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UPDATE ON LIPID-LOWERING THERAPIES

-  **Hypercholesterolaemia is a major risk factor for the development of cardiovascular disease (CVD).**
-  **Statins are the drug of choice in the secondary prevention of CVD, irrespective of an individual's cholesterol level.**
-  **Patients with established CVD, those with a 10 year risk of $\geq 5\%$ of developing a fatal CVD event, Type 2 diabetes and Type 1 diabetes with microalbuminuria and patients with particularly elevated single risk factors should also be considered for statin treatment.**
-  **Fibrates are the drug of choice in patients with marked hypertriglyceridaemia.**

INTRODUCTION

Cardiovascular disease (CVD) continues to be a major cause of premature death in European populations¹, despite improvements in most Western countries over the last 20 years². Figures for Ireland show that it remains above the European Union average for premature deaths from CVD³. Hypercholesterolaemia is a major risk factor for the development of cardiovascular disease. Although the clinical benefits of lowering cholesterol in both primary and secondary prevention of coronary heart disease are well established, cholesterol levels are still under-treated, with many patients not achieving their target. This bulletin will focus on the different types of lipid-lowering agents and their uses.

HYPERLIPIDAEMIA

There are different ways of classifying hyperlipidaemias (including the Frederickson/WHO classification), however, from a therapeutic aspect, it is useful to classify them as hypercholesterolaemia, hypertriglyceridaemia or mixed hyperlipidaemia. It is important to identify those with familial hyperlipidaemia, as they have an increased incidence of ischaemic heart disease at an early age. In general, hyperlipidaemia is primary, however it is important to identify secondary causes. Secondary causes of hyperlipidaemia include diabetes mellitus, alcohol abuse, hypothyroidism, renal failure, nephrosis, cholestasis and therapy with oral oestrogen, isotretinoin, protease inhibitors and thiazide diuretics⁴.

Hypertriglyceridaemia is associated with pancreatitis when levels are $>10\text{mmol/l}$.

ASSESSMENT

The exact cholesterol concentration requiring treatment depends on the patient's overall cardiovascular risk. Whole population screening for hyperlipidaemia is not recommended and a population-directed lifestyle programme with a targeted high-risk approach should be adopted⁵. In recent years in patients with high cardiovascular risk, there has been an emphasis on achieving lower cholesterol levels^{6,7}, with multiple trials demonstrating the benefit of aggressive lipid treatments, especially in groups with established disease^{8,9,10}.

The assessment of risk is dependent on different risk factors and should be estimated using an appropriate risk calculator, or by clinical assessment for people for whom an appropriate risk calculator is not available (for example, older people, people with diabetes or people in high-risk ethnic groups)¹¹. There are various national and international guidelines available on risk assessment for the prevention of CVD in clinical practice¹². Ireland follows the European guidelines (Third Joint Task Force of European and other Societies on Cardiovascular Disease Prevention in Clinical Practice), which assesses the 10 year risk of total fatal CVD events using the SCORE risk assessment system, which is derived from a large dataset of prospective European studies¹. Asymptomatic patients are considered at high risk if their 10 year risk is $\geq 5\%$.

Table 1: People who are considered at high risk of developing a fatal cardiovascular event (European guidelines)¹

1. Patients with established cardiovascular disease
2. Asymptomatic people who have:
 - a. Multiple risk factors resulting in a 10 year risk $\geq 5\%$, or will become $\geq 5\%$ if the individual's risk is projected to age 60 years
 - b. Markedly raised levels of single risk factors: total cholesterol $\geq 8\text{mmol/l}$, LDL cholesterol $\geq 6\text{mmol/l}$, blood pressure $\geq 180/110\text{ mmHg}$
 - c. Type 2 diabetes or type 1 diabetes with microalbuminuria

In general total cholesterol should be $<5\text{mmol/l}$ and low-density lipoprotein cholesterol (LDL-C) $<3\text{mmol/l}$. **For patients with clinically established CVD and patients with diabetes the treatment goals should be lower – total cholesterol $<4.5\text{mmol/l}$ and LDL-C $<2.5\text{mmol/l}$.**

No specific goals are defined for high-density lipoprotein cholesterol (HDL-C) and triglycerides, but concentrations of HDL-C and triglycerides are used as markers of increased risk. HDL-C $<1.0\text{mmol/l}$ in men and $<1.2\text{mmol/l}$ in women and fasting triglycerides $>1.7\text{mmol/l}$ serve as markers of increased cardiovascular risk.

Table 2: Management of asymptomatic patients ¹.

Individual's total 10 year CVD risk <5%, total cholesterol ≥5mmol/l *

• Lifestyle advice to reduce their total cholesterol below 5mmol/l and LDL-C below 3mmol/l and followed up at a **minimum** of 5 year intervals
(* Individuals with total cholesterol >8mmol/l and LDL cholesterol >6mmol/l do not require assessment of risk as they are already considered to have a high total risk of CVD)

Individual's total 10 year CVD risk ≥5% and total cholesterol ≥5mmol/l

These individuals should have a full analysis of plasma lipoproteins, including total cholesterol, HDL-C and triglycerides and calculation of LDL-C. They require intensive lifestyle advice, particularly dietary advice. They should be reviewed after 3 months and the lipid profile repeated. If after this time:

1. Total cholesterol has fallen to <5 mmol/l and LDL-cholesterol to <3mmol/l

- If a further risk assessment is <5% individuals should be advised to continue with lifestyle changes and be reviewed on an annual basis to review CVD risk
- If however the individual's risk remains ≥5%, consideration should be given to lowering total cholesterol to <4.5mmol and LDL-C to <2.5mmol/l with lipid-lowering therapy (first choice statins)

2. Total cholesterol remains ≥5 mmol/l or LDL-C ≥ 3 mmol/l

- These individuals will require lipid-lowering therapy (first choice statins) in addition to continuing their lifestyle changes
- They will require regular follow-up and some patients may require an increased statin dose, a switch to a more potent statin, or the addition of another lipid-lowering agent to achieve their goal. Patients also need to be monitored for drug toxicity.

People with metabolic syndrome are also at high risk of CVD and management should focus on weight loss and increased physical activity, with the evidence suggesting that these patients also require statins ¹³.

MANAGEMENT

Both non-pharmacological and pharmacological therapies are important to consider in the management of a patient with hyperlipidaemia.

Before drug therapy is initiated, secondary causes of hyperlipidaemia should be excluded, particularly in those patients with isolated elevated cholesterol or triglycerides. In particular, consideration should be given to measuring thyroid function in patients whose cholesterol is > 8mmol/l ¹⁴. Treatment of the disorder causing secondary hyperlipidaemia may obviate the need for treatment with hypolipidaemic drugs ⁴. In addition hypothyroidism may predispose to statin toxicity.

NON-PHARMACOLOGICAL THERAPY

All patients should receive instruction in relation to therapeutic lifestyle change. Maintaining or achieving ideal body weight – by eating a diet low in saturated fat and cholesterol, which includes polyunsaturated fats and fish oils, and high in fresh fruit and vegetables, in addition to regular exercise – is the cornerstone of managing hyperlipidaemia ⁷.

Plant sterols and stanols, which reduce the absorption of cholesterol from the gastrointestinal tract have been incorporated into foods (in particular margarine). Randomised controlled trials have shown that polyunsaturated margarines with added plant sterols or stanols reduce LDL-C, with doses of ≥2g per day giving an average reduction of 0.33 – 0.54 mmol/L in LDL-C¹⁵, but there is no outcome data to show benefits.

PHARMACOLOGICAL THERAPY

There is a range of lipid-lowering therapy with different modes of action available. The drugs of choice for primary and secondary prevention of CVD are the statins.

Statins

The role of statins in lowering cholesterol has been recognised for many years. Multiple randomised controlled trials (RCTs) have shown evidence of their efficacy in both the primary ¹⁶⁻¹⁸ and secondary ¹⁹⁻²³ prevention of cardiovascular disease in patients. They have been shown to safely reduce the 5-year incidence of major coronary events, coronary revascularisation, and stroke by about one-fifth per 1 mmol/l reduction in LDL-C, largely irrespective of the initial lipid profile or other presenting characteristics ²⁴. They have also been shown to be of benefit in individuals with cerebrovascular disease ^{21,25}. The benefits of statins in trials also extend to the community, including the elderly ²⁶, those with diabetes ^{19,20} and women ^{19,27}.

Mode of action - Statins are competitive inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which leads to an increased synthesis of LDL-C receptors resulting in reduced LDL-C. They rapidly lower serum total cholesterol, particularly LDL-C (by 20-55% depending on the dose and statin used); they have a lesser effect on very low-density lipoproteins (VLDL) and triglycerides and can cause a small rise in HDL-C. Statins also decrease fibrinogen concentrations and viscosity, increase activation of endothelial nitric acid synthase and decrease C-reactive protein ⁸.

The following statins are authorised in Ireland: simvastatin, fluvastatin, pravastatin, atorvastatin, and rosuvastatin. All the statins are authorised for hypercholesterolaemia; with simvastatin, pravastatin, fluvastatin and atorvastatin also authorised for either primary and/or secondary CVD prevention (the individual Summary of Product Characteristics (SPC) are available on www.medicines.ie and should be consulted for each statin) ²⁸⁻³². The lipid-lowering effects of the statins are dose-dependent. Furthermore, comparator studies have shown that rosuvastatin and atorvastatin are more potent than simvastatin and pravastatin ^{33,34}. Hepatic cholesterol synthesis is maximal between midnight and 2:00 am; therefore statins with a half-life of 4 hours or less (simvastatin, immediate release fluvastatin and pravastatin) should be taken in the evening. The choice of which statin and dose to use depends on the amount of LDL-C reduction required, the safety profile of the drug and concomitant drug use ⁸.

Adverse effects of statins

Drug interactions - The use of higher doses of statins increases the risk of adverse effects, particularly those occurring as a result of drug interactions ³⁵. Not all statins are metabolised the same way and they differ in their interactions. Simvastatin is extensively metabolised by the Cytochrome P450 isoenzyme CYP3A4, and any drugs that inhibit this enzyme can cause marked rises in simvastatin levels ³⁶. Atorvastatin is metabolised by CYP3A4 but has a low affinity for this isoenzyme; however inhibition of CYP3A4 can still cause potentially serious elevations in its levels. Fluvastatin is metabolised primarily by CYP2C9. Rosuvastatin is metabolised by CYP2C9 and CYP2C19, although the majority of it is excreted unchanged. The Cytochrome P450 system does not appear to be involved in the metabolism of pravastatin. It is important that the individual SPC is reviewed for more detailed information on potential drug interactions.

Liver disease – the cause of minor hepatic enzyme abnormalities occurring in patients receiving statins is unknown ³⁵. Most minor elevations resolve spontaneously with continued treatment ^{35,37}. Statins are contra-indicated in the presence of active liver disease and for those patients with persistent elevations of serum transaminases ²⁸⁻³². They should be used with caution in patients with a history of alcohol abuse and those who have a history of liver disease.

Practical Advice - Liver function tests should be checked prior to starting statins, after 3 months of treatment and following any

increase in dose²⁸⁻³². They should also be performed if the patient develops any signs or symptoms suggestive of liver injury. **Statins should be stopped if serum transaminase increases to > 3 x upper limit of normal (ULN).**

Myopathy – Muscle complaints appear to be very common in patients treated with statins in clinical practice,³⁵ however the occurrence of clinically significant myopathy with statins is rare and unpredictable³⁷, occurring in 0.1% to 0.5% of those treated with statins in RCTs^{38,39}. The most serious risk associated with statins is rhabdomyolysis – defined as muscle symptoms with marked creatinine kinase (CK) (substantially >10 times ULN) and creatinine elevation leading to acute renal failure³⁷. (Cerivastatin, which had a higher reported incidence of rhabdomyolysis compared to the other statins was withdrawn due to this complication⁴⁰). The risk of rhabdomyolysis is increased by factors that increase the serum concentration of statins, such as small body size, advanced age, renal or hepatic dysfunction, diabetes, hypothyroidism and some drugs. **Drugs, which interfere with the metabolism of statins are the most important risk factor for rhabdomyolysis, and include fibric acid derivatives, ciclosporin, niacin, azole antifungals, macrolide antibiotics, protease inhibitors, verapamil, diltiazem, amiodarone and grapefruit juice (as previously discussed not all statins are metabolised the same way and the individual SPC should be consulted)**³⁵.

Practical Advice - There is no evidence that screening or monitoring of CK will identify those patients at risk of myopathy, myositis or rhabdomyolysis^{37,41}. Measurement of CK however is recommended in patients prior to starting statins if the patient has predisposing factors, including renal impairment, hypothyroidism, personal or family history of hereditary muscular disorders, previous history of muscular toxicity with a statin or fibrate, previous history of liver disease and/or where substantial quantities of alcohol are consumed, and in patients >70 years of age²⁸⁻³². If CK levels are significantly elevated at baseline > 5 x ULN, statins should be withheld and CK rechecked in 5-7 days. On starting treatment with any statin, all patients should be warned about the rare risk of myopathy and asked to report unusual or unexplained muscle pain or weakness³⁷. In this situation the patient's CK should be checked and if the level is > 5 x ULN, the statin should be stopped. Even if CK is < 5 x ULN and muscular symptoms are severe, treatment discontinuation should be considered. If symptoms resolve and CK levels return to normal, reintroduction of the statin or the introduction of an alternative statin may be considered at the lowest dose and with close monitoring²⁸⁻³². Persistent elevations of CK not in the diagnostic range for myopathy should trigger a search for other causes, of which hypothyroidism is the most common. The main limitation of statin therapy in clinical practice is **poor adherence to treatment**. Although 80-90% of patients remain on statin therapy for up to 5 years in clinical trials, >50% of patients in clinical settings discontinue treatment within 2 years³⁵. Evidence suggests that patients who are prescribed statins for primary prevention are less likely to persist with treatment than those prescribed for secondary prevention⁴².

An Irish study looking at the prescribing rates of statins between 1998-2002 (in a specific patient population) also showed that even though there were consistent and significant increases in statin prescribing rates for that period, the rate of prescribing was still below that recommended for the population in general and for at-risk groups such as ischaemic heart disease (IHD) and diabetic patients in particular⁴³.

Heartwatch, a programme of chronic disease management in the secondary prevention of coronary heart disease has shown up to a 53% relative improvement in cholesterol levels from baseline⁴⁴. From an economic point of view, a recent study showed that statins were cost-effective in the primary prevention of CVD in high-risk individuals in Ireland⁴⁵. In the future the use of generic formulations may help to reduce the costs of statins.

Statins should be used conservatively in young patients who are at very low risk, even when hyperlipidaemia is present, because the long-term effects of these drugs are not yet known. Diet and exercise are more appropriate approaches for this population. Statins are contra-indicated in pregnancy and breast feeding⁸.

Fibrates

The lipid regulating properties of fibrates were first described about 40 years ago. Clofibrate, the first fibrate to be widely used, has been replaced by gemfibrozil and fenofibrate, which are both authorised in Ireland. They cause a marked reduction in circulating VLDL and hence triglyceride (up to 50%⁷), with a reduction in LDL-C (up to 30%⁴⁶) and an increase in HDL-C (up to 30%⁴⁶). They are the drug of choice for marked hypertriglyceridaemia. Several large intervention trials investigating the potential of fibrates to reduce cardiovascular disease, have shown varied results⁴⁷. Primary (Helsinki Heart Study) and secondary prevention (Veteran Affairs Trial) studies however have shown that gemfibrozil has cardioprotective effects⁴⁷. Even in those patients with low HDL-C, evidence suggests that a statin rather than a fibrate would be the drug of first choice in the absence of marked hypertriglyceridaemia³⁷.

Mode of action – Fibrates act as a ligand for peroxisome proliferator-activator receptor alpha (PPAR-alpha) which, by inducing fatty acid oxidation, leads to reduced uptake of fatty acids into triglyceride-rich VLDLs and a reduction in triglyceride levels.

Adverse effects - Important adverse effects include gastrointestinal symptoms (especially gemfibrozil), erectile dysfunction, myositis (particularly in patients with renal impairment) and hepatitis⁸. Fibrates also increase biliary cholesterol concentrations and can cause gallstones.

Drug interactions – Fibrates interact with warfarin and intensive monitoring of the INR is required in these patients^{48,49}. The combination of gemfibrozil and repaglinide is contra-indicated and the combination of gemfibrozil and statins should be avoided⁴⁸. Please see individual SPCs for more details of drug interactions.

Ezetimibe

Ezetimibe is a new class of drug, which is a cholesterol absorption inhibitor. It is rapidly absorbed and is highly protein bound. It reduces total cholesterol by 15% and LDL-C by 18% when given alone. Experience with its use is limited and there is no current evidence of any long-term reduction in CVD. It is useful in those patients already on statins who require further LDL-C lowering and in those who are intolerant of statins³⁷. (A combination of simvastatin and ezetimibe is also presently licensed).

When ezetimibe is administered with a statin, **liver function tests should be monitored at initiation of treatment and according to the recommendations for the statin**. Cases of myopathy and rhabdomyolysis have been reported with ezetimibe in combination with a statin and rarely in those on ezetimibe alone. Care should be taken when prescribing ezetimibe with ciclosporin (serum levels of which can increase) and warfarin (post-marketing reports of increased INR). **It is not recommended to combine it with fibrates**⁵⁰.

Nicotinic acid

Nicotinic acid has been known to effectively lower cholesterol since the 1950's⁵¹, however its use has been limited due to the side-effects associated with it. A modified release preparation is available which is better tolerated. Patients receiving the modified release preparation report fewer flushing episodes, which generally occur during early treatment and the dose titration phase⁵². It is used as adjunctive therapy with the statins and can be used as monotherapy in those who are intolerant of the statins⁵². It is the most effective agent for increasing HDL-C. At the maximum recommended dose of 2g daily, decreases in LDL-C, and triglycerides averaged 17% and 35%, whereas HDL-C increased by 24%⁵¹. Nicotinic acid has been shown to reduce total cholesterol, with a significant reduction in mortality after 5 years, with its benefit seen following the first year of therapy⁵³.

Mode of action – It reduces the release of esterified fatty acids from adipose tissue, which in turn diminishes hepatic triglyceride synthesis and VLDL secretion from the liver. This leads to lower cholesterol and triglycerides and increased HDL-C.

Adverse effects – The use of nicotinic acid has been limited due to the unpleasant frequent side-effects of flushing and itching, which may be reduced by prior administration of aspirin⁵⁴. It should be taken at bedtime following a low-fat snack⁵². Hepatic dysfunction, hyperglycaemia, hyperuricaemia and gastrointestinal upsets have also been reported with its use⁵¹. Nicotinic acid may also affect platelet count and prothrombin time⁵².

Omega-3 fatty acids (fish oils)

The long chain polyunsaturated fatty acids, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) reduce triglyceride levels in a dose-dependent manner; 4g daily will reduce triglycerides up to 40%⁵⁵. There are two preparations authorised in Ireland – omega-3-acid ethyl esters and omega-3-marine triglycerides both containing DHA and EPA. They are useful as adjunctive therapy in those with marked hypertriglyceridaemia and omega-3-acid ethyl esters is also authorised as adjunctive therapy for CVD prevention following myocardial infarction⁵⁶. A recent systematic review showed that omega-3 fatty acids had no clear effect on total mortality and combined cardiovascular events⁵⁷. Evidence however does suggest that they are associated with anti-arrhythmic properties⁵⁸.

Adverse effects -With high doses there can be an associated increase in bleeding time and careful monitoring is required for those on anticoagulants⁵⁶. There is no experience with its use in combination with fibrates.

Resins

The anion-exchange resins, including colestyramine, which is authorised for use in Ireland, bind to bile acids preventing their reabsorption. They are moderately effective at lowering LDL-C (15-20%), however they have a tendency to increase triglycerides. Trials have shown a reduction in CHD events, but non-significant increase in non-coronary mortality. They are second-line agents to statins⁸, and may be combined with statins, but administration should be separated by at least 1 hour before or 4-6 hours after the resin⁵⁹.

Adverse effects - These include abdominal fullness, gas and constipation⁸. They reduce the absorption of certain drugs including digoxin, warfarin and levothyroxine. Prolonged use may be associated with increased bleeding tendency⁵⁹.

Combination therapy

Monotherapy with statins does not always result in the optimal cholesterol level and it is often necessary to combine them with other lipid-lowering agents, especially in those patients with familial hypercholesterolaemia. In patients with mixed hyperlipidaemia, statin therapy on its own may fail to reduce triglycerides and raise HDL-C to the level required, and it may be necessary to add nicotinic acid or a fibrate.

Studies suggest that both nicotinic acid and fibrates are useful adjuncts to statins, the choice of which depends on tolerability and safety. The safety of combined statin/fibrate treatment has been questioned because of concerns regarding rhabdomyolysis. Most of the reported cases have been seen in association with statins and gemfibrozil⁵¹. Rhabdomyolysis has also been seen with combinations of statins and other lipid-lowering therapies, including nicotinic acid⁵² and ezetimibe⁵⁰.

Table 3: Summary of lipid-lowering treatment therapy⁵¹

Type	First Choice	If Refractory
Hypercholesterolaemia	Statin	Add cholesterol absorption inhibitor, fibrate (caution with gemfibrozil), resin or nicotinic acid
Hypertriglyceridaemia	Fibrate	Add nicotinic acid
Mixed hyperlipidaemia	Statin	Substitute or add fibrate (not gemfibrozil + statin)
Low HDL cholesterol	Statin	Substitute or add nicotinic acid or fibrate

Check liver function before and after three months on statin
 Check renal function before and after one month on fibrate
 Check serum CK at baseline if patient has predisposing factors for myalgia or if myalgia occurs during statin treatment

Evidence suggests that patients at very high risk of coronary artery disease benefit from treatment that lowers LDL-C levels to ≤ 1.81 mmol/l and that patients with ≥ 2 risk factors benefit from treatment that lowers LDL-C to <2.59 mmol/l⁹, as recommended by the National Cholesterol Education Programme in the United States.

Can cholesterol levels be lowered too much? - A J-shaped or U-shaped relation between serum cholesterol levels and total mortality has been seen in some epidemiological studies. Increased mortality at low cholesterol levels appears to be caused by an increase in some cancers, hepatic disease and haemorrhagic stroke. The consensus of most experts is that higher mortality with low cholesterol is a consequence of chronic diseases that lower cholesterol and that lowering cholesterol does not increase mortality^{7,35}.

Table 4: Commonly prescribed lipid lowering therapy with dose ranges and costs per pack (taken from GMS database March 2006)

Drug	Daily dose range	Pack size	Average cost per pack (Euros)
Atorvastatin	10-80mg	28	25.17 – 76.58
Pravastatin	10-40mg	28	17.17 – 54.29
Rosuvastatin	5-40mg*	28	21.44 – 44.19
Simvastatin	10-80mg	28	17.00 – 42.41
Fluvastatin	40-80mg	28	20.17 – 26.73
Ezetimibe	10mg	28	39.53
Omega-3-acid ethyl esters	2 – 4 capsules daily	28 capsules	20.67
Gemfibrozil	900-1200mg	300mg x 100 – 600mg x 56	33.53 – 37.56
Fenofibrate	200mg	30 capsules	21.56
Nicotinic acid (prolonged release)	1,000-2,000mg	500mg x 56 – 1,000mg x 56	24.99 – 45.02
Colestyramine	12-24g	4g x 50 sachets	24.04 – 34.33

* 40mg dose of rosuvastatin only to be used under specialist supervision

SUMMARY

The primary goal in the treatment of hyperlipidaemia is to avoid future morbidity and mortality from CVD. One of the most important aspects over the last ten years in lipid-lowering management, in addition to the introduction of statins, is the evidence that statins have an important role in the primary and secondary prevention of CVD in individuals. In asymptomatic individuals, it is important to estimate their CVD risk in order to determine an overall strategy for cholesterol management. In addition to lipid-lowering therapy, where statins are the drugs of choice, it is important to emphasize the benefits of diet, exercise and weight control.

References available on request. Date prepared: November 2006. 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 SPC for information on specific drugs

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