Lipid Management for the Primary and Secondary Prevention of Cardiovascular Disease

Medscape UK X Guidelines
Primary Care Hacks

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Key Principles

1. **Review LDL-C and aim for levels as low as possible, as quickly as possible, for as long as possible**
2. **Healthy lifestyle changes can improve overall CV health and aid in achieving LDL-C targets, and should be reinforced at every person contact**
3. **Do not over-rely on QRISK3 and 10-year CV risk; calculating lifetime CV risk may offer a more holistic view of a person's life story**
4. **Consider tighter European LDL-C targets over the current, more lenient UK targets**
5. **Statins are safe and effective and should be utilised when indicated**
6. **Statin intolerance is rare, and should be approached appropriately**
7. **Raised triglycerides are a marker of residual CV risk that may warrant further lifestyle and pharmacological management**
8. **Lp(a) is an independent CV risk factor that, when raised, should act as a prompt to mitigate all other CV risk factors and review lifestyle choices**
9. **Combination LLT should be considered standard practice for high-risk and very high-risk individuals**
10. **Familial hypercholesterolaemia is underdiagnosed in primary care, and should be suspected in individuals with a total cholesterol >7.5 mmol/l and/or LDL-C >4.9 mmol/l.**

See the flowchart on the final page for a comprehensive lipid management pathway for primary care practitioners

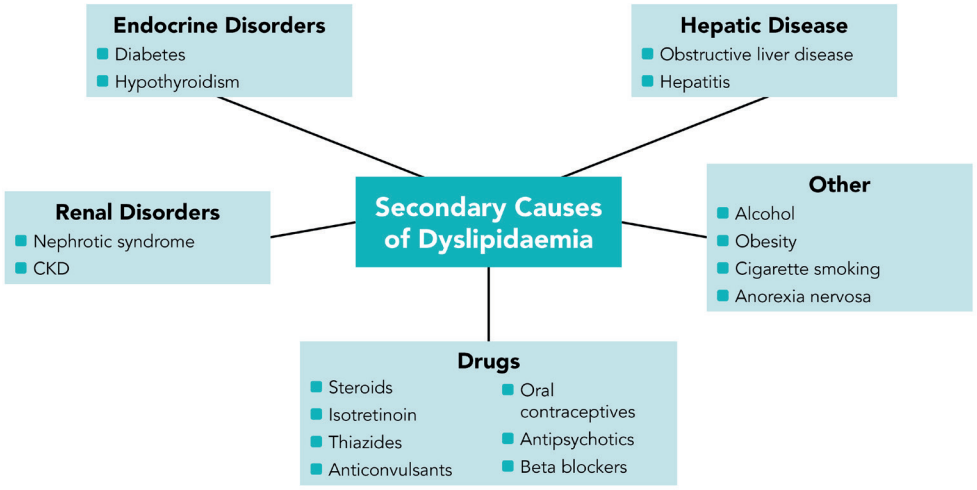
1. Overview of Lipid Management and Assessment

- The relationship between LDL-C levels and risk of major CV events is well established: **lower LDL-C translates into a lower risk of ASCVD, regardless of how it is achieved**[1–4]
  - evidence suggests that lowering LDL-C as quickly as possible and maintaining lower levels long-term significantly reduces risk of major CV events[1,3,4]
  - recent evidence also demonstrates that significant non-HDL-C reduction in the 2 months after an MI improves outcomes irrespective of baseline LDL-C, especially when sustained long-term[5]
- When reviewing cholesterol, focus on LDL-C or non-HDL-C rather than total cholesterol[1,6]—**the aim of therapy should be to lower LDL-C, to reduce the risk of ASCVD**
- NICE NG238 recommends a full lipid profile—including total cholesterol, HDL-C, LDL-C, and TGs—for comprehensive CV risk assessment.[6] **A fasting sample is not mandated**[1,6]
  - however, if lab results indicate a TG level >4.5 mmol/l or do not report an LDL-C due to high TGs, a retest should be conducted using a fasting blood sample[6]
- Although HDL-C has traditionally been viewed as protective, its exact role in CV health remains unclear and is still the subject of ongoing research[1,7]
  - **Heart UK** estimates that the protective effects of HDL-C reach a limit at around 1.4 mmol/l, with levels >2.3 mmol/l potentially increasing risk of ASCVD, especially in perimenopause/menopause[7]
- When reviewing a patient, it is essential to **identify and address secondary causes of dyslipidaemia and modifiable CV risk factors** (see Figure 1 and *2. Lifestyle Interventions*).[6,8,9]

2. Lifestyle Interventions

- Lifestyle interventions are fundamental in managing CV risk and cholesterol levels, and in promoting overall CV health over and above cholesterol[1,6]
- **Heart UK** advises the following as key strategies:
  - maintaining a balanced, heart-healthy diet[11]
  - regular physical activity (adults should aim for ≥150 minutes of moderate-intensity activity or ≥75 minutes of intense activity every week—if they can do more, that's even better)[12]
  - smoking cessation[13]
  - maintaining a healthy weight[14]
- Heart UK has published a helpful guide explaining how to carry out a quick dietary assessment and provide tailored dietary advice based on the person's responses
- Although lifestyle changes can lower LDL-C, the reduction may be modest, typically around 20%[15]
  - therefore, it is important not to delay medical treatment, especially in individuals at higher risk of CVD.

Figure 1: Secondary Causes of Dyslipidaemia[9,10]



3. Risk Estimation

- Although QRISK3[16] is a valuable tool for estimating 10-year CV risk, it should not be solely relied upon,[6] especially in younger people with CV risk factors or those with risk factors that accumulate over time—**early intervention is key to prevention of CVD**
  - **NICE NG238 recommends assessing both short-term CV risk (with QRISK3) and lifetime CV risk** for a more comprehensive assessment that informs discussions of CV risk; this helps to identify people with a high lifetime risk even if their short-term risk appears low[6]
    - risk assessments can be carried out in those as young as 25 years[6,16]
  - lifetime CV risk can be assessed using tools such as QRISK3-lifetime[6,17]
  - do not depend exclusively on QRISK3 to determine whether to start statins[6]
- A more pragmatic approach may be to gauge risk based on the individual's age and the number of LTCs they have, alongside any CV risk calculations—for example, an under-40-year-old living with multiple LTCs or CV risk factors is likely to have a high lifetime risk and therefore benefit from early intervention, independent of any risk calculation
- According to NICE guidance, QRISK3 should **not** be used in certain groups, including people:[6]
  - with FH or another form of genetic dyslipidaemia
  - with pre-existing CVD
  - aged ≥85 years
  - with CKD (stages 3–5)
  - with T1D, for whom specific guidance is applied regardless of QRISK3
- Furthermore, QRISK3 may **underestimate** risk in certain groups, including people:[6]
  - who have recently stopped smoking
  - living with HIV
  - living with severe mental illness
  - already taking medicines to treat CV risk factors
  - taking medicines that can cause dyslipidaemia, such as immunosuppressant drugs
  - living with autoimmune disorders and other systemic inflammatory disorders.

See the flowchart on the final page for a comprehensive lipid management pathway for primary care practitioners

4. LDL-C Targets

- NICE NG238[6] sets more lenient LDL-C targets than the equivalent ESC/EAS guidance (see the table below),[1] notably for individuals at **high** or **very high** CV risk
  - note: definitions of 'high' and 'very high' CV risk differ, are malleable, and can be complicated (see the ESC/EAS guideline for details[1]); the following is a simplified way of remembering the key difference:
    - **high risk**—mostly 'primary prevention' patients (no history of CVD) with raised CV risk, such as from a raised QRISK3/lifetime CV risk, FH without other risk factors, or multiple CV risk factors[1]
    - **very high risk**—mostly 'secondary prevention' patients (history of CVD)[1]
- The ESC's tighter targets are based on evidence that **achieving lower LDL-C levels significantly reduces the risk of ASCVD[1]**
  - **it has been estimated that each 1.0 mmol/l reduction of LDL-C causes a relative risk reduction of 23% for major CV events[18]**
  - regardless of the specifics, the modelling suggests that managing patients to more relaxed targets would lead to more CV events.

Comparison of LDL-C Targets[1,6]

CV Risk Level	NICE NG238[6]	ESC/EAS 2019[1]
Very High	• LDL-C ≤2.0 mmol/l or non-HDL-C ≤2.6 mmol/l (for secondary prevention).	• ≥50% LDL-C reduction from baseline • LDL-C <1.4 mmol/l.
High	• >40% reduction in non-HDL-C (for primary prevention).	• ≥50% LDL-C reduction from baseline • LDL-C <1.8 mmol/l.
Moderate[A]		• LDL-C ≤2.6 mmol/l.
Low[A]		• LDL-C <3.0 mmol/l.

[A] NICE offers a standard lipid target for all forms of primary prevention; for further explanation of moderate- and low-risk categories, see the ESC/EAS guideline.

6. Statin Intolerance

- **True statin intolerance—where patients cannot tolerate any dose or type of statin—is relatively rare, recently estimated at 5.9–9.1%[29]**
- The NHS AAC statin intolerance pathway[30] provides an in-depth summary of how to handle statin intolerance
  - if intolerance occurs, options include using a lower dose, switching to an alternative statin, or considering nonstatin therapies[1,6,30]
- **We suggest here a pragmatic approach of using only two statins—atorvastatin and rosuvastatin, both high-potency statins—before moving to nonstatin agents** (reflecting NHS AAC guidance[30]):
  - atorvastatin is lipophilic, whereas rosuvastatin is hydrophilic;[31] therefore, if the patient is intolerant or has side effects with one, it would be sensible to try the other
  - rosuvastatin can be initiated at doses as low as 5 mg once a week, and then slowly increased to maximum tolerated doses.[25]

5. Statins

- **Statins are safe and effective drugs widely used to lower LDL-C and reduce CV risk.** They have been extensively studied and have been demonstrated to significantly lower the risk of major adverse CV events in both primary- and secondary-prevention populations[1,19]
  - clinicians should educate individuals on their efficacy and safety, to dispel any incorrect information they may have been exposed to[6]
- Muscle ache (myalgia) is a common adverse effect, as are mild digestive issues and headaches.[1,20] More serious side effects are rare[1,4,20]
- Although statins have been associated with a slightly increased risk of developing T2D, the CV benefits far outweigh this risk for most individuals (as explained by the BHF)[1,4,21]
  - NICE states the following: *'Do not stop statins because of an increase in blood glucose level or HbA_{1c}'*[6]
- Concerns about haemorrhagic stroke are very rare and largely theoretical, and fears of dementia have been dispelled by studies showing no link between statin use and cognitive decline[1,22]
- The benefit of statins is clear:
  - in primary prevention, the NNT over 10 years (NNT_{10}) to prevent one CV event is estimated by NICE to be 25–50, depending on the threshold of treatment[23]
  - in secondary prevention, the NNT_{10} to prevent one CV event is lower, at around 18–21 for high-intensity statins.[24]

Blood Tests for Statin Monitoring

- The following baseline blood tests should be undertaken before commencement of statins:[6]
  - full lipid profile
  - diabetes status (HbA_{1c})
  - renal function
  - ALT or AST (alone, or as part of LBTs)
  - TSH
- In general, statins exert their effect within 4 weeks,[25,26] so a repeat lipid profile can be performed as soon as 4–6 weeks after initiation
  - however, to improve practicalities in primary care, repeat blood tests should be performed 2–3 months after initiation[6]
- Statins can cause a transient rise in liver aminotransferases but **do not cause liver disease**[27]
  - current monitoring of LBTs for statins is unnecessary and costly[27]
  - a single baseline ALT is all that is required—if this is <3x ULN, commence the statin and repeat ALT only if clinically indicated (note: NICE[6] and NHS AAC[28] guidelines do recommend further measurements of ALT/AST as part of early statin monitoring).

7. Raised Triglycerides

- Raised TGs are an important marker of residual CV risk (that is, persistent risk of CV events despite achievement of treatment goals for LDL-C, BP, and glycaemia[32]), especially when LDL-C is within target[32–34]
  - although the exact mechanism is unknown, elevated TGs are linked to an increased risk of ASCVD and other complications[1,32–34]—**the higher the TGs, the higher the risk**[1]
- If a nonfasting lipid profile indicates a TG level >4.5 mmol/l or does not return an LDL-C result due to high TGs, a retest should be conducted using a fasting blood sample[6]
- Clinicians should determine why TGs are raised and treat any underlying secondary cause[6,9,34]
  - **primary causes of raised TGs include genetic conditions** such as familial hypertriglyceridaemia[9]
  - **secondary causes of raised TGs include:[9,34]**
    - a sedentary lifestyle and an unhealthy diet, particularly one high in saturated fats and sugars
    - alcohol
    - obesity
    - the metabolic syndrome, including MASLD and chronic hyperglycaemia in diabetes
    - hypothyroidism
    - CKD
    - certain medications (such as steroids, certain diuretics, beta blockers, antipsychotics)
- **When treating raised TG levels, non-fasting TGs >2.3 mmol/l, or fasting TGs >1.7 mmol/l indicate increased residual CV risk that should be addressed[35]**
- Lifestyle interventions are the cornerstone of management for high TGs (see *2. Lifestyle Interventions*)[33,34]
- Medication may be required if TGs remain elevated despite lifestyle changes and treatment of secondary causes, to reduce risk of both CVD and pancreatitis
  - statins are typically used first-line due to their overall CV benefit[6,33,34]
  - fibrates or omega-3 fatty acids (such as EPA), can be used to reduce TG levels, but it should be noted that reducing TG levels has no proven CV benefit[33,34]
- The REDUCE-IT trial has demonstrated that treatment with icosapent ethyl, a purified form of EPA, significantly reduced CV events in people with elevated TGs on top of statin therapy[36,37]
  - individuals in the trial had a 25% relative risk reduction in major CV events, but reductions in TGs were less significant than with fibrates or omega 3 fatty acids[37]
  - in July 2022, NICE published a TA for icosapent ethyl as a treatment to reduce the risk of CV events in adults,[36] recommending it in people who:
    - have a high risk of CV events
    - have raised fasting TGs (≥1.7 mmol/l)
    - are taking statins
    - have established CVD (defined as a history of acute coronary syndrome [such as MI or unstable angina needing hospitalisation], coronary or other arterial revascularisation procedures, CHD, ischaemic stroke, or PAD)
    - have LDL-C levels >1.04 mmol/l and ≤2.60 mmol/l
- If TG levels are very high (>20 mmol/l), the risk of acute pancreatitis is significantly higher and urgent discussion with a lipid specialist is recommended.[6]

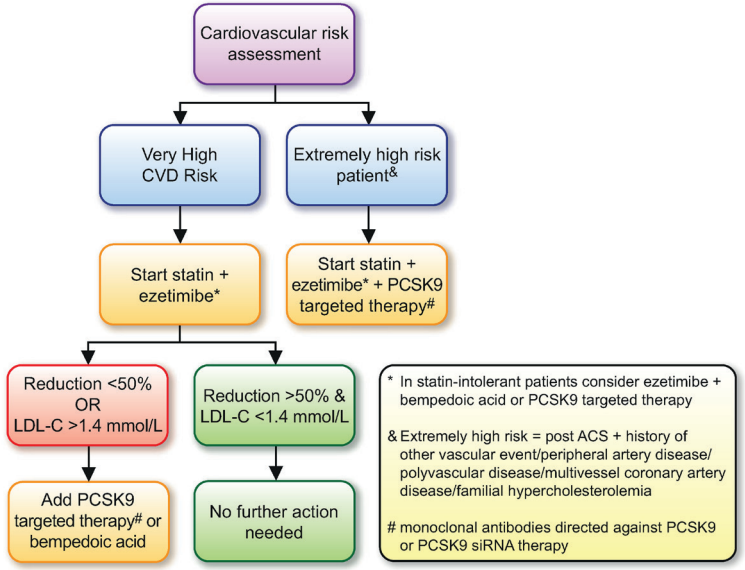
8. Lipoprotein(a)

- **Lp(a) is an independent risk factor for both CVD and calcific aortic valve stenosis**, as elevated Lp(a) levels contribute to atherogenesis, thrombosis, and inflammation[38–40]
- Elevated Lp(a) levels are largely genetically determined, with an autosomal codominant inheritance[38–40]—**unlike LDL-C, Lp(a) levels are not significantly affected by lifestyle choices or statins**[1,41]
  - **one in five people in the UK has raised Lp(a) levels**[38]
- New therapies targeting Lp(a) are in development, which may transform the management of high-risk individuals[40,41]
- Family screening for Lp(a) levels is important due to its hereditary nature, and early detection can guide preventive care[1,38,40]
- Heart UK has published *Consensus statement on Lp(a): a call to action*, making the following key recommendations:[40]
  - serum Lp(a) levels should be measured in those with:
    - a personal or family history of premature ASCVD (<60 years)
    - a first-degree relative with high serum Lp(a) levels (>200 nmol/l)
    - FH, or another genetic dyslipidaemia
    - calcific aortic valve stenosis
    - a borderline increased (but <15%) 10-year risk of a CV event
  - Lp(a) only needs to be measured once (unless a secondary cause is suspected, or specific treatment is undertaken to lower it)
  - CV risk resulting from elevated Lp(a) is determined by Lp(a) serum concentration:
    - minor: 32–90 nmol/l
    - moderate: 90–200 nmol/l
    - high: 200–400 nmol/l
    - very high: >400 nmol/l
  - mitigate CV risk with aggressive lipid management and targeting of all other CV risk factors
    - for those with Lp(a) levels >90 nmol/l, initiate a high-intensity statin and aim for a >50% reduction in non-HDL-C (and an LDL-C <1.8 mmol/l or non-HDL-C <2.5 mmol/l)
- Consider referral to a specialist lipid clinic for those with high Lp(a) levels (such as >200 nmol/l),[40,42] but manage all CV risk factors while waiting for them to be seen.

9. Combination Lipid-Lowering Therapy

- There persists a therapeutic gap between guideline-recommended LDL-C targets (see *4. LDL-C Targets*) and what is achieved in real-world practice[43,44]
- **Rule of 6:** in terms of LDL-C lowering, it is widely accepted that most of the efficacy of statins is at lower doses, and that doubling the dose provides a further 6% lowering of LDL-C, on average[45]
  - therefore, in individuals at high or very high CV risk, combination therapy may be necessary to achieve lower LDL-C targets;[1,4,46] it may be beneficial to initiate the patient on a high-intensity statin and then swiftly add in a second agent, if needed
- An expert consensus statement from the ESC recommends **a shift away from an 'intensive statin therapy first' to an 'intensive lipid-lowering therapy' approach encompassing combination LLT as a first-line strategy for very high-risk individuals** (see Figure 2)[43]
- Fixed-dose combination tablets may help to reduce pill burden, but local guidance should be consulted.

Figure 2: Combination LLT as First-Line Strategy in Very High-Risk Patients[43]



10. Familial Hypercholesterolaemia

- **FH is a common inherited condition** caused by gene mutations encoding key proteins involved in LDL-C receptor pathways, which results in elevated LDL-C levels[47]
- It is an easily missed diagnosis! Many people with FH are asymptomatic, so case-finding is pivotal
- FH affects 0.2–0.5% of people in the UK, and if untreated is a major risk factor for premature ASCVD[47]
  - **for a typical GP practice with 10,000 patients, there will be around 20–50 individuals with FH**
- **FH is an autosomal dominant condition.**[8] Therefore:
  - a child of a parent with FH has a 50% chance of inheriting the condition[8]
  - men and women are equally likely to have the mutation, and sons and daughters are equally likely to inherit it
- **Untreated, FH leads to a ≥30% risk of CHD in women by the age of 60 years and a >50% risk of CHD in men by the age of 50 years due to lifetime exposure to increased LDL-C**[47]
  - if treated early, affected individuals can expect the same life expectancy as the general population[48,49]
- **Suspect FH as a possible diagnosis in adults with:**
  - total cholesterol >7.5 mmol/l[8] and/or LDL-C >4.9 mmol/l[28]
    - it would also be practical to consider FH in those with persistent hyperlipidaemia despite current therapy (for example, LDL-C >2.6 mmol/l when on a high-intensity statin with adherence confirmed), especially in those with a history of premature CHD (an event at <60 years)
    - estimate **untreated** LDL-C in those on current therapy—FH Wales has produced a useful tool for this purpose
  - a personal or family history of premature CHD (an event at <60 years in them or a first-degree relative)[8]
  - family history of suspected or confirmed FH[8,48]
  - presence of tendon xanthomata, xanthelasma, or corneal arcus[50]
    - note: the absence of these features does **not** exclude a diagnosis of FH[8]
- Use the Simon Broome criteria or the Dutch Lipid Clinic Network criteria to aid clinical diagnosis of FH in primary care[8]
  - assessment should be made by a healthcare professional competent in using the criteria[8]
  - suspect a clinical diagnosis of FH in people who have a DLCN score >5 or meet the Simon Broome criteria for 'possible' or 'definite' FH[8]
- Exclude secondary causes of hyperlipidaemia (see Figure 1) before a diagnosis of FH is considered[8]
- **NICE CG71[8] suggests systematically searching primary care records for people with:**
  - total cholesterol >7.5 mmol/l in those aged <30 years
  - total cholesterol >9.0 mmol/l in those aged ≥30 years
- **Risk estimation tools such as QRISK3 should not be used for people with FH, as they are already at high risk of premature CAD**[1,6]
- When FH is suspected (according to the Simon Broome or DLCN criteria):
  - initiate treatment with a high-intensity statin or combination LLT,[8] with suggested LDL-C targets of <1.8 mmol/l in those with no other risk factors or <1.4 mmol/l in those with CV risk factors or pre-existing ASCVD[1]
  - refer to the specialist lipid clinic for review and confirmation of diagnosis[8] but **DO NOT** wait to treat, as waiting lists to be seen by specialist lipid clinics in many parts of the UK are >12 months
  - advise cascade testing to all first-degree relatives[8]
  - consider Lp(a) testing to better determine CV risk[40]
  - advise lifestyle modification and interventions (see *2. Lifestyle Interventions*), especially a diet low in cholesterol and saturated fats.[8]

Abbreviations
AAC=Accelerated Access Collaborative; **ACS**=acute coronary syndrome; **ALT**=alanine aminotransferase; **ASCVD**=atherosclerotic cardiovascular disease; **AST**=aspartate aminotransferase; **BHF**=British Heart Foundation; **BMI**=body mass index; **BP**=blood pressure; **CAD**=coronary artery disease; **CG**=Clinical Guideline; **CHD**=coronary heart disease; **CKD**=chronic kidney disease; **CV**=cardiovascular; **CVD**=cardiovascular disease; **DLCN**=Dutch Lipid Clinic Network; **EAS**=European Atherosclerosis Society; **eGFR**=estimated glomerular filtration rate; **ESC**=European Society of Cardiology; **EPA**=eicosapentaenoic acid; **FH**=familial hypercholesterolaemia; **HbA_{1c}**=glycated haemoglobin; **HDL-C**=high-density lipoprotein cholesterol; **LBT**=liver blood test; **LDL-C**=low-density lipoprotein cholesterol; **LLT**=lipid-lowering therapy; **Lp(a)**=lipoprotein(a); **LTC**=long-term condition; **MASLD**=metabolic dysfunction-associated steatotic liver disease; **MI**=myocardial infarction; **NG**=NICE Guideline; **NNT**=number needed to treat; **od**=once daily; **PAD**=peripheral arterial disease; **PCSK9**=proprotein convertase subtilisin/kexin type 9; **siRNA**=small interfering RNA; **SPC**=summary of product characteristics; **T1D**=type 1 diabetes; **T2D**=type 2 diabetes; **TA**=Technology Appraisal; **TFT**=thyroid function test; **TG**=triglyceride; **TIA**=transient ischaemic attack; **TSH**=thyroid-stimulating hormone; **U&E**=urea and electrolytes; **ULN**=upper limit of normal.

Lipid Management Pathway for Primary Care

INITIAL CONSIDERATIONS

- Measure U&Es, ALT/AST (alone, or as part of LBTs), TFTs, **nonfasting** full lipid profile (total cholesterol, HDL-C, non-HDL-C, LDL-C, TGs), and HbA_{1c} as part of an initial baseline assessment; measure BP, BMI, and waist-to-height ratio[6,28]
- When treating lipids, concentrate on LDL-C and non-HDL-C as they are the main causal ASCVD risk factors;[1,6] plan therapy to ensure targets are achieved as efficiently as possible; If LDL-C is not available locally, add 0.7 to the below LDL-C values for target non-HDL-C levels
- Consider secondary causes of hyperlipidaemia (e.g. diabetes, excess alcohol, poor diet, hypothyroidism) and manage as needed[6,8,9]
- Check **Lp(a) levels** if there is a personal or family history of premature ASCVD (<60 years), a first-degree relative with Lp(a) >200 nmol/l, calcific aortic valve stenosis, or a borderline increased (but <15%) 10-year risk of a CV event[40]
- If **nonfasting TGs >2.3 mmol/l**, refer to the main text of this Primary Care Hack (*7. Raised Triglycerides*); if **nonfasting TGs >4.5 mmol/l** or LDL-C is not reported because TGs are too high, retest with a fasting sample
- Ensure shared decision-making with patients when discussing lipid management[6]

It is important to remember the reduction each LLT will achieve on LDL-C:

- high-intensity statin: 40–55%[28]
  - doubling statin dose only lowers LDL-C by ~6%[28,45]
- ezetimibe: 15–22%[1]
- bempedoic acid:[A] 17–28%[51]
- ezetimibe + bempedoic acid: ~38%[52]
- inclisiran:[B] 50%[28]

This pathway is based on the authors' clinical experience and interpretation of relevant guidance, evidence, and SPCs. Local guidance may differ.

PRIMARY PREVENTION

- Consider statin therapy for adults who do not have established CVD but fall into the categories below
- Use the QRISK3 risk assessment tool,[16] where appropriate
- Identify and address all modifiable risk factors—diet, lifestyle, physical activity, smoking, weight, alcohol intake, BP, CKD, HbA_{1c}
- Refer to the main text of this Primary Care Hack for reasons to check Lp(a)—*8. Lipoprotein(a)*

Moderate/low risk of CVD (QRISK <10%)

Do not rule out statin treatment if CV risk is low/moderate, especially if lifestyle modification is ineffective or inappropriate, LDL-C >3 mmol/l despite lifestyle modifications, or there is concern that risk is underestimated[1,6]

Offer **atorvastatin 20 mg od**

Aim for LDL-C <2.6 mmol/l[C]

High risk of CVD (e.g. QRISK ≥10%, OR presence of T1D, CKD, or multiple comorbidities, OR Lp(a) >90 nmol/l)

Aim for LDL-C <1.8 mmol/l[C]

Offer atorvastatin 20 mg od or another high-intensity statin

(atorvastatin = lipophilic | rosuvastatin = hydrophilic)

If the patient has a suspected intolerance or side effects to multiple statin treatments, initiate **ezetimibe** and/or **follow the NHS AAC statin intolerance pathway**[1,6,30]

If LDL-C >1.8 mmol/l and <50% reduction in LDL-C[C] at review (within 3 months), **optimise therapy as follows:**

Current LDL-C 1.8–1.9 mmol/l

Increase statin dose if able to maximum tolerated dose OR add ezetimibe

(if already on ezetimibe, optimise to combination ezetimibe + bempedoic acid)

Current LDL-C 1.9–2.1 mmol/l

Add ezetimibe

(if already on ezetimibe, optimise to combination ezetimibe + bempedoic acid; if ezetimibe not tolerated, add bempedoic acid)

Current LDL-C >2.1 mmol/l

Add combination ezetimibe + bempedoic acid

If LDL-C >1.8 mmol/l and <50% reduction in LDL-C[C] still not achieved despite triple therapy, seek advice from a local lipid clinic or specialist

SEVERE HYPERCHOLESTEROLAEMIA

Suspect FH if:[8,28,48,50]

- total cholesterol >7.5 mmol/l and/or LDL-C >4.9 mmol/l (use the FH Wales tool to estimate those already being treated with statins)
- personal and/or family history of premature CHD (<60 years)
- family history of FH
- characteristic symptoms (tendon xanthomata, xanthelasma, or corneal arceus)

Do not use QRISK3

Offer atorvastatin 20 mg od or another high-intensity statin

(atorvastatin = lipophilic | rosuvastatin = hydrophilic)

AND

Use Simon Broome or DLCN criteria to make a clinical diagnosis of FH[8]

Identify and address all modifiable risk factors[8]—diet, lifestyle, physical activity, smoking, weight, alcohol intake, BP, CKD, HbA_{1c}

If clinical diagnosis of possible FH or definite FH using Simon Broome criteria, or DLCN score >5:

Refer patient to the lipid clinic for further assessment and genetic testing[8]

Aim for LDL-C ≤1.8 mmol/l, or ≤1.4 mmol/l if major CVD risk factors or existing CVD[C]

SECONDARY PREVENTION

For adults with existing CVD—this includes angina, previous MI, revascularisation, stroke or TIA, or PAD

Aim for LDL-C ≤1.4 mmol/l[C]

Identify and address all modifiable risk factors—diet, lifestyle, physical activity, smoking, weight, alcohol intake, BP, CKD, HbA_{1c}

Do not delay statin treatment in secondary prevention while managing modifiable risk factors. This should be one of the first-line treatments offered

Prescribe a high-intensity statin, e.g. atorvastatin 80 mg od (or alternative)

(atorvastatin = lipophilic | rosuvastatin = hydrophilic)

Use a lower dose of atorvastatin if there is a potential drug interaction, high risk/experience of adverse effects, or patient preference.[6] Offer atorvastatin 20 mg od if CKD (eGFR <60 ml/min/1.73 m^2)[6]

If LDL-C >1.4 mmol/l[C] after 4–6 weeks despite high-intensity statin treatment, **add additional LLT depending on current LDL-C levels**

If the patient has suspected intolerance or side effects to multiple statin treatments, initiate **ezetimibe** and/or **follow the NHS AAC statin intolerance pathway**[1,6,30]

Current LDL-C 1.4–1.9 mmol/l

Add ezetimibe

Current LDL-C 1.9–2.5 mmol/l

Add combination ezetimibe + bempedoic acid

Only if patient is **not** on atorvastatin >40 mg, rosuvastatin >20 mg (due to the theoretical increased risk of myopathy with high-intensity statins), or simvastatin >40 mg (a contraindication)

If bempedoic acid is not suitable, offer ezetimibe 10 mg; if further reductions then needed, seek advice from a local lipid clinic or specialist

Current LDL-C >2.5 mmol/l

Consider inclisiran before oral agents (only if not already on PCSK9 inhibitor monoclonal antibody therapy)

Additional oral therapies can be offered AFTER inclisiran has been considered, if LDL-C is not to target

Current LDL-C ≥3.5 mmol/l

Consider inclisiran

OR

Refer to lipid clinic for PCSK9 inhibitor monoclonal antibody treatment (consider waiting times)

Check TG levels and manage according to guidelines (also see the main text of this Primary Care Hack—*7. Raised Triglycerides*)

At any point, consider icosapent ethyl in addition to statins and/or other therapies, if a person has all of:[36]

- **established CVD**
- **fasting TGs ≥1.7 mmol/l**
- **LDL-C 1.04–2.60 mmol/l, despite maximum LLT**

See NICE TA805

For context on particular medications being recommended here, see also:[36,53–58]

- NICE TA385 (ezetimibe)
- NICE TA694 (bempedoic acid with ezetimibe)
- the bempedoic acid SPC
- NICE TA733 (inclisiran)
- NICE TA393 (alirocumab)
- NICE TA394 (evolocumab)
- NICE TA805 (icosapent ethyl)

When prescribing combination ezetimibe + bempedoic acid: to reduce pill burden and support cost-effective prescribing, prescribe the combination production (bempedoic acid 180 mg + ezetimibe 10 mg tablets)

Only prescribe if patient is **not** on atorvastatin >40 mg, rosuvastatin >20 mg (due to the theoretical increased risk of myopathy with high-intensity statins), or simvastatin >40 mg (concomitant use with simvastatin >40 mg is a contraindication)

Prescribe 1 month of ezetimibe as an acute, and add ongoing combination ezetimibe + bempedoic acid as a repeat

If bempedoic acid is not suitable (e.g. history of gout, CKD stage 4 or 5, or another caution or contraindication that precludes its use), offer ezetimibe 10 mg; if further reductions are then needed, seek advice from a local lipid clinic or specialist

All patients requiring lipid management should be reviewed after the initiation of treatment, after any dose changes (review within 1–3 months), and then annually with a lipid panel. Annual reviews should reassess LDL-C targets and therapies, check adherence, and offer support for diet and lifestyle

Footnotes

[A] Bempedoic acid has demonstrated evidence of CV risk reduction[51]

[B] Inclisiran has not yet demonstrated evidence of CV risk reduction

[C] LDL-C targets are based on the 2019 ESC/EAS guideline.[1] See the main text of this Primary Care Hack for explanation of LDL-C targets for low, moderate, high, and very high CV risk (*4. LDL-C Targets*).

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For references and to view this Primary Care Hack online, go to **medscape-uk.co/Hack-lipids**

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