

# Medicines Optimisation Update

## Other Lipid modifying drugs

### What this includes:

Number of prescription items for bile acid sequestrants, fibrates, nicotinic acid and Omega-3 fatty acid compounds (BNF 2.12 sub-set) as a percentage of total items for BNF 2.12.

### Identifying the problem:

NICE Guidance CG71 states: When deciding on lipid modification therapy for the prevention of cardiovascular disease (CVD), drugs are preferred for which there is evidence in clinical trials of a beneficial effect on CVD morbidity and mortality. Choice focuses on proven outcomes and not simply lowering cholesterol levels.

### Background:

Statins are the key evidence based lipid modification treatment for both primary and secondary prevention. The Cholesterol Treatment Trialist meta-analysis showed that overall each 1mmol/l reduction in LDL-C (low density lipoprotein cholesterol) resulted in 22% reduction in the risk of CVD. Atorvastatin 20mg typically produces a reduction in LDL-C of 43%. **For a person with an LDL-C of 5mmol/l, that is an expected decrease of 2.15mmol/l reduction and a 40% reduction in the risk of CVD.**

**Patient informed decision making:** Using the online QRISK2 tool provides helpful ,patient-specific information, which helps people see their 10 year CVD risk and the impact a statin (and other modifiable risks) will have on risk reduction. NICE have provided tables of numbers needed to treat for statins (see below).

### NICE (CG71) "Do Not Do" Recommendations:

- Do not routinely offer fibrates
- Do not offer omega-3 fatty acid
- Do not offer a bile acid sequestrant (anion exchange resin) to any of the following:
  - people who are being treated for primary prevention
  - people who are being treated for secondary prevention
  - people with CKD, people with type 1 diabetes
  - people with type 2 diabetes

Condition (subpopulation)	Drug	Comparison	Outcome	"Number needed to treat" per year (95% CI)
Cardiovascular disease (secondary prevention)	Statins	Placebo	CV mortality	Need to treat 239 people for 1 year to prevent one cardiovascular death.
Cardiovascular disease (primary prevention)				Need to treat 1949 people for 1 year to prevent one cardiovascular death.

### Actions:

- **Bile acid sequestrants:** Are no longer indicated for the treatment of primary or secondary prevention of heart disease. Note: colesvelam and colestipol are **ONLY** licensed for lipid modification. All patients should be identified and their lipid modification treatment reviewed in the light of this guidance. Cholestyramine has other licensed indications.
- **Omega-3** should not be prescribed for the treatment and prevention of cardiovascular disease. All patients should be identified and their lipid modification treatment reviewed in the light of this guidance.
- **Fibrates:** In addition to the recommendation above, Cochrane meta-analysis of all fibrate trials failed to identify any clinical benefit from prescribing or co-prescribing a fibrate. Studies also failed to any clinical benefit that reductions in triglyceride levels by fibrates will improve patient outcomes and experience; they concluded that more research is required. If however, after due consideration of the above, a fibrate is still considered to be indicated, prescribe a fibrate with the lowest acquisition cost (see page 2). The ACCORD lipid trial involved 5,518 participants and researchers found that, overall, the combination therapy was safe, but it did not lower LDL-C levels or the risk of heart attack, stroke, or death from cardiovascular disease any further.

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**Triglycerides:** Raised triglycerides were the main reason for prescribing fibrates in the past. NICE CG 181 states: In people with a triglyceride concentration between 10 and 20 mmol/litre:

- Repeat the triglyceride measurement with a fasting test (after an interval of 5 days, but within 2 weeks).
- Review for potential secondary causes of hyperlipidaemia.
- Seek specialist advice if the triglyceride concentration remains above 10 mmol/litre.

Triglycerides can be raised because of: diabetes, smoking, inactivity, obesity, high carbohydrate diet, thyroid disorders and raised alcohol consumption (all themselves major CVD risk factors). An elevated triglyceride level may, in some cases, be a marker for cardiovascular disease rather than a causal factor. Blood test needs to be fasting as non-fasting triglyceride levels can be 5-10 times higher.

Guidance is to treat the cause, not the triglycerides: e.g. thyroid, diabetes, alcohol, encourage weight loss, exercise and smoking cessation. However, fibrates are the first-line treatment in patients with hypertriglyceridemia *who are at risk of pancreatitis*, defined as (i) Severe hypertriglyceridemia (11.3 to 22.6 mmol/litre) or (ii) Very severe (>22.6 mmol/litre)

Bezafibrate and fenofibrate are safe and cost effective options, at approximately £100/year, whilst ciprofibrate costs over £1,000/year. When prescribed with a statin fenofibrate is the safest option. Gemfibrozil should never be co-prescribed with a statin.

**Familial hypercholesterolemia (FH)** NICE CG 71: states: Healthcare professionals should consider prescribing a high-intensity statin to achieve a recommended reduction in LDL-C concentration of greater than 50% from baseline (that is, LDL-C concentration before treatment).

**Ezetimibe:** IMPROVE-IT Trial: In contrast to fibrates and bile acids, ezetimibe *was* associated with reductions in LDL-C levels (23% reduction), but more importantly it *did* improve cardiovascular outcomes prompting NICE CG 181 to state: *Statins are unsuitable for some people, for example if side effects are too troublesome. If statins are not suitable for you, you may be offered an alternative drug called ezetimibe.* For patients who fail to reduce their cholesterol despite being on an optimised or maximum tolerated statin clinicians may wish to add ezetimibe (e.g. FH).

**Lipid Modification should focus on evidence based treatments that save lives and reduce CVD events.**

### Resources:

- National Institute of Health and Care Excellence: Multi-morbidity: clinical assessment and management. September 2016: <https://www.nice.org.uk/Guidance/ng56/resources>
- QRISK2 tool: <https://www.qrisk.org/>

### References

- Familial hypercholesterolaemia: identification and management. Clinical guideline [CG71]. Updated July 2016. Available at: <https://www.nice.org.uk/guidance/cg71>
- Cholesterol, Not just cardiovascular risk, Is important in deciding who should receive a statin. Eur Heart J. 2015; 36(43): 2975-83: <http://eurheartj.oxfordjournals.org/cgi/pmidlookup?view=long&pmid=26242714>
- Cholesterol Treatment Trialists (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet 2010;376:1670–1681. [http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(14\)61368-4/abstract](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(14)61368-4/abstract)
- NICE CG 181 – <https://www.nice.org.uk/guidance/CG181>