Clinical & Commissioning Pathway
for the Prevention and Management
of Dyslipidaemia and Familial Hypercholesterolaemia
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Introduction

This clinical pathway has been developed to support providers, public health commissioners and NHS commissioners in the development of services to improve clinical practice for those people at increased risk of CVD, who have dyslipidaemia, including Familial Hypercholesterolaemia (FH). It is hoped that it will prove to be a practical guide that will encourage discussion and collaboration between different stakeholders and help to deliver clinically effective and coordinated holistic services for people at increased CVD risk with dyslipidaemia and familial hypercholesterolaemia across the full pathway of care.

This pathway focuses on the standard of care that individuals with dyslipidaemia (including FH) would expect to receive using both a diagnostic and prognostic approach, from initial detection to post CVD event management. It does not however, comprehensively cover every single anomaly that may arise in clinical practice.

Why Effective Commissioning for Dyslipidaemia and Familial Hypercholesterolaemia is Essential

The NHS (1) and Public Health Outcome Frameworks (2) together with the Clinical Commissioning Outcome Indicator Set, (3) focuses on a reduction in mortality in people under 75 years of age from CVD. The main causes of mortality are heart disease and stroke. The inclusion of the under 75 mortality rates from CVD means all commissioners across the pathway will have a major role to play in ensuring that services focus on identifying people who are at increased risk of CVD. This will include:

- Treating those who have a diagnosis of dyslipidaemia with appropriate clinical treatment and lifestyle education.
- Treating those who have a diagnosis of CVD with appropriate clinical intervention.
- Identifying, diagnosing and treating people who have FH.

Aim of the Pathway

This pathway provides expert guidance concerning the identification of patients who should be screened for lipid disorders and the approach to be adopted in prevention and management of lipid disorders once identified. Introducing and implementing a pathway for dyslipidaemia and FH across different care settings is based on four core principles:

- Population Health Lifestyle Intervention.
- Primary Prevention of CVD.
- Secondary Prevention of CVD.
- Treatment of Dyslipidaemia and FH across primary, secondary and tertiary sectors.

Who is this Document for?

- Health care professionals in primary care, community care, integrated care, secondary care and tertiary care healthcare services.
- Commissioners.
- Service development managers across clinical commissioning groups.
- Local Authority and Public Health services.
The Pathway

This clinical and commissioning pathway recommends four stages of care: (1.) Population health intervention (e.g. Services are available to the population to encourage and enable self-help). (2.) Primary prevention: assessment, identification and management. (3.) Secondary prevention: assessment, identification and management. (4.) Specialist lipid / familial hypercholesterolaemia services the identification, assessment and management.

The following diagram sets out the four essential stages of patient management across the pathway for the prevention and management of dyslipidaemia and FH. Clinical management is effective in managing cholesterol, however population health interventions should be considered and discussed across all stages of the pathway.

The detailed steps provided at each stage of the pathway are incorporated into five elements:

- A flow chart on how to manage someone with dyslipidaemia or suspected familial hypercholesterolaemia.
- A set of indicators (process and outcome measures).
- Guidelines.
- Standards.
- Recognised competencies (if appropriate).

This format provides validity in the measurement, efficiency and clinical effectiveness across the pathway, thus providing confidence in the commissioning and provision of care.
First Stage: Population Health Interventions

Healthy lifestyle messages should be delivered throughout the patient’s management pathway. Individualised consistent signposting to relevant lifestyle advice and interventions can promote behaviour change and willingness to change can happen through education on lifestyle. Lifestyle intervention should be a consistent message. The diagram on page 6 demonstrates tools that can be accessed and from where in the system they are available. This is not an exhaustive list but promotes and highlights the tools available.

Purpose of this Stage

Population health can be supported by a wide variety of lifestyle advice, services and interventions. Lifestyle advice should be embedded into all advice / education given to patients who have or are at increased risk of CVD.

A wide range of services are available across all sectors of the NHS, including community services. All opportunities for interventions, signposting and referral to services should be taken to support clinical management, self-management and education.

Importance of this Stage

CVD is the leading cause of death in England and Wales, accounting for almost one-third of deaths [1]. In 2010, 180,000 people died from CVD – around 80,000 of these deaths were caused by coronary heart disease and 49,000 were caused by strokes. Of the 180,000 deaths, 46,000 occurred before the age of 75 years, and 70% of those were in men. Death rates from CVD peaked in the 1970s & 1980s and have more than halved since then. Rates have fallen more rapidly in older age groups compared with younger ones, with a reduction of approximately 50% in the 55–64 year age group compared with a 20% reduction in men aged 35–44 years. In spite of evidence that mortality from CVD is falling, morbidity appears to be rising.

CVD has significant financial implications and was estimated to cost the NHS in England almost £6,940 million in 2003, rising to £7,880 million in 2010.

Consequences of not Following this Stage

Failure to promote and support health lifestyles in the population is a missed opportunity to reduce cardiovascular disease risk.

Rationale Behind the Indicators Chosen

Prevention of dyslipidaemia is an important approach as it will reduce the impact upon the NHS, both in terms of time and resources. The benefits of lifestyle interventions to the individual are far greater than preventing dyslipidaemia alone and the population shift in reduced risk of CVD will be enhanced.
## Population Health Interventions

<table>
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<tr>
<th>Core Components of Population Health Interventions</th>
<th>Milestones &amp; Guidance</th>
</tr>
</thead>
</table>
| **Indicators**                                    | Life expectancy at 65 (Male)  
Life expectancy at 65 (Female)  
Percentage of adults aged 18+ classified as overweight or obese  
Percentage of physically active adults  
Proportion of the population meeting recommended 5 fruit or vegetable portions a day  
Proportion of adults achieving at least 150 mins of physical activity per week  
Prevalence of tobacco smoking among persons aged 18+  
Cumulative percentage of eligible population aged 40 – 74 offered an NHS Health Check  
Cumulative percentage of eligible population aged 40 – 74 offered an NHS Health Check who received an NHS Health Check  
Age standardised rate of mortality for causes considered preventable for alcohol-related diseases excluding external causes  
Age standardised rate of mortality for all cardiovascular diseases in persons less than 75 that are considered preventable |
| **Guidance**                                      | NICE guidance CG181, 2014  
JBS 3  
NICE public health guidance 10  
NICE public health guidance 21  
Physical activity guidelines for adults at NHS Choices  
NHS Choices  
NICE clinical guideline 43 |
| **Competencies**                                  | All clinical staff are continuing to follow best practice  
All NHS staff trained in delivery of lifestyle interventions  
All NHS partners trained in delivery of lifestyle interventions  
Online resources to deliver lifestyle interventions must be validated and resources must link to pathways capable of identifying high-risk patients |
Population Health Interventions

Some services will be assessed and delivered in multiple settings across primary, community, integrated, secondary and tertiary services, they are not isolated to the service locality described above.
Notes on this Section

Making Every Contact Count (MECC)

Making every contact count\(^{(11)}\) is about making and maximising every opportunity to support people in considering healthy lifestyle changes to improve physical, mental health and emotional wellbeing, such as stopping smoking or becoming more physically active. The Five Year Forward View\(^{(12)}\) called for a radical upgrade in prevention and public health. If MECC were to be fully integrated and delivered at scale the impact on population health, both locally and nationally would be significant. The Five Year Forward View states that “health needs to be thought of in a different way” - therefore a culture change is required and the introduction of tools to support this will include MECC.

Dietary Advice

Advise people at high risk of (or established) CVD to do the following:

- Reduce their saturated fat intake from animal sources.
- Choose wholegrain varieties of starchy food and reduce intake of sugar/food products containing refined sugars (including fructose).
- Eat at least 5 portions of fruit and vegetables per day.
- Eat at least 2 portions of fish per week, including a portion of oily fish.
- Eat at least 4 to 5 portions of unsalted nuts, seeds and legumes per week.
- Refer to health improvement teams / local public health / lifestyle services for more support and advice – see MECC resource for referral options.

Further information and advice can be found at NHS Choice and Cheshire & Merseyside Public Health Services – Public Health Collaborative CHAMPS\(^{(13)}\). Resources are available to patients via charity i.e. BHF\(^{(14)}\), HEART UK\(^{(15)}\).

Alcohol Intake

Men and women should not regularly drink more than 14 units per week. People should avoid binge drinking. Further information can be found at NHS Choices.

Lifestyle Options

Lifestyle services / options available to patients for secondary prevention of cardiovascular disease:

- GP exercise referral schemes / council exercise schemes
- Diabetes community management programmes, education and exercise
- Weight management services
- Dietitian services
- Healthy Lifestyle hubs / living centres
- Wellness centres
- Alcohol cessation service
- Smoking cessation services
- Drug services – change / grow / live
- Mental Health Physical screens
- Healthy living pharmacy
- Anxiety and depression clinics – The Improving Access to Psychological Therapies services IAPT / social services / mental health
Physical Activity

The recommendation for physical activity per week is:

- At least 150 minutes of moderate intensity aerobic activity or 75 minutes of vigorous intensity aerobic activity or a mix of moderate and vigorous aerobic activity.
- To do muscle-strengthening activities on 2 or more days that work all major muscle groups (legs, hips, back, abdomen, chest, shoulders and arms).

For those people who are unable to perform moderate intensity physical activity because of comorbidity, medical conditions or personal circumstances, to exercise at their maximum safe capacity.

Advice about physical activity should take into account a person’s needs, preferences and circumstances. Agree goals and provide written information about the benefits of activity and local opportunities to be active.

Weight Management

Offer people at high risk of (or established CVD), who are overweight or obese, a referral to a local weight management service. Give appropriate advice and support to work towards achieving and maintaining a healthy weight.

Smoking Cessation

Advise all people who smoke to stop, in line with the advice provided by Smoking Cessation services. Offer people who want to stop smoking support and advice, and referral to an intensive support service. If a person is unable or unwilling to accept a referral to an intensive support service, offer pharmacotherapy in line with Smoking Cessation services.
Second Stage: Primary Prevention Assessment & Identification

The diagram on page 10 outlines the assessment of CVD risk in people without clinical evidence of existing CVD i.e. Primary Prevention. The importance of identifying possible familial hypercholesterolaemia is highlighted. An informed discussion with the patient concerning the process of risk assessment should take place before starting a formal assessment.

Purpose of this Stage

To estimate CVD risk for patients and provide opportunities for lifestyle behaviour change as well as lifestyle interventions where appropriate. Offer information to patients about their absolute CVD risk and assess their initial response.

Importance of this Stage

To identify patients at increased CVD risk or with FH at an early stage, in order to reduce morbidity and mortality. Patients with FH are at high CVD risk and should be managed according to the FH Pathway.

In patients already on statin or other lipid-lowering therapy, a total cholesterol (TC) level <7.5 mmol/L cannot be used to exclude the possibility of FH.

Consequences of not Following this Stage

Missing the opportunity to identify and optimally manage patients who are at risk of developing CVD potentially exposes patients to future avoidable CVD events.

Rationale Behind the Indicators Chosen

All patients who are at high risk of developing CVD should be given the opportunity to make lifestyle modifications. Patients who are offered statin therapy must also be counselled to make lifestyle change in order to attain the maximum possible reduction in their CVD risk.

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<tr>
<th>Core Components of Population Health Interventions</th>
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<td>Indicators</td>
<td>Number of people under the age of 40 deemed at risk of CVD (see flow chart for criteria)</td>
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<tr>
<td></td>
<td>Proportion of the number of people under the age of 40 that have had a CVD risk assessment such as QRISK2 / QRISK3</td>
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<td>Proportion of the number of people under the age of 40, defined as low-risk, following assessment</td>
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<tr>
<td></td>
<td>Proportion of the number of people under the age of 40, defined as low-risk, that have had lifestyle advice</td>
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<td>Proportion of the number of people under the age of 40, defined as low-risk, following assessment</td>
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<td>Proportion of the number of people under the age of 40 defined as high-risk that have had repeat bloods in 3 months</td>
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<td></td>
<td>Proportion of the number of people under the age of 40 defined as possible FH</td>
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<td>Proportion of the number of people under the age of 40 defined as possible FH referred to FH service</td>
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<td>Standards</td>
<td>NICE Quality Standard - QS10b</td>
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<td>QRISK 2</td>
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<td>JBS 3</td>
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<tr>
<td>Competencies</td>
<td>All primary care staff interpreting CVD risk assessment tools are competent in delivery of risk assessment results to the patient</td>
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<tr>
<td></td>
<td>Knowledge of lifestyle advice referral pathways to patients with high CVD risk within their locality</td>
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<tr>
<td></td>
<td>Knowledge of clinical management pathway for medical management</td>
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</table>
Exclusion criteria for the use of QRISK should be adhered to, please refer to page 12 regarding advice of when not to use QRISK tool.
Exclude secondary causes of dyslipidaemia, before starting treatment.

If optimal clinical targets are not achieved after progressing through the flow chart consider referral to specialist lipid services.

Primary Prevention Clinical Management Flow Chart

Discuss benefits of lifestyle modification, refer to exercise schemes to support lifestyle change and optimise the management of all other modifiable CVD risk factors before commencing statin therapy.

A repeat lipid profile (fasting if previous triglyceride level >4.0 mmol/L) is required, together with LFTs, before commencing statin therapy.

For people with a 10% or greater 10-year risk of developing CVD or CKD (3 or above) or type II DM who consent to stain therapy commence on a statin such as Atorvastatin 20 mg

* Current NICE guidance only recommends statin therapy for type 2 diabetics after performing a QRISK assessment. In contrast, JBS3 guidelines mandate statin therapy for all patients with type 2 DM age > 40years.

Once statin therapy initiated and tolerated, repeat lipid profile and liver transaminases 3 months later. Aim for a reduction of >40% in Non-HDL-C

If not achieved discuss:
- Adherence to timing of dose
- Optimise adherence to diet & lifestyle
- Consider increasing the dose if at high-risk because of comorbidities

When statin dosage is optimal, offer annual review, including lipid profile, to check adherence to target and development or additional cardiovascular risk factors. Check liver transaminases after 12 months of statin therapy but not again (unless clinically indicated)
Notes on this Section

Lipid Profile

Lipid profile or lipid panel is a panel of blood tests that serves as an initial screening tool for abnormalities in lipids, such as cholesterol and triglycerides. The test includes: Total cholesterol (TC), HDL cholesterol (HDL-C), Non-HDL cholesterol (Non-HDL-C = TC minus HDL-C), Triglycerides (TG). The results of this test can identify certain genetic diseases and can determine approximate risks for cardiovascular disease, certain forms of pancreatitis, and other diseases.

Secondary Dyslipidaemia

Secondary dyslipidaemia is the identifiable secondary condition plausibly contributing to the patient’s dyslipidaemia. Numerous disorders are identifiable, with uncontrolled diabetes mellitus, hyperthyroidism, liver disease, nephrotic syndrome and excessive alcohol being the most common.

Establish CVD risk:

Classification of Low-risk:-
An individual’s estimated risk of CVD events over the subsequent 10 years is <10%

Classification of High-risk:-
An individual’s estimated risk of CVD events over the subsequent 10 years is ≥10%

NHS Health Check

NHS health checks are available to people in England between the ages of 40 and 74. The health check consists of an appointment with a healthcare professional during which people are asked about their family history and lifestyle and have their body mass index, blood pressure and cholesterol concentration measured.

NICE 2014 QRISK 2 or 3

QRISK 2 is the first choice algorithm in current practice. It is a prediction algorithm for CVD that uses traditional risk factors together with body mass index, ethnicity, measures of deprivation, family history, chronic kidney disease, rheumatoid arthritis, atrial fibrillation, diabetes mellitus, and antihypertensive treatment.

QRISK 3 is an updated version that uses additional factors for assessment.

Heart Age Tool
– The Heart Age Test:

Provides estimated heart age compared to your real age. Explains why it’s important to know your blood pressure and cholesterol numbers and gives advice on how to reduce your heart age.

JBS3

The JBS3 Risk Calculator has measures and communication tools, aiming to empower patients to make appropriate choices about their lifestyle and drug treatments, based on a better understanding of their personal CVD risks. It helps GPs and clinicians to address three key questions for their patients;

Why should I start CVD risk factor modification?
When should I start?
What should I do?

The JBS3 Risk Calculator demonstrates how a delay in beginning risk factor reduction (for example stopping smoking) greatly reduces the lifetime benefits that can be achieved. It also shows that, for most changes or interventions, it is never too late to obtain some benefit for the individual. It is possible to calculate the age at which beginning risk factor intervention gives the greatest lifetime benefit and, for the healthcare provider, the balance of clinical versus cost effectiveness of treatments at different ages can also be estimated. This type of mathematical modelling addresses the important issue of when best to start drug treatment from both a clinical and economic perspective.
Lifetime Risk

CVD appears to be related to long-term and combined exposure to risk factors (such as smoking and having high blood pressure). There is an opportunity to change CVD progression in an individual by earlier intervention on risk factors. CVD risk over a lifetime can be estimated and takes into account both risk from CVD and competing diseases such as cancer. As with 10-year risk levels, lifetime risk estimates represent the average figures taken from studying large groups of people; so caution should be applied in their use with individual patients. Nevertheless, lifetime risk is a novel way of communicating risk to individuals in a clinical setting, such as a GP surgery.

While the concept of a lifetime risk approach may still be relatively new for the medical community, it has been applied by the insurance industry for many years to determine appropriate levels of insurance premiums. They have long understood that disease and death caused by CVD risk factors increases with the length of exposure and that the benefits gained from interventions depend on the time point that the intervention begins (whether it is through lifestyle or drug therapy).

Lifetime risk measurement should be used in addition to the estimate of 10-year risk. It is not intended primarily as a guide for GPs to decide upon drug initiation but as a way to show an individual the lifetime consequences from their current lifestyle/medical risk factors and the substantial opportunity to reduce/delay future CVD events by early appropriate lifestyle changes and drug treatments.

Patients at High-Risk of CVD:

Patients at high risk (CVD risk 10% or above) should be offered lifestyle advice and the impact of such interventions / changes in behaviour should be explained. Referral to programmes such as exercise or obesity clinics should always be considered, irrespective of any discussion or decisions concerning statin therapy. Reassess their CVD risk after giving them opportunity to modify their lifestyle.

Rule out secondary causes of dyslipidaemia by checking TFT, LFT, renal functions, glycated haemoglobin.

Treat CVD risk factors and advocate smoking cessation and moderation of alcohol consumption. Treat hypothyroidism once identified.

If CVD risk is high on reassessment then offer high intensity statin therapy, such as Atorvastatin 20 mg.

Patient Decision Aids

The outputs of CVD risk estimation algorithms can be poorly understood by patients and, as a consequence, the merits of prevention interventions may not be fully appreciated. The development of patient decision aids by NICE was intended to be used by healthcare professionals to aid the patient consultation and explain the benefits and risks of treatment. Patient Decision Aids can be helpful when discussing primary prevention and risk reduction with a patient.
Education for Population on the Importance of Statins

The decision whether or not to start statin therapy should be made after an informed discussion between the clinician and the patient on the risks and benefits of statin treatment, whilst taking into account the potential benefits of all relevant lifestyle modifications. Informed patient preference must be explored and should be the priority. Comorbidities, polypharmacy, general frailty and life expectancy may also be relevant.

Advise People who are Offered Statin Therapy:

- That other drugs, some foods (for example, grapefruit juice) and some supplements may interfere with statins and to always consult the patient information leaflet, a pharmacist or prescriber for advice when starting other drugs or thinking about taking supplements.
- To report persistent generalised unexplained muscle pain, whether associated or not with previous lipid-lowering therapy. If they have, measure creatine kinase levels. If creatine kinase levels are more than 5 times the upper limit of normal, re-measure creatine kinase after 7 days. If creatine kinase levels are still 5 times the upper limit of normal, do not start statin treatment. If creatine kinase levels are raised but less than 5 times the upper limit of normal, start statin treatment at a lower dose.
- To seek medical advice if they develop muscle symptoms (pain, tenderness or weakness) once statin therapy has been initiated. If this occurs, measure creatine kinase.
- Restart the statin if they stopped taking it because of drug interactions or intercurrent illnesses once these issues have been resolved.

Possible insight as to why people with raised cholesterol are reluctant to start a statin.
- Adverse effects of statins such as muscle pain, joint pain, insomnia, abnormal LFTs, risk of diabetes mellitus.
- Media reports which question the efficacy of statin (in terms of CVD risk reduction) whilst exaggerating the side effects of statins.

Benefits of Statins

Statins are prescribed for their potent effect on LDL-C levels and are the most studied class of drugs in CVD prevention. The overall benefits of statin therapy include:
- Reduction in CVD morbidity and mortality.
- Primary and secondary prevention of acute CVD events.
- Slow progression / promote regression of coronary atherosclerosis.

Meta-analysis of trials, 1 mmol/L reduction in LDL-C:
- 20% reduction in coronary heart disease related mortality
- 10% reduction in all-cause mortality
- 23% reduction in major coronary events
- 17% reduction in atherothrombotic stroke

No increase in any non-CVD cause of death*.

* https://www.ncbi.nlm.nih.gov/pmc/articles/pmc3437972

Statin Intolerance

Intolerance to initial statin therapy 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.

If someone reports adverse effects when taking a high-intensity statin discuss the following possible strategies with them:
- Stopping the statin and trying again when the symptoms have resolved to check if the symptoms are related to the statin.
- Reducing the dose within the same intensity group.
- Changing the statin to a lower intensity group.

The response should be assessed at 6 to 8 weekly intervals and treatment intensified as required.
Third Stage: Secondary Prevention Assessment & Identification

Purpose of this Stage

To promote high quality clinical management of all patients with established CVD through the adoption of national standards. To favourably impact on future CVD event risk through interventions including lifestyle risk factor modification and appropriate lipid modulation.

Importance of this Stage

Supports the clinical management and lifestyle modification of patients who have been diagnosed with CVD, and directs to services that will support identification of FH at an early stage in order to reduce morbidity and mortality.

Consequences of not Following this Stage

Missing the opportunity to identify and effectively manage patients with existing CVD is likely to result in additional CVD-related morbidity, premature mortality and exaggerated strain on limited NHS resources.

Rationale Behind the Indicators Chosen

Adults with a confirmed diagnosis of atherothrombotic CVD should be offered Atorvastatin 80 mg. A proportion of adults reporting side effects from a high-intensity statin should be offered a lower dose or alternative statin.

Secondary Prevention Assessment & Identification

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<td>Proportion of patients receiving statin therapy post CVD event</td>
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<td>Proportion of patients referred to tertiary care for lipid management</td>
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<td>Proportion of patients at acceptable secondary prevention targets for CVD</td>
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<td>Standards</td>
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<td>Competencies</td>
<td>A competency framework for all prescribers [25]</td>
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</table>
Secondary Prevention Assessment & Identification

The diagram below demonstrates a robust pathways for lipid management in patients with established atherothrombotic CVD, which includes important elements for the identification of FH. There is a general agreement that the lower the LDL-C level, the lower the risk of further CVD events.

In patients already on statin or other lipid-lowering therapy, a total cholesterol (TC) level <7.5 mmol/L cannot be used to exclude the possibility of FH.

It is essential when patients are discharged from secondary care after their CV event that they are followed up in Primary Care. Patients should receive routine follow up to include measurement of their lipid levels and have their care optimised to ensure their CV risk is reduced as far as possible. If it is not possible to achieve an appropriate level of care then consider consulting a lipid specialist.
Secondary Prevention Clinical Management Flow Chart

Patient with established atherothrombotic CVD including history of stroke/TIA/MI/PVD; high dose high intensity statin treatment is recommended

Atorvastatin 80 mg (20 mg if CKD3-5, see box below)
Aim for >40% reduction in non-HDL-C, dose titration may be helpful.

Lower dose of Atorvastatin to be used if any of the following apply:

- Potential drug interaction
- High-risk of adverse effects
- Patient preference
- CKD3 or above (see notes below)

Patients who appear to have intolerance of statins should only be progressed to next stage therapy once 3 statins have been trialled with the same resultant side effects. Patients should NOT be documented as statin intolerant until other statins have been trialled. If optimum secondary prevention targets are not achieved referral to Lipid clinic is advisable.

STATIN INTOLERANCE & EFFICACY

Do not delay statin treatment in secondary prevention, if patient does not tolerate Atorvastatin 80 mg offer:
- Atorvastatin 40 mg
- Rosuvastatin 5 mg

(Refer to BNF for the recommended statins and doses, and in conjunction with other drugs)

If statins contraindicated offer Ezetimibe 10 mg

If the patient does not achieve a 40% reduction in non-HDL cholesterol after all clinical management options have been explored consider referral to specialist lipid service or cardiology services for further assessment and treatment.

A PCSK9 Inhibitor may be an appropriate treatment option for treating hypercholesterolaemia or mixed dyslipidaemia but referral to specialist lipid or cardiology services will be needed for assessment and treatment.

CKD 3 or above - Do not delay statin treatment in secondary prevention:
- If patient has CKD offer Atorvastatin 20 mg
- Increase the dose if a greater than 40% reduction in non-HDL-C is not achieved
- Agree the use of higher dose with a renal specialist if eGFR is <30ml/min/1.73m²
Renal Disease Clinical Management

An extremely rare but robustly reported severe complication of statin therapy is rhabdomyolsis and the risk of this is increased in patients renal disease. However, the presence or renal disease, particularly CKD3 or more is a powerful predictor of future CVD events irrespective of the presence or absence of other known CVD risk factors. Therefore, the overall benefits of statin therapy far outweigh the risks but is important that this class of drugs are used with a degree of caution. Atorvastatin 20 mg would appear to be a reasonable starting dose with subsequent titration as required, if eGFR is >30ml/min, then increase to a maximum dose of 80 mg, providing there are no side effects. If combinations are to be used i.e. other lipid lowering agents alongside statins, the risks increase and referral to a lipid / metabolic clinic would be advisable. However, as a caveat, the use of Ezetimibe does not appear to be associated risk of complications and can be trialled.

Secondary Dyslipidaemia
Refer to Primary Prevention Notes section, page 12.

Lipid Profile
Refer to Primary Prevention Notes section, page 12.

Lifestyle Options
Refer to Population Health Notes section, page 7.

Cardiovascular Prevention & Rehabilitation Programmes (CPRPs)

CPRPs offer the coordinated sum of activities required to influence favourably the underlying cause of CVD, as well as to provide the best possible physical, mental and social conditions, so that the patients may, by their own efforts, preserve or resume optimal functioning in their community and through improved health behaviour, slow or reverse progression of disease. The CPRPs aim to offer a service that takes a multidisciplinary biopsychosocial approach in order to best influence uptake, adherence and long-term healthier living. The involvement of partners, other family members and carers is also important.

CVD Event
Cardiovascular disease (CVD) is a class of diseases that involve the heart and/or arterial blood vessels. Acute CVD events include acute coronary syndromes (ACS/ with or without myocardial infarction (MI)), transient ischaemic attack (TIA) and stroke (CVA). Chronic forms of atherothrombotic CVD may affect the coronary arteries and result in stable angina or the peripheral arteries (PAD) with symptoms such as intermittent claudication.

Notes on this Section

CVD Event

Secondary Dyslipidaemia
Refer to Primary Prevention Notes section, page 12.

Lipid Profile
Refer to Primary Prevention Notes section, page 12.

Lifestyle Options
Refer to Population Health Notes section, page 7.

Cardiovascular Prevention & Rehabilitation Programmes (CPRPs)
Proprotein Convertase Subtilisin / Kexin Type 9 inhibitors (PCSK9)

In June 2016, NICE recommended two PCSK9 inhibitors – evolocumab (Repatha®) and alirocumab (Praluent®). This class of drugs have a particularly powerful effect on LDL-C levels and are appropriate for use in certain patients with primary hypercholesterolemia or mixed dyslipidemia, in whom statins and other treatments, such as ezetimibe, either cannot lower cholesterol to recommended levels or cannot be tolerated.

Evolocumab was also recently (June 2018) granted a secondary prevention licence in adults with established atherosclerotic cardiovascular disease (myocardial infarction, stroke or peripheral arterial disease) to reduce cardiovascular risk by lowering LDL-C levels. This licence extension follows the 2017 FOURIER CV outcomes trial results [26].

PCSK9 inhibitors are still a relatively new treatment and patients who may be suitable for one of these medicines should be referred for specialised assessment (Lipid service or Cardiologist with expertise in Lipid management) to assess for eligibility based on the NICE criteria.

The licence is subject to local guidelines and formulary.

<table>
<thead>
<tr>
<th></th>
<th>Without CVD</th>
<th>With CVD</th>
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<tbody>
<tr>
<td><strong>Primary non-familial hypercholesterolaemia or mixed dyslipidaemia</strong></td>
<td>Not recommended at any LDL-C concentration</td>
<td>Recommended only if LDL-C concentration is persistently above 4.0 mmol/litre</td>
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<tr>
<td><strong>Primary heterozygous-familial hypercholesterolaemia</strong></td>
<td>Recommend only if LDL-C concentration is persistently above 5.0 mmol/litre</td>
<td>Recommend only if LDL-C concentration is persistently above 3.5 mmol/litre</td>
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1 High risk of CVD is defined as a history of any of the following: Acute coronary syndrome [such as myocardial infarction or unstable angina needing hospitalisation]; coronary or other arterial revascularisation procedures; coronary heart disease; ischaemic stroke; peripheral arterial disease.

2 Very high risk of CVD 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.

Exclude secondary causes of dyslipidaemia, before starting treatment. If optimal clinical targets are not achieved after progressing through the flow chart consider referral to Specialist Lipid Services.
Specialist Lipid Clinics provide support to individuals with abnormal lipid levels, especially those who are at increased risk of cardiovascular disease.

Although many people, who need lipid lowering treatment, can be managed effectively in a Primary Care setting, there are some cases for which specialist referral may be indicated:

- Individuals with existing cardiovascular disease, or those at high risk, who have not been able to tolerate statin therapy: at least three statins should be tried before a patient is labelled as statin-intolerant. [Intolerance to statins is defined by NICE as "the presence of clinically significant adverse effects that represent an unacceptable risk to the patient, or that may reduce compliance with therapy".]
- Individuals with existing cardiovascular disease, or those at high risk, who have not achieved target lipid levels, despite being prescribed the maximum tolerated dose of a statin.
- Individuals, who fulfil the Simon Broome criteria for the diagnosis of Definite or Possible FH*.
  * https://cks.nice.org.uk/hypercholesterolaemia-familial
- First-degree relatives of individuals, who have been diagnosed with FH, especially children, who should be referred to a Paediatric Lipid Service.
- Individuals, for whom there is uncertainty as to the need for lipid lowering therapy.
- Individuals with significant hypertriglyceridaemia i.e. fasting triglycerides greater than 10 mmol/L, without poorly controlled diabetes or alcohol excess [hypertriglyceridaemia should respond to appropriate management of these clinical scenarios].

### Purpose of this Stage

To provide education and support across NHS structures, to ensure the identification, diagnosis and optimal management of patients with dyslipidaemia and, in particular, FH.

### Importance of this Stage

Many forms of dyslipidaemia are associated with an increased risk of cardiovascular disease but there is incontrovertible evidence that this risk can be ameliorated by effective treatment.

Individuals with FH are at a particularly high-risk of developing coronary heart disease (CHD): without effective treatment, the risk of a coronary event by the age of 55 years is at least 50% in men and approximately 30% in women. Data from the UK Register for FH (Simon Broome Register) has shown that, before effective treatment (statins) became available, mortality from CHD was increased nearly 100-fold in young adults (20-39 years) and approximately 4-fold for those aged 40–59 years.

Since statins became widely available (1992), the outcome for patients with FH has been transformed: with early intervention and appropriate follow-up, the excess CHD risk and premature mortality associated with FH can be effectively eliminated.

Although there is evidence that those patients identified with FH and managed in specialist Lipid Clinics are being treated effectively, it is thought that only 15-20% of people with FH in the UK have been formally diagnosed. Failure to identify FH is a particular issue in relation to younger individuals who, in fact, are those that accrue the greatest benefit from effective treatment.
Consequences of not following this stage

As the estimated population prevalence in the UK of FH is in the region of 1:250, there may be as many as 9600 affected individuals in Cheshire and Merseyside. A failure to identify and treat such patients would be a missed opportunity to prevent the associated excess atherothrombotic CVD risk and premature mortality.

Rationale behind the indicators chosen

Healthcare professionals should offer all people with FH, or suspected FH, a referral to a specialist with expertise in FH for confirmation of diagnosis, initiation of appropriate management and cascade testing of relatives.

Familial Hypercholesterolaemia Assessment & Identification

<table>
<thead>
<tr>
<th>Core Components of Population Health Interventions</th>
<th>Milestones &amp; Guidance</th>
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<tbody>
<tr>
<td><strong>Indicators</strong></td>
<td>Proportion of patients with suspected FH who are:</td>
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<tr>
<td></td>
<td>• Referred to specialist lipid clinic or FH service for expert diagnosis and treatment</td>
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<tr>
<td></td>
<td>• Offered genetic testing for FH</td>
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<tr>
<td></td>
<td>• Undergo genetic testing for FH</td>
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<td></td>
<td>• Treated to accepted lipid targets with statin therapy or other approved treatments</td>
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<tr>
<td></td>
<td>• Proportion of children (less than 16) with proven FH offered treatment.</td>
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<tr>
<td></td>
<td>Proportion of relatives of patients with FH, who are themselves screened for FH.</td>
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<tr>
<td><strong>Standards</strong></td>
<td>NICE Quality Standard QS41 FH [27]</td>
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<tr>
<td><strong>Guidance</strong></td>
<td>NICE CG71 [28]</td>
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<td></td>
<td>NICE CG181</td>
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<td></td>
<td>NICE Pathways: Lipid modification therapy for preventing CVD [29]</td>
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<td>NICE Technology Appraisal TA393 &amp; TA394</td>
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<td><strong>Competencies</strong></td>
<td>Patient counselling services</td>
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<td>A competency framework for prescribers</td>
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<td>Clinical examination</td>
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The diagram below demonstrates a process of referral and management for patients with suspected FH after either a primary or secondary prevention assessment or identification process or incidental finding.

**Familial Hypercholesterolaemia Assessment & Management**

- **Identification**
  - Incidental Finding
  - Primary Prevention
  - Secondary Prevention
  - Registered with Lipid Clinic

**FH Service Referral Proforma using Simon Broome Criteria (Ref, See Pg23)**

- **Clinical Review – FH Coordinator & FH MDT**
  - FH Coordinator/Lipidologist/ Cardiologist /Paediatric Specialist
  - Assessment / Counselling / Identification of relatives

- **DNA testing offered**
  - FH Mutation Positive
  - Contact relatives: Advise lipid measurement and genetic cascade testing

- **DNA testing not offered**
  - FH Mutation Negative
  - Contact relatives: Advise lipid measurement

- MDT will advice re lipid management / CVD risk
- Follow-up plan agreed (Lipid Clinic / Primary Care)
- (Paediatric Lipid support specialist service)

- **Structured Annual Review**
  - Primary / Secondary Care
The PCSK9 gene

PCSK9 is an enzyme involved in the breakdown of LDL receptors. Alterations in this gene may result in a form of the enzyme, which increases the rate of breakdown of LDL receptors so that there are fewer on cell surfaces. This reduces the removal of LDL particles from the blood and, therefore, LDL-C accumulates in the blood. This is the least common genetic alteration found in cases of FH.

FH shows an autosomal dominant pattern of inheritance so that most people with this condition are heterozygotes i.e. they have one abnormal gene, inherited from one parent, alongside a normal gene inherited from their other parent. Heterozygous FH is a relatively common condition, with an estimated population prevalence in the UK of approximately 1 in 250 - therefore approximately 9,600 affected individuals in Cheshire and Merseyside.

A clinical diagnosis of FH is made using the Simon Broome Criteria* but genetic testing is possible, allowing identification of the gene alteration in most cases. Whilst a DNA test is more expensive than lipid measurements alone, it has been shown that its use improves the cost effectiveness of cascade testing and it is strongly recommended in CG71 and in the NICE Quality Standard QS41 for FH.

* Simon Broome Criteria for the diagnosis of Definite or Possible Familial Hypercholesterolaemia.

www.nice.org.uk/guidance/cg71

Definite Familial Hypercholesterolaemia

a. Total cholesterol > 6.7 mmol/L or LDL cholesterol above 4.0 mmol/L in a child < 16 years
or Total cholesterol > 7.5 mmol/L or LDL cholesterol above 4.9 mmol/L in an adult.

PLUS

b. Tendon xanthomas in patient, or in 1st degree relative (parent, sibling, child), or in 2nd degree relative (grandparent, uncle, aunt)

OR

c. DNA-based evidence of an LDL receptor mutation, familial defective apo B-100 or PCSK9 gain of function mutation

Familial Hypercholesterolaemia

Familial hypercholesterolaemia is an inherited metabolic disorder which causes raised LDL cholesterol (LDL-C) levels from birth, resulting in a greatly enhanced risk of CVD, particularly CHD.

FH is caused by a gene alteration in one of three key genes:

- The LDL receptor gene
  This is the most common gene alteration in patients with FH. The LDL receptor is a protein on cell surfaces, which is a key component in the removal of LDL-C from the blood. Alterations in the LDL receptor gene results in reduced LDL receptor activity and, therefore, LDL-C accumulates in the blood.

- The ApoB gene
  This gene is responsible for the main protein in LDL particles: apolipoprotein B (apoB). This protein interacts with the LDL receptor so that the LDL can be removed from the blood. Alterations in apoB may affect this interaction so that the LDL cannot be removed and, therefore, LDL-C accumulates in the blood.

- The PCSK9 gene
  PCSK9 is an enzyme involved in the breakdown of LDL receptors. Alterations in this gene may result in a form of the enzyme, which increases the rate of breakdown of LDL receptors so that there are fewer on cell surfaces. This reduces the removal of LDL particles from the blood and, therefore, LDL-C accumulates in the blood. This is the least common genetic alteration found in cases of FH.
Possible Familial Hypercholesterolaemia is defined as:

a. Total cholesterol > 6.7 mmol/L or LDL cholesterol above 4.0 mmol/L in a child < 16 years
or Total cholesterol > 7.5 mmol/L or LDL cholesterol above 4.9 mmol/L in an adult.

PLUS

b. Family history of myocardial infarction: below age of 50 in a second degree relative or below age 60 in a first degree relative

OR

c. Family history of raised cholesterol: > 7.5 mmol/L in adult first or second degree relative or
> 6.7 mmol/L in child or sibling under 16

NICE Clinical Guideline (CG) 71

This guidance published in 2008, and updated in 2017, addressed the identification and management of FH.

Key recommendations included:

- Recognition of the possibility of FH in individuals with raised cholesterol, especially when there is a personal or family history of premature CHD.
- Referral of all patients with a clinical diagnosis of FH (Simon Broome Criteria) to a specialist with expertise in FH.
- Confirmation of diagnosis by DNA genetic testing.
- Cascade testing: ie systematic testing of first-degree relatives of a patient with FH (who have a 50% chance of also having FH), using a combination of lipid measurements and DNA testing. In general, it is found that most individuals with FH will have at least two affected first-degree relatives (parent, sibling or child).
- Children at risk of FH should be tested before the age of 10 years.
- Children and young people diagnosed with, or being investigated for, FH should be offered a referral to a specialist with expertise in FH in children and young people.
- If lipid lowering therapy is being considered in females of reproductive age, information and counselling should be provided with respect to the need for contraception and the steps required to avoid the risks associated with taking such treatment whilst pregnant.
- Treatment with high intensity statins, in order to achieve a reduction in LDL-C of at least 50% from baseline. Where this cannot be achieved using statins, there is now the option to use a PCSK9 inhibitor in FH patients (NICE TA 393 and NICE TA 394).
- As the clinical expression of FH is affected by lifestyle (diet, smoking), all individuals with this diagnosis should be offered individualised nutritional advice if appropriate (and access to smoking cessation services).

FH Service

This should be a regional service, which facilitates the implementation of agreed priorities in the identification and management of patients with suspected FH e.g. NICE CG71 and NICE QS41 for FH.

1. FH Coordinator
The individual undertaking this role will coordinate referrals to the FH Service, from multiple sites, across all NHS sectors. Once a referral is accepted by the FH Multi-disciplinary Team (MDT), the FH Coordinator will facilitate the steps of assessment, diagnosis (including genetic testing), treatment and follow up. The FH Coordinator will also manage the cascade screening of family members, who may also have FH.

2. FH MDT
The FH Service Multi-Disciplinary Team includes a range of professionals, who will support the Service in the assessment and treatment of those patients, and their relatives, who are suspected and / or diagnosed with FH. Primary professionals will include local Lipidologists, Cardiologists and Paediatricians with a special interest in lipid management.
Quality Improvement Tools

PRIMIS FHC™ is one example of a quality improvement tool available to help practices by generating a list of patients who may have FH but who do not have a coded diagnosis. This will establish a more accurate prevalence rate for FH within the practice population and identify patients who are at increased risk of developing FH and categorising them by level of risk.

The tool highlights patients with the disease who are currently untreated, identifying opportunities to optimise lipid lowering treatment regimes for all patients with the disease. It provides a mail merge function to generate letters to send to high risk patients about discussing their family history. It offers a comparative analysis service via CHART Online, which enables comparison with other practices, locally or nationally, and highlights recording rate of important family history information.
**Lipid Pathway Reference**


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23. NICE Technology appraisal guidance [TA393]. Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia. Available at: https://www.nice.org.uk/guidance/ta393

24. NICE Technology appraisal guidance [TA394]. Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia. Available at: https://www.nice.org.uk/guidance/ta394


30. Familial Hypercholesterolaemia (FH) quality improvement tool; University of Nottingham, England. Available at: https://www.nottingham.ac.uk/primis/tools-audits/tools-audits/familial-hypercholesterolaemia.aspx
“This pathway has been developed by the NHS as part of a joint working initiatives with Amgen Ltd, with facilitated support from Salvera Services Limited, EQE Health Ltd and Interface Clinical Services.”