Lipid Update – NICE Guidance, IMPROVE-IT and some practical lipid problems

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Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease

NICE clinical guideline 181

Issued: July 2014 last modified: September 2014

http://www.nice.org.uk/guidance/cg181
Downloaded 29th September 2014
Cardiovascular disease (CVD) is one of the most significant causes of death in England and Wales, accounting for almost one third of deaths.

The epidemic of CVD is caused by the process of atherosclerosis.

Atherosclerosis is an age-dependent process affecting blood vessel (vascular) walls driven by environmental and genetic risk factors in which lipid (including cholesterol)-laden macrophages play a key role.

CVD has significant cost implications and was estimated to cost the NHS in England almost £6940 million in 2003, rising to £7880 million in 2010.
Identifying and assessing CVD risk

- Primary prevention in primary care - use a systematic strategy to identify people likely to be at high risk
- Prioritise full formal risk assessment if the estimated 10-year risk of CVD is >10%
- People older than 40 years should have their estimate of CVD risk reviewed on an ongoing basis
- Use QRISK2 risk assessment tool
  - For primary prevention of CVD in people up to and including age 84yrs
  - To assess CVD risk in type 2 diabetes use
  - QRISK2 - changes compared to QRISK
    http://www.gpnotebook.co.uk/simplepage.cfm?ID=x20150114123718862850
- Do not use a risk assessment in
  - Type 1 diabetes
  - People with eGFR < 60mi/min/1.73m³ and/or albuminuria
    - be aware of new CKD classification based on eGFR and albuminuria
    - http://www.gpnotebook.co.uk/simplepage.cfm?ID=x20140903131721906919
  - People with pre-existing CVD
  - for people who are at high risk of developing CVD because of familial hypercholesterolaemia (FH) or other inherited disorders of lipid metabolism

Identifying and assessing CVD risk

- Recognise that standard CVD risk scores will underestimate risk in people who have additional risk because of underlying medical conditions or treatments.

- These groups include: people treated for HIV
  - people with serious mental health problems
  - people taking medicines that can cause dyslipidaemia such as antipsychotic medication, corticosteroids or immunosuppressant drugs
  - people with autoimmune disorders such as systemic lupus erythematosus, and other systemic inflammatory disorders
  - recognise that CVD risk will be underestimated in people who are already taking antihypertensive or lipid modification therapy, or who have recently stopped smoking. Use clinical judgement to decide on further treatment of risk factors in people who are below the CVD risk threshold for treatment
  - Obesity
    - [http://www.gpnotebook.co.uk/simplepage.cfm?ID=x20090815154002037722](http://www.gpnotebook.co.uk/simplepage.cfm?ID=x20090815154002037722)
    - aged > 84y
    - [http://www.gpnotebook.co.uk/simplepage.cfm?ID=-596967351](http://www.gpnotebook.co.uk/simplepage.cfm?ID=-596967351)

cardiovascular calculator and how to use one
[http://www.gpnotebook.co.uk/simplepage.cfm?ID=x20150114123718862850](http://www.gpnotebook.co.uk/simplepage.cfm?ID=x20150114123718862850)
Lipid Modification therapy

• Measure both **total cholesterol** (TC) and **high-density lipoprotein cholesterol** (HDL-C)

• Before starting therapy for primary prevention of CVD take at least 1 lipid sample to measure full lipid profile
  – TC, HDL-C, non-HDL-C and triglyceride
  – Non-fasting sample

• Exclude secondary causes
  – Excess alcohol, uncontrolled diabetes, hypothyroidism, liver disease and nephrotic syndrome

• Consider possibility of familial hypercholesterolaemia
  – TC > 7.5mmol/L
  – Family history of premature coronary heart disease

**LDL-C vs non-HDL-C**

- **LDL-C**
  - Calculated using The Friedewald equation
  - Requires a fasting sample and triglycerides below 4.5 mmol/l
  - Derived from a small number of patients (130) with very few patients with diabetes (<30)
  - Large database analysis revealed excess variance and bias in the calculation of LDL-C such that
    a complicated table of correction factors would have to be applied by clinical laboratories\(^1\)
  - The formula is limited in its utility at low LDL-C levels as seen with high-intensity statin treatment\(^2\)
  - The use of direct LDL-C measurement is limited by cost and availability in the NHS
  - European guidelines use LDL targets based on risk – very high risk e.g. Established CVD has
    LDL target < 1.8 mmol/l; diabetes without end organ damage or CVD risk factors < 2.5 mmol/l
  - LDL used as end points in major lipid trials

- **Non-HDL-C**
  - Difference between TC and HDL-C
  - Superior predictive value of non-HDL-C on CV events\(^3\)
  - Does not require a fasting blood sample.
  - The GDG deemed the use of non-HDL-C preferable to calculated or measured LDL-C

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GDG – Guideline Development Group
Therapy

• Be aware that when deciding on lipid modification therapy for the prevention of CVD, drugs are preferred for which there is evidence in clinical trials of a beneficial effect on CVD morbidity and mortality.

• When a decision is made to prescribe a statin use a statin of high intensity† and low acquisition cost.

† See table on next slide.
# Grouping of statins

<table>
<thead>
<tr>
<th>Dose (mg/day)</th>
<th>5</th>
<th>10</th>
<th>20</th>
<th>40</th>
<th>80</th>
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<tbody>
<tr>
<td>Fluvastatin</td>
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<td>-</td>
<td>21%</td>
<td>27%</td>
<td>33%</td>
</tr>
<tr>
<td>Pravastatin</td>
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<td>24%</td>
<td>29%</td>
<td>-</td>
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<tr>
<td>Simvastatin</td>
<td>-</td>
<td>27%</td>
<td>32%</td>
<td>37%</td>
<td>42%*</td>
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<tr>
<td>Atorvastatin</td>
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<td>37%</td>
<td>43%</td>
<td>49%</td>
<td>55%</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>38%</td>
<td>43%</td>
<td>48%</td>
<td>53%</td>
<td>-</td>
</tr>
</tbody>
</table>

* MHRA advice: there is an increased risk of myopathy associated with high-dose (80mg) simvastatin. The 80mg dose should be considered only in patients with severe hypercholesterolaemia and high risk of cardiovascular complications who have not achieved their treatment goals on lower doses, when benefits are expected to outweigh the potential risks.

- Low intensity; 20%-30%
- Medium intensity; 31%-40%
- High intensity; above 40%

Adapted from NICE clinical guidance 181. Appendix A: Grouping of statins.  
http://www.nice.org.uk/guidance/cg181/resources. Downloaded 29th September 2014
Statin therapy: Primary Prevention

• Offer **atorvastatin 20mg** for
  – Primary prevention of CVD to people with a 10% or greater 10-year risk of developing CVD*
  – For people 85 years
  – Type 1 diabetes if
    • >40 years or
    • Have diabetes for more than 10 years or
    • Have established nephropathy or
    • Have other CVD risk factors
  – Type 2 diabetes – if 10% or greater 10-year risk of developing CVD*
  – CKD
    • Increase dose if greater than 40% reduction in non-HDL-C is not achieved and eGFR is 30ml/min/1.73 m³ or more
    • Agree a higher dose with a renal specialist if eGFR is less than 30ml/min/1.73 m³


*Estimate CVD risk using QRISK2
Statin Therapy: Secondary Prevention

• Start with atorvastatin 80mg*

• Use a lower dose if
  – Potential drug interactions
  – High risk of adverse effects
  – Patient preference

• Acute coronary syndrome – do not delay treatment
  – Take a lipid sample on admission and 3 months after treatment

*At the time of publication (July 2014), atorvastatin did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council’s “Good practice in prescribing and managing medicines and devices” for further information

Follow-up on statin treatment

• Measure TC, HDL-C, non-HDL-C on all people started on high-intensity statin

• Repeat at 3 months

• Aim for > 40% reduction in non-HDL-C

• If greater than 40% reduction in non-HDL-C is not achieved:
  – Discuss adherence and timing of dose
  – Optimise adherence to diet and lifestyle
  – Consider increasing the dose if started on less than 80mg atorvastatin

• Provide annual medication reviews

• Consider annual non-fasting blood test for non-HDL-C

• Discuss changing to high-intensity statin at medication review and agree with the person whether a change is needed

Other lipid lowering treatment

- Do not routinely offer either alone or as combination therapy:
  - Fibrates
  - Nicotinic acid
  - Bile acid sequestrants
  - Omega-3 fatty acid compounds
Ezetimibe

• Consider use of ezetimibe treatment in line with NICE technology appraisal guidance (TAG) 132

• The population groups covered by the ezetimibe NICE TAG 132 are:

  – adults with primary (heterozygous familial and non-familial) hypercholesterolaemia who are candidates for treatment with statins on the basis of their CVD status or risk and

  – whose condition is not appropriately controlled with a statin alone or

  – in whom a statin is considered inappropriate or is not tolerated

The term “not appropriately controlled with a statin alone” is defined as failure to achieve a target lipid level that is appropriate for a particular group or individual. It also assumes that statin therapy is optimised and tolerated.


IMPproved Reduction of Outcomes: Vytorin Efficacy International Trial

A Multicenter, Double-Blind, Randomized Study to Establish the Clinical Benefit and Safety of Vytorin (Ezetimibe/Simvastatin Tablet) vs Simvastatin Monotherapy in High-Risk Subjects Presenting With Acute Coronary Syndrome

Presented at American Heart Association November 2014
Goals

• **IMPROVE-IT**: First large trial evaluating clinical efficacy of combination ezetimibe/simvastatin vs. simvastatin (i.e., the addition of ezetimibe to statin therapy):
  – Does lowering LDL-C with the non-statin agent ezetimibe reduce cardiac events?
  – “Is (Even) Lower (Even) Better?”
    (estimated mean LDL-C ~1.3 vs. 1.7 mmol/L)
  – Safety of ezetimibe
Patient Population

• Inclusion Criteria:
  – Hospitalization for STEMI, NSTEMI/UA < 10 days
  – Age ≥ 50 years, and ≥ 1 high-risk feature:
    • New ST chg, + troponin, DM, prior MI, PAD, cerebrovasc, prior CABG > 3 years, multivessel CAD
    – LDL-C 1.3-3.2 mmol/L (1.3-2.6 mmol/L if prior lipid-lowering Rx)

• Major Exclusion Criteria:
  – CABG for treatment of qualifying ACS
  – Current statin Rx more potent than simva 40mg
  – Creat Cl < 30mL/min, active liver disease
Primary Endpoint — ITT

Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke

HR 0.936 CI (0.887, 0.988)

p=0.016

Treatment effect 6.4%

Simva — 34.7%
2742 events

EZ/Simva — 32.7%
2572 events

NNT= 50

7-year event rates
Messages for Primary Care management of lipids

• Use of QRISK2 replaces QRISK and Framingham
• Primary prevention suggested intervention if QRISK2 ≥10%
• QRISK2 for type 2 diabetes
• Statin treatment for type 1 diabetes if criteria met
• Statin treatment if eGFR < 60
• Use of atorvastatin 20mg in primary prevention
• Use of atorvastatin 80mg in secondary prevention
• Use of statins and/or ezetimibe for cholesterol lowering
• IMPROVE-IT – lower LDL better; agent other than statin with evidence base
• Use of non-HDL cholesterol for treatment target
  – Use of 40% reduction; LDL targets in European guidance

http://www.gpnotebook.co.uk/simplepage.cfm?ID=x20090621090009398225

Interesting problems in lipid management

• 54 year old man; type 2 diabetes; metformin 1g bd; ramipril 5mg od; HbA1c 62; renal function normal; LFTs ALT 160; BMI 33; cholesterol 6.7 mmol/l; TG 5.2 mmol/l; HDL 0.8 mmol/l

  – What is significance of lipid profile
  – What is the next step in management of his lipids

  – See GPnotebook – ALT in diabetes - http://www.gpnotebook.co.uk/simplepage.cfm?ID=x20050727084644160230

Interesting problems in lipid management

- 54 year old man; BMI 28; no pmhx of note; routine blood tests; no fhx of hyperlipidaemia; no fhx of IHD

➢ Cholesterol 28 mmol/l; TG 39 mmol/l
  - What is this condition and how should it be managed
  - See GPnotebook
  - Management of high triglycerides
    [Link](http://www.gpnotebook.co.uk/simplepage.cfm?ID=1422917684&linkID=71192&cook=yes)
  - T3 [Link](http://www.gpnotebook.co.uk/simplepage.cfm?ID=x20081205121326480651)

NICE CG 181. [Link](http://www.nice.org.uk/guidance/cg181). Downloaded 29th September 2014
Interesting problems in lipid management

• 54 year old man; phx MI 2002; intolerant of statins – atorvastatin, simvastatin > myalgia but normal CK; similar side effects on ezetimibe

➢ cholesterol 6.4 mmol/l; HDL 1.2 mmol/l

See GPnotebook
– Management of statin intolerance
  – http://www.gpnotebook.co.uk/simplepage.cfm?ID=x20090520180900630520

Thank You

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