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PCCS Lipid QI Programme

Treatment and management

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This programme has been solely funded by Novartis. Novartis were not involved in the development of the programme, content, selection of speakers or their arrangements. All content has been independently developed by PCCS.

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Prof. Raj Thakkar disclosures

- AstraZeneca
- Bayer
- Boehringer Ingelheim
- Novartis
- Amgen
- Medtronic
- Edwards
- Heathy.io
- Abbott

Dr Jim Moore disclosures

- Amgen
- AstraZeneca
- Bayer
- Boehringer Ingelheim
- Cuviva
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- Novo Nordisk
- VIFOR
- Amarin
- Medtronic
- Roche

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Contents

- Lifestyle and drug therapy for lipid management
- National guidance for managing lipids
- Monitoring and follow-up
- Management of statin intolerance and use of alternative lipid lowering therapies beyond statins

Primary and secondary prevention of CVD: baseline tests

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- **Baseline blood tests:**
  - Full lipid profile (TC, HDL-C, non-HDL-C and TG)
    - Fasting sample is not needed
    - Excessive alcohol use, uncontrolled diabetes and ketogenic diets can raise TG
  - Creatine kinase
    - If persistent generalised unexplained muscle pain present
  - LFTs (ALT or AST)
  - eGFR and urine ACR (as per NICE NG203)
  - HbA1c
  - TSH
    - If symptoms of underactive or overactive thyroid present
- Clinical assessment to include alcohol consumption, BP, BMI, smoking and diabetes status

Lipid levels	Action
Age < 30 years: TC > 7.5 mmol/L + family history of premature CHD Age ≥ 30 years: TC > 9.0 mmol/L	Consider possibility of FH
TC > 9.0 mmol/L or non-HDL-C > 7.5 mmol/L (even in absence of first-degree family history of premature CHD)	Arrange for specialist assessment
TG > 20 mmol/L (not related to excess alcohol or poor glycaemic control)	Refer for urgent specialist review
TG 10-20 mmol/L	Repeat TG check with a fasting test (after 5 days but within 2 weeks) Review for potential secondary causes of hyperlipidaemia and seek specialist advice if the TG remains > 10 mmol/L
TG 4.5-9.9 mmol/L	CVD risk may be underestimated by risk assessment tools, optimise management of other CVD risk factors present Seek specialist advice if non-HDL-C > 7.5 mmol/L

Statin treatment should not be delayed in secondary prevention to manage modifiable risk factors.

ALT, alanine transaminase; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; FH, familial hypercholesterolaemia; HbA1c, haemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LFTs, liver function tests; TC, total cholesterol; TG, triglycerides; TSH, thyroid stimulating hormone. 1. NICE CKS. Lipid modification – CVD prevention: Scenario: Lipid therapy – primary prevention of CVD. Available at: https://cks.nice.org.uk/topics/lipid-modification-cvd-prevention/management/lipid-therapy-primary-prevention-of-cvd/. Accessed June 2023; 2. NICE CKS. Lipid modification – CVD prevention: Scenario: Lipid therapy – secondary prevention of CVD. Available at: https://cks.nice.org.uk/topics/lipid-modification-cvd-prevention/management/lipid-therapy-secondary-prevention-of-cvd/. Accessed June 2023; 3. NICE. Chronic kidney disease: assessment and management (NG203). Available at: https://www.nice.org.uk/guidance/ng203. Accessed August 2023; 4. NICE CKS. Hypercholesterolaemia – familial. Available at: https://cks.nice.org.uk/topics/hypercholesterolaemia-familial/. Accessed August 2023; 5. Cleveland Clinic. Triglycerides. Available at: https://my.clevelandclinic.org/health/articles/11117-triglycerides. Accessed August 2023; 6. Chan JT, et al. Cureus 2022;14(1):e20879.

Exclusion of secondary hyperlipidaemias – key investigations

	Tests exclude[1-3]
Renal profile (Na+, K+, Creatinine, eGFR)	Renal failure
Liver profile (TProt, Alb, ALP, ALT)	Cholestasis, M protein
Thyroid profile (TSH, FT4)	Hypothyroidism
HbA1c	Diabetes
Dipstick urinalysis, protein creatinine ratio	Nephrotic syndrome
Also consider at baseline	
Creatine kinase (CK)	High baseline
Review diet (alcohol intake/ketogenic diet)	Diet/lifestyle induced hypertriglyceridemia

Alb, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; FT4, free thyroxine; HbA1c, haemoglobin A1c; K+, potassium; Na+, sodium; Tprot, total protein; TSH, thyroid stimulating hormone. 1. NICE. Cardiovascular disease: risk assessment and reduction, including lipid modification (CG181). Available at: https://www.nice.org.uk/guidance/cg181. Accessed July 2023; 2. Cleveland Clinic. Triglycerides. Available at: https://my.clevelandclinic.org/health/articles/11117-triglycerides. Accessed August 2023; 3. Chan JT, et al. Cureus 2022;14(1):e20879.

Optimal prevention seeks to minimise the risk from all known risk factors[1]

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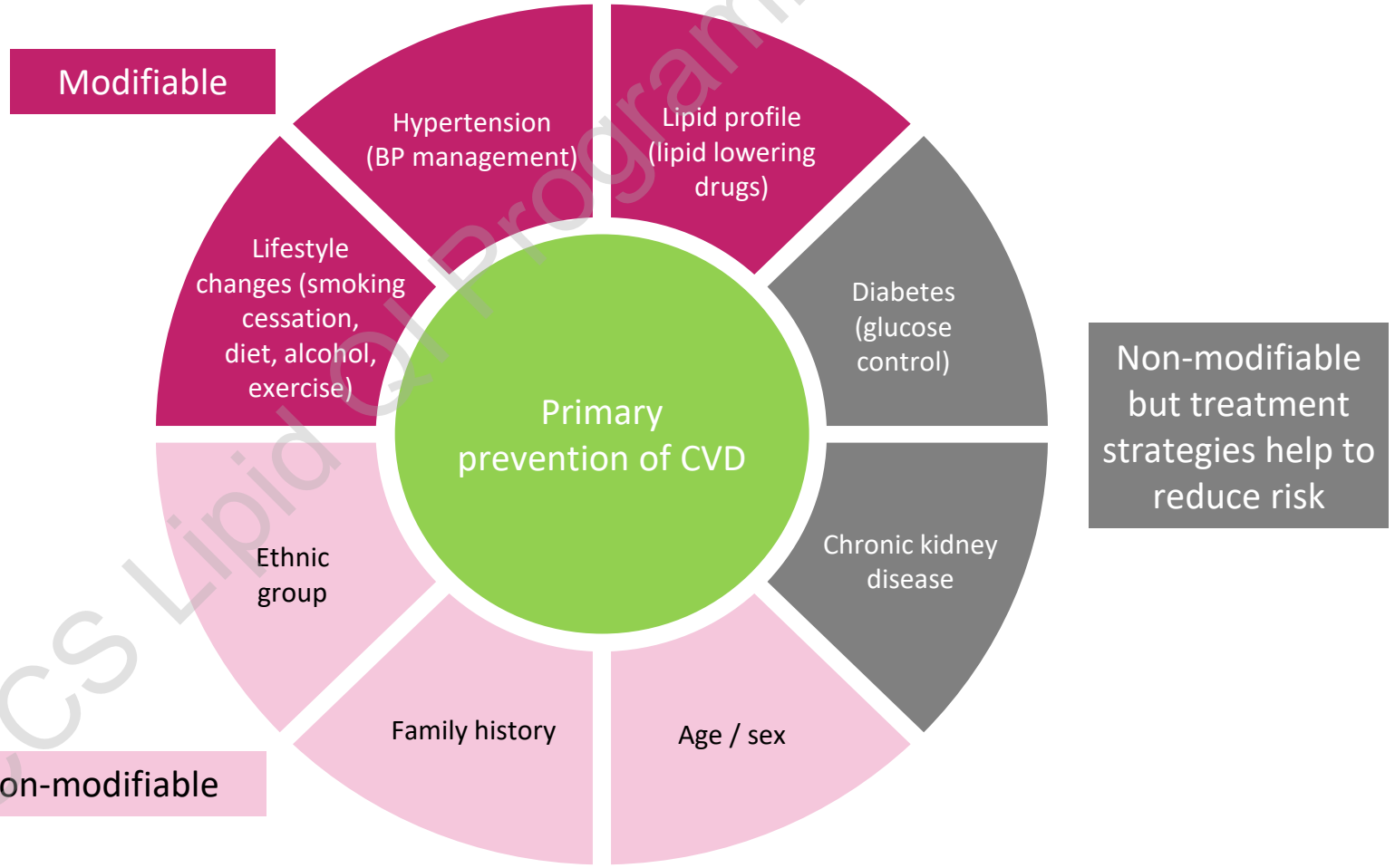
- Lifestyle changes underpin all strategies for risk factor management
- Aspirin is not recommended for primary prevention of CVD



BP, blood pressure; CVD, cardiovascular disease.

Adapted from 1. NICE. Cardiovascular disease: risk assessment and reduction, including lipid modification (CG181). Available at: https://www.nice.org.uk/guidance/cg181. Accessed July 2023.

Dietary recommendations[1,2]

Based on the ESC/EAS 2019 guidelines:

- Reduce intake of foods high in saturated fat
- Replace some saturated fats with unsaturated fats
- Increase (soluble) fibre intake

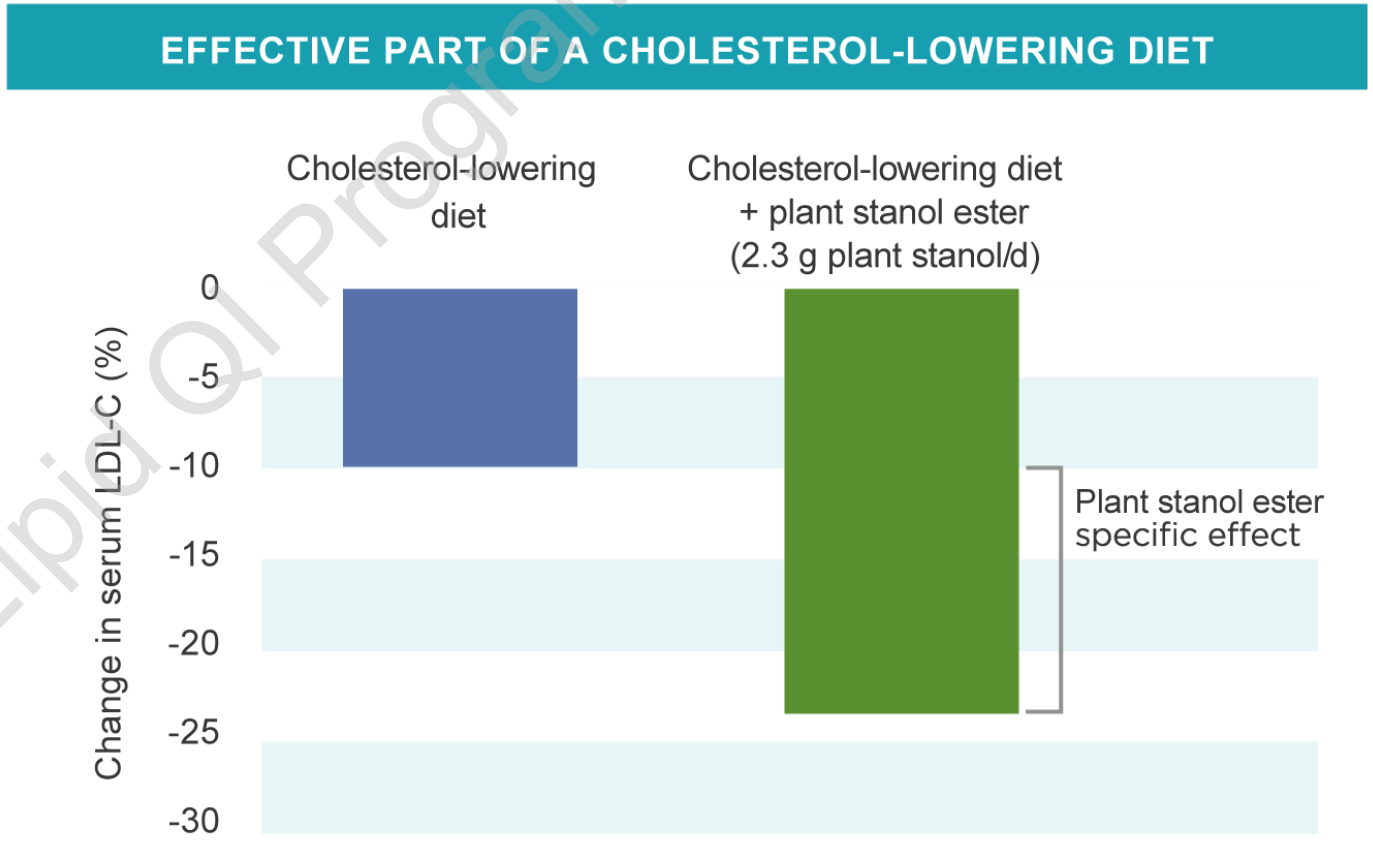
Unhealthy choice		Healthier option
Crisps or roasted, salted peanuts	→	Handful of unsalted nuts
Refined cereal such as cornflakes	→	Wholegrain cereals, such as muesli or porridge
White bread	→	Wholemeal bread
White pasta	→	Wholemeal pasta
Butter	→	Vegetable spreads with added plant stanols and sterols
Coconut oil	→	Olive oil or rapeseed oil
Full-fat cheese	→	Reduced fat cheese
Full-fat milk	→	Low-fat milk
Sausages	→	Lean meat such as chicken
Frying food	→	Grill, boil or steam food

EAS, European Atherosclerosis Society; ESC, European Society of Cardiology.

1. Mach F, et al. Eur Heart J 2020; 41(1):111–188; 2. British Heart Foundation. Healthy eating. Available at: https://www.bhf.org.uk/informationsupport/support/healthy-living/healthy-eating. Accessed July 2023.

Plant stanol esters are effective as part of a cholesterol-lowering diet[1]

- Plant stanol ester in addition to a cholesterol-lowering diet reduced LDL-C by a further 9–14% vs the cholesterol-lowering diet alone



LDL-C, low-density lipoprotein cholesterol.

1. Hallikainen MA, et al. Am J Clin Nutr 1999;69:403–410.

Guidance on phytosterols

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According to the ESC/EAS 2019 guidelines and EAS consensus panel papers, foods enriched with plant sterols/stanols may be considered:[1–3]

- In those with high cholesterol levels at intermediate/low global CVD risk who are not eligible for cholesterol-lowering drugs
- In combination with cholesterol-lowering drugs in high/very high-risk patients who fail to achieve LDL-C targets on statins or have statin intolerance
- In adults and children (>6 years) with familial hypercholesterolaemia
- In patients with statin-associated muscle symptoms

NICE do not advise plant stanols or sterols for CVD prevention for:[4]

- Primary and secondary prevention
- Patients with CKD
- Patients with type 1 and 2 diabetes

CVD, cardiovascular disease; EAS, European Atherosclerosis Society; ESC, European Society of Cardiology; LDL-C, low-density lipoprotein cholesterol.

1. Mach F, et al. Eur Heart J 2020;41(1):111–188; 2. Gylling H, et al. Atherosclerosis 2014;232(2):346–360; 3. Stroes ES, et al. Eur Heart J 2015;36(17):1012–1022; 4. NICE. Cardiovascular disease: risk assessment and reduction, including lipid modification (CG181). Available at: https://www.nice.org.uk/guidance/cg181. Accessed July 2023.

Primary prevention[1]

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Offer atorvastatin 20mg to:

- Up to age 84 years with 10% or greater risk of CVD over 10 years
- CKD
- Type 1 diabetes
  - Over 40 years old or
  - For 10 years or
  - Concomitant nephropathy or CVD risk factors

Consider atorvastatin 20mg:

- All adults with type 1 diabetes
- Over 85 years old

GDG: "Why atorvastatin 20mg?"

- QALY £4,125 (in men aged 60 at QRISK of 10%)[2]
- "Most clinically and cost-effective option for primary prevention"

When considering primary prevention for at-risk individuals, always undergo an individualised patient assessment, considering aspects such as frailty.

CKD, chronic kidney disease; CVD, cardiovascular disease; GDG, guideline development group; QALY, quality-adjusted life year.

1. NICE. Cardiovascular disease: risk assessment and reduction, including lipid modification (CG181). Available at: https://www.nice.org.uk/guidance/cg181. Accessed July 2023; 2. NICE. Lipid modification: Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. Clinical guideline: Methods, evidence and recommendations. Available at: https://www.nice.org.uk/guidance/cg181/evidence/lipid-modification-update-full-guideline-243786637. Accessed August 2023.

Secondary prevention[1]

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Start atorvastatin 80mg (unlicensed) daily in:

- Established CVD
- Without delay in ACS

Use lower dose of atorvastatin if:

- Potential drug interactions
- High risk of side effects
- Patient preference

GDG:
"Why atorvastatin 80mg?"[2-4]

- QALY £3,275 (in men aged 60)
- High intensity statins are cost effective as a group in secondary prevention
  - NNT = 26 (atorvastatin 80 mg vs. "moderate" statin therapy
- Equivalent or greater benefits, with a lower risk of myopathy than simvastatin 80 mg

High dose, high intensity statin recommended

ACS, acute coronary syndrome; CKD, chronic kidney disease; CVD, cardiovascular disease; GDG, guideline development group; QALY, quality-adjusted life year.

1. NICE. Cardiovascular disease: risk assessment and reduction, including lipid modification (CG181). Available at: https://www.nice.org.uk/guidance/cg181. Accessed July 2023; 2. NICE. Cardiovascular risk assessment and lipid modification (QS100). Available at: https://www.nice.org.uk/guidance/qs100/chapter/quality-statement-6-statins-for-secondary-prevention#:~:text=High%E2%80%91intensity%20statins%20are%20the,a%20heart%20attack%20or%20stroke. Accessed August 2023; 3. NICE. Lipid modification: Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. Clinical guideline: Methods, evidence and recommendations. Available at: https://www.nice.org.uk/guidance/cg181/evidence/lipid-modification-update-full-guideline-243786637. Accessed August 2023; 4. Midlands Therapeutics Review and Advisory Committee. Verdict & Summary: Atorvastatin 80 mg daily - For the secondary prevention of cardiovascular events. Available at: https://ccg.centreformedicinesoptimisation.co.uk/download/873b29c592c59d9f06c44d59955dd6b8/Atorvastatin-80-Verdict-Sep-06.pdf#:~:text=Atorvastatin%20at%20the%20dose%20of,syndrome%20or%20established%20cardiovascular%20disease. Accessed August 2023.

Triglycerides help identify adult statin-treated patients with remaining CV risk[1–3]

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- Epidemiological studies have shown that elevated levels of TGs are an independent marker of CV risk[4]
- International guidelines recognise that CV risk is increased with TGs over 1.7 mmol/L[5]
- In a US observational study, ~40% of adults with diabetes have TG levels ≥1.7 mmol/L regardless of statin use[6]

TG levels	Action
TG > 20 mmol/L (not related to excess alcohol or poor glycaemic control)	Refer for urgent specialist review
TG 10-20 mmol/L	Repeat TG check with a fasting test (after 5 days but within 2 weeks) Review for potential secondary causes of hyperlipidaemia and seek specialist advice if the TG remains > 10 mmol/L
TG 4.5-9.9 mmol/L	CVD risk may be underestimated by risk assessment tools, optimise management of other CVD risk factors present Seek specialist advice if non-HDL-C > 7.5 mmol/L

CV, cardiovascular; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; US, United States.

1. Lawler PR, et al. Eur Heart J 2020;41(1):86–94; 2. Toth PP, et al. J Am Heart Assoc 2018;7:e008740; 3. Schwartz GG, et al. J Am Coll Cardiol 2015;65(21):2267–2275; 4. Ganda OP, et al. J Am Coll Cardiol 2018;72(3):330–343; 5. Visseren FLJ, et al. Eur Heart J 2021;42(34):3227–3337; 6. Fan W, et al. Diabetes Care 2019;42:2307–2314.

“The rule of 6”: Doubling the dose of statins does not double the LDL-C reduction[1,2]

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When the dose of a statin is doubled there is a ~6% increase in LDL lowering efficacy for atorvastatin and fluvastatin[1]

Approximate reduction in LDL-C

Statin dose mg/day	5	10	20	40	80
Fluvastatin			21%	27%	33%
Pravastatin		20%	24%	29%	
Simvastatin		27%	32%	37%	42%
Atorvastatin		37%	43%	49%	55%
Rosuvastatin	38%	43%	48%	53%	
Atorvastatin + ezetimibe 10 mg		52%	54%	57%	61%

Low-intensity statins: 20–30% LDL-C reduction

Medium-intensity statins: 31–40% LDL-C reduction

High-intensity statins: >40% LDL-C reduction

Simvastatin 80 mg is not recommended due to risk of muscle toxicity

Add-on therapy can be used to help patients to reach their target[2–5]

Figure adapted from AAC lipid management pathway, 2022. AAC, Accelerated Access Collaborative; LDL-C, low-density lipoprotein cholesterol. 1. GP notebook. Rule of 6 cholesterol lowering (LDL). Available at: https://gpnotebook.com/simplepage.cfm?ID=x20130329130701685340. Accessed July 2023; 2. Khatib R & Neely D on behalf of the AAC Clinical Subgroup. November 2022. Pathway approved by NICE November 2022. Available at: https://www.england.nhs.uk/aac/publication/summary-of-national-guidance-for-lipid-management/. Accessed July 2023; 3. ESC/EAS Guidelines for the management of dyslipidaemias. Mach F, et al. Eur Heart J 2020;41:111–188; 4. Fox KM, et al. Clin Res Cardiol 2018;107:380–388; 5.NICE. Bempedoic acid with ezetimibe for treating primary hypercholesterolaemia or mixed dyslipidaemia (TA694). Available at: https://www.nice.org.uk/guidance/TA694. Accessed July 2023; 6. Baigent C, et al. Lancet 2010;376:1670–1681.

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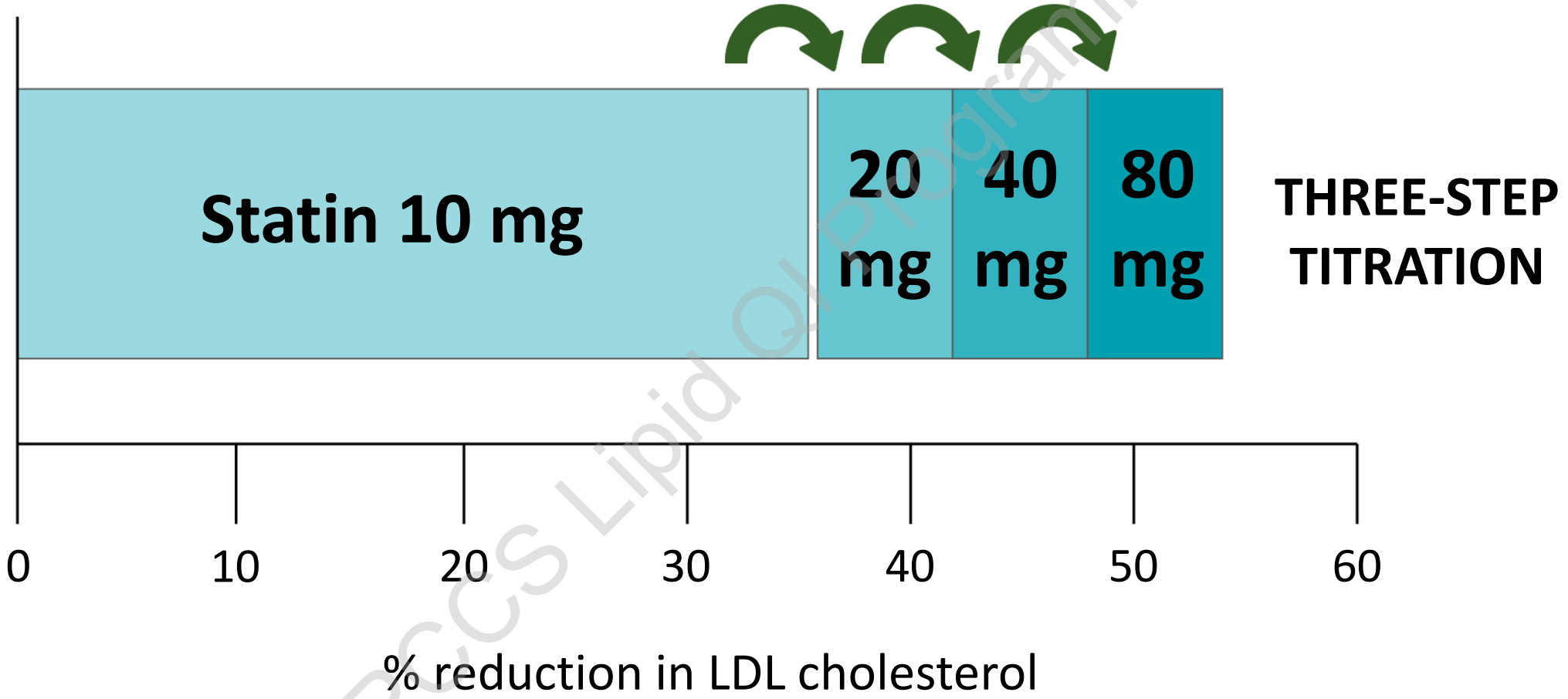
Statin therapy – “the rule of 6”



LDL, low-density lipoprotein.

Brinton E. Unmet Needs in Lipid Management. Available at: https://www.ajmc.com/view/unmet-needs-in-lipid-management. Accessed July 2023.

Follow up and targets in primary and secondary prevention[1-5]

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Primary Prevention	Secondary Prevention
Measure TC, HDL-C, LDL-C and non-HDL-C within 3 months	Measure TC, HDL-C, LDL-C and non-HDL-C within 3 months
Aim for a greater than 40% reductio	l/L and/or LDL-C <1.8mmol/L
ESC recommendations for patients • LDL-C reduction ≥50% from bas	tients at very high-risk: m baseline and LDL-C goal <1.4 mmol/L

Very high risk is defined as:
- ASCVD (clinical/imaging)
- SCORE ≥10%
- FH with ASCVD or with another major risk factor
- Severe CKD (eGFR <30 mL/min)
- DM & target organ damage: ≥3 major risk factors; or early onset of T1DM of long duration (>20 years)

If not achieved:
- Consider adherence issues, dose ti
- Consider increasing statin dose if on < atorvastatin 80 mg and the patient is at higher risk due to comorbidities, risk score or based on clinical judgement
- Consider combination treatment with other lipid lowering therapies

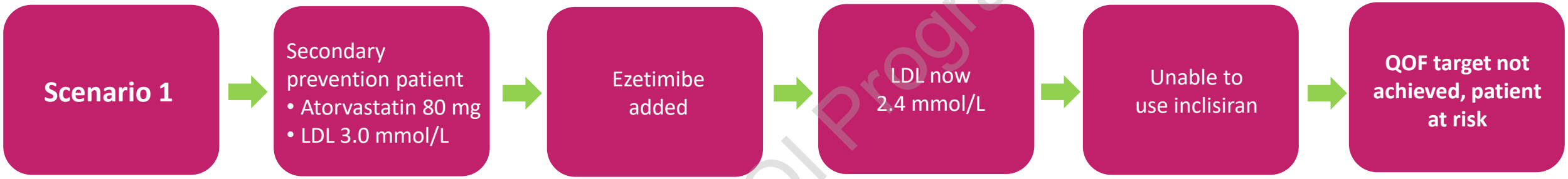
Provide annual medication reviews for patients taking statins (consider an annual non-fasting non-HDL-C blood test to inform the discussion):
- Discuss medication adherence, lifestyle changes and address CVD risk factors
- Discuss with patients taking low or medium intensity statins, the benefits and risks of high intensity statins

CVD, cardiovascular disease; ESC, European Society of Cardiology; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol.

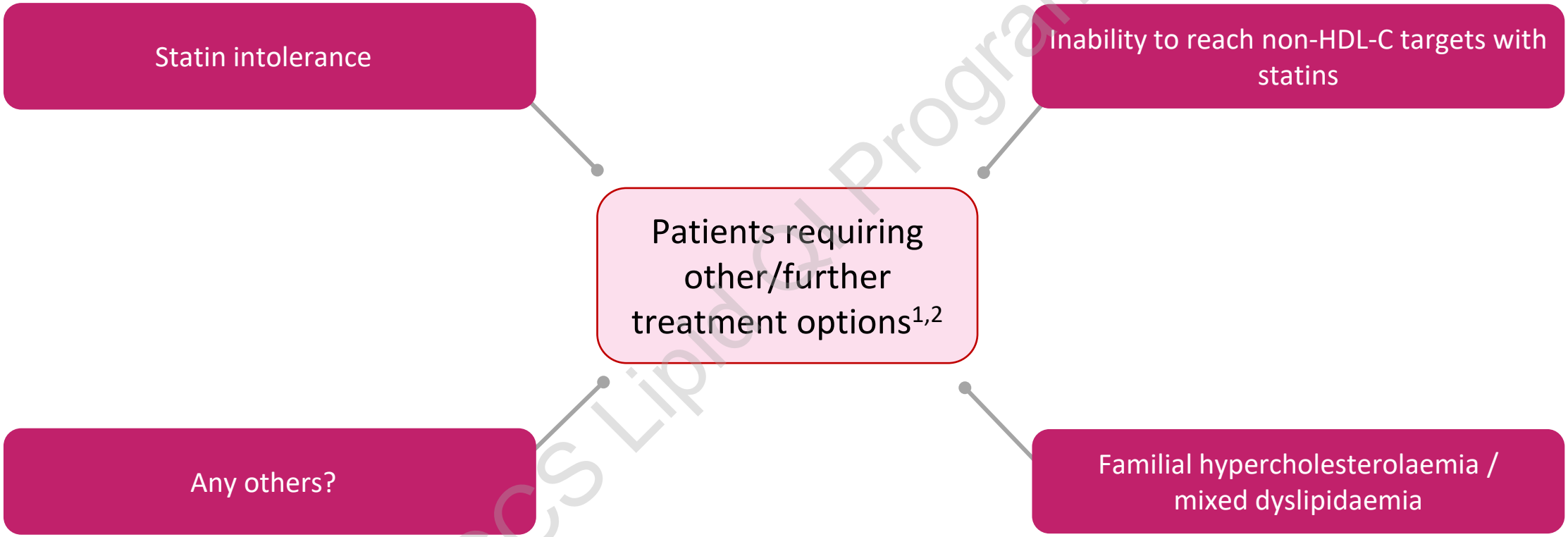
1. NICE. Cardiovascular disease: risk assessment and reduction, including lipid modification (CG181). Available at: https://www.nice.org.uk/guidance/cg181. Accessed July 2023; 2. Health Innovation Network. Lipid Optimisation Pathway for Secondary Prevention in Primary Care. Available at: https://thehealthinnovationnetwork.co.uk/programmes/cardiovascular-disease/lipid-management-and-familial-hypercholesterolemia/lipid-management-pathways/. Accessed November 2023; 3. NICE. Inclisiran for treating primary hypercholesterolaemia or mixed dyslipidaemia (TA733). Available at: https://www.nice.org.uk/guidance/ta733. Accessed August 2023; 4. Mach F, et al. Eur Heart J 2020;41:111-188; 5. Khatib R and Neely D on behalf of the AAC Clinical Subgroup. Summary of National Guidance for Lipid Management for Primary and Secondary Prevention of CVD. November 2022. Available at: https://www.england.nhs.uk/aac/publication/summary-of-national-guidance-for-lipid-management/. Accessed August 2023.

If targets not achieved

Inclisiran lockout risk



What about scenarios in which high intensity statins are not effective enough at lipid lowering?



HDL-C, high-density lipoprotein cholesterol.

1. NICE. Ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia (TA385). Available at: https://www.nice.org.uk/guidance/ta385. Accessed July 2023; 2. NICE CKS. Lipid modification – CVD prevention: Scenario: Lipid therapy - secondary prevention of CVD. Available at: https://cks.nice.org.uk/topics/lipid-modification-cvd-prevention/management/lipid-therapy-secondary-prevention-of-cvd/. Accessed July 2023.

Up to 80% of patients with ASCVD* who use moderate or high intensity statins do not achieve the recommended LDL-C goal† of <1.8 mmol/L[1-3]

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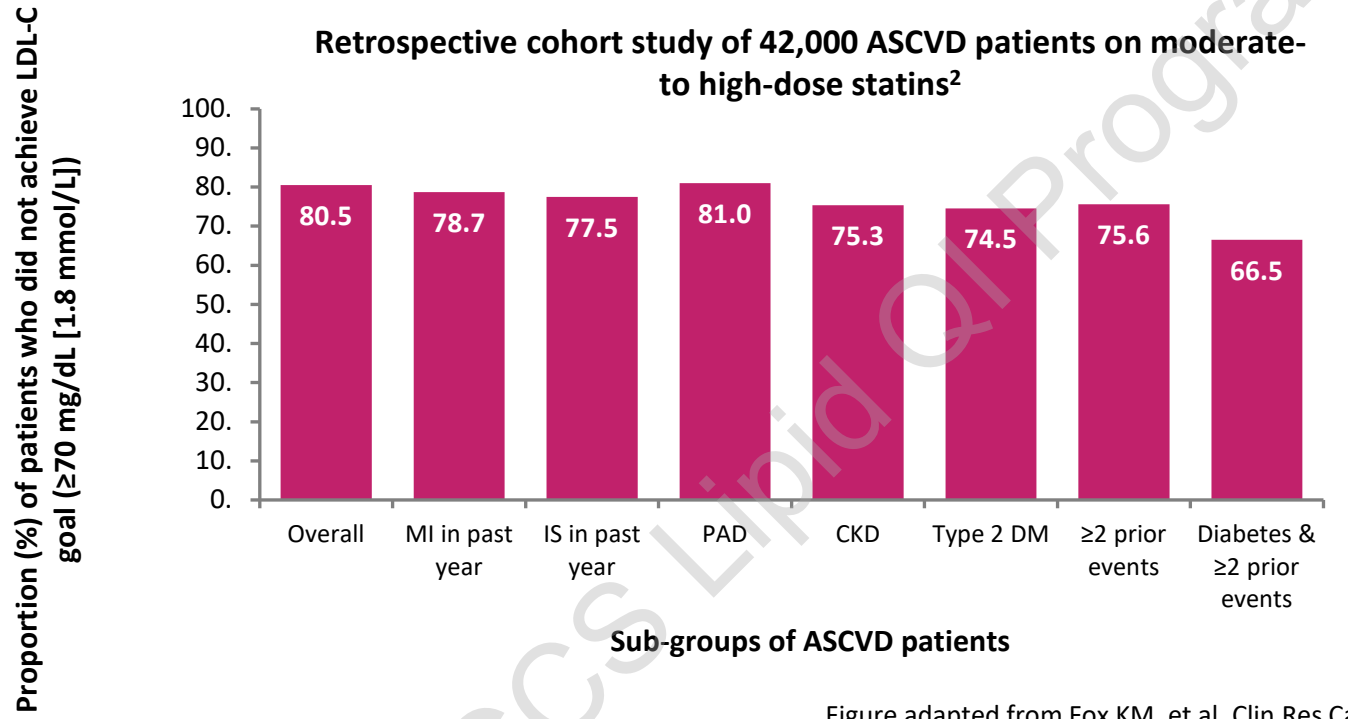

Too many patients, particularly those with ASCVD or other risk factors, have difficulties achieving treatment goals and remain at residual risk for a CV event[4]

Figure adapted from Fox KM, et al. Clin Res Cardiol 2018.

*Documented ASCVD included a history of acute MI, silent MI, unstable angina, coronary revascularisation procedures, clinically significant CHD, symptomatic peripheral arterial disease or cerebrovascular atherosclerotic disease.[1] †The updated ESC/EAS Guidelines recommend an LDL-C reduction of ≥50% from baseline and LDL-C goals of 1.8 mmol/L and 1.4 mmol/L in high risk and very high risk patients, respectively.[1]

ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; DM, diabetes mellitus; LDL-C, low-density lipoprotein cholesterol; IS, ischaemic stroke; MI, myocardial infarction; PAD, peripheral artery disease.

1. Mach F, et al. Eur Heart J 2020;41:111–188; 2. Fox KM, et al. Clin Res Cardiol 2018;107:380–388; 3. Kotseva K, et al. Eur J Res Prev Cardio 2019;26:824–835; 4. Ruscica M, et al. Expert Opin Drug Discov 2019;14:843–847.

Patients with CVD treated and reaching target treatment goals with lipid lowering therapy*

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82% of patients aged 18 and over with GP recorded CVD (narrow definition), who are currently treated with lipid lowering therapy.

28% of these patients had a most recent blood cholesterol level (measured in the preceding 12 months) of non-HDL-C < 2.5 mmol/l or LDL-C < 1.8 mmol/l

*Data to March 2023.

CVD, cardiovascular disease; GP, general practitioner; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

CVDPREVENT. Data Explorer. Available at: https://www.cvdprevent.nhs.uk/data-explorer?period=8. Accessed August 2023.

The NICE guidelines recommend intensive reduction of non-HDL-C[1]

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- The NICE guidelines recommend starting with atorvastatin 20 mg for the primary prevention of CVD in patients who have a 10% or greater 10-year risk of developing CVD and aiming for a >40% reduction in non-HDL-C. In patients with established CVD, NICE recommend starting with atorvastatin 80 mg[1]

If a person is not able to tolerate a high-intensity statin, aim to treat with the maximum tolerated dose[1]

If the original statin was not tolerated, another statin of similar intensity should be tried before resorting to a lower intensity group[1]

For patients at high risk of CVD or those with CVD who are intolerant to 3 different statins, advice should be sought from a specialist about other possible treatment options[1]

Alirocumab or evolocumab are recommended as options in certain patients with primary non-familial hypercholesterolaemia or mixed dyslipidaemia, or primary HeFH if specific LDL-C targets have not been reached[2,3]

Intensive reduction of non-HDL-C aims to reduce CV risk[1]

CV, cardiovascular; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; NICE, National Institute for Health and Care Excellence. 1. NICE. Cardiovascular disease: risk assessment and reduction, including lipid modification (CG181). Available at: https://www.nice.org.uk/guidance/cg181. Accessed July 2023; 2. NICE. Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia (TA393). Available at: https://www.nice.org.uk/guidance/ta393. Accessed July 2023; 3. NICE. Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia (TA394). Available at: https://www.nice.org.uk/guidance/ta394. Accessed July 2023.

The NHS Accelerated Access Collaborative have published guidance for lipid management for primary and secondary prevention of CVD[1]

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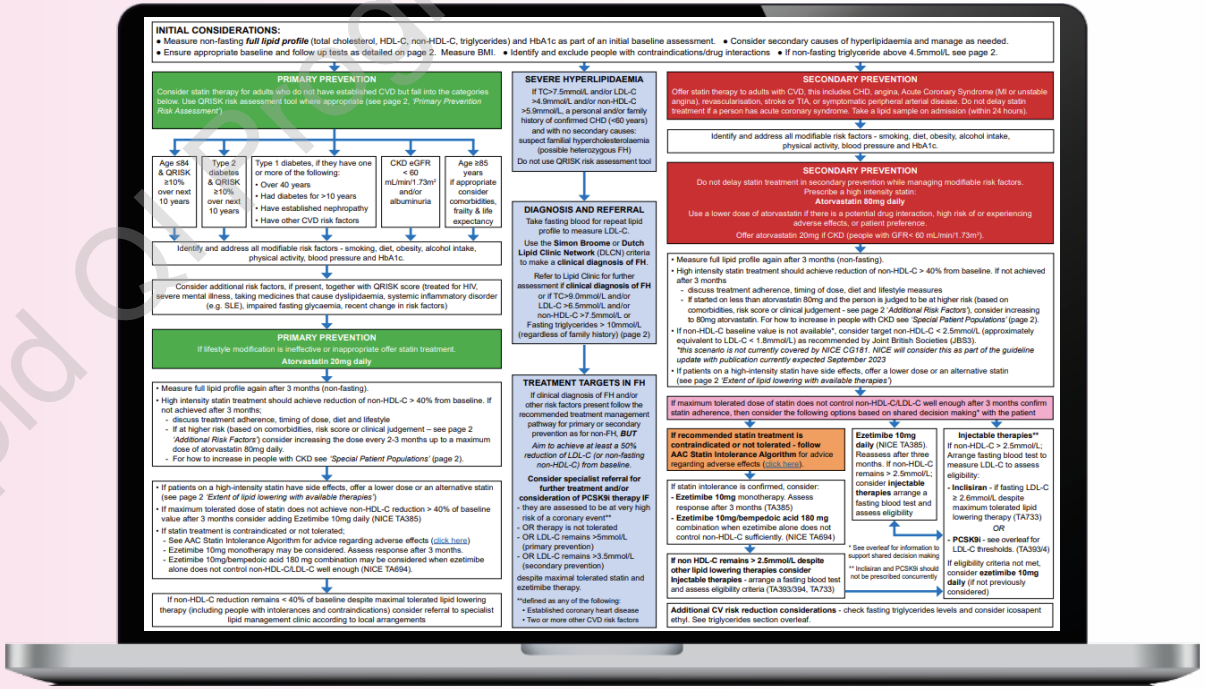
Management:

- If statin therapy is contraindicated, not tolerated or not effective, consider first ezetimibe, then ezetimibe / bempedoic acid, then inclisiran or PCSK9 inhibitor
- Use of ezetimibe / bempedoic acid is not precluded when prior low-dose statin is used due to intolerance to higher-intensity statin (check SPC for interactions)



AAC, Accelerated Access Collaborative; CVD, cardiovascular disease; NHS, National Health Service; PCSK9, proprotein convertase subtilisin/kexin type 9; SPC, summary of product characteristics.

1. Khatib R and Neely D on behalf of the AAC Clinical Subgroup. Summary of National Guidance for Lipid Management for Primary and Secondary Prevention of CVD. November 2022. Available at: https://www.england.nhs.uk/aac/publication/summary-of-national-guidance-for-lipid-management/. Accessed July 2023.

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

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INITIAL CONSIDERATIONS

- Measure non-fasting full lipid profile and HbA1c
- Consider secondary causes of hyperlipidaemia and manage as needed
- Ensure appropriate baseline and follow-up tests
- Measure BMI
- Identify/ exclude people with contraindications/ drug interactions

PRIMARY PREVENTION

Consider statin therapy for adults who do not have established CVD but fall into the categories below. Use QRISK risk assessment tool where appropriate

- Age ≤84 & QRISK ≥10% over next 10 years
- Type 2 diabetes & QRISK ≥10% over next 10 years
- Type 1 diabetes, if they have one or more of the following:
  - Over 40 years
  - Had diabetes for >10 years
  - Have established nephropathy
  - Have other CVD risk factors
- CKD eGFR <60mL/min/1.73m^2 and/or albuminuria
- Age ≥85 years if appropriate consider comorbidities, frailty & life expectancy

Identify and address all modifiable risk factors: smoking, diet, obesity, alcohol intake, physical activity, BP and HbA1c

Consider additional risk factors, if present, together with QRISK score (treated for HIV, severe mental illness, taking medicines that cause dyslipidaemia, systemic inflammatory disorder (e.g. SLE), impaired fasting glycaemia, recent change in risk factors).

BMI, body mass index; BP, blood pressure; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA1c, haemoglobin A1c; HIV, human immunodeficiency virus; SLE, systemic lupus erythematosus. Adapted from 1. Khatib R and Neely D on behalf of the AAC Clinical Subgroup. Summary of National Guidance for Lipid Management for Primary and Secondary Prevention of CVD. November 2022. Available at: https://www.england.nhs.uk/aac/publication/summary-of-national-guidance-for-lipid-management/. Accessed August 2023.

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

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PRIMARY PREVENTION
If lifestyle modification is ineffective or inappropriate offer statin treatment.
Atorvastatin 20mg daily

- Measure full lipid profile again after 3 months (non-fasting).
- High intensity statin treatment should achieve reduction of non-HDL-C >40% from baseline. If not achieved after 3 months;
  - Discuss treatment adherence, timing of dose, diet and lifestyle
  - If at higher risk (based on comorbidities, risk score or clinical judgement consider increasing the dose every 2-3 months up to a maximum dose of atorvastatin 80mg daily.
  - For how to increase in people with CKD see 'Special Patient Populations'.

- If patients on a high-intensity statin have side effects, offer a lower dose or an alternative statin
- If maximum tolerated dose of statin does not achieve non-HDL-C reduction >40% of baseline value after 3 months consider adding Ezetimibe 10mg daily (NICE TA385)
- If statin treatment is contraindicated or not tolerated;
  - See AAC Statin Intolerance Algorithm for advice regarding adverse effects.
  - Ezetimibe 10mg monotherapy may be considered. Assess response after 3 months.
  - Ezetimibe 10mg/bempedoic acid 180 mg combination may be considered when ezetimibe alone does not control non-HDL-C/LDL-C well enough (NICE TA694).

If non-HDL-C reduction remains < 40% of baseline despite maximal tolerated lipid lowering therapy (including people with intolerances and contraindications) consider referral to specialist lipid management clinic according to local arrangements

Special Patient Populations:

Chronic Kidney Disease

- Offer atorvastatin 20mg for the primary or secondary prevention of CVD to people with CKD (eGFR less than 60 mL/min/1.73m^2 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/1.73m^2 or more
- Agree the use of higher doses with a renal specialist if eGFR is less than 30 mL/min/1.73m^2

Type 1 diabetes

- While NICE recommends offering statins to patients with T1D as per the algorithm, it also states to consider statins in all adults with T1D

AAC, Accelerated Access Collaborative; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NICE, National Institute for Health and Care Excellence; T1D, type 1 diabetes. Adapted from 1. Khatib R and Neely D on behalf of the AAC Clinical Subgroup. Summary of National Guidance for Lipid Management for Primary and Secondary Prevention of CVD. November 2022. Available at: https://www.england.nhs.uk/aac/publication/summary-of-national-guidance-for-lipid-management/. Accessed August 2023.

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

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INITIAL CONSIDERATIONS

- Measure non-fasting full lipid profile and HbA1c
- Consider secondary causes of hyperlipidaemia and manage as needed
- Ensure appropriate baseline and follow-up tests
- Measure BMI
- Identify/ exclude people with contraindications/ drug interactions

SECONDARY PREVENTION

Offer statin therapy to adults with CVD, this includes CHD, angina, Acute Coronary Syndrome (MI or unstable angina), revascularisation, stroke or TIA, or symptomatic peripheral arterial disease. Do not delay statin treatment if a person has acute coronary syndrome. Take a lipid sample on admission (within 24 hours)

Identify and address all modifiable risk factors: smoking, diet, obesity, alcohol intake, physical activity, BP and HbA1c

Do not delay statin treatment in secondary prevention while managing modifiable risk factors. Prescribe a high intensity statin: **Atorvastatin 80 mg OD**
Use a lower dose of atorvastatin if there is a potential drug interaction, high risk of or experiencing adverse effects, or patient preference.
Offer atorvastatin 20 mg if CKD (people with GFR< 60 mL/min/1.73m^2)

- Measure full lipid profile again after 3 months (non-fasting)
- High intensity statin treatment should achieve reduction of non-HDL-C > 40% from baseline. If not achieved after 3 months:
  - Discuss treatment adherence, timing of dose, diet and lifestyle measures
  - If started on less than atorvastatin 80 mg and the person is judged to be at higher risk (based on comorbidities, risk score or clinical judgement consider increasing to 80mg atorvastatin.
  - For how to increase in people with CKD see 'Special Patient Populations'
- If non-HDL-C baseline value is not available,* consider target non-HDL-C <2.5 mmol/L (approximately equivalent to LDL-C < 1.8 mmol/L), as recommended by Joint British Societies (JBS3)
  (**This scenario is not covered by NICE CG181)*
- If patients on a high-intensity statin have side effects, offer a lower dose or an alternative statin

Special Patient Populations:
Chronic Kidney Disease

- Offer atorvastatin 20mg for the primary or secondary prevention of CVD to people with CKD (eGFR less than 60 mL/min/1.73m^2 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/1.73m^2 or more
- Agree the use of higher doses with a renal specialist if eGFR is less than 30 mL/min/1.73m^2

BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA1c, haemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; NICE, National Institute for Health and Care Excellence; OD, once daily; TIA, transient ischaemic attack. Adapted from 1. Khatib R and Neely D on behalf of the AAC Clinical Subgroup. Summary of National Guidance for Lipid Management for Primary and Secondary Prevention of CVD. November 2022. Available at: https://www.england.nhs.uk/aac/publication/summary-of-national-guidance-for-lipid-management/. Accessed August 2023.

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

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If maximum tolerated dose of statin does not control non-HDL-C/LDL-C well enough after 3 months confirm statin adherence, then consider the following options based on shared decision making with the patient

If recommended statin treatment is contraindicated or not tolerated – follow **AAC Statin Intolerance Algorithm** for advice regarding adverse effects

If statin intolerance is confirmed, consider:

- **Ezetimibe 10 mg** monotherapy. Assess response after 3 months (TA385)
- **Ezetimibe 10 mg/bempedoic acid 180 mg** combination when ezetimibe alone does not control non-HDL-C sufficiently (NICE TA694)

If non HDL-C remains > 2.5 mmol/L despite other lipid lowering therapies consider Injectable therapies – arrange a fasting blood test and assess eligibility criteria (TA393/394, TA733)

Ezetimibe 10 mg daily (NICE TA385). Reassess after 3 months. If non-HDL-C remains >2.5 mmol/L, consider **injectable therapies**; arrange a fasting blood test and assess eligibility

Injectable therapies[†]

If non-HDL-C > 2.5 mmol/L; arrange fasting blood test to measure LDL-C to assess eligibility:

- **Inclisiran** – If fasting LDL-C ≥ 2.6 mmol/L despite maximum tolerated lipid lowering therapy (TA733) OR
- **PCSK9i** (TA393/4)

If eligibility criteria are not met, consider **ezetimibe 10 mg daily** (if not previously considered)

Additional CV risk reduction considerations – check fasting triglycerides levels and consider icosapent ethyl.

[†]Inclisiran and PCSK9i should not be prescribed concurrently.

AAC, Accelerated Access Collaborative; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NICE, National Institute for Health and Care Excellence; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitors. Adapted from 1. Khatib R and Neely D on behalf of the AAC Clinical Subgroup. Summary of National Guidance for Lipid Management for Primary and Secondary Prevention of CVD. November 2022. Available at: https://www.england.nhs.uk/aac/publication/summary-of-national-guidance-for-lipid-management/. Accessed August 2023.

The NHS Accelerated Access Collaborative have also published a statin intolerance pathway[1]* based on published NICE guidance

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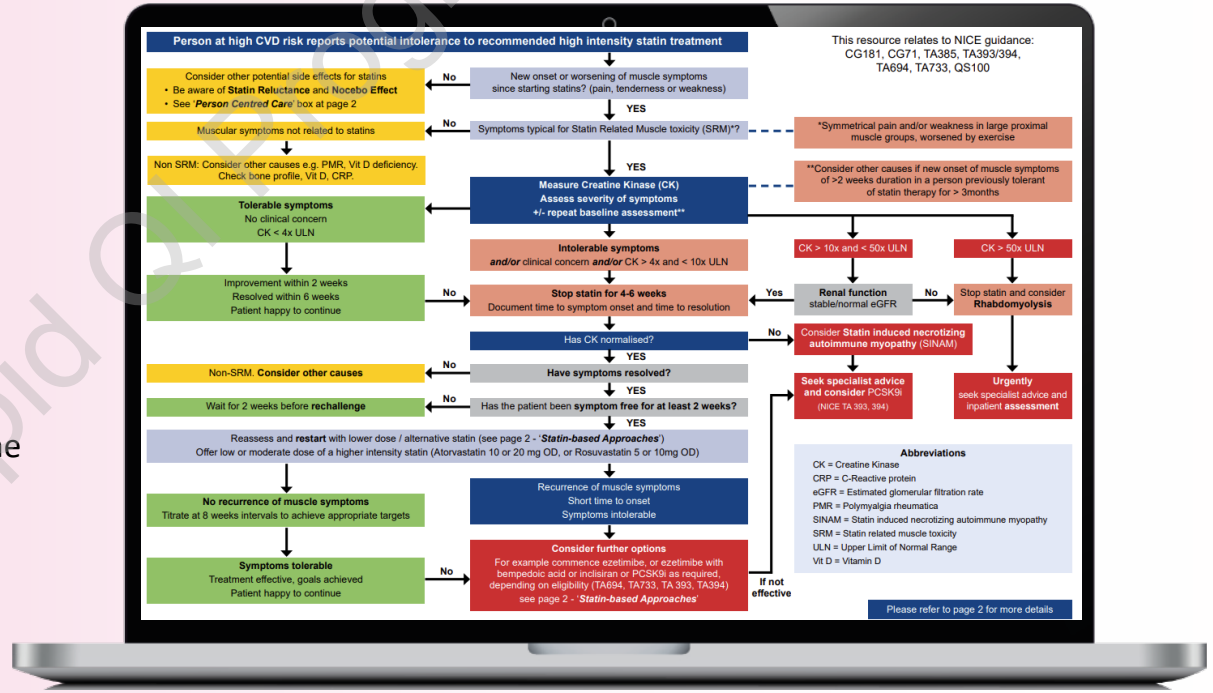
Consider further options:

For example

- Add ezetimibe or give as monotherapy and if needed
- Add bempedoic acid, ahead of inclisiran or PCSK9i
- Noting that statin intolerance does not preclude the use of low-dose statins



*This resource relates to NICE guidance: CG181, CG71, TA385, TA393/394, TA694, TA733, QS100.

AAC, Accelerated Access Collaborative; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor.

1. Khatib R and Neely D on behalf of the AAC Clinical Subgroup. Statin Intolerance Pathway. January 2022. Available at: https://www.england.nhs.uk/aac/publication/statin-intolerance-pathway/. Accessed July 2023.

Statin intolerance pathway

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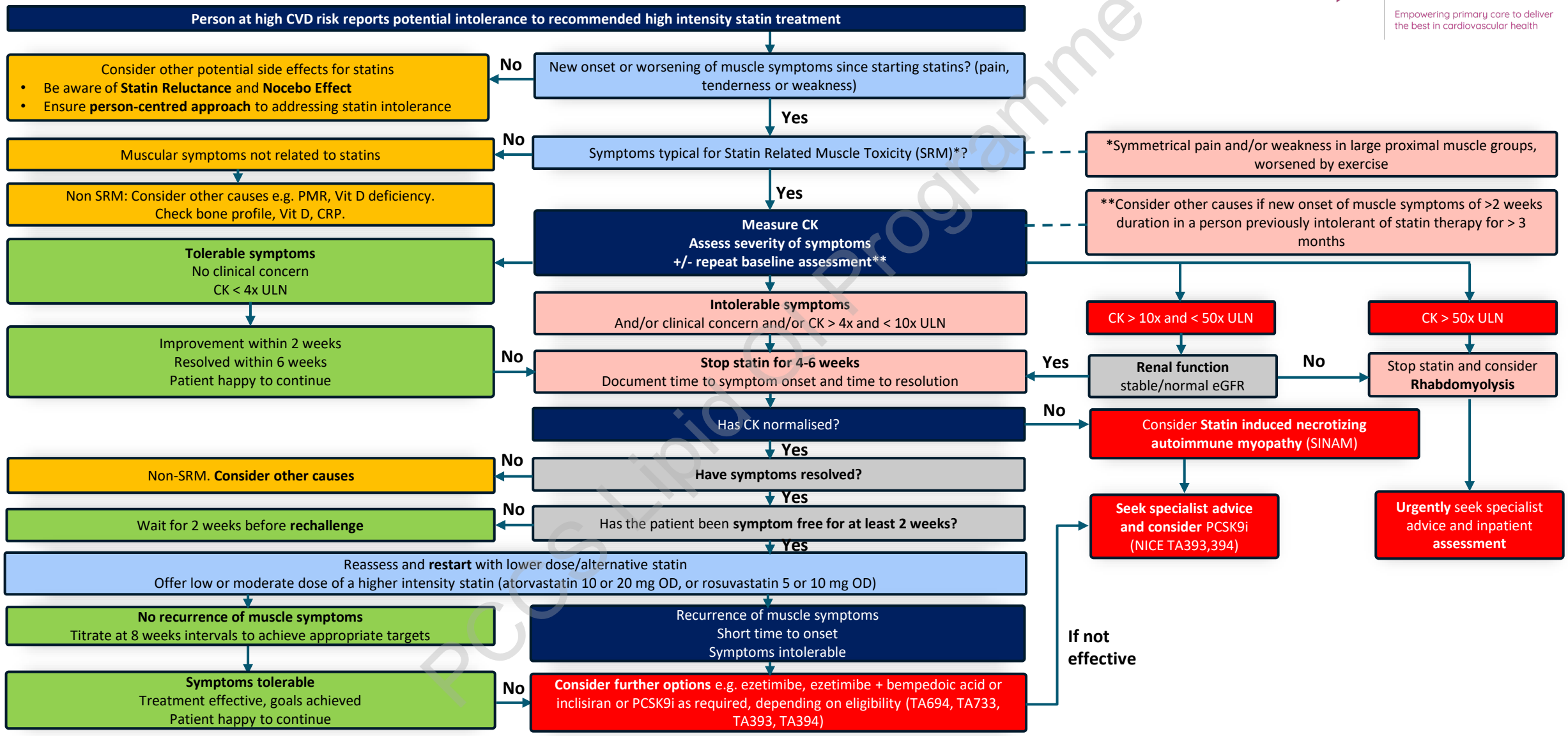

CK, creatinine kinase; CRP, C-Reactive protein; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; NICE, National Institute for Health and Care Excellence; OD, once daily; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitors; PMR, polymyalgia rheumatica; ULN, upper limit of normal range; Vit D, Vitamin D.

1. Khatib R and Neely D on behalf of the AAC Clinical Subgroup. Statin Intolerance Pathway. January 2022. Available at: https://www.england.nhs.uk/aac/publication/statin-intolerance-pathway/. Accessed August 2023.

Statins and the nocebo effect

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- NOCEBO effect: Patient's awareness and concerns regarding possible AEs may lead to a negative outcome
- Comparison of blinded and unblinded statin trials have shown that statin muscle intolerance is associated with a nocebo effect

- A retrospective cohort study was conducted between January 2010 and December 2019 to evaluate whether the high frequency of reported statin AEs may be associated with the nocebo effect
- Subjective AE's included:
  - Fatigue
  - Subjective muscular
  - Nervous system
- Objective AEs were defined as:
  - Hepatic
  - Objective muscular

Of 2,994,487 overall AE reports:

- More subjective than objective AEs were reported per quarter ($P<0.0001$) and over time ($P<0.001$)
- Women reported more subjective AEs than men per quarter
  - Fatigue ($P=0.035$)
  - Subjective muscular AEs ($P<0.0001$)
  - Nervous system AEs ($P<0.0001$)
- Women reported fewer objective muscular AEs ($P<0.0001$)
- Simvastatin-associated reports showed signals for higher objective muscular AEs than all other statins

Specific subjective statin AEs, often associated with a nocebo effect have increased.
Objective statin AEs have shown consistently low reporting patterns over the last decade.

AEs, adverse effects.
Moon J, et al. Circ Cardiovasc Qual Outcomes 2021;14:e007480.

Lipid Optimisation Pathway following an Acute Cardiovascular Event: Acute IS / TIA or ACS

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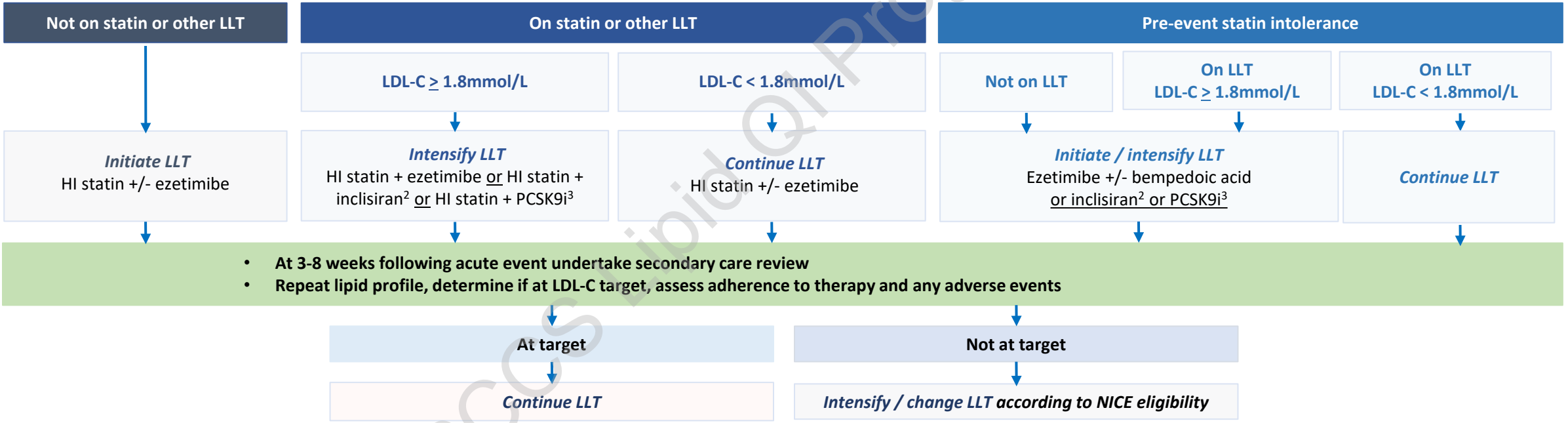
- **Obtain Lipid Profile on Admission preferably LDL-C**
- **Review pre-event lipid lowering therapy including statin therapy tolerance and adherence**
- **Provide lifestyle advice**
- **Commence / optimise all patients on high intensity statin unless statin intolerant**
- **Use shared-decision making and incorporate patient preference in treatment and care decisions**
- **Set LDL-C target. Aim is to achieve for most patients LDL-C < 1.8mmol/L[1]; or non HDL-C < 2.5 mmol/l if no LDL-C result available**



1. Following ACS a lower LDL-C target < 1.4 mmol/l may be appropriate. 2. Inclisiran is a NICE approved option where LDL-C > 2.6 mmol/l despite maximum tolerated statin therapy. 3. PCSK9is are a NICE approved option where LDL-C > 3.5 mmol/l very high risk (recurrent CV events or multiple vascular beds) or > 4.0 mmol/l high risk patients (ACS, ischaemic stroke). ACS, acute coronary syndrome; HDL-C, high-density lipoprotein cholesterol; HI, high intensity; IS, ischaemic stroke; LDL-C, low-density lipoprotein cholesterol; LLT, lipid lowering therapy; NICE, National Institute for Health and Care Excellence; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; TIA, transient ischaemic attack.

Adapted from: Health Innovation Network. Lipid Optimisation Pathway following an Acute Cardiovascular Event: Acute Ischaemic Stroke / Transient Ischaemic Attack (TIA) or Acute Coronary Syndrome (ACS). Available at: https://thehealthinnovationnetwork.co.uk/programmes/cardiovascular-disease/lipid-management-and-familial-hypercholesterolemia/lipid-management-pathways/. Accessed November 2023.

Version 4
20/01/23

Lipid Optimisation Pathway for Secondary Prevention in Primary Care

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Is patient on high dose, high intensity statin[1]?
(atorvastatin 80mg or equivalent)

No

Initiate / increase to high dose high intensity statin[2] and reinforce lifestyle and diet measures

Yes

Review within 3 months:
Is non-HDL-C less than 2.5mmol/L[7] or LDL less than 1.8 mmol/L ?

No

Check adherence to statin[5] and lifestyle measures

Yes

Consider ezetimibe 10mg daily

Review within one to three months.
If non-HDL-C remains ≥2.5mmol/L: consider injectable therapies arrange a fasting blood test and assess eligibility

Consider injectable therapies

If non-HDL-C ≥ 2.5 mmol/l: obtain lipid profile, preferably fasting, to assess eligibility:

- **Inclisiran - if fasting LDL-C ≥ 2.6mmol/L OR**
- **Refer for PCSK9i (mAB)[6] if fasting LDL-C > 4mmol/L (or > 3.5mmol/L if recurrent events)**

If eligibility criteria are not met, consider ezetimibe 10mg daily (if not previously considered)

Review annually for adherence to drugs and support for diet and lifestyle measures

Optimal High Intensity Statin for secondary prevention (High intensity statins are substantially more effective at preventing cardiovascular events than low/medium intensity statins)	
Atorvastatin	80mg
Rosuvastatin	20mg

1. Dose may be limited, for example if:
   - eGFR<30ml/min
   - Drug interactions
   - Intolerance
   - Older age / frailty
2. See statin intensity table. Use shared-decision making and incorporate patient preference in treatment and care decisions.
3. NICE CG181 CVD Risk Assessment and Reduction
4. NICE approved Summary of National Guidance for Lipid Management
5. If statin not tolerated, follow statin intolerance pathway and consider ezetimibe 10mg daily +/- bempedoic acid 180mg daily. If non HDL-C remains ≥ 2.5mmol/L despite other lipid lowering therapies consider injectable therapies.
6. NICE Guidance: Evolocumab, Alirocumab
7. Non-HDL LDL targets are identified in order to aid optimal lipid management, current NICE Guidance (under review) recommends a greater than 40% reduction in non-HDL-C

Version 6
03/02/23

CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; mAB, monoclonal antibody; NICE, National Institute for Health and Care Excellence; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitors. Health Innovation Network. Lipid Optimisation Pathway for Secondary Prevention in Primary Care. Available at: https://thehealthinnovationnetwork.co.uk/programmes/cardiovascular-disease/lipid-management-and-familial-hypercholesterolemia/lipid-management-pathways/. Accessed November 2023.

Do not offer as monotherapy or in combination with statins the following:[1-4]

- Fibrates (routinely)
- Nicotinic acid
- Bile acid sequestrants
- Omega 3 fatty acid compounds

This includes in patients with:

- CKD
- Type 1 diabetes
- Type 2 diabetes

For ezetimibe follow NICE (TA385) guidance (use statin where possible)

For bempedoic acid (TA694) and inclisiran (TA733) follow NICE guidance

CKD, chronic kidney disease; NICE, National Institute for Health and Care Excellence.

1. NICE. Cardiovascular disease: risk assessment and reduction, including lipid modification (CG181). Available at: https://www.nice.org.uk/guidance/cg181. Accessed July 2023; 2. NICE. Ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia (TA385). Available at: https://www.nice.org.uk/guidance/ta385. Accessed July 2023; 3. NICE. Bempedoic acid with ezetimibe for treating primary hypercholesterolaemia or mixed dyslipidaemia (TA694). Available at: https://www.nice.org.uk/guidance/ta694. Accessed July 2023; 4. NICE. Inclisiran for treating primary hypercholesterolaemia or mixed dyslipidaemia (TA733). Available at: https://www.nice.org.uk/guidance/ta733. Accessed July 2023.

Bempedoic acid with ezetimibe for treating primary hypercholesterolaemia or mixed dyslipidaemia (TA694)

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- Bempedoic acid with ezetimibe is recommended as an option for treating primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia as an adjunct to diet in adults. It is recommended only if:
  - Statins are contraindicated or not tolerated
  - Ezetimibe alone does not control low-density lipoprotein cholesterol well enough and
  - The company provides bempedoic acid and bempedoic acid with ezetimibe according to the commercial arrangement

NICE. Bempedoic acid with ezetimibe for treating primary hypercholesterolaemia or mixed dyslipidaemia (TA694). Available at: https://www.nice.org.uk/guidance/ta694. Accessed July 2023.

Bempedoic acid with ezetimibe in practice[1,2]

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- Statins are contraindicated or not tolerated[1]
  - Use of ezetimibe/bempedoic acid is not precluded when prior low-dose statin is used due to intolerance to higher-intensity statin (check SPC for interactions)[2-4]
- It is a simple once-daily oral therapy[3,4]
- It can be used for primary and secondary prevention patients[3,4]
- It can be used ahead of PCSK9i[2]
- Can be used either as a single tablet or a FDC with ezetimibe[3,4]
- Increased risk of gout with bempedoic acid

FDC, fixed-dose combination; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; SPC, summary of product characteristics.

1. NICE. Bempedoic acid with ezetimibe for treating primary hypercholesterolaemia or mixed dyslipidaemia (TA694). Available at: https://www.nice.org.uk/guidance/ta694. Accessed July 2023; 2. Khatib R and Neely D on behalf of the AAC Clinical Subgroup. Statin Intolerance Pathway. January 2022. Available at: https://www.england.nhs.uk/aac/publication/statin-intolerance-pathway/. Accessed July 2023; 3. Nilemdo SmPC; 4. Nustendi SmPC.

Inclisiran is available to prescribe for eligible patients

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NICE recommends inclisiran, within its licensed indication,[1] as an option for the treatment of adult patients who:[2]

1 **Have already had certain cardiovascular events,*** and

2 **Have persistently elevated LDL-C levels (≥2.6 mmol/L)** despite maximum tolerated statins with or without other lipid-lowering therapies, or other lipid-lowering therapies when statins are not tolerated or are contraindicated

NICE recommends inclisiran should be considered for patients after treatment with a maximally tolerated statin, with **OR** without ezetimibe, as an adjunct to diet.

Funding by NHSE&I is now in place; inclisiran has been available to prescribe in the UK since 1 September 2021.

*Acute coronary syndrome (such as myocardial infarction or unstable angina needing hospitalisation), coronary or other arterial revascularisation procedures, coronary heart disease, ischaemic stroke or peripheral arterial disease.[2]

LDL-C, low-density lipoprotein cholesterol; NHSE&I, National Health Service England and Improvement; NICE, National Institute for Health and Care Excellence.

1. Inclisiran SmPC; 2. NICE. Inclisiran for treating primary hypercholesterolaemia or mixed dyslipidaemia (TA733). Available at: https://www.nice.org.uk/guidance/ta733. Accessed July 2023.

Inclisiran in practice

- Use for secondary prevention patients where LDL-C persistently 2.6 mmol/l or more, despite maximum tolerated lipid-lowering therapy[1]
- Or other lipid-lowering therapies when statins are not tolerated or are contraindicated[1]
- It is injected initially, again at 3 months, then every 6 months thereafter[2]
- Inclisiran is recommended only in research for treating adults who have no history of cardiovascular events[1]

LDL-C, low-density lipoprotein cholesterol.

1. NICE. Inclisiran for treating primary hypercholesterolaemia or mixed dyslipidaemia (TA733). Available at: https://www.nice.org.uk/guidance/ta733. Accessed July 2023; 2. Inclisiran SmPC.

When to inject?

The recommended dose of inclisiran is 284 mg in a single subcutaneous injection: initially, again at 3 months, followed by a dose every 6 months.[1]

No mandated safety lab monitoring or required dose adjustments for patients: with mild or moderate hepatic impairment;* mild, moderate or severe renal impairment or end-stage renal disease;† or elderly patients.[1]

GP practices can order inclisiran from the wholesaler (AAH), administer to the patient and then request reimbursement via the FP34D route.[2]

*No data are available in patients with severe hepatic impairment. Inclisiran should be used with caution in these patients.[1]

†There is limited experience with inclisiran in patients with severe renal impairment. Inclisiran should be used with caution in these patients. The effect of haemodialysis on inclisiran pharmacokinetics has not been studied. Haemodialysis should not be performed for at least 72 hours after inclisiran dosing.[1] 1. Inclisiran SmPC; 2. NHS England. Summary information on the funding and supply of inclisiran (Leqvio®). Version 2.0. April 2023. Available at: https://www.england.nhs.uk/aac/wp-content/uploads/sites/50/2023/04/B1913-summary-information-on-the-funding-and-supply-of-inclisiran-v-april-2023.pdf. Accessed August 2023.

NICE has recommended icosapent ethyl for the secondary prevention of CV risk (TA805)[1]

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- Icosapent ethyl is recommended as an option for reducing the risk of cardiovascular events in adults. It is recommended if they have a high risk of cardiovascular events and raised fasting triglycerides (1.7 mmol/L or above) and are taking statins, but only if they have:[1]
  - Established cardiovascular disease (secondary prevention), defined as a history of any of the following:
    - Acute coronary syndrome (such as myocardial infarction or unstable angina needing hospitalisation)
    - Coronary or other arterial revascularisation procedures
    - Coronary heart disease
    - Ischaemic stroke
    - Peripheral arterial disease, and
  - LDL-C levels above 1.04 mmol/L and below or equal to 2.60 mmol/L

LDL-C, low-density lipoprotein cholesterol.

NICE. Icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in people with raised triglycerides (TA805). Available at: https://www.nice.org.uk/guidance/ta805. Accessed July 2023.

LDL-Cholesterol lowering therapies

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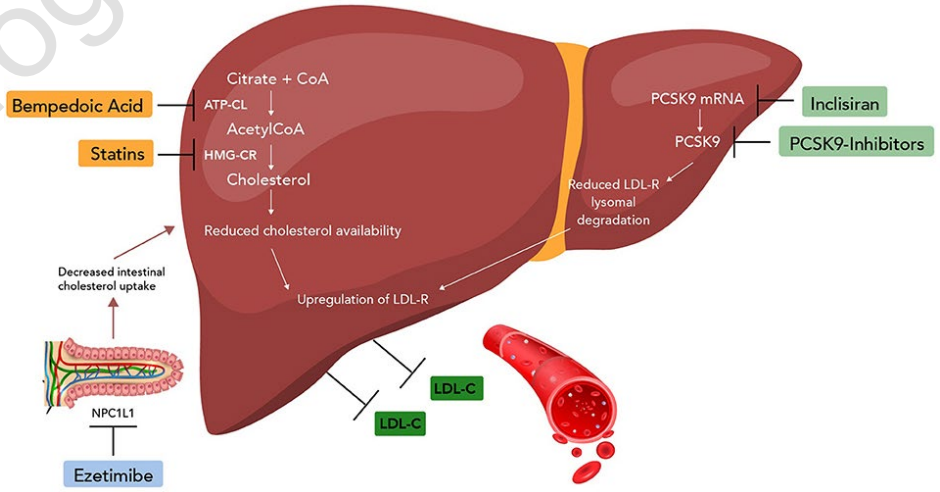
Mechanism of action

Statins	**↓ cholesterol synthesis**
	HMG CoA reductase inhibitor
Ezetimibe	**Impairs cholesterol and biliary absorption**
	Inhibits Niemann-Pick C1 like protein in the intestine and liver
Bempedoic acid	**↑ expression LDL receptors**
	Inhibits adenosine triphosphate-citrate lyase
PCSK9i's	**Prevents inhibition of LDL receptors on hepatocytes**
	Inhibits PCSK9 that binds to LDL receptors
Inclisiran	**↓ production PCSK9**
	Gene silencing by small interfering RNA



HMG CoA, hydroxymethylglutaryl-coenzyme A; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; RNA, ribonucleic acid. 1. Atorvastatin SmPC; 2. Ezetimibe SmPC; 3. Bempedoic acid SmPC; 4. Evolocumab SmPC; 5. Alirocumab SmPC; 6. Inclisiran SmPC.

LDL-C lowering capabilities of therapies

Lipid-lowering therapies	LDL-C ↓	Points to note
Atorvastatin 80 mg OD	55%	Cost effective in all patients
Ezetimibe 10 mg OD	19%	
Bempedoic acid 180 mg OD	~28% (when combined with ezetimibe)	Use if statins not tolerated and LDL-C not controlled on ezetimibe
NICE cost-effective in high-risk patients at NICE specified LDL-C cut-offs:		
Evolocumab 2-4 weekly	~50%	LDL-C > 3.5/4 mmol/L
Alirocumab 2-4 weekly	~50%	
Inclisiran 3-6 monthly	~50%	LDL-C ≥ 2.6 mmol/L

Thresholds for inclisiran use are different in Wales	LDL-C cut-offs
Patients with high risk due to previous CV events	LDL-C ≥4.0 mmol/L
Patients with recurrent/polyvascular disease	LDL-C ≥3.5 mmol/L
Patients with HeFH for secondary prevention of CV events	LDL-C ≥3.5 mmol/L
Patients with HeFH for primary prevention of CV events	LDL-C ≥5.0 mmol/L

CV, cardiovascular; HeFH, heterozygous familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; NICE, National Institute for Health and Care Excellence; OD, once daily. 1. Atorvastatin SmPC; 2. Ezetimibe SmPC; 3. Bempedoic acid SmPC; 4. Evolocumab SmPC; 5. Alirocumab SmPC; 6. Inclisiran SmPC; 7. Khatib R and Neely D on behalf of the AAC Clinical Subgroup. Summary of National Guidance for Lipid Management for Primary and Secondary Prevention of CVD. November 2022. Available at: https://www.england.nhs.uk/aac/publication/summary-of-national-guidance-for-lipid-management/. Accessed October 2023; 8. NICE. Bempedoic acid with ezetimibe for treating primary hypercholesterolaemia or mixed dyslipidaemia (TA694). Available at: https://www.nice.org.uk/guidance/ta694. Accessed October 2023; 9. All Wales Therapeutics and Toxicology Centre. Inclisiran (Leqvio®). Available at: https://awttc.nhs.wales/accessing-medicines/medicine-recommendations/inclisiran-leqvio/. Accessed October 2023.

Advice and monitoring[1]

- Liver transaminases
  - Check ALT/AST at baseline, 3 months and one year of statin therapy and not routinely thereafter
  - Do not withdraw if ALT/AST increases up to x3 ULN
- Creatine Kinase
  - Measure pre-statin if generalised muscle aches only
    - if persistently raised x5 ULN withhold statin
    - if raised but less than x5 ULN then start statin at lower dose
  - If patients develop significant muscle symptoms taking statin then measure CK

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; ULN, upper limit of normal.

1. NICE. Cardiovascular disease: risk assessment and reduction, including lipid modification (CG181). Available at: https://www.nice.org.uk/guidance/cg181. Accessed July 2023.

Statin-associated muscle symptoms (SAMS)[1–3]

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- SAMS are the most significant side effect of statin therapy because they impair long-term drug adherence
- Exact mechanism causing symptoms unknown
- No specific markers for diagnosis
- Comprehensive medical history, temporal associations and response to withdrawal and re-exposure to statins are important
- With careful guidance 90% of patients can be treated with statins long term
- If adequate cholesterol targets not achieved in SAMS patients – consider combination with other lipid-lowering therapy

1. Ward NC, et al. Circ Res 2019;124(2):328–350; 2. American College of Cardiology. Statin Intolerance: Not a Myth. August 2015. Available at: https://www.acc.org/latest-in-cardiology/articles/2015/08/11/09/16/statin-intolerance-not-a-myth. Accessed July 2023; 3. Laufs U, et al. Dtsch Arztebl Int 2015;112(44):748–755.

UCLPartners Proactive Care Framework

UCLPartners. UCLPartners Proactive Care Framework: Lipid Management including Familial Hypercholesterolaemia. Available at: https://s42140.pcdn.co/wp-content/uploads/Cholesterol-Framework-Dec-2022-Version-8.pdf. Accessed July 2023.

Cholesterol – Secondary Prevention (pre-existing CVD)

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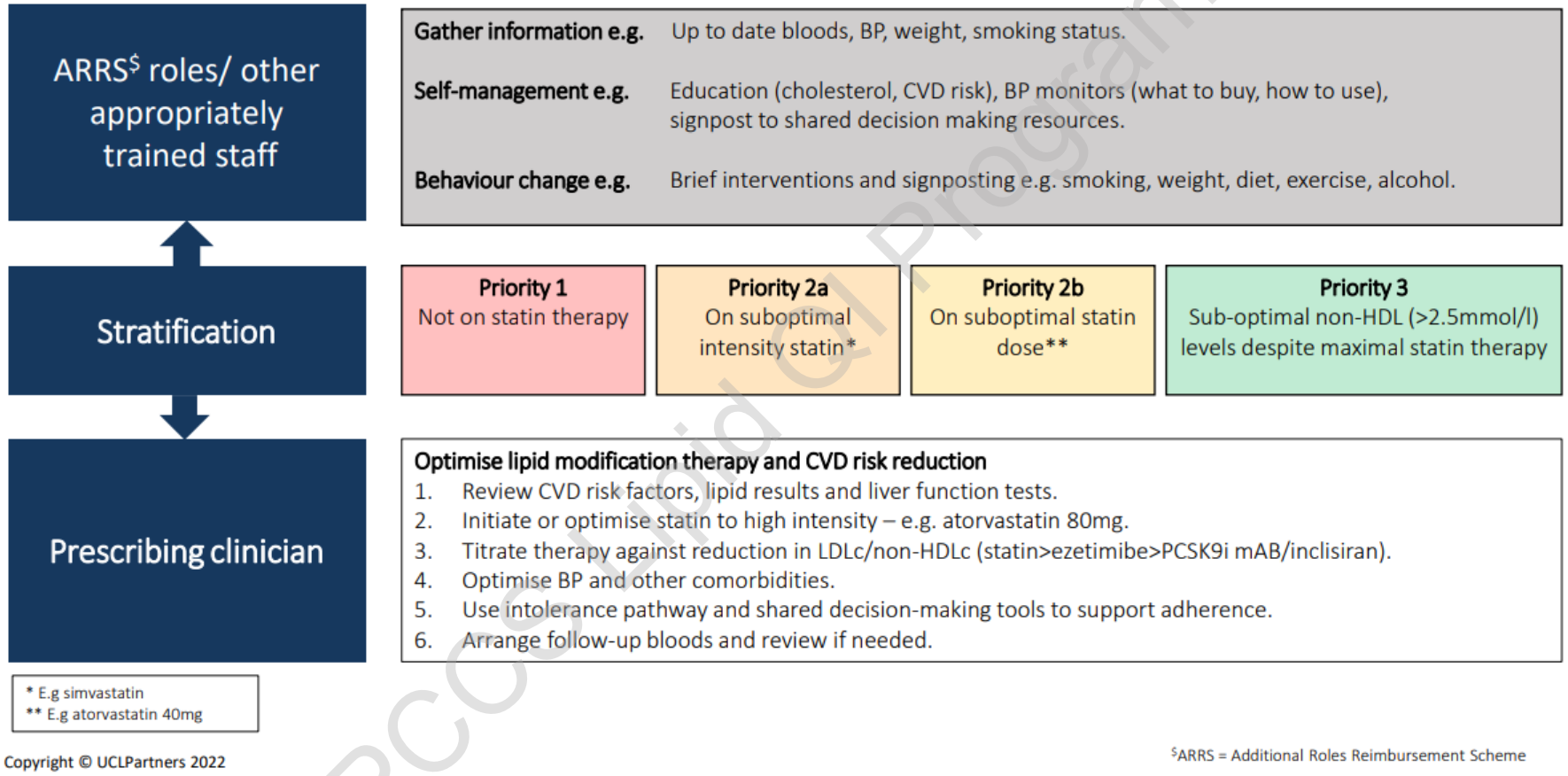

$ARRS = Additional Roles Reimbursement Scheme

BP, blood pressure; CVD, cardiovascular disease; HDLc, high-density lipoprotein cholesterol; LDLc, low-density lipoprotein cholesterol; mAB, monoclonal antibody; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitors.

UCLPartners. UCLPartners Proactive Care Framework: Lipid Management including Familial Hypercholesterolaemia. Available at: https://s42140.pcdn.co/wp-content/uploads/Cholesterol-Framework-Dec-2022-Version-8.pdf. Accessed July 2023.

Cholesterol – Primary Prevention (no pre-existing CVD)

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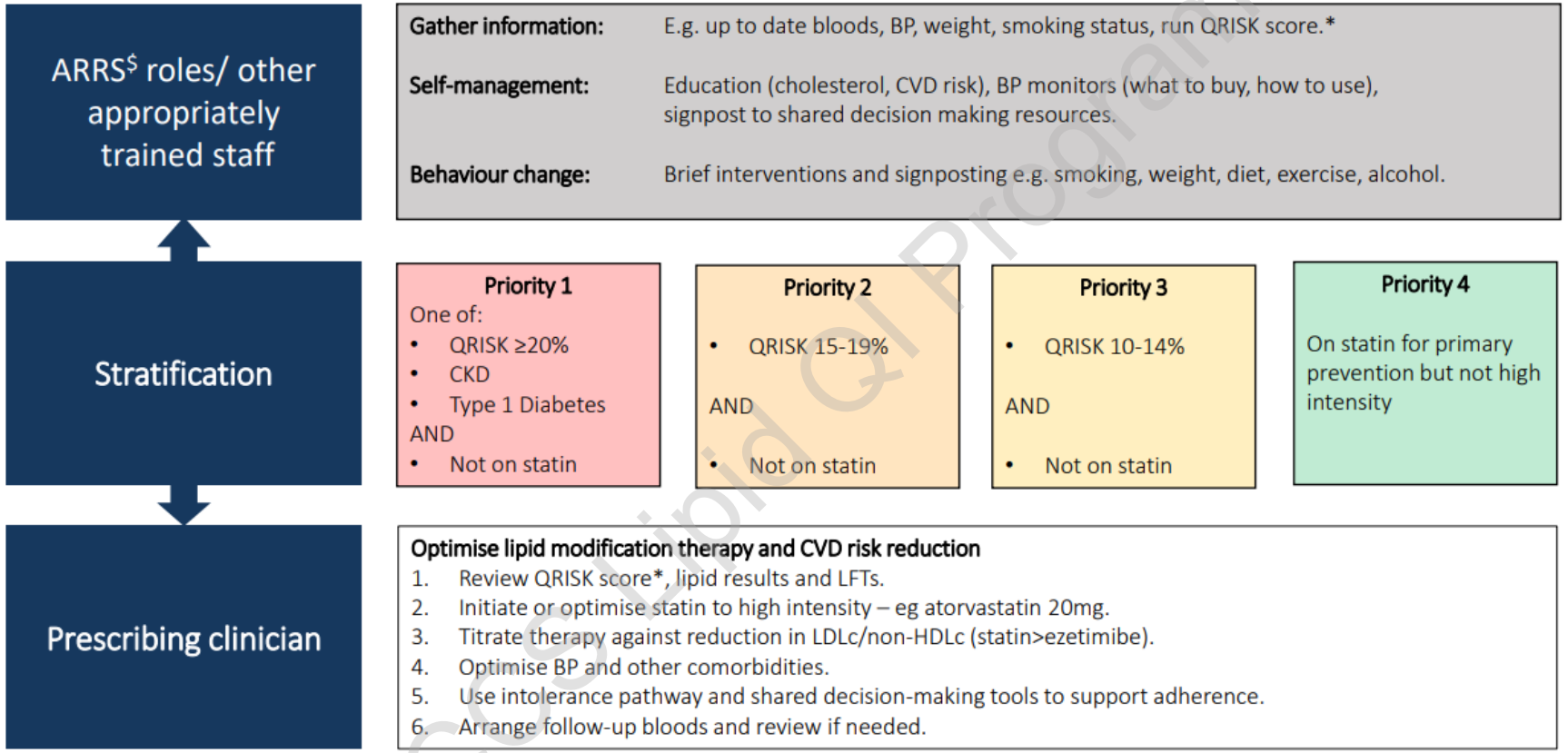
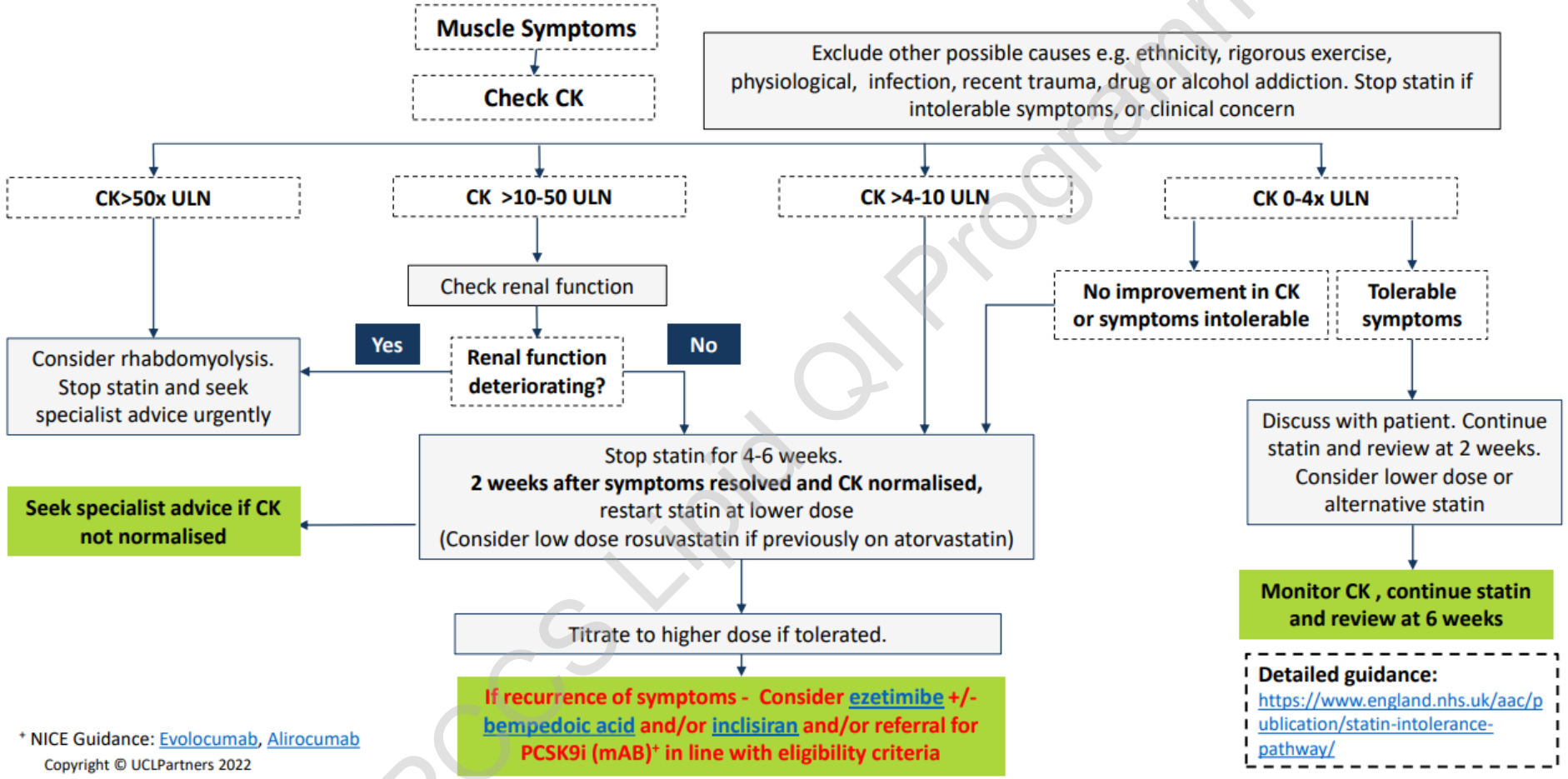


*QRISK 3 score is recommended to assess CV risk for patients with Severe Mental Illness, Rheumatoid Arthritis , Systemic Lupus Erythematosus, those taking antipsychotics or oral steroids; $ARRS = Additional Role Reimbursement Scheme

$ARRS = Additional Roles Reimbursement Scheme

BP, blood pressure; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; HDLc, high-density lipoprotein cholesterol; LDLc, low-density lipoprotein cholesterol; LFTs, liver function tests. UCLPartners. UCLPartners Proactive Care Framework: Lipid Management including Familial Hypercholesterolaemia. Available at: https://s42140.pcdn.co/wp-content/uploads/Cholesterol-Framework-Dec-2022-Version-8.pdf. Accessed July 2023.

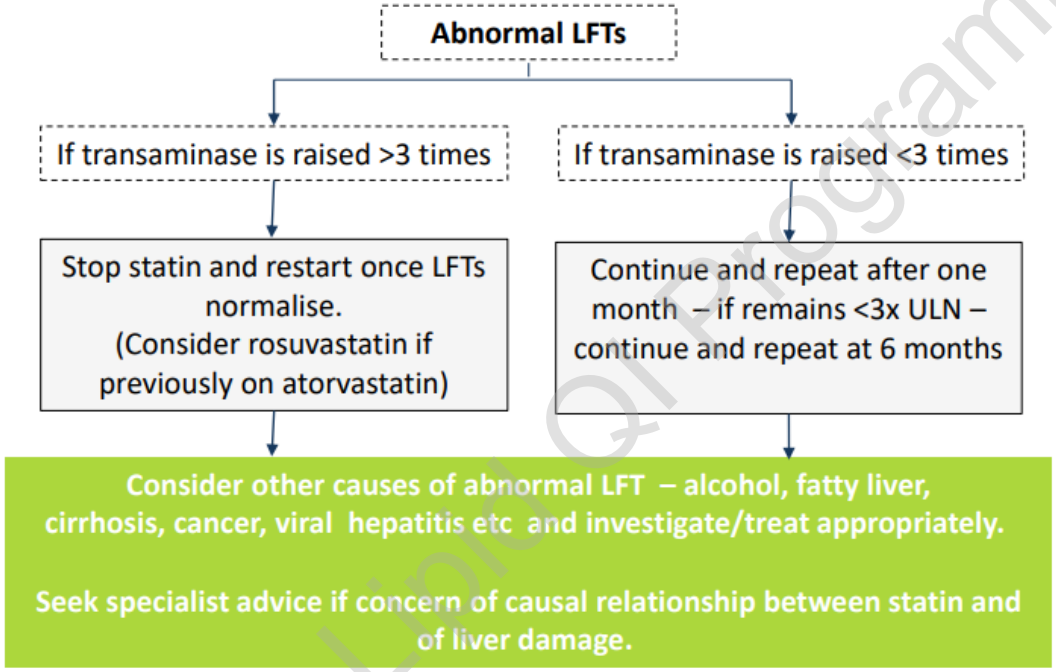
Muscle Symptoms Pathway



CK, creatinine kinase; mAB, monoclonal antibody; NICE, National Institute for Health and Care Excellence; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitors; ULN, upper limit of normal.

UCLPartners. UCLPartners Proactive Care Framework: Lipid Management including Familial Hypercholesterolaemia. Available at: https://s42140.pcdn.co/wp-content/uploads/Cholesterol-Framework-Dec-2022-Version-8.pdf. Accessed July 2023.

Abnormal Liver Function Test (LFT) Pathway



- Do not routinely exclude from statin therapy people who have liver transaminase levels that are raised but are less than 3 times the upper limit of normal.
- Most adults with fatty livers are likely to benefit from statins and this is not a contraindication.
- Check liver function at baseline, within 3 months and 12 months after initiation of statin therapy.

LFTs, liver function tests; ULN, upper limit of normal.

UCLPartners. UCLPartners Proactive Care Framework: Lipid Management including Familial Hypercholesterolaemia. Available at: https://s42140.pcdn.co/wp-content/uploads/Cholesterol-Framework-Dec-2022-Version-8.pdf. Accessed July 2023.

Summary

- Management of lipid levels for the primary prevention of CVD is centred around addressing modifiable and non-modifiable risk factors[1]
  - This include lifestyle changes, lipid lowering therapy and management of comorbidities
- Statin therapy with atorvastatin is first-line for the primary and secondary prevention of CVD[1]
  - Choose statin of high intensity and low acquisition cost
- Ezetimibe, bempedoic acid, inclisiran or PCSK9 inhibitors are alternative NICE recommended lipid-lowering therapies where statins are ineffective or not tolerated or contraindicated[2]
- Multiple lipid management guidelines are available to support primary care in optimising lipids[1-6]

CVD, cardiovascular disease; PCSK9, proprotein convertase subtilisin/kexin type 9.

1. NICE. Cardiovascular disease: risk assessment and reduction, including lipid modification (CG181). Available at: https://www.nice.org.uk/guidance/cg181. Accessed July 2023; 2. Khatib R and Neely D on behalf of the AAC Clinical Subgroup. Summary of National Guidance for Lipid Management for Primary and Secondary Prevention of CVD. November 2022. Available at: https://www.england.nhs.uk/aac/publication/summary-of-national-guidance-for-lipid-management/. Accessed July 2023; 3. Health Innovation Network. Lipid Optimisation Pathway following an Acute Cardiovascular Event: Acute Ischaemic Stroke / Transient Ischaemic Attack (TIA) or Acute Coronary Syndrome (ACS). Available at: https://thehealthinnovationnetwork.co.uk/programmes/cardiovascular-disease/lipid-management-and-familial-hypercholesterolemia/lipid-management-pathways/. Accessed November 2023; 4. Health Innovation Network. Lipid Optimisation Pathway for Secondary Prevention in Primary Care. Available at: https://thehealthinnovationnetwork.co.uk/programmes/cardiovascular-disease/lipid-management-and-familial-hypercholesterolemia/lipid-management-pathways/. Accessed November 2023; 5. UCLPartners. UCLPartners Proactive Care Framework: Lipid Management including Familial Hypercholesterolaemia. Available at: https://s42140.pcdn.co/wp-content/uploads/Cholesterol-Framework-Dec-2022-Version-8.pdf. Accessed July 2023; 6. Khatib R and Neely D on behalf of the AAC Clinical Subgroup. Statin Intolerance Pathway. January 2022. Available at: https://www.england.nhs.uk/aac/publication/statin-intolerance-pathway/. Accessed July 2023.