THE ROLE OF STATINS IN PREVENTION OF CORONARY HEART DISEASE

SUMMARY

- Hyperlipidaemia is a major risk factor for coronary heart disease (CHD), the main cause of death in Ireland
- Treatment goals are total cholesterol < 5.0 mmol/L and LDL cholesterol < 3.0 mmol/L
- Dietary and lifestyle modification is the first-line intervention with management of other risk factors
- Statins are the agents of choice and are particularly recommended for hyperlipidaemic patients with CHD or other atherosclerotic disease, and those at > 20% risk of developing a coronary event in the next 10 years
- Choice of statin should be evidence based, cost-effective and tailored to the patient

INTRODUCTION

Coronary heart disease (CHD) is the leading cause of morbidity and mortality in Europe.[1-3] Mortality rates are higher in urban areas and in areas of social and economic deprivation.[4] Hyperlipidaemia is a major risk factor for atherosclerosis and cardiovascular disease and its control is essential to prevention of CHD.[5-7] In Ireland, an estimated 21% of adults are at risk of CHD because of high cholesterol levels.[8] This presents a major economic burden to the Irish health service.

The clinical benefits of lowering cholesterol in both primary and secondary prevention of CHD are well established.[9-12] Dietary and lifestyle modification are key components in the treatment of hyperlipidaemia, although may not achieve treatment goals.[13-7] The majority of patients will require pharmacological intervention.[17-9] The HMG Co-A reductase inhibitors (**statins**) are the most effective and best tolerated lipid-lowering agents available.[11,18,20-2] Large scale intervention trials have established that the use of statins significantly reduces coronary events and death.[23-6] Despite this evidence, undertreatment of hyperlipidaemia is common; many patients who may benefit are not prescribed a statin.[27-9] Moreover, there is widespread variation in prescribing of statins by medical practitioners.[30-1]

HOW DO STATINS WORK

There are currently five statins available namely, **simvastatin**, **pravastatin**, **fluvastatin**, **atorvastatin** and **cerivastatin**, all of which share the same mode of action. They competitively inhibit the enzyme HMG Co-A reductase, the rate limiting enzyme in cholesterol synthesis.[16,32-4] The fall in hepatocellular cholesterol, results in an upregulation of hepatic LDL receptors, which bind circulating LDL cholesterol. The increased uptake of LDL-cholesterol reduces plasma cholesterol levels. This is accompanied by a slight increase in HDL-cholesterol and triglycerides.[16] Statins achieve on average, a 25-30% reduction in cholesterol. In addition to their lipid-lowering properties, angiographic studies have shown that statins slow the rate of progression of atherosclerosis, promote plaque regression and stabilise atherosclerotic plaques prone to rupture.[35-43] Stabilisation mechanisms suggested include antithrombotic, anti-inflammatory and antioxidant mechanisms, together with restoration of endothelial function.[35,44-5]

WHOM TO TREAT

Targeting statin treatment within constraints of healthcare budgets is a major challenge to prescribers.[46] The use of statins must be targeted where most benefit can be acheived. In clinical practice, the first priority should be hyperlipidaemic patients with CHD or other atherosclerotic disease (**secondary prevention**); the second priority are individuals considered at high risk of developing CHD or other atherosclerotic disease because of hyperlipidaemia, hypertension, diabetes, or a combination of these and other risk factors (**primary prevention**).[9,22] CHD is a multi-factorial disease and it is essential that other modifiable risk factors (see **Table 1**) are also controlled effectively.[9] All patients should receive dietary (see **Table 2**) and lifestyle advice. Ultimately, **treatment goals** are total cholesterol < 5.0mmol/L and LDL cholesterol < 3.0 mmol/L.[9] Secondary causes of hyperlipidaemia e.g. hypothyroidism, alcoholism, obstructive jaundice, drugs (thiazides, beta-blockers) should be excluded and corrected, accordingly.[47-8]

MEASURING SERUM LIPIDS

There is presently no rationale for routine cholesterol screening in general practice. Screening should be targeted at high risk individuals. A random blood test is usually appropriate for initial screening of total cholesterol (TC). Where statin treatment is being considered (TC >5.0 mmol/L), at least two fasting lipid profiles (TC, HDL, TG) are needed. The TC:HDL ratio is useful for assessing coronary risk.[9,22] Risk is proportional to the concentration of TC and LDL cholesterol and inversely proportional to the concentration of HDL cholesterol.[49] Elevated triglycerides (TG) is an independent risk factor for CHD.[46,50]

Table 1 CHD risk factors

Modifiable	Non-modifiable
Hyperlipidaemia	Age and gender
Hypertension (>140/90)	men > 45 years
Diabetes mellitus	women > 55years / premature menopause
Obesity	
Physical inactivity	Family history of premature CHD
Cigarette smoking	male relative < 55 years
High saturated fat intake	female relative < 65 years
Excessive alcohol intake	Inherent disorders of lipid metabolism
Hypertriglyceridaemia	

Table 2 Dietary advice

- Reduce total fat intake (<30%)
- Reduce saturated fats (<10%)
- Substitute with unsaturates
- Decrease dietary cholesterol
- Increase fibre intake
- Reduce alcohol intake
- Achieve ideal body weight

SECONDARY PREVENTION

The benefits of statins in secondary prevention are well established, reducing the incidence of fatal and non-fatal MIs by 30-35%.[23-4,26] The landmark **4S**, **CARE** and **LIPID** trials have proven that simvastatin and pravastatin significantly reduce CHD morbidity and mortality (see **Table 3**).[23-4,26] A **summary** of these trials is available from the Centre. In secondary prevention, statin treatment should be instigated at a cholesterol level >5.0 mmol/L i.e. about 80% of patients. Undertreatment of secondary prevention is common in about two-thirds of patients, and not acceptable.[5,27,51-2] Appropriate instigation of a statin in hospitalised patients post-MI may promote seamless care and reduce this deficit.[47,53]

PRIMARY PREVENTION

Rational targeting of statin treatment for primary prevention represents more difficulty.[22,30,54] Many GPs are unsure when to instigate a statin for primary prevention.[30] This requires an estimate of CHD risk rather than interpretation of lipid levels. For example, a patient with a cholesterol of 7.5 mmol/L may be at lower absolute risk of CHD than a patient with a cholesterol of 6.0 mmol/L, depending on other variables (see **Table 1**). Primary prevention of CHD will utilise more resources than secondary prevention (see **Table 3**). At lower levels of risk, numbers of patients meeting criteria for statin treatment will be higher.[11,54] Until recently, patients with a CHD risk of > 30% were considered candidates for a statin. The European Societies' Guidelines suggest a threshold of 20%.[12] Recent British guidelines suggest a lower threshold of 15%.[9] The Irish Cardiac Society have endorsed adoption of the European recommendations in general practice. Patients considered at a > 20% risk should receive intensive risk factor modification and lifestyle intervention (see below). If TC remains > 5.0 mmol/L, treatment with a statin is indicated. The **WOSCOPS** primary prevention trial (**summary** also available) showed a 31% reduction in risk of non-fatal MI or death in hyperlipidaemic men treated with pravastatin.[25] Autopsy findings of coronary atherosclerosis in noncardiac trauma victims under 35 years support the need for primary prevention.[55]

ASSESSING CHD RISK

The European Societies' Guidelines include colour CHD prediction charts for men and women. These charts will be circulated to GPs by the Irish Cardiac Society this year. Copies are also available from the Centre. They are based on a 2-D model of continuous BP and cholesterol measurements and take into account age, gender, cigarette smoking and diabetes. The charts enable estimation of absolute risk of developing CHD over the next 10 years.

Table 3 The Prevention of CHD events if 1000 patients were treated for 5 years with a statin

	Primary prevention	Secondary prevention		
Reduction in events	**WOSCOPS (TC > 6.5)**	**4S (TC=5.5-6.1)**	**CARE (TC=4.8-6.1)**	**LIPID (TC=4.0-7.0)**
Myocardial infarctions	**20**	**70**	**26**	**40**
Deaths (CHD)	**7**	**40**	**11**	**29**

DIETARY AND LIFESTYLE ADVICE

The first-line management of hyperlipidaemia is dietary and lifestyle intervention.[13-7] Dietary recommendations are given in **Table 2**. Long-term compliance with dietary changes can be poor.[17-9] Patients should also be advised to take more exercise, lose weight and stop smoking. Smoking cessation is three times more effective than other interventions in CHD prevention. Meta-analysis of all dietary trials in hyperlipidaemia reveal an approximate 10% reduction in LDL cholesterol.[47,56] This has significant benefits for patient prognosis and prevention of other disease onset. Dietary response should be assessed after a period of 3-6 months.[19] Even when drug therapy is instigated, diet and lifestyle

changes should still be reinforced. Statins are usually started after a diet and lifestyle trial of 3 months; in secondary prevention, most patients will require immediate statin treatment.

WHICH STATIN

Choice of statin should be evidence based and cost-effective. The licensed dosage ranges and relative costs are given in **Table 4**. Pravastatin or simvastatin should be prescribed first-line in accordance with the trial evidence. Doses should be the same as those used in the trials and increased every 4-6 weeks to achieve treatment goals.[9] The dose should be taken before bedtime as cholesterol synthesis increases at night. The commonest dose in use in Ireland, 10 mg, was not employed in the definitive studies and also would not usually be expected to achieve the goal of TC< 5.0 mmol/L. Fluvastatin is the cheapest; it is also the least potent.[57] Atorvastatin is much more potent than simvastatin and pravastatin and has a role in the management of severe hyperlipidaemia.[2,58-61] It also has a favourable effect on triglyceride levels[2], however it lacks an evidence base in CHD to support its use as first-line therapy. Clinical experience with cerivastatin, the most potent statin, is limited. Until more data is available, drugs used in landmark trials are preferred.[57,62]

Table 4 Doses and costs of the statins

Statin	Licensed dose range(mg)	Cost (£) - 28 days*
Simvastatin	10 - 40	19.65 - 43.75
Pravastatin	10 - 40	17.80 - 42.36
Fluvastatin	20 - 40	13.48 - 15.89
Cerivastatin	0.1 - 0.3	13.95 - 20.05
Atorvastatin	10 - 80	19.82 - 52.29

(*prices Jan '99 MIMS)

Over 120,000 prescriptions for statins were dispensed in 1997, costing the GMS £3.3 million pounds. Statin prescriptions account for 94% of all lipid lowering drugs prescribed and 1.8% of the total GMS spend on medicines in 1997. Stain expenditure is expected to increase to over £5 million for 1998.

ADVERSE EFFECTS

The statins are generally very well-tolerated.[62-3] In major trials, tolerability and drug withdrawal have not differed significantly from placebo groups.[23-6] Adverse effects are usually class effects, however individual statins do not necessarily cause the same problem when used in the same patient.[11] **Gastrointestinal effects** (nausea, dyspepsia, constipation, diarrhoea and flatulence) are the most commonly reported.[16,19,61,63] **Headache**, **dizziness** and **rash** are also common complaints.[19,63] **Sleep disturbance** may be a problem, although more so with the lipophilic statins (simvastatin, atorvastatin).[2] The most serious, although infrequent, adverse events encountered with statins are **hepatotoxicity** and **myositis**. Elevated serum transaminases (AST, ALT) are a recognised class effect and often asymptomatic. Most cases of significant LFT elevations occur within the first 2-5 months of treatment.[64] If LFTs exceed three times the upper limit of normal, drug withdrawal is warranted.[11] Other underlying pathology should always be considered. Myopathy and frank rhabdomyolysis occur rarely.[19] The risk of muscle damage is higher if the patient is hypothyroid or renally impaired.[19] Baseline LFTs and creatine kinase (CK) levels should be checked prior to initiating treatment with a statin, then again 2-3 months after treatment is started and on a regular basis, thereafter.[11] Patients with a history of statin-related liver dysfunction should be referred to a lipid specialist before considering further lipid lowering treatment.[11]

DRUG INTERACTIONS

The statins vary in their drug interaction profiles. **Simvastatin**, **atorvastatin** and **cerivastatin** are metabolised via the cytochrome P4503A4 (CYP3A4) enzyme in the liver. Concomitant therapy with CYP3A4 inhibitors e.g. **macrolide antibiotics**, **azole antifungals**, **protease inhibitors**, **cyclosporin**, **gemfibrozil** and **nefazadone** may potentiate statin levels and increase the risk of myositis.[2,6,61,65] For example, concomitant erythromycin can increase the bioavailabilty of atorvastatin by 38%.[11] The most severe of these is with gemfibrozil; this combination should be carefully monitored. **Pravastatin** is not specific for CYP3A4 and so has a lower propensity to interact with these drugs.[65] **Fluvastatin** differs from all other statins in that it is specific for CYP2C9. Fluvastatin clearance is increased by **rifampicin**.[6] Absorption of fluvastatin is increased in the presence of ranitidine, cimetidine and omeprazole.[65] **Simvastatin** and **atorvastatin** may enhance the effect of **warfarin**.[19,63] Many patients are prescribed this combination post-MI and close monitoring of INRs is needed. Pravastatin, fluvastatin and cerivastatin do not affect warfarin and may be preferable for patients requiring oral anticoagulation.[6,19,62] Atorvastatin and simvastatin may also potentiate serum **digoxin** levels and initial monitoring is needed.[63,65] Drugs that affect endogenous steroid production e.g. **spironolactone**, **cimetidine**, **ketoconazole** should be used with caution.[65] Patients also taking **cholestyramine**, should take the statin one hour before or four hours after the sequestrant.[62,65]

PRESCRIBING STATINS IN SPECIAL POPULATIONS

ELDERLY

The use of statins for CHD prevention in the elderly is evolving.[11] The absolute risk of CHD and other cardiovascular disease is higher in the elderly than any other group. The association between hyperlipidaemia and CHD risk is however weaker.[66] Elderly patients do benefit from statins.[67-70] Sub-group analysis of 60-70 year old patients from the 4S study revealed significant benefit from simvastatin in this age-group, as did patients aged up to 75 years in the LIPID trial.[23,71] However, decision to treat should not only be based on chronological age, but biological age.[68-9]

WOMEN

The absolute risk of CHD is lower in women than men at all ages. Lifetime risk of CHD at the age of 40 is one in three for women and one in two for men.[71] However, CHD is the most common cause of death in the female population, incidence increasing markedly **post-menopause**.[72] Moreover, women with CHD have a higher mortality rate post-infarction and are a greater operative risk for CABG and angioplasty.[72] Serum cholesterol concentrations increase steadily in women between the ages of 35-60 years, but remain relatively constant in men. Evidence of efficacy of statin treatment is however lacking. In the 4S and LIPID studies, only 19% of study populations were female, this power being too low to demonstrate significant improvement in survival. Nevertheless, treatment with either pravastatin or simvastatin reduced the risk of coronary events.[23,26] Women should be treated as aggressively as men.[74-5] Statins are significantly more effective in lowering cholesterol in post-menopausal women than HRT.[76] The combination of HRT and a statin may have a synergistic effect.[77]

Statins are teratogenic in rodents and there have been anecdotal reports of congenital abnormalities in infants born to women exposed to statins during pregnancy. Pravastatin and fluvastatin are excreted into milk and this is likely true for other statins.[78] Cholesterol is an important component of steroid synthesis and cell membrane function, both essential to healthy fetal and infant development.[60] Hence statins are contra-indicated in **pregnancy** and **lactation**.

DIABETES

The risk of CHD in diabetic patients with hyperlipidaemia is equal to that of patients with CHD. Over 70% of diabetics die from macrovascular disease, mainly CHD.[9] Diabetics who develop proteinuria are at particularly high risk of CHD and should be treated according to secondary prevention guidelines.[9] Simvastatin reduces microalbuminuria in NIDDM patients in addition to its lipid lowering effect.[82] Fibrates are particularly useful in diabetics with hypertriglyceridaemia, and of the statins, atorvastatin has the most favourable effect on triglycerides.[83]

FAMILIAL HYPERCHOLESTEROLAEMIA

Familial hypercholesterolaemia (FH) is an autosomal dominant condition, affecting 1 in 500 of the population; the primary defect is a gene mutation of the LDL receptor. Typically, patients will display classical signs of FH, severe hypercholesterolaemia and premature CHD. Statins are the drugs of choice and all patients with FH, including children and women of child-bearing age, should be treated aggressively.[9,84] Patients with FH should be referred to a lipid specialist.

STROKE PROPHYLAXIS

Statin therapy for CHD prevention is also associated with a significant reduction in the incidence of stroke. Stroke is the third leading cause of death after CHD and cancer.[35] Meta-analyses of secondary prevention studies observed a 30% (range 29-32) reduction in stroke risk in patients treated with a statin.[35,85-7] Stroke, a significant endpoint in the CARE trial, was reduced by 31% in patients treated with pravastatin.[24] Considering the significant physical and mental disability suffered by stroke victims and its considerable burden on healthcare resources, statins may have a future role in stroke prophylaxis.[67] Futher clinical data is required to address this question. Effective blood pressure control is a primary goal in stroke prevention.

PHARMACOECONOMICS

The cost-effectiveness of statin treatment for secondary prevention is well established. In the landmark secondary prevention trials, costs of statin treatment were off-set by reduction in direct costs associated with hospitalisation and revascularisation procedures. Primary prevention will however utilise considerably more healthcare resources than secondary prevention; the cost per life year gained with a statin varying from £2500 (for high risk secondary prevention) to £50,000 (for low risk primary prevention) for each life year saved. Treating all patients with a CHD risk of > 20 % in the next 10 years will have significant cost implications for GP prescribing budgets. Lifestyle options (the most cost-effective treatment strategy) and targeting statin treatment to high risk patients, are a priority.

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