Lothian lipid guideline update 2023

RefHelp / PLIG webinar

Dr Jonathan Malo (Clin Biochem + Lipid Clinic)

Overview

- Why are we updating?
- What are the main changes?

- Non-HDL cholesterol (and briefly – triglycerides)
- A tour of the updated guideline

- When / how to intensify lipid-lowering medication
- New(ish) lipid-lowering drugs (available to primary care)
- Lipid clinic referral & advice

Lothian lipid guideline – why the update?

Current version last updated 2017, largely based on NICE CG181 (2014)

Proposed update based on a hybrid of guidelines:

- NICE CG181 (2014)
- SIGN 149 (2017)
- JBS-3 (2014)
- EAS / ESC (2019)

- atorvastatin – “standard” therapy
- greater emphasis on confirming chol-lowering efficacy
- dose titration for higher ASCVD risk

... and slow but steady move across UK, to use non-HDL cholesterol.

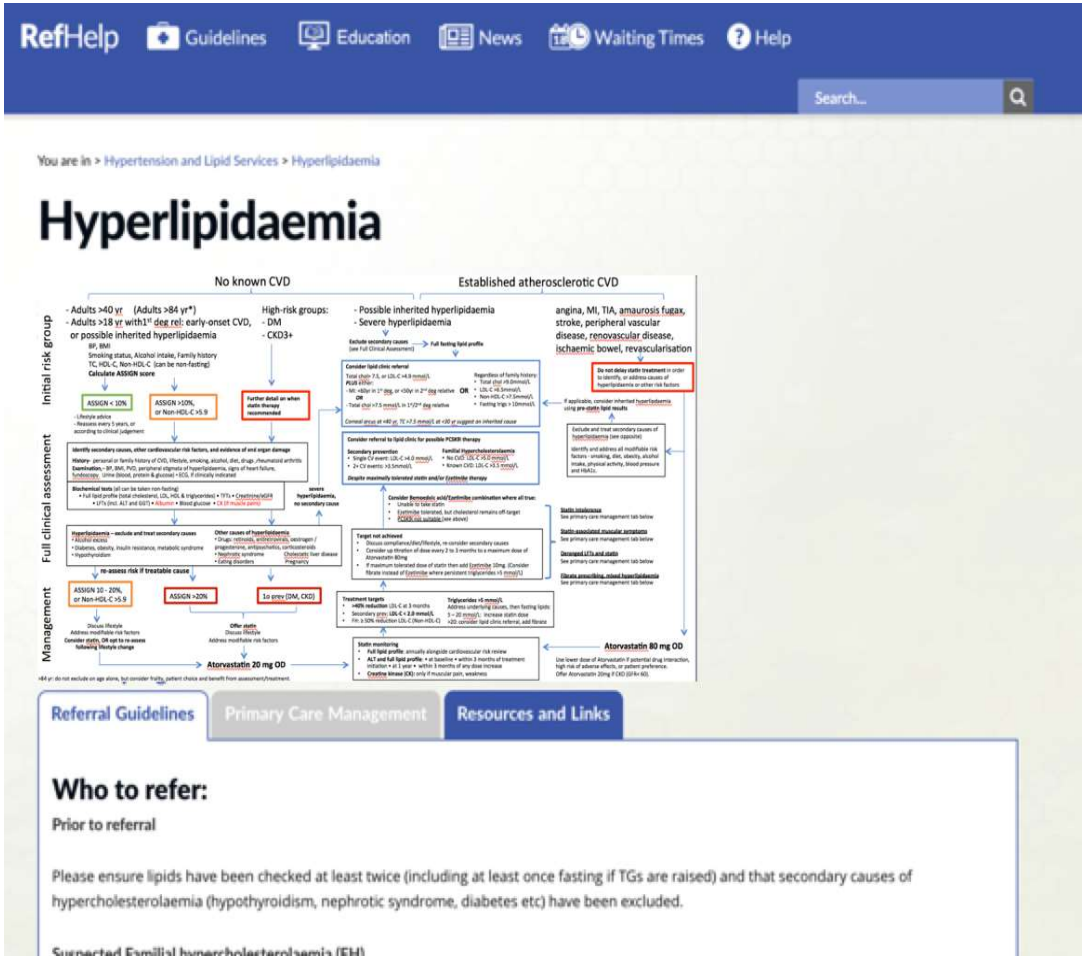
SMC approval of several new lipid-lowering drugs:

- Evolocumab, Alirocumab (monoclonal PCSK9 inhibitors)
- Inclisiran (siRNA PCSK9i)
- Bempedoic acid (ACL inhibitor)

SMC decision *not yet published*: icosapent ethyl (omega-3 ethyl ester)

Lothian lipid guideline – main changes

Change in format…



- flow diagram (summary)
- tabs underneath (more detail)

Lothian lipid guideline – main changes

Changes to content:

A "new" test: ***non-HDL cholesterol***

Rationalise ICE lipid test ordersets
– reduce chol-alone, full lipid profile requesting...
– in favour of: TC, HDL-C, Non-HDL-C as "standard"

?Review reference ranges, thresholds for flagging lipid tests

Primary prevention

- Assess those with hyperlipidaemia, defined by non-HDL-C ≥6.0 mmol/L, (*even where 10-year CV risk is low*) -- and consider statin primary prevention
- Repeat lipids within 3 months of starting statin
  -- and where higher risk, consider up-titrating from atorvastatin 20 mg

Rosuvastatin, Ezetimibe

Options in either primary or secondary prevention
Ezetimibe can be used as monotherapy, or alongside statin

} *Lipid Clinic advice not required*

New drugs

Monoclonal PCSK9 inhibitors (Evolocumab, Alirocumab)
ACL inhibitor (Bempedoic acid)

} *Lipid Clinic initiation*

Introducing... *non-HDL cholesterol*

Why is it useful? And what is it?

Non-HDL-C = total cholesterol – HDL-cholesterol

In simple terms, all cholesterol that isn't HDL-C... is **atherogenic**

-- strong evidence that non-HDL-C is the best (non-specialist) lipid test in terms of predicting ASCVD

-- better than total chol, which underestimates risk when HDL-C is low, overestimates risk when HDL-C is high

-- easier to assess trends over time compared to *TC:HDL-C* ratio

Introducing... *non-HDL cholesterol*

Why is it useful? And what is it?

Non-HDL-C = total cholesterol – HDL-cholesterol

Calculated LDL-C is also a good measure, since LDL has high atherogenic potential. But calculated LDL-C:

-- does not take into account high/low HDL-C

-- requires a triglyceride measurement

-- *underestimates* atherogenicity where trigs are slightly raised (common in obesity, pre-diabetes, diabetes

-- cannot be calculated when trig >4.5 mmol/L. Limits use in mixed hyperlipidaemia, or in non-fasting state.

Non-HDL-C recommended by NICE (since 2014), and SIGN (since 2017)

Introducing... *non-HDL cholesterol*

Non-HDL cholesterol - disadvantages

New... so clinicians & patients will be less familiar with it

Yet to be adopted as primary end-point for new cholesterol-lowering drugs. So NICE / SMC eligibility criteria continue to cite LDL-C. Of most relevance for high-risk patients, potentially eligible for PCSK9i.

Familial Hypercholesterolaemia screening cut-offs use LDL-C

... solutions to latter two problems could include either:

- full lipid profile (LDL-C included) for 2o prev, ?FH
- auto-request full lipid profile, where non-HDL-C > *x* mmol/L

Introducing... *non-HDL cholesterol*

Non-HDL cholesterol - summary

- Plan is to add non-HDL-C to lab reports shortly

- Aim is to make default lipid profile:

Total chol, ***HDL chol, Non-HDL chol****, Total chol:HDL-C ratio*

- Reduce *total chol alone* testing
- Reserve full lipid profiles (include LDL-C, triglycerides) to:
    - Secondary prevention
    - Familial Hypercholesterolaemia (FH)

Triglycerides... *in brief*

Guideline for hypertriglyceridaemia **not** being changed (yet)

- Triglycerides do not confer (significant) extra risk to primary prev. risk scoring – hence not in ASSIGN / QRISK3
- Non-fasted >5 mmol/L (new result), merits **fasted** repeat
- Most useful in pointing toward secondary causes of hyperlipidaemia *e.g. alcohol, diabetes, untreated hypothyroidism*

Try to address secondary causes first

Recommended action where <u>fasted</u> trigs:

5 – 10 mmol/L AND 1o-prev, start / increase statin dose
5 – 10 mmol/L **AND 2o-prev**, *seek lipid clinic advice*
>10 mmol/L *seek lipid clinic advice*
>20 mmol/L *urgent lipid clinic advice*

<u>Reduce risk of pancreatitis</u>
Avoid alcohol, fatty foods
Diabetes – improve glycaemic control
May require fenofibrate

A tour of the updated lipid guideline...

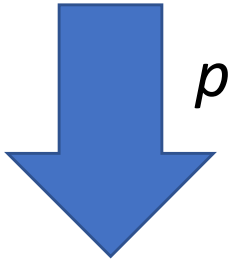
¡ Work in progress !

Revised with feedback from PLIG, GP RefHelp advisor (but no formal sign-off from either, as yet)

***Hopefully*, largely finished – some scope for feedback / revision**

*Guide*line, not a mandate...

multiple continuous risk factors



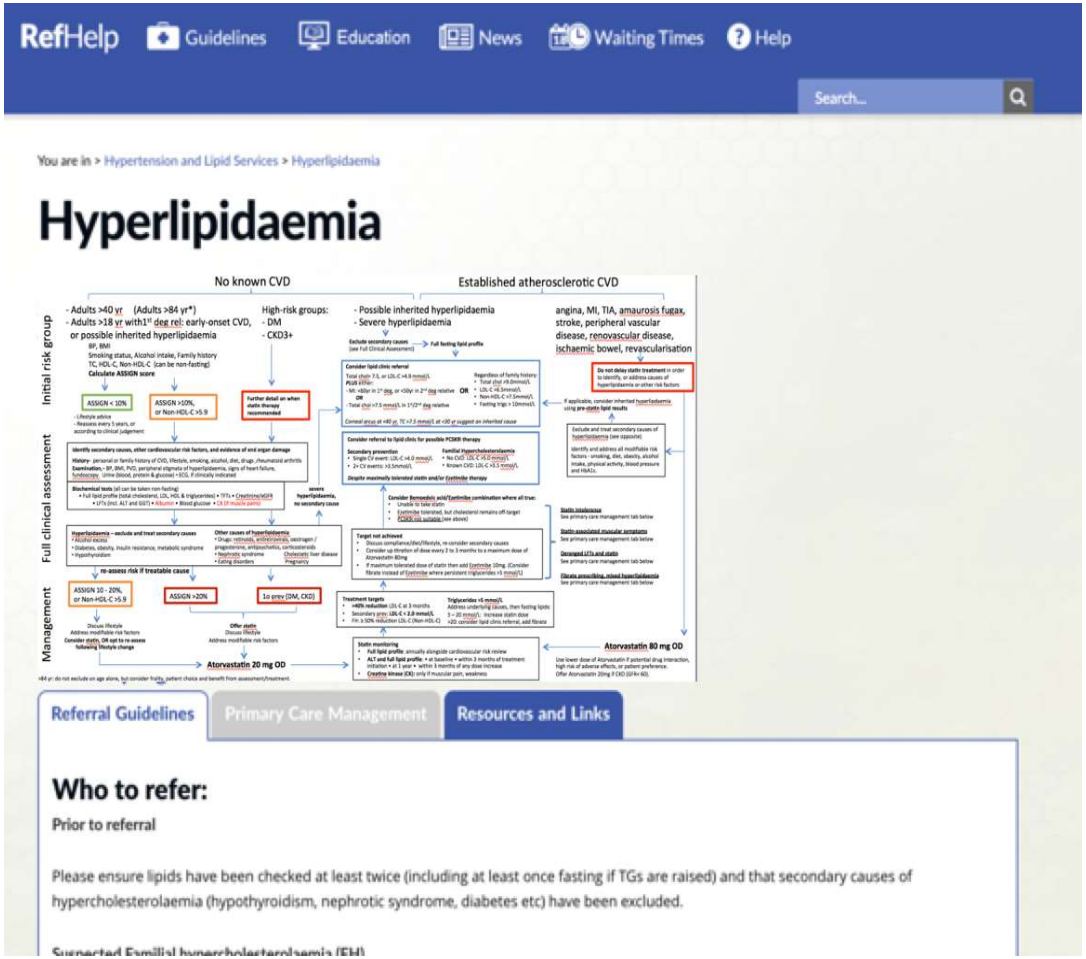
precise cut-offs

YES / NO outcomes

-- Some (many?) clinical scenarios will NOT neatly fit

-- Not a substitute for clinical judgement, but hopefully a “rough guide”

Change in format…



- flow diagram (summary)
- tabs underneath (more detail)
  - ***Who to refer***
  - ***Primary care management***
  - ***?Hypertrig. guideline***
  - ***Resources and links***

Lipid guideline for prevention of atherosclerotic cardiovascular disease (ASCVD) in adults

NHS Lothian, April 2023

(For ***suspected inherited hyperlipidaemia*** – see "Who to refer" tab below)

Primary prevention

Consider ASCVD risk in all adults >40 years
(or younger adults, with 1st deg rel. ASCVD <60 yr)
Frail or elderly – consider whether appropriate

Total chol, HDL-C
(can be non-fasting)

Calculate ASSIGN score

ASSIGN < 10%
and
Non-HDL-C <6.0

- Lifestyle advice
- Reassess every 5 years, or according to clinical judgement

ASSIGN >10%
or
Non-HDL-C ≥6.0

Full lipid profile
(can be non-fasting)

ASSIGN NOT required for:

Diabetes
Age >40 yr, OR
Age <40 yr, and any of:
- diabetes for >20 yr
- end-organ damage
- other significant CV risk factors

Chronic kidney disease
eGFR <60, and/or
Micro- or macroalbuminuria

Familial Hyperchol. (FH)

Secondary prevention

Full lipid profile
(can be non-fasting)

ASSIGN NOT required for:

Angina, MI,
TIA, amaurosis fugax, stroke,
peripheral vascular disease,
renovascular disease,
ischaemic bowel

Do not delay statin treatment in order to identify, or address causes of hyperlipidaemia or other risk factors

ASSIGN < 10%
and
Non-HDL-C <6.0

- Lifestyle advice
- Reassess every 5 years, or according to clinical judgement

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Familial Hyperchol. (FH)

Angina, MI,
TIA, amaurosis fugax, stroke, peripheral vascular disease, renovascular disease, ischaemic bowel

Do not delay statin treatment in order to identify, or address causes of hyperlipidaemia or other risk factors

Non-inherited causes of hyperlipidaemia – identify and /or address

Common:
- alcohol excess
- diabetes **(glucose / HbA1c)**
- obesity **(BMI)**
- hypothyroidism **(TFTs)**
- pregnancy

Other causes:
- keto-or high-fat diets
- eating disorders
- nephrotic syndrome **(albumin, urine ACR)**
- cholestatic liver disease **(LFTs)**
- drugs: oestrogen, retinoids, antiretrovirals, antipsychotics, corticosteroids, ciclosporin

Inherited hyperlipidaemia suspected?
- Non-inherited cause excluded
- Family history of ASCVD <60 yr, or hyperlipidaemia
- See **"Who to refer" tab** below

After identifying / addressing non-inherited causes:
- If large cholesterol reduction likely (for example – after patient significantly reduces high alcohol intake), consider arranging: full lipid profile and (where required) re-calculation of ASSIGN score.
- Hypothyroidism - do not start a statin until managed adequately
- For trigs >4.5 mmol/L, see *RefHelp Hypertriglyceridaemia guideline*

- obesity **(BMI)**
- hypothyroidism **(TFTs)**
- pregnancy

- cholestatic liver disease **(LFTs)**
- drugs: oestrogen, retinoids, antiretrovirals, antipsychotics, corticosteroids, ciclosporin

- Non-inherited cause excluded
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ASSIGN 10 - 20%
or
Non-HDL-C ≥6.0

- Discuss lifestyle
- Address modifiable risk factors
- Any additional risk factors?*
- **Consider statin, OR re-assess after lifestyle change**

ASSIGN >20%

Non-ASCVD high risk group

Offer statin
Discuss lifestyle
Address modifiable risk factors

Atorvastatin 20 mg OD

Atorvastatin 80 mg OD

- Use lower dose of Atorvastatin if potential drug interaction, high risk of adverse effects, or patient preference
- Offer Atorvastatin 20mg if CKD (eGFR< 60)

Risk factors not captured by ASSIGN

- Indian, Pakistani, or Bangladeshi ethnicity
- Physical inactivity
- Systemic inflammatory disease
- Mental health disorders
- Early menopause

***** Patient groups that may***

- Physical inactivity
- Systemic inflammatory disease
- Mental health disorders
- Early menopause

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***** Patient groups that may benefit from annual TC, HDL-C:***
- Secondary prevention
- Diabetes
- Familial hypercholesterolaemia
- Long-term therapies causing hyperlipidaemia (see "Non-inherited causes" above)
- Strong family history of ASCVD at age <60 yr
- Poor medication compliance

Frequency of monitoring may be tailored according to CV risk, patient choice and consistency of cholesterol reduction.

Statin monitoring

- **ALT and Total chol, HDL-C**: within 3 months of initiation, or any dose increase
- **Total chol, HDL-C**: annually alongside cardiovascular risk review for ***selected*** patients**
- **Creatine kinase (CK):** only if muscular pain, weakness

Primary prevention

>40% reduction in non-HDL-C or LDL-C
(FH: ≥50% reduction in LDL-C)

Secondary prevention

Non-HDL-C <2.5 and LDL-C <1.8 mmol/L

Where above not achieved

- Discuss compliance / diet / lifestyle, re-consider secondary causes e.g. diabetes, alcohol
- Consider intensification of therapy **for highest risk patients** (**secondary prevention**; FH; diabetes with end-organ damage; diabetes or CKD or family history 1st deg rel ASCVD <60yr plus adverse risk factor***):
  - increase atorvastatin dose until target achieved
  - rosuvastatin may be used if atorvastatin not tolerated, or ineffective
  - if max. tolerated dose of statin then add Ezetimibe 10mg
  (consider lipid clinic advice to use fibrate instead of Ezetimibe where persistent trigs >5 mmol/L)
- See below options where:

at age <60 yr
- *Poor medication compliance*

Frequency of monitoring may be tailored according to CV risk, patient choice and consistency of cholesterol reduction.

Primary prevention
>40% reduction in non-HDL-C or LDL-C
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  (consider lipid clinic advice to use fibrate instead of Ezetimibe where persistent trigs >5 mmol/L)
- See below options where:
  - secondary prev. AND LDL-C >3.5 mmol/L
  - primary or secondary prev. AND unable to take statin

*** long-standing: smoking, poorly-controlled BP or hyperlipidaemia

See **Primary Care Management tab** below for:

Statin intolerance

Deranged LFTs and statins

Fibrates, mixed hyperlipidaemia

Options beyond statins and ezetimibe

Consider referral to lipid clinic for possible PCSK9i therapy

Familial Hypercholesterolaemia
- No CVD: LDL-C >5.0 mmol/L
- Known CVD: LDL-C >3.5 mmol/L

Secondary prevention
- Single CV event: LDL-C >4.0 mmol/L
- 2+ CV events: >3.5mmol/L

despite (well-tolerated) maximal statin and/or Ezetimibe therapy

PCSK9 inhibitors

SMC have recommended:

- Evolocumab, Alirocumab (monoclonal PCSK9 inhibitors)
- Inclisiran (siRNA PCSK9i)

<u>Evolocumab, Alirocumab (monoclonal PCSK9 inhibitors)</u>

- self-administered s/c injection every 2 weeks
- approx 30 – 60% reduction in LDL-C
- Evolocumab 140 mg (no other dose)
- Alirocumab 75 mg, 150 mg (approx equiv. efficacy to Evolocumab)

<u>Inclisiran</u>

- HCP-administered s/c injection every 6 months
- similar reduction in LDL-C to monoclonals
- **as yet, no CV event data**

PCSK9 inhibitors – prescribing in Lothian

Patient eligible for PCSK9i?

Secondary prevention
- Single CV event: LDL-C >4.0 mmol/L
- 2+ CV events: >3.5mmol/L

Familial Hypercholesterolaemia
- No CVD: LDL-C >5.0 mmol/L
- Known CVD: LDL-C >3.5 mmol/L

despite maximal statin and/or Ezetimibe therapy

refer to lipid clinic

LIPID CLINIC

review indication for PCSK9i

start 8-week prescription (Evolocumab)

repeat lipids: effective? tolerated?

See shared-care agreements on Evolocumab / Alirocumab - for further detail...

Recommend long-term GP Evolocumab prescription

Long-term management (GP)
- Annual lipid profile
- Re-refer if adverse effects, or self-administration

Evolocumab, Alirocumab – key points

- **NOT** immunosuppressants

- Reasonably well-tolerated
- Most common adverse-effects: local injection site reactions (redness, pain, bruising), flu-like symptoms, nasopharyngitis, back pain, arthralgia, rash and nausea

- No “special” monitoring required e.g. no need to track LFTs, U&Es etc.
- Appear safe in renal, liver impairment – but recommend lipid clinic advice if eGFR <30, or severe/active liver disease
- Should not be prescribed in pregnancy

- Long-term lipid monitoring required to track efficacy, compliance
- Appear most effective (largest LDL-C reduction) when used with statin

organ damage, diabetes or CKD or family history 1st deg rel ASCVD <60yr plus adverse risk factor ***).

- increase atorvastatin dose until target achieved
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- if max. tolerated dose of statin then add Ezetimibe 10mg

(consider lipid clinic advice to use fibrate instead of Ezetimibe where persistent trigs >5 mmol/L)

- See below options where:
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Secondary prevention
- Single CV event: LDL-C >4.0 mmol/L
- 2+ CV events: >3.5mmol/L

despite (well-tolerated) maximal statin and/or Ezetimibe therapy

Consider Bempedoic acid/Ezetimibe combination if ALL true:

- Primary prevention (only highest risk), or secondary prevention
- Unable to take statin
- Ezetimibe tolerated, but cholesterol remains off-target
- PCSK9i not suitable (see SMC criteria above)

Pre-initiation - recommend seeking lipid clinic advice via SCI-gateway, or email: RIE.BioLipidsAdvice@nhslothian.scot.nhs.uk

Bempedoic acid – background

Adenosine triphosphate citrate lyase (ACL) inhibitor – inhibits cholesterol synthesis in the liver, thereby lowering LDL-cholesterol

- ACL is an enzyme a couple of steps before HMG-CoA reductase (enzyme inhibited by statins). Like statins reduces LDL-C and hsCRP.

- Unlike statins... bempedoic acid is only converted to its active form by an enzyme present within hepatocytes (and not within skeletal muscle)

- So, ***if....*** the muscular symptoms associated with statins are caused by inhibition of cholesterol synthesis in skeletal muscle... bempedoic acid ***should*** avoid causing similar adverse effects

Recently published outcomes data (earlier this month) show that bempedoic acid ***does reduce CV events***

Bempedoic acid – key points (lipid clinic)

- SMC requires prescription alongside Ezetimibe. So best prescribed as combination tablet called *Nustendi.*

- **Most common adverse effects**: anaemia, **gout, hyperuricaemia**, dizziness, headache, diarrhoea, constipation, flatulence, nausea, back pain, myalgia, arthralgia, pain in extremity.

- **Less common adverse effects**: deranged LFTs, increased creatinine, increased urea

Some similar adverse effects to those seen with statins and fibrates – when initiating need to repeat U&Es, LFTs. Avoid if eGFR <30, or hepatic imp.

Avoid in gout, and where urate >ULN
(RCT – rate of gout was 3.1% vs 2.1% for BA vs placebo. Urate reduced to baseline where BA was discontinued.)

Bempedoic acid – key points (GP)

Shared-care agreement summarises initiation (lipid clinic), long-term prescribing (GP)

- **Long-term monitoring – recommend annual bloods**
  - full lipid profile
  - urate – *only if symptoms of gout*
  - CK – only if muscular pain or weakness
- **Interactions:** warfarin, ciclosporin (may require more freq monitoring)
- **Contraindicated in pregnancy, breast-feeding** – provide advice on contraception. (We advise stopping 8 weeks before trying for pregnancy.)
- **Re-refer to lipid clinic** where adverse-effects or ineffective (consider compliance, secondary causes of hyperlipidaemia first)

Suspected inherited hyperlipidaemia

Excerpts from the "Who to refer" tab

Consider referring patients with the following to the lipid clinic:

- suspected Familial Hypercholesterolaemia (FH)
- mixed hyperlipidaemia (total chol >7.0 AND trig >3.0 mmol/L) in the absence of a secondary cause
- raised lipoprotein(a)
- severe (fasting) hypertriglyceridaemia (>10 mmol/L) in the absence of a secondary cause, particularly if history of acute pancreatitis

Suspected inherited hyperlipidaemia

Familial Hypercholesterolaemia

- affects up to 1 in 250 people in Scotland
- confers a high-risk of early-onset cardiovascular disease (over half of untreated men will suffer an MI before the age of 50)
- under-diagnosed

- autosomal dominant, most commonly involves a mutation in the LDL receptor gene
- **life-long raised LDL-C** and (typically) **normal triglyeride** levels
- can be confirmed via a sensitive genetic screen
- upon identification of a case, family screening for close relatives is offered throughout Scotland, Wales, NI and parts of England

Suspected inherited hyperlipidaemia

Familial Hypercholesterolaemia – Simon-Broome criteria

Consider referral if patient has had at least 2 lipid profiles, and the answers below are 'YES' to: (1 or 2) AND any of (3, 4 or 5).

1. Total cholesterol >7.5 (predominantly due to raised LDL-C)
2. LDL cholesterol >4.9 and, where available, persistently high historic LDL-C levels

3. Total cholesterol >7.5 in 1st or 2nd degree relative
4. Tendon Xanthoma in patient or 1st or 2nd degree relative
5. MI < 60yrs in 1st, or <50yrs in 2nd degree relative

Suspected inherited hyperlipidaemia

Familial Hypercholesterolaemia – Simon-Broome criteria

Consider referral if patient has had at least 2 lipid profiles, and the answers below are 'YES' to: (1 or 2) AND any of (3, 4 or 5).

1. Total
2. LDL c
LDL-C l

3. Total
4. Tend
5. MI <

gh historic

Prior to referral

1. Exclude secondary causes
new diabetes diagnosis, alcohol excess, untreated hypothyroidism, nephrotic syndrome

2. If overweight with raised triglycerides (as well as) LDL-C then most likely **polygenic hypercholesterolaemia** which may respond to lifestyle intervention – for these patients ***repeating lipids prior to referral after a period of lifestyle*** changes may be appropriate as genetic testing for FH is unlikely to be helpful

Suspected inherited hyperlipidaemia

Familial Hypercholesterolaemia – Simon-Broome criteria

Consider referral if patient has had at least 2 lipid profiles, and the answers below are 'YES' to: (1 or 2) AND any of (3, 4 or 5).

1. Total
2. LDL c … gh historic LDL-C l

3. Total
4. Tend
5. MI <

Also worth considering pre-referral...

FH is UNLIKELY if the patient has had a previous (off-statin) LDL-C below 4.5 mmol/L, since the age of 25 years

FH is MORE LIKELY if:

- LDL-C >4.9 before age of 40
- corneal arcus under the age of 40
- tendon xanthoma at any age

RIE.BioLipidsAdvice@nhslothian.scot.nhs.uk

Thank you...

Lipid clinic: Sara Jenks, Nicola Shand, Jennifer Simpson, Kirsty McCance

CV risk clinic: Simon Maxwell, Iain MacIntyre

PLIG: too many to mention!

RefHelp: Caroline Wiggins

Clinical Biochemistry: too many to mention!

Questions?