Hyperlipidaemia

COOPER, A., O'FLYNN, N. ON BEHALF OF THE GUIDELINE DEVELOPMENT GROUP (2008): Risk assessment and lipid modification for primary and secondary prevention of cardiovascular disease: summary of NICE guidance. *BMJ* **336**:1246-8.

BHATNAGAR, D. ET AL. (2008): Hypercholesterolaemia and its management. *BMJ* **337**:503-8.

Hypercholesterolaemia
- Major cause of atherosclerosis
- Whilst there are other risk factors, hypercholesterolaemia is the permissive factor that allows other risk factors to operate

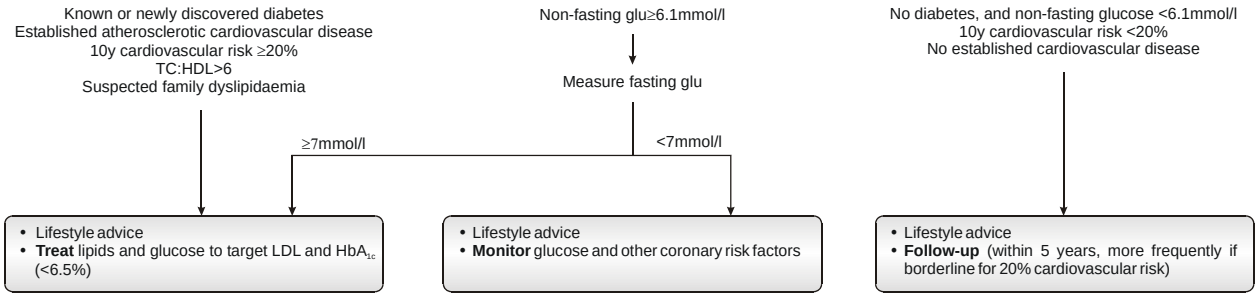
Hx
- FH
- Occupational Hx
- Smoking, EtOH, diet

Ex
- BP
- Weight, height, waist circumference
- Xanthomata

Ix
- Blood sample for lipid profile and glu taken after at least 10h of fasting
- Also check LFT, CK, crea and urine dipstick for protein before starting cholesterol-lowering Rx

Indications for treatment

Summary of Joint British Societies guidelines



NB
- Risk assessment should be systematic rather than opportunistic
- Risk levels are financially constrained and set pragmatically
- Framingham risk equation underestimates risk for
  - Blacks or Asians
  - Patients with dyslipidaemias, or a strong FH of premature IHD
  - Patients with chronic renal impairment
  - Premenopausal women

Treatment options
- Correct any secondary causes
- Dietary modification
- Drug treatment (usually statin)

Treatment comments[1]
- How soon after starting drug treatment should lipids be rechecked?
  - 8 (±4) weeks after starting Rx or adjusting dose
- How often should lipids be rechecked once target reached?

[1] STUART, W. & SMELLIE, A. (2006): Testing pitfalls and summary of guidance in lipid management. *BMJ* **333**:83-6.

- Annually

Statins

Mechanism of action

- Competitive inhibitors of HMG (hydroxymethyl glutaryl)-CoA reductase, the final step in cholesterol synthesis
- Upregulate LDL-R
- Hence ↓LDL ↑HDL; minimal effect on triglycerides
- May also influence the process of atherosclerosis directly

Evidence base

>>5 placebo-controlled trials show efficacy in primary and secondary prevention

- WOSCOPS, AFCAPS/TexCAPS (lovastatin): primary prevention
- 4S, MRC HPS, SPARCL: secondary prevention

For each 1mmol/l decrease in LDL, coronary and stroke events fall by ca. 21%, accompanied by a decrease in all cause mortality. This linear decrease extends down to current LDL targets of 2mmol/l.[2]

Prescribing a statin

Which statin?

Efficacy is a class effect – no convincing evidence to support any particular agent.

Points

- NICE recommends simvastatin 40mg as first line for primary and secondary prevention
- Different potency – equivalent doses :
  - Pravastatin, fluvastatin 80mg
  - Simvastatin, lovastatin 40mg
  - Atorvastatin 10mg
  - Rosuvastatin 5mg
- Short $t_{1/2}$ (~2h, except atorvastatin at 14h) but effective with once daily administration
- 'Old' statins coming off license → cheaper (e.g. simvastatin patent expired 2003)

Also…

- Give at night
  - Block endogenous cholesterol synthesis, which mostly occurs overnight → better efficacy
  - Applies mostly to simvastatin/pravastatin; can give atorvastatin anytime due to long duration of action
- Ask patient to report muscle pain, tenderness or weakness; if asymptomatic, CK monitoring is not indicated
- Dose
  - Primary prevention: no further monitoring of lipids, unless clinical judgement or patient preference require it (NICE)
  - Secondary prevention: up-titrate to reach target
- Re-check lipids 6w after dose adjustment

Targets

- HT guidelines/JBS2 guidelines: TC<4.0/25%, LDL<2.0/30%

What if targets are not achieved on maximum tolerated dose? Give a combination, usually under specialist supervision.

- Add a resin: although rarely used alone because of poor tolerance, statin + resin combinations can be very effective at reducing LDL by >50%
- Add a fibrate: used alone they are very effective at lowering triglyceride, but can also lower LDL. Statin + fibrate combinations have increased risk of myopathy.
- Add nicotinic acid: combination handicapped by adverse effects of NA.

Adverse effects

Common

[2] CHOLESTEROL TREATMENT TRIALISTS' (CTT) COLLABORATORS (2005): Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* **366**:1267-78.

- Mild GI upset
- Tiredness
- CNS disturbance (e.g. insomnia, vivid dreams) – only with lipid-soluble agents, e.g. simvastatin

Rare

- Myopathy up to rhabdomyolysis (1:100,000; more likely if e.g. lipophilic statin[3], high dose, renal impairment, untreated hypothyroidism or fibrate co-therapy; stop if CK >10-fold ULN, or intolerable symptoms with lesser CK elevation)[4]
    - Inhibition of HMG-CoA reductase reduces mevalonate production, an intermediate required for both cholesterol and ubiquinone. Lack of ubiquinone may cause the mitochondrial respiratory chain to fail, causing myopathy.
    - Do not use with other statins or fibrates
    - Ezetimibe might be appropriate
- Deranged LFTs up to hepatitis (usually deranged transaminases – stop if >3-fold ULN; check LFT before, after 1-3m and at 1y)

Interactions

P_{450} metabolism of atorvastatin, fluvastatin, simvastatin – usual interactions; may enhance effect of warfarin
Pravastatin is cleared by sulfation and may be useful where above interactions are problematic

Anion-exchange resins

E.g. cholestyramine

Mechanism of action

- Bind bile acids and prevent their reabsorption (enterohepatic circulation), encouraging the liver to convert cholesterol into bile acids
- Increased hepatic LDL-R expression
- May aggravate hypertriglyceridaemia

Adverse effects

- Constipation, flatulence, abdominal pain

Interactions

- Impaired absorption of fat-soluble vitamins and polar drugs (e.g. ***statins***, thyroxine, digoxin, warfarin)
    - Give other drugs at least 1h before or 4-6h after

Ezetimibe

Mechanism of action

- Inhibits intestinal cholesterol transporter
- Metabolised to glucuronide
    - 400x higher potency
    - Prolonged action by enterohepatic cycling
- Unlike resin, no ↑hypertriglyceridaemia

Indications

- Adjunct in primary and homozygous familial hypercholesterolaemia
- Adjunct in homozygous sitosterolaemia

No major adverse effects or drug interactions

Contraindications

- Breastfeeding

[3] Relatively lipophilic: simvastatin, atorvastatin, lovastatin; relatively hydrophilic: pravastatin, rosuvastatin, fluvastatin

[4] SATHASIVAM, S. & LECKY, B. (2008): Statin-induced myopathy. *BMJ* **337**:1159-65.

Fibrates

E.g. bezafibrate, ciprofibrate, fenofibrate

Mechanism of action

- PPARα ligands (also see thiazolidinediones/glitazones in diabetes)
- ↑fatty acid oxidation in liver and muscle, ↑lipolysis in liver
- Mainly ↓triglycerides

NB also ↑glu tolerance and uricosuric

Adverse effects

- GI (e.g. nausea, gastric pain)
- Gallstones
- Myositis, esp. if also on statin
- Pruritus
- ↑creatinine

Contraindications

- Severe hepatic or renal impairment
- Hypoalbuminaemia
- Pregnancy, breastfeeding

Interactions

- Potentiate warfarin

Nicotinic acid

Mechanism of action

- Lowers both cholesterol and triglyceride by inhibiting synthesis
- ↑HDL by 30% (highest of all agents)

Adverse effects

Limit its use

- Vasodilatation (prostaglandin mediated; less with acipimox)
- Pruritus
- Acanthosis nigricans
- ↑glu, ↑uric acid

May be used in combination to avoid high doses.

Fish oils

Two commercial preparations now available.

Review article summary[5]

- Humans lack enzyme to convert the abundant omega 6- into omega 3 fatty acids
- Omega 3 fatty acids protect against CHD - mechanisms
    - Not fully understood but include: anti-arrhythmic, anti-thrombotic, anti-atherosclerotic/plaque-stabilising, anti-inflammatory, anti-vasospasm, triglyceride lowering
    - Unravelling them may lead to the identification of novel therapeutic targets
- Secondary prevention: established trial evidence – give 1g/day, but note trial weaknesses: not in conjunction with current treatment (DART)/not double blind (GISSI-Prevenzione)/not Western (Indian)
- Primary prevention: epidemiological association – encourage eating fish twice a week; for trial, large groups would be required, and there might be an unsustainable increase in demand
- Almost no adverse effects (mercury contamination can lessen cardioprotective effects, halitosis)
- Future: further trials – give what when

[5] JEHANGIR ET AL. (2004): Omega 3 fatty acids and cardiovascular disease – fishing for a natural treatment. *BMJ* **328**:30-5.

Plant sterols

Margarines and drinks containing plant sterols or stanols rather than saturated fat can decrease plasma cholesterol by up to 10%[6]

[6] KATAN M.J. ET AL. (2003): Efficacy and safety of plant stanols and sterols in the management of blood cholesterol levels. *Mayo Clin Proc* **78**:965-78.