Cardiovascular disease (CVD) is a substantial cause of death and disability worldwide; coronary heart disease (CHD) is the principal cause of premature death while 10% of the global disease burden is attributed to CVD. Hypercholesterolaemia is a major cardiovascular risk factor; there is a continuous association between total cholesterol and CVD risk. Although CVD mortality is decreasing in Ireland, it is still the single largest cause of death; 2008 figures showed that 35% of all deaths were due to diseases of the circulatory system, the majority of which were due to coronary heart disease (CHD) and stroke. Moreover, there has been a greater than two-fold increase in CVD procedures (including angiography and angioplasty procedures) and prescribing of medications for CVD over the last decade or so in Ireland. Therefore CVD continues to represent a substantial public health burden in Ireland.

This bulletin outlines the options available for managing lipid levels and reviews the current guidance on lipid modification in the management of CVD in clinical practice.

**INTRODUCTION**

Cardiovascular disease (CVD) is a major cause of mortality and morbidity worldwide; coronary heart disease (CHD) is the principal cause of premature death while 10% of the global disease burden is attributed to CVD. Hypercholesterolaemia is a major cardiovascular risk factor; there is a continuous association between total cholesterol and CVD risk. Although CVD mortality is decreasing in Ireland, it is still the single largest cause of death; 2008 figures showed that 35% of all deaths were due to diseases of the circulatory system, the majority of which were due to coronary heart disease (CHD) and stroke. Moreover, there has been a greater than two-fold increase in CVD procedures (including angiography and angioplasty procedures) and prescribing of medications for CVD over the last decade or so in Ireland. Therefore CVD continues to represent a substantial public health burden in Ireland.

**LIPOID METABOLISM**

Cholesterol and triglycerides are insoluble in plasma. Therefore they bind to proteins known as apoproteins to form lipoproteins. These lipoproteins transport the lipids to the various tissues in order to undertake their many functions, including energy expenditure, steroid hormone production and bile acid formation. There are 5 major classes of lipoproteins, which are closely interlinked, each of which has a different function in lipid metabolism (see Table 1).

**Table 1: Characteristics of the 5 major classes of lipoproteins**

<table>
<thead>
<tr>
<th>Type</th>
<th>Synthesis</th>
<th>Method of Metabolism</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chylomicrons (CM)</td>
<td>Dietary lipids bound to Apo B in intestine → CM.</td>
<td>LPL releases FFAs for skeletal muscle and adipose tissue.</td>
<td>Source of lipids in plasma.</td>
</tr>
<tr>
<td>Very-low-density lipoproteins (VLDL)</td>
<td>Produced in liver using circulating FFAs.</td>
<td>LPL releases FFAs for skeletal muscle and adipose tissue. VLDL1 → VLDL2 → IDL.</td>
<td>Source of triglycerides in plasma (Plasma TG level) + LDL (VLDL levels).</td>
</tr>
<tr>
<td>Intermediate-density lipoprotein (IDL)</td>
<td>Formed by release of TG from VLDL.</td>
<td>Taken up by liver and transformed into LDL.</td>
<td>Intermediate step between breakdown of VLDL → LDL.</td>
</tr>
<tr>
<td>Low-density lipoprotein (LDL)</td>
<td>Hepatic lipase acts on IDL → LDL.</td>
<td>Cleared by LDL receptor, primarily situated in liver (rate = VLDL levels).</td>
<td>Major carrier of cholesterol in plasma (atherogenic lipoprotein).</td>
</tr>
<tr>
<td>High-density lipoprotein (HDL)</td>
<td>Formed in extracellular space (bound to Apo A-I).</td>
<td>Taken up by liver and broken down → cholesterol → excreted in bile.</td>
<td>Binds cholesterol and some phospholipids in plasma. Thought to be anti-atherogenic.</td>
</tr>
</tbody>
</table>

**Importance of the various lipid components:** Most of the clinical evidence on lipid-related CVD risk is based on measurement of total cholesterol (TC) or low density lipoprotein cholesterol (LDL-C) since most of the cholesterol in plasma is carried in the form of LDL-C (see Table 1). Dietary saturated fatty acids are the dietary factor with the strongest impact on LDL-C levels. This may explain the international differences in CVD. TC levels are also affected by other factors such as genetic factors and weight loss (due to reduced energy intake). Triglycerides (TGs) are also an independent risk factor for CVD but the association is less strong than that reported with high TC levels. Raised TGs tend to be associated with central obesity, low levels of high density lipoprotein cholesterol, raised blood sugar and hypertension; these should be looked for if raised TGs are identified. Very high TGs are associated with pancreatitis. High density lipoprotein cholesterol (HDL-C) is thought to be anti-atherogenic as it binds cholesterol and delivers it to the liver for excretion via the bile; moreover, a low HDL-C level has been a widely replicated biomarker for CVD risk. However the nature of the association between HDL-C levels and CVD is still uncertain since no consistent effects on CVD prevention have been shown for any agent which medically increase HDL-C levels. Apoprotein B (ApoB) is the main apoprotein of atherogenic lipoproteins and measurement of ApoB has been used as a risk marker for CVD similar to LDL-C levels; it may be particularly helpful in the early diagnosis of familial hyperlipidaemia. Measurement of plasma lipids: Many guidelines recommend that plasma lipid levels are measured after a 12-hour fast, because TG levels rise post-prandially and an accurate TG level is required to calculate the LDL-C level. Neither non-HDL-C (calculated by subtracting HDL-C from TC) nor ApoB appears to be greatly influenced by the non-fasting state and recent studies have suggested that measurement of TC and non-HDL-C (with or without ApoB) may be at least as good as a fasting LDL-C sample in monitoring response to lipid lowering therapy. Therefore, it may be possible to use non-fasting samples to monitor plasma lipids and response to therapy.

**DYSLIPIDAEMIAS**

Dyslipidaemias cover a broad spectrum of lipid abnormalities, most of which are due to the interaction between genetic predisposition and environmental factors (primary dyslipidaemia). Increased TC and LDL-C are major risk factors for CVD, therefore management of lipid levels (through lifestyle changes and lipid lowering therapies as appropriate) is one of the important elements of CVD prevention. Secondary causes of dyslipidaemia include hypothyroidism, diabetes mellitus (DM), alcohol abuse, liver or renal disease and treatment with certain medicines (oral oestrogen, isoretinoin, thiazide diuretics and protease inhibitors); these causes should be ruled out as they will impact on the need...
for choice of therapy. 

Familial hyperlipidaemia is an inherited disorder in which a 2 to 5-fold increased risk for accelerated CVD is the clinical hallmark due to the burden of markedly elevated plasma LDL-C levels from birth; early diagnosis is essential to prevent development of overt premature CVD.

CARDIOVASCULAR RISK ASSESSMENT

Risk factors for CVD are divided into modifiable and non-modifiable factors. Non-modifiable risk factors include age (CVD predominantly affects people >50 years), gender, family history of CVD and ethnicity. 

CVD risk has also been associated with low income and social deprivation. Modifiable risk factors include smoking, hypertension, obesity and TC levels. In addition, CVD risk will be higher with certain co-morbid states including DM and chronic kidney disease.

Risk factor screening for CVD may be considered in adult men ≥40 years old and in women ≥50 years old (or postmenopausal) particularly in the presence of other risk factors. In addition to clinical evaluation (e.g. age, presence of co-morbidities) a risk assessment tool may be used to improve risk estimation. There are several calculator tools available, which estimate a person’s 10-year risk of CVD, based on various risk factors (see Table 2).

LIPID MODIFICATION IN THE MANAGEMENT OF CVD

The strategy for the management of CVD is based on interventions at population and individual level; lipid modification is an important element of the overall management plan. However, CVD is generally the result of several interacting risk factors, and therefore dyslipidaemia should not be considered in isolation. For example, a 60-year old man with a TC of 5 mmol/L who smokes and has uncontrolled hypertension may have a 10-fold higher CVD risk than a normotensive, non-smoking 60-year old woman with a TC of 8 mmol/L.

Population interventions are important for the overall management of CVD risk since the largest number of CVD events will occur in those at low risk. These interventions include programmes to (1) optimise management of smoking cessation, (2) ensure adequate control of blood pressure, weight and cholesterol and (3) increase physical activity levels.

Interventions at individual level are aimed at those with established CVD or those at high risk of CVD.

LIPID-LOWERING INTERVENTIONS

Lifestyle interventions should be recommended for all patients with dyslipidaemia. As noted previously, dietary saturated fatty acids are the principal dietary determinant of LDL-C levels; there is an estimated LDL-C increase of 0.02-0.04 mmol/L for every additional 1% of energy coming from saturated fat, therefore advice on dietary modification should be given (to reduce saturated and trans fats and to increase dietary fibre and fish). A recent review showed modest reductions in TC with use of a Mediterranean type diet (-0.23 mmol/L in TC) compared with -0.06 mmol/L in TC for those not on this diet; however, data were limited. Foods enriched with phytosterols (plant sterols and stanols) are reported to be effective in lowering LDL-C by 8-10% at levels of 2g/day, without adverse effects, but there is a lack of clinical trial data on CVD outcomes to establish clinical benefit from their use. The European Atherosclerosis Society has recently recommended that functional foods with plant sterols/stanols may be considered in individuals with high TC levels at intermediate or low global CVD risk who do not qualify for pharmacotherapy, as an adjunct to pharmacotherapy in high and very high risk patients who fail to achieve LDL-C targets on statins or are statin-intolerant, and in adults and children (>6 years) with familial hypercholesterolaemia, in association with current guidance. However, they should be used in conjunction with, and not as a replacement for, the other recommended dietary modifications.

Lifestyle interventions should also include (1) a total smoking ban (2) weight reduction if necessary (aim to achieve a BMI of 20-25 with waist circumference of <94cm and <80cm for men and women respectively) (3) modification of alcohol and (4) increase in physical activity (30-60 minutes of moderate physical activity on most days) all of which have shown beneficial effects on the plasma lipid profile.

Pharmacological Therapy: There are several classes of pharmacological agents used to reduce plasma lipid levels in individual patients, in conjunction with lifestyle interventions. Each class has a different mechanism of action; Table 3 outlines the principal agents, used in the management of dyslipidaemias.

Statins are the class of lipid lowering agents for which the largest body of clinical evidence exists for a proven beneficial effect on CVD outcomes. Several studies have demonstrated a beneficial effect on CVD outcomes associated with reduction in LDL-C. It has been estimated that lowering LDL-C by 1 mmol/l reduces CVD events by 21% and total mortality by 12%, irrespective of baseline CVD risk. Therefore statin therapy is considered first-line in the management of hypercholesterolaemia and moderate hypertriglyceridaemia requiring pharmacotherapy.

Concerns have been raised regarding the long-term effects of statin therapy, due to their multiple non-cardiovascular effects, especially when used as primary prevention; their safety profile has been reported in several studies. Most have reported a modest increased risk of myositis (and/or myalgia) with statin usage, especially at higher doses, or when used with interacting medicines. Abnormalities in liver function tests (>3 X ULN) were usually related to the dose of statin.
statin used and were generally reversible. One study estimated the rate of liver failure in statin users to be one case per million person years of use, which is similar to that in the overall US population. Statins have been reported to increase the rate of incident diabetes, although findings suggest that this may be confined to patients with pre-existing risk. Insufficient information was found in relation to potential statin effects on cognition, nephropathy or the development of cataracts and no evidence of any excess risk of cancers has been found. Therefore, based on currently available evidence, the overall cardiovascular benefits of statins outweigh the non-cardiovascular effects.

**Fibrates** have been shown to be particularly useful in hypertriglyceridaemia, but evidence for their effectiveness in reducing CVD is limited. Addition of **omega-3-fatty acids** to fibrates may be beneficial in severe hypertriglyceridaemia (≥10mmol/L) in order to reduce the risk of pancreatitis. **Statin/fibrate combination therapy** has been shown to produce a significantly stronger reduction in LDL-C and TGs, and a greater elevation of HDL-C than monotherapy with either agent. However, since each class is associated with a risk of myopathy, the risk is greater with the combination, especially if higher doses of statin are used or when gemfibrozil is combined with a statin. In addition, the risk of myopathy is greater if the combination is used in those already receiving medicines metabolised through the cytochrome P450 system (Table 3). Therefore **statin/fibrate combination therapy (but never gemfibrozil)** should be used only when absolutely necessary, with specialist monitoring.

**Resins or ezetimibe** are most commonly used in combination with a statin to improve control of hypercholesterolaemia; they may also be used as monotherapy in patients intolerant of statins. Although **nicotinic acid** has been shown to reduce plasma TC and TGs, it is poorly tolerated due to its toxicity profile (Table 3). Currently, there are no authorised nicotinic acid products in Ireland.

**Table 3: Lipid-lowering agents**

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Mode of Action</th>
<th>Safety Profile</th>
<th>Drug Interactions (DDI)*</th>
<th>Practice points*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Statins</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Inhibition of HMG CoA reductase leads to ↓ synthesis of cholesterol</td>
<td>GI upset; myalgia, rarely myositis / rhabdomyolysis; ↑ LFTs; ↑ risk of developing Type 2 DM. Not to be used during pregnancy.</td>
<td>DDI risk with drugs which inhibit CYP3A4 with simvastatin+++ and atorvastatin+ [consider dose ↓ or temporary discontinuation of statin if used with these drugs]. Ciclosporin ↑ plasma levels of all statins. Use of rosuvastatin and warfarin may lead to an ↑ INR.</td>
<td>Use with fibrates, (especially simvastatin) may ↑ risk of myopathy, not necessarily due to ↑ plasma levels. LFTs should be monitored.</td>
</tr>
<tr>
<td>Pravastatin</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Atorvastatin</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Rosuvastatin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluvastatin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fibrates</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Gemfibrozil**</td>
<td>↑ lipoprotein lipolysis + hepatic FA uptake; ↓ hepatic TG production; ↓ removal of LDL from plasma</td>
<td>GI upset; ↑ LFTs. Dose to be ↓ in ↓ renal function; rarely associated with pancreatitis. Avoid use during pregnancy.</td>
<td>Use of fibrates + warfarin may lead to an ↑ INR. Use with ciclosporin ↑ risk of renal dysfunction. Use with a glitazone may result in a paradoxical ↓ in HDL-C.</td>
<td>Use with statins may ↑ risk of myopathy, not necessarily due to ↑ plasma levels (especially with gemfibrozil). Renal function should be monitored.</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Intestinal inhibitors</strong></td>
<td>↓ absorption of cholesterol in small intestine</td>
<td>GI upset; ↑ LFTs; myalgia. Avoid use during pregnancy.</td>
<td>Use with ciclosporin may affect plasma level of either drug. Use with warfarin may lead to an ↑ INR.</td>
<td>Use with fibrates may ↑ risk of gallbladder disease.</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Resins</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Colesteyramine</td>
<td>↓ absorption of cholesterol from bile salts in gut</td>
<td>GI upset and constipation; stays in gut, therefore may affect absorption of many drugs.</td>
<td>Interferes with absorption of many drugs including COC, l-thyroxine, warfarin, ciclosporin. May ↓ Vit K absorption (results in an enhanced anti-coagulant effect).</td>
<td>Not generally used as monotherapy.</td>
</tr>
<tr>
<td>Colesevelam</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Omega-3 Fatty Acids</strong>*</td>
<td>↓ synthesis of TG</td>
<td>GI upset; ↑ in bleeding time; risk of ↑ LFTs.</td>
<td>Use with anti-coagulants must be monitored and may require ↓ in dose of anti-coagulant.</td>
<td>Authorised for use in hypertriglyceridaemia only.</td>
</tr>
<tr>
<td><strong>Nicotinic acid (niacin)</strong>*</td>
<td>↓ release of FAs which results in ↓ synthesis of TG</td>
<td>Flushing; itch; GI upset; ↑ LFTs. May affect PTT.</td>
<td>Use with statins may ↑ risk of myopathy.</td>
<td>No authorised nicotinic acid product in Ireland at present.</td>
</tr>
</tbody>
</table>

FA=fatty acids; TG=triglycerides; GI=gastrointestinal; LFTs=liver function tests; INR=international normalised ratio; HDL-C=high density lipoprotein cholesterol; PTT=prothrombin time; COC=combined oral contraceptives

*The Summary of Product Characteristics for each medicine should be consulted for full prescribing information.

**use in combination with a statin is contraindicated because of risk of serious myopathy, including rhabdomyolysis

***not reimbursed on Primary Care Reimbursement Service (PCRS) community drug schemes

**LIPID MODIFICATION IN CLINICAL PRACTICE**

All clinical guidelines highlight the importance of engaging with the individual patient in the management of CVD risk. The individual should be made aware of his/her estimated 10-year CVD risk and encouraged to work with the relevant healthcare professional in order to manage/reduce this risk on a long-term basis. The management plan should take into account the individual’s needs and preferences, and existing diseases. Lifestyle interventions remain a cornerstone of management for all patients, irrespective of their level of CVD risk. These should be discussed with the patient at every visit and barriers to their implementation dealt with if possible (e.g. need for smoking cessation pharmacotherapy, advice on dietary modification or physical activity plans, adherence to pharmacotherapy if applicable). The need for lipid lowering therapy depends on (1) the level of dyslipidaemia, (2) whether the person has established CVD or co-morbidity and (3) the estimated level of CVD risk for those with no overt CVD (primary prevention). Guidelines differ in their recommendations regarding target LDL-C levels when using statins; however, a recent meta-analysis of statin trials showed that the lower the level of LDL-C achieved, the greater the level of CVD risk reduction recorded in the patients. Figure 1 outlines the current European Joint Prevention Guidelines risk categories (based on a total risks approach) and recommended targets for lipid modification in the management of CVD.


**Table 4: Costs of reimbursed lipid lowering therapies in Ireland* **

<table>
<thead>
<tr>
<th>Name</th>
<th>Daily Dose Range</th>
<th>Reimbursed Price* (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simvastatin</td>
<td>10 – 40mg</td>
<td>2.52 (10mg); 3.47 (20mg); 5.04 (40mg)</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>10 – 40mg</td>
<td>3.36 (10mg); 5.88 (20mg); 7.84 (40mg)</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>10 – 40mg</td>
<td>3.47 (10mg); 5.46 (20mg); 9.14 (40mg); 10.53 (80mg)</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>5 – 40mg**</td>
<td>5.88 (5mg); 7.28 (10mg); 11.76 (20mg); 12.32 (40mg)</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>40 – 80mg</td>
<td>5.28 (20mg); 6.22 (40mg); 8.25 (80mg)</td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td>900-1200mg</td>
<td>30.70 (300mg x 100); 22.84 (600mg x 56)</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>67 – 200mg</td>
<td>13.75 (67mg x 90); 8.07 (145mg x 30); 9.24 (200mg x 30)</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>10mg</td>
<td>35.65 (10mg)</td>
</tr>
<tr>
<td>Ezetimibe/ Simvastatin</td>
<td>DM 10/20 – 10/80mg</td>
<td>40.82 (10/20); 47.63 (10/40); 50.35 (10/80)</td>
</tr>
<tr>
<td>Colestyramine</td>
<td>12-24mg</td>
<td>21.41 (4gram sachets x 50)</td>
</tr>
<tr>
<td>Colesevelam</td>
<td>4 – 6 tablets (625mg tablet)</td>
<td>130.71 (625mg x 180)</td>
</tr>
</tbody>
</table>

*PCRS reimbursed price, 5th August 2014 (www.pcrs.ie/) for a 28-day pack unless otherwise stated. **Rosuvastatin 40mg under specialist supervision only.

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List of references available on request. Date of preparation: August 2014

Every effort has been made to ensure that this information is correct and is prepared from the best available resources at our disposal at the time of issue.

Prescribers are recommended to refer to the individual Summary of Product Characteristics (SmPC) for specific information on a drug.

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**Summary**

- Lipid modification should always be considered within the broader framework of CVD prevention and therefore **assessment of total CVD risk** is recommended when deciding on the management of dyslipidaemia in clinical practice.
- **Secondary causes** of dyslipidaemia should always be considered in the initial evaluation.
- Management of dyslipidaemias must always include education and advice on lifestyle interventions, including total smoking cessation, weight and dietary modification, and increased physical activity.
- Statins are the drug of first choice for dyslipidaemias; they should be prescribed up to the highest recommended tolerated dose in order to achieve the target LDL-C level appropriate for the patient. [A useful table on the relative intensity of the lipid-lowering effect of statins is available at: [http://www.nice.org.uk/Guidance/GC181/chapter/appendix-a-grouping-of-statins]](http://www.nice.org.uk/Guidance/GC181/chapter/appendix-a-grouping-of-statins)
- CVD risk increases with age; therefore low-risk individuals should be reassessed regularly.

- The **Medicines Management Programme** in Ireland recommends **simvastatin** as the statin of first choice for patients who require statin therapy, and who have no contraindications to its use.


42. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials (The Cholesterol Treatment Trialists Collaboration). The Lancet 2012; 380: 581-90

43. Desai C et al, non-cardiovascular effects associated with statins. BMJ 2014; 349:g3743
