

**Cheshire and
Merseyside**
Health and Care Partnership

Lifespan Pathway for Lipid Management 2024

**Guidance for all those caring for
people with raised CVD risk.**



Who is this document intended for?

- Non-specialist clinicians prescribing lipid therapies
- Providers of primary care services
- Providers of cardiovascular disease services
- Patients
- Integrated Care Board
- Place based commissioners

Acknowledgements

Health Innovation North West Coast and Cheshire and Merseyside Clinical Cardiac Network have developed the Lifespan Pathway for Lipid Management 2024 in association with clinicians and specialists from across the region.

We would like to acknowledge and thank all the contributors who have provided their expertise and commitment to ensure that the development of this pathway has been possible:

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Introduction

Cardiovascular disease (CVD) includes all conditions affecting the heart and blood vessels, i.e. coronary heart disease, cerebrovascular disease which causes strokes and transient ischaemic attack (TIA) and peripheral arterial disease (PAD) which includes aortic disease and aneurysm.

Addressing modifiable risk factors and using lipid therapies can help prevent CVD. Increased lipids in the blood stream (hyperlipidaemia), and especially low-density lipoprotein cholesterol (LDL-C), have a linear relationship to the development of CVD and are a significant modifiable risk factor for CVD [1]. The Lifespan Approach for the Management of Lipids 2024 is a best practice clinical pathway, underpinned by national guidance and evidence relating to the diagnosis of hyperlipidaemia and use of lipid therapies.

This pathway has been developed by Cheshire and Merseyside clinicians and managers to support improvement in clinical outcomes for people at risk of, or who already have CVD, and would benefit from lipid interventions to reduce their risk of new, or additional CVD burden, which would otherwise increase morbidity and mortality.

Key message for commissioners

In 2023 CVD accounted for 25% of all deaths in England, and nearly 7 million are living with the impact of CVD, causing chronic symptoms and disability. CVD is the largest cause of premature death in deprived areas and is preventable for many.

CVD is the largest area where the NHS can save lives in the next 10 years. Furthermore, risk factors for CVD are involved in the development of cancers and Alzheimer's disease. Optimising lipid therapies, and especially statin therapy, has been shown to be the most cost-effective intervention for CVD prevention to save the NHS money in the first 5 years of use.

CVD prevention is detailed in the NHS Long Term Plan, and the Advancing CVD Prevention In Cheshire and Mersey strategy, with the aim of helping people live longer and remain healthy. [2] [3] [4] [5] [6]

High Cholesterol	
75%	Of people aged 40-74 years have a formal validated CVD risk assessment including cholesterol reading recorded in last 5 years by 2029.
60%	Of people aged 25-84 years with a CVD risk > 20% are on lipid lowering therapy.
25%	Of the expected number of people with FH are diagnosed and treated according to NICE by 2024.

Figure 1. Cardiovascular Disease Ambitions for England

Improving the use of lipid therapies to reduce morbidity and mortality from CVD, will require clinical pathways and services to support early identification and timely treatment. Familial hypercholesterolaemia (FH) is an important genetic condition affecting approximately 1 in 250 people and can lead to high levels of LDL-C and premature CVD, yet FH remains underdiagnosed and undertreated across the UK [2].

At the time of writing, the Cheshire and Mersey FH genetic testing service, vital to make a diagnosis of FH, is a pilot yet to be commissioned for the long term. The National Institute for Health and Care Excellence (NICE) recommends a childhood diagnosis is achievable, and required, to improve access to treatment by the age of 10 years. Child-Parent Screening Services (CPSS), designed to detect FH in childhood, then screen family members, is an NHS England commissioned pilot until 2025 when review and recommendations are expected.

Identifying babies with FH, via CPSS, or through cascade testing (genetic testing family members), will require providers to prescribe lipid therapies for children. This new work will impact on primary care and paediatric specialist services; development of workforce and pathways to support this work will be essential to improve outcomes for those at risk of premature CVD due to FH. [7] [8]

Aims

- Define opportunities using technology and innovations, throughout the average lifespan, to recommend when lipid assessment and intervention should be considered.
- Early identification and treatment of familial hypercholesterolaemia (FH) to include cascade testing of families to reduce the burden of premature vascular disease.
- Optimal identification and treatment for people who will benefit from primary prevention lipid therapies to reduce their CVD risk.
- Optimal identification and treatment for people who will benefit from secondary prevention lipid therapies to reduce their CVD risk.
- Provide guidance for special considerations, such as pre-natal counselling, use of lipid therapies in pregnancy, and treatment decision aids for children with FH.
- Define lifestyle interventions to reduce CVD risk tailored to age and comorbidities.
- Support clinicians to de-prescribe lipid therapies when no longer appropriate and potentially harmful for people with frailty or end of life conditions.

The Pathway Overview

The essential stages and their key aim for the Lifespan Approach to the Management of Lipids 2024 are detailed in Figure 2. The stages take an age-focused approach to illustrate current and potential opportunities for assessment, diagnosis

and treatment throughout a normal lifespan. The detail of each pathway stage includes a flowchart summary of the main recommendations, whilst the narrative explains key aims, diagnosis and management, with special considerations.

Lifespan Approach: Stages and Key Aims

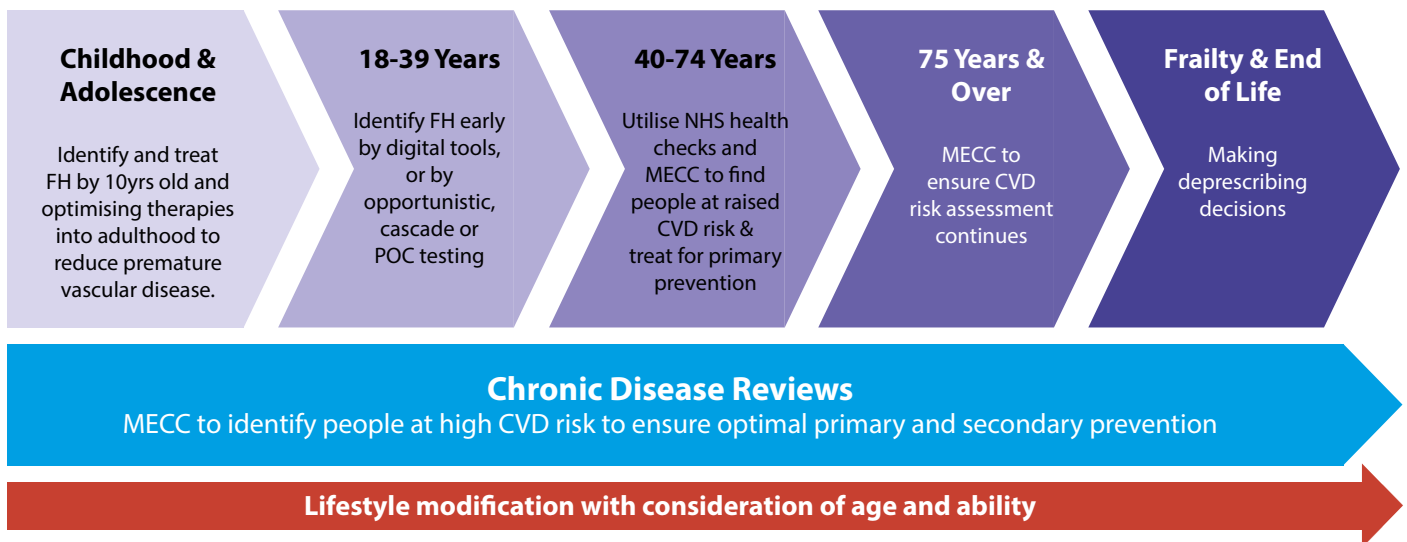


Figure 2. Lifespan Approach to the Management of Lipids 2024

The key issue for all people with raised CVD risk, is that for every 1mmol/L reduction in LDL-C there is a 22% reduction in the annual risk of developing CVD, irrespective of the treatment used to lower LDL-C [9]. This pathway explains how to proactively determine who may benefit from lipid therapies, and how to structure clinical care to deliver comprehensive, timely management. Lifestyle modification and lipid

therapies work together to optimise CVD prevention, i.e. improvements in diet, weight, physical activity, stopping smoking, and reducing alcohol intake benefit everyone, from infancy through to old age. Lipid management pathways are usually medication decision aids focusing on CVD risk or presence of CVD to divide treatment into primary and secondary prevention.

This approach to lipid medication use is important, and the Summary of National Guidance for Lipid Management for Primary and Secondary Prevention of CVD, called the NHS Lipid Pathway (Appendix A), is referenced as a decision aid for prescribing lipid therapies. [10]

An estimated 50% of adults may benefit from intervention to reduce hyperlipidaemia. For people with FH, this can begin in childhood. This pathway discusses child-parent screening as an option for detecting FH prior to the development of premature CVD; this supports NICE recommendations to initiate lipid therapies for people with FH by age 10 years. It describes the long term treatment of FH from childhood, into teenage years and adulthood, with recommendations about the range of lipid therapies available, whilst considering prenatal counselling regarding the risks of conceiving a child with FH, and perinatal use of lipid therapies. [5] [11]

NHS Health Checks, for fit and well people aged 40-74 years, are commissioned to find those at risk of developing CVD who may benefit from modification of hyperlipidaemia. This check excludes people with established CVD and other high-risk conditions such as diabetes and chronic kidney disease (CKD). This pathway considers how people over 74 years, and therefore no longer eligible for an NHS Health Check, can still receive CVD risk assessment.

The chronic disease review section cuts across all generations to make every contact count (MECC), to optimise CVD risk in people with pre-existing chronic long term conditions (LTCs) already attending regular reviews, e.g. CVD, hypertension, diabetes, CKD and respiratory conditions such as chronic obstructive pulmonary disease (COPD), as many are smokers or ex-smokers, and likely to have a higher risk of CVD. Conversely, for people with complex multimorbidity, frailty or receiving palliative treatment, this pathway lends support for discussions on prescribing or de-prescribing lipid therapies to balance any benefit and avoid risks of harm.

The lipid profile

This pathway, and its use of lipid therapies, relies on accurate interpretation of the lipid profile. National guidance recommends the clinician evaluate either non-high-density lipoprotein cholesterol (non-HDL-C) or LDL-C, to make clinical and therapeutic decisions; non-HDL-C ≤ 2.6 mmol/L is equivalent to LDL-C ≤ 2.0 mmol/L. [12]

Random (non-fasting) lipid profile blood tests are recommended for most people and are accurate unless triglyceride levels are very high (>9 mmol/L), when a fasting profile is needed. Laboratory calculations, e.g. Friedewald or Samson equations, can be used to calculate LDL-C from a random lipid profile if triglycerides are <9 mmol/L, or an estimate can easily be accessed using an online calculator; see Appendix C.

Whilst total cholesterol and total cholesterol:HDL ratio are also reported, both are unhelpful for clinical therapeutic decisions, though total cholesterol can be used as one variable in considering possible FH diagnosis.

Once treated with lipid therapies, it is vital to achieve target lipid levels for optimal risk reduction. This pathway recommends the following treatment targets for cholesterol;

1. All secondary prevention: Non-HDL-C ≤ 2.6 mmol/L or LDL-C ≤ 2.0 mmol/L.
2. Genetically diagnosed and suspected FH primary prevention: $>50\%$ reduction from baseline LDL-C.
3. Non-FH primary prevention: Non-HDL-C ≤ 2.6 mmol/L or LDL-C ≤ 2.0 mmol/L. [13][14][15]

Whilst NICE currently recommend a non-HDL-C reduction of $>40\%$ for primary prevention, ESC (European Society for Cardiology) recommend a target LDL-C <1.4 - 3.0 mmol/L, tailored to the individual CVD risk. The authors of this pathway propose that a numeric target facilitates effective path lab reporting of the lipid profile, ensuring cut-off ranges are represented to support timely clinical intervention. Whilst the ideal target of non-HDL-C ≤ 2.6 mmol/L is recommended, this may not be achievable for all people in the non-FH primary prevention population, within the limitations of medications currently licensed for this purpose. Therefore, targets should be tailored to the individual.

Summary of lipid therapies

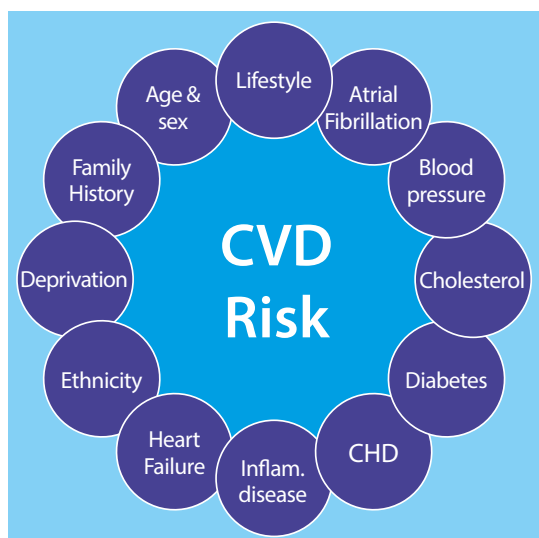
This pathway will discuss how, and when, to use the therapies summarised in Figure 3. Always check the latest regional formularies for local variations and the

Electronic Medicines Compendium for the SPC; links available in Appendix C.

Statins	Ezetimibe	Bempedoic acid
<ul style="list-style-type: none"> • First line therapy for people at high risk of, or already have CVD, is always a high intensity statin, i.e. <ul style="list-style-type: none"> ◦ Atorvastatin ≥ 20mg OD, ◦ Rosuvastatin ≥ 10mg OD • Achieves 40-50% non-HDL-C reduction. • NICE recommends LFT at baseline, with each titration, at 12 months but not again if normal. (See page 17 for more information on liver function.) • Manage “intolerance” using Statin Intolerance Pathway. 	<ul style="list-style-type: none"> • Add on to statin • Provides an extra 10-20% non-HDL-C reduction on top of statin. <ul style="list-style-type: none"> ◦ Monotherapy in people who are statin intolerant, ◦ In combination with Bempedoic Acid if target not achieved. • No monitoring. • Well tolerated. 	<ul style="list-style-type: none"> • NICE approved 2021. <ul style="list-style-type: none"> ◦ Recommended in combination therapy with Ezetimibe. • 38% non-HDL-C reduction with Bempedoic acid & Ezetimibe. • Works like a statin but less effect on skeletal muscle. • Only monitor renal/liver function if severe impairment. • Side effects; <ul style="list-style-type: none"> ◦ Possible increase in uric acid & risk of gout. ◦ Possible risk of tendon rupture.
Inclisiran	PCSK9i; Alirocumab or Evolocumab	
<ul style="list-style-type: none"> • NICE approved 2021. • Primary care and secondary care use. • For people with CVD and LDL-C>2.5mmol/L, if, <ul style="list-style-type: none"> ◦ Maximum tolerated dose of high intensity statin +/- Ezetimibe, or, ◦ Ezetimibe monotherapy, or, ◦ Ezetimibe & Bempedoic acid combination, or, ◦ Unable to tolerate any oral therapy. • Reduces production of PCSK9 protein by reducing mRNA coding for PCSK9 rather than antibody inhibition. • Given at baseline, 3 months then 6 monthly. • Provides 50% LDL-C reduction. • Well tolerated and minimal side effects. 	<ul style="list-style-type: none"> • NICE approved 2016. • Secondary care use only. • For people with FH if, <ul style="list-style-type: none"> ◦ LDL-C>5mmol/L for primary prevention, or, ◦ LDL-C>3.5mmol/L for secondary prevention. • For people with CVD alone if, <ul style="list-style-type: none"> ◦ LDL-C >4.0mmol/L or, ◦ LDL-C >3.5mmol/L with poly-vascular disease. • Provides 50-75% non-HDL-C reduction. • 2 weekly subcutaneous self-injector. • These are monoclonal antibodies that inhibit PCSK9 protein, which then reduces LDL receptor degradation, thus increasing the number of LDL receptors helping to reduce serum cholesterol. 	
Icosapent ethyl	Other specialist-only lipid therapies	
<ul style="list-style-type: none"> • NICE approved 2022. • Highly purified fish oil. • Two capsules twice daily. • Add-on therapy to reduce CVD risk, if, <ul style="list-style-type: none"> ◦ Taking statin, plus, ◦ Fasting triglycerides ≥1.7mmol/L and LDL-C levels >1.04mmol/L and ≤2.60mmol/L. • No target lipid level. • Side effects include arrhythmias, flatulence, gout and peripheral oedema. 	<ul style="list-style-type: none"> • Fibrates (usually fenofibrate) are for specialist consideration only, though not generally recommended for most people. Sometimes used by specialists to treat severe raised triglycerides and can be combined with Ezetimibe, but particularly risk rhabdomyolysis with statins. • Cholestyramine, Colesevelam and Nicotinic Acid are rarely used now. 	

Figure 3. Overview of Lipid Therapies used in This Pathway [16] [17] [18] [19] [20]

Key Messages Arising From The Pathway



Hyperlipidaemia is one of the main drivers for atherosclerosis (build of fatty plaques that narrow and block arteries); atherosclerosis begins in childhood, becoming clinically significant by causing CVD in later life. In some, this process is accelerated by FH, leading to premature CVD.

By taking a lifespan approach to lipid management, this pathway guides the reader to understand and visualise the opportunities for lipid interventions throughout a person's life. Embedding this lifespan approach in clinical practice will support holistic assessment of CVD risk factors required for optimal prevention.

Each section details practical recommendations for service delivery to make every contact count.

Early identification and treatment of familial hypercholesterolaemia.

UK population health data shows significant underdiagnosis of FH which affects 1 in 250 people, risking premature vascular disease. This pathway considers novel ways to increase the numbers diagnosed and treated at an earlier age.

Understanding CVD risk and use of calculators such as QRISK^{®3}.

Application of CVD calculators to direct the use of lipid therapies for primary prevention are widespread in the NHS, however, incorrect use may underestimate risk, leaving people untreated. This pathway outlines how and when calculators should, and should not, be used for specific patient cohorts to avoid underestimating CVD risk.

Optimising lipid therapy treatments safely and effectively.

The Summary of National Guidance for Lipid Management for Primary and Secondary Prevention of CVD (NHS Lipid Pathway; Appendix A), and Statin Intolerance Pathway (Appendix B), underpin lipid therapy decisions for adults with lipid disorders in this lifespan approach.

This pathway discusses lipid therapies in children, prenatal counselling, use of statins during childbearing age and de-prescription of lipid therapies during end-of-life care. Data search tools are outlined as a resource to aid case finding and risk stratification.

Lifestyle modification for everyone.

Supporting people to understand how to improve their cardiovascular health, whatever their age or co-morbidities, to help drive autonomy and enable best possible outcomes for CVD prevention.

The Pathway Stages

Childhood and Adolescence



Key aim – Child-parent screening as one evidence-based option for early diagnosis of FH with a management plan to transition into adulthood.

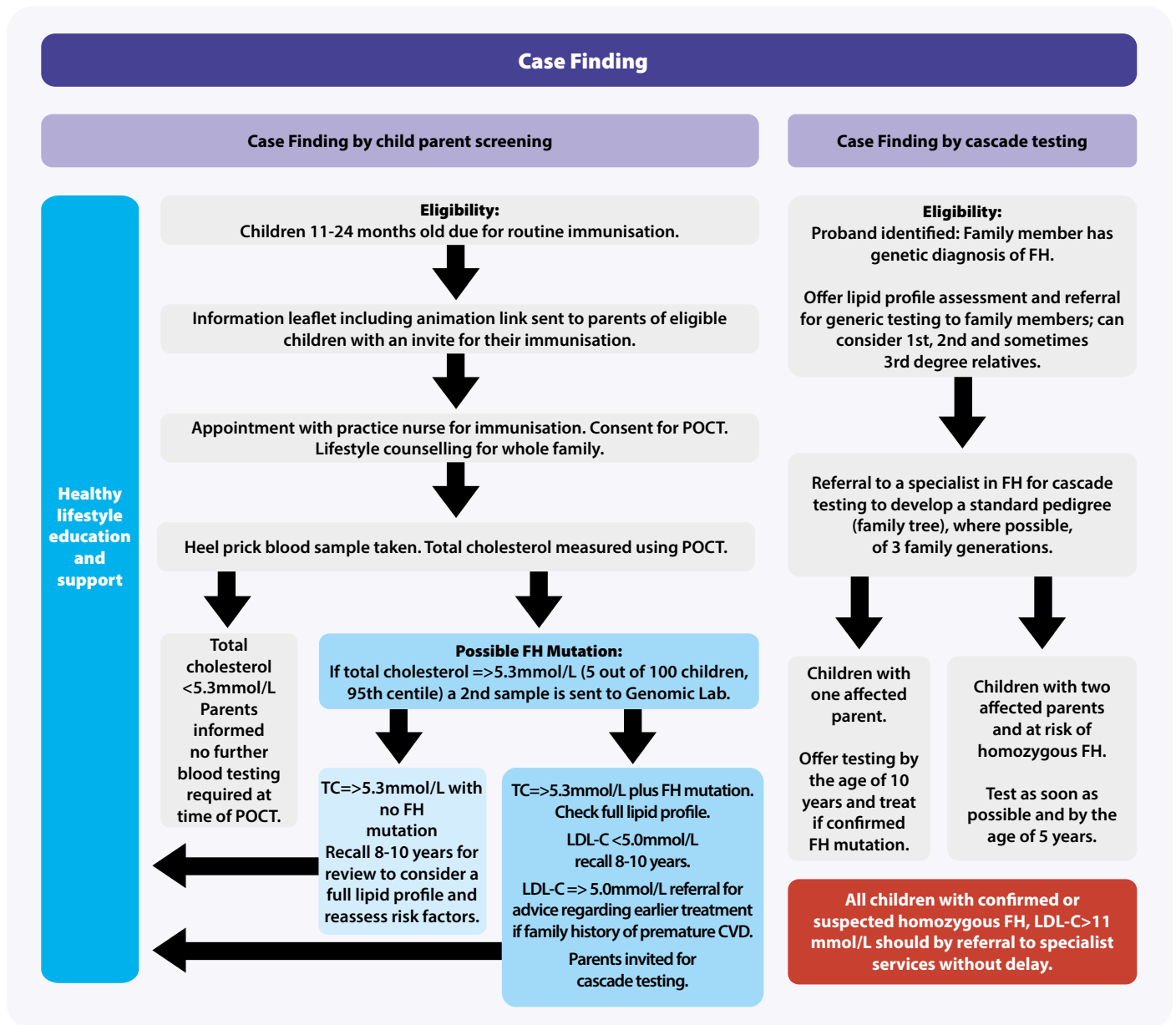


Figure 4. Child Case Finding Algorithm [11]

FH is an autosomal dominant condition; heterozygous FH (one gene from one parent), affects 1 in 250 people, whilst homozygous FH (two genes, one gene from each parent) has an estimated prevalence of 1 in 170,000-300,000 and is responsible for causing CVD in childhood [21].

This pathway refers to people with heterozygous FH unless otherwise specified. All people with FH have a high risk of premature CVD, often under 40 years of age. They are 100 times more likely to have

a myocardial infarction than people without FH, whilst lipid therapies can effectively and significantly reduce their risk.

The aim of lipid assessment at this pathway stage is early identification of FH, to maximise prevention of premature vascular disease by facilitating lifestyle modification and consideration of lipid therapies by the age of 10 years where possible, as well as cascade testing family members. [11][22]

Early diagnosis and case finding

Children with FH can potentially be detected in a variety of ways:

- 1. Child-parent screening (CPSS)** in primary care (Figure 4), using a calibrated and validated, point of care capillary blood test (POCT), is one innovative approach to diagnosing FH in children aged around 12 months. At the time of writing, this service is at pilot stage, commissioned by NHS England until 2024 prior to re-evaluation. Screening at 12 months, to coincide with childhood immunisations, is an opportune time to influence lifestyle and nutrition, when parents are developing family eating and activity habits. Infants with a confirmed genetic diagnosis will then need a full lipid profile check to confirm the severity of hypercholesterolaemia. Parents of infants with a genetic mutation for FH are offered genetic screening, allowing early initiation of lipid therapies to optimise CVD prevention. Research shows CPSS has a high level of acceptability for parents, whilst not impacting on delivery of baby immunisations [11].
- 2. Cascade testing** offers genetic testing to identify members of the family when one member has a genetic diagnosis of FH. To allow treatment to commence by age 10, NICE recommends children should have genetic testing by 10 years if one parent is affected, or 5 years if both. [7]
- 3. POCTs**, using a validated POCT machine, although not currently commissioned, provide an innovative way to find this important condition early in other venues e.g. at school during routine school nurse health checks or immunisations, or during hospital paediatric appointments.
- 4. Opportunistic full lipid profiles**, though at the time of writing not in guidelines or commissioned pathways, could be offered as an FH screen for children already having blood tests in primary or secondary care.

Recall, review and treatment

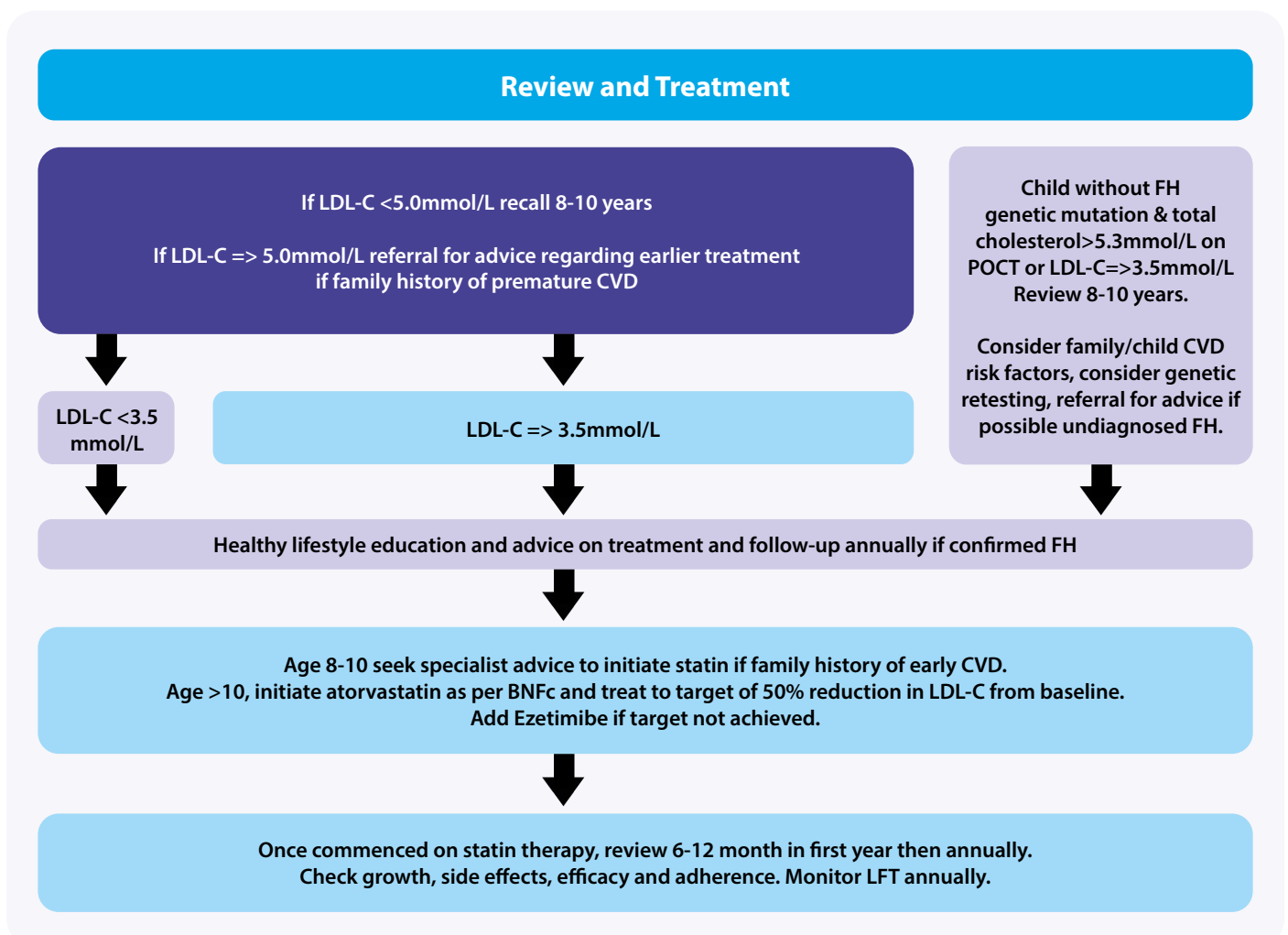


Figure 5. Child Review and Treatment Algorithm for Known or Suspected FH [8]

For children with elevated cholesterol, lifestyle modification for the whole family should be supported (see page 24). At the time of genetic diagnosis, the family of a child with FH should receive written information about the age their child should be considered for initiation of lipid therapies, with a process in place to safely recall the child by 8-10 years. Earlier reassessment should be considered if LDL-C \geq 5.0mmol/L and there is a known family history of premature vascular disease.

Children with confirmed or suspected homozygous FH (LDL-C \geq 11mmol/L) should always be referred to specialist paediatric services without delay, as tertiary care is usually required, including apheresis and possible liver transplant. All children with raised lipids should be reviewed by 8-10 years (Figure 5). Not all genetic mutations are currently identifiable, therefore checking CVD risk factors and periodically reviewing developments in genetic testing is advised [23].

As with adults, a high intensity statin is the mainstay of lipid therapy for children with FH. Statins are usually well tolerated by children, who don't experience the same frequency of side effects as the older population with comorbidities that increase the risk of statin related problems. The principles of using statins in children is the same as in adults and they are considered a safe and effective treatment to initiate and titrate in primary care, as with adults.

At the time of writing, atorvastatin is licensed from age 10 years, whilst rosuvastatin is licensed from 6 years, though recommended for specialist initiation in children. Ezetimibe can be used as an add-on therapy, but other lipid treatments, e.g. PCSK9i, Bempedoic acid and Inclisiran are not licensed for children. Target cholesterol levels for primary prevention in people with FH are a 50% reduction from baseline.

Paediatric specialist referral

Advice and guidance or specialist opinion is recommended if;

1. Homozygous FH or severe hypercholesterolaemia; LDL-C \geq 11mmol/L.
2. Children with significant comorbidities e.g. type 1 diabetes or a family history of very premature CVD in their 20s or 30s.
3. Children who may be high risk if there is a family history of premature CVD and require initiation of therapy under the age of 10 years.
4. Unable to achieve target LDL-C levels where rosuvastatin may be required.

Special considerations

Prenatal counselling

The timing of prenatal counselling will depend on the young person, but should be considered for all people with FH and will need to be considered during adolescence. This should include the risks of conceiving a child with FH. Couples who both have heterozygous FH and therefore at risk of having a child with homozygous FH, are eligible to be considered for pre-implantation genetic testing for monogenic disorders (PGT-M); a specialist procedure which involves checking the genes or chromosomes of an embryo for a specific genetic condition.

Because embryos need to be tested in a lab, people need to have IVF. Embryos which have been tested and are free from the condition are placed back inside the womb to continue to develop. Historically, the embryo was usually transferred two to six days after being created (i.e. a fresh embryo transfer) but now, the embryo is more often frozen and transferred later.

[24]

Statin therapy

People with FH who wish to become pregnant should be advised on how to manage their statin therapy due to the possible risk of preterm birth and low birth weight, and theoretical risk of congenital malformations, though research suggests further studies are needed. Currently people should be advised to stop statin therapy three months before pregnancy, and usually not to restart until breastfeeding is completed.

Advice and guidance can be sought from specialist lipid services when considering cessation of lipid therapies prior to pregnancy, as consideration of continuing medication in pregnancy, or an early restart of treatment when breastfeeding, may be safer for people with high-risk FH. For people who become pregnant whilst taking statin medication, advice should be sought from an obstetrician regarding monitoring requirements. [25]



Key aim – A single lipid check for young people who have not had childhood screening to ensure diagnosis and treatment of FH before the development of premature vascular disease.

FH Case Finding Options				
Child-parent screening <ul style="list-style-type: none"> • 12 month vaccination 	Cascade testing <ul style="list-style-type: none"> • Proband relative 	POCT <ul style="list-style-type: none"> • Routine vaccination • Health bus • Social event 	Single random lipid profile <40 years	Primary care systematic search <ul style="list-style-type: none"> • Digital tools (see Appendix C) • Bespoke search
When to suspect FH: Use a combination of cholesterol level, examination*, and history and history of premature CVD to direct genetic testing for FH (exclude secondary causes**)				
Cholesterol mmol/L	Adult <30 years	Any age	Premature Coronary Heart Disease (CHD)	Genetic diagnosis
Total cholesterol (mmol/L)	>7.5	>9.0	Use the following to consider FH, rather than strict lipid cut-off values alone, <ul style="list-style-type: none"> • Personal history and/or, • Family history <60 years old, plus, • No secondary cause 	Use an FH calculator to check if genetic testing would be appropriate, <ul style="list-style-type: none"> • Simon Broome • Dutch Lipid Clinic Network • Welsh Score • Refer to specialist if testing indicated
And/or				
LDL-C (mmol/L)	>4.9	>6.5		
And/or				
Non-HDL-C (mmol/L)	>5.9	>7.5		
*Xanthomata are suggestive of FH but their absence does not exclude FH. **Check for secondary causes of hyperlipidaemia by clinical assessment plus renal and liver profile, TFT and HBA1c. Exclude hypothyroidism, diabetes mellitus, significant renal impairment (especially nephrotic syndrome) and cholestatic liver disease. Assessment of rare causes such as Cushing's syndrome and Pheochromocytoma should be directed by the clinical context. It is important to consider that FH can co-exist with other conditions and specialist advice should be sought in complex cases.				
FH Key Points for Treatment				
Lifestyle modification <ul style="list-style-type: none"> • See page 24 for details 	Treat as for Primary & Secondary Prevention; Figures 7 & 11 <ul style="list-style-type: none"> • High intensity statin first line • Multi-drug approach can include, <ul style="list-style-type: none"> ◦ Ezetimibe ◦ Ezetimibe/Bempedoic acid ◦ Inclisiran ◦ PCSK9i 		Homozygous FH <ul style="list-style-type: none"> • Specialist referral and treatment 	
	Target Lipid Level			
	Primary Prevention 50% reduction in LDL-C from baseline	Secondary Prevention Non-HDL-C ≤2.6mmol/L		

Figure 6. FH case finding, Overview of Diagnosis and Key Treatment Steps [7] [10]

Young people do not have a routine lipid profile until they become eligible for an NHS Health Check at the age of 40, risking undiagnosed FH and

preventable premature vascular disease. This stage explores finding and treating young people with this important and potentially serious condition.

Case finding

Figure 6 describes the potential options to identify FH within the population. These include;

1. **Child-parent screening** offers an exciting possibility to improve effective long term early detection of FH and could reduce the need to at 18–39 years.
2. **One opportunistic random lipid profile** under 40 years, for young people having blood tests for other reasons.
3. **POCT in venues accessible to this population** would aid earlier detection prior to NHS Health Check.
4. **Bespoke searches or validated digital tools** can be run on primary care IT systems to identify people who have already had a lipid profile which may indicate FH, to flag those who would benefit from further evaluation [7][26].

Diagnosis

Figure 6 provides an overview to making a biochemical diagnosis based on the lipid profile, whilst ensuring secondary causes are excluded.

To check eligibility for genetic testing, a validated FH calculator is recommended. These include the Simon Broome Criteria, the Dutch Lipid Clinic Network Criteria and the Welsh Genetic Testing Calculator. The latter is currently used for referral to the Cheshire and Merseyside FH genetic testing service; a pilot service with the aim of becoming fully commissioned at the time of writing. People meeting the criteria for suspected FH should be referred to specialist services to undertake genetic testing.

For people who do not have a genetic diagnosis of FH following testing, but who have elevated lipid levels, lifestyle modification should be advised, alongside information about their CVD risk and that their risk will increase with age, and signposting to re-assessment every five years from the age of 40, via an NHS Health Check (see page 14, Figure 7).

Treatment

Key points to treating people with FH are detailed in Figure 6 and include;

1. All people with FH are considered high risk for CVD and should be treated with lipid therapies as per the algorithms for primary and secondary prevention (see Figures 7 and 11).
2. NICE guidance recommends for people with FH requiring primary prevention, that LDL-C should be reduced by 50% from baseline. For people with CVD, the secondary prevention target level is non-HDL-C \leq 2.6mmol/L (equivalent to LDL-C \leq 2.0mmol/L).
3. Referral should be considered for specialist advice and treatment for primary prevention if a 50% reduction in LDL-C is not achieved, especially if LDL-C remains above 5.0mmol/L, when an injectable therapy, called a PCSK9 inhibitor (PCSK9i), can be initiated by a specialist. PCSK9i can also be used for people with FH requiring secondary prevention, though the eligibility criteria is an LDL-C $>$ 3.5mmol/L, whilst Inclisiran can be used if LDL $>$ 2.5mmol/L (see Chronic Disease Review Section, page 19, for details). [27][7]

Special considerations

Prenatal counselling regarding the risks of conceiving a child if one or more parents has a diagnosis of FH, and the use of lipid therapies in pregnancy, should be discussed at each annual medication review, to provide up to date support and advice (see page 11).



Key aim – NHS Health Checks to identify people who would benefit from primary prevention lipid therapies to reduce their risk of developing CVD.

Case finding & treatment for primary prevention

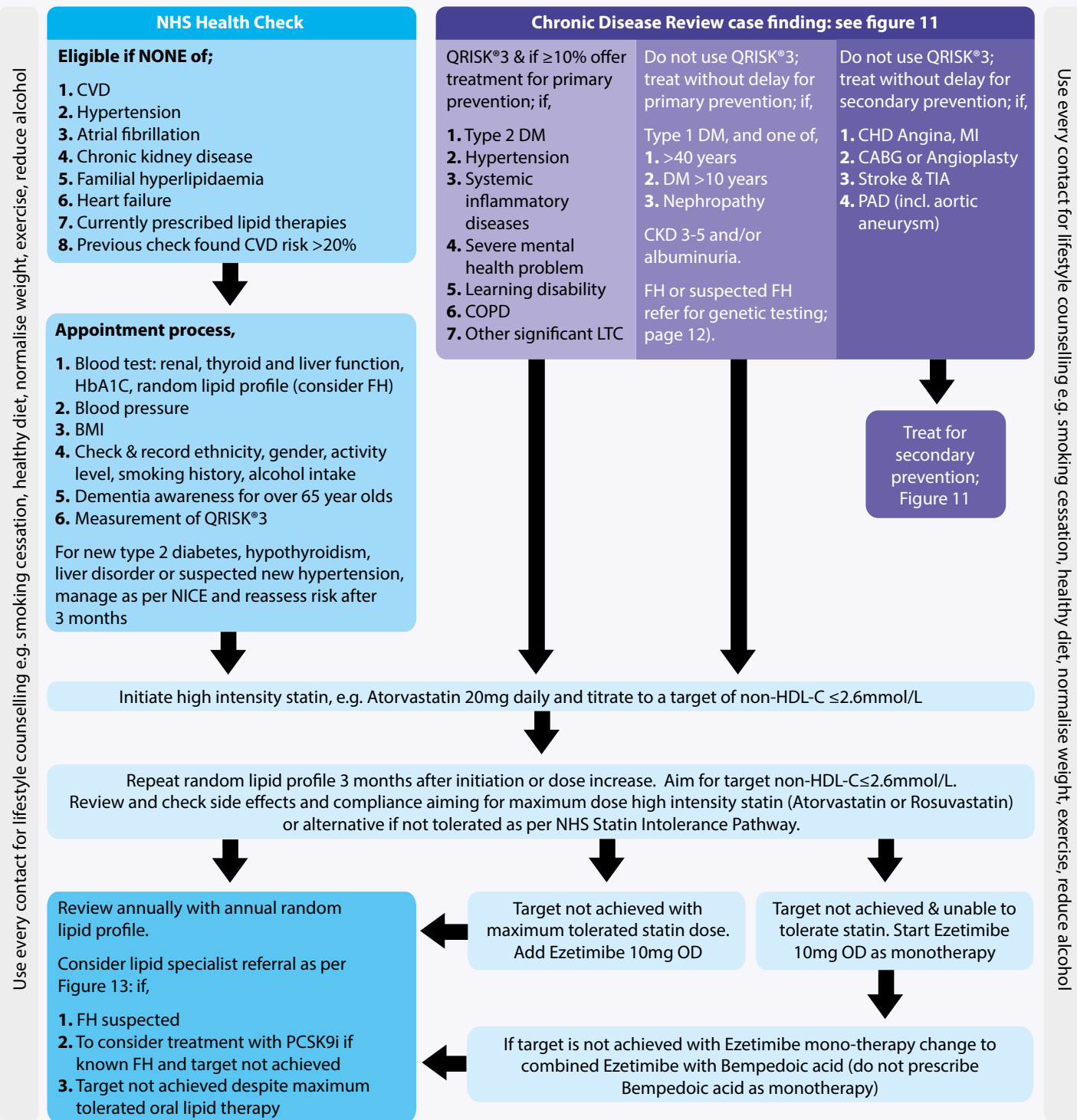


Figure 7. Case finding at NHS Health Checks & Lipid Therapy for Primary Prevention [10] [28]

This section focuses on people who are eligible for an NHS Health Check due to their age and are otherwise fit and well, to find and treat those at risk of developing CVD. Conversely, the Chronic Disease Review section (page 19), details case finding primary and secondary prevention for those not eligible for an NHS Health Check, but who attend annual reviews for long term conditions. Understanding CVD risk and initiating long term therapy can be challenging for patients and clinicians; this section provides a guide to this process.

Diagnosis: The NHS Health Check and CVD risk assessment

NHS Health Checks are an important service delivered by primary care to find people with high CVD risk and associated conditions, e.g. hypertension, CKD and diabetes. Figure 7 summarises this check, underpinned by CVD risk

assessment every five years, with an offer of a blood test, then face to face consultation. The check is designed to detect and offer lipid therapies to people who have 10% or more risk of developing CVD in the subsequent 10 years.

CVD risk is measured using a validated risk calculator, NICE recommends QRISK[®]3 (Appendix C) at time of writing, which can measure CVD risk from 25 to 84 years. NICE also advises people with a risk below 10% should be offered lipid therapy according to their preference if their risk is likely to be underestimated by a risk calculator.

QRISK[®]3-lifetime (Appendix C) is an additional online resource which illustrates an individual lifetime prediction to facilitate discussion about starting treatment, if QRISK[®]3 risk is less than 10%. Figure 8 illustrates when risk may be underestimated and when not to use QRISK[®]3 at all as the patient is already high risk. [13]

QRISK [®] 3 may underestimate of risk if;	Do NOT use QRISK [®] 3 if;
<ul style="list-style-type: none"> • Current HIV treatment • Medications that worsen the lipid profile e.g. immunosuppressants, chemotherapy, illicit drugs • Triglycerides >4.5mmol/L • Significant lifestyle changes e.g. recently stopping smoking • Systemic inflammatory disorders e.g. severe generalised psoriasis, seronegative inflammatory arthritis • Previous cancer • Fatty liver disease • Chronic obstructive pulmonary disease (COPD) 	<ul style="list-style-type: none"> • Established CVD • MI • Angina • Revascularisation e.g. angioplasty or CABG • Stroke/TIA • Peripheral arterial disease (PAD) • Chronic kidney disease (CKD) • Familial Hypercholesterolaemia (FH) • Suspected FH <ul style="list-style-type: none"> ◦ Premature vascular disease, or ◦ Total cholesterol >9.0mmol/L, or ◦ LDL-C >6.5mmol/L, and/or ◦ Non-HDL-C >7.5mmol/L • Type 1 Diabetes • Age over 84 years

Figure 8. When QRISK[®]3 may Underestimate Risk and When People are Already High Risk

Innovative means of case finding and offering CVD risk assessment should be considered to improve population coverage, as many people do not take up the offer of an NHS Health Check. This could include a validated POCT as a screen, e.g. from opticians or pharmacies or redeployed health buses used for immunisations during the covid pandemic. Furthermore, data tools run on primary care computer systems are able to estimate CVD risk, using information already held, to risk stratify and prioritise those at highest risk for full assessment [13] [29].

Treatment and risk management

For people with a CVD risk of 10% or more, lifestyle changes should always be recommended; see page 24. Short term, i.e. 3 months of lifestyle intervention can be considered, to avoid or delay initiating medication.

However, there is evidence highlighting the challenges patients routinely encounter when trying to adopt and maintain such lifestyle changes and the low likelihood that lifestyle changes alone will be sufficient.

Therefore, the decision to delay the start of lipid therapy in favour of lifestyle change recommendations should always be balanced against benefit. CVD risk prediction in healthy people is most strongly correlated with risk factors that are not modifiable; especially age. Even significant changes to the lipid profile make little difference to an individual's overall CVD risk prediction.

Evidence tells us that a single random lipid profile to exclude FH, can facilitate long term CVD risk assessment without repeated blood tests. As with age, CVD risk increases. Using QRISK[®]3 online or QRISK[®]3 Lifetime to visualise changes to CVD risk, can predict when risk will exceed 10%. This remains accurate provided no significant change occurs in clinical conditions, e.g. CVD, diabetes, hypertension or CKD, when risk should be reassessed (see Chronic Disease Review section, page 19) [30].

QRISK[®]3 provides a percentage risk of developing CVD in the next 10 years, but for patients this percentage risk can be confusing. It can help to express risk by explaining; e.g. for people with a CVD risk score of 10%, 1 in 10 people will develop CVD in the next 10 years, and offer resources to help patients visualise the benefits of reducing their risk such as the NICE decision aid (Appendix C) which uses pictures to illustrate a range of CVD risk outcomes, with or without treatment. An example is shown in Figure 9.

If your QRISK score is 10% over the next 10 years

On average, for every 100 people with this risk score who do not take a statin, over 10 years 10 people will get heart disease or have a stroke and 90 will not.



If 100 people take a statin, over 10 years on average:




-  about 90 people will not get heart disease or have a stroke, but would not even if they had not taken a statin
-  about 4 people will not get heart disease or have a stroke because they take a statin
-  about 6 people will get heart disease or have a stroke even though they take a statin

Figure 9. NICE Patient Decision Aid for CVD risk [31]

Lipid therapies should be initiated and titrated as per Figure 7, with detail about specific drug therapies outlined in Figure 3; always being mindful about the use of lipid therapies in people of childbearing age (page 11). People will receive maximum benefit from their lipid therapies for CVD risk reduction, by titrating to a target non-HDL-C ≤ 2.6 mmol/L; this may require a multi-drug approach.

People with new diagnoses of diabetes, hypertension, CKD or liver disease will benefit from treatment and optimisation of these conditions, as well as optimisation of their lipids to improve cardiovascular health. For people with previously undiagnosed CKD 3-5, QRISK[®]3 assessment should not be used to measure CVD risk and lipid therapies should be offered (see Chronic Disease Reviews; page 19). Raised serum triglycerides do not preclude CVD risk assessment but may require specific assessment and treatment (see below).

Special considerations

Statin intolerance

Optimising statin therapy to reduce CVD risk has been shown to provide the most cost-effective benefit of any CVD prevention intervention within the first 5 years of use [3]. However, people often incorrectly label themselves as intolerant to statins, but with clinician support can usually take either a different statin or different dose without problem [32].

The NHS Statin Intolerance Pathway (Appendix B) illustrates the necessary steps to help consider alternative causes for suspected side effects, and options to try to maintain a dose of statin, as well as when to consider serious but rare statin related problems. The Statin Intolerance Pathway should always be utilised before labelling people as truly unable to take statin therapy.

Raised triglycerides

Raised serum triglycerides are commonly due to secondary causes such as poor diet, excess alcohol, or diabetes, therefore lifestyle modification and improving diabetes control is vital. But triglycerides can also be elevated due to inherited causes such as familial combined hyperlipidaemia (FCH). Very high triglycerides can increase the risk of pancreatitis and may require urgent attention; referral criteria are detailed in Figure 13.

For people with CVD with persistent raised serum triglycerides, Icosapent ethyl is recommended to reduce CVD risk if fasting triglycerides ≥ 1.7 mmol/L despite achieving LDL-C 1.04-2.6mmol/L with standard lipid therapies [18].

Renal and liver disease

Routine Liver Function Test (LFT) monitoring has not clearly been associated with improvement in diagnosis or prevention of liver injury. Whilst statins have not been shown to cause liver disease, transient mild, non-clinically significant rises in liver enzymes are common.

All patients should be advised to report the development of potential symptoms of significant liver impairment, e.g. pruritis and jaundice, but for people with a diagnosis of fatty liver disease, which is an independent risk factor for CVD, statin therapy should not be withheld as these patients continue to derive significant benefit. [33] [34]

Using lipid therapies in severe or advanced renal (CKD 4 or 5), or liver disease, may pose clinical challenges due to an increased risk of adverse effects due to polypharmacy and multiple health conditions; the long term benefit and CVD risk reduction potential may need to be tailored to the individual (page 23) and advice from their specialist should be considered, as increased monitoring is likely to be required. For people with mild to moderate renal (e.g. CKD 3) or liver impairment, initiating a high intensity statin at a lower dose, i.e. atorvastatin 20mg daily or rosuvastatin 10mg daily, and titrating slowly to achieve target lipid levels, is recommended.

Lipoprotein(a)

Lipoprotein(a) is an LDL-like particle that is inherited and is an independent risk factor for CVD; although genetic tests are available, these are not widely used. Heart UK guidance [35] suggests five patient groups to consider checking lipoprotein(a) levels;

1. A personal or family history of premature vascular disease with no clear cause
2. First degree relatives with raised lipoprotein(a) levels (>200 nmol/L)
3. FH or another genetic dyslipidaemia
4. Calcific aortic valve disease
5. Borderline 10-year CVD risk

Finally, lipoprotein(a) assessment should be considered in people who fail to respond to conventional lipid therapies, but specialist lipidologist referral and advice is recommended as effective treatment remains unclear [36].



Key aim – To identify people no longer eligible for an NHS Health Check who would benefit from primary prevention lipid therapies to reduce their CVD risk.

>75 years, no CVD, no chronic disease & not already on lipid therapies			
No previous CVD risk assessment	CVD risk previously <10%	CVD risk previously ≥10%	≥85 years
<ul style="list-style-type: none"> • Offer CVD risk assessment periodically. • Likely to be high risk due to age alone. • Check for undiagnosed chronic disease, e.g. hypertension and diabetes, if no prior assessment. 		<ul style="list-style-type: none"> • High CVD risk; QRISK[®]3 not needed. • Review reasons for no treatment if previously noted to be high risk e.g. statin intolerance. • Offer lipid therapies, discussing the benefits in the context of; <ul style="list-style-type: none"> • Biological age • Frailty • Life expectancy • Use of Statin Intolerance Pathway • Patient choice 	

Figure 10. When to Consider Lipid Therapies for Primary Prevention from 75+ years

Diagnosis

Most people aged 75 years and older will already be at high risk of CVD; assessment and diagnosis remain the same as in the 40-74 age group.

Figure 10 serves as a reminder that CVD risk assessment should be considered for those not already treated with lipid therapies. In people over the age of 70 years, increasing age is the strongest predictor for major adverse cardiac events (MACE), followed by female gender and declining renal function [37]. Although CVD risk calculators are effective in measuring risk in people under 65 years, for older people these calculators may perform less accurately [38].

Furthermore, people with younger biological age (rather than chronological) may have a lower CVD risk, compared to those with evidence of vascular ageing due to poor lifestyle, environment and comorbidities, who may benefit more from reducing CVD risk with lipid therapies [39].

Treatment

Treating older people with lipid therapies carries a greater risk of adverse reactions which must be balanced against the potential benefit of preventing CVD events.

Age is the strongest risk factor for the development of CVD, but chronic conditions e.g. diabetes, liver and renal disease can increase the risk of drug toxicity and adverse effects; these conditions are all more common with age but it is less clear if age alone can lead to more side effects [40]. Whilst treatment algorithms remain the same as for the 40–74-year-old group, tailoring drug treatment to the individual and titrating therapies gradually is recommended.

Chronic Disease Reviews



Key aim – Identify people at high risk of CVD in those attending chronic disease reviews with long term conditions (LTC) and ensure a holistic approach to optimise lipid interventions.

Chronic long term conditions review, including disabilities and severe mental health problems

Secondary Prevention

Do not use QRISK[®]3; treat without delay for secondary prevention; if,

1. CHD, Angina, MI
2. CABG or Angioplasty
3. Stroke and TIA
4. PAD (incl. aortic aneurysm)

Start high intensity statin, e.g., Atorvastatin 80mg, or 20mg if CKD (consider 20mg if high risk of side effects or patient preference).

Address modifiable & lifestyle risk factors concurrently.

Primary Prevention

QRISK[®]3 & if $\geq 10\%$ offer treatment for primary prevention; if,

1. Type 2 DM
2. Hypertension
3. Systemic inflammatory diseases
4. Severe mental health problem
5. Learning disability
6. COPD
7. Other significant LTC

Do not use QRISK[®]3; treat without delay for primary prevention; if, Type 1 DM and one of;

1. >40 years
 2. DM >10 years
 3. Nephropathy
- CKD 3-5 and/or albuminuria.
FH or suspected FH (refer for genetic testing; page 12).

Initiate & optimise lipid therapies for primary prevention; see Figure 7

Repeat random lipid profile 3 months after initiation or dose increase, to achieve target non-HDL-C $\leq 2.6\text{mmol/L}$. Review and check side effects and compliance aiming for maximum dose high intensity statin (Atorvastatin or Rosuvastatin) or alternative if not tolerated as per NHS Statin Intolerance Pathway.

Consider addition of Icosapent ethyl if fasting triglycerides $\Rightarrow >1.7\text{mmol/L}$ but, LDL-C $>1.04\text{mmol/L}$ AND $\leq 2.6\text{mmol/L}$.

Consider referral for consideration of PCSK9i if eligibility met and unable to achieve target non-HDL-C $\leq 2.6\text{mmol/L}$.*

Review annually with random lipid profile.

Target non-HDL-C $\leq 2.6\text{mmol/L}$ not achieved on max. tolerated statin, consider the following options;

$\leq 20\%$ non-HDL-C reduction needed to achieve target; add Ezetimibe 10mg OD.
Review at 3 months and if target still not achieved check fasting LDL-C and if $>2.5\text{mmol/L}$ initiate Inclisiran*.

$>20\%$ non-HDL-C reduction needed to achieve target; check fasting LDL-C and if $>2.5\text{mmol/L}$ initiate Inclisiran*.
If target not achieved after 3 months add Ezetimibe 10mg OD.

Unable to tolerate any statin;

Start Ezetimibe 10mg OD as monotherapy.
If target not achieved at 3 months, change to Ezetimibe & Bempedoic acid combination (Do not use Bempedoic acid monotherapy).
Review at 3 months and if not to target, check fasting LDL-C and if $>2.5\text{mmol/L}$ initiate Inclisiran*.

Target non-HDL-C $\leq 2.6\text{mmol/L}$ not achieved despite maximum tolerated therapy using multi-drug approach detailed above; consider lipid clinic referral

*Injectable therapies

Secondary prevention

Start Inclisiran if LDL-C $>2.5\text{mmol/L}$ Consider PCSK9i if LDL-C $>4\text{mmol/L}$ or $>3.5\text{mmol/L}$ if polyvascular disease.

Primary prevention and FH

Consider PCSK9i if LDL-C $>3.5\text{mmol/L}$ if CVD or $>5\text{mmol/L}$ if primary prevention.

Primary prevention without FH

Not indicated. Continue oral therapies.

Figure 11. Case Finding at Chronic Disease Reviews & Lipid Therapy for Secondary Prevention (see Figure 7 for primary prevention lipid therapy treatment algorithm) [10]

Opportunities for lipid assessment should be considered as part of a holistic review for people with long term chronic conditions. This may include annual medication reviews, structured medication reviews, learning disability checks, physical health checks for people with severe mental health problems,

and people on immunosuppressant therapies requiring regular monitoring. Some people will require CVD risk assessment prior to initiating lipid therapies, but for some, using a CVD risk calculator will underestimate their risk significantly.

Diagnosis

Do NOT use QRISK®3: Already at high risk		Assessment Needed
Secondary prevention	Primary prevention	
<p>Established CVD, including;</p> <ul style="list-style-type: none"> • MI • Angina • Revascularisation (stent or CABG) • Stroke & TIA • PAD • Aortic aneurysm 	<p>Risk already ≥10%;</p> <ul style="list-style-type: none"> • CKD 3-5 • Type 1 diabetes and one of; <ul style="list-style-type: none"> ◦ Aged >40 years ◦ Type 1 diabetes for >10 years ◦ Another CVD risk factor e.g. nephropathy • Familial hypercholesterolaemia • Age ≥84 years (comorbidities and life expectancy should be considered) 	<ul style="list-style-type: none"> • Hypertension • Type 2 diabetes • COPD • Learning disabilities • Severe psychiatric illness • Systemic inflammatory disease e.g. rheumatoid arthritis, severe psoriasis
Treat with lipid therapies as per Figure 11	Treat with lipid therapies as per Figure 7	
Consider undiagnosed FH if high baseline cholesterol meets biochemical diagnostic criteria (Figure 6) or premature CVD (<60 years), or lipids remain significantly elevated despite lipid therapies.		

Figure 12. Using CVD Risk Assessment (QRISK®3) at a Chronic Disease Review

Treatment

Secondary Prevention

Lifestyle and risk factor modification is vital for all people who have elevated lipids, but lipid therapies for secondary prevention for people with established CVD should be initiated and titrated without delay, and as soon after a vascular event as possible (Figure 11). Patient information to detail the risk and benefit of lipid therapies should be provided (see Appendix C). Support to undertake lifestyle modification should be sought and all people should be offered exercise-based cardiac rehabilitation to include education about lifestyle modification following an acute vascular event.

Primary Prevention

People who do not have CVD already should be treated according to the primary prevention algorithm; Figure 7. Initiation of lipid therapies plus optimisation of lifestyle and co-morbidities can be

undertaken concurrently if intervention is unlikely to reduce CVD risk, or prior to initiation of lipid therapies if their risk is bordering 10% and a significant change can be made to reduce their risk.

Referral

Figure 13 details a selection of the most common reasons to consider referral to a lipid clinic for specialist advice or outpatient assessment. This list is not exhaustive and any patient who is unable to be treated effectively in primary care regarding FH, mixed hyperlipidaemia, or CVD prevention, should be considered for specialist assessment.

As more children are identified with FH, expertise to initiate and titrate therapies may require specialist support in the first instance. People with complex multimorbidity or palliative conditions may benefit from referral to the appropriate specialist to aid lipid therapy decisions, e.g. nephrologist, hepatologist, frailty specialist or palliative care services.

Referral Criteria

- People with or without CVD, not achieving target non-HDL-C ≤ 2.6 mmol/L despite maximal tolerated therapy.
- Person with suspected FH requiring genetic testing to confirm diagnosis and undertake cascade testing.
- People with FH not achieving target 50% reduction in LDL-C from baseline for primary prevention who may benefit from a PCSK9i.
- People with FH not achieving target non-HDL-C ≤ 2.6 mmol/L for secondary prevention despite maximum tolerated therapy.
- Children with FH needing to commence lipid therapies where primary care expertise will not support initiation.
- Children with FH with significant co-morbidities.
- People with FH requiring prenatal counselling.
- Complex hyperlipidaemia e.g. significant renal or liver impairment.
- Refer immediately if triglycerides are >20 .
- Refer if triglycerides remain >10 as per NHS lipid pathway.
- People with concurrent medical conditions making lipid therapy decisions difficult or complex e.g. advanced renal or liver disease.
- Consider specialist advice for use of lipid therapies in conditions where guidelines & evidence do not provide clear recommendations on prescribing such as retinal vein occlusion.

Figure 13. Referral Criteria for Lipid Specialist Clinic



Key aim – Considering life-limiting conditions when discussing the benefits and risks of lipid therapies for people with frailty, complex multi-morbidity or receiving palliative care.

Identifying People for a Tailored Approach to Lipid Therapies	
Life-limiting conditions	Frailty
<ul style="list-style-type: none"> • Metastatic cancer • On Gold Standards Framework (GSF) register • Organ failure with progressive decline • Dementia with progressive decline • Complex multimorbidity 	<ul style="list-style-type: none"> • Recurrent falls • Recurrent hospitalisations • Increasing social care needs • Complex multimorbidity
Complex Multimorbidity >3 long term conditions, especially three of;	
<ul style="list-style-type: none"> • Polypharmacy > ≥10 regular repeat medications • Heart failure • Atrial Fibrillation (AF) • Diabetes 	<ul style="list-style-type: none"> • Asthma or COPD • Coronary Artery Disease (CAD) • Mental health condition • Hypertension

Figure 14. Summary of Conditions to Consider a Tailored Approach to Lipid Therapies [41]

Clinical trials and guidelines are usually single condition focused and fail to clarify use of therapies in people with complex conditions with reduced life expectancy. NICE multimorbidity guidelines suggest a tailored approach to the initiation or continuation of therapies in this instance; supporting clinicians to exercise clinical judgement whilst considering patient values and choice.

Figure 14 outlines the conditions and characteristics of patients that clinicians should consider for a tailored approach to using lipid therapies for prevention. Furthermore, research shows that the elderly gain benefit from lipid therapies for prevention, therefore, age alone should not be used as an indicator to recommend stopping or not starting treatment. [42]

Diagnosis

Identifying people who may benefit from this tailored approach is often difficult as conversations with patients and their families are emotive, but to avoid adding unnecessary burden from treatments that may be unhelpful, or add to symptom burden, it is important to make an active diagnosis of frailty or end of life.

Frailty can be measured and flagged by IT tools on GP computer systems which provide frailty calculations based on clinical data within the patient record. Referral to a frailty specialist for diagnosis may be required and there are a range of validated tools available to support clinicians to assess frailty further. These include;

- Timed get up and go test (>12 seconds indicates frailty)
- Formal gait speed assessment (>5 seconds to walk 4 meters indicates frailty)
- PRISMA-7 questionnaire (scores ≥3 indicates frailty) [41]

End-of-life diagnoses are aided by a multidisciplinary approach; the GSF question and prognostic indicators detailed in Figure 15 are a reminder of when a palliative diagnosis should be considered.

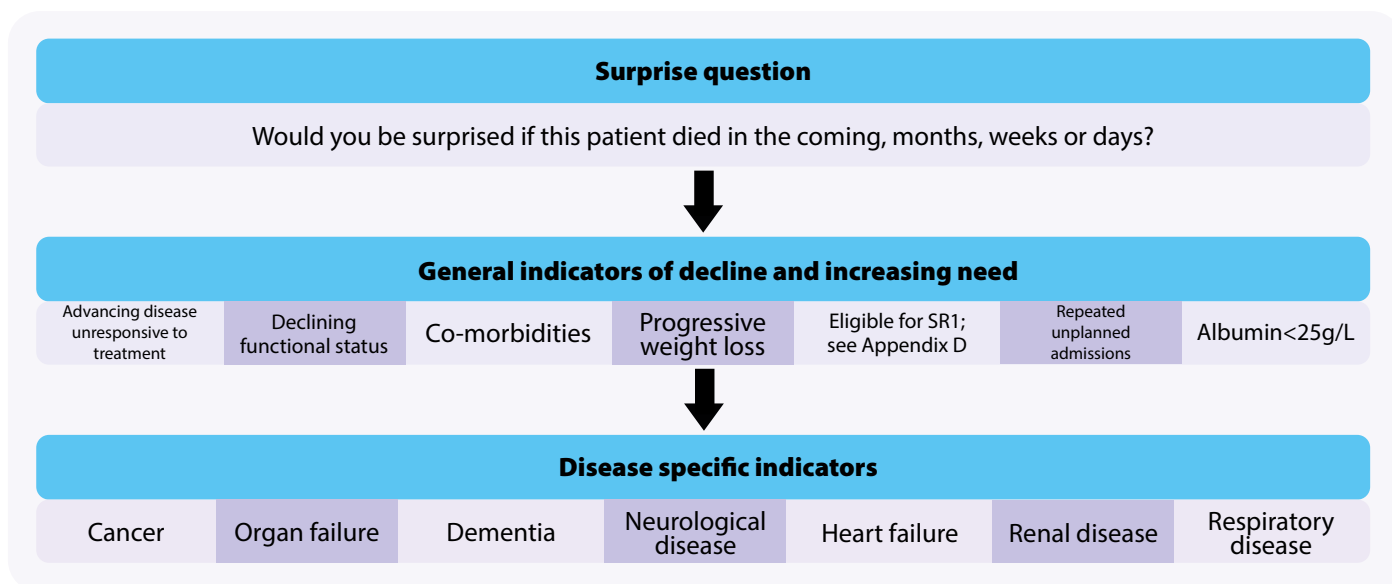


Figure 15. GSF Prognostic Indicators [43]

Treatment

Initiation

Consideration of the burden of polypharmacy and disease should be balanced against any potential benefits of using lipid therapies prior to initiation, particularly to reduce the risk of contributing to physical disability due to stroke or cardiac event. Understanding an individual's goals and priorities, plus helping the person to understand the risks and benefits of treatment, including risks of adverse events is important, particularly as evidence suggests that statin side effects such as myopathy and liver impairment increase with multimorbidity.

If there is agreement to initiate therapies for hyperlipidaemia, these should be used as detailed in this pathway for primary and secondary prevention (Figures 7 and 11). However, using lower doses with gradual titration may be safer to allow monitoring for adverse effects.

Continuation

For people already on lipid therapies who develop severe frailty or end of life conditions, agreement with the patient about criteria of when to stop treatment in advance of physical deterioration, may support easier individualised deprescribing. Remote monitoring, supported by a nominated carer or family member, can be offered for many patients, being mindful to reduce the burden of health care by streamlining blood tests, appointments and interventions. Decisions to stop treatments should be made using a shared decision making approach; the use of the STOP-START tool (Appendix C) may help to identify people at risk of medicine-related safety issues. [42] [45]

Special considerations

Clinicians should be aware of the possibility of reduced capacity to make difficult treatment decisions, and whether the patient has an Advance Care Plan or Lasting Power of Attorney.

The Mental Capacity Act (MCA) sets out provision for assessing whether a person can make a decision regarding specific questions, and how we can support people in making their own decisions, or when the decision should be taken in their best interests. [46]

Lifestyle Modification



Key aim – To achieve effective CVD prevention, lifestyle modification should be supported across every stage in this pathway.



Figure 16. Summary of Lifestyle Modification

Lifestyle modification should be recommended at all stages of this pathway and include all areas detailed in Figure 16.

For people who require lipid therapies for primary prevention, there may be an opportunity prior to the initiation of medication to improve CVD risk by lifestyle changes.

For people who require lipid therapies for secondary prevention, lifestyle modification should be undertaken at the same as initiating and titrating medication to target cholesterol levels.

Information to support patients to learn more about lifestyle modification can be found on the British Heart Foundation, Heart UK and the Cheshire and Merseyside Happy Hearts websites (Appendix C).

[47] [48] [49]

Healthy diet

Figure 17 summarises the main dietary considerations to reduce CVD risk. Changes should be tailored to the individual and consider their stage of behaviour change as well as comorbidities.

Eating a healthy diet	Achieving a normal weight	Foods to reduce cholesterol
<p>Fats <30% of energy consumed. Saturated fats <7% of total energy eaten. Use mono- or poly-unsaturated fats; e.g. olive oil or rapeseed oil instead. Avoid fried or roast food, processed food & takeaways. Cook by grilling, baking, steaming and poaching.</p> <p>Carbohydrates Wholegrain. Less refined starches & sugars.</p> <p>Protein Lean protein. More plant-based protein.</p> <p>Focus on, ≥5 a day of fruit & veg. ≥2 portions of fish per week. ≥4-5 Legumes, nuts & seeds per week. Use herbs & spices to flavour instead of butter & salt.</p>	<p>Measure BMI of children and adults using validated calculator. Help goal setting. Specialist/bariatric services for high BMI.</p> <p>Tailored approach with emphasis on,</p> <ul style="list-style-type: none"> • healthy diet • control eating pace • behaviour change • relapse prevention <p>Control triggers for over-eating.</p> <p>Reward achievement especially children.</p> <p>Support self-monitoring of weight & waist circumference. Social support networks.</p>	<p>Aim for >30g/day of dietary fibre. Mediterranean balanced diet is recommended to reduce CVD risk, with plenty of,</p> <ol style="list-style-type: none"> 1. Fruit 2. Vegetables 3. Nuts 4. Seeds 5. Legumes 6. Fish. <p>Do not routinely recommend plant stanols & sterols, fish oils, omega 3.</p>

Figure 17. Healthy Eating to Reduce the Risk of CVD [30] [50]

Getting enough exercise

Being physically inactive increases the risk of developing a chronic disease, so minimising sedentary time is important. Physical activity and exercise can reduce the risk of CVD by 35% and type 2 diabetes by 40%, as well as reducing the risk of cancers, falls and joint pains. In childhood, physical activity reduces the development of obesity and improves health. People with chronic illness, disability, frailty and cognitive impairment benefit from reducing sedentary time and increasing activity. See Figure 18 for recommendations on tailoring exercise to an individual based on their age and abilities.

Stopping smoking

Smoking tobacco is one of the major causes of CVD; smoking is not only prothrombotic but accelerates the development of widespread atherosclerosis caused by changes to cholesterol metabolism. Stopping smoking is one of the best things we can advise people to do for their cholesterol, CVD risk and overall health, with rapid and measurable health benefits evident from smoking cessation. Overall health begins to improve within days and within a year the risk of heart disease is halved [52].

Under 5	5-18 years	Adults	Disability & frailty
<p>Under 1 year 30 minutes tummy time or floor-based activity e.g. crawling or rolling spread across the day. Aim to gradually increase activity over time.</p> <p>Toddler (1-2 years) 3 hours per day mixed activity indoors & outside.</p> <p>Pre-school 3 hours per day mixed activity indoors & outside, more is better and should include 60 minutes of moderate to vigorous activity.</p>	<p>An average of at least 60 minutes per day of moderate or vigorous intensity activity.</p> <p>Variety of types and intensities of activities to develop movement skills, muscles & bones, spread across the week, e.g.</p> <ul style="list-style-type: none"> • jumping • running around the playground • P.E. • skipping • dancing. 	<p>150 minutes per week of moderate intensity aerobic exercise (getting a little bit out of breath and a bit sweaty), or, at least 75 minutes of vigorous intensity aerobic exercise per week (getting quite out of breath and sweaty).</p> <p>Two sessions per week of muscle strengthening exercises e.g. carrying heavy shopping bags, yoga, heavy gardening or body weight exercises.</p> <p>Balance exercises 2 days per week helps to reduce frailty and risk of falls especially for people over 65.</p>	<p>Any increase in volume of activity with aim of 150 minutes of exercise per week.</p> <p>Any reduction in sedentary time is beneficial.</p> <p>Focus on strengthening and balance exercises</p>

Figure 18. Summary of Recommended Physical Activity [51]

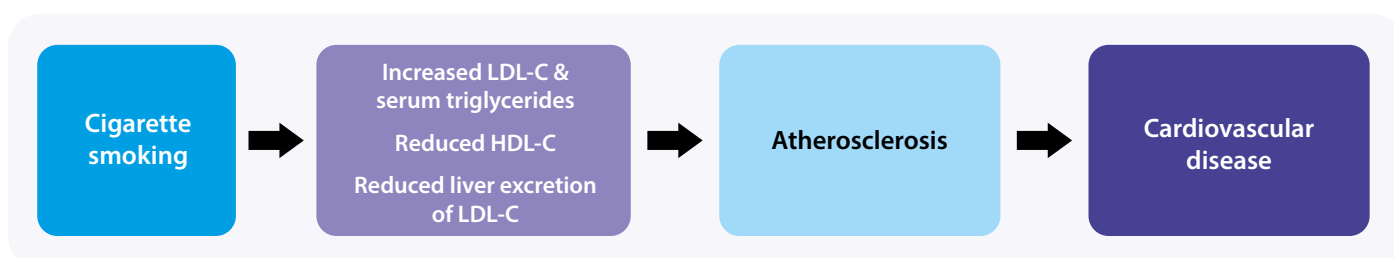


Figure 19. Impact of Smoking on Cholesterol Metabolism [53]

Providing support for people to quit smoking significantly increases the chances of success; referral to NHS stop smoking services should be recommended as this improves the cessation rate by three times [52]. There are a variety of locations to support communities across the UK; see Appendix C to locate services near you [54].

Stopping smoking immediately is an effective way to quit. NHS patient information at time of writing suggests e-cigarettes are a safer alternative to cigarette smoking, as well as a means to quitting [55]. Nicotine replacement therapy (NRT) remains an option to support cessation, and although Bupropion medication remains within guidance to support quitting, it is, however, unavailable in the UK at the time of writing, whilst Varenicline has been removed from the UK market at present.

For people not ready to quit, brief advice on cutting down, use of NRT or signposting to support can aid behaviour change.

Reducing alcohol intake

Alcohol related illness is estimated to cost the NHS £3.5 billion per year impacting significantly on working years lost for people affected as well as around 200,000 children living with an alcohol

dependant parent [56]. Reducing alcohol intake helps to lower cholesterol and triglycerides, reduce weight and blood pressure as well as improving mental health and sleep. Raised triglycerides are a factor in the development of fatty liver, leading to liver fibrosis and cirrhosis. Impaired liver function reduces clearance of LDL-C and increases atherosclerosis. Although, drinking alcohol in moderation was previously considered beneficial, this is now thought unlikely.

Alcohol content is measured in units, e.g. 14 units is equivalent to 6 pints of average strength beer, or 10 small glasses of lower strength wine. Online tools can help people check units of alcohol more easily, e.g. see Appendix C for Alcohol Change UK online calculator. [57]

UK guidance recommends;

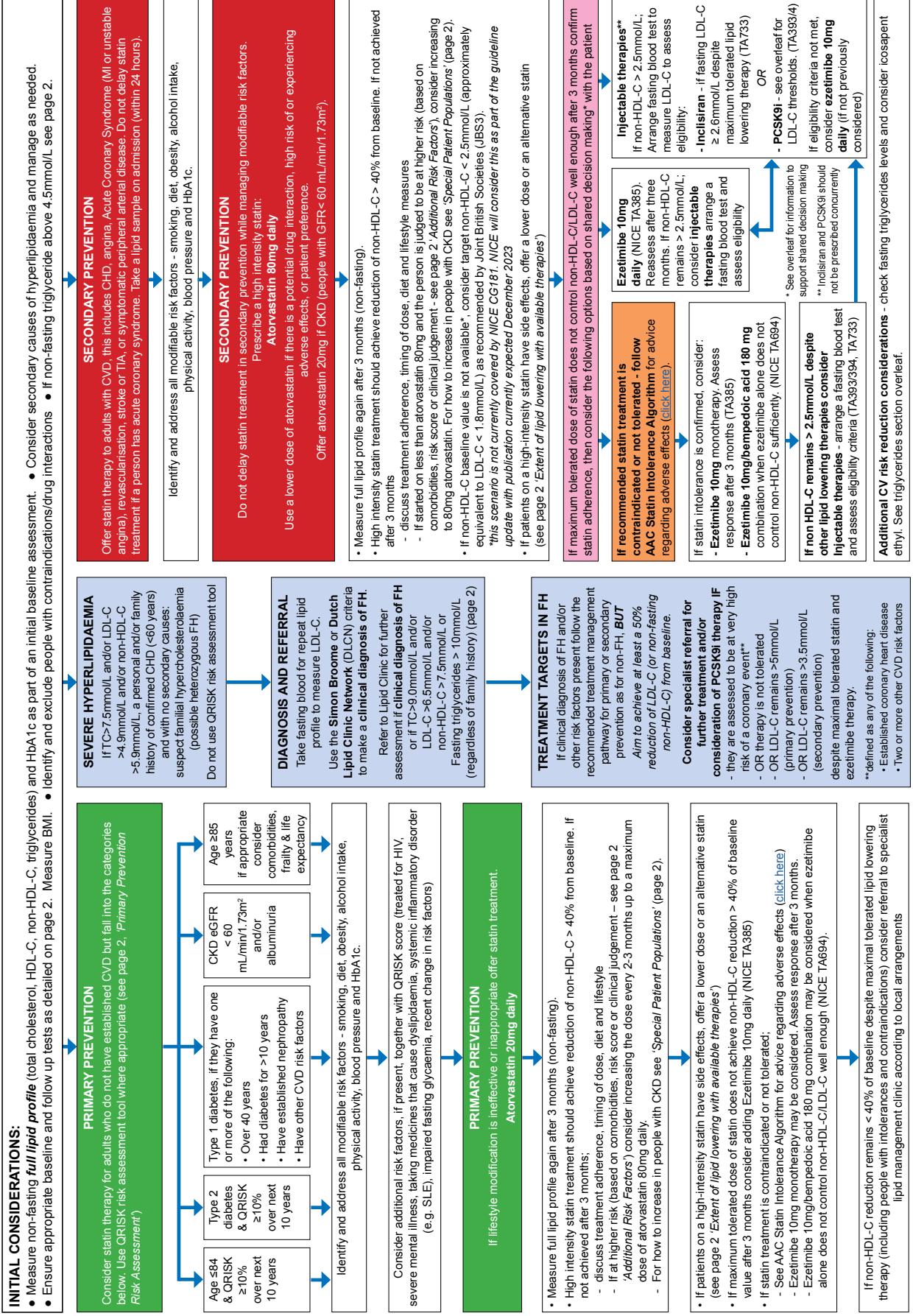
1. Men and women should not drink more than 14 units of alcohol per week on a regular basis.
2. Spread drinking over 3 or more days if regularly drinking as much as 14 units per week.
3. To cut down on alcohol, have several drink free days per week.

Top tips for reducing alcohol								
Swap to lower strength options	Only drink while having a meal	Take the bottle off the table while you're eating, so you won't top up without thinking	Alternate alcoholic drinks with soft drinks	Make your drinks last longer by adding ice, water or mixers	Try drinking more slowly	Watch out for very large glasses	Choose smaller amounts, such as a bottle of beer instead of a pint	Buy a measure so you know how much you're drinking

Figure 20. Top Tips to Reduce Alcohol from Heart UK, 2022



Summary of National Guidance for Lipid Management for Primary and Secondary Prevention of CVD



MANAGEMENT

his guidance applies to new patients and may also be taken into consideration for those already on statins at their annual review. If 40% reduction of non-HDL-C is achieved, offer high intensity statins. Discuss with people who are stable on a low- or medium-intensity statin the likely benefits and potential risk of side effects changed to a high-intensity statin when they have a medication review and agree with the person whether a change is needed.

ezetimibe, alicrocumab, evolocumab or inclisiran can be added when patients' LDL-C levels are not lowered enough with the maximally tolerated dose of statins. Bempedoic acid with ezetimibe is an option when statins are contraindicated or not tolerated, and when ezetimibe alone does not control LDL-C well enough. Do not offer a fibrate, niacin, bile acid binder or mega-3 fatty acids alone or in combination with statins, for the prevention of CVD (check NICE CG181 and TA805 for exceptions).

PRIMARY PREVENTION RISK ASSESSMENT

QRISK3 is the current version of the QRISK calculator. www.qrisk.org/three

Do not use this risk assessment tool for people with established CVD or those who are at high risk of developing CVD because of FH or other inherited disorders of lipid metabolism.

Do not use a risk assessment tool to assess CVD risk in people with type 1 diabetes, or eGFR less than 60 mL/min/1.73 m² and/or albuminuria.

Consider people aged ≥ 85 at increased risk of CVD because of age alone particularly people who smoke or have raised BP.

Additional Risk Factors

Age, standard CVD risk scores including QRISK may underestimate risk in people who have additional risk because of underlying medical conditions or treatments. These groups include the following groups of people:

- severe obesity (BMI > 40kg/m²) increases CVD risk
- treated for HIV
- serious mental health problems

taking medicines that can cause dyslipidaemia such as antipsychotic medication, corticosteroids or immunosuppressant drugs

autoimmune disorders such as SLE, and other systemic inflammatory disorders

non-diabetic hyperglycaemia

significant hypertriglyceridaemia (fasting triglycerides 4.5-9.9mmol/L)

recent risk factor changes e.g. quit smoking, BP or lipid treatment

consider socio-economic status as an additional factor contributing to CVD risk

If QRISK < 10% over the next 10 years - Give lifestyle advice and ensure regular review of CVD risk in line with guidance.

SPECIAL PATIENT POPULATIONS

type 1 Diabetes

While NICE recommends offering statins to patients with Type 1 diabetes as detailed in the algorithm, it also states to consider statins in all adults with type 1 diabetes.

chronic Kidney Disease

Offer atorvastatin 20mg for the primary or secondary prevention of CVD to people with CKD (eGFR less than 60 mL/min/1.73m² and/or albuminuria)

Increase the dose if a greater than 40% reduction in non-HDL-C is not achieved and eGFR is 30 mL/min/1.73m² or more.

Give the use of higher doses with a renal specialist if eGFR is less than 30 mL/min/1.73m²

ABBREVIATIONS

- LDL-C: low density lipoprotein cholesterol
- LDL-C: non-HDL-C: non-high density lipoprotein cholesterol
- PCSK9i: proprotein convertase subtilisin kexin 9 monoclonal antibody inhibitor
- SLE: systemic lupus erythematosus
- SPC: summary of product characteristics
- TC: total cholesterol

References:

353, 2014. www.ipsrisk.com/pages/6.htm

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NICE 2016. TA385 www.nice.org.uk/guidance/ta385

NICE 2016. TA393 www.nice.org.uk/guidance/ta393

NICE 2016. TA394 www.nice.org.uk/guidance/ta394

NICE 2014. CG181 www.nice.org.uk/guidance/cg181

EXTENT OF LIPID LOWERING WITH AVAILABLE THERAPIES

Statin dose mg/day	Approximate reduction in LDL-C					
	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%	49%	55%		
Atorvastatin + Ezetimibe 10mg		52%	54%	57%	61%	

- Low intensity statins** will produce an LDL-C reduction of 20-30%
- Medium intensity statins** will produce an LDL-C reduction of 31-40%
- High intensity statins** will produce an LDL-C reduction above 40%
- Simvastatin 80mg** is not recommended due to risk of muscle toxicity
- Rosuvastatin** may be used as an alternative to atorvastatin if compatible with other drug therapy. Some people may need a lower starting dose (see BNF).
- Low/medium intensity statins should only be used if intolerance or drug interactions.
- Ezetimibe** when combined with any statin is likely to give greater reduction in non-HDL-C or LDL-C than doubling the dose of the statin.
- PCSK9i** (NICE TA393, TA394) alone or in combination with statins or ezetimibe produce an additional LDL-C reduction of approximately 50% (range 25-70%).
- Bempedoic acid** when combined with ezetimibe (TA694) produces an additional LDL-C reduction of approximately 28% (range 22-33%) but no clinical outcome evidence is currently available.
- Inclisiran** (TA733) alone or in combination with statins or ezetimibe produces an additional LDL-C reduction of approximately 50% (range 48-52%) but no clinical outcome evidence is currently available.

MONITORING

Baseline Measurements

In addition to full lipid profile, measure renal, thyroid and liver profiles (including albumin) and HbA1c to exclude secondary causes and co-morbidities.

Measure baseline liver transaminase (ALT or AST) before starting a statin.

Measure CK if unexplained muscle pain before starting a statin.

CK should not be measured routinely especially if a patient is asymptomatic.

	Primary Prevention		Secondary prevention	
	Lipid Profile	ALT or AST	Lipid Profile	ALT or AST
Baseline	✓	✓	✓	✓
3 months	✓	✓	✓	✓
6-9 months			If <40% non-HDL-C reduction, up titration required. Repeat full lipid profile and ALT or AST within 3 months of each up-titration of statin dose or addition of ezetimibe as required	
12 months	✓	✓	✓	✓
Yearly	✓	✓	✓	✓

Provide annual medication reviews for people taking statins to discuss effectiveness of therapy, medicines adherence, lifestyle modification and address CVD risk factors

*Consider an annual non-fasting full lipid profile to inform the discussion around effectiveness of lipid lowering therapy and any medicines non-adherence.

Monitoring

Repeat full lipid profile is non-fasting.

Measure liver transaminase within 3 months of starting treatment and then within 3 months of every additional up titration and then again at 12 months, but not again unless clinically indicated.

- If ALT or AST are greater than 3 times the upper limit of normal then do not initiate a statin or discontinue statin therapy already prescribed and repeat the LFTs in a month.
- If ALT or AST are elevated but are less than 3 times the upper limit of normal then:
 - Continue the statin and repeat in a month.
 - If they remain elevated but are less than 3 times the upper limit of normal then continue statin and repeat again in 6 months.

NICE 2008. CG71 www.nice.org.uk/guidance/cg71

NICE 2021. TA694 www.nice.org.uk/guidance/ta694

NICE 2021. TA733 www.nice.org.uk/guidance/ta733

NICE 2022. TA805 www.nice.org.uk/guidance/ta805

TITRATION THRESHOLD / TARGETS

	NICE titration threshold	JBS3
Primary Prevention	Intensify lipid lowering therapy if non-HDL-C reduction from baseline is less than 40%	non-HDL-C <2.5mmol/L (LDL-C <1.8mmol/L)
Secondary Prevention		
FH	Optimise lipid lowering therapy to achieve at least 50% reduction in LDL-C (or non-HDL-C)	

If baseline cholesterol is unknown in the setting of secondary prevention use the use Joint British Societies' JBS3 consensus recommendation.

Non-HDL-C = TC minus HDL-C

LDL-C = non-HDL-C minus (Fasting triglycerides*2.2)

*valid only when fasting triglycerides are less than 4.5 mmol/L

SPECIALIST SERVICES

Scope of specialist service available locally may include: lipid clinic, PCSK9i clinic (offering initiation and subsequent follow up), FH genetic diagnosis and cascade testing, lipoprotein apheresis service. NICE eligibility criteria for PCSK9i and fasting LDL-C thresholds are summarised below.

NICE TA393 Ailrocumab	Without CVD	With CVD
NICE TA394 Evolocumab	High risk ¹	Very high risk ²
Primary non-FH or mixed dyslipidaemia	Not recommended	LDL C > 4.0 mmol/L
Primary heterozygous-FH	LDL C > 5.0 mmol/L	LDL C > 3.5 mmol/L

¹ History of any of the following: ACS; coronary or other arterial revascularisation procedures; CHD, ischaemic stroke; PAD; Recurrent CV events or CV events in more than 1 vascular bed (that is, polyvascular disease).

Bempedoic acid/ezetimibe and inclisiran are available in primary care and do not require initiation by specialist services. PCSK9i may be available for prescribing in primary care: see local initiation pathways.

TRIGLYCERIDES

Triglyceride concentration	Action
Greater than 20mmol/L	Refer to lipid clinic for urgent specialist review if not a result of excess alcohol or poor glycaemic control. At risk of acute pancreatitis.
10 - 20mmol/L	Repeat the TG measurement with a fasting test (after an interval of 5 days, but within 2 weeks) and review for potential secondary causes of hyperlipidaemia. Seek specialist advice if the TG concentration remains > 10mmol/Litre. At risk of acute pancreatitis
4.5 - 9.9mmol/L	If non-fasting triglycerides are greater than 4.5mmol/L, repeat with a fasting TG measurement. Be aware that the CVD risk may be underestimated by risk assessment tools, optimise the management of other CVD risk factors present and seek specialist advice if non-HDL-C concentration is > 7.5 mmol/litre.

Icosapent ethyl (TA805)

- Check fasting triglycerides levels.
- Manage secondary causes of hypertriglyceridaemia
- Consider icosapent ethyl (TA805) if patient has established cardiovascular disease (secondary prevention) and
 - on statins and fasting TG ≥ 1.7mmol/L and LDL-C* between 1.04[†] and ≤2.6mmol/L
 - See table above and refer as appropriate.
- LDL-C cannot be calculated using Friedewald's formula if TG > 4.5. Discuss with your lab. Consider using an alternative equation (eg Sampson, doi: 10.1001/jama.2020.0013) or beta-quantification. † labs don't report calculated LDL-C beyond one decimal point

STATIN INTOLERANCE

Statin intolerance 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 adherence to therapy being compromised. For people who are intolerant of the recommended statin treatment see the NHSE AAC statin intolerance algorithm, available on the NHSE AAC page ([Click here](https://www.nhs.uk))

Authors: Dr. Ranj Khatib & Dr Dermot Neely on behalf of the AAC Clinical Subgroup. Nov 2022. Review date: Jan 2024.

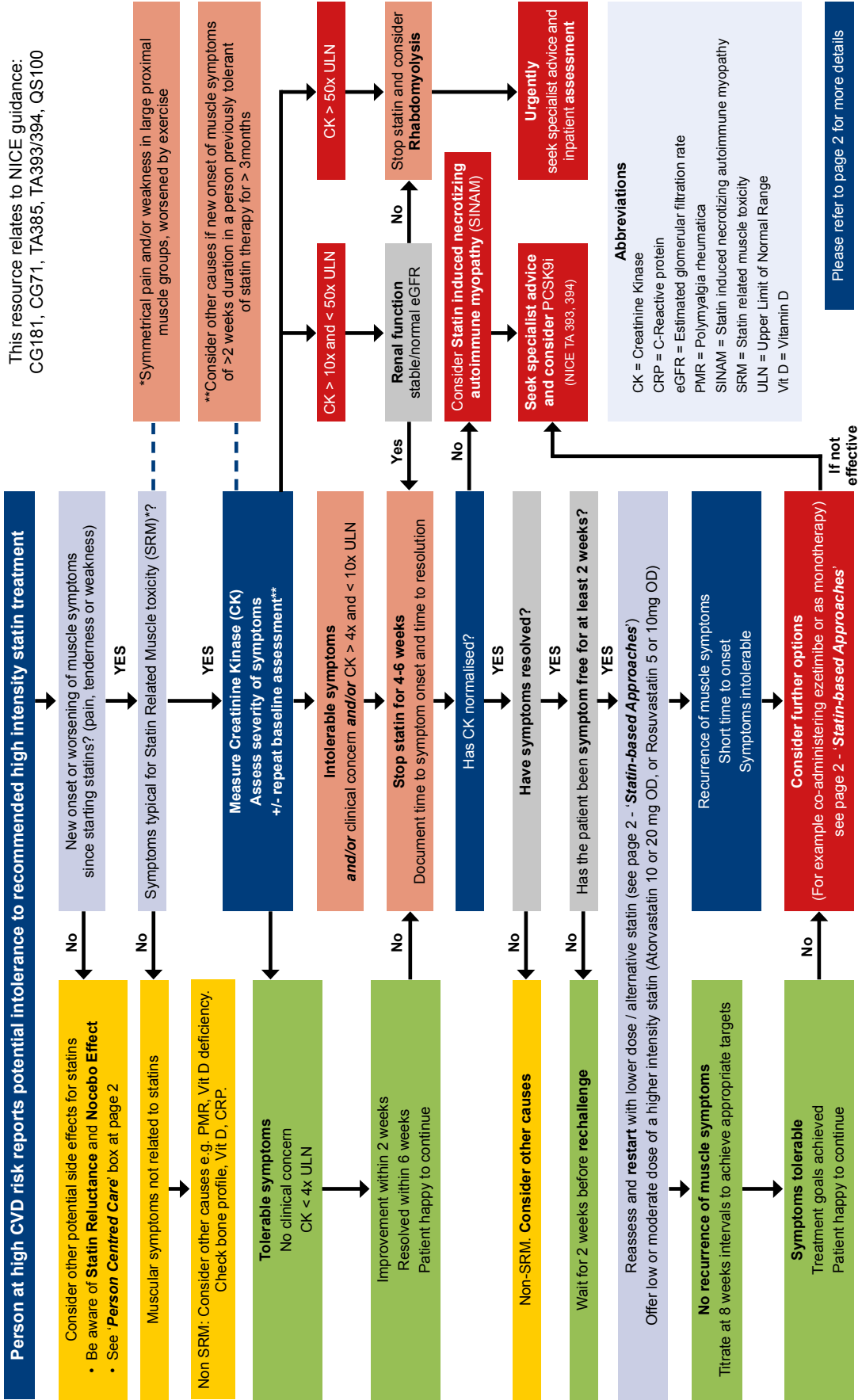
NICE confirmed that its guidance is accurately represented, Nov 2022.

NHS

Appendix B

NHS Statin Intolerance Pathway

Statin Intolerance Pathway



Introduction

Statins are the cornerstone for prevention and treatment of cardiovascular (CV) disease with a substantial evidence of reduction of morbidity and mortality. Refer to Lipid Management Pathway and related NICE guidelines (CG181, CG71) for guidance on initiation, titration and monitoring of statin therapy.

In clinical trials, statins were found to be largely well tolerated (often with a similar adverse effect (AE) profile to placebo), however this is not reflected in clinical practice where up to 75% of people started on a statin will discontinue treatment within 2 years.

Stopping statin therapy is associated with an increased risk of major CV events and there is growing concern that clinicians are labelling patients as 'statin intolerant' too quickly. Indeed statin discontinuation is significantly associated with negative media coverage.

Definition of Statin Intolerance

Intolerance to initial statin therapy 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.

Other definition: any adverse event (AEs) considered unacceptable by the patient, and/or some laboratory abnormalities, both attributed to statin treatment and leading to its discontinuation.

statin-associated muscle symptoms (SAMS)

SAMS are one of the principal reasons for statin non-adherence and/or discontinuation. However, not all such symptoms should lead to a label of 'statin intolerance' as they may not be truly statin related muscle toxicity (SRM) as demonstrated by resolution on de-challenge and recurrence with re-challenge.

Ion-Statins related musculoskeletal symptoms (Non SRM)

If patients report symptoms that are not typical of SRM (e.g. asymmetric distribution, failure to resolve with de-challenge despite normal CK) consider other musculoskeletal disorders, metabolic, degenerative or inflammatory e.g. Vitamin D deficiency, polymyalgia rheumatica. Check Bone profile, Vit D, CRP.

Considerations when starting a statin to reduce risk of SRM

Check baseline thyroid, liver and renal function, any potential drug interactions, and avoid the highest doses in at risk groups (See "Risk Factors" below).

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 CK. If CK levels are > 4x ULN do not start statin - investigation required.

Do not measure CK if person is asymptomatic.

Warn patients about AEs, 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 CK (see page 1).

Risk factors for SRM and statin intolerance

Indogenous factors

- Female gender
- Advanced age (> 75 yrs)
- Frailty (reduced lean body mass)
- History of muscle disorder or high CK
- Impaired renal or hepatic function
- Personal or family history of intolerance to lipid-lowering therapies.
- Hypothyroidism

Exogenous Factors

- Excessive alcohol intake
- High intensity exercise
- Dehydration
- Drug interactions with statins (including herbal medicines)
- Vitamin D deficiency

Classification of statin related muscle toxicity (SRM)

Allfirev, A. et al. Clin Pharm Ther. 2014; 96:470-476

SRM	Phenotype	Incidence	Definition
SRM 0	CK elevation <4x ULN	1.5-26%	No muscle symptoms
SRM 1	Myalgia, tolerable	190/100,000 Patient-years; 0.3-33%	Muscle symptoms without CK elevation
SRM 2	Myalgia, intolerable	0.2-2/1,000	Muscle symptoms, CK <4x ULN, complete resolution on dechallenge
SRM 3	Myopathy	5/100,000 Patient-years	CK elevation >4x ULN <10x ULN ± muscle symptoms, complete resolution on dechallenge
SRM 4	Severe myopathy	0.11%	CK elevation >10x ULN <50x ULN, muscle symptoms, complete resolution on dechallenge
SRM 5	Rhabdomyolysis	0.1-8.4/100,000	CK elevation >10x ULN with evidence of renal impairment + muscle symptoms or CK >50x ULN
SRM 6	Autoimmune-mediated necrotizing myositis (SINAM)	~2/million per year	Detection of HMGR antibodies, HMGR expression in muscle biopsy showing autoimmune myositis, incomplete resolution on dechallenge

HMGR = 3-hydroxy-3-methylglutaryl coenzyme A reductase ULN = upper limit of normal

- SRM is a spectrum from myalgia to severe myopathy
- SRM 0 - does not preclude statin therapy, consider reducing starting dose
- SRM 1-3 manage according to pathway
- When SRM4 is suspected, without evidence of impaired renal function, discontinue statin therapy immediately and refer for outpatient assessment. Assess and treat possible contributory factors and re-assess the need for a statin. Intensify lifestyle modifications and consider alternative lipid lowering regimens.
- If rhabdomyolysis (SRM5) is suspected, immediately stop statins, urgently refer to inpatient assessment and management including intravenous rehydration as required to preserve renal function. Do not wait for measurement of urinary myoglobin. Post recovery, manage as for SRM4.
- Statin induced necrotizing autoimmune myositis (SINAM) (SRM6) should be suspected in patients with progressive muscle weakness and ongoing CK elevation despite statin withdrawal. Requires immunosuppressive treatment and avoidance of re-exposure to statins. Re-assess the need for lipid lowering therapy - may be eligible for treatment with PCSK9 inhibitor (NICE TA 393, 394).

Non-muscle related statin side effects

May vary between different statins. In clinical trials some side effects often associated with statins are not statistically different from placebo.

Most commonly reported: gastrointestinal disturbance and asymptomatic increases in hepatic transaminases (ALT or AST). May affect up to 1 in 10 statin users.

Rarer side effects include: Hepatotoxicity, new onset Type 2 Diabetes (benefits outweigh risk, do not stop statin), Renal insufficiency, proteinuria, Neurocognitive and neurological impairments (no apparent link from RCTs), Intracranial haemorrhage (conflicting evidence, benefit outweigh possible harm), Interstitial lung disease, Pancreatitis, Skin disorders including alopecia, Lupus-like reaction, Sleep disturbance, headache, dizziness, fatigue, depression, sexual dysfunction.

Management: If symptoms appear statin related, consider de-challenge and re-challenge or change to a different statin (e.g. hydrophilic instead of lipophilic).

Liver enzyme abnormalities - minor increases in liver enzymes (<2x ULN) may be seen within the first three months of statin therapy; temporary discontinuation and further assessment is warranted if levels exceed 3x ULN. Several studies have confirmed that the cardiovascular benefits of statin treatment in high-risk populations outweigh the rare adverse effects, such as rhabdomyolysis.

Person-centred approach to address statin intolerance

Initial Consultation

- Be aware of "nocebo effect"¹ and "statin reluctance"²
- Reinforce healthy lifestyle habits (e.g. exercise, reducing weight)
- Listen to the concerns of each patient.
- Explain LDL-C targets and strategies to lower LDL-C/non-HDL-C
- Discuss options to reduce LDL-C/non-HDL-C with pros and cons

- Nocebo effect** is negative expectations of the patient regarding a treatment leading to reporting more negative effects even if they are prescribed a placebo.
- Statin reluctance** is an attitudinal state of aversion to taking statins (often without prior exposure).

Statin-based approaches to manage muscle symptoms

- Adopt person-centred approach as described above.
- Therapy with a lower dose statin is preferred to no statin
- Apply a repetitive "De-Challenge" - "Re-Challenge" approach to establish if symptoms are caused by a statin(s) and the best statin regimen for each patient.
- Switch to a different statin or re-challenge with the same statin using a lower dose or frequency (intermittent dosages)
- Patients who do not tolerate statins on a daily basis, alternate day or twice-weekly dosing is a good option.
- Rosuvastatin and atorvastatin have longer half-lives, permitting their use on a non-daily regime.
- Adding ezetimibe to a lower dose statin may be better tolerated with robust reduction of LDL-C / non-HDL-C.

- Once a new regime is tolerated, dose / frequency can be up-titrated slowly to achieve LDL-C / non-HDL-C goals with minimal or no muscle complaints.

It is important to note that cardiovascular benefits have not been proven for all the above approaches but any reduction of LDL-C / non-HDL-C is beneficial.

LDL-C lowering options for patients with genuine statin intolerance

- Refer to the AAC Lipid Management Algorithm. ([click here](#))
- Consider ezetimibe, (NICE TA 385) therapy as per algorithm
- Consider ezetimibe combined with bempedoic acid (NICE TA 694) as per algorithm
- Consider inclisiran if eligible for treatment according to NICE TA 733
- Consider PCSK9i if eligible for treatment according to NICE TA 393, 394

Appendix C

Patient information and clinician resources

Alcohol units calculator

Alcohol Change UK

<https://alcoholchange.org.uk/alcohol-facts/interactive-tools/unit-calculator>

BMI calculator

<https://www.nhs.uk/live-well/healthy-weight/bmi-calculator/>

Child-parent screening

Scan the QR code for child-parent screening information for parents in several languages



PGT-M patient information

<https://www.hfea.gov.uk/i-am/i-have-a-genetic-disease-in-my-family/>

Digital case finding tools

- NHS Digital Lipid management Searches
<https://digital.nhs.uk/services/lipid-management-searches>
- UCL Partners Proactive Care Framework
<https://uclpartners.com/our-priorities/cardiovascular/proactive-care/search-and-risk-stratification-tools/>
- Clinical Digital Resource Collaborative
https://cdrc.nhs.uk/2023/04/20/using-cdrc-searches-to-meet-new-qof-cholesterol-indicators/?utm_source=All+Health+Contacts&utm_campaign=1feab3d0b7-EMAIL_CAMPAIGN_2022_06_17_02_07_COPY_01&utm_medium=email&utm_term=0_969ba08df5-1feab3d0b7-439253012&mc_cid=1feab3d0b7&mc_eid=d38a9ece1d
- Ardens Healthcare Informatics
<https://support.ardens.org.uk/support/solutions/articles/31000120344-cvd-screening-prevention>

Electronic Medicines Compendium

Recommended source to check latest drug SPC and licencing, <https://www.medicines.org.uk/emc#gref>

FH calculators and criteria

- Welsh Genetic testing calculator
<https://fhwalescriteria.co.uk/assistant.html>
- Simon Broome Criteria
<https://www.mdcalc.com/calc/3817/simon-broome-diagnostic-criteria-familial-hypercholesterolemia-fh>
- DLCN criteria
<https://www.mdcalc.com/calc/3818/dutch-criteria-familial-hypercholesterolemia-fh>

Frailty Resources

- PRISMA-7
https://www.cgakit.com/_files/ugd/2a1cfa_917397e853c644f1bb499fc91b83e2f4.pdf
- NICE multimorbidity: Clinical Assessment and Management 2016
<https://www.nice.org.uk/guidance/ng56/chapter/Recommendations>

Healthy lifestyle patient information

- British Heart Foundation
<https://www.bhf.org.uk/informationsupport/support/healthy-living/healthy-eating>
- Cheshire and Merseyside Happy Hearts website patient information
<https://www.happy-hearts.co.uk/lifestyle-choices>
- Heart UK patient information
<https://www.heartuk.org.uk/healthy-living/introduction>
- Finding NHS Stop Smoking Services
<https://www.nhs.uk/better-health/quit-smoking/find-your-local-stop-smoking-service/>

LDL-C estimate calculator

<https://www.mdcalc.com/calc/70/ldl-calculated>

Patient decision aid information | Cardiovascular disease: risk assessment and reduction, including lipid modification | Guidance | NICE
<https://www.nice.org.uk/guidance/ng238/resources/patient-decision-aid-information-243780160>

QRISK®3

<https://qrisk.org/>

QRISK®3-lifetime

<https://qrisk.org/lifetime/index.php>

Regional medicines management drug formularies

Cheshire: <https://www.cheshireformulary.nhs.uk/>
Merseyside: <https://www.panmerseyapc.nhs.uk/formulary/>
NB: Plans to merge these formularies in due course may change website links

STOPP-START Medication Review Tool

<https://www.cgakit.com/m-2-stopp-start>

Weight management

<https://www.england.nhs.uk/digital-weight-management/>

Appendix D

A-Z Glossary of abbreviations and terminology

- **BMI** *Body mass index: Ratio between height and weight. Should be measured using a validated calculator.*
- **CVD** *Cardiovascular disease: Conditions affecting the heart and blood vessels, sometimes referred to as ASCVD or atherosclerotic cardiovascular disease. These include heart attack, angina, stroke, coronary bypass graft or stent, stroke or TIA, peripheral arterial disease and aortic aneurysm.*
- **CKD** *Chronic kidney disease: Any impairment of the kidneys which will not get better. Can range from mild to severe.*
- **COPD** *Chronic obstructive pulmonary disease: A progressive lung disease causing breathing problems, often related to cigarette smoking.*
- **e-GFR** *Estimated glomerular filtration rate is a measure of kidney function commonly used to define the categories of CKD from 1-5.*
- **FH** *Familial hypercholesterolaemia: An inherited form of high cholesterol that can cause premature blood vessel disease.*
- **GSF** *Gold Standards Framework: A tool used to enable early identification and effective care of people requiring a palliative approach to treatment.*
- **HDL-C** *High-density lipoprotein cholesterol: The main good fat particle in the blood stream.*
- **LDL-C** *Low-density lipoprotein cholesterol: The main bad fat particle in the blood stream.*
- **LFT** *Liver function test: Blood test which provides a measure of how the liver is working.*
- **LTC** *Long term condition: A health condition requiring ongoing management over years or decades that is not cured but controlled with medication and/or therapies.*
- **MCA** *Mental Capacity Act: Law that supports and protects people who are not able to make decisions for themselves.*
- **MACE** *Major adverse cardiac events: Used as a composite end point in research to include cardiac diagnostic codes and endpoints.*
- **MECC** *Make every contact count: A process to ensure time and resources are used effectively to improve health outcomes.*
- **NRT** *Nicotine replacement therapy: Treatment options to reduce craving for cigarettes, used while trying to stop smoking.*
- **Non-HDL-C** *Non-high-density lipoprotein cholesterol: All blood fats that are not HDL-C.*
- **PAD** *Peripheral arterial disease: Atherosclerotic blood vessel disease usually affecting the legs though also other large arteries e.g. aortic aneurysm.*
- **PGT-M** *Pre-implantation genetic testing for monogenic disorders: A fertility treatment used for couples who both have FH and want to screen regarding the potential to have child with homozygous FH.*
- **POCT** *Point of care capillary blood test: A term often used for a test done at the time a person is consulting a medical practitioner, to avoid a further appointment for the test; it is important this is performed using calibrated and validated test equipment.*
- **SPC** *Summary of product characteristics is a description of a medicine's properties and conditions of use. It explains how to safely use and prescribe a medicine.*
- **SR1** *Medical Report Form: A form used to claim benefits under special rules for people with a terminal illness.*
- **TIA** *Transient ischaemic attack: A temporary disruption to blood flow in the brain causing the same symptoms of stroke that all resolve completely within 24 hours.*

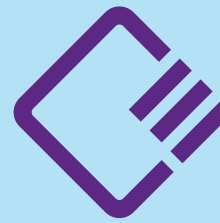
Appendix E

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