Advances in the diagnosis and management of dyslipidaemia

Yee Ping Teoh MRCP, FRCPath

Tackling the early stages of dyslipidaemia can help in the reduction of the risk of CVD. Our drug review outlines primary and secondary prevention measures and the need for patient-centred care which includes individual assessment of overall cardiovascular risk, followed by an analysis of the prescription data.

Cardiovascular disease (CVD) due to atherosclerosis of the arterial vessel wall and thrombosis is one of the primary causes of premature mortality and morbidity across Europe. The main clinical entities of this are coronary artery disease, ischaemic stroke and peripheral arterial disease. Atherosclerosis is an age-dependent process affecting vascular walls that is driven by both environmental and genetic factors; abnormal lipid metabolism (dyslipidaemia) plays a crucial role in its pathogenesis. Lipid metabolism can be disturbed in different ways, leading to changes in plasma lipoprotein concentration and role. This, when added to other cardiovascular risk factors such as hypertension, smoking, diabetes, metabolic syndrome and chronic inflammation, will predispose a person to an earlier onset of atherosclerosis. Population studies have repeatedly demonstrated a strong correlation between dyslipidaemia and earlier onset of atherosclerosis events.

Dyslipidaemia is usually asymptomatic, with the majority of patients only identified during routine screening or following further investigation after having a cardiovascular event. Generally, dyslipidaemia can be classified into primary (inherited) and secondary (acquired) causes. The three most common dyslipidaemia patterns seen in our population include (see Table 1 and Figure 1):

- predominantly hypercholesterolaemia consisting mainly of raised low-density lipoprotein (LDL).
- predominantly hypertriglyceridaemia (mainly raised triglycerides, TGs).
- mixed dyslipidaemias, which consist of raised TGs and LDL with potentially low high-density lipoprotein (HDL).

Although all three lipid patterns have known primary (monogenic) causes, the vast majority of dyslipidaemias are caused by interactions between environmental and genetic factors (polygenic). A particular atherogenic lipid triad that is relatively common in the population consists of increased very low-density lipoprotein (VLDL) manifesting as mildly raised TGs, increased small-dense LDL particles and reduced HDL.
The traditional Fredrickson classification of dyslipidaemia (types I to V), although providing information about the types of lipoprotein abnormalities observed, adds little to the clinical management of the different conditions. It is more important to exclude secondary contributory causes of dyslipidaemia, and this can be done from history taking and performing additional laboratory investigations such as thyroid stimulating hormone (TSH), renal and liver function, urine protein quantitation and HbA1c.

**Laboratory measurement of lipids**

Before commencing lipid modification therapy for CVD, it is recommended that at least one full lipid profile is measured for all patients. Most laboratories will provide analysis of either fasting (full) lipids or non-fasting lipids. A full lipid profile usually comprises of total cholesterol, TG, HDL and calculated LDL. Serum LDL is normally calculated from the Friedewald equation, although direct LDL assays may be available in some laboratories. A fasting sample is ideal (12 hour fast) for a full lipid profile, but it is not necessary in individuals where dietary chylomicron contributions remain minimal.

**Guidelines on dyslipidaemia management**

A large number of European and UK guidelines have been issued in recent years that attempt to quantify individual cardiovascular risks and provide a recommended approach to dealing with dyslipidaemia. In the last year, two significant national guidelines were published in the UK: the Joint British Societies’ Consensus Recommendations for the Prevention of Cardiovascular Disease (JBS3) in April 2014 and the NICE guideline for lipid modification (CG181) in July 2014.

One of the novel aspects of JBS3 is the availability of an individual’s ‘lifetime risk’ of cardiovascular events. This allows the inclusion of young individuals and women who may have a high lifetime risk due to the presence of other risk factors but would otherwise not have benefited from early lifestyle modifications. The JBS3 calculator provides an estimate of a person’s ‘heart age’ that is designed to communicate the long-term consequences of an individual’s lifestyle with its associated risk factors and the substantial lowering of the CVD risk obtained through early lifestyle changes. It is hoped that these individuals will modify some of their lifestyle factors early on to reduce their overall long-term CVD risks.

The management of dyslipidaemia can be divided into three groups: primary and secondary prevention, and those patients with high underlying CVD risks.

### Table 1. Classification of dyslipidaemia

<table>
<thead>
<tr>
<th>Predominantly hypercholesterolaemia</th>
<th>Elevated measured lipid parameters</th>
<th>Actual lipoprotein abnormalities</th>
<th>Monogenic condition</th>
<th>Frequency in the population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polygenic hypercholesterolaemia</td>
<td>TC + LDL +/- TG TC + LDL</td>
<td>LDL +/- VLDL</td>
<td>No</td>
<td>1:50</td>
</tr>
<tr>
<td>Familial hypercholesterolaemia,</td>
<td></td>
<td></td>
<td>Yes</td>
<td>1:500 (heterozygous)</td>
</tr>
<tr>
<td>familial defective Apo B-100 and</td>
<td></td>
<td></td>
<td></td>
<td>1:1,000,000 (homozygous)</td>
</tr>
<tr>
<td>familial increased function of PCSK9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Predominantly hypertriglyceridaemia</td>
<td>TG +/- TC TG &gt;&gt; TC</td>
<td>VLDL +/- LDL</td>
<td>No</td>
<td>1:50</td>
</tr>
<tr>
<td>Polygenic hypertriglyceridaemia</td>
<td></td>
<td></td>
<td>Yes</td>
<td>1:200</td>
</tr>
<tr>
<td>Familial hypertriglyceridaemia</td>
<td></td>
<td></td>
<td></td>
<td>1,000,000</td>
</tr>
<tr>
<td>Lipoprotein lipase and Apo C-II</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>deficiency</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Predominantly combined dyslipidaemia</td>
<td>TC+TG TC+ TG TC+TG</td>
<td>VLDL+LDL</td>
<td>No</td>
<td>1:50</td>
</tr>
<tr>
<td>Polygenic mixed dyslipidaemia</td>
<td></td>
<td>VLDL+ LDL</td>
<td>Yes</td>
<td>1:200</td>
</tr>
<tr>
<td>Familial combined hyperlipidaemia</td>
<td></td>
<td>IDL</td>
<td>Yes</td>
<td>1:100(ApoE2/E2) plus other</td>
</tr>
<tr>
<td>Remnant hyperlipidaemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TC – Total cholesterol, TG – Triglycerides, VLDL – Very Low Density Lipoprotein, LDL – Low Density Lipoprotein

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The management of dyslipidaemia can be divided into three groups: primary and secondary prevention, and those patients with high underlying CVD risks.

### Primary prevention

Primary prevention is outlined in Figure 2. NICE CG181 recommends that a systematic strategy is used to identify patients between the ages of 40 and 74 who are likely to be at high risk of CVD. Three online risk assessment calculators are currently available to perform this: QRISK2 (preferred by NICE), JBS3 and Framingham. All three will provide an estimation of an individual patient’s 10-year CVD and lifetime risks. However, the following group of individuals should be excluded from these risk assessment tools: patients with pre-existing CVD, patients with type 1 and 2 diabetes, patients with chronic kidney disease stages 3–5, and patients with suspected familial hypercholesterolaemia (FH) or other familial dyslipidaemia, as these risk tools will underestimate their CVD risk.
NICE CG181 recommends that the UK Prospective Diabetes Study (UKPDS) risk engine tool should be considered in type 2 diabetes patients instead of QRISK2. NICE also recommends that all patients with 10-year risk of 10 per cent or more for developing CVD should be offered commencement of a statin such as atorvastatin 20mg for primary prevention of CVD. In addition to this, appropriate lifestyle changes should be identified at the earliest opportunity and incorporated in the advice given. This includes advice on smoking cessation, diet, weight reduction, exercise and alcohol consumption. Hypertension, if detected and confirmed, should be treated appropriately.

Secondary prevention in patients with established vascular disease
Secondary prevention is outlined in Figure 2. Patients with established underlying atherosclerosis history (previous myocardial infarction, angina, coronary revascularisation, peripheral vascular disease, transient ischaemic attack and ischaemic stroke) are at the highest risk of a repeated vascular event. For these patients, atorvastatin 80mg is advised by NICE CG181. However, if patients are unable to tolerate this dose due to either drug interactions, side-effects or patient preference, a lower dose of atorvastatin can be used.

Patients with underlying high CVD risks
Type 2 diabetes patients with a UKPDS CV risk score of above 6 per cent will benefit from the commencement of atorvastatin 80mg. NICE recommends atorvastatin 20mg initially for all type 2 diabetes patients with UKPDS CV risk score between 4.8 and 6 per cent, all type 1 diabetes patients and patients with chronic kidney disease stages 3–5.

Patients with FH or other familial dyslipidaemic conditions associated with CVD should not have a cardiovascular risk assessment performed and should be considered for treatment as they are at high risk. Consider FH in an adult patient if their total cholesterol is >7.5mmol/L and LDL >4.9mmol/L in a setting whereby there is a family history of either premature coronary artery disease or hypercholesterolaemia. The presence of tendon xanthomas in these patients or their relatives is pathognomonic for the condition. Consider familial combined hyperlipidaemia (FCH) if there is evidence of mixed dyslipidaemia (TG >2.0mmol/L and total cholesterol >6.0mmol/L) in a setting whereby there is a strong family history of premature coronary artery disease in first-degree relatives. For this group of familial dyslipidaemia patients, again early commencement of statin treatment is advised.

Lipid-lowering therapy
It is important that the decision as to whether to start statin therapy is made after an informed consultation with the patient; taking into account the risks and benefits of statin treatments, other co-morbidity issues and patients’ preferences. Statins as a class still have by far the most amount of clinical outcome evidence for reducing cardiovascular mortality. For every 1.0mmol/L reduction in LDL, it is estimated from population studies that a person’s cardiovascular risk can be reduced by 20 per cent. Statins are generally safe, with trial evidence showing no effects on non-cardiovascular mortality or incidence with cancer. There is a small increase in the development of diabetes especially related to higher intensity statins, but the benefits of cholesterol lowering by statins will far exceed any potential CVD risk of impaired glucose tolerance associated with statin therapy. Statins are contraindicated in pregnancy.
Figure 2. Primary and secondary prevention of CVD

**Primary prevention**

- Check TFTs, U&Es, LFTs and HbA₁c to exclude secondary causes of dyslipidaemia
- Measure full lipid profile (baseline) which include total cholesterol, HDL, non-HDL, TG and LDL measurements
- Document family history of premature CVS, smoking, alcohol consumption, BP, BMI and ethnicity
- Use QRISK2 tool to assess CVD risk
- Offer atorvastatin 20mg if 10 year risk is 10% or greater
- Emphasise lifestyle modifications for all patients – diet, exercise and smoking cessation
- Check baseline CK if patients have unexplained muscle symptoms prior to commencement of statin
- Measure LFTs at 3 months and 12 months
- Review statin and consider discontinuation if AST/ALT >3x upper limit of normal
- Measure CK if muscle symptoms occur post statin commencement
- Consider stopping statin if CK >5x ULN if no other contributory causes of CK elevation are identified
- Measure total cholesterol, HDL, non-HDL cholesterol after 3 months of treatment
- Aim for >40% reduction in non-HDL cholesterol by further atorvastatin titration
- Check statin adherence and lifestyle modifications at review
- If dose of statin is not tolerated, consider a low dose or an alternative statin such as pravastatin

**Secondary prevention**

- Establish baseline measurements for full lipid profile (TC, HDL, non-HDL cholesterol, LDL and TG) and LFTs
- Obtain baseline CK in patients who have unexplained muscle symptoms prior to commencement of statin
- Offer atorvastatin 80mg for the majority of these patients
- Do not delay statin treatment to manage other CVS risk factors
- Consider a lower dose of atorvastatin if there is potential drug interactions or adverse side-effects associated with a higher dose
- Emphasise lifestyle modifications, which include stopping smoking, healthy diet, weight reduction, increased physical activity and limiting alcohol intake
- Measure LFTs at 3 months and 12 months interval
- Review statin and consider discontinuation if AST/ALT >3x ULN
- Measure CK if muscle symptoms occur post statin commencement
- Only consider stopping statin if CK >5x ULN if no other contributory causes of CK elevation are identified
- Measure total cholesterol, HDL, non-HDL cholesterol after 3 months of treatment
- Check statin adherence and lifestyle modifications at review
- If not tolerating atorvastatin 80mg, consider a lower dose and aim to treat with the maximum tolerated dose or change to an alternative statin

**Patients with high CVS risk that should not be assessed under the primary prevention flowchart include:**
- Patients with type 1 and type 2 diabetes
- Patients with CKD stage 3 or greater
- Patients with pre-existing CVD
- Patients with familial dyslipidaemia including familial hypercholesterolaemia
- All these patients should be considered for higher intensity statin therapy

**For treatment of patients who have established CVD including:**
- established underlying atherosclerosis history (previous MI, angina, coronary revascularisation, peripheral vascular disease, transient ischaemic attack and ischaemic stroke)
- patients with ACS
- patients with type 2 diabetes
Since May 2010, the Medicines and Healthcare products Regulatory Agency has advised that simvastatin 80mg should not be started in new patients unless no other alternatives are available. Both atorvastatin and simvastatin have interactions with drugs that are metabolised by cytochrome CYP3A4. In these situations, the use of a lower dose of atorvastatin or simvastatin, or an alternative statin such as pravastatin or rosuvastatin (Crestor), which are not metabolised by cytochrome CYP3A4, is advised. If statin intolerance is reported, a stepwise dose reduction or switching to another statin is recommended.

A baseline liver function test (LFT) is recommended before commencement of statins and a repeat LFT within 2–3 months post statin commencement is advised. Consider stopping a statin if the LFTs (alanine transaminase or aspartate transaminase) increase by more than three times the upper limit of normal. Recheck LFTs again after statin discontinuation to confirm that the abnormal rise was due to statin. A baseline creatine kinase (CK) is not needed before statin commencement but if a patient has ongoing unexplained muscle aches, obtaining a baseline CK prior to treatment will be useful. All patients who report the development of muscle symptoms (pain, tenderness or weakness) should have their CK measured. Patients with a CK level that is five times above the upper limit (of which no other contributory muscle activities are identified) should have their statin discontinued and CK checked again.

The recent IMPROVE-IT trial comparing simvastatin 40mg/ezetimibe 10mg with simvastatin 40mg monotherapy in high-risk post acute coronary syndrome patients has shown positive clinical outcomes (reduction of cardiovascular events) in the group on combination of simvastatin and ezetimibe. It has also re-affirmed the LDL hypothesis that the lower the LDL is (less than 1.8mmol/L), the fewer cardiovascular events are observed.

Although lipid-lowering agents other than statins and ezetimibe, such as fibrates, omega-3 fish oils, bile acid sequestrants and nicotinic acid formulations, have been shown to improve lipid parameters, they lack clinical outcome evidence for reducing CV mortality. These drugs do have a role in the treatment of hypertriglyceridaemia and FH (as second- and third-line agents after statins), as well as in patients with statin intolerance or where dose intensification of a potent statin is limited by side-effects. Patients with severe hypertriglyceridaemia (TG >10mmol/L) would be at risk of acute pancreatitis. For these patients, treatment with a fibrate may be required and a referral for a specialist opinion is recommended.

Conclusion

The principal lipids present in blood are cholesterol, TGs and phospholipids. Lipids have essential functions in our cellular structure and metabolism, but the major clinical interest in them derives from the relationship between plasma cholesterol and the risk of developing atherosclerosis. The management of dyslipidaemia in patients needs to be patient-centred and requires individual assessment of the patient’s overall cardiovascular risk using some of the available risk assessment tools such as the QRISK2 calculator, which is advocated by NICE. It is important to ensure that patients with familial (genetic) dyslipidaemias should not have their cardiovascular risk assessment done using these risk calculators; they should be considered for early treatment and referral to specialist lipid centres if they are at high risk.

Declaration of interests

Dr Teoh has received speaker fees from Merck Sharp Dohme and Astra Zeneca for providing educational presentations during 2013–2014.

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Preparation analysis: statins

In 2013, GPs in England wrote 67 million prescriptions for lipid-lowering agents at a cost of £242 million. Statins accounted for 95 per cent of volume and 64 per cent of spending.

The pattern of spending on statins has been transformed by the loss of patent protection for atorvastatin, which became available as a generic in mid-2012. Prescribing volume for lipid-lowering drugs in 2011 was marginally lower than in 2013 but spending on atorvastatin alone totalled £311 million. The average cost per prescription for atorvastatin was then £27.37; it is now less than one-tenth of that.

Almost two-thirds of statin prescribing is for simvastatin, which accounts for about one-third of spending. Nearly 60 per cent of simvastatin prescriptions are for the 40mg tablet. Atorvastatin now makes up just under 30 per cent of volume and costs. The most expensive statin is now the other high potency agent rosuvastatin which, though accounting for only 3 per cent of volume, consumes 30 per cent of spending. Ezetimibe is even more expensive, especially in combination with simvastatin.

<table>
<thead>
<tr>
<th>Drug</th>
<th>No. prescriptions (000s)</th>
<th>NIC (£000)</th>
<th>Mean NIC per prescription (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>atorvastatin</td>
<td>18,250</td>
<td>42,420</td>
<td>2.32</td>
</tr>
<tr>
<td>fluvastatin</td>
<td>154</td>
<td>1,141</td>
<td>7.41</td>
</tr>
<tr>
<td>pravastatin</td>
<td>3,016</td>
<td>7,260</td>
<td>2.41</td>
</tr>
<tr>
<td>rosuvastatin</td>
<td>1,817</td>
<td>45,643</td>
<td>25.13</td>
</tr>
<tr>
<td>simvastatin</td>
<td>39,856</td>
<td>54,568</td>
<td>1.37</td>
</tr>
<tr>
<td>simvastatin/ezetimibe</td>
<td>58</td>
<td>2,842</td>
<td>49.09</td>
</tr>
<tr>
<td>ezetimibe</td>
<td>1,798</td>
<td>56,660</td>
<td>31.52</td>
</tr>
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</table>


Table 2. Number and cost of prescriptions for statins and ezetimibe, England, 2013