FAMILIAL HYPERCHOLESTEROLAEMIA (FH)

The NICE guideline on familial hypercholesterolaemia (FH) was updated in October 2019, and it has some significant implications for General Practice. The original guideline was published in 2008 with the aim of identifying individuals and families with FH in order to get them appropriately treated and to get family members tested for the FH gene. With improvements in diagnostic testing, further data on high-intensity statin therapy, and more safety data on the use of statins in children and young people, NICE have updated their guideline with a 'push' to identify more people with FH. **We have a crucial role to play in helping to identify potential FH cases**, making appropriate referrals, and checking these patients are treated with high-intensity statins. The recent European lipid guideline 2019 also has implications for people with FH, by suggesting much more aggressive lipid targets, with increasing use of the PCSK9 inhibitors if required (see also our lipid and statin chapter).

► *What is FH?*

FH is an inherited genetic defect causing high cholesterol levels and early atherosclerotic disease, leading to premature coronary artery disease. It is an autosomal dominant gene and is **more common than we think** estimated to have a prevalence of between 1:250 and 1:500, equating to 130,000-260,000 cases in the UK, many of which are undiagnosed. Heterozygous FH leads to a greater than 50% risk of coronary heart disease in men by the age of 50 years and at least 30% in women by the age of 60 years. Homozygous disease is rare and often presents in childhood.

► *Why is FH important for General Practice?*

Is this not just for specialists? Well yes, and no. Yes, the testing for FH and most of the management is likely to be undertaken by specialists, but **we are the crucial cog in the pathway to identify these patients and families and refer them** as highlighted in the updated NICE guidance. Based on primary care data from Medway, a practice of 10,000 patients would expect to have ~30 patients with FH, many of whom are undiagnosed.

► *The good news*

Whilst the outcomes of untreated FH are very poor, the good news is that treatment with statins can give patients with FH dramatic improvements. A landmark study published in 2008 (BMJ 2008;337:a2423) found that treating FH, even with modest statin doses, in patients >55 **improved life expectancy to near normal population levels**.

► *So what has changed in this guideline?*

Whereas much of the guidance on testing and treatment is similar, the key change for us in General Practice is to start systematically identifying individuals and families with possible FH and get them referred for genetic cascade testing. It is recommended 1st, 2nd, and where possible 3rd-degree relatives should be offered cascade testing. The guideline recommends that we:

- **Systematically search primary care records for people:**
  - <30 years old with total cholesterol>7.5mmol/l and ≥ 30 years old with total cholesterol >9.0 mmol/l
  - With a family history of premature coronary heart disease (event <60 years old in 1st-degree relative) whose total cholesterol is unknown, and offer to measure their cholesterol
- We then need to use the **Simon Broome criteria or Dutch Lipid Clinical Network criteria** to identify potential cases and refer (see below KISS)
- Importantly **we should NOT use standard CVD risk assessment tools** e.g. QRISK as these SIGNIFICANTLY underestimate risk in people with suspected FH

► *What treatment options are available?* NICE CG71 Oct 2019 SIGN 149 2017 European guideline 2019

Whilst the treatment for people with FH may be delivered by specialists it's worth being aware of the treatment options available, as in some areas once the diagnosis of FH is made initial prescribing may fall on the GP. The range of options has increased over the last few years.

- **High-dose and high-intensity statins should remain the mainstay of treatment for people with FH** - we have good evidence they both reduce lipid levels and improve CVD outcomes (see evidence above); however, we know some may not tolerate statins, or may not reach their target lipid levels on statins, so others options include:
- **Ezetimibe, ideally as an add-on to statin treatment** (but can be used as monotherapy if statins are not tolerated or contraindicated) is recommended as the next step of treatment by both NICE, SIGN and the European guidelines.
- If patients **do not reach their target (see below) with statins +/- ezetimibe we should refer them** (if not already done so) to a specialist with expertise with FH.
- **PCSK9 inhibitors** are recommended in both the European guidelines, and by SIGN and NICE if patients with FH have not reached their lipid targets with statins +/- ezetimibe, but they will need to be prescribed by specialists. **PCSK9 inhibitors are monoclonal antibodies** that inhibits PCSK9, an enzyme involved in down-regulation of LDL receptors. Thus they increase receptor density and lowers low-density lipoprotein cholesterol (LDL-C). They are given by sub-cut injections every 2 or 4 weeks and are extremely expensive. The 2 recommended by NICE are:
  - Evolocumab - TA394
  - Alirocumab - TA393
- **Bempedoid acid** has been recently approved by NICE in April 2021 (TA694), and although it is unlikely to be on our primary care prescribing formularies it will be available for specialist initiation. Bempedoic acid is now an option for people with familial or non-familial hypercholesterolaemia or mixed dyslipidaemia, in combination with ezetimibe (as separate tablets or fixed-dose combination) for those in whom statins are contraindicated or not tolerated AND whom don't reach LDL target with stand-alone ezetimibe. There is no direct comparison data between bempedoic acid and the PCSK9 inhibitors, but indirect comparisons suggest it is not as effective as either alirocumab or evolocumab, and although not cheap at ~£55/month it is considerably cheaper than the eye-waveringly expensive PCSK9 inhibitors (~£340/month to >£1000/month).

► *Treatment targets?*

- NICE recommend aiming for a reduction in baseline LDL of >50%.
- The more recent European guidelines make more stringent recommendations by recommending a reduction in baseline LDL of >50% AND an LDL goal of <1.8 mmol/L, with a lower LDL goal of <1.4 mmol/L if they have confirmed CVD or another major risk factor.

KISS: Familial Hypercholesterolaemia (FH) NICE guideline 2019

Case finding

- **Suspect FH in adults with:**
  - Total cholesterol > 7.5 mmol/l and/or
  - Personal or family history of premature CHD (event <60 in an index case or 1st-degree relative).
- **Systematically search primary care records for people:**
  - <30 with total cholesterol>7.5 mmol/l.
  - ≥30 with total cholesterol >9.0 mmol/l.
  - With personal or family history of premature CHD (event <60 in an index case or 1st-degree relative) whose total cholesterol is unknown, and offer to measure it.

Diagnosis

- Exclude secondary causes of hypercholesterolaemia and do 2 LDL measurements (expert opinion in CKS FH suggests tests should be fasting but NICE does not specify).
- **Do NOT use standard CVD risk estimation tools** e.g. QRISK.
- Use either the Simon Broome criteria or Dutch Lipid Clinical Network (DLCN) criteria:
- **Simon Broome criteria** (and click here for DLCN criteria):
  - **Definite FH:**
    - A) Total chol > 6.7 mmol/l or LDL > 4.0 mmol/l in a child < 16 years or total chol>7.5 mmol/l or LDL > 4.9 mmol/l in an adult, PLUS
    - B) Tendon xanthomas in patient, or in 1st-degree relative (parent, sibling, child), or in 2nd-degree relative (grandparent, uncle, aunt).
  - **Possible FH:**
    - As above for A) PLUS ONE OF C) OR D):
    - C) Family history of MI <50 in 2nd-degree relative or <60 in 1st-degree relative
    - D) Family history of raised cholesterol >7.5 mmol/l in adult 1st or 2nd-degree relative or > 6.7 mmol/l in child or sibling under 16.

Referral to specialist FH service for DNA testing

- If either possible or definite FH on Simon Broome criteria or DLCN score >5.
- Genetic cascade testing should be offered to 1st, 2nd and if possible 3rd-degree relatives.

Treatment

- Although drug therapy is crucial, relevant lifestyle changes are also vital.
- **High intensity statin with NICE recommending >50% reduction in baseline LDL +/- Ezetimibe** as an option if statins are contraindicated or not tolerated, or as an add-on to statins if target LDL not reached with a maximum tolerated statin dose.
- In addition 2019 European lipid guideline advises LDL goal of <1.8mmol/L, with lower LDL goal <1.4 mmol/L if they have confirmed CVD or another major risk factor.
- **Refer to a specialist with expertise in FH:**
  - If target LDL not reached with statin +/- ezetimibe consider PCSK9 inhibitors (NICE TA393, TA394) or bempedoic acid (NICE TA 694).
  - If established CHD, family history of premature CHD or ≥2 other CVD risk factors.
  - All children - they should be offered statins by age 10 or as soon after as possible.
- **Patient information** can be found on the British Heart Foundation website