Familial hypercholesterolaemia

1. Familial hypercholesterolaemia

Why does familial hypercholesterolaemia matter?

- By the age of 60y, 50% of men and 30% of women with familial hypercholesterolaemia will have had an MI (BJGP 2009;59:777).
- Treatment returns cardiovascular risk to near-population risk (BMJ 2008;337:a2423). However, over a third of people with the condition in the UK are under-treated, leaving them at increased risk of CV events (BJGP 2024;e174).

How common is it?

- Worldwide, it affects 1 in 310 people (BMJ 2023;382:e073280). Most familial hypercholesterolaemia genes are inherited in an autosomal dominant pattern. Homozygous states are rare, but need very specialist management: liver transplant may be considered.
- In the UK, the prevalence is about 1 in 608, less than expected, suggesting that familial hypercholesterolaemia is under-recognised in UK primary care (BJGP 2024;e174).

Aim of treatment?

- Reduce LDL by more than 50% from pre-treatment levels.
- Lipids clinic will try to do cascade testing to identify other family members affected.

The NICE FHc guideline (NICE 2008, CG71) was last updated in 2019. The following recommendations caught our eye:

- We should systematically search our records for people at high risk of FHc (cholesterol >7.5 if <30y, >9 if ≥30y).
- The Dutch Lipid Clinic Criteria can be used as an alternative to the Simon Broome Criteria to make a diagnosis of suspected FHc in primary care.

This article was updated in May 2024.

Before we start, just a reminder of who our relatives are:

- ***First-degree relatives*** *are parents, siblings, children.*
- ***Second-degree relatives*** *are grandparents/grandchildren, aunts/uncles, nieces/nephews, half siblings.*

1.1. NICE on familial hypercholesterolaemia

NICE asks us to do two things:

1. Systematically search our records for those who have elevated cholesterols but have not been identified as having familial hypercholesterolemia.
2. Identify new potential cases when filing blood results/talking to patients about their family history.

REMEMBER:

- **When measuring LDL, do 2 readings because of biological and analytical variations in levels** *(NICE gives no indication about the interval needed between readings!).*
- **If someone has a known mutation, refer regardless of LDL.**

The NICE guidance is summarised in this GEMS. Please follow the link for a PDF version of the GEMS for download/printing: Familial hypercholesterolaemia: GEMS

NICE on familial hypercholesterolaemia
1. DIAGNOSIS

NICE 2008 (updated 2019) CG71

Red Whale GEMS
Guidelines & Evidence Made Simple

NICE asks us to identify new potential cases when filing cholesterol results/taking a family history, and to systematically identify patients at high risk by searching our records for those with high cholesterol.

Identify new potential cases based on cholesterol levels/personal or family history

From history

CHD under 60y in patient or first-degree relative

From cholesterol levels (>16y)

Total cholesterol >7.5

Systematic search for those at high risk

Total cholesterol >9 if ≥30y
or
>7.5 if <30y

Why so high? NICE balanced the likelihood of having FHc against the time/cost effort involved. These levels are >99th centile for age, so highly likely to have FHc. Lower thresholds would result in more false positives and significant additional workload/costs

Suspect HOMOZYGOUS FHc if:
LDL >13 if ≥16y
LDL >11 if <16y
AND REFER
(do not use Simon Broome/Dutch criteria)

Assess likelihood of FHc: use Simon Broome criteria or Dutch Lipid Clinical Network criteria

REFER for genetic testing, management and 'cascade testing' of relatives if:
Simon Broome or Dutch Lipid Clinical Network criteria met OR HOMOzygous disease suspected

Simon Broome criteria

Total cholesterol >7.5 or LDL >4.9

(If <16y: total cholesterol >6.7 or LDL >4)

PLUS any ONE of

Tendon xanthomas (rarely appear <30y) in patient or 1st or 2nd degree relative

Family history of MI <60y in 1st degree relative <50y in 2nd degree relative

High cholesterol in 1st or 2nd degree relative
Total cholesterol >7.5 in adults
Total cholesterol >6.7 in children

OR

Confirmed mutation

Those with tendon xanthomas or confirmed mutation have definite FHc. The others have possible FHc but still need referral

Dutch Lipid Clinical Network criteria
(easier using online calculator, e.g. MDCalc)

'Premature' is <55y (males) and <60y (females)

		Score
1st degree relative with...	Premature CHD/CVD or LDL >95th centile (on chart)	1
	Tendon xanthomas/arcus OR <18y with LDL >95th centile (on chart)	2
Clinical history	Premature coronary artery disease	2
	Premature cerebral/peripheral vascular disease	1
Physical findings	Tendon xanthoma	6
	Arcus cornealis <45y	4
LDL	LDL ≥8.5	8
	LDL 6.5–8.4	5
	LDL 5.0–6.4	3
	LDL 4.0–4.9	1
DNA	Mutation in relevant genes	8

REFER if Simon Broome criteria met or Dutch Lipid score >5

Which criteria to use? NICE says either can be used. Simon Broome is easier but is based on a UK database started in the 1980s; the BMJ suggested it may not be as applicable to other populations, including Asian populations, who tend to have lower cholesterols (BMJ 2023;382:e073280).

NICE on familial hypercholesterolaemia
2. REFERRAL and MANAGEMENT
NICE 2008 (updated 2019) CG71

Red Whale
GEMS
Guidelines & Evidence Made Simple

Referral

- Referral should be offered to all with suspected FHc. This is for:
  - Initiation of treatment.
  - Assessment of personal and family risk.
  - Cascade testing to identify asymptomatic relatives.
- If there are symptoms/signs of coronary heart disease, refer to cardiologist.
- In those with suspected HOMOZYGOUS FHc:
  - Refer to specialist centre: LDL apheresis/liver transplant may be offered.

NICE doesn't recommend testing for secondary causes, but the BMJ review suggests:
- Hypothyroidism.
- Liver disease.
- Renal disease.
- Ketogenic diet.
- Medication, e.g. highly-active retroviral drugs.

Cascade testing

This involves using the index case to identify other potentially-affected family members through detailed family history and testing. It is a systematic secondary care process: a BMJ review suggested that *'Tell your relatives to get tested*' was not effective! (BMJ 2012;344:e3228) **NICE recommends:**

- **In families where a mutation has been identified**, genetic testing should be offered to those at risk (don't use LDL concentration in these individuals). If found NOT to carry the gene, manage CV risk as you would for the rest of the population (80% will have a known mutation).
- **In families where a mutation has NOT been identified,** use age- and sex-standardised LDL concentrations to diagnose family members with FHc (provided in the NICE guidance but not here because this is secondary care territory). Do not use the Simon Broome criteria in these people as it underestimates risk.
- **Consider screening all first- and second-degree relatives. Include third-degree relatives if possible** (great grandparents, great grandchildren, great aunts/uncles/niece/nephews, first cousins).

Testing children of affected adults

If one parent is affected: test offspring by age 10y (or as soon as possible after this):
- Offer DNA testing if family mutation present.
- Measure LDL concentration if no known family mutation. Repeat after puberty to exclude diagnosis.

If both parents are affected (or clinical signs in child): test by age 5y (or as soon as possible after this) by measuring LDL concentration. If LDL >11, consider diagnosis of FHc and manage appropriately.

Management

- **Aim is to reduce LDL by more than 50% from pretreatment levels.**
- All the usual lifestyle advice should be offered (smoking, diet, activity, weight management, alcohol).
- Never use a risk estimator (e.g. QRISK3) to assess risk: these tools will significantly underestimate risk!
- Statins are first line in adults and children. Ezetimibe may be considered alongside statins in those with FHc (or as monotherapy if statins not tolerated/contraindicated) (NICE 2016, TA385). Treatment is for life.
- PCSK-9 inhibitors may be initiated by specialist if NICE criteria met (TA393, TA394 (2016), TA733 (2021)).

	Evolocumab or alirocumab	Inclisiran
In those WITHOUT CVD	LDL persistently >5mmol/l	Research trials only
In those WITH CVD	LDL persistently >3.5mmol/l	LDL persistently ≥2.6mmol/l

More on these drugs in the Lipids and statins article.

Females: NICE says COCP not contraindicated, but it may increase CV risk so alternatives may be preferred. Statins are not recommended during pregnancy (risk of congenital malformation) or breastfeeding (but women can breastfeed on bile acid sequestrants).

In children with FHc: specialist will offer statins by the age of 10y or at the earliest opportunity thereafter.

Annual review

- Check smoking status (NICE doesn't mention other CV risks, e.g. BP/lifestyle, but logical to include!).
- Check LDL levels, and review medication side-effects and compliance.
- Review progress of cascade testing and update family history (new CHD events, etc.).
- Look for symptoms/signs of CHD (consider an ECG).

1.2. Is the presence of xanthelasma relevant?

Only 50% of those with xanthelasma (yellowish deposits in the skin around the eyes) have a lipid disorder. The other common causes are type 2 diabetes, hypothyroidism, diet, excess alcohol intake (J Am Acad Dermatol 1994;30:236, Clin Cosmet Investig Dermatol 2018;11:1).

1.3. What if people don't meet the criteria?

Clearly, some people who have dyslipidaemia will not meet the criteria for FHc, for example those with hypertriglyceridaemia. Although the NICE guidelines do not offer any advice on the management of these individuals, it would seem sensible to refer them too – they may have another lipid disorder.

1.4. Does treating those with FHc make a difference?

Yes!

Obviously, it would be impossible to do an RCT allocating some to statins and others to placebo, but this study was able to look at patients who started treatment immediately compared with those in whom there was a delay in initiating treatment. The study involved over 2000 patients in lipid clinics diagnosed with FHc before 1990 (when simvastatin became available in the Netherlands, where this study took place). Of these, 66% had a mean delay in starting therapy of 4.3y. The two groups were slightly different in other ways – those who received immediate statins were more likely to be older (by 3.5y), have higher LDLs and total cholesterols, and lower HDLs, and be hypertensive. Mean follow-up was 8.5y (BMJ 2008;337:a2423).

- For MIs, risk reduction was 76% in the early treatment group compared with the delayed treatment group (hazard ratio 0.24, CI 0.18–0.3).
- **Risk of MI in the early treatment group was similar to that of the normal population.**
- Average statin dose was significantly lower than that currently recommended for FHc (mean dose 33mg simvastatin), but the impact was nevertheless impressive. 85% did not have LDLs reduced by 50% from baseline, the current recommendation – although mean reduction of LDL was close at 44%.

What does this mean in practice?

- **This study confirms that early treatment reduces risk of MI significantly – almost to population risk.**
- **The editorial encourages us to aim to reduce LDL by 50%, as suggested by NICE.**

What about treating children?

A 20-year follow-up of 200+ children with familial hypercholesterolaemia and their siblings showed that, with treatment, there was a dramatically lower rate of CV events and deaths compared with their parents at a similar age (NEJM 2019;381:1547).

At age 39y, for those who had been treated since childhood:

- **There was a 1% risk of CV events compared with 26% in their parents at the same age.**
- **CV mortality rates were 0% vs. 7% in their parents.**

- **This was on a background average fall in LDL of 32%.**

Great news and a reminder of why it is so important to cascade test and identify affected families early.

Familial hypercholesterolaemia

- Consider the diagnosis of FHc in anyone with a total cholesterol of >7.5, and then assess them against the Simon Broome or Dutch Lipid Clinic criteria. Refer if appropriate.
- Systematically search for any patients meeting the criteria below, and assess them against the Simon Broome/Dutch Lipid Clinic criteria.
    - <30y with a cholesterol >7.5 or
    - ≥30y with a cholesterol >9.
- Refer anyone with suspected homozygous disease (≥16y with LDL >13 or <16y with LDL >11).
- Aim for a 50% reduction in LDL on treatment.
- Cascade testing is required, including testing any children who may be affected. DNA testing should be used when a family mutation is known.
- Don't use CV risk calculators as they significantly underestimate CV risk.
- Offer specialist referral to all for management and cascade testing.
- Remember, early treatment significantly reduces the risk of having an MI.

Run a search to systematically identify any patients <30y with a cholesterol >7.5 or ≥30y with a cholesterol >9, as NICE suggests. These people need assessing against the Simon Broome/Dutch Lipid Clinic criteria.
You could also do a broader search looking for anyone with a cholesterol >7.5, and see whether they have had an LDL measurement of >4.9 or any assessment for FHc.

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