higher intensity statins are being considered appropriate, start with a low dose and titrate slowly. Treatment with a low dose statin started once weekly and then gradually titrated at monthly intervals has been an effective strategy in some case series of patients with myalgia induced by statins. Some people may only tolerate alternate day statins.
9. If myalgia recurs with low doses of statin or other statins, try non-statin treatment. NICE TA385 recommends ezetimibe 10 mg daily monotherapy as an option for the treatment of adults with hypercholesterolaemia who would otherwise be started on a statin but are intolerant. (Intolerance defined as the presence of clinically significant adverse effects that represent an unacceptable risk to the patient or that may reduce compliance with therapy)
10. Statin associated necrotising autoimmune myopathy is a rare condition in which discontinuation of the statin does not lead to recovery, and immunosuppression may need to be considered. Referral to a neurologist specialising in myopathy is required.

Source BMJ 2012;345:e5348 doi: 10.1136/bmj.e5348

Rosuvastatin (Green 2nd line to atorvastatin)
Local consultant advice rosuvastatin may be a treatment option in patients with:

- **Complete intolerance*** of atorvastatin due to myalgia. Less than once daily dosing strategy may be adopted (which includes atorvastatin 10mg every other day). Rosuvastatin to be prescribed initially 5mg less than daily and titrated to 5mg daily if possible. Tolerance of higher doses is not likely but can be tried.

- **Partial tolerance*** of other statins at low-moderate doses (simvastatin 40mg, pravastatin 40mg and atorvastatin 20mg max tolerated dose) but not reaching target 40% reduction in non-HDL lipids- In

these patients it is appropriate to commence rosuvastatin with titration to maximum tolerated/ minimum necessary dose to achieve target reduction (dose range 5mg-40 mg daily).

- Patients >70 years of age - start dose of 5 mg is recommended
- Patients of Asian ancestry- recommended start dose 5mg; 40mg dose contraindicated.
- Mild to moderate renal impairment- no dose adjustment necessary
    - Moderate renal impairment (CrCl <60ml/min)- recommended start dose 5mg; 40mg dose contraindicated.
    - Severe renal impairment (CrCl<30ml/min)- contraindicated for all doses
- An assessment of renal function should be considered during routine follow-up of patients treated with a dose of 40mg

* Intolerance is defined as the presence of clinically significant adverse effects that represent an unacceptable risk to the patient or that may reduce compliance with therapy.

Appendix 2 Lifestyle advice

- At initial assessment and at each review assess modifiable risk factors and the patient's readiness to change.
- Give tailored advice in line with NICE Public Health Guidance 6 Behaviour Change https://www.nice.org.uk/guidance/ph6
- For all areas of behaviour change offer brief advice and referral to specialist services if appropriate

Cardioprotective diet

- Advise people at high risk of or with CVD to eat a diet in which total fat intake is 30% or less of total energy intake, saturated fats are 7% or less of total energy intake, and where possible saturated fats are replaced by mono-unsaturated and polyunsaturated fats, such as olive and rapeseed oil.
- Increase wholegrain, reduce sugar including fructose, aim for 5 fruits/ vegetables per day, 2 portions of fish and 4-5 portions of nuts/ seeds/ pulses per week.

Physical Activity

- Advise 150 minutes of moderate intensity or 75 minutes of vigorous intensity aerobic exercise per week.
- Advise muscle strengthening exercise on at least 2 days per week.
- Agree goals and provide written information in line with NICE Public Health Guidance 2 https://www.nice.org.uk/guidance/PH2

Weight

- Ensure advice is given in line with NICE Guidance 43 https://www.nice.org.uk/guidance/cg43

Alcohol

- Assess using the AUDIT questionnaire
- Advise that the safe limits for alcohol are 14 units per week over at least 3 days for men& women

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Smoking

- Give advice consistent with NICE Public Health Guidance 10 http://www.nice.org.uk/guidance/ph10
- Provide support and pharmacotherapy for those who do not wish to be referred.

Appendix 3- statin intensity (as defined by NICE NG238)

Above 40%	High intensity	atorvastatin 20-80mg rosuvastatin 10-40mg
30-40%	Medium intensity	atorvastatin 10mg rosuvastatin 5mg simvastatin 20-40mg Fluvastatin 80mg
20-30%	Low intensity	simvastatin 10mg pravastatin 5-40mg Fluvastatin 20-40mg

Drug	Daily dose (mg)				
	5	10	20	40	80
Fluvastatin			21%	27%	33%
Pravastatin		20%	24%	29%	
Simvastatin		27%	32%	37%	42%*
Atorvastatin		37%	43%	49%	55%
Rosuvastatin	38%	43%	48%	53%	-

% = percentage reduction in LDL cholesterol

*Advice from the MHRA: there is an increased risk of myopathy associated with high-dose (80mg) simvastatin. This dose should only be considered in patients with severe hypercholesterolaemia and high risk of cardiovascular complications who have not achieved their treatment goals on lower doses, when the benefits are expected to outweigh the potential risks.

This table is based on: Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. BMJ 2003; 326: 1423.

Appendix 4 Simvastatin and Atorvastatin drug interactions

Please refer to the current BNF or SPC for a full and up-to-date list of drug interactions

agents	Simvastatin	Atorvastatin
Ketoconazole Posaconazole Erythromycin Telithromycin Itraconazole Clarithromycin	Contraindicated	Avoid if possible; consider temporary suspension of atorvastatin if interacting drug is taken for a short period. If unavoidable a lower starting and maximum doses of atorvastatin should be considered and appropriate clinical monitoring is recommended. See SPC for maximum doses.
Miconazole oral gel (See SPS- Using miconazole oral gel to treat oral thrush in adults taking a statin)	Do not use miconazole in combination with simvastatin. Instead use a different antifungal, e.g., nystatin. If essential to use miconazole, simvastatin must be temporarily stopped whilst the individual is using miconazole.	Do not use miconazole oral gel, if possible. Instead use a different antifungal, e.g., nystatin. If miconazole oral gel must be used, it may be prudent to: • temporarily withhold atorvastatin, whilst the individual is using miconazole, to avoid possible adverse effects or, • use a lower dose of atorvastatin and monitor for toxicity.
Ciclosporin	Contraindicated	Maximum dose 10mg daily atorvastatin
Danazol	Contraindicated	No specific recommendation
HIV protease inhibitors	Contraindicated	Avoid if possible. See SPC for maximum recommended doses
Gemfibrozil	Contraindicated	Lower starting dose and clinical monitoring is recommended
Other fibrates	Do not exceed 10 mg simvastatin daily (except fenofibrate)	Lower starting dose and clinical monitoring is recommended
Ezetimibe	Additive risk of myopathy can't be ruled out	Additive risk of myopathy cannot be ruled out
Amlodipine	Do not exceed 20 mg simvastatin daily	No specific recommendation
Amiodarone	Do not exceed 20 mg simvastatin daily	Consider lower maximum dose;

Verapamil Diltiazem		appropriate clinical monitoring is required
Fusidic acid (systemic)	Patients should be closely monitored. Temporary suspension of simvastatin treatment may be considered.	Concurrent use is not recommended. Temporary suspension of atorvastatin may be considered.
Grapefruit juice	Avoid grapefruit juice when taking simvastatin	Concomitant intake of large quantities of grapefruit juice and atorvastatin is not recommended

Appendix 5 Common secondary causes of dyslipidaemia

- Excess alcohol intake: Counsel patients on safe limits of drinking alcohol and signpost to alcohol services (where required)
- Uncontrolled diabetes: Ensure ongoing review of diabetes management from primary care (or secondary care where warranted) and refer to diabetes specialist/nurse for further support if required.
- Hypothyroidism: optimise thyroid control through treatment and monitoring
- Liver disease: includes alcoholic-related liver disease, non-alcoholic fatty liver disease, hepatitis, haemochromatosis and primary biliary cholangitis. Refer to specialist.
- Nephrotic Syndrome: offer dietary advice and review treatment options with GP/nephrologist.
- Obesity: Offer support through health and wellbeing coaches or signpost to weight management programmes