

## **FATS7**

### ***A strategy for the use of cholesterol lowering drugs in Newcastle, North Tyneside and Northumberland***

**A summary of the evidence used to develop FATS7 from FATS6**

***The recommendations are presented in summary form as a quick reference  
guide on the first page after the index***

FATS Steering Group December 2014  
(Appendices updated November 2016)

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- This is a lipid lowering drug strategy. It should be used as part of an overall management plan, discussed and agreed with the patient.
- It is assumed that people with contraindications / drug interactions will be identified and excluded (refer to the BNF/SPCs).
- This summary should be used with the supporting notes / appendices

**All people being considered for statin treatment (for doses see below)**

- Measure lipid profile (total cholesterol, HDL cholesterol, non-HDL cholesterol, triglycerides). Fasting is not required.
- Measure ALT. Measure CK if unexplained muscle pain.
- If ALT < 3 x normal, CK normal (if measured) prescribe statin

**Routine monitoring in all patients (primary and secondary prevention)**

- Measure total cholesterol, HDL-C and non-HDL cholesterol at 3 and 12 months, then annually, ALT after 3 months and 12 months.
- If non-HDL cholesterol reduction < 40%, discuss treatment concordance, lifestyle measures, consider increasing dose of atorvastatin if not maximal.
- Ensure annual review

**People with symptomatic or prior occlusive vascular disease**

- **Drug flow:** start Atorvastatin 80 mg od, **but:**
- Reconsider choice and or statin dose if there are drug interactions / intolerances / CKD / increased risk of adverse effects – see extra notes

**Primary prevention in groups not requiring 10 year cvd risk assessment**

**Type 1 diabetes:** all adults ( $\geq 18$  years) should be considered for statin treatment and in particular, target those with:

- Microalbuminuria/proteinuria
- Aged > 40 years
- Had diabetes for > 10 years
- Established nephropathy
- Other cardiovascular risk factors (use clinical judgement)

**CKD** (see NICE / local CKD guideline for diagnosis): offer statin treatment for primary and secondary prevention

**Drug flow:** Atorvastatin 20 mg od (discuss with specialist if eGFR < 30 ml/min/1.73m<sup>2</sup>) if no interactions/intolerances/increased risk of adverse effects, and titrate as appropriate

**Familial hypercholesterolaemia:** see appendix 2

**Primary prevention in all others (no occlusive vascular disease, Type 1 diabetes, or CKD)****Type 2 diabetes**

- Assess 10 year cardiovascular risk using QRISK2
- Offer statin treatment if 10 year cardiovascular risk  $\geq 10\%$
- Ensure lifestyle measures are optimised

**Primary prevention (no diabetes, CKD or occlusive vascular disease)**

- Assess 10 year cardiovascular disease risk using QRISK2
- Undertake a full clinical assessment and support lifestyle modification
- Discuss and agree about statin treatment if 10 year cardiovascular risk  $\geq 10\%$  and lifestyle modifications are ineffective or inappropriate

**Additional risk factors**

Consider additional risk factors when considering drug treatment, together with the QRISK2 risk score, when estimating 10 year CVD risk, notably people:

- Treated for HIV
- With severe mental illness
- Taking medicines that can cause dyslipidaemia (eg antipsychotics, corticosteroids, immunosuppressants)
- With systemic autoimmune disorders or other systemic inflammatory conditions (eg SLE)
- With impaired fasting hyperglycaemia
- Who have made recent changes eg quit smoking, treated BP, lipids etc

**Drug flow**

- Start Atorvastatin 20 mg od (discuss with specialist if eGFR < 30 ml/min/1.73m<sup>2</sup>), if no interactions/intolerances/increased risk of adverse effects, and titrate as appropriate

**Additional notes (see full supporting notes / appendices):**

1. People intolerant of recommended statin – see appendix 3
2. Consider FH if TC > 7.5 mmol/l - see appendix 2. Do not use QRISK2
3. If triglycerides > 4.5 mmol/l: see notes
4. Consider secondary causes of hyperlipidaemia – alcohol / thyroid / diabetes / nephrotic syndrome / liver disease / drug induced
5. If ALT raised at baseline, refer to local LFT guidelines.
6. Patients already treated with statins – review percent reduction in non-HDL cholesterol from baseline, consider switching to / uptitrating atorvastatin
7. Treatment in general frailty and older people; see supporting notes

FATS7 developed in the light of monitoring of FATS1, 2, 3, 4, 5 & 6

Agreed with Primary and Secondary Care Users North of Tyne, incorporating the NICE Lipid modification GL

## INTRODUCTION

FATS6 has been reviewed to develop FATS7 following publication of the updated NICE lipid modification guideline. The underpinning principles remain the same in that FATS7 is evidence based, whilst also taking into consideration the need for implementation and cost.

This is not intended to duplicate the NICE lipid modification guideline (CG181)<sup>1</sup>, but rather to summarise and obtain a shared understanding between clinicians locally to support implementation. Clinicians are also encouraged to read the NICE guideline.

***FATS is a drug treatment strategy and should only be implemented within an overall management plan which has been discussed and agreed with the patient.***

*FATS advice is based **on risk** not **cholesterol**, discuss **risk** not just **cholesterol***

During the discussion about FATS7 the importance of a meaningful discussion between the clinician and the patient when considering management of cardiovascular risk, including the benefits and risks of starting and or up-titrating statin treatment, was emphasised. This was considered to be an important part of the implementation, but extended beyond discussion about statins, and the details about this are not part of the scope of this guideline.

The NICE guideline recommends atorvastatin as the first line statin, not simvastatin. Comparative costs of these and other statins are included in [appendix 1](#).

The previous supplementary guidance to aid in the identification of patients with possible familial lipid disorders has also been updated, and is included in [appendix 2](#).

More detailed recommendations for the recognition and management of statin intolerance have also been developed, and are included in [appendix 3](#).

Appendix 3 also includes [details](#) of average LDL cholesterol lowering with different intensity statins.

FATS7 is intended for all clinicians in the Newcastle, North Tyneside, Northumberland areas involved in treating people for primary and secondary prevention of cardiovascular disease, including coronary disease, cerebro-vascular disease and peripheral arterial disease, and implemented as part of a wider management plan.

A [summary](#) of the recommendations that can be printed is included at the beginning. This can be laminated if that is required (folded as a double sided A5 or as a single sided A4 sheet). The [supporting notes](#) provide additional information.

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<sup>1</sup> <http://www.nice.org.uk/guidance/cg181>

## SUPPORTING NOTES

- **This is a lipid lowering drug strategy. It should be used as part of an overall management plan which is discussed and agreed with the patient.**

All patients should have the opportunity for an assessment and informed discussion about management of their cardiovascular risk, with a healthcare professional with the appropriate skills and knowledge to do that. Details of that are beyond the scope of this guideline, and clinicians should refer to the NICE lipid modification guideline and other local guidance.

- **It is assumed that people with contraindications / drug interactions will be identified and excluded (refer to the BNF/SPCs).**

Statins and fibrates are contra-indicated in pregnancy. In all women in whom pregnancy is possible, the following should be specifically clarified before starting treatment; whether pregnant, contraceptive status and future pregnancy plans or possibility of pregnancy.

Reference should be made to the BNF and relevant SPCs, and the MHRA have previously published recommendations for interactions with simvastatin<sup>2</sup> (see table on [page 11](#))

The SPC for atorvastatin (available at <http://www.medicines.org.uk/emc/medicine/1424>) states that concomitant treatment with medicinal products that are inhibitors of CYP3A4 or transport proteins may lead to increased plasma concentrations of atorvastatin and an increased risk of myopathy.

Potent CYP3A4 inhibitors include ciclosporin, telithromycin, clarithromycin, delavirdine, stiripentol, ketoconazole, voriconazole, itraconazole, posaconazole and HIV protease inhibitors. If co-administration of these medicinal products with atorvastatin cannot be avoided lower starting and maximum doses of atorvastatin should be considered as recommended in the SPC, with appropriate clinical monitoring.

Moderate CYP3A4 inhibitors include erythromycin, diltiazem, verapamil and fluconazole and may increase plasma concentrations of atorvastatin and a lower maximum dose of atorvastatin should be considered eg atorvastatin 40 mg daily, with appropriate clinical monitoring.

### **All people being considered for statin treatment (for doses see below)**

- Measure lipid profile (total cholesterol, HDL cholesterol, non-HDL cholesterol, triglycerides). Fasting is not required.
- Measure ALT. Measure CK if unexplained muscle pain.
- If ALT < 3 x normal, CK normal (if measured) prescribe statin

### **Routine monitoring in all patients (primary and secondary prevention)**

- Measure total cholesterol, HDL-C and non-HDL cholesterol at 3 and 12 months, then annually, ALT after 3 months and 12 months.

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<sup>2</sup> Drug Safety Update Aug 2012 vol 6, issue 1: S1

- If non-HDL cholesterol reduction < 40%, discuss treatment concordance, lifestyle measures, consider increasing dose of atorvastatin if not maximal.
- Ensure annual review

This is self explanatory and is concordant with the recommendations in the NICE lipid modification guideline.

A fasting sample is not required to measure the initial lipid profile. All people presenting with ACS/acute MI should also have a full lipid profile measured on presentation, taking note of the timing of the sample from the onset of symptoms, but this should not delay initiation of treatment.

The NICE guideline recommends using non-HDL cholesterol to monitor response, using a percent reduction rather than the same target for all patients. Calculation of a 40% reduction in non-HDL cholesterol for each patient should be included as part of the initial discussion with the patient when agreeing the management plan and treatment with a statin.

NICE recommend that all patients, whether treated for primary or secondary prevention, have the response to statins monitored with further review and discussion about concordance and lifestyle behaviours, and possible up titration of atorvastatin dose, when the reduction in non-HDL cholesterol is less than 40%.

Past iterations of FATS have not recommended monitoring LFTs on treatment, unless patients are treated with high dose statins or if clinically indicated. However, as more patients are likely to be treated with a high dose statin, and to be compliant with the NICE guideline, measurement of ALT is recommended at 3 and 12 months, at the same time as the lipid profile will be measured, without further monitoring of LFTs thereafter unless clinically indicated.

As noted in FATS6, the main purpose of measuring ALT before treatment is to identify people with abnormal results prior to starting drug treatment, but *not* to exclude them from treatment. Fatty liver is one cause of a raised ALT and is not an indication to exclude people from treatment, and cardiovascular risk modification is an important aspect of their management. Clinicians should refer to the local LFT guideline for further information. In some people with raised liver enzymes a lower dose of statin may be started initially.

Members of the FATS group in the past felt that statins were sometimes inappropriately stopped in people who develop abnormal LFTs, and clinical status, repeat blood testing and other causes of abnormal LFTs (refer to the local guideline) should often be considered first before statins are stopped.

Routine measurement of CK is not recommended, but should be considered before starting a statin in patients with unexplained muscle pain (although will not be meaningful in patients with an acute MI).

- If the CK is more than 4 times upper limit of normal<sup>3</sup>, the CK should be re-measured after 7 days and if still more than 4 times upper limit of normal, statin treatment should not be started and specialist advice obtained.

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<sup>3</sup> 4 fold increase in CK is used, recognising the current 'normal levels' reported by local biochemistry labs (not 5 fold as included in NICE guidance)

- If the CK levels are raised but less than 4 times normal, a statin can be started at a lower dose ([see appendix 3](#)).

#### **People with symptomatic or prior occlusive vascular disease**

- **Drug flow:** start Atorvastatin 80 mg od, **but:**
- Reconsider choice and or statin dose if there are drug interactions / intolerances / CKD / increased risk of adverse effects – see extra notes

This is self explanatory. Occlusive vascular disease includes people with coronary heart disease, atheromatous stroke disease and people with peripheral arterial disease. When starting treatment with atorvastatin in patients with established vascular disease, atorvastatin 80 mg od is first line, unless there are concerns about tolerability or interactions.

A lower dose of atorvastatin may be considered initially in patients with co-morbidity which increases the risk of adverse side effects or who are taking other drugs that interact with the statin, with a view to titration dependent on response and tolerability. In some cases the maximum dose may also be lower. This may include patients who are older, have a lower body weight and with other conditions such as CKD or conditions which increase the risk of muscle side effects. Previous iterations of FATS have identified the following groups:

- CKD with eGFR  $\leq 30$  ml/min/1.73m<sup>2</sup>
- Older people particularly those who are frail and or have a low muscle mass
- Untreated muscle disorder, or other conditions which may be associated with 'vulnerable' muscles eg PMR (CK measurement recommended at baseline in these groups, but not in all people)
- Untreated hypothyroidism (until corrected)
- Alcohol abuse

The BNF and SPC provide details of potential drug interactions, and some information is also included above.

#### **Primary prevention in groups not requiring 10 year cvd risk assessment**

**Type 1 diabetes:** all adults ( $\geq 18$  years) should be considered for statin treatment and in particular, target those with:

- Microalbuminuria/proteinuria
- Aged > 40 years
- Had diabetes for > 10 years
- Established nephropathy
- Other cardiovascular risk factors (use clinical judgement)

**CKD** (see NICE / local CKD guideline for diagnosis): offer statin treatment for primary and secondary prevention

**Drug flow:** Atorvastatin 20 mg od (discuss with specialist if eGFR < 30 ml/min/1.73m<sup>2</sup>) if no interactions/intolerances/increased risk of adverse effects, and titrate as appropriate.

**Familial hypercholesterolaemia:** see [appendix 2](#).

These recommendations are consistent with those in the NICE lipid modification guideline, and a 10 year cardiovascular risk assessment with a risk assessment tool is not required to inform the decision to offer statin treatment in those with Type 1 diabetes and or CKD (recommendations for making a diagnosis of CKD are available in the associated NICE guideline for chronic kidney disease and from local CKD guidelines). The initial recommended dose of atorvastatin is 20 mg od, unless there are concerns about tolerability or drug interactions (see above) and the NICE lipid



modification guideline recommends discussing with a specialist if the eGFR is < 30 ml/min/1.73m<sup>2</sup> ie CKD 4 and 5.

**Primary prevention in all others (no occlusive vascular disease, Type 1 diabetes, or CKD)**

**Type 2 diabetes**

- Assess 10 year cardiovascular risk using QRISK2
- Offer statin treatment if 10 year cardiovascular risk  $\geq$  10%
- Ensure lifestyle measures are optimised

**Primary prevention (no diabetes, CKD or occlusive vascular disease)**

- Assess 10 year cardiovascular disease risk using QRISK2
- Undertake a full clinical assessment and support lifestyle modification
- Discuss and agree about statin treatment if 10 year cardiovascular risk  $\geq$  10% and lifestyle modifications are ineffective or inappropriate

**Additional risk factors**

Consider additional risk factors when considering drug treatment, together with the QRISK2 risk score, when estimating 10 year CVD risk, notably people:

- Treated for HIV
- With severe mental illness
- Taking medicines that can cause dyslipidaemia (eg antipsychotics, corticosteroids, immunosuppressants)
- With systemic autoimmune disorders or other systemic inflammatory conditions (eg SLE)
- With impaired fasting hyperglycaemia
- Who have made recent changes eg quit smoking, treated BP, lipids etc

**Drug flow**

- Start Atorvastatin 20 mg od (discuss with specialist if eGFR < 30 ml/min/1.73m<sup>2</sup>), if no interactions/intolerances/increased risk of adverse effects, and titrate as appropriate

The recommendations in the updated NICE guideline have led to a substantial revision in FATS7 compared to FATS6. Statins are not now recommended routinely for patients with type 2 diabetes aged over 40 years, but rather that those with Type 2 diabetes have a 10 year cardiovascular risk assessment first. However, those with CKD (those with albuminuria or with eGFR <60 ml/min/1.73m<sup>2</sup> with or without albuminuria), should be considered to be at greater risk of cardiovascular disease, and routinely be offered statins (see above).

NICE have maintained the recommendation to use a 10 year cardiovascular disease risk assessment, rather than a lifetime risk assessment and have specifically recommended that the QRISK2 tool (available at <http://www.qrisk.org/>) is used in those up to and including 84 years of age. QRISK2 incorporates more risk factors than other tools such as Framingham for example. However, there are some conditions which are not incorporated, including those noted in the summary. These were also recognised in FATS6.

An initial assessment of patients being considered for treatment with statins for primary prevention should include as a minimum;

- Smoking status
- Alcohol consumption
- Blood pressure
- BMI and or other measures of obesity
- Non-fasting lipid profile ((total cholesterol, HDL cholesterol, non-HDL cholesterol, triglycerides)
- HbA1c



- Renal function and eGFR
- Family history of premature coronary disease
- Ethnicity
- Socioeconomic status
- Secondary causes of dyslipidaemia (see below)
- A review to ensure there are no symptoms to suggest undiagnosed vascular disease which warrants further investigation.

The initial recommended dose of atorvastatin is 20 mg od, unless there are concerns about tolerability or drug interactions (see above).

**Additional notes (see full supporting notes / appendices):**

1. People intolerant of recommended statin – see [appendix 3](#)
2. Consider FH if TC > 7.5 mmol/l - see [appendix 2](#). Do not use QRISK2.
3. If triglycerides > 4.5 mmol/l: see notes
4. Consider secondary causes of hyperlipidaemia – alcohol / thyroid / diabetes / nephrotic syndrome / liver disease / drug induced
5. If ALT raised at baseline, refer to local LFT guidelines.
6. Patients already treated with statins – review percent reduction in non-HDL cholesterol from baseline, consider switching to / uptitrating atorvastatin
7. Treatment in general frailty and older people; see supporting notes

1. Previous iterations of FATS have made some recommendations about managing statin intolerance. This has now been further developed to support implementation of FATS7 and is now included as [appendix 3](#).

2. A pathway for assessment of patients with lipid profiles which could be consistent with a familial disorder was developed as an appendix to FATS5 and maintained unchanged for FATS6. This has been updated at the same time as FATS7 has been developed and is included as [appendix 2](#).

3. Serum triglyceride concentrations are affected by the fasting status and if non fasting triglycerides are greater than 4.5 mmol/l a fasting measurement should be considered. All patients with raised triglycerides should be reviewed for secondary causes, including excess alcohol consumption, poor glycaemic control in diabetes and adverse effects of other co-prescribed drugs. If secondary causes are identified, these should be addressed, but if no secondary cause is found or their modification is limited, referral should be made for urgent specialist review if the triglycerides are above 20 mmol/l.

In patients with an initial triglyceride concentration between 10 and 20 mmol/l, a repeat fasting measurement should be made after an interval which is more than 5 days, but within 2 weeks together with a review for secondary causes as above. If the fasting measurement remains above 10 mmol/l specialist advice should be obtained.

In patients with triglyceride measurements between 4.5 mmol/l and 9.9 mmol/l, cardiovascular risk may be underestimated by the risk assessment tools. Cardiovascular risk factors should be optimised, in particular lifestyle changes. If the non-HDL cholesterol is more than 7.5 mmol/l specialist advice should be obtained.

Fibrates, either alone or in combination with a statin, may be appropriate in patients with severe hypertriglyceridaemia at risk of pancreatitis, but are no longer routinely

recommended for cardiovascular disease prevention, including those with Type 2 diabetes. Patients currently treated with fibrates should be reviewed, the impact of additional treatment examined and a decision made whether the benefit of continuing treatment is justified.

4. The recommendation to exclude secondary causes of dyslipidaemia is consistent with previous iterations of FATS and the updated NICE lipid modification guideline. All people with dyslipidaemia being considered for lipid lowering drug treatment should have secondary causes of dyslipidaemia excluded. The table below describes some of the causes of secondary dyslipidaemia.

### Secondary causes of dyslipidaemias

Poor diet, some “fad diets” and lack of physical activity will have an adverse effect on the lipid profile. Other causes include:

Condition / drug treatment	Lipid change		
	Cholesterol	Triglycerides	HDL cholesterol
Diabetes mellitus		++/+	-
Untreated hypothyroidism	++		
Alcohol excess		++/+	+
Obesity		+	-
Chronic renal failure	+	++	-
Nephrotic syndrome	++	+	
Cholestasis	++		
Gout		+	
Pregnancy	+/-	+/++	
Anorexia nervosa	+		
Hypopituitarism	+/////	++/+	-
<b>Long term drug treatment</b>			
Anticonvulsants			+/++
Androgens			-/--
Atypical antipsychotics	+/////	+/////	-
Beta blockers		+	
Corticosteroids	+	+	-
Ciclosporin	+	+	-
HIV/anti-retroviral drugs		+/++	
Oral oestrogens		+	+
Retinoids		++/+	-

6. The local LFT guideline should be referred to if the ALT is raised.

7. Percent reduction in non-HDL cholesterol from baseline should be assessed wherever possible in patients already treated with statins. Patients treated with an alternative statin, other than atorvastatin, such as simvastatin and a non-HDL cholesterol reduction of less than 40% from baseline, should be considered for switching to atorvastatin, and in those already treated with atorvastatin for up-titration of dose. In all patients concordance with treatment and lifestyle measures should be reviewed and encouraged.

Simvastatin 80 mg od was not recommended in FATS6, due to the increased risk of myopathy. However, there may be some patients still treated with this and if so, these patients should be reviewed and switched to atorvastatin 40 to 80 mg od. In patients maintained on a lower dose of simvastatin, the maximum dose co-prescribed with other agents should be consistent with the recommendations from the MHRA<sup>4</sup>, and a summary table of some drugs is included below. Further information about interactions with atorvastatin is included on [page 5](#).

All statins are contra-indicated in pregnancy.

<b>DRUG INTERACTIONS WITH SIMVASTATIN ASSOCIATED WITH AN INCREASED RISK OF MYOPATHY / RHABDOMYOLYSIS (FROM MHRA 2012)</b>	
<b>INTERACTING AGENTS</b>	<b>PRESCRIBING RECOMMENDATIONS</b>
Itraconazole Ketoconazole Posaconazole Erythromycin Clarithromycin Telthromycin HIV protease inhibitors eg nelfinavir Nefazodone Ciclosporin Danazol Gemfibrozil	Contra-indicated with simvastatin. Do not co-prescribe
Other fibrates (except fenofibrate) Dronedarone	Do not exceed simvastatin 10 mg daily
Amiodarone Amlodipine Diltiazem Verapamil	Do not exceed simvastatin 20 mg daily
Fusidic acid	Patients should be closely monitored. Temporary suspension of simvastatin treatment may be considered.
Grapefruit juice	Avoid grapefruit juice when treated with simvastatin.

### **Treatment in older people; see supporting notes**

This was discussed for FATS4 and has been maintained since with some notable additions. The following was noted during the initial discussion when developing FATS4;

- Life expectancy in people of different ages (this included all people, not just those who are well) was reviewed. At the age of 80 years, the average life expectancy in men is about 7 years and in women 9 years. At the age of 90 years, the average life expectancy in both men and women is about 4 years
- People who are older are more likely to have a circulatory death than those who are younger. If statins are of benefit, that benefit may be greater in an older person than a younger
- Correcting for frailty, co-morbidity and first year events, cholesterol is a risk factor in older people
- The statin trials show no trend suggesting a difference in efficacy of statin treatment with older age

<sup>4</sup> Drug Safety Update Aug 2012 vol 6, issue 1: S1

The updated NICE lipid modification guideline has recommended the use of QRISK2 to estimate 10 year cardiovascular disease risk in those aged up to and including the age of 84 years. The NICE guideline has further recommended that people aged 85 years and older are at increased risk of cardiovascular disease because of age alone, particularly people who smoke or have raised blood pressure, and that atorvastatin 20 mg od may be of benefit in reducing the risk of non-fatal MI.

Members of the FATS group expressed concern about the potential for indiscriminate prescribing of statins in older people, in particular the use of high dose statins, given the increased risk of adverse effects in older people, and the lack of evidence showing reduced mortality in the very elderly. However, equally of concern is that older people may be denied access to treatment, purely on the basis of their age, and older patients should be assessed for the likely benefit based on such factors as life expectancy, underlying conditions increasing cardiovascular risk and individual patient preferences as well as factors which increase the risk of adverse effects, including general frailty, co-morbidities and polypharmacy. When statins are prescribed, a lower dose than that recommended routinely may be appropriate.

# APPENDICES

## Appendix 1

### Examples of statin / ezetimibe costs - 28 days (December 2014)

Simvastatin 10 mg od	£0.90
Simvastatin 20 mg od	£0.98
Simvastatin 40 mg od	£1.23
Atorvastatin 10 mg od	£1.19
Atorvastatin 20 mg od	£1.45
Atorvastatin chewable 20 mg od (30)	£26.40
Atorvastatin 40 mg od	£1.67
Atorvastatin 80 mg od	£2.68
Pravastatin 40 mg od	£2.00
Rosuvastatin 5 mg od	£18.03
Rosuvastatin 10 mg od	£18.03
Rosuvastatin 20 mg od	£26.02
Rosuvastatin 40 mg od	£29.69
Ezetimibe 10 mg od	£26.31



*The NHS in Newcastle, North Tyneside  
and Northumberland*

**People with possible or definite familial  
hypercholesterolaemia (FH); supplementary  
guidance to FATS**

***To be read in conjunction with current iteration of FATS***

FATS Steering Group December 2014

## **Background and definition of Familial Hypercholesterolaemia (FH)**

It is estimated that about 4% of the primary care population will have hypercholesterolaemia with total cholesterol > 7.5 mmol/l and or LDL cholesterol > 4.9 mmol/l. About 1 in 20 of these will have FH. FH is a condition which shows an autosomal dominant pattern of inheritance within families (half of first degree and a quarter of second degree relatives will also be affected) and is associated with a very high risk of premature coronary heart disease if left untreated (>20% of males before 40 years, 50% by 50 years; 50% of females by age 60 years). The concentration of LDL cholesterol is doubled from birth in those affected, but primary prevention with lifestyle changes and statin treatment (to reduce LDL-C by >50%) is effective in reducing mortality to population levels or below. The estimated prevalence of FH in the UK population is 1 in 500 or a total of 6000 in the North East, of whom it is estimated that currently less than 1000 have been identified and treated.

The Simon Broome criteria are used for a clinical diagnosis of familial hypercholesterolaemia (FH). That is in adults;

### ***Definite FH***

Total cholesterol > 7.5 mmol/l (either pre-treatment or highest on treatment) in adults over 16 years, or LDL cholesterol > 4.9 mmol/l  
*plus*

Either tendon xanthomata in the person or 1<sup>st</sup> or 2<sup>nd</sup> degree relative and/or DNA-based evidence of an LDL receptor mutation or familial defective apoB-100.

### ***Possible FH***

Total cholesterol > 7.5 mmol/l (either pre-treatment or highest on treatment) in adults over 16 years, or LDL cholesterol > 4.9 mmol/l  
*plus one of the following*

Family history of myocardial infarction before age 50 years in 2<sup>nd</sup> degree relative or before 60 years in 1<sup>st</sup> degree relative

Family history of raised total cholesterol > 7.5 mmol/l in 1<sup>st</sup> or 2<sup>nd</sup> degree relative.

Non-HDL cholesterol thresholds are also included and is a valid measure from non fasting samples.

## **Diagnosis and management of people with total cholesterol greater than 7.5 mmol/l and or LDL cholesterol > 4.9 mmol/l, and or non HDL cholesterol > 5.9 mmol/l**

### **Introduction**

This is additional guidance developed to supplement FATS. It specifically makes recommendations for the assessment and management of all people with a total cholesterol > 7.5 mmol/l and or a LDL cholesterol > 4.9 mmol/l, and or non HDL cholesterol > 5.9 mmol/l. FATS already recognises that such people should be further assessed for a diagnosis of Familial Hypercholesterolaemia (FH). The current document also includes guidance about how people with possible or definite FH can be identified and distinguished from others with a high cholesterol to facilitate targeted family cascade screening taking into account the recommendations in the



NICE clinical guideline 71, Identification and management of familial hypercholesterolaemia<sup>5</sup>.

The [flow chart](#) below outlines the steps to take when a total cholesterol > 7.5 mmol/l and or LDL cholesterol > 4.9 mmol/l and or non-HDL cholesterol > 5.9 mmol/l is found and identifies which patients should be referred to the lipid clinic.

[A referral form](#) to refer a patient with possible familial hypercholesterolaemia or other suspected familial lipid disorder to the lipid clinic is included below. Patients referred for other reasons, such drug intolerance, should be referred by written letter.

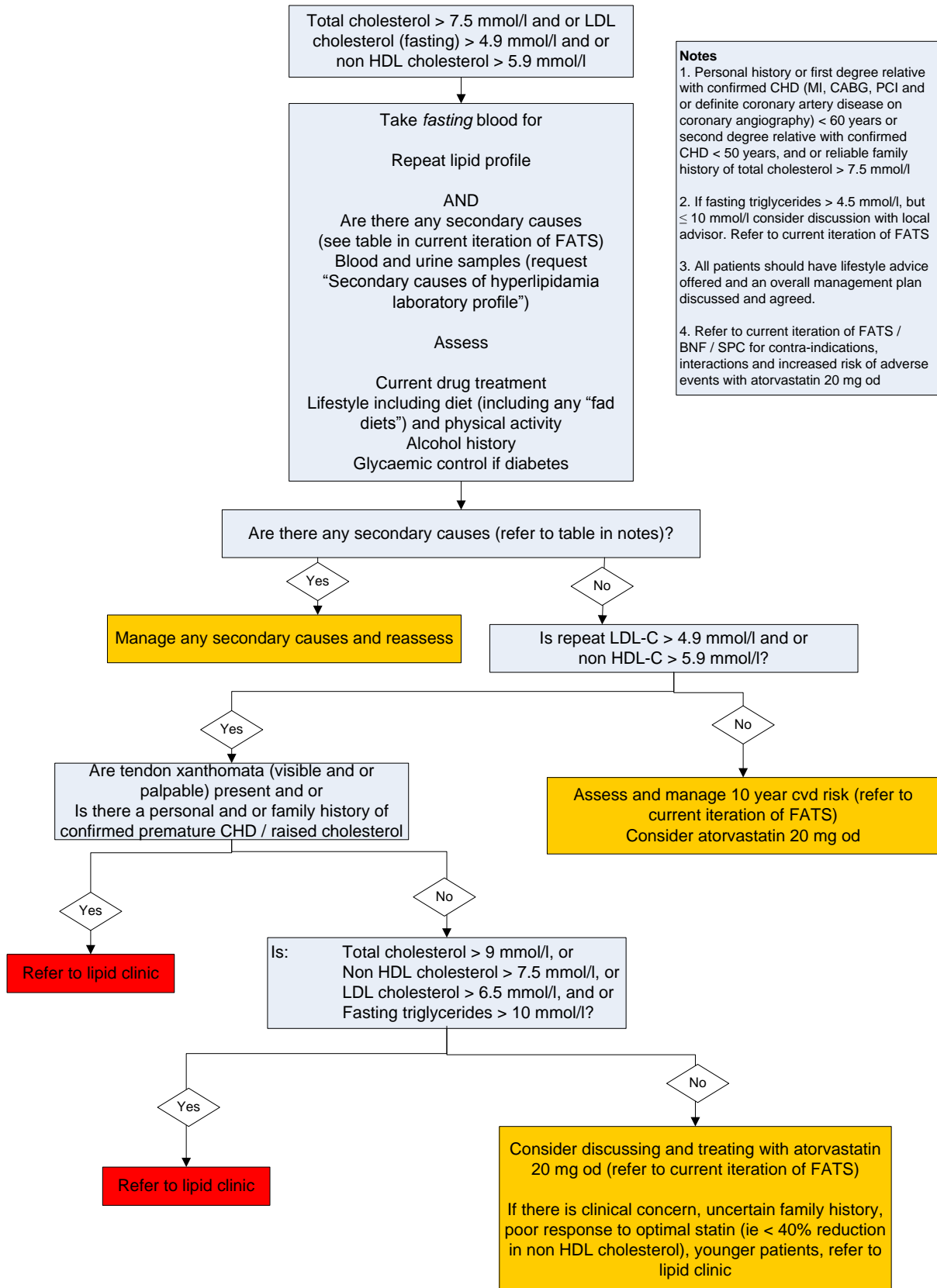
This guidance is intended for all clinicians in the Newcastle, North Tyneside, Northumberland areas involved in treating people for primary and secondary prevention of cardiovascular disease, and should be used in conjunction with the current iteration of FATS.

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<sup>5</sup> available at <http://guidance.nice.org.uk/CG71>

# Flow chart for the assessment of severe hypercholesterolaemia

Patient with total cholesterol > 7.5 mmol/l and or LDL cholesterol > 4.9 mmol/l



## Secondary causes of dyslipidaemias

Some of these are summarised in the current iteration of [FATS](#).

### People with occlusive vascular disease

The above [flow chart](#) should be adopted for all people presenting with a total cholesterol > 7.5 mmol/l or LDL cholesterol (measured from a fasting sample) > 4.9 mmol/l, but the following was noted.

### People with coronary heart disease

People with a personal history of confirmed coronary heart disease may not have the results of the initial lipid profile confirmed before treatment with a statin is started. These patients should still have secondary causes excluded (as above) and should be considered for referral to the lipid clinic if they have;

- a total cholesterol > 7.5 mmol/l, LDL cholesterol (fasting) > 4.9 mmol/l, non-HDL cholesterol > 5.9 mmol/l **AND**
- a personal history of confirmed CHD age < 60 years, and or
- tendon xanthomata, and or
- a family history which meets the Simon Broome criteria (see above)

### People with stroke disease and PAD

People with a personal history of stroke and PAD should be managed as recommended in the flow chart, although a fasting lipid profile may not always be taken before a statin is started, particularly in those with an acute presentation.

### Lipid clinic

The lipid clinic will;

- Confirm a clinical diagnosis of FH or alternative diagnosis and recommend coding in primary care  
EMIS code for familial hypercholesterolaemia C3200  
SYSTMONE code C3200
- Provide lifestyle and dietetic advice
- Start and/or titrate lipid lowering drug treatment.  
Intensive statin treatment will be offered to people with FH, aiming to lower LDL cholesterol (or non-HDL cholesterol) by 50% or more. A non generic statin (rosuvastatin) and combination therapies may be needed, although these should only be used following recommendation from specialist care.
- Provide information, including about CHD risk and in women of child bearing age, the importance of avoiding statins for 3 months before conception and throughout pregnancy.
- Identify and arrange investigation if there are any symptoms or signs of cardiovascular disease
- Use the Dutch Lipid Clinics Network score to determine the likelihood of familial hypercholesterolaemia and prioritise those with a score  $\geq 6$  for genetic testing.
- Recommend if family cascade screening is appropriate, using measurement of lipid profiles in other family members (see below)
- Arrange follow up and an annual structured review (see below)

### Follow up and annual review

All people with FH require an annual structured review. This may be done in the lipid clinic or in primary care dependent on clinical need, and as a minimum includes;

- Fasting lipid profile; comparison to previous level of LDL cholesterol and review of LDL lowering from baseline
- Current drug treatment, concordance and any problems with side effects
- Lifestyle and dietetic review and advice
- Identify any symptoms or signs of cardiovascular disease or new cardiovascular event, and arrange appropriate investigation
- Update any family history of CHD events and progress with cascade screening.

### Family cascade screening for Familial Hypercholesterolaemia

Genotyping is being introduced in the North East for patients most likely to have a familial hypercholesterolaemia, following assessment in the lipid clinic. The lipid clinics will use the Dutch Lipid Clinics Network score. Patients with a score  $\geq 6$  are anticipated to have an estimated pick up rate of a positive genotyping of approximately 40% or more, whilst those with a score  $\geq 10$  a pick up of more than 80%. Patients being considered for genotyping will be seen by a specialist nurse who will complete a family history with them and arrange appropriate further testing.

The Dutch Lipid Clinics Network Score is calculated from the table below and is used in the lipid clinic, but **should not** be used to decide if a patient should be referred to the lipid clinic.

Dutch Lipid Clinics Network Score			
<b>A. Family History</b>			
Enter Number of relatives at 50% risk: <input type="text"/>		Number of relatives at 25% risk	
I.	First degree relative with premature CHD and/or CVD*	Y / N	
II.	First degree relative with LDL cholesterol >5.5	Y / N	1
III.	First degree relative with xanthoma or corneal arcus	Y / N	
IV.	First degree relative age <18 with LDL cholesterol >3.9	Y / N	2
*Premature CHD and/or CVD in men <55 years, women <60 years			
<b>B. Personal History</b>			
I.	History of premature CHD (M <55, F <60)	Y / N	2
II.	History of premature PAD or CEVD	Y / N	1
<b>C. Physical Examination</b>			
I.	Tendon xanthomas	Y / N	6
II.	Premature corneal arcus (<45 years)	Y / N	4
<b>D. Fasting LDL cholesterol with triglycerides &lt;2.3**</b>			
**LDL cholesterol for calculation of the score is highest without drug treatment.			
I.	LDL cholesterol >8.5	Y / N	8
II.	LDL cholesterol 6.5 – 8.4	Y / N	5
III.	LDL cholesterol 5.0 – 6.4	Y / N	3
IV.	LDL cholesterol 4.0 – 4.9	Y / N	1
Add HIGHEST score from each of domains A + B + C + D =		Total	

Patients who do not fulfil the criteria for genotyping, but in whom cascade family screening is recommended, will have this explained in the lipid clinic and if they wish will be given information and a letter which their first degree relatives can take to their own GPs to have a lipid profile measured.

The results of the fasting lipid profile in family members should be interpreted using the tables for first degree relatives in the NICE clinical guideline 71, Identification and management of familial hypercholesterolaemia. Pages 43 to 45 of the NICE guideline are pasted [below](#). Family members who fall into the 'red zone' or 'grey zone' should be considered for referral to the lipid clinic. Those in the 'red zone' are very likely to have familial hypercholesterolaemia and those in 'grey zone' require further specialist assessment for diagnosis.

## Tables for interpretation of lipid profiles if used in family cascade testing

NICE clinical guideline 71, Identification and management of familial hypercholesterolaemia. Pages 43 to 45, available at <http://guidance.nice.org.uk/CG71>

### ***Gender- and age-specific LDL-C criteria for the diagnosis of FH in relatives of a person with FH***

These gender- and age-specific LDL-C criteria are to be used for the diagnosis of FH in the relatives of an index case with FH where the family mutation has not been identified. These are intended for use by healthcare professionals with expertise in FH.



Relatives with LDL-C levels in the green zone are unlikely to have FH. In these instances, manage the person's coronary heart disease risk as in the general population (see 'Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease', NICE clinical guideline 67).



Relatives with LDL-C levels in the red zone are likely to have a clinical diagnosis of FH.



The diagnosis of FH for relatives in the grey zone is uncertain. A further measurement of LDL-C concentration should be carried out, and if the level is still in the grey zone this should be repeated annually. If the person's LDL-C concentration remains in the grey zone then coronary heart disease risk should be assessed and managed as in the general population (see 'Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease', NICE clinical guideline 67).

## LDL-C females\*

LDL-C females					
Age (years)					
0 to 14	15 to 24	25 to 34	35 to 44	45 to 54	55 and older
5.3	5.3	5.3	5.3	5.3	5.3
5.2	5.2	5.2	5.2	5.2	5.2
5.1	5.1	5.1	5.1	5.1	5.1
5.0	5.0	5.0	5.0	5.0	5.0
4.9	4.9	4.9	4.9	4.9	4.9
4.8	4.8	4.8	4.8	4.8	4.8
4.7	4.7	4.7	4.7	4.7	4.7
4.6	4.6	4.6	4.6	4.6	4.6
4.5	4.5	4.5	4.5	4.5	4.5
4.4	4.4	4.4	4.4	4.4	4.4
4.3	4.3	4.3	4.3	4.3	4.3
4.2	4.2	4.2	4.2	4.2	4.2
4.1	4.1	4.1	4.1	4.1	4.1
4.0	4.0	4.0	4.0	4.0	4.0
3.9	3.9	3.9	3.9	3.9	3.9
3.8	3.8	3.8	3.8	3.8	3.8
3.7	3.7	3.7	3.7	3.7	3.7
3.6	3.6	3.6	3.6	3.6	3.6
3.5	3.5	3.5	3.5	3.5	3.5
3.4	3.4	3.4	3.4	3.4	3.4
3.3	3.3	3.3	3.3	3.3	3.3
3.2	3.2	3.2	3.2	3.2	3.2

\* From Starr B, Hadfield SG, Hutten BA, Landsberg P, Leren TP, Damgaard D, Neil HAW and Humphries SE (2008) Development of sensitive and specific age- and gender-specific low density lipoprotein cholesterol cutoffs for diagnosis of first-degree relatives with familial hypercholesterolaemia in cascade testing. *Clinical Chemistry and Laboratory Medicine* 46 (6): 791–803.

## LDL-C males\*

LDL-C males					
Age (years)					
0 to 14	15 to 24	25 to 34	35 to 44	45 to 54	55 and older
5.3	5.3	5.3	5.3	5.3	5.3
5.2	5.2	5.2	5.2	5.2	5.2
5.1	5.1	5.1	5.1	5.1	5.1
5.0	5.0	5.0	5.0	5.0	5.0
4.9	4.9	4.9	4.9	4.9	4.9
4.8	4.8	4.8	4.8	4.8	4.8
4.7	4.7	4.7	4.7	4.7	4.7
4.6	4.6	4.6	4.6	4.6	4.6
4.5	4.5	4.5	4.5	4.5	4.5
4.4	4.4	4.4	4.4	4.4	4.4
4.3	4.3	4.3	4.3	4.3	4.3
4.2	4.2	4.2	4.2	4.2	4.2
4.1	4.1	4.1	4.1	4.1	4.1
4.0	4.0	4.0	4.0	4.0	4.0
3.9	3.9	3.9	3.9	3.9	3.9
3.8	3.8	3.8	3.8	3.8	3.8
3.7	3.7	3.7	3.7	3.7	3.7
3.6	3.6	3.6	3.6	3.6	3.6
3.5	3.5	3.5	3.5	3.5	3.5
3.4	3.4	3.4	3.4	3.4	3.4
3.3	3.3	3.3	3.3	3.3	3.3
3.2	3.2	3.2	3.2	3.2	3.2
3.1	3.1	3.1	3.1	3.1	3.1
3.0	3.0	3.0	3.0	3.0	3.0

\* From Starr B, Hadfield SG, Hutten BA, Landsberg P, Leren TP, Damgaard D, Neil HAW and Humphries SE (2008) Development of sensitive and specific age- and gender-specific low density lipoprotein cholesterol cutoffs for diagnosis of first-degree relatives with familial hypercholesterolaemia in cascade testing. *Clinical Chemistry and Laboratory Medicine* 46 (6): 791–803.



## REFERRAL OF ADULTS (≥16 yrs) WITH POSSIBLE FAMILIAL HYPERCHOLESTEROLAEMIA (FH) or OTHER FAMILIAL HYPERLIPIDAEMIA TO THE LIPID CLINIC

This form can be used to refer adults with possible/definite FH or possible FH to the lipid clinic. The local guidelines for patients with possible or definite FH provide more information.

Date of Referral;

Referring G.P: .....

Address:.....  
.....  
.....  
..... Post Code: .....

Telephone No: .....

Fax No: .....

Patient's Surname: .....

Previous Surname (if married): .....

Forename(s): .....

Address: .....

.....  
..... Postcode: .....

Telephone No. Daytime: .....

Evening: .....

D.O.B.         Age: .....

NHS No: .....

Hospital ID No if available: .....

Special Needs: (e.g. hearing loss, physical disability)

Interpreter Required:     Yes                       No

Language:.....

**BIOCHEMICAL RESULTS TO ACCOMPANY THE REFERRAL**

Lipid profiles (at least one fasting), preferably including highest pre-treatment results.

Date       Total chol   .  HDL-C  .  Trigs   .  LDL-C (fasting)   .

Date       Total chol   .  HDL-C  .  Trigs   .  LDL-C (fasting)   .

Date       Fasting glucose                        .                       Date       HbA1C

Date       TSH                        .

Date       LFT    Albumin      Bilirubin      Alk phos       ALT

Date       Urine protein quantification (PCR or ACR (ring one))    .

**CLINICAL INFORMATION and DRUG HISTORY**

Is this the first degree relative of a confirmed familial hypercholesterolaemia case?                      Yes  No

Is there a personal history of coronary disease < 60 years?                      Yes  No

Are there first degree relatives with proven coronary disease < 60 years?                      Yes  No

Are there second degree relatives with proven coronary disease < 50 years?                      Yes  No

Is there a personal history of other premature CVD < 60 years ?                      Yes  No

Is there a family history of other premature CVD < 60 years?                      Yes  No

Is there a family history of cholesterol > 7.5 mmol/l?                      Yes  No

Are tendon xanthomata present?                      Yes  No

Alcohol consumption (units per week)                     

**List any recent drugs which may cause hyperlipidaemia (attach list of all current drugs)**

\_\_\_\_\_

**Please send completed forms with a copy of the patient's current drug history and details of any other relevant history to the Lipid Clinic**  
**Dr D Neely, Lipid Clinic, Royal Victoria Infirmary, Newcastle upon Tyne Hospitals NHS Foundation Trust**  
**Dr P McKenna, Lipid Clinic North Tyneside Hospital, Northumbria Healthcare NHS Foundation Trust**

## Appendix 3

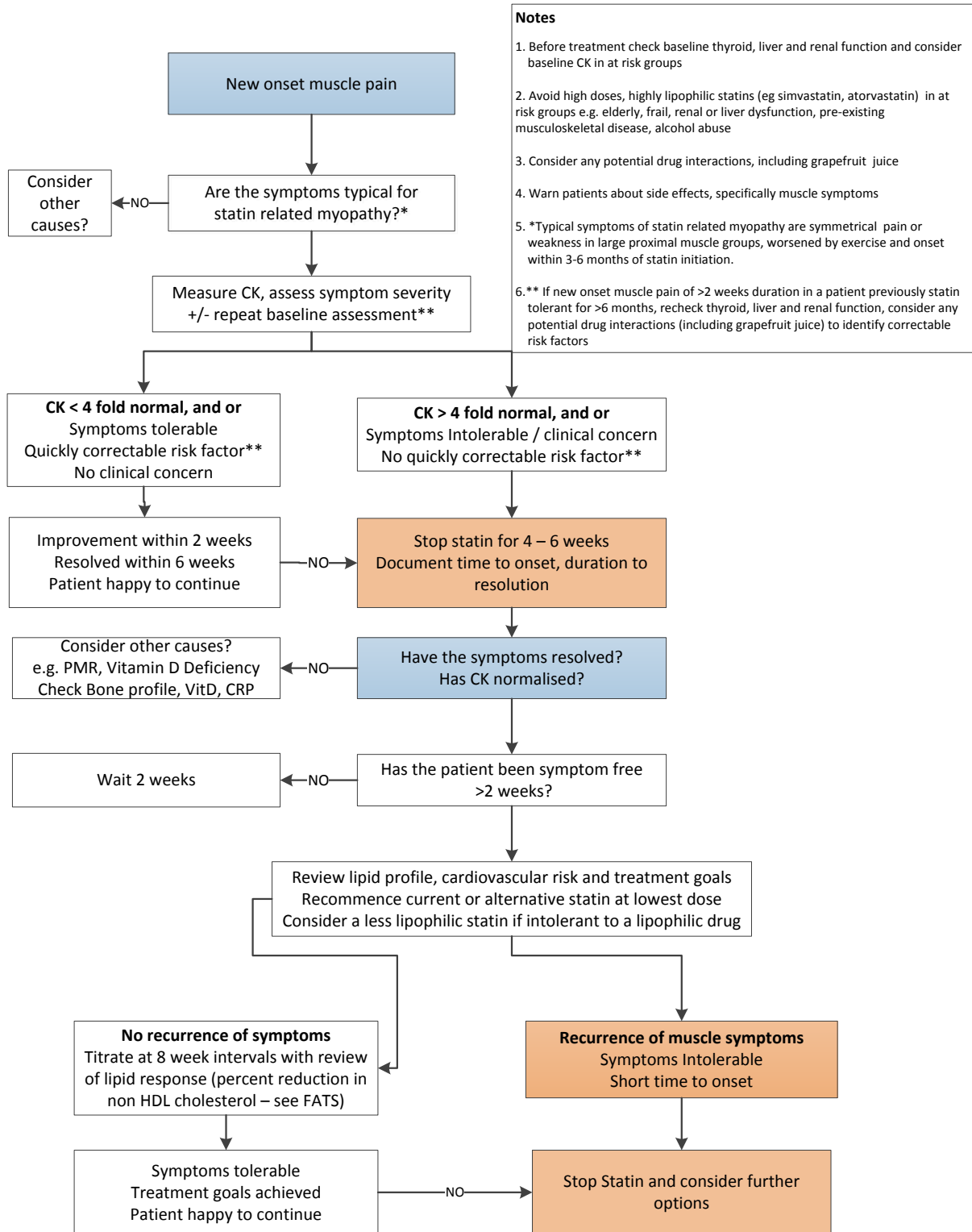
### Additional guidance for assessment and management of statin intolerance

#### Statin intolerance definition

Intolerance to initial statin therapy is defined as the presence of clinically significant adverse effects from statin therapy that are considered to represent an unacceptable risk to the patient or that may result in compliance with therapy being compromised. Adverse effects include evidence of new-onset muscle pain (which may be associated with increased serum levels of the muscle enzyme CK, indicating of muscle damage), increased levels of liver function enzymes, significant gastrointestinal disturbances. Musculoskeletal are the most frequently reported adverse effects, however more severe forms of muscle toxicity are infrequent (see [Table SRM Classification, page 29](#)) and almost always avoidable if simple precautions are observed.

Recommendations for the assessment and management of adverse muscle side effects in patients being considered for, or treated with statins, were developed as a consensus by the FATS group. These are presented as a [flow chart](#) and [notes](#), which should be read together.

## Flowchart for Assessment of Suspected Statin Related Myopathy



## Notes for advice and monitoring for adverse effects ([see flow chart](#))

1. Before offering a statin, ask the person if they have had persistent generalised unexplained muscle pain, whether associated or not with previous lipid-lowering therapy. If they have, measure creatine kinase levels (CK).
  - If creatine kinase levels are more than 4 times the upper limit of normal, re-measure creatine kinase after 7 days.
  - If creatine kinase levels are still 4 times the upper limit of normal, do not start statin treatment.
  - If creatine kinase levels are raised but less than 4 times the upper limit of normal, start statin treatment at a lower dose. Unless free of symptoms of muscle pain re-measure creatinine kinase in 6 weeks.
2. Before prescribing a statin, check baseline thyroid, liver and renal function and consider any potential drug interactions and avoid the highest doses in at risk groups such as elderly, female, those with musculoskeletal disease, renal or liver dysfunction.
3. Warn patients about adverse effects, specifically muscle symptoms. Advise people who are being treated with a statin to seek medical advice if they develop muscle symptoms (pain, tenderness or weakness).
  - If this occurs, measure creatine kinase (CK)
  - If CK levels are raised more than 4 times the upper limit of normal, stop statin treatment immediately.
  - The dose of statin used, time to onset and the anatomical distribution of symptoms should be documented
4. If people report muscle pain or weakness while taking a statin, explore other possible causes of muscle pain or weakness (with or without raised CK) particularly if the symptoms are not typical of statin related muscle toxicity, or if they have previously tolerated statin therapy for more than 3 months.
5. If someone reports adverse effects when taking high-intensity statins discuss the following possible strategies with them:
  - a. stopping the statin and trying again when the symptoms have resolved to check if the symptoms are related to the statin
  - b. reducing the dose within the same intensity group
  - c. changing the statin to a lower intensity group.In all cases, the recommendations in the event of muscle side effects should be followed (see above)
6. If a person is not able to tolerate a high-intensity statin aim to treat with the maximum tolerated dose. Tell the person that any statin at any dose reduces cardiovascular disease risk.
7. Seek specialist advice about options for treating people at high risk of cardiovascular disease who are intolerant (SRM 2 or above) to 3 different statins or who develop myopathy (SRM 3-6)

Treatment options for people at high cardiovascular risk who are intolerant to 3 different statins:

1. Low dose, non-daily long acting statin (atorvastatin 10 mg or rosuvastatin 5mg one to three days per week)
2. Ezetimibe, coadministered with maximum tolerated generic statin therapy, when dose titration is limited by intolerance to statin therapy (as defined above)
3. Ezetimibe monotherapy is an option for those who are intolerant to low dose, non-daily statin therapy (as defined above).
4. Lipoprotein apheresis should be considered as a last resort in patients with Familial Hypercholesterolaemia and LDL-Cholesterol greater than 5 mmol/L despite maximum tolerated statin therapy or in people with progressive vascular disease who are intolerant of statin therapy. These patients should be assessed in a specialist lipid clinic.

The table describes average percent reduction in LDL cholesterol with different statins/doses (taken daily). Similar reductions in non-HDL cholesterol can be assumed.

Dose (mg/day)	Reduction in LDL cholesterol				
	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%	–
20%–30%: low intensity					
31%–40%: medium intensity					
Above 40%: high intensity					

## Statin related myotoxicity (SRM) classification

Table. Statin Related Myotoxicity (SRM) Classification			
	Phenotype	Incidence	Definition
<b>SRM 0</b>	CK elevation <4XULN	1.5-26%	No muscle symptoms
<b>SRM 1</b>	Myalgia, tolerable	190/100,000 patient years; 0.3 to 33%	Muscle symptoms without CK elevation
<b>SRM 2</b>	Myalgia, intolerable	0.5%	Muscle symptoms, CK <4xULN, complete resolution on dechallenge
<b>SRM 3</b>	Myopathy	5/100,000 patient years	CK elevation >4xULN <10xULN ± muscle symptoms, complete resolution on dechallenge
<b>SRM 4</b>	Severe myopathy	0.11%	CK elevation >10 x ULN<50x ULN ± muscle symptoms complete resolution on dechallenge
<b>SRM 5</b>	Rhabdomyolysis	0.1-8.4/100,000 patient years	CK elevation >10xULN with evidence of renal impairment + muscle symptoms or CK>50x ULN
<b>SRM 6</b>	Autoimmune- mediated necrotising myositis	~2/million per year	HMGCR antibodies, HMGCR expression in muscle biopsy incomplete resolution on dechallenge

## Appendix 4

### **Lipid management in patients with primary heterozygous familial hypercholesterolaemia and or vascular disease and recommendations for use of Alirocumab and Evolocumab**

NICE have published TAGs recommending the PCSK9 inhibitors, Alirocumab<sup>6</sup> and Evolocumab<sup>7</sup>, (monoclonal antibodies that inhibits proprotein convertase subtilisin/kexin type 9 (PCSK9), an enzyme involved in down regulation of low-density lipoprotein receptors) as options for treatment of high risk patients with uncontrolled severe hypercholesterolaemia or mixed dyslipidaemia. These TAGs set out criteria for these drugs (given as a subcutaneous injection) to be considered as an option in lipid management.

Patients with primary heterozygous familial hypercholesterolaemia (HeFH) and LDL-C concentration persistently above 5 mmol/l despite maximum tolerated lipid lowering therapy and who may be eligible for treatment with one of these agents should already be under the care of a specialist clinic for lipid management and if not should be referred.

Some non-FH patients with vascular disease are also eligible for treatment. [The flow chart](#) below describes a pathway to assess patients with atheromatous vascular disease (coronary, cerebrovascular disease and peripheral arterial disease) and which patients should be referred to a specialist clinic for lipid management.

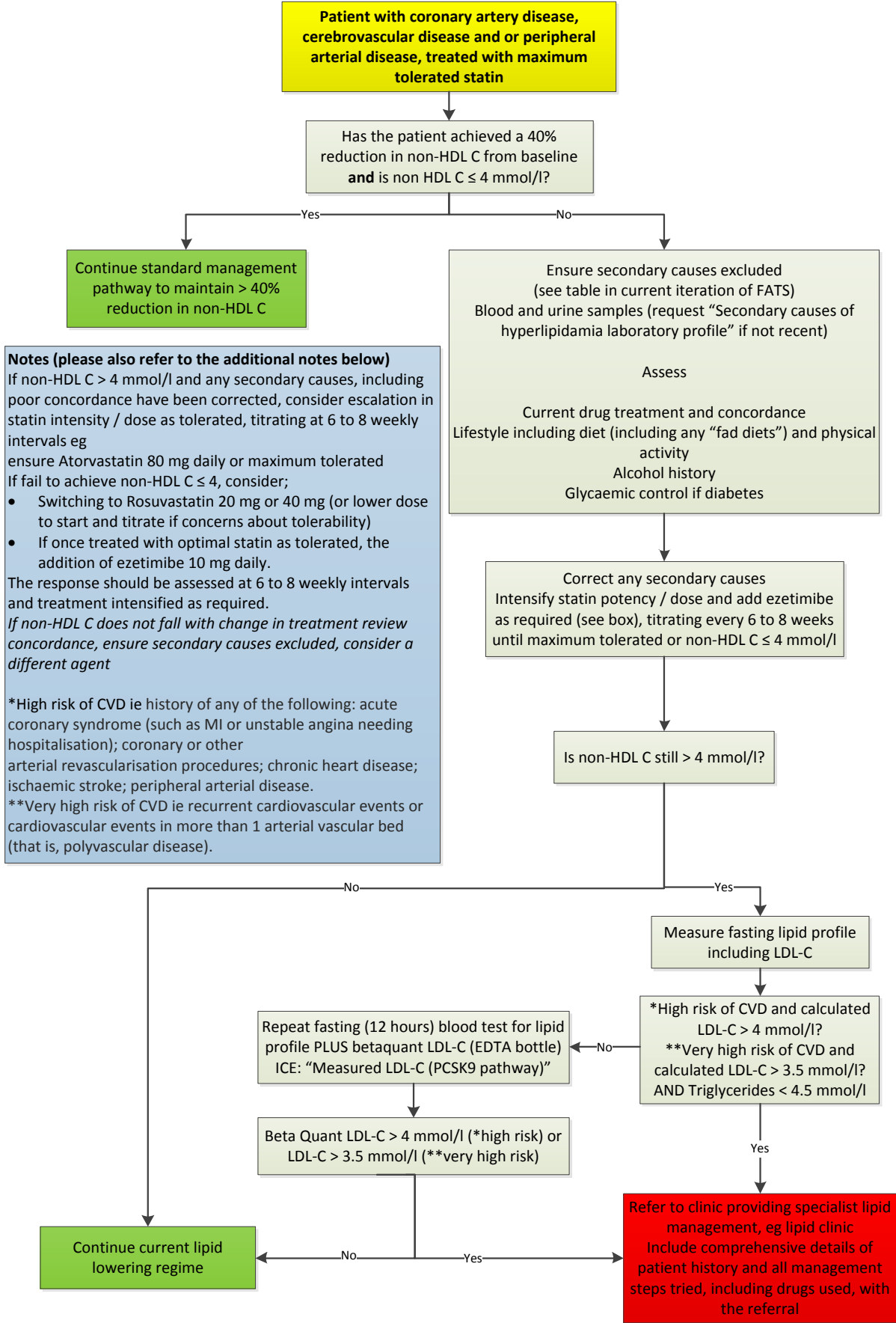
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<sup>6</sup> <https://www.nice.org.uk/guidance/ta393>

<sup>7</sup> <https://www.nice.org.uk/guidance/ta394>



# Assessment of patients with vascular disease in primary care and hospital clinics



**Notes (please also refer to the additional notes below)**  
 If non-HDL C > 4 mmol/l and any secondary causes, including poor concordance have been corrected, consider escalation in statin intensity / dose as tolerated, titrating at 6 to 8 weekly intervals eg ensure Atorvastatin 80 mg daily or maximum tolerated  
 If fail to achieve non-HDL C ≤ 4, consider;

- Switching to Rosuvastatin 20 mg or 40 mg (or lower dose to start and titrate if concerns about tolerability)
- If once treated with optimal statin as tolerated, the addition of ezetimibe 10 mg daily.

The response should be assessed at 6 to 8 weekly intervals and treatment intensified as required.  
*If non-HDL C does not fall with change in treatment review concordance, ensure secondary causes excluded, consider a different agent*

\*High risk of CVD ie history of any of the following: acute coronary syndrome (such as MI or unstable angina needing hospitalisation); coronary or other arterial revascularisation procedures; chronic heart disease; ischaemic stroke; peripheral arterial disease.  
 \*\*Very high risk of CVD ie recurrent cardiovascular events or cardiovascular events in more than 1 arterial vascular bed (that is, polyvascular disease).

### **Additional notes about the pathway**

\*High risk patients of CVD are identified by NICE as being those with a history of any of the following: acute coronary syndrome (such as MI or unstable angina needing hospitalisation); coronary or other arterial revascularisation procedures; chronic heart disease; ischaemic stroke; peripheral arterial disease and \*\*very high risk of CVD those with recurrent cardiovascular events or cardiovascular events in more than 1 arterial vascular bed (that is, polyvascular disease).

Patients who have a non-HDL cholesterol greater than 4 mmol/l following correction of any secondary causes and optimisation of statin treatment, with or without ezetimibe should be further assessed with a LDL cholesterol. Initially this is a calculated LDL-C from a fasting lipid profile with referral to a specialist clinic for lipid management if the criteria are met (see the flow chart). If the LDL-C criteria are not met, or the triglycerides are greater than 4.5 mmol/l and hence the LDL-C cannot be calculated accurately, blood should be taken for a Beta Quant LDL-C measurement with a repeat fasting lipid profile at the same time. This should be requested on ICE as “Measured LDL-C (PCSK9) pathway”.

### **Specialist clinic for lipid management**

- Following referral to a specialist clinic for lipid management, patients will have specialist assessment including a detailed dietary assessment.
- Patients who are otherwise optimally managed and who have a LDL-C confirmed as fulfilling the criteria for considering treatment with a PCSK9 inhibitor will have this discussed with them.
- The PCSK9 inhibitor with the lowest acquisition costs will generally be preferred.
- If treatment with a PCSK9 inhibitor is being started, patients will receive appropriate education about this and patients being treated with one of these agents will remain under the management of the specialist clinic for their prescribing and monitoring (by non-fasting non-HDL-Cholesterol).
- Patients treated with a PCSK9 inhibitor who fail to achieve at least a 20% reduction in non-HDL-Cholesterol within 3 months will be reassessed to ensure concordance with management, including appropriate dietary compliance, and to ensure that no secondary causes have developed.
- Primary non-responders to treatment (less than 20% reduction in non-HDL-Cholesterol) will have their management reviewed including whether they should still continue treatment with a PCSK9 inhibitor.

## Appendix 5

### Membership of the FATS steering group

Dr Jane Skinner, Consultant Community Cardiologist, Newcastle upon Tyne Hospitals NHS Foundation Trust (guideline co-ordinator)

Anne-Marie Bailey, Pharmaceutical Advisor, NHS North of England Commissioning Support Unit

Dr Stuart Bennett, Consultant in Diabetes, Northumbria Healthcare NHS Foundation Trust

Dr John Bourke, Consultant Cardiologist, Newcastle upon Tyne Hospitals NHS Foundation Trust

Dr Andrew Chalmers, GP, Beaumont Park, Whitley Bay

Rebecca Coon (Samantha Wood from December 2014), Pharmacist, Northumbria Healthcare NHS Foundation Trust

Dr Helen Coundon, GP and prescribing lead, North Tyneside CCG

Dr Richard Curless, Northumbria Healthcare Trust

Dr Anand Dixit, Consultant in Stroke Medicine, Newcastle upon Tyne Hospitals NHS Foundation Trust

Dr J Colin Doig, Consultant Cardiologist, Northumbria Healthcare NHS Foundation Trust

Dr A Gall, GP and prescribing lead, Newcastle North and East CCG

Dr Sharon Gandy, GP, North Shields

Dr Akif Gani, Consultant in Elderly Care, Newcastle upon Tyne Hospitals NHS Foundation Trust

Dr Ifti Haq, Consultant Cardiologist, Newcastle upon Tyne Hospitals NHS Foundation Trust

Dr Suren Kanagasundaram, Consultant in Renal Medicine, Newcastle upon Tyne Hospitals NHS Foundation Trust

Dr N Leech, Consultant Diabetologist, Newcastle upon Tyne Hospitals NHS Foundation Trust

Dr Nick Lewis-Barned, Consultant in Diabetes, Northumbria Healthcare NHS Foundation Trust

Matthew Lowery, Formulary Pharmacist, Newcastle upon Tyne Hospitals NHS Foundation Trust

Dr Paul McKenna, Consultant Chemical Pathologist, Northumbria Healthcare NHS Foundation Trust

Dr Frances Naylor, GP and LTC lead, Northumberland CCG

Dr Dermot Neely, Consultant in Clinical Biochemistry and Metabolic Medicine, Newcastle upon Tyne Hospitals NHS Foundation Trust

Dr Wan-Fai Ng, Consultant Rheumatologist, Newcastle upon Tyne Hospitals NHS Foundation Trust

Dr Craig Runnett, Consultant Cardiologist, Northumbria Healthcare NHS Foundation Trust

Dr Mike Scott, GP, Newburn Surgery, Newcastle

Dr Caroline Sprake, GP and LTC lead, North Tyneside CCG

Prof Gerry Stansby, Consultant Vascular Surgeon, Newcastle upon Tyne Hospitals NHS Foundation Trust

Deb Stone, Dietician, Healthy Hearts, Northumbria Healthcare NHS Foundation Trust

Claire Thomas, Medicines Management Lead, Northumberland Tyne and Wear NHS Trust

Dr Simon Thomas, Consultant Physician, Newcastle upon Tyne Hospitals NHS Foundation Trust

Amanda Thompson, Practice Nurse and cardiovascular lead, Northumberland CCG

Susan Turner, Pharmaceutical Advisor, NHS North of England Commissioning Support Unit

Dr Mark Walker, Consultant Physician, Newcastle upon Tyne Hospitals NHS Foundation Trust

Dr Nicola Weaver, GP and prescribing lead, Newcastle West

Dr Andre Yeung, Consultant in Public Health Medicine, Newcastle upon Tyne

Dr Azfar Zaman, Consultant Cardiologist, Newcastle upon Tyne Hospitals NHS Foundation Trust

### **Declared conflicts of interest**

JCD has received travel grants and speaker fees from drug companies which have been associated with lipid lowering agents. IH is the PI for the HPS3/TIMI55/REVEAL study in Newcastle (<http://www.ctsuo.ox.ac.uk/research/mega-trials/hps3-reveal>) which is funded by, but independent of MSD. PM was an investigator in the HPS, SEARCH and HPS-2/THRIVE trials and is an investigator in the REVEAL trial organised by the CTSU, Oxford and has received travel grants from various pharmaceutical companies that manufacture lipid lowering drugs. RDGN is a Trustee and board member of the Heart UK the Cholesterol Charity, represented Heart UK on the Joint British Societies (JBS3) Guideline Development Group, and was a member of the NICE Lipid Modification Guideline Development Group (CG181). RDGN is Clinical Lead for the North East Cardiovascular Network Lipid Specialists Advisory Group, has been Newcastle upon Tyne Hospital NHS Foundation Trust Site Investigator for clinical trials sponsored by KaraBio, MSD, Sanofi, Amgen and ISIS, has received honoraria for participation in advisory boards for Aegerion, Amgen, Genzyme, Roche and Sanofi and has received sponsorship from MSD to attend an educational meeting.

### **Date of review**

December 2017