

# NENC Lipids & FH Pathways & Guidelines:Interpretation and Application

AHSN-NENC QOF Targets
The Durham Centre
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### Disclosures

- Research: Sanofi, Novartis, Daiichi Sankyo
- Collaborative Working Projects :- Amarin, Novartis, GENinCode
- Advisory:- Amgen, Novartis
- Speaker Fees:- Lilly, Sanofi, Daiichi Sankyo, Amarin, Novartis
- Meeting Sponsorship:- NovoNordisk, Lilly, Sanofi, Boehringer Ingelheim, Amarin



# Why develop a Regional Lipid Guideline?

- Historically subregional guidelines (FATS/SLiMS/NEATS)
- Based on NICE Guidelines (CG 71; 181)
  - Technology Appraisals (TA 385;393;394; )
- Increasingly developing regional approach to Lipid management
  - FH Genetic testing
  - Primary Care FH searches
  - Lipid Optimisation
- Useful to have a single regional resource that we can signpost to for issues pertaining to Lipid Management



### What have we learnt?

- Avoided "too much detail" = Secondary Care Guideline
- Single Sheet Summary stick it on a wall
- Flowcharts more of the same
- Colour coded sections
  - Ease of access
  - Ease of update
- Developed guidelines to cover the gaps
- Incorporated NICE approved AAC Pathways
- Googleable

# **Contact with Reality**

- Feedback mostly positive
- "Too Complicated"; "Don't have time to wade through that"
- TA 694; TA 733; TA 805
- Added :-
- Problem based Signposting to relevant section
- Updated Secondary Prevention beyond standard therapy
- Frailty Guidance
- Inclisiran FAQ
- 2023 Version with updates AAC pathway awaiting NTAG approval



### Northern England Evaluation and Lipid Intensification guideline

| Section<br>Description | Primary Secondary prevention   | Statin Intolerance  | Severe<br>Hypercholesterolaemia   | Severe<br>Hypertriglyceridaemia | Pregnancy   | FH in Children<br>and Young<br>People | Supplementary<br>information  |
|------------------------|--|---|---|---------------------------------|---|---------------------------------------|---|
| Section Guideline      |  |   | Simon Broome criteria<br>for diagnosis of Familial<br>Hypercholesterolaemia |                                 | Lipid<br>management<br>and medication<br>issues in<br>pregnancy |                                       | Frailty Guidelines  Common drug interactions  Lipid Clinic referral criteria  Lipoprotein (a)  Regional Lipid clinics |
| Flow charts            | National Guidance for lipid management  Secondary prevention treatment beyond standard therapy | Statim intolerance<br>flow chert                                      | Assessment pathway  | Assessment pathway              |   | Assessment pathway                    |   |
|                        | NHS  | NHS Foundation Trust  NHS  Of Tyne, Gateshead and North Cumbria South | Tyneside and Sunderland In Prescribing Committee                            | Academ Science                  | South Tyneside  Network  Gateshea                               | NHS Foundation Trust NHS Fo           | NHS<br>h Cumbria<br>rated Care<br>sundation Trust   |

### Result based reference guide and link to relevant guideline detail

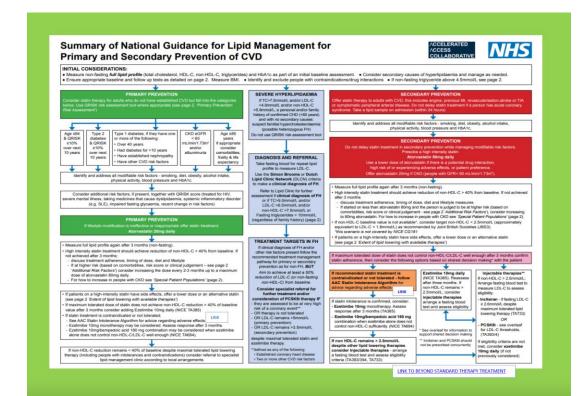
Alternative lipid lowering options - beyond Atorvastatin

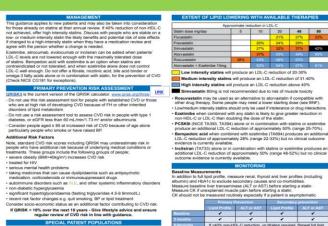
| Medication                    | Notes                                  | When to prescribe   | Section link        |
|-------------------------------|--|---|---------------------|
| Rosuvastatin                  | Water soluble statin                   | First line alternative medication   |                     |
| Ezetimibe                     |  | Additional if non HDLc above target or alternative if statin intolerant   | Red section         |
| Ezetimibe +<br>Bempedoic acid | Available as a single tablet           | Consider in non HDLc above target on Ezetimibe monotherapy  | <u>ited section</u> |
| Evolocumab/<br>Alirocumab     | Secondary care presciption only        | Secondary prevention: single event LDLc>4mmol/l; two or more events LDLc>3.5mmol/l; Familial Hypercholesterolaemia LDLc>5mmol/l | Green section       |
| Inclisiran                    | Primary or Secondary care prescription | Secondary prevention; LDLc ≥2.6mmol/l   | <u> </u>            |

**Guidance related to Interpretation of lipid profile** 

| Parameter                       | Value      | Clinical scenario  | Section link   |
|---------------------------------|------------|--|----------------|
| non HDLc                        | >5.9mmol/l | Assessment for severe hypercholesterolaemia  | Peach section  |
| HOH HOLC                        | ≥2.5mmol/l | Need to intensify lipid lowering in secondary prevention patients  | Green section  |
| Triglycerides                   | >5mmol/l   | Measure fasting lipid profile  | Yellow section |
| Apolipoprotein<br>B100          |            | Measured if fasting triglycerides >10mmol/l  |                |
| Total cholesterol               | >7.5mmol/l | + Personal or first degree relative history of IHD/CVD event <60yrs <b>OR</b>  | Peach section  |
| LDLc<br>(fasting lipid profile) | >4.9mmol/l | + First /second degree relative with total cholesterol >7.5mmol/l or LDL>4.9mmol/l Consider Familial Hypercholesterolaemia                     |                |
| Lipoprotein (a)                 |            | Consider measuring if personal or first degree relative with history of IHD/CVD <60yrs or lipoprotein (a)>200nmol/l in a first degree relative | Blue section   |

# AAC NICE Approved 1ry/2ry Pathway





albumin) and HhA1c to exclude secondary causes and cour CK should not be measured routinely especially if a patient is asymptomal

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

<2.5mmol/L (LDL-C <1.8mmol/L)

If baseline cholestern) is unknown in the setting of secondary prevention use the Non-HDL-C = TC minus HDL-C

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

valid only when fasting triglycerides are less than 4.5 mmol/l

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

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

tory of any of the following: ACS; coronary or other anterial revascularisation procedures; CHD, semic stroke; PAD, <sup>2</sup> Recurrent CV events or CV events in more than 1 vascular bed (that is,

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<br>20mmol/L   | Refer to lipid clinic for urgent specialist review if not a result of<br>excess alcohol or poor glycaemic control. At risk of acute pancreatil   |  |  |  |
| 10 - 20mmo#L               | Repeat the TG measurement with a fasting test (after an interval of days, but within 2 weeks) and review for potential secondary cause 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 managemen of other CVD risk factors present and seek specialist advice if non-HDL-C concentration is 2.7.5 mmol/life. |  |  |  |

Statin intolerance is defined as the presence of clinically significant adverse to the patient or that may result in adherence to therapy being compromised

LINK

FH: familial hypercholesterolaemia SPC: summary of product characteristics

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 diabeter

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/1.73m<sup>2</sup> or more.

Agree the use of higher doses with a renal specialist if eGFR is less than 30 mL/ min/1.73m<sup>2</sup>

LDL-C: low density lipoprotein cholesterol

SLE: systemic lupus erythematosus

PCSK9t: proprotein convertase subfilisin kexin 9 monoclonal antibody inhibitor

Chronic Kidney Disease



















# Basically.....

- Measure full fasted lipid profile and assess risk
- Address Secondary causes / Lifestyle issues
- Primary Prevention
  - Atorvastatin 20 mg OD
  - Aim for 40% reduction from baseline NonHDL-C
  - Up titrate and add Ezetimibe if not to target
- Secondary Prevention
  - Atorvastatin 80 mg OD (start with 20mg if eGFR < 60 or interaction)
  - Aim for NonHDL-C < 2.5 mmol/L [or LDL < 1.8 mmol/L]
  - Consider additional therapy if eligible

# **Grouping of Statins**

|                          | Reduction in LDL |     |     |     |             |  |
|--------------------------|------------------|-----|-----|-----|-------------|--|
| Dose<br>mg / day         | 5                | 10  | 20  | 40  | 80          |  |
| Fluvastatin              |                  |     | 21% | 27% | 33%         |  |
| Pravastatin              |                  | 20% | 24% | 29% |             |  |
| Simvastatin              |                  | 27% | 32% | 37% | 42%<br>MRHA |  |
| Atorvastatin             |                  | 37% | 43% | 49% | 55%         |  |
| Rosuvastatin             | 38%              | 43% | 48% | 53% |             |  |
| Atorvastatin + Ezetimibe |                  | 52% | 54% | 57% | 61%         |  |

### **NICE QOF Indicators**

**CHOL 001** = 14 Points

70-95%

% CHD, PAD, CVA/TIA or CKD prescribed statin or alternative lipid lowering therapy

**CHOL 002** = 16 Points

20-35%

% CHD, PAD, CVA/TIA with NonHDL < 2.5 or LDL < 1.8 mmol/l

**DM022** = 4 Points

50-90%

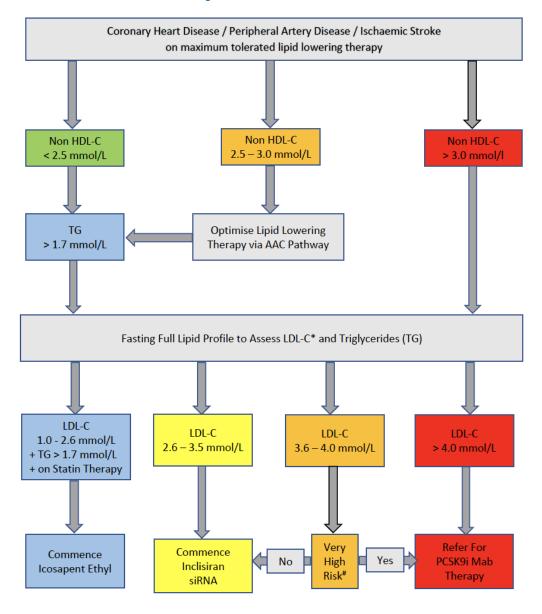
% Patients with DM >40yr without CVD or mod/severe Frailty prescribed statin (exclude T2DM with QRisk < 10%)

**DM023** = 2 Points

50-90%

% Patients with DM with CVD (excl haemorrhagic stroke) prescribed statin

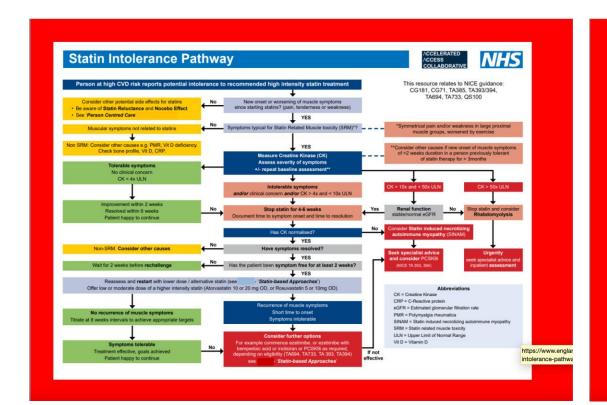
# Secondary Prevention Beyond Standard Therapy



## Measure Fasting LDL if CVD + NonHDL not to target

- Non HDL < 2.5 mmol/L</li>
  - To Target; Consider Vazkepa if TG > 1.7mmol/L and LDL 1.0 2-6 mmol/L
- Non HDL 2.5 3.0 mmol/L
  - Optimise Statin / Ezetimibe therapy
  - Consider Vazkepa if TG > 1.7mmol/L and LDL 1.0 2-6 mmol/L
- NonHDL ≥ 3.0 mmol/L
  - LDL > 4.0 mmol/L → Refer for PCSK9i MaB
  - LDL > 3.5 mmol/L → Refer for PCSK9i MaB if Very High Risk
    - → Start Inclisiran if High Risk
  - LDL > 2.6 mmol/L → Start Inclisiran
  - LDL = 1.0 2.6 mmolL  $\rightarrow$  Consider Vazkepa if TG > 1.7 mmol/L

# **AAC Statin Intolerance Pathway**



- . Statins are the cornerstone for prevention and treatment of cardiovascular (CV) isease with a substantial evidence of reduction of morbidity and mortality Refer to Lipid Management Pathway and related NICE guidelines (CG181 CG71) for guidance on initiation, titration and monitoring of statin therapy.
- In clinical trials, statins were found to be largely well tolerated (often with a similar adverse effect (AE) profile to placebo), however this is not reflected in clinical practice where up to 75% of people started on a statin will
- Stopping statin therapy is associated with an increased risk of major CV events and there is growing concern that clinicians are labelling patients as 'statin intolerant' too quickly. Indeed statin discontinuation is significantly associated with negative media coverage.

### Definition of Statin Intolerance

- Intolerance to initial statin therapy is defined by NICE as the presence of clinically significant adverse effects that represent an unacceptable risk to the patient or that may reduce compliance with therapy.
- Other definition: any adverse event (AEs) considered unaccentable by

### Statin-associated muscle symptoms (SAMS)

SAMS are one of the principal re 'statin intolerance' as they may not be truly statin related muscle toxicity (SRM) as demonstrated by resolution on de-challenge and recurrence with

### Non-Statin related musculoskeletal symptoms (Non SRM) . If patients report symptoms that are not typical of SRM (e.g. asymmetric

in pasema report symptoms trat are not system to row (e.g. asymmetric distribution, failure to resolve with de-challenge despite normal CK) consider other musculoskeletal disorders, metabolic, degenerative or inflammatory e.g. Vitamin D deficiency, polymyalgia rheumatica. Check Bone profile, Vit D, CRP.

- and avoid the highest doses in at risk groups (See "Risk Factors" below).
- Ask the person if they have had persistent generalised unexplained muscle pain, whether associated or not with previous lipid-lowering therapy. If they have, measure CK. If CK levels are > 4x ULN do not start statir

Warn patients about AEs, specifically muscle symptoms. Advise people who are being treated with a statin to seek medical advice if they develop muscle symptoms (pain, tenderness or weakness). If this occurs, measure

Exogenous Factors

Dehydration

Excessive alcohol intake

(including herbal medicines)

### Endogenous factors · Female gender

- . Frailty (reduced lean body mass) History of muscle disorder or high CK
- Impaired renal or hepatic function
- · Personal or family history of intolerance

### 0.2-2/1.000 Muscle symptoms, CK <4x ULN, CK elevation >4x ULN <10x ULI muscle symptoms, complet resolution on dechallenge Rhabdomyolysis 0.1-8.4/100,000 CK elevation >10x ULN with evidence of renal impairment. dence of renal impairme muscle symptoms or CK >50x ULN

### . SRM is a spectrum from myalgia to severe myopathy

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

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

Most commonly reported: gastrointestinal disturbance and asymptomatic increases in hepatic transaminases (ALT or AST). May affect up to 1 in 10 statin users. Rarer side effects include: Hepatotoxicity, new onset Type 2 Diabetes (benefits outweigh risk, do not stop statin), Renal insufficiency, proteinuria, Neurocognitiv and neurological impairments (no apparent link from RCTs), Intracranial haemorrhage (conflicting evidence, benefit outweigh possible harm), Interstitial lung disease, Pancrealitis, Skin disorders including alopecia, Lupus-like reaction, Sleep disturbance, headache, dizziness, fatigue, depression, sexual dysfunction

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

### Initial Consultation

### Be aware of "nocebo effect" and

- Reinforce healthy lifestyle habits Listen to the concerns of each patient
- . Explain LDL-C targets and strategies to lower LDL-C/non-HDL-C
- Explain the benefits of statins
- Evaluate and identify any risk factors

### and address (e.g. drug interactions) · Work with patients to identify and

### . Follow up on agreed plan and address any issues/concer

- . Ongoing patient education and regular
- review helps addressing concerns around medicine safety and underline the importance of adherence.

### agree best options and next steps

- · Adopt person-centred approach as described above.
- Therapy with a lower dose statin is preferred to no statin
- . Apply a repetitive "De-Challenge" "Re-Challenge" approach to establish if
- reptoms are caused by a statin(s) and the best statin regimen for each patient. . Switch to a different statin or re-challenge with the same statin using a lower dose
- . Patients who do not tolerate statins on a daily basis, alternate day or twice-weekly
- dosing is a good option
- Rosuvastatin and atorvastatin have longer half-lives, permitting their use on a non-daily regime.
- Adding ezetimibe to a lower dose statin may be better tolerated with robust reduction of LDL-C / non-HDL-C. . Once a new regime is tolerated, dose / frequency can be up-titrated slowly to
- achieve LDL-C / non-HDL-C goals with minimal or no muscle complaints It is important to note that cardiovascular benefits have not been proven for all the above approaches but any reduction of LDL-C / non-HDL-C is beneficial.

- Refer to the AAC Lipid Management Algorithm. | Click here
- . Consider ezetimibe, (NICE TA 385) therapy as per algorithm
- . Consider ezetimibe combined with bempedoic acid (NICE TA 694) as per algorithm
- . Consider inclisiran if eligible for treatment according to NICE TA 733

### . Consider PCSK9i if eligible for treatment according to NICE TA 393, 394

assessment is warranted if levels exceed 3x ULN. Several studies have confirmed that the cardiovascular benefits of statin treal

https://www.england.nhs.uk/aac/publication

COLLABORATIVE

### Statin Intolerance

- Affects up to 10% of patients
- Significant nocebo effect :- reinforced by health professionals
- More likely in certain subgroups (female, hypothyroid, alcohol excess)
- Ask, reassure, advise
- Check Creatinine Kinase if symptoms suggestive of myalgia
- Aim for max tolerated dose (low better than no)
- Re-try at lower dose after 4-6 week wash out period
- Switch to Rosuvastatin 10 mg
- Consider lower intensity statin
- Use Ezetimibe as statin sparing agent or as monotherapy
- Consider addition of Bempedoic acid to Ezetimibe if NonHDL

### Additional Sections

- Severe Hypercholesterolaemia
  - Simon Broome criteria
  - Pathway
- Severe Hypertriglyceridaemia
  - Use of Apo B100 alongside Full Fasted Lipid Profile
- Pregnancy
- FH in Children and Young People
- Supplementary
  - Frailty
  - Common Drug Interactions
  - Lipid Clinic Referral Criteria
  - Lipoprotein (a)
  - Regional Lipid Clinics
  - Inclisiran FAQ

### FH Diagnosis

Simon Broome Criteria

- 1. Total Chol > 7.5 or LDL > 4.9
- 2. Tendon Xanthoma
- 3. Family history of Premature MI\*
- 4. Family history of hypercholesterolaemia@



\* <60 yr if  $1^{\circ}$  Rel or < 50 yr  $2^{\circ}$  Rel @ Total Chol > 7.5 or LDL > 4.9 in  $1^{\circ}$  /  $2^{\circ}$  Rel

1+2 = Definite FH 1+ 3 or 4 = Probable FH

Dutch Lipid Clinic Network score ≥6 used to determine whether or not to do genetic testing





## Referring FH

- Use Simon Broom Criteria to determine whether "could" have FH
  - 1 in 250 patients have FH = 0.4%
  - Population with Chol > 7.5 mmol/l = 4%
  - Hypercholesterolaemia common in women > 50 yrs
- Don't use DLCS; determines whether eligible for genetic testing
  - LDL > 6.4 mmol/L + family history premature MI / LDL > 5.5 mmol/L
  - LDL > 4.9 + personal MI < 60 yr + family history
  - Bilateral TX
  - TG < 2.3 mmol/L
- Refer via A+G if
  - > 30 yr with Chol > 9.0 mmol/L or NonHDL > 7.5 mmol/l or LDL > 6.5 mmol/L
  - < 30 yr with Chol > 7.5 mmol/L or NonHDL > 6.0 mmol/l or LDL > 4.9 mmol/L

# Criteria for Lipid Clinic Referral

- All Regional Lipid Clinics offer A+G
- Refer if
- Clinical Diagnosis of FH according to SB criteria
  - Relatives who require genetic testing (FH Nurses)
  - Children with FH (Paediatric Clinic)
- Total Chol > 9.0 mmol/L or NonHDL-C > 7.5 mmol/L
- TG > 10 mmol/L (Urgently if > 20 mmol/L)
- Other Lipid disorders (Remnant / FCH / Familial HyperTG)
- Patients with CVD and NonHDL-C > 4 mmol/L
- Patients for PCSK9i Mab therapy

### Where can I find it?

NTAG Website

https://ntag.nhs.uk/wp-content/uploads/2022/09/NEELI-edit-v2022.2-FINAL-NTAG.pdf

- 2023 update awaiting NTAG approval
- Update existing weblinks

# Any Questions?

