LIPID LOWERING TO DELAY THE PROGRESSION OF CORONARY ARTERY DISEASE

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There is now substantial evidence from outcome trials, in individuals who have clinically manifest coronary artery disease (CAD), confirming the benefits of treating plasma lipids as one of the key factors in retarding the progression of clinical atherosclerotic disease. Over the past decade there have been an increasing number of clinical trials which have evaluated lipid lowering treatments, confirming the pathophysiological and epidemiological associations between plasma lipids and the progression of artery disease. CAD is demonstrated by angiographic confirmation of coronary artery lumen narrowing and has its clinical manifestations (coronary heart disease—CHD) as angina, unstable angina, myocardial infarction or revascularisation procedures such as percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft surgery (CABG).

While acknowledging the important public health message of risk factor modification, in particular lipid lowering, for the primary prevention of CHD, this review covers the secondary prevention of CHD by focusing on the role of lipid lowering (that is, the treatment of total and low density lipoprotein (LDL) cholesterol, serum triglycerides, and high density lipoprotein (HDL) cholesterol) in delaying the progression of the clinical and angiographic findings in patients with clinically manifest CHD.

This review is divided into three parts: background evidence; treatment thresholds and targets for secondary prevention of coronary heart disease; and practical management issues.

BACKGROUND EVIDENCE

The clinical importance of secondary prevention of CHD is highlighted by the observation in the secondary prevention trials that cardiovascular events account for 75% of the observed mortality in individuals with existing coronary disease.[1] A pronounced increase—up to 20 fold—in coronary death over a 10 year follow up was observed when there is a history of CHD,[2] compared to an individual without a history of CHD. The increased risk parallelled the degree of cholesterol elevation.

The major lipid alterations associated with the progression of coronary artery disease include not only increases in concentrations of total and LDL cholesterol, but also increases in serum triglycerides, a decrease in HDL cholesterol, as well as compositional changes in HDL and LDL cholesterol. Triglyceride-rich LDL, intermediate density lipoprotein (IDL), and chylomicron remnants are considered to be atherogenic due, in part, to their relative ease of oxidative modification enhancing foam cell production. A raised triglyceride may therefore reflect triglyceride enrichment of these particles as well as other atherogenic features including postprandial lipaemia, and a shift in the particle distribution to small/dense HDL and LDL particles and activation of clotting factors. A triglyceride elevation above 1.7 mmol/l is associated with a compositional change in LDL with a preponderance of small, dense LDL. These LDL particles (also called LDL type B or LDL-III) have the propensity to be oxidised more readily than normal sized LDL, and are cleared less efficiently by the normal receptor mediated clearance allowing more residence time in the plasma and exposure to the arterial wall.

The link of HDL to the atherosclerotic process is through the role of HDL in "reverse cholesterol transport" and the removal of atherogenic particles from the circulation by a complex process of lipid exchange and lipoprotein clearance mechanisms. A low HDL reflects an inefficient mechanism and is proposed as one mechanism to explain the epidemiological link of a low HDL and progression of CAD.

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Pathological processes in preventing progression of coronary artery disease

Cholesterol originating from plasma LDL has been shown to accumulate in subendothelial monocyte derived macrophages. Foam cells, the hallmark of the atherosclerotic plaque, occur in these macrophages when oxidised LDL is taken up by the scavenger receptor. Smooth muscle cells also become foam cells by the accumulation of lipid. Foam cells are commonly observed in the precursor (fatty streak) lesion, as well as the early fibrous and the advanced atherosclerotic plaques.

Table 1 Non-drug lipid lowering trials in subjects with coronary heart disease: trials with clinical CHD end points

	Treatments (duration)	Lipid lowering (% change)			Reduction in CHD end point
		Chol	Trig	HDL	
Medical Research Council (1969)[w1]	Soya bean (4 years)	−14			↓18% CHD
Diet and Reinfarction Trial (DART) (1989)[w2]	Low fat, fish, low fibre (2 years)	−4		0	No effect on CHD; ↓29% all cause mortality (fish diet group)
Program on the Surgical Control of the Hyperlipidemias (POSCH) (1990)[w3]	Partial ileal bypass surgery (5 years)	−28			↓35% CHD
	(10 years)	−22	+5	+5	
Cardioprotective diet study (1992)[w4]	Low fat + (high fruit, vegetables, nuts grains) *v* low fat (1 year)	−13			↓70% angina
Lyon Diet Heart Study	Mediterranean α-linolenic acid-rich diet *v* usual post-infarct prude diet	−5	−14		↓73% MI; ↓70% CV mortality
(1994)[w5]	(27 months)	↓ saturated fat, chol, PUFA (ω-6)			↓65% fatal/non-fatal MI
(1999)[w6]	(46 months)	↑ polyunsaturated fat (ω-3, ω-9)			

Baseline mean cholesterol 5.8–7.1 mmol//l.
CHD, coronary heart disease; Chol, cholesterol; CV, cardiovascular, HDL, high density lipoprotein; MI, myocardial infarction; PUFA, polyunsaturated fatty acid; Trig, triglyceride

Atherosclerotic plaques are described as stable or vulnerable (unstable), depending on the ratio between media thickness, the fibrous cap, and the lipid core. Stable lesions appear to have relatively thicker fibrous caps. Rupture of the vulnerable plaques with the subsequent clinical event is caused by biochemical/cellular processes rather than by direct mechanical factors. One proposed explanation for the reduction in clinical events with lipid lowering treatment is the effect on lipid and foam cell content of the plaque and its risk of fissuring. Lipid lowering treatment depletes lipid from the crucial lesions with a large lipid core and a preponderance of macrophages. This stabilisation effect on the lesions decreases clinical events.

Several studies have shown that inflammatory as well as thrombogenic mechanisms are associated with both the initiation and progression of atherosclerosis. Vulnerable plaques are characterised by a thin fibrous cap, a large lipid core, an abundance of macrophages and T lymphocytes, and reduced concentrations of smooth muscle cells. They are prone to rupture and have been implicated in acute coronary syndromes. Lipid lowering may reduce the risk of acute clinical events by also decreasing thrombogenicity, improving endothelial function, modifying the inflammatory response, and reducing the influx and deposition of lipids to the lipid core of the atherosclerotic plaque.[3]

Randomised controlled trials of lipid lowering assessing progression of CAD

Trial outcomes

A number of trials have measured: (1) clinical end points (including CHD events of non-fatal myocardial infarction, unstable/worsening angina, cardiac death—some trials have reported cardiovascular events of stroke and cardiovascular death); and/or (2) quantitative coronary angiography, which assessed either regression (increased diameter) and/or a slowing in the progression (defined as reduction in luminal diameter) of coronary anatomy. The angiographic trials measure continuously variable end points in up to 10 coronary artery segments in each subject, giving greater statistical power and allowing smaller and shorter trials than are needed to assess clinical outcomes.

Trial design

The studies have usually been randomised, placebo controlled comparisons of lipid lowering interventions including non-drug or drug treatments. Drug treatment has usually been initiated 1–3 months after a clinical coronary event or revascularisation procedure. A few trials have had lipid lowering treatment introduced within the first week following a clinical event. Most trials, with assessments over several years (see tables) have used unifactorial treatment (that is, only lipid lowering) and not modification of multiple risk factors.

Table 2 Non-drug lipid lowering trials in subjects with coronary heart disease: angiographic trials confirming reduced CAD progression

	Treatments	Duration
Lifestyle Heart Trial (1990)[w7]	Diet, exercise, anti-smoking, stress management	1 year
Program on the Surgical Control of the Hyperlipidemias (POSCH) (1990)[w3]	Partial ileal bypass surgery	5 years, 10 years
Heidelberg study (1992)[w8]	Ddiet + exercise	1 year
St Thomas' Atherosclerosis Study (STARS) (1992)[w9]	Diet	3 years

Cholesterol: baseline mean 6.1–7.2 mmol/l.
Lipid reduction: cholesterol −9% to −53%, triglyceride −8% to −38%.

Table 3 Statin based trials in subjects with coronary heart disease: trials with clinical CHD end points

	Treatment (duration)	Lipid lowering (% change)			Reduction in CHD end point
		Chol	Trig	HDL	
Scandinavian Simvastatin Survival Study (4S) (1994)[w10]	Simvastatin (5.4 years)	–25	–10	+8	↓34%; ↓42% CHD death
Cholesterol and Recurrent Events (CARE) (1996)[w11]	Pravastatin (5 years)	–20	–14	+5	↓24%; ↓20% CHD death
Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) (1998)[w12]	Pravastatin (6 years)	–18	–11	+6	↓24%; ↓24% CHD death
Atorvastatin versus Revascularization Treatment (AVERT) (1999)[w13]	Atorvastatin *v* angioplasty + other lipid treatment (1.5 years)	–31	–11	+8	↓36% "ischaemic events" (angioplasty, CABG, hospitalisation for angina)
Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) (2000)[w14]	Pravastatin (6.2 years)	–18	–11	+4	↓26%
Fluvastatin in Acute Myocardial Infarction (FLORIDA) (2002)[w15]	Fluvastatin (1 year)	–23 (LDL)			NS
Effects of Atorvastatin on Early Recurrent Ischemic Events in Acute Coronary Syndromes (MIRACL) (2001)[w16]	Atorvastatin (16 weeks)	–27	–16	+4	NS (only ↓re-hospitalisation for symptomatic myocardial ischaemia)
Heart Protection Study (HPS) (2002)[w17]	Simvastatin (5 years)	–20	–16	+3	↓24%
Lescol Intervention Prevention Study (LIPS) (2002)[w18]	Fluvastatin (3.9 years)	-27 (LDL)	–22	+22	↓26% (cardiac death, MI or revascularisation)

NS, non-significant/no change.
Baseline mean cholesterol 5.3 –6.9 mmol/l.

Some recent trials have included newer drugs or used higher doses against other lipid lowering ("usual" or "standard" care) as the treatment comparator. All classes of lipid lowering have been assessed, although most trials have used a statin based regimen because of their enhanced efficacy and tolerability.

Trial results

Tables 1–6 summarise the randomised controlled trials of lipid lowering in subjects with established CHD where there has been an assessment of the progression of coronary atherosclerosis by either clinical end points or angiography. The baseline cholesterol, lipid lowering and clinical CHD (fatal/non-fatal myocardial infarction, angina) or angiographic end points are presented for the treatment group only in the tables.

The consistent and statistical slowing in the rate of progression of coronary stenoses has been demonstrated in most trials with only small differences (in millimetres) in the mean measured diameter between treatment and control groups. Regression, while not always assessed, was not a consistent finding. By comparison the magnitude of clinical CHD benefit observed (with lipid lowering) raises the possibility that the angiographic studies which only assess anatomical changes underestimate the full benefit of lipid treatment.

The benefits of lipid lowering were observed for both high and low baseline lipid concentrations (baseline mean cholesterol concentrations are detailed in the tables) in both clinical end point and angiographic studies.

TREATMENT THRESHOLDS AND TARGETS FOR SECONDARY PREVENTION OF CORONARY HEART DISEASE

There are several recent published guidelines derived from clinical trials before 2002, with treatment thresholds and targets for the management of lipids in patients with clinical CHD (table 7). All guidelines endorse lipid lowering treatments and other risk factor modifications in order to reduce progression of coronary artery disease (secondary prevention).[4–8]

The current guidelines (table 7) have an LDL treatment threshold, but only the Canadian recommendations have included HDL (as a cholesterol:HDL cholesterol ratio). It is of interest that LDL is not usually directly measured, but is calculated by the Friedwald formula which requires parameters of measured total cholesterol, HDL cholesterol, and a fasting triglyceride. The formula is imprecise when triglycerides are > 4.5 mmol/l.

New evidence: treatment targets, dose, and when to start treatment

While epidemiological data indicate that there is no threshold effect for the link between raised serum lipids and clinical CHD, the benefits of lipid lowering in the major trials have not been consistent at lower lipid concentrations. Data from CARE indicate no added clinical CHD benefit with a treatment LDL cholesterol of < 3.2 mmol/l, and the Pravastatin Pooling Project results support this observation.[9] In the angiographic studies there appears to be no added benefit for regression with treatment of LDL cholesterol below 2.4 mmol/l. By contrast the more recent HPS study indicates clinical benefit with treatment of cholesterol < 3.5 mmol/l or LDL cholesterol < 2.0 mmol/l.

Two separate treatment paradigms have emerged from the above trial data: (1) similar to the "aspirin-for-all"' paradigm which supports the role of statin treatment regardless of the lipid concentration (and perhaps regardless of cost); and (2) "lipid paradigm" which uses lipid concentrations to guide treatment and dose adjustments in order to achieve targets. This area of therapeutics may be resolved with the results of newer trials and pharmacoeconomic data. The trials have usually used mid to high dose statins and have not assessed any dose effect. Importantly statins at low dose exert most of

Table 4 Statin based trials of lipid lowering in subjects with coronary heart disease (angiographic trials)

Angiographic trials confirming reduced CAD progression	Treatments	Duration
Familial Atherosclerosis Treatment Study (FATS)(1990)[w19]	Nicotinic acid + colestipol Lovastatin + colestipol	2.5 years
University of California, San Francisco Arteriosclerosis Specialised Center of Research Intervention Trial (UCSF-SCOR) (1990)[w20]	Colestipol/nicotinic acid/lovastatin	2 years
Monitored Atherosclerosis Regression Study (MARS) (1993)[w21]	Lovastatin	2.2 years
Canadian Coronary Atherosclerosis Intervention Trial (CCAIT) (1994)[w22]	Lovastatin	2 years
Stanford Coronary Risk Intervention Project (SCRIP) (1994)[w23]	Exercise + colestipol/nicotinic acid/ gemfibrozil/ lovastatin/probucol	4 years
Multicenter Anti-Atheroma Study (MAAS) (1994)[w24]	Simvastatin	4 years
Familial Hypercholesterolaemia Regression Study (FHRS) (1995)[w25]	LDL apheresis + simvastatin Colestipol + simvastatin	2.1 years
Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC 1) (1995)[w26]	Pravastatin	3 years
Regression Growth Evaluation Statin Study (REGRESS) (1995)[w27]	Pravastatin	2 years
LDL-Apheresis Atherosclerosis Regression Study (LAARS) (1996)[w28]	LDL apheresis + simvastatin Simvastatin	2 years
Lipoprotein and Coronary Atherosclerosis Study (LCAS) (1997)[w29]	Fluvastatin Fluvastatin + cholestyramine	2.5 years
Post Coronary Artery Bypass Graft Trial (Post-CABG) (1997)[w30]	Lovastatin	4.3 years (reduced rate of revascularisation)
HDL-Atherosclerosis Treatment Study (HATS) (2001)[w31]	Simvastatin + niacin Antioxidants Simvastatin + niacin + antioxidants	3 years

Baseline mean cholesterol 4.2–9.9 mmol/l. Lipid reduction: cholesterol –13% to –53%, triglyceride –8% to –27%.

Angiographic trial *not* confirming reduced CAD progression	Treatment	Duration
Harvard Atherosclerosis Reversibility Project (HARP) Group (1994)[w32]	Pravastatin/nicotinic acid/cholestyramine/gemfibrozil	2.5 years

Baseline mean cholesterol 5.5 mmol/l. Lipid reduction: cholesterol –26%, triglyceride –20%.

their biological effect in lipid lowering and have a reduced side effect potential. A doubling of dose does not double the lipid response but has a small increment of benefit.

Most trials have introduced lipid lowering treatment after a minimum of 1–3 months following a clinical event. A few randomised trials have assessed outcome following early initiation (1–14 days) of statin treatment. No benefit in definite clinical CHD end points of myocardial infarction or angina was observed in the MIRACL and FLORIDA studies, while treatment benefits were observed in the LIPS trial. The recent SYMPHONY study[10] showed no improvement with early drug initiation in clinical outcome over 12 months.

New evidence: HDL cholesterol

The majority of trials which are statin based have clearly shown delay in progression of CAD manifested by a reduced number of CHD events. However, importantly in these trials all new clinical events were not abolished by treatment. This finding underscores the key role of other factors besides the concentration of LDL, and includes HDL, compositional (size)

Table 5 Non-statin based trials in subjects with coronary heart disease: trials with clinical CHD end points

		Lipid lowering (% change)			
	Treatment	Chol	Trig	HDL	Reduction in CHD end point
Coronary Drug Project (1975)[w33]	Nicotinic acid Clofibrate	–10 –7	–26 –22		↓23% ↓23%
Stockholm Ischaemic Heart Disease Secondary Prevention Study (1988)[w34]	Clofibrate + nicotinic acid	–13	–19		↓36%
Veterans Affairs Cooperative Studies Program: High Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) (1999)[w35]	Gemfibrozil	–4	–31	+6	↓22%
Bezafibrate Infarction Prevention (BIP) Study (2000)[w36]	Bezafibrate	–4	–21	+18	NS (↓40% only in Trig >2.3)

Baseline mean cholesterol 4.5–6.5 mmol/l.

Table 6 Non-statin based trials in subjects with coronary heart disease: angiographic trials confirming reduced CAD progression

	Treatments	Duration
Finnish regression study (1983)[w37]	Clofibrate + nicotinic acid	7 years
NHLBI coronary intervention study (1984)[w38]	Cholestyramine	5 years
Cholesterol Lowering Atherosclerosis Study (CLAS I) (1987)[w39], (CLAS II) (1990)[w40]	Nicotinic acid + colestipol	2 years, 4 years
St Thomas' Atherosclerosis Study (STARS) (1992)[w9]	Cholestyramine	3 years
Bezafibrate Coronary Atherosclerosis Intervention Trial (BECAIT) (1996)[w41]	Bezafibrate	5 years
Lopid Coronary Angiography Trial (LOCAT) (1997)[w42]	Gemfibrozil	2.6 years
Diabetes Atherosclerosis Intervention Study (DAIS) (2001)[w43]	Fenofibrate	3 years

Baseline mean cholesterol 5.4–8.0 mmol/l.
Lipid reduction: Cholesterol –9% to –27%, triglyceride –18% to –40%.

changes of LDL, and raised serum triglycerides as well as non-lipid factors. Additionally, from the trial data, CHD risk of a low HDL is not altered by statin treatment.[9] It is of interest that there are emerging recommendations for an HDL treatment target, in addition to LDL, in preventing progression of CAD.[11]

New evidence: diabetes

The emerging awareness of a diabetes epidemic underscores the importance of the high CHD rates contributing to the 80% cardiovascular mortality in type 2 diabetes.

Current guideline recommendations have not incorporated fully the positive trial results of the diabetic subgroups in 4S, LIPID, CARE, BIP, VA-HIT, and the recent HPS, as well as the fibrate trial data (DAIS) in exclusively diabetic coronary subjects assessed for angiographic coronary regression. The recent subgroup analysis from the Pravastatin Pooling Project indicated that at low LDL cholesterol, the higher rates of CHD progression in those subjects with diabetes were reduced by treatment to the rates observed in the non-diabetic group.[12]

The benefits of lipid lowering, even at low LDL concentrations, and improving the raised triglyceride and low HDL concentrations (the "diabetic dyslipidaemia"), have already been incorporated in recent international diabetes management guidelines.

PRACTICAL ISSUES IN THE MANAGEMENT LIPID LOWERING

In order to achieve lipid treatment targets, both dietary and drug interventions have a role as both been shown to have clinical benefit. Additional advice to attain ideal body weight (such as calorie restriction or reduction of excess alcohol to a moderate intake), stop smoking, and increase aerobic exercise all have a modest effect on increasing HDL and variable effects on lowering triglyceride and LDL cholesterol.

Primary/secondary causes of hyperlipidaemia

Common genetic factors may be the underlying aetiological factor in the presentation of hypercholesterolaemia. These include polygenic hypercholesterolaemia (prevalence 1:200) or less commonly familial hypercholesterolaemia (prevalence of 1:500 in the heterozygous form). An elevation in both cholesterol and triglyceride may be a feature of familial combined hyperlipidaemia (prevalence 1:250).

Important secondary and modifiable causes of a raised cholesterol include thiazide diuretics, often used at higher than conventional dose, and untreated hypothyroidism. Lower dose thiazide or alternative diuretic and thyroid replacement, if indicated, may in some cases achieve desirable lipid targets.

Is there a role for dietary modification?

Diet "responders" may be able to reduce lipid concentrations and achieve treatment targets. Although the response is variable, greater effects with triglyceride lowering than with cholesterol lowering may be observed, in particular with weight loss. Guideline recommendations include a reduction of total fat $< 30\%$ of energy intake, saturated fat to 7–10% of total calories, and dietary cholesterol intake < 300 mg/day. In practical terms this requires a reduction in foods containing these constituents.

Reducing saturated fat content of the diet may, in some cases, reduce plasma LDL by up to 5–20%. Trans fatty acids (that is, *trans* configuration) which are produced by catalytic hydrogenation of polyunsaturated fats result in solidification of fats, which are used by the food industry in the production of margarines, biscuits, and peanut butter. These fats have an LDL and triglyceride elevating effect as well as an effect in reducing

Non-drug treatment trials (tables 1 and 2): key points

- Baseline mean cholesterol in the non-drug treatment trials ranged from 5.8–7.2 mmol/l
- Dietary modification alone or surgical intervention (one trial) lower both cholesterol and triglycerides and raise HDL. They are associated in the angiographic trials with reduced progression of coronary atherosclerosis. This has been supported by the significant reduction in some, but not all, trials in the incidence of clinical coronary end points. Diet modification affecting progression included reductions in intakes of energy and saturated (palmitic and stearic) fat and trans-fatty acids
- The type of dietary intervention appears to be an important factor for CHD reduction as a reduced fat diet alone has not been shown to be clinically effective, while other more specific diets were associated with reduced CHD, despite having no significant lipid lowering effect
- The most effective diet for secondary prevention is low in saturated fat and is supplemented with polyunsaturated (ω-3) fatty acids which are in vegetables, oily fish, and some nuts. The enhanced clinical benefit has been ascribed to both lipid lowering and the effects on thrombosis as well as atherogenesis

Drug (statin and non-statin) treatment trials (tables 3–6): key points

- Baseline or pretreatment mean cholesterol in the drug treatment clinical end point trials ranged between 5.3–6.9 mmol/l and in the drug treatment coronary angiography trials between 4.2–9.9 mmol/l
- Lipid lowering (monotherapy or combination) drug treatment in the trials was associated with pronounced reductions in both cholesterol and serum triglycerides, but also an increase in HDL. There was a near universal finding in the angiographic trials of 1–2% reduced progression of coronary artery stenoses. By contrast in the clinical outcome trials there was a greater percentage reduction (between 24–34%) in the incidence of clinical CHD end points (fatal/non-fatal myocardial infarction, unstable angina) with lipid lowering. The relatively small improvements in the severity in the stenotic lesions compared with the pronounced changes in clinical benefits suggests that there are also other physiological treatment benefits (beyond the scope of this review). In some trials (4S, CARE, LIPID, HPS) other cardiovascular end points (stroke, revascularisation procedures, and congestive cardiac failure) were also reduced with effective lipid lowering
- Subgroup analyses were reported in the clinical end point trials, and confirmed similar CHD risk reductions in the following:
  - younger compared with older age groups
  - the presence of other risk factors (smoking, hypertension)
  - diabetes
  - across the population range for cholesterol, HDL, and triglyceride
- The CARE study was one of the first randomised controlled trials to assess inflammatory markers. The study confirmed that the inflammatory markers C reactive protein and serum amyloid were higher in those with highest coronary risk. This risk was attenuated by lipid lowering with statin treatment. In some trials (SCRIP, 4S, LIPID) where substantial improvements in lipids were observed, the decreased rate of progression of coronary atherosclerosis was translated into reduced hospitalisations for clinical cardiac events
- Concerns regarding non-CHD mortality with lipid lowering treatment were allayed following the results of 4S in 1994 where there was a 30% reduction in all cause mortality. Several subsequent studies have confirmed this finding—POSCH, LIPID (–22%), and HPS (–12.9%). In these trials, there appeared a lag phase of 1–2 years before a treatment benefit was seen for fatal outcomes

HDL. Reduction of trans fatty acids and cholesterol, although small components of diet, may also assist in reducing cholesterol concentrations. The addition of monounsaturated (for example, olive oil) and polyunsaturated fats (of the natural occurring *cis* configuration) reduce total and LDL cholesterol.

Fish oils which are high in ω-3 polyunsaturated fats as part of the usual diet in the form of fish portions have minimal effects on lipid lowering, but appear to have benefits with regards to clinical coronary disease which has been attributed to the effects on thrombogenesis. Pharmacological doses of fish oils have a pronounced triglyceride lowering effect and are indicated in severe hypertriglyceridaemia (for example, triglycerides > 10 mmol) in order to reduce the risk of pancreatitis. In the absence of a raised triglyceride, pharmacological doses of fish oils may elevate LDL cholesterol and are therefore not recommended in routine management of raised cholesterol in order to reduce the progression of clinical coronary disease.

Plant sterols (phytosterols) and stanols inhibit the absorption of cholesterol from the gut. The esterification of sterol and stanols permits their incorporation into foods such as margarine spreads and yoghurts without altering taste or texture of the food substance. Sterol products may reduce LDL cholesterol by up to 10–15%. There is emerging information of a small additive LDL lowering effect when used in combination with statin drugs.

What if diet and lifestyle change are not enough? The role of drug treatment

Pravastatin and simvastatin (at the 40 mg dose) have been the main statin drugs used in trials confirming reductions in definite clinical end points of myocardial infarction or angina and CHD mortality. There is one recent study with fluvastatin (80 mg). In several angiographic trials, treatment with either pravastatin, simvastatin, lovastatin (currently not available in the UK) or fluvastatin has produced a decrease in coronary progression. The trials based on fibrate, nicotinic or bile acid sequestrant lipid lowering are fewer in number than statin based trials; however, similar benefits were confirmed with regards to reduced progression as a result of the treatment induced lipid lowering.

Statins: efficacy/tolerability/safety

The most effective and widely used cholesterol lowering drugs are the statins (HMG CoA reductase inhibitors). These drugs inhibit the rate limiting enzyme (3-hydroxy 3-methylglutaryl CoA reductase) in cholesterol biosynthesis, thereby reducing the formation of cholesterol in the liver. This lowering of intracellular cholesterol results in upregulation of hepatic LDL receptors with enhanced clearance of plasma LDL, thereby lowering total cholesterol. A lowering of both small and large LDL particles are observed with the statin induced reduction in LDL. Triglyceride lowering is also observed with all statins in a dose dependent fashion (up to 10–20% triglyceride reductions), which appears to correlate with LDL lowering. An HDL increase of 5–12% appears to be independent of statin dose used.

Table 8 lists the number of patients needed to treat over five years to prevent one CHD event in the secondary prevention trials.

Currently available statins in the UK include the first generation fungal metabolites, simvastatin and pravastatin, and the synthetic second generation compounds, atorvastatin and fluvastatin. These drugs have different dose efficacy with regards to LDL lowering, and according to dose may achieve lowering of cholesterol of up to 55%. Many individuals will achieve target lipid concentrations at the lowest dose of statin used. If pretreatment lipid concentrations are high or if lipid lowering response is poor, uptitration to maximum dose may be necessary to maximise lipid lowering effect.

In the statin clinical trials, drug induced side effects were similar to that observed in placebo. In routine practice these drugs are generally well tolerated; however, idiosyncratic adverse effects are observed in some individuals—abdominal pain, dyspepsia, myalgia (without creatine kinase (CK) rise), erectile dysfunction or sleep disturbance. Additional biochemical effects include the risk of raised liver enzymes, reportedly between 1–2% per year. A much rarer side effect, in the order of 1:1000, is myopathy. The potentially fatal side effect of rhabdomyolysis is extremely rare.

Variations in the physical properties of the statins may account for some pharmacodynamic observations. Atorvastatin and fluvastatin do not appear to be influenced significantly

Table 7 Current guidelines for management of patients with clinical CHD ("secondary prevention")

Guidelines	Treatment thresholds			Treatment targets		
	Cholesterol (mmol/l)	LDL-C (mmol/l)	Chol:HDL-C ratio	Cholesterol (mmol/l)	LDL-C (mmol/l)	Chol:HDL-C ratio
Joint British Societies (1998)[4]	≥5.0	≥3.0		<5.0	<3.0	
National Service Framework for coronary heart disease (2000)[5]				<5.0 or –25% reduction	<3.0 or –30% reduction	
Joint European Societies (1998)[6]	≥5.0	≥3.0		<5.0	<3.0	
USA (NCEP-ATP III) (2001)[7]		≥2.6 (therapeutic lifestyle change) ≥3.4 (drug)			<2.6	
Canadian Recommendations (2000)[8]		≥3.5 or	>5.0	<2.5 and	<2.0 and	<4.0

Table 8 Number of patients needed to treat (NNT) over five years to prevent one CHD event (fatal or non-fatal myocardial infarction) in secondary prevention trials

Cholesterol (mean) (mmol/l)		Trial data	NNT
"High"	6.8 (range 5.5–8)	4S (statin)	22
"Average-high"	5.9 (above 3.5)	HPS (statin)	32
"Average-high"	5.6 (range 4.0–7.0)	LIPID (statin)	28
"Average"	5.4 (below 6.2)	CARE (statin)	33
"Low"	4.5	VA-HIT (fibrate)	23

by renal impairment. There is a suggestion that the differences in the lipophilicity of the statins may influence both their clinical efficacy and tissue side effect profile with regards to specific tissues (for example, muscle toxicity). Pravastatin and fluvastatin are considered to be hydrophilic while simvastatin and atorvastatin are lipophilic. In clinical practice borderline elevation in liver function tests and muscle enzymes (in the absence of myalgia) may occur with all statins and should be monitored without withdrawal of statin treatment. Significant increases in liver enzymes (3× the upper limit of normal) and CK (10× the upper limit of normal—defined as "myositis") are clear indications for statin withdrawal. Myalgia without CK elevation is also an indication for withdrawal/change to an alternative statin. Occasionally changing to an alternative compound with different metabolic or lipophilic characteristics or reducing the dose may result in clinical efficacy without undesirable effects.

Drug interactions may depend upon the cytochrome P450 enzyme system which is the metabolic pathway for all statins (except for pravastatin which is metabolised by sulfation, oxidation, and glutathione conjugation). Potential adverse drug interactions resulting from the cytochrome P450 pathway include the use of statins in combination with erythromycin, warfarin, anticoagulants, azol antifungals (ketoconazole), some oral contraceptives, nicotinic acid, cyclosporin, grapefruit juice, and protease inhibitors.

Is there a role for non-statin drug treatment?

There is now trial evidence supporting the use of drugs other than statin compounds, particularly fibrate acid derivatives (bezafibrate, fenofibrate, and gemfibrozil).[13] These drugs have been also recommended if there is statin intolerance/lack of effect or there is a hypertriglyceridaemia and/or a low HDL. Fibrates have been shown to have a notable triglyceride lowering effect, but they also lower LDL and increase HDL, with confirmed clinical benefit regarding reduced CAD

Table 9 Decrease in new CHD according to percentage cholesterol reduction in the cholesterol lowering drug trials versus tryglyceride lowering drug trials (adapted from Durrington *et al*[13])

	Trial	% Cholesterol reduction in trial	% Decrease in new CHD per 1% cholesterol reduction
Cholesterol (total-LDL) lowering treatment			
Bile acid sequestrant	*LRCC[w44]	–11	2.2
HMG Co-A reductase inhibitors (statins)	*WOSCOPS[w45]	–20	1.6
	*AFCAPS/TexCAPS[w46]	–18	2.1
	4S[w10]	–29	1.1
	CARE[w11]	–20	1.2
	LIPID[w12]	–18	1.3
Triglyceride lowering treatment			
Fibrate	*WHO[w47]	–9	2.2
	*Helsinki Heart Study[w48]	–10	3.4
	Scandinavian Secondary Prevention Study[w34]	–13	3.2
	*SENDCAP[w49]	–7	9.7
	VA-HIT[w35]	–4	5.5

*Primary prevention trials.

progression. Clofibrate is currently no longer recommended because of its association with gallstones and adverse surgical outcome.

There is evidence that fibrates have an effect in altering the composition of LDL towards a less atherogenic particle size—that is, a shift from small/dense to larger/more buoyant LDL. Statins lower the concentration of LDL particles. This has been one of the proposed mechanisms for the notable clinical benefit in the triglyceride lowering trials, where there were only modest reductions in cholesterol lowering (table 9).

Reported fibrate side effects are similar to those of statins and also include drug rash. Potential drug interactions include anticoagulants as there appears to be displacement of plasma proteins which could adversely effect the anticoagulant effect.

The role of other lipid lowering drugs including resins and nicotinic acid have been assessed in a limited number of randomised controlled trials. Although the few trials to date have shown successful lipid lowering and clinical benefits, both drugs are limited by their side effect profiles. Combining resin and statin produces a synergistic effect on cholesterol lowering, while nicotinic acid should not be routinely combined with statin treatment because of the risk of myopathy. The nicotinic acid associated flushing can be blocked by aspirin, indicating a prostaglandin induced effect. A gradual increase in dose may ameliorate the frequency of side effects.

Lipid lowering drug combinations

While combinations of lipid lowering drugs do not have specific licence, there are several clinical studies on the enhanced efficacy (for example, for refractory cases) of combining lipid lowering drugs with different modes of action. Studies have shown safety over several years, but have included only highly selected patients, in particular those who are tablet compliant, avoid alcohol excess, have normal renal function, and are not on other multiple medications.[14 15] Most of the reported hazards have been associated with the use of statins, in particular lovastatin or cervastatin, in combination with fibrates—mainly gemfibrozil (this drug has a distinct chemical structure compared to the other fibric acid derivatives).

THE FUTURE

In the next five years several treatment trials will be completed which should provide data on "which statin dose" and "how low should lipids be lowered" in order to achieve clinical benefit,[16] as well as clear pharmacoeconomic data, and the therapeutic role for an HDL ± triglyceride target. Additionally the future introduction of newer lipid lowering drugs[15] with greater cholesterol lowering efficacy ("superstatins"), as well as drugs with different modes of action (for example, cholesterol absorptive inhibitors), will add further options for managing the lowering of lipids in order to delay the progression of coronary artery disease.

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Additional references appear on the *Heart* website—www.heartjnl.com/supplemental