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Lipid management: case study on implementation of the proactive care frameworks in BHR

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CVD burden remains a significant unmet need; however, recent UK policy reflects the importance of lipid management

CVD in the UK[1]
- >7 million people have CVD
- CVD has an annual total healthcare cost of £9 billion
- CVD is one of the biggest cause of death despite the availability of medical interventions and strategies

The NHS Long-Term Plan:[2]
Up to 10 year outlook for a variety of healthcare topics
- Cholesterol was highlighted for the first time in a decade
- CV risk management is a combined approach: ABC (AF, Blood pressure, Cholesterol)

160,000 deaths/year from CVD; **43,000** are premature[1]

Improve early detection and treatment of CVD
NHS Long-Term Plan[2]

>100,000 hospital admissions/year for an MI[1]
>100,000 strokes/year[1]

Prevent 150,000 heart attacks, strokes and dementia cases
NHS Long-Term Plan[2]

Up to **260,000** people in the UK have HeFH[3]

Expand access to genetic testing for identification of FH cases to at least 25% in 5 years
NHS Long-Term Plan[2]

References

- AF, atrial fibrillation; CV, cardiovascular; CVD, cardiovascular disease; FH, familial hypercholesterolaemia; HeFH, heterozygous familial hypercholesterolaemia; MI, myocardial infarction; UK, United Kingdom.
- 1. BHF. UK Factsheet, August 2019. Available at: https://www.bhf.org.uk/what-we-do/our-research/heart-statistics Accessed: May 2022. 2. NHS Long-Term Plan. Available at: https://www.longtermplan.nhs.uk/wp-content/uploads/2019/08/nhs-long-term-plan-version-1.2.pdf Accessed: May 2022. 3. NICE Clinical Guidance [CG71]. Available at: https://www.nice.org.uk/guidance/cg71/ Accessed: May 2022.

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

ACCELERATED ACCESS COLLABORATIVE

NHS

INITIAL CONSIDERATIONS:

● Measure non-fasting **full lipid profile** (Total cholesterol, HDL-C, non-HDL-C, triglycerides) and HbA1c as part of an initial baseline assessment. ● Consider secondary causes of hyperlipidemia and manage as needed. ● Ensure appropriate baseline and follow up tests as detailed on page 2. Measure BMI. ● Identify and exclude people with contraindications/drug interactions ● If non-fasting triglyceride above 4.5mmol/L see page 2.

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 (see page 2, 'Primary Prevention Risk Assessment')

- 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 < 60 mL/min/1.73m2 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, blood pressure and HbA1c.

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

PRIMARY PREVENTION

If lifestyle modification is ineffective or inappropriate offer statin treatment.
Atorvastatin 20mg OD

- 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 – see page 2 'Additional Risk Factors') 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' (page 2)

- If patients on a high-intensity statin have side effects, offer a lower dose or an alternative statin (see page 2 'Extent of lipid lowering with available therapies')
- 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 recommended statin therapy is contraindicated or not tolerated;
- Ezetimibe monotherapy may be considered. Assess response after 3 months
  - See local statin intolerance guidance / pathway where available
  - 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.

SEVERE HYPERLIPIDAEMIA

If TC>7.5mmol/L and/or LDL-C >4.9mmol/L and/or non-HDL-C >5.9mmol/L, a personal and/or family history of confirmed CHD (<60 years) and no secondary causes: suspect Familial Hypercholesterolemia (Possible Heterozygous FH)
Do not use QRISK risk assessment tool

DIAGNOSIS AND REFERRAL

Take fasting blood for repeat lipid profile to measure LDL-C.
Use the Simon Broome or Dutch Lipid Clinic Network (DLCN) criteria to make a clinical diagnosis of FH.
Refer to Lipid Clinic for further assessment if clinical diagnosis of FH
or if TC>9.0mmol/L and/or
LDL-C >6.5mmol/L and/or
non-HDL-C >7.5mmol/L or
Fasting triglycerides > 10mmol/L
(regardless of family history) (page 2)

TREATMENT TARGETS IN FH

If clinical diagnosis of FH and/or other risk factors present, follow the recommended treatment management pathway for primary or secondary prevention as for non-FH, BUT
Aim to achieve at least a 50% reduction of LDL-C (or non-fasting non-HDL-C) from baseline.
Consider specialist referral for further treatment and/or consideration of PCSK9i therapy IF
- they are assessed to be at very high risk of a coronary event**
- OR therapy is not tolerated
- OR LDL-C remains >5mmol/L (primary prevention)
- OR LDL-C remains >3.5mmol/L (secondary prevention)

Despite maximal tolerated statin and Ezetimibe therapy.
**defined as any of the following:
• Established coronary heart disease.
• Two or more other CVD risk factors

SECONDARY PREVENTION

Offer statin therapy to adults with CVD, this includes angina, previous MI, 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, blood pressure and HbA1c.

SECONDARY PREVENTION

Do not delay statin treatment in secondary prevention while managing modifiable risk factors. Prescibe a high intensity statin: Atorvastatin 80mg 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 20mg if CKD (people with GFR< 60 mL/min/1.73m2).

- 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 80mg and the person is judged to be at higher risk (based on comorbidities, risk score or clinical judgement – see page 2 'Additional Risk Factors'), consider increasing to 80mg Atorvastatin. For how to increase in people with CKD see 'Special Patient Populations' (page 2).
- If non-HDL-C baseline value is not available*, consider target non-HDL-C < 2.5mmol/L (approximately equivalent to LDL-C < 1.8mmol/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 (see page 2 ''Extent of lipid lowering with available therapies')

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 (click here).

If statin intolerance is confirmed, consider:
- Ezetimibe 10mg monotherapy. Assess response after 3 months (TA385)
- Ezetimibe 10mg/bempedoic acid 180 mg combination when ezetimibe alone does not control non-HDL-C sufficiently. (NICE TA694)

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

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

* See overleaf for information to support shared decision making
** Inclisiran and PCSK9i should not be prescribed concurrently

Injectable therapies**
If non-HDL-C > 2.5mmol/L; Arrange fasting blood test to measure LDL-C to assess eligibility:
- Inclisiran - if fasting LDL-C ≥ 2.6mmol/L despite maximum tolerated lipid lowering therapy (TA733)
OR
- PCSK9i - see overleaf for LDL-C thresholds. (TA393/4) If eligibility criteria are not met, consider **ezetimibe 10mg daily** (if not previously considered)

MANAGEMENT

This guidance applies to new patients and may also be taken into consideration for those already on statins at their annual review. If 40% reduction of non-HDL-C not achieved, offer high intensity statins. Discuss with people who are stable on a low- or middle-intensity statin the likely benefits and potential risk of side effects if changed to a high-intensity statin when they have a medication review and agree with the person whether a change is needed.

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

PRIMARY PREVENTION RISK ASSESSMENT

QRISK3 is the current version of the QRISK calculator www.qrisk.org/three
- Do not use this risk assessment tool for people with established CVD or those who are at high risk of developing CVD because of FH or other inherited disorders of lipid metabolism.
- Do not use a risk assessment tool to assess CVD risk in people with type 1 diabetes, or eGFR less than 60 mL/min/1.73 m2 and/or albuminuria.
- Consider people aged ≥ 85 at increased risk of CVD because of age alone particularly people who smoke or have raised BP.

Additional Risk Factors
Note, standard CVD risk scores including QRISK may underestimate risk in people who have additional risk because of underlying medical conditions or treatments. These groups include the following groups of people;
- severe obesity (BMI>40kg/m2) increases CVD risk
- treated for HIV,
- serious mental health problems,
- taking medicines that can cause dyslipidaemia such as antipsychotic medication, corticosteroids or immunosuppressant drugs
- autoimmune disorders such as systemic lupus erythematosus, and other systemic inflammatory disorders
- non-diabetic hyperglycaemia
- significant hypertriglyceridaemia (fasting triglycerides 4.5-9.9mmol/L)
- recent risk factor changes e.g. quit smoking, BP or lipid treatment

Consider socio-economic status as an additional factor contributing to CVD risk.
If QRISK < 10% over the next 10 years - give lifestyle advice and ensure regular review of CVD risk in line with guidance.

SPECIAL PATIENT POPULATIONS

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

Chronic Kidney Disease
Offer atorvastatin 20mg for the primary or secondary prevention of CVD to people with CKD (eGFR less than 60 mL/min/1.73m2 and/or albuminuria).
Increase the dose if a greater than 40% reduction in non-HDL-C is not achieved and eGFR is 30 mL/min/1.73m2 or more.
Agree the use of higher doses with a renal specialist if eGFR is less than 30 mL/min/1.73m2.

ABBREVIATIONS

ALT: alanine aminotransferase LDL-C: low density lipoprotein cholesterol
AST: aspartate aminotransferase non-HDL-C: non-high density lipoprotein cholesterol
CHD: coronary heart disease PCSK9i: proprotein convertase subtilisin kexin 9
CKD: chronic kidney disease monoclonal antibody inhibitor
CVD: cardiovascular disease SLE: systemic lupus erythematosus
FH: familial hypercholesterolaemia SPC: summary of product characteristics
LDL-C: low density lipoprotein cholesterol
non-HDL-C: non-high density lipoprotein cholesterol
PCSK9i: proprotein convertase subtilisin kexin 9
SLE: systemic lupus erythematosus
SPC: summary of product characteristics
TC: total cholesterol

Authors: Dr Rani Khatib & Dr Dermot Neely on behalf of the AAC Clinical Subgroup. Nov 2021.
Review date: Nov 2022. NICE endorsed Dec 2021.

EXTENT OF LIPID LOWERING WITH AVAILABLE THERAPIES

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 10mg		52%	54%	57%	61%

Low/moderate intensity statins will produce an LDL-C reduction of 20-30%

Medium intensity statins will produce an LDL-C reduction of 31-40%

High intensity statins will produce an LDL-C reduction above 40%

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

- **Rosuvastatin** may be used as an alternative to Atorvastatin for primary or secondary prevention if compatible with other drug therapy. Lower starting dose maybe needed in some. See BNF.
- **Other statins** should only be used in intolerance or drug interactions.
- **Ezetimibe** when combined with any statin is likely to give greater reduction in non-HDL-C/LDL-C than doubling the dose of the statin.
- **PCSK9i** (NICE TA393,394) alone or in combination with statins or Ezetimibe produce an additional LDL-C reduction of approximately 50% (range 25-70%).
- **Bempedoic acid** when combined with ezetimibe (TA694) produces an additional LDL-C reduction of approximately 28% (range 22-33%) but no clinical outcome evidence is currently available.
- **Inclisiran** (TA733) alone or in combination with statins or ezetimibe produces an additional LDL-C reduction of approximately 50% (range 48-52%) but no clinical outcome evidence is currently available.

MONITORING

Baseline Measurements
In addition to full lipid profile, measure renal, thyroid and liver profiles (including albumin) and HbA1c to exclude secondary causes and co-morbidities.
Measure baseline liver transaminase (ALT or AST) before starting a statin.
Measure CK if unexplained muscle pain before starting a statin.
CK should not be measured routinely especially if a patient is asymptomatic.

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

Provide annual medication reviews for people taking statins to discuss effectiveness of therapy, medicines adherence, lifestyle modification and address CVD risk factors.
**Consider an annual non-fasting full lipid profile to inform the discussion around effectiveness of lipid lowering therapy and any medicines non-adherence.*

Monitoring
Repeat full lipid profile is non-fasting.
Measure liver transaminase within 3 months of starting treatment and then within 3 months of every additional up titration and then again at 12 months, but not again unless clinically indicated.
If ALT or AST are greater than 3 times the upper limit of normal then do not initiate a statin or discontinue statin therapy already prescribed and repeat the LFTs in a month.
If ALT or AST are elevated but are less than 3 times the upper limit of normal then:
- Continue the statin and repeat in a month.
- If they remain elevated but are less than 3 times the upper limit of normal then continue statin and repeat again in 6 months.

TITRATION THRESHOLD/TARGETS

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

If baseline cholesterol is unknown in the setting of secondary prevention use the use Joint British Societies' JBS3 consensus recommendation.
Non-HDL-C = TC minus HDL-C
LDL-C = non-HDL-C minus (Fasting triglycerides [a] /2.2)
[a] valid only when fasting triglycerides are less than 4.5 mmol/L

SPECIALIST SERVICES

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

	Without CVD	With CVD	
		High risk 1	Very high risk 2
Primary non-FH or mixed dyslipidaemia	Not recommended	LDL C > 4.0 mmoL/L	LDL C > 3.5 mmoL/L
Primary heterozygous-FH	LDL C > 5.0 mmoL/L	LDL C > 3.5 mmoL/L	

[1] History of any of the following: ACS; coronary or other arterial revascularisation procedures; CHD, ischaemic stroke; PAD. 2 Recurrent CV events or CV events in more than 1 vascular bed (that is, polyvascular disease).

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

TRIGLYCERIDES

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

STATIN INTOLERANCE

Statin Intolerance is defined as the presence of clinically significant adverse effects from statin therapy that are considered to represent an unacceptable risk to the patient or that may result in adherence to therapy being compromised.
For people who are intolerant of the recommended statin treatment see the NHSE AAC statin intolerance algorithm, available on the NHSE AAC page (Click here)

References:
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NICE 2021. TA694 www.nice.org.uk/guidance/TA694
NICE 2021. TA733 www.nice.org.uk/guidance/TA733

Approved by the National Institute for Health and Care Excellence (NICE), Dec 2021

What health professionals can do to improve cardiovascular disease management

1. FIND THEM

make system audits **routine** and **detect** those at risk

2. TREAT THEM

treat in line with NICE guidelines

3. MANAGE THEM

many with unmanaged co-morbidities present an **'early wins'** cohort

eg. start or switch from low-intensity to ***high-intensity statins***

Public Health England. Feb 2019. Health matters: preventing cardiovascular disease. Available at Health matters: preventing cardiovascular disease - GOV.UK (www.gov.uk) Accessed May 2022

Cholesterol – Secondary Prevention (pre-existing CVD)

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Healthcare assistants/other appropriately trained staff

Gather information e.g.	Up to date bloods, BP, weight, smoking status.
Self-management e.g.	Education (cholesterol, CVD risk), BP monitors (what to buy, how to use), signpost to shared decision making resources.
Behaviour change e.g.	Brief interventions and signposting e.g. smoking, weight, diet, exercise, alcohol.

Stratification

Priority One	Priority Two	Priority Three	Priority Four– routine follow up
Not on statin therapy	On suboptimal intensity statin*	On suboptimal statin dose**	Sub-optimal non-HDL (>2.5mmol/l) levels despite maximal statin therapy

Prescribing clinician

Optimise lipid modification therapy and CVD risk reduction

1. Review CVD risk factors, lipid results and liver function tests.
2. Initiate or optimise statin to high intensity – e.g. atorvastatin 80mg.
3. Titrate therapy against reduction in LDLc/non-HDLc (statin>ezetimibe>PCSK9i)mAB)/inclisiran).
4. Optimise BP and other comorbidities.
5. Use intolerance pathway and shared decision-making tools to support adherence.
6. Arrange follow-up bloods and review if needed.

* E.g simvastatin
** E.g atorvastatin 40mg

Cholesterol – Primary Prevention (no pre-existing CVD)

Healthcare assistants/other appropriately trained staff

Gather information: E.g. up to date bloods, BP, weight, smoking status, run QRISK score.*

Self-management: Education (cholesterol, CVD risk), BP monitors (what to buy, how to use), signpost to shared decision making resources.

Behaviour change: Brief interventions and signposting e.g. smoking, weight, diet, exercise, alcohol.

Stratification

Priority One

One of:

- QRISK ≥20%
- CKD
- Type 1 Diabetes

AND

- Not on statin

Priority Two

- QRISK 15-19%

AND

- Not on statin

Priority Three

- QRISK 10-14%

AND

- Not on statin

Priority Four

On statin for primary prevention but not high intensity

Prescribing clinician

Optimise lipid modification therapy and CVD risk reduction

1. Review QRISK score, lipid results and LFTs.
2. Initiate or optimise statin to high intensity – eg atorvastatin 20mg.
3. Titrate therapy against reduction in LDLc/non-HDLc (statin>ezetimibe).
4. Optimise BP and other comorbidities.
5. Use intolerance pathway and shared decision-making tools to support adherence.
6. Arrange follow-up bloods and review if needed.

*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

UCLPartners Proactive Care Frameworks

UCLPartners has developed a series of frameworks for local adaptation to support proactive management of long-term conditions in post-COVID primary care.

- Led by clinical team of GPs and pharmacists
- Supported by patient and public insight
- Working with local clinicians and training hubs to adapt and deliver

Core principles:

1. Virtual where appropriate and face to face when needed
2. Mobilising and supporting the wider workforce (e.g. pharmacists, HCAs, and others) to optimise clinical care and holistic care
3. Step change in support for self-management
4. Digital innovation including apps for self-management and technology for remote monitoring

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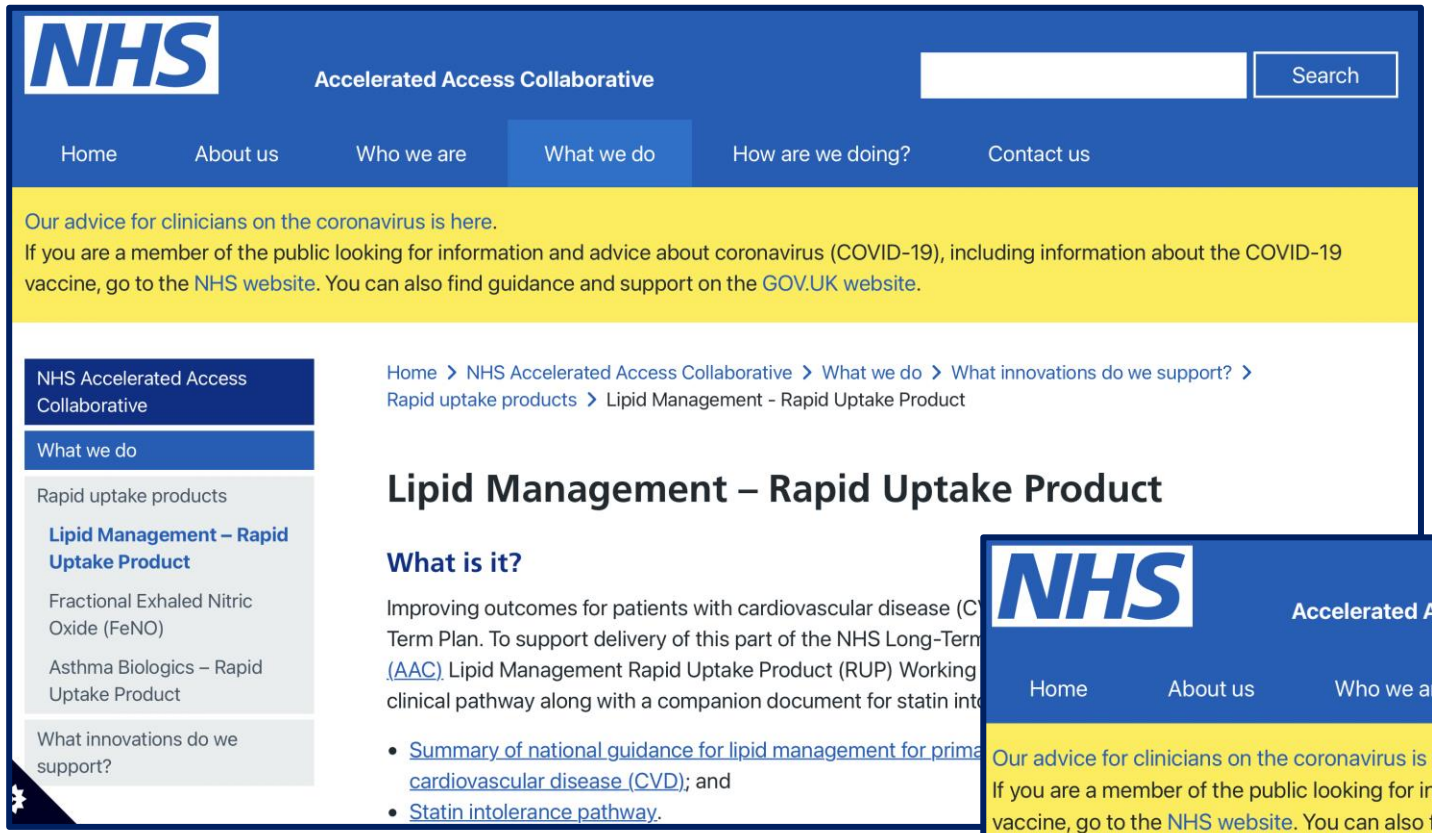
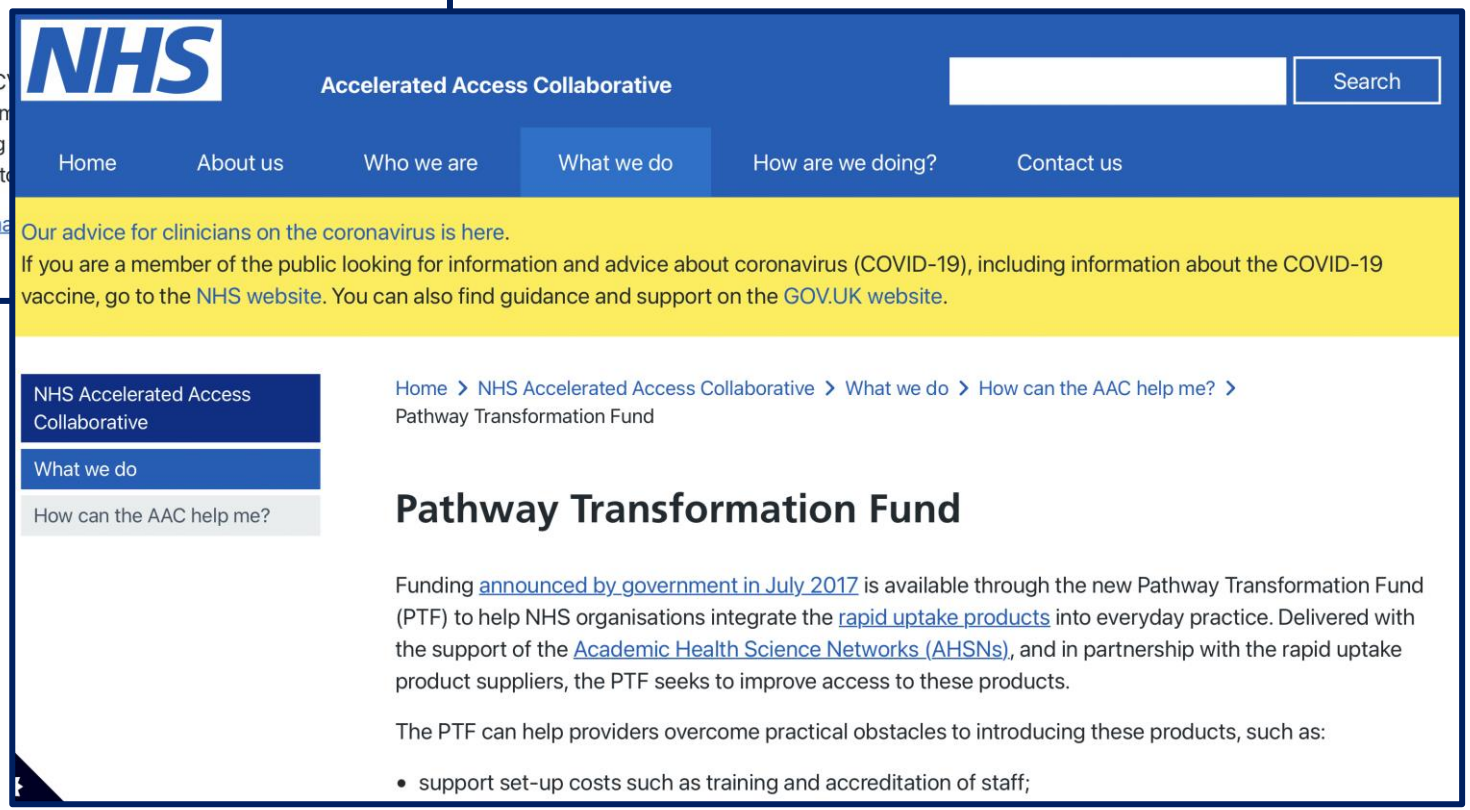
Project Transformation Fund





Lipid pathway transformation project

CCG 1 Lipid Management Cohort 2021/22

- 42 Practices cross 6 Primary Care Networks
- 37 Practices EMIS + 5 Practices System ONE

Aged 18+ with IHD,PAD or Stroke/TIA

11233

Priority One
Not on statin therapy

2220

BHC ELOPE NEL lipid pathway transformation data

Data supplied by Sotiris Antoniou.
CCG, clinical commissioning group; IHD, Ischemic heart disease; PAD, Peripheral arterial disease; TIA, Transient ischemic attack.

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Priority One Not on statin therapy	Priority Two (A) On suboptimal intensity statin*	Priority Two (B) On suboptimal statin dose**
2220	4347	2430

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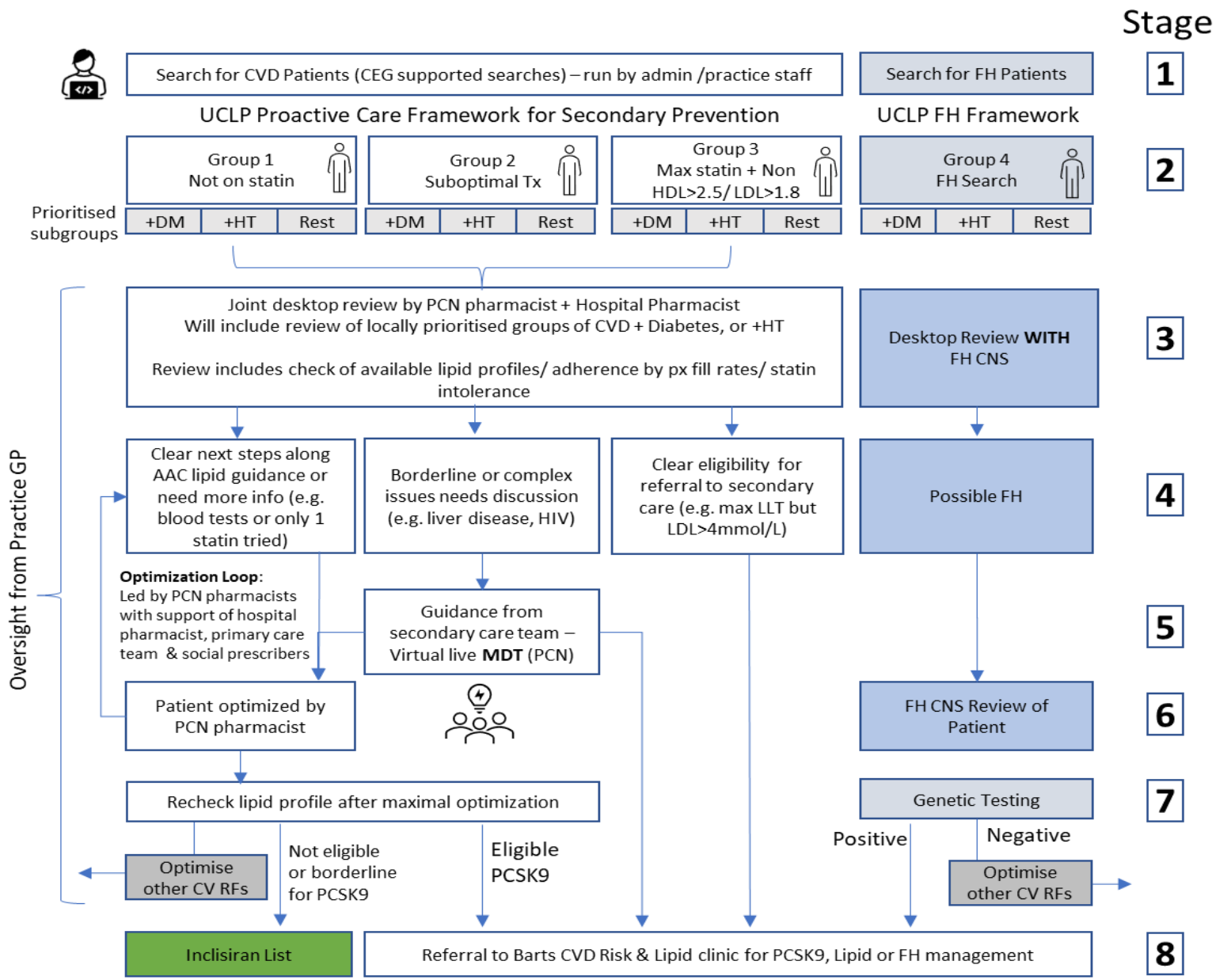
11233

Priority One Not on statin therapy	Priority Two (A) On suboptimal intensity statin*	Priority Two (B) On suboptimal statin dose**	Priority Three – routine follow up Sub-optimal non-HDL (>2.5mmol/l) levels despite maximal statin therapy
2220	4347	2430	908

BHC ELOPE NEL lipid pathway transformation data

Data supplied by Sotiris Antoniou.

CCG, clinical commissioning group; IHD, Ischemic heart disease; PAD, Peripheral arterial disease; TIA, Transient ischemic attack.



BHC ELOPE NEL lipid pathway

Data supplied by Sotiris Antoniou.

Search for CVD Patients (CEG supported searches) – run by admin /practice staff

Search for FH Patients

UCLP Proactive Care Framework for Secondary Prevention

UCLP FH Framework

	Priority One Not on statin therapy			Priority Two (A) On suboptimal intensity statin*		Priority Two (B) On suboptimal statin dose**		Priority Three – routine follow up Sub-optimal non-HDL (>2.5mmol/l) levels despite maximal statin therapy			Group 4 FH Search		
Prioritised subgroups	+DM	+HT	Rest	+DM	+HT	Rest		+DM	+HT	Rest	+DM	+HT	Rest

ceg Clinical Effectiveness Group

APL - CVD Cardiovascular Disease Tool v1

Barts and The London School of Medicine and Dentistry

CVD (IHD, Stroke/TIA and PAD) Prescribed Statin Page

Date of last run: 19/Jul/2019

Filters

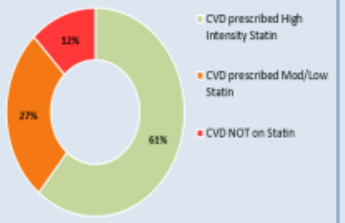
Disease	☐ IHD	☐ Stroke/TIA	☐ PAD	☐ AF	☐ Hypertension	☐ Diabetes	☐ CKD
Statin	○ Any Statin	○ High Intensity Statin	○ Mod/Low Statin	○ Not on Statin			
Frailty	☐ Severe	☐ Moderate	☐ Mild	Other Risks	☐ SMI	☐ Learning Difficulty	
Total Cholesterol	Greater Than Or Equal To		Less Than		Age	>=	<
Statin Exclusion	☐ Contraindicated	☐ Declined					

Reset Filters

Practice Summary

Denominator Population (CVD)	420
CVD prescribed ANY Statin	369
CVD prescribed High Intensity Statin	256
CVD prescribed Mod/Low Statin	113
CVD NOT on Statin	51
CVD Statin Contraindicated	14
CVD Statin Declined	5

Prescribing CVD patients



Full Name	Patient Reference no.	Usual GP	Age	Sex	Statin Prescription	Statin Intensity (High, Mod/Low, None)	Presc. Ezetimibe	Presc. Fibrate	Frailty Breakdown	Statin Exclusion	Blood Pressure	Total Cholesterol	Medication Review (Pharmacist or detailed GP review)	
245265b8-afcb-f941-6c3b-b1d059cb7767	xxxxxx	JP	28	Male		None	No	No	None	NO				
f92dcad7-e421-e185-b943-80e278381792	xxxxxx	KB	44	Female		None	No	No	None	NO	140/83	5		
ba5af7b5-98a5-3b34-b645-572d339ebbd1	xxxxxx	SA	45	Male		None	No	No	None	NO	115/47	4.7	GP	30-Oct-12
2316e84e-009b-19e6-d1c6-e601631cd4d4	xxxxxx	SA	46	Male		None	No	No	None	NO	122/68	4		
ae1b3b58-d2d6-c45e-485d-75259893a691	xxxxxx	KP	50	Female		None	Yes	No	None	Declined	113/69	5.2	GP	14-Jan-15
cf61c8b6-0d5d-68c0-8a4f-726b1158f084	xxxxxx	JT	51	Male		None	No	No	None	NO	105/78	3.9		
cb3af926-62a7-c310-da55-f29d68c062e7	xxxxxx	JP	52	Female		None	No	No	None	NO	132/86	6.1		
e456e9c5-4ca8-295b-63f2-de6df44920ae	xxxxxx	JL	54	Male		None	No	No	None	NO	113/64	6.2		

BHC ELOPE NEL
lipid pathway

Data supplied by Sotiris Antoniou.

Joint desktop review by PCN pharmacist + Hospital Pharmacist
Will include review of locally prioritised groups of CVD + Diabetes, or +HT

Review includes check of available lipid profiles/ adherence by px fill rates/ statin intolerance

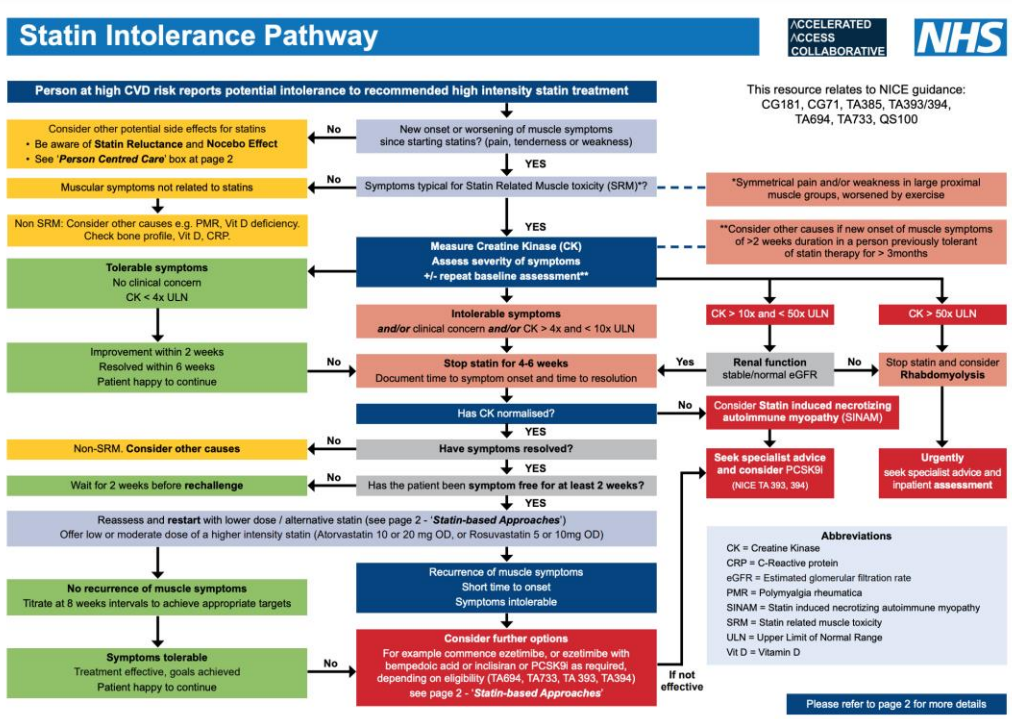
Desktop Review **WITH** FH CNS

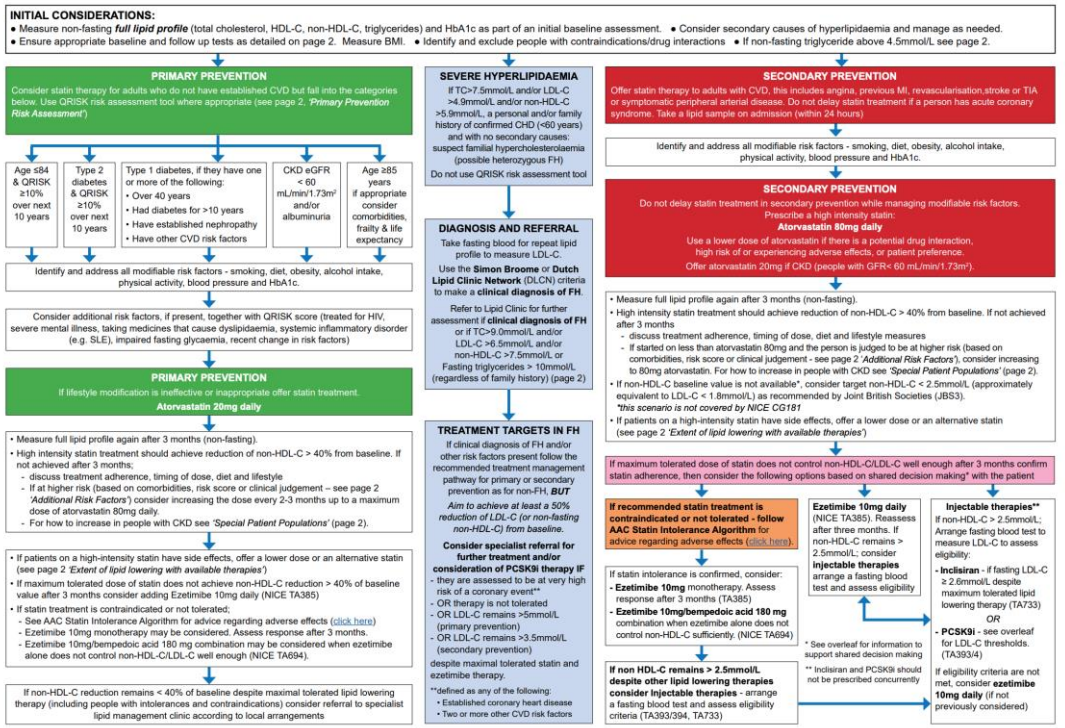
Clear next steps along AAC lipid guidance or need more info (e.g. blood tests or only 1 statin tried)

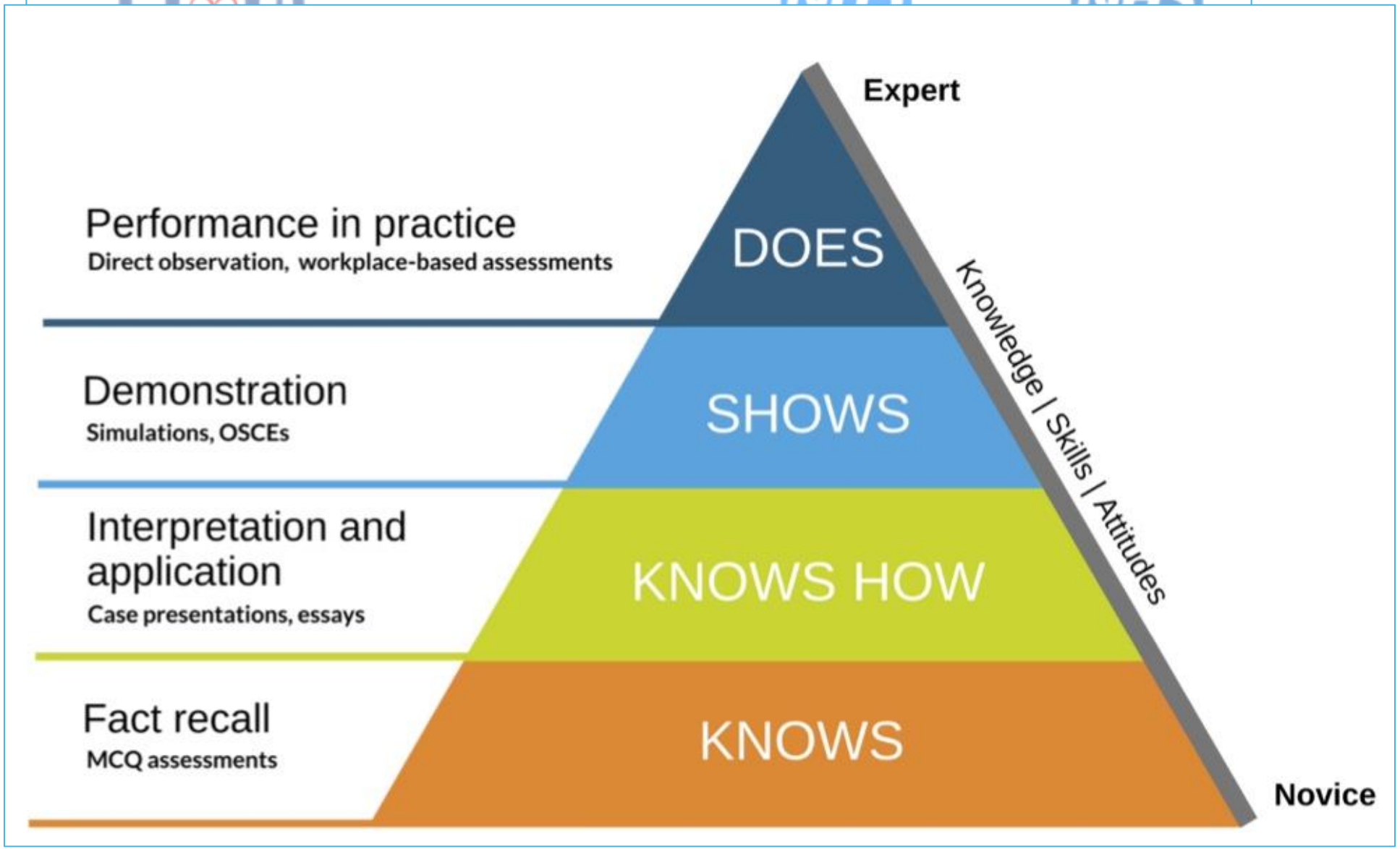
Borderline or complex issues needs discussion (e.g. liver disease, HIV)

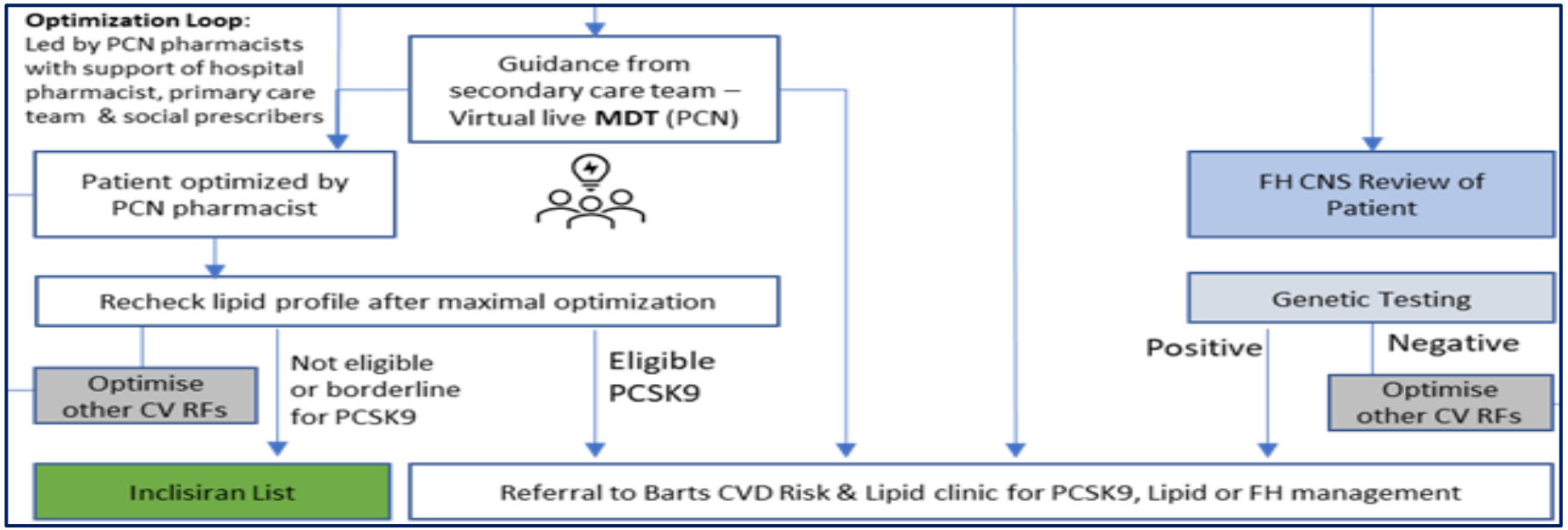
Clear eligibility for referral to secondary care (e.g. max LLT but LDL>4mmol/L)

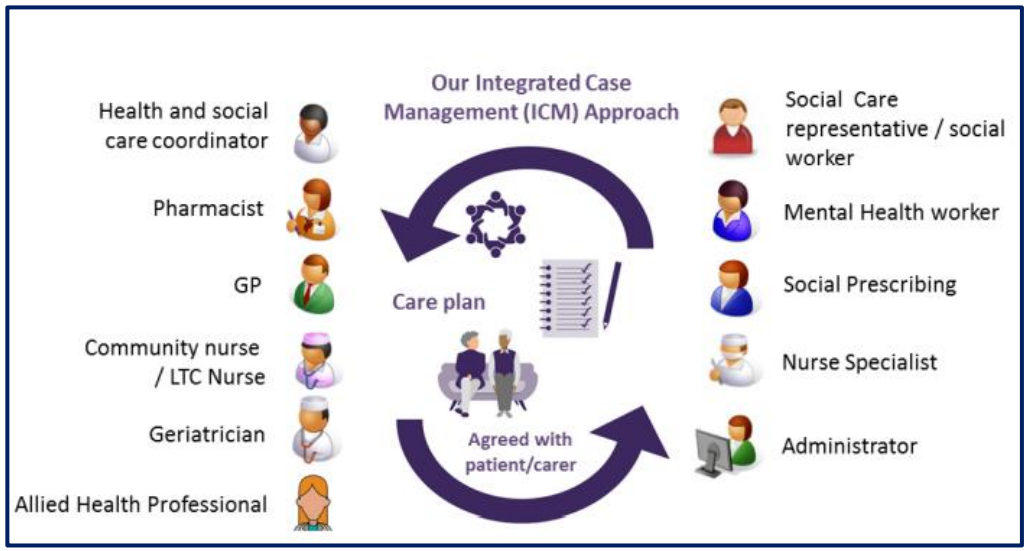
Possible FH











SPECIALIST SERVICES

Scope of specialist service available locally may include; Lipid Clinic, PCSK9i clinic (offering initiation and subsequent follow up), FH Genetic Diagnosis and Cascade testing, Lipoprotein Apheresis service. NICE eligibility criteria for PCSK9i and fasting LDL-C thresholds are summarised below.

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

BHC ELOPE NEL
lipid pathway

Data supplied by Sotiris Antoniou.

Optimisation Pathway for Secondary Prevention

UCLPartners

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

Yes

No

Initiate / increase to high dose high intensity statin
*** and re-enforce lifestyle and diet measures

Non-HDL-C reduced by 40% or more from baseline at 3 months? ****
(if baseline non-HDL not available, consider intensification of therapy if non-HDL-C > 2.5mmol/L)[7]

Yes

No

Check adherence to statin and lifestyle measures **

Consider ezetimibe 10mg daily
Reassess after 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 chol > 2.5mmol/L; Arrange fasting blood test to assess eligibility:

- **Inclisiran** - if fasting LDL-C ≥ 2.6mmol/L despite maximum tolerated lipid lowering therapy **OR**
- **Refer for PCSK9i** 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

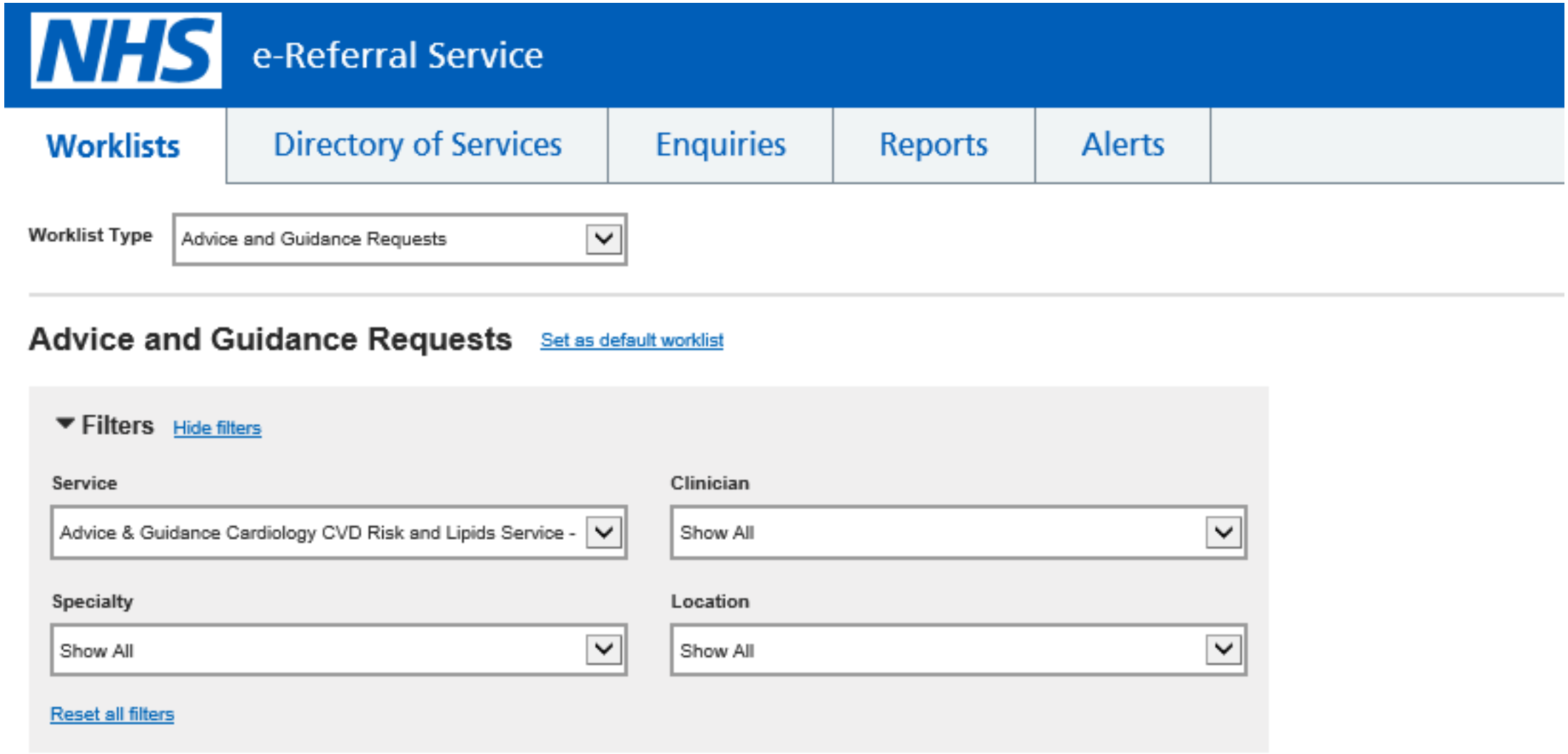
* Dose may be limited if:

- eGFR<30ml/min
- Drug interactions
- Intolerance
- Older age / frailty

** **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.

*** See statin intensity table

**** Current NICE Guidance recommends a 40% reduction in non- HDL cholesterol



CCG 1 Lipid Management Cohort 2021/22

- 42 Practices cross 6 Primary Care Networks
- 37 Practices EMIS + 5 Practices System ONE

Aged 18+ with IHD,PAD or Stroke/TIA

11233

Priority One
Not on statin therapy

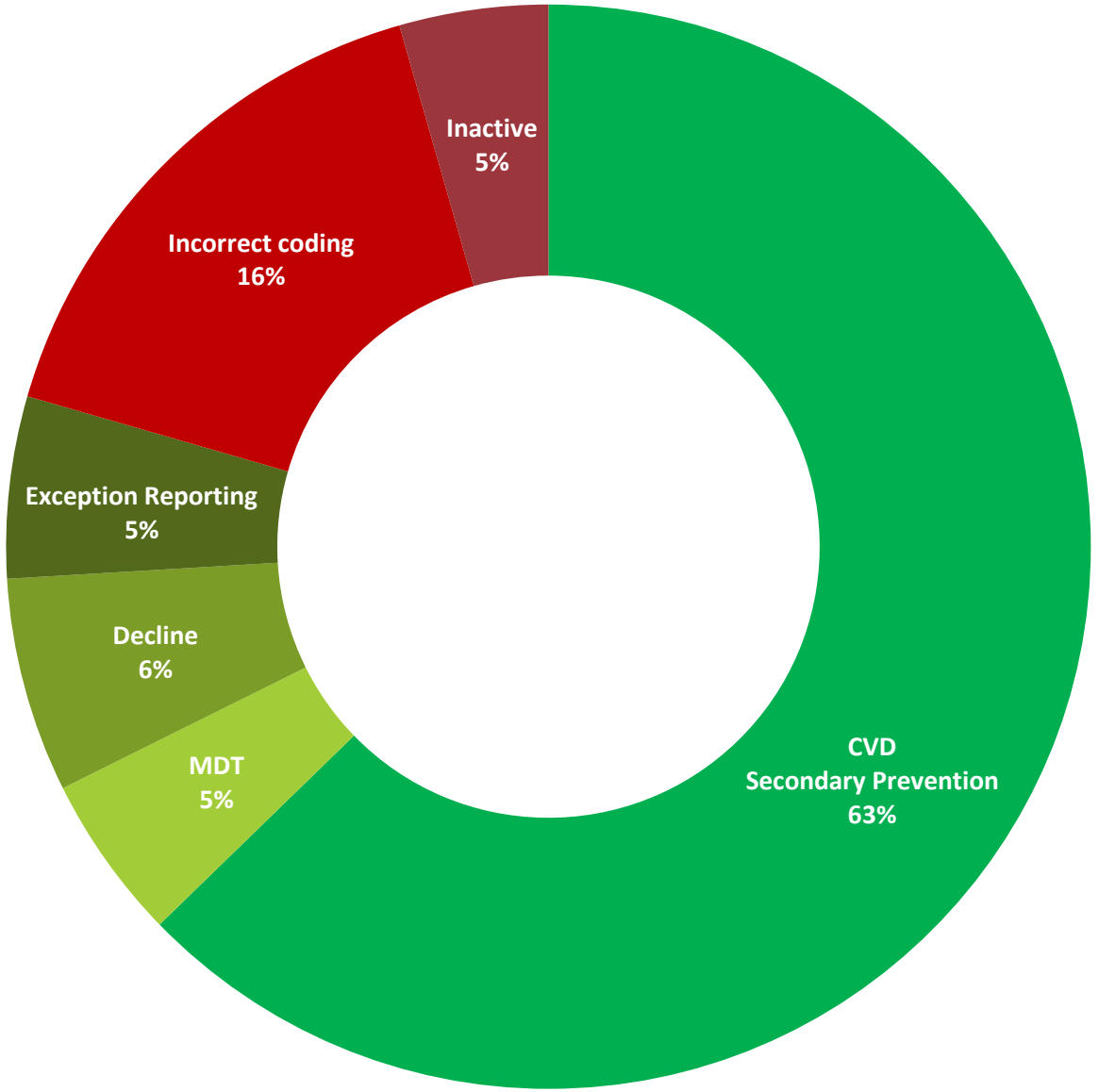
2220

BHC ELOPE NEL lipid pathway transformation data

Data supplied by Sotiris Antoniou.
CCG, clinical commissioning group; IHD, Ischemic heart disease; PAD, Peripheral arterial disease; TIA, Transient ischemic attack.

Redbridge Lipid Management Program

- Desk top notes review of 600 Patients
  - 63% CVD Secondary Prevention Lipid Management
    - 35% Statin
    - 2% Ezetimibe
    - 2% Other Tx
    - 20% GP/Consultant discussion
    - 2% repeat bloods
  - 6% Declined
  - 5% MDT
  - 5% Exception Reporting
  - 16% Incorrect coding
  - 5% Inactive



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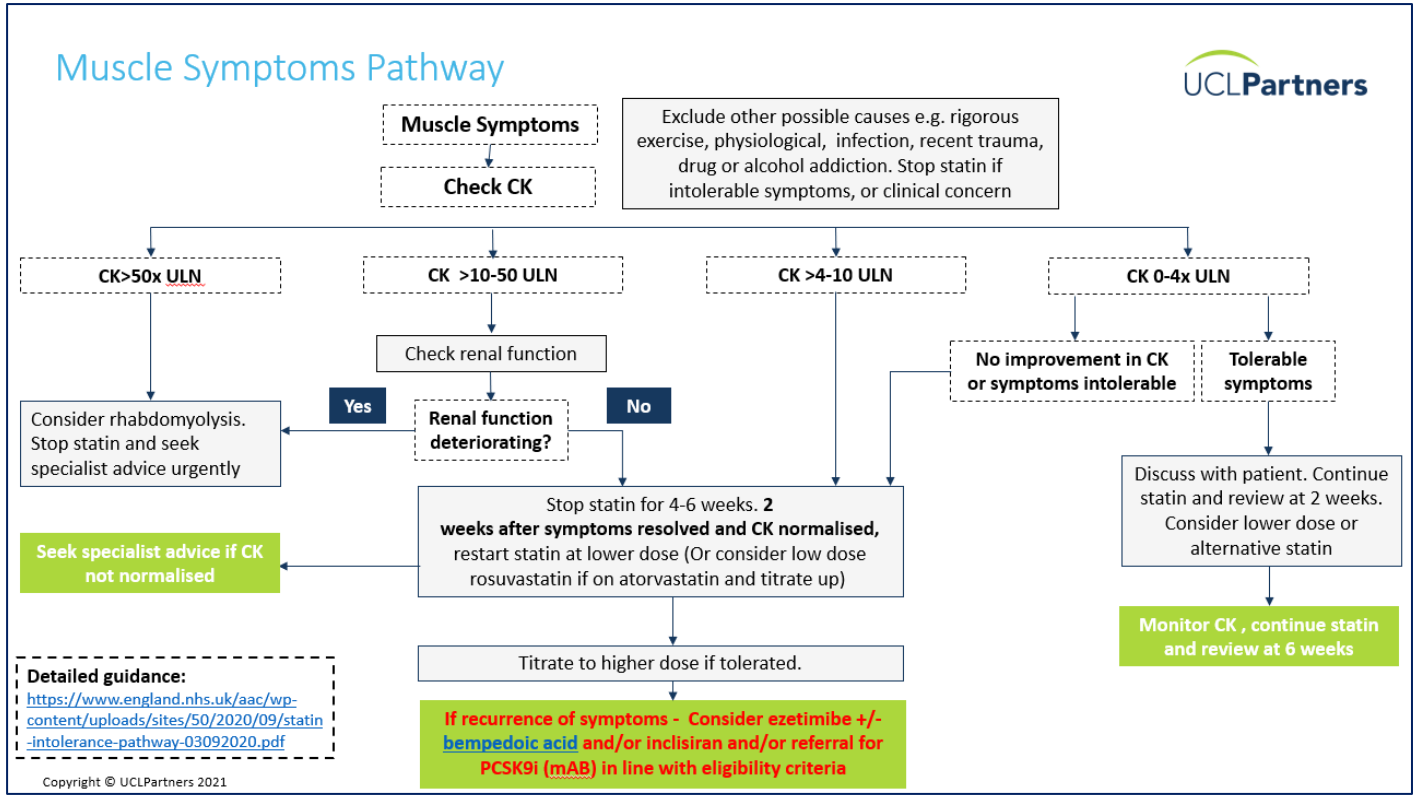
Case Studies

Case study 1

- Mrs AS - 67F
- Hx of ACS
- Atorvastatin 80mg OD
  - Discontinued Oct 2020 due to muscle pain
- Bloods (Sept 2020)
  - TC 5.2 mmol/L
  - LDL 3.3 mmol/L
  - HDL 1.4 mmol/L
  - Trig 1.17
  - TFTs / LFTs / U&Es / HbA1c – unremarkable
  - BP 109/63 mmHg; Wt 62kg; BMI 22kg/m^2; smoker



BHC Fictional case study for illustrative purposes

BP, Blood pressure; BMI, Body mass index; CVD, Cardiovascular disease; HbA1c, Hemoglobin A1c; HDL, High-density lipoprotein; LDL, Low-density lipoprotein; LFT, Liver function test; TC, Total cholesterol; TFT, Thyroid function test; U&E, Urea and electrolytes, Wt weight

Case study continued

- Offer lifestyle advice (smoking cessation)
- Assess symptoms (nature / onset)
- Rechallenge with lower intensity statin
- Measure CK
  - 720 U/L (range 22-198 U/L)
- Stop statin 4-6 weeks
- Reassess symptoms and CK
  - 134 U/L with resolution of symptoms

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 10mg		52%	54%	57%	61%

Low/moderate intensity statins will produce an LDL-C reduction of 20-30%

Medium intensity statins will produce an LDL-C reduction of 31-40%

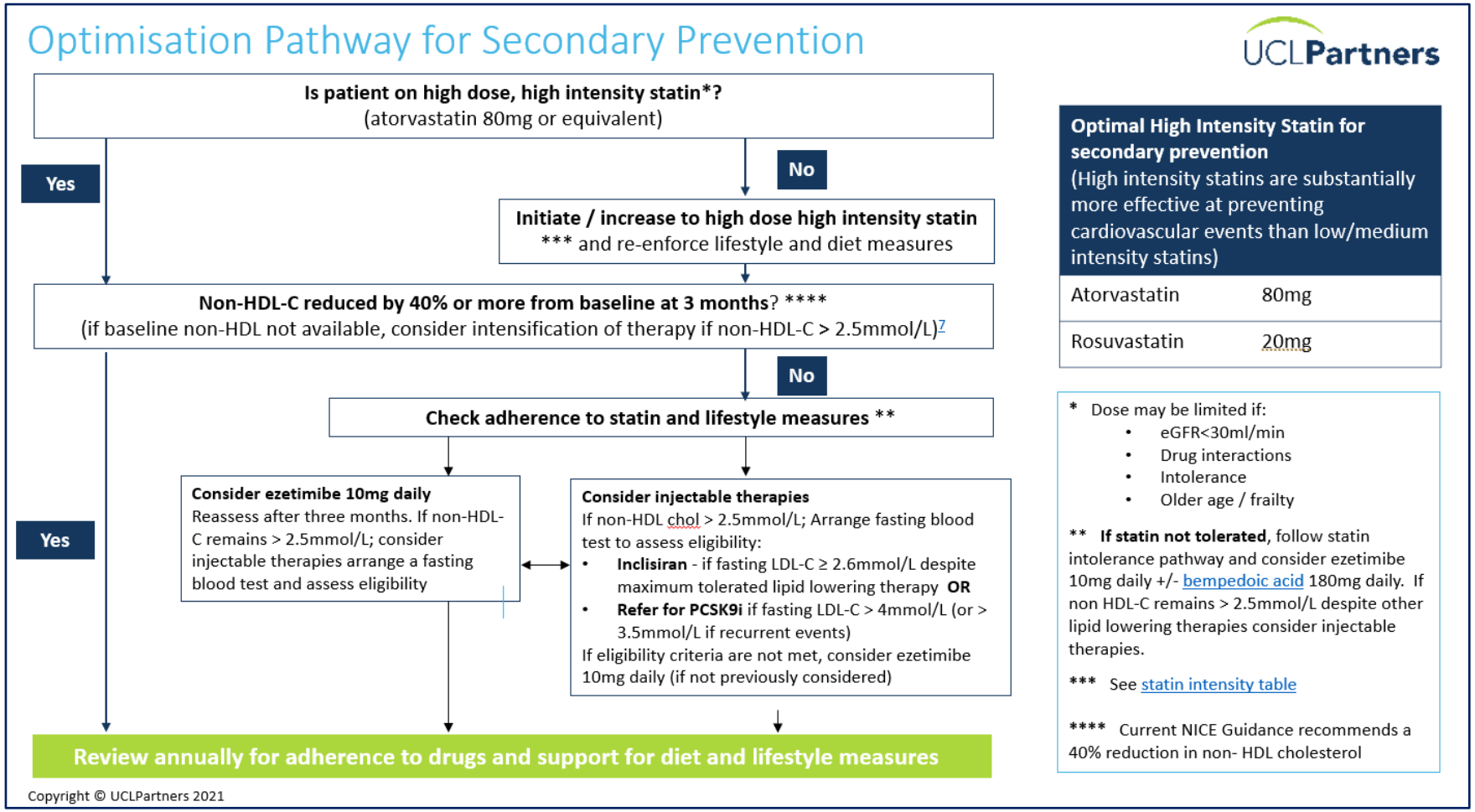
High intensity statins will produce an LDL-C reduction above 40%

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

*BHC Fictional case study for illustrative purposes
CK, Creatine kinase: HDL, High-density lipoprotein; OD, Once-daily.

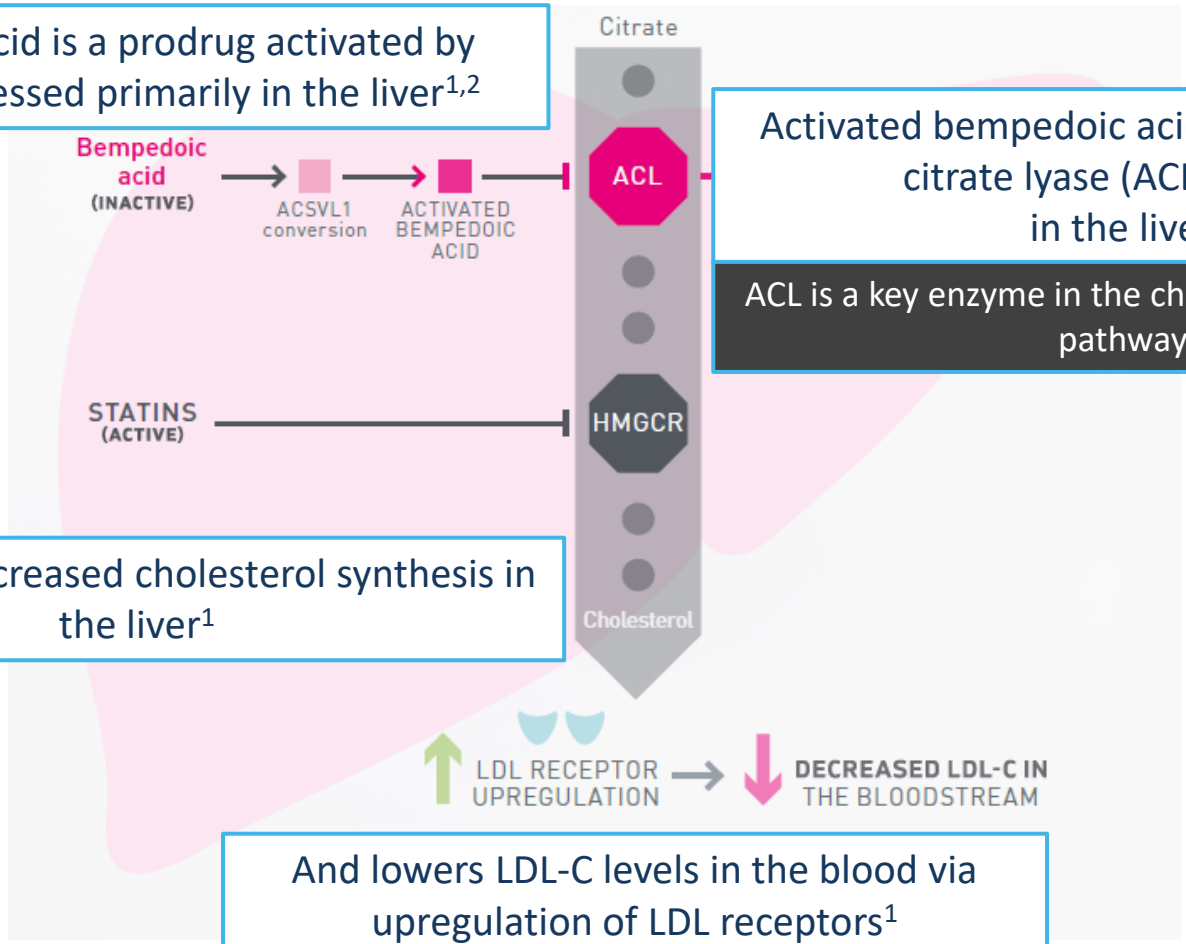
Case Study continued

- Start ezetimibe 10mg daily
- Repeat non-HDLc after 3 months
  - <40% reduction from baseline
- Add bempedoic acid



The mechanism of action of bempedoic acid is complementary yet distinct from statins[1]

Bempedoic acid is a prodrug activated by ACSVL1, expressed primarily in the liver[1,2]



Activated bempedoic acid inhibits the ATP-citrate lyase (ACL) enzyme in the liver[1]

ACL is a key enzyme in the cholesterol biosynthesis pathway[2]

Resulting in decreased cholesterol synthesis in the liver[1]

And lowers LDL-C levels in the blood via upregulation of LDL receptors[1]

Adapted from Pinkosky SL, *et al.* 2016.

ACL: ATP-citrate lyase; ACSVL1: Very long-chain acyl-CoA synthetase-1; HMGR: 3-hydroxy-3-methylglutarate-CoA reductase; LDL: Low-density lipoprotein; LDL-C: Low-density lipoprotein cholesterol.

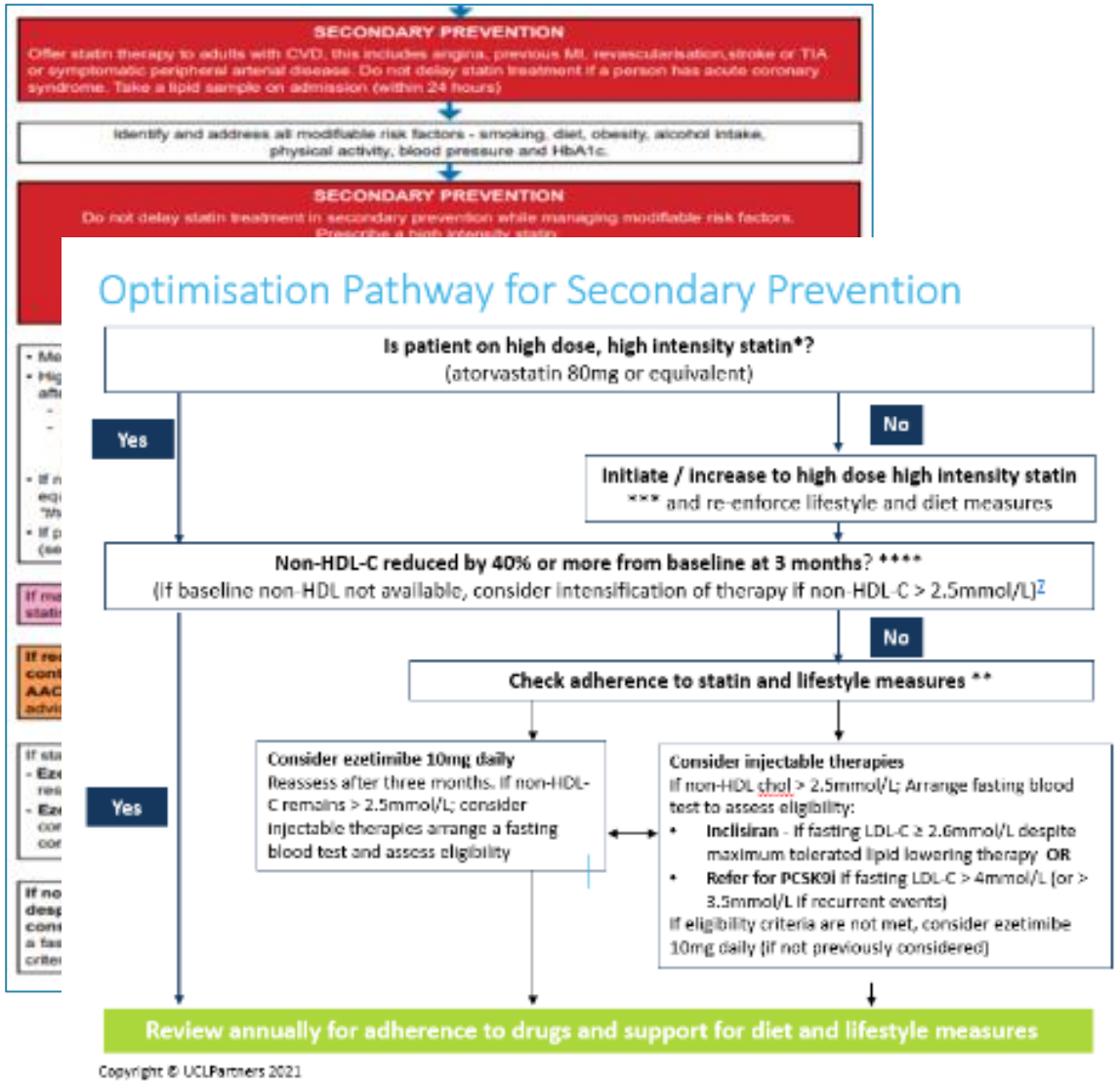
- 1. Pinkosky SL, *et al.* Liver-specific ATP-citrate lyase inhibition by bempedoic acid decreases LDL-C and attenuates atherosclerosis. *Nat Commun*. 2016; 7: 13457. 2. NILEMDO®. Summary of Product Characteristics. Available at https://www.medicines.org.uk/emc/product/11743. Accessed May 2022.

Bempedoic acid for use in statin intolerance

- 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
- Bempedoic acid with ezetimibe can be used as separate tablets or a fixed-dose combination
- The recommended dose is one film-coated tablet of 180 mg taken once daily
- Bempedoic acid lowers LDL-C by an additional 28% (range 22-33%) when combined with ezetimibe
- Bempedoic acid was associated with a slightly increased risk of hyperuricaemia and gout.
- More information on bempedoic acid can be found at: https://www.medicines.org.uk/emc/product/11743/smpc#gref

Case study 2

- Mr MP
- 56 Male
- STEMI and PCI to RCA (2019)
- Atorvastatin 80 mg OD
- Bloods (June 2021)
  - TC 6.2 mmol/L
  - LDL 4.5 mmol/L
  - HDL 1.1 mmol/L
  - Trig 1.32 mmol/L
  - TFTs / LFTs / U+Es / HbA1c – unremarkable
- BP 132/74 mmHg; Wt 83 kg; BMI 27 kg/m^2; non-smoker



Fictional case study for illustrative purposes

Case study 2 continued

- Offer lifestyle advice (diet and exercise for weight loss)
- Confirm adherence
- Add ezetimibe 10 mg OD

> • If maximum tolerated dose of statin does not achieve non-HDL-C reduction > 40% of baseline value and/or non-HDL-C < 2.5mmol/L after 3 months consider adding Ezetimibe 10mg OD (NICE TA385)

- Repeat lipid panel after 3 months

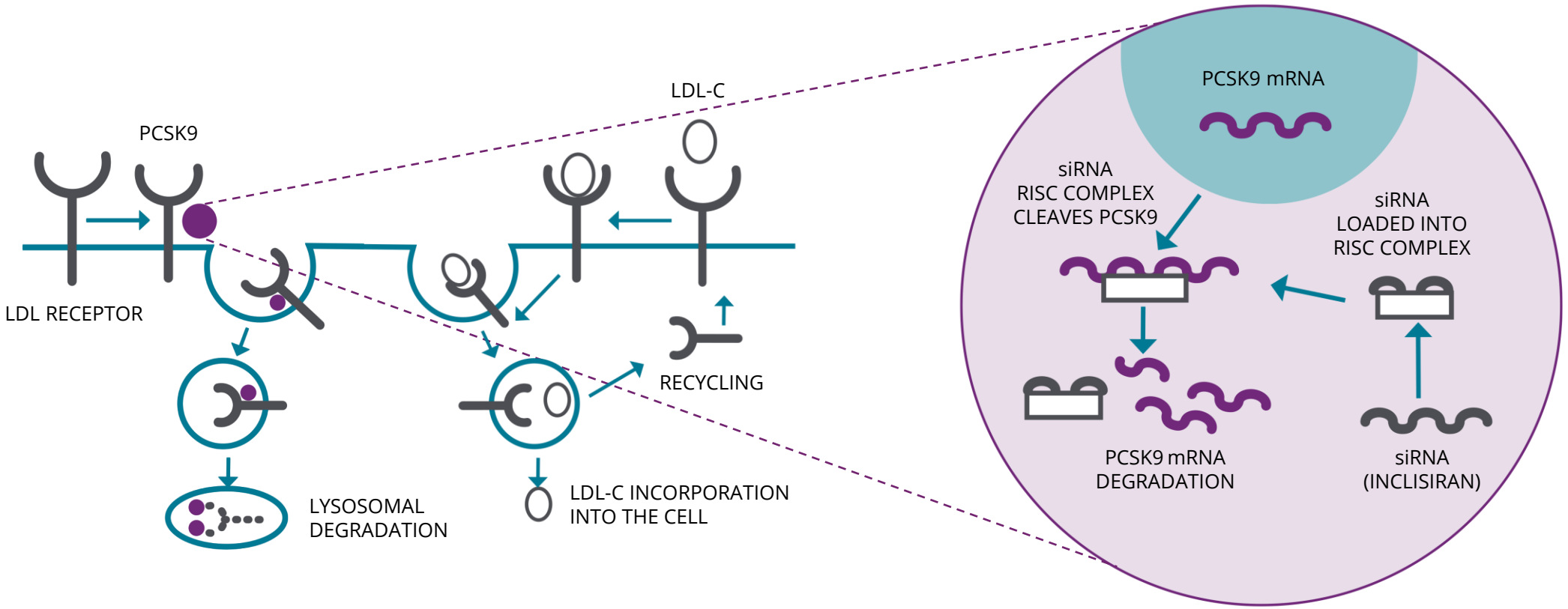
  - TC 5.0 mmol/L
  - LDL 3.6 mmol/L
  - HDL 1.0 mmol/L
  - Trig 0.89 mmol/L

SPECIALIST SERVICES			
Scope of specialist service available locally may include; Lipid Clinic, PCSK9i clinic (offering initiation and subsequent follow up), FH Genetic Diagnosis and Cascade testing, Lipoprotein Apheresis service. NICE eligibility criteria for PCSK9i and fasting LDL-C thresholds are summarised below.			
NICE TA393 Alirocumab **NICE TA394 Evolocumab**	**Without CVD**	**With CVD**	
		High risk [1]	**Very high risk [2]**
Primary non-FH or mixed dyslipidaemia	Not recommended	LDL C > 4.0 mmoL/L	LDL C > 3.5 mmoL/L
Primary heterozygous-FH	LDL C > 5.0 mmoL/L	LDL C > 3.5 mmoL/L	

- Possible FH + CVD + LDL > 3.5 mmol/L
  - Refer for specialist assessment and consideration of PCSK9i or inclisiran

Inclisiran an siRNA LDL-C-lowering therapy[1-3]

Inclisiran uses the intrinsic process of RNAi to increase hepatic LDL-C uptake and reduce LDL-C levels in the bloodstream[1-3]



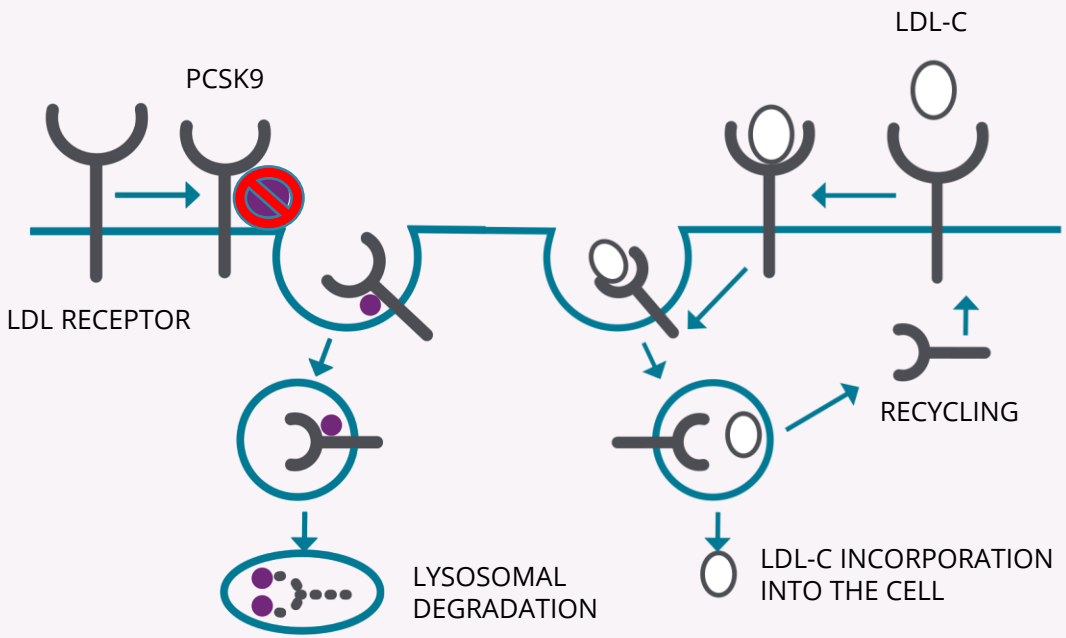
Adapted from Kosmas CE et al. Diseases 2018.[4]

LDL – low-density lipoprotein; LDL-C – low-density lipoprotein cholesterol; mRNA – messenger ribonucleic acid; PCSK9 – proprotein convertase subtilisin/kexin type 9; RISC – RNA-induced silencing complex; RNAi – ribonucleic acid interference; siRNA – small interfering ribonucleic acid

References: 1. Leqvio® Summary of Product Characteristics. **2.** Stoekenbroek RM et al. Future Cardiol 2018;14(6):433-442. **3.** Klinovski M et al. CADTH Issues in Emerging Health Technologies, 2019. Canadian Agency for Drugs and Technologies in Health. **4.** Kosmas CE et al. Diseases 2018;6(3):63.

PCSK9i LDL-C-lowering therapy

PCSK9i are monoclonal antibodies that blocks PCSK9 from binding to LDL receptors to increase hepatic LDL-C uptake and reduce LDL-C levels in the bloodstream



Adapted from Kosmas CE et al. Diseases 2018.[4]

PCSK9i for secondary prevention

- PCSK9i are indicated only for patients:
  - Low-density lipoprotein concentrations are persistently above the thresholds specified below, despite maximal tolerated lipid-lowering therapy. That is, either the maximum dose has been reached or further titration is limited by intolerance

- PCSK9i lower LDL-C by approx. 60%.

- PCSK9i dosing:
  - Alirocumab 150mg s/c every 2 weeks
  - Evolocumab 140mg s/c every 2 weeks

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

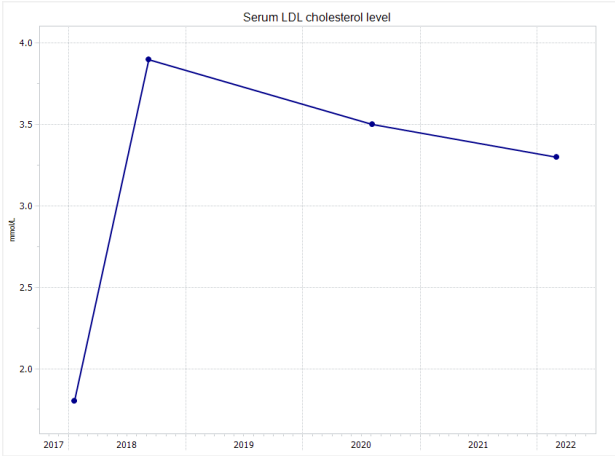
- The most common adverse reactions associated with PCSK9i are injection site reactions, pruritis and upper respiratory tract signs and symptoms

- More information on PCSK9i can be found at:
  https://www.medicines.org.uk/emc/product/8093/smpc#gref
  https://www.medicines.org.uk/emc/product/6962

Inclisiran for secondary prevention

- Inclisiran is indicated only for patients:
  - With established CVD
  - On optimal oral lipid lowering therapy including high intensity statins where tolerated
  - Where LDL-C remains ≥ 2.6mmol/L
- Inclisiran lowers LDL-C by approx. 50%, but there are currently no long term CVD outcome data or safety data which should be taken into account when making a shared decision with the patient about appropriate treatment choices
- Inclisiran (Leqvio®) is administered at a dose of 284mg by subcutaneous injection
- It should be given at month 0 (initiation), month 3, month 9 and then every 6 months thereafter.
  - If a planned dose is missed by more than 3 months, a new dosing schedule should be started – inclisiran should be administered initially, again at 3 months, followed by every 6 months.
  - It should be administered by a healthcare professional into the abdomen; alternative injection sites include the upper arm or thigh.
- The only adverse reactions associated with inclisiran reported to date are injection site reactions (8.2%)
- More information on inclisiran can be found at: https://www.medicines.org.uk/emc/product/12039/smpc#gref

Case study 3



- Mrs JP
- 74F
- IHD with revascularisation to LAD 2008, NSTEMI and revascularisation with stents to OM1 (+ LAD/LCx medical management) 2017, ACS with medical management 2021
- PMH: Heart failure, Atrial fibrillation, CKD,
- Statin History: Atorvastatin 40mg; Pravastatin 10mg; Rosuvastatin 10mg, Simvastatin 40mg caused myalgia and nightmares
- Weight 74kg; BMI 30kg/m2; non-smoker; Alcohol consumption: 4 units/week; BP 114/68mmHg
- Lipid profile results: TC 6.1mmol/L; LDL 3.3mmol/L; HDL 1.0mmol/L; non-HDL 5.1mmol/L; Triglycerides 3.92mmol/L
- Cr 162mmol/L; CrCl 31ml/min; ALT 13iu/L ; HbA1c 39mmol/mol; TSH 0.81mU/L
- Current medication: **Ezetimibe 10mg daily**; bisoprolol 5mg daily, ISMN MR 60mg daily, bumetanide, 1mg morning, Dabigatran 110mg twice daily, omeprazole 20mg daily, co-dydramol 1 or 2 tablets up to four times a day

Primary care Process Summary

NHS Barts Health NHS Trust

Inclisiran suitability checklist

1. **Does the patient have a CVD history?** (Tick all that apply)
   - ☐ Acute Coronary Syndrome (ACS) eg NSTEMI/STEMI or Coronary Heart Disease (CHD) eg angina
   - ☐ Previous coronary/arterial revascularisation eg PCI/CABG
   - ☐ Ischaemic stroke/transient ischaemic attack (TIA)
   - ☐ Peripheral arterial disease (PAD)

2. **Check LDL**: Enter result here.....

   If LDL ≥2.6mmol/L – continue to question 3
   If LDL < 2.6mmol/L – inclisiran not indicated

3. Has the patient taken a **maximum tolerated dose of a high intensity statin such as atorvastatin or rosuvastatin for at least 3 months** prior to this referral?

   If Yes – go to question 5
   If No – optimise and / or go to question 4

4. If **statin intolerance**- have you followed the AAC statin intolerance pathway?

   If Yes – go to question 5
   If No – follow pathway and reassess

5. Does your patient have any **cautions/contra-indications** to inclisiran? (tick any that apply)
   - ☐ Severe renal impairment (eg CrCl <30ml/min) or requiring haemodialysis
   - ☐ Severe liver impairment (eg Child-Pugh score >3)
   - ☐ Pregnancy/breastfeeding
   - ☐ Age <18 years

6. Prior to referral, please ensure you have undertaken shared decision making and discussed the following with your patient:
   a. Need to attend regular appointments for injections at least every 6 months (noting second dose is repeated at 3 months and then 6 monthly thereafter).
   b. Informed consent, including the absence of long term cardiovascular benefit and unknown long term safety profile of this new and novel medication (see supporting sheet overleaf).
   c. As with any black triangle drug, the need to report all side-effects, however minor, via the MHRA "yellow card" scheme.

7. Send this request via eRS (e-Referral Service advice and guidance) to **Cardiology CVD Risk** and Lipids Service - Cardiology (SBH) - Barts Health NHS Trust - R1H

Patient eligible for Inclisiran
Established CVD & LDL ≥2.6mmol/L

↓

Patient consultation

↓

CVD risk & Lipids A&G

↓

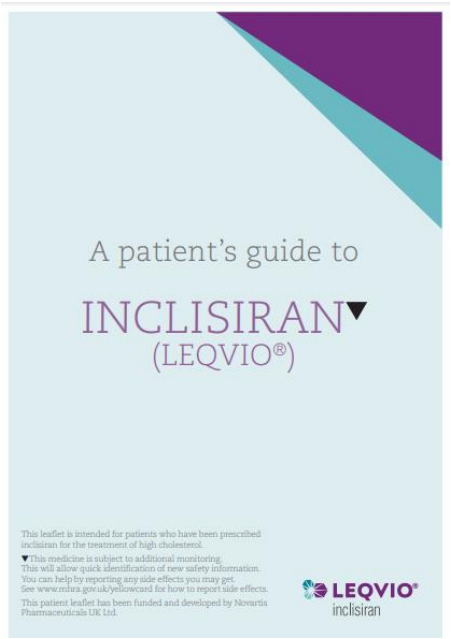
Prescribing/ordering Inclisiran

↓

Appointment for initial injection

↓

Diary Recall Process for 3 months injection & repeat blood test



consultation notes

'Patient consents to treatment with Inclisiran and is aware that there is no long term cardiovascular outcome data or long term safety data at present. Patient has agreed to report all side effects, however minor so that MHRA yellow cards can be completed'

UCLPartners

Thank you

For more information please contact:

primarycare@uclpartners.com

www.uclpartners.com
@uclpartners