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Medical Lipid-Regulating Therapy
Current Evidence, Ongoing Trials and Future Developments

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Abstract

Coronary heart disease (CHD) is a major cause of morbidity and mortality worldwide. Elevated low density lipoprotein-cholesterol (LDL-C) and reduced high density lipoprotein-cholesterol (HDL-C) levels are well recognised CHD risk factors, with recent evidence supporting the benefits of intensive LDL-C reduction on CHD risk. Such observations suggest that the most recent National Cholesterol Education Program Adult Treatment Panel III guidelines, with LDL-C targets of 2.6 mmol/L, may result in under-treatment of a significant number of patients and form the basis for the proposed new joint European Societies treatment targets of 2 and 4 mmol/L, respectively, for LDL and total cholesterol. HMG-CoA reductase inhibitors (statins) reduce LDL-C by inhibiting the rate-limiting step in cholesterol biosynthesis and reduced CHD event rates in primary and secondary prevention trials. The magnitude of this effect is not fully accounted for by LDL-C reduction alone and may relate to effects on other lipid parameters such as HDL-C and apolipoproteins B and A-I, as well as additional anti-inflammatory effects. With increasing focus on the benefits of intensive cholesterol reduction new, more efficacious statins are being developed. Rosuvastatin is a potent, hydrophilic enantiomeric statin producing reductions in LDL-C of up to 55%, with about 80% of patients reaching European LDL-C treatment targets at the 10 mg/day dosage.

The Heart Protection Study (HPS) demonstrated that LDL-C reduction to levels as low as 1.7 mmol/L was associated with significant clinical benefit in a wide range of high-risk individuals, including patients with type 2 diabetes mellitus, or peripheral and cerebrovascular disease, irrespective of baseline cholesterol levels, with no apparent lower threshold for LDL-C with respect to risk. Various large endpoint trials, including Treating to New Targets (TNT) and Study of Effectiveness of Additional reductions in Cholesterol and Homocysteine (SEARCH) will attempt to further address the issue of optimal LDL-C reduction. At low LDL-C levels, HDL-C becomes an increasingly important risk factor and is the primary lipid abnormality in over half of CHD patients, with the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study set to assess the effect of raising HDL-C on cardiovascular events in patients with low HDL-C and LDL-C levels below 3 mmol/L.

A variety of agents are being developed, which affect both LDL-C and HDL-C metabolism, including inhibitors of acyl-coenzyme A-cholesterol acyl transferase, microsomal transfer protein and cholesterol ester transfer protein, as well as specific receptor agonists. Ezetimibe is a selective cholesterol absorption inhibitor, which produces reductions in LDL-C of up to 25 and 60% reduction in chylomicron cholesterol content with a 10 mg/day dosage.

A 1 mmol/L reduction in LDL-C results in a 25% reduction in cardiovascular risk, independent of baseline LDL-C levels. Growing evidence supports the concept that lower is better for LDL-C and that increasing HDL-C represents an important therapeutic target. Furthermore, there is growing appreciation of the role of inflammation in atherogenesis. Consequently, increasing numbers of people should receive lipid-regulating therapy with the development of newer agents offering potential mechanisms of optimising lipid profiles and thus risk reduction. In addition, the pleiotropic anti-inflammatory effects of lipid lowering therapy may provide further risk reduction.

Despite major advances in the pharmacological and surgical treatment of cardiovascular disease, coronary heart disease (CHD) remains the leading cause of death in the industrialised world,[1] with the global burden of disease continuing to increase in association with the increasing prevalence of type 2 diabetes mellitus, obesity and the metabolic syndrome.[2] Elevated levels of total cholesterol and low density lipoprotein cholesterol (LDL-C) are well recognised CHD risk factors[3] and the reduction of total cholesterol and LDL-C is associated with numerous sequelae, which attenuate atherogenesis including improved endothelial function, reduced oxidative stress and reduced inflammation.[4,5] Cholesterol reduction is associated with a reduced risk of CHD,[6,7] with recent evidence from the Medical Research Council/British Heart Foundation Heart Protection Study (HPS) demonstrating that the benefits of cholesterol-lowering therapy extend into all forms of atherosclerotic vascular disease including peripheral vascular disease and cerebrovascular disease.[8]

Observational studies indicate a continuous and positive relationship between plasma cholesterol levels and cardiovascular risk, with no apparent lower threshold level at which there is no increased risk.[9,10] This relationship is approximately linear when plotted on a logarithmic scale, implying that the proportional reduction in relative risk is similar throughout the range of cholesterol levels.

Several large randomised trials have shown that LDL-C reduction with the HMG-CoA reductase inhibitors (statins) of 25–35% is associated with a 24–37% decrease in cardiovascular mortality.[11-13] Furthermore, reductions in coronary death of up to 24% with a long-term difference of 1 mmol/L in LDL-C levels in individuals with and without diagnosed vascular disease, irrespective of baseline

LDL-C levels,[8] raise questions regarding optimal target levels for cholesterol and imply a 'lower the better' approach to cholesterol reduction.

Currently there are five main classes of drugs available for the treatment of dyslipidaemia: bile acid binding agents (resins); fibric acid derivatives (fibrates); nicotinic acid (niacin); HMG-CoA reductase inhibitors (statins); and ezetimibe and the phytostanols and esters, although these are not yet in widespread use. The statins are the most potent LDL-C-lowering agents, but have variable effects on high density lipoprotein-cholesterol (HDL-C). This is a potential limitation with respect to optimal CHD risk reduction with statin therapy, since low HDL-C is the primary lipid abnormality in approximately half of CHD patients.[14]

In this article we review the most recent evidence and guidelines regarding lipid lowering and vascular risk reduction, and how these may influence the design and objectives of future clinical trials. In addition, with increasing focus on the potential benefits of intensive lipid modification, we also discuss recent advances in lipid-lowering therapy and how these may relate to future treatment strategies.

1. Cholesterol Lowering: Completed Trials and Current Evidence

Despite the clear epidemiological association between cholesterol and cardiovascular risk, the majority of individuals who develop vascular disease do not have particularly elevated cholesterol levels.

Epidemiological evidence supporting the notion that lower LDL-C levels are associated with lower CHD risk comes from, among others, studies of men in rural China, where subjects in the lowest quartile of LDL-C (<3.0 mmol/L) had coronary event rates 75% lower than those in the highest quartile.[15] Further evidence in support of this notion comes from the Seven Countries study,[16] as well as prospective longitudinal studies such as the Prospective Cardiovascular Munster (PROCAM) study and the Framingham study.[17,18] Every major clinical endpoint trial of statin therapy has demonstrated that lower LDL-C levels are associated with a reduced atherosclerotic disease burden.[6] Such observations suggest that there may be no threshold for LDL-C reduction beyond which additional cardiovascular benefit may not be achieved.

Controversy thus remains with respect to the magnitude of LDL-C reduction required to maximise clinical benefit. The results of the HPS[8] demonstrated a similar 25% event rate reduction with 1 mmol/L reduction in LDL-C independent of pretreatment levels, with continuing benefit seen with LDL-C reduction to levels as low as 1.7 mmol/L. These observations suggest that there appears to be no baseline threshold for initiation of statin therapy, and current guidelines such as the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III and the 2nd European Joint Task Force recommendations,[19,20] with LDL-C goals of 2.6 and 3.0 mmol/L, respectively, may lead to under-treatment of at-risk individuals who present with LDL-C levels at or near these levels. The question that remains is how low these treatment goals should be, a situation which may be addressed by the new Joint European Societies guidelines, which are due to be published in mid 2004 and are set to define treatment goals of 2 and 4 mmol/L, respectively, for LDL and total cholesterol.

In HPS the chief determinants of CHD risk were pre-existing vascular disease (CHD, cerebrovascular disease, peripheral vascular disease), the presence or absence of type 2 diabetes, or some combination of these conditions, with significant reductions in risk produced by statin therapy irrespective of pretreatment LDL-C levels. On the basis of such observations it appears logical to include peripheral vascular disease, cerebrovascular disease and CHD in assessing the need to commence statin therapy.

The benefits of LDL-C reduction in individuals with LDL-C levels at or near present target values was further illustrated in a post-coronary percutaneous intervention study using fluvastatin,[21] while the benefits of intensive cholesterol lowering on cardiovascular events are further supported by the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial.[22] The Atorvastatin versus Simvastatin on Atherosclerosis Progression (ASAP) and Arterial Biology for the Investigation of the Treatment Effects of Reducing cholesterol (ARBITER) studies[23,24] demonstrated the effects of intensive cholesterol reduction on the

Table I. Future studies evaluating the clinical benefits of more aggressive cholesterol lowering

Trial	No. of participants	Treatment	Primary endpoint
IDEAL[26]	7600	Atorvastatin 80mg or simvastatin 20–40mg	Coronary death or nonfatal MI
SEARCH[27]	12 000	Simvastatin 80 or 20mg ± vitamin B12 and folic acid (2mg)	Coronary death or nonfatal MI
BELLES[28]	600	Atorvastatin 80mg or pravastatin 40mg	Calcium content of coronary arteries by EBCT
REVERSAL[26]	600	Atorvastatin 80mg or pravastatin 40mg	Coronary artery intimal medial accumulation of lesions as measured by IVUS
TNT[29]	>10 000	Atorvastatin 10 or 80mg	Coronary death or nonfatal MI
HPS II[30]	10 000	Simvastatin 80 or 20–40mg ± vitamin B12 and folic acid (2mg)	Major cardiovascular events

BELLES = Beyond Endorsed Lipid Levels Evaluation Study; **EBCT** = electron beam computerised tomography; **HPS II** = Heart Protection Study II; **IDEAL** = Incremental Decrease in End points through Aggressive cholesterol Lowering; **IVUS** = intravascular ultrasound; **MI** = myocardial infarction; **REVERSAL** = Reversal of Atherosclerosis with Lipitor Study; **SEARCH** = Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine; **TNT** = Treating to New Targets.

early structural changes of atherosclerosis in the form of reduction in carotid intima media thickness.

The Antihypertensive and Lipid-Lowering Treatment to prevent Heart Attack Trial (ALLHAT-LLT), in which more than 10 000 moderately hypercholesterolaemic, hypertensive individuals were randomised to receive either usual care or pravastatin 40 mg/day, demonstrated no significant difference in CHD mortality between both groups.[25] Because of the use of non-trial statins and crossovers in the usual-care group, there were only modest differences in total cholesterol (9.6%) and LDL-C (16.7%) between the two groups. This observation, that less cholesterol lowering produces less clinical benefit, provides further indirect support for the hypothesis that robust LDL-C reduction is required to produce significant outcome benefits. The results of ALLHAT-LLT also suggest that cholesterol lowering remains central to the benefits produced by statin therapy for CHD prevention and that the reported pleiotropic effects do not appear to significantly contribute to the therapeutic benefits of statins.

The pertinent clinical question, therefore, is whether larger reductions in LDL-C may produce greater risk reductions, an issue that is the subject of various ongoing randomised trials.

2. Ongoing Clinical Trials of Lipid-Lowering Therapy

A number of clinical trials assessing the potential benefits of aggressive cholesterol lowering are under way (table I). In the Treating to New Targets (TNT) trial, more than 10 000 patients have been enrolled to assess the effects of LDL-C reduction to below 2.6 mmol/L in patients aged 35–75 years who have had a major coronary event within the previous 5 years.

In the Incremental Decrease in Endpoints through Aggressive Lipid lowering (IDEAL) trial, 7600 patients with a history of myocardial infarction will be randomised to atorvastatin 80 mg/day or simvastatin 20 mg/day, titrated to 40mg/day if total cholesterol remains >5 mmol/L. A follow-up period of 5.5 years is planned and a large segment of elderly patients will be studied.

The Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) is a secondary prevention trial of 12 000 patients with a 2×2 factorial design to simvastatin 80 mg/day or simvastatin 20 mg/day with or without folate (2 mg/day)/vitamin B12. Other studies using electron beam computerised tomography or intravascular ultrasound to evaluate changes in anatomic features of atherosclerosis are also under way. In the Beyond Endorsed Lipid Levels Evaluation Study (BELLES) and the Reversal of Atherosclerosis with Lipitor (REVERSAL) study, the effects of high-dose (80 mg/day) atorvastatin and pravastatin 40 mg/day on coronary atherosclerosis will be studied over 12- and 18-month periods, respectively.

The Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) study has a 2×2 factorial design and will compare the effects of atorvastatin 80 mg/day and pravastatin 40 mg/day on major cardiovascular events. The second limb

includes evaluating the effects of gatifloxacin, a fluoroquinolone, against placebo on cardiovascular events and will provide the first major endpoint evidence relating to the importance of addressing low-grade infection on cardiovascular risk.

It has been recently suggested that at low LDL-C, elevated plasma triglyceride and low HDL-C levels become increasingly important with respect to determining vascular risk.[31] Future studies will be required to specifically address the potential additional cardiovascular benefits of treating hypertriglyceridaemia and low HDL-C in patients with low LDL-C levels, particularly in view of the increasing focus on lower LDL-C treatment targets. Indeed, a clinical trial is already under way to evaluate the benefits of raising HDL-C and lowering triglyceride levels in patients with type 2 diabetes and modest LDL-C levels. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial is due to report in 2005.[32]

The clinical significance of the pleiotropic effects of statin therapy is controversial. However, a recent post hoc analysis of the West of Scotland Coronary Prevention Study (WOSCOPS) data suggested that pravastatin therapy may actually reduce incident type 2 diabetes.[33] The insulin resistance or metabolic syndrome is a recognised risk factor for both cardiovascular disease and the development of type 2 diabetes, and is estimated to affect up to 30% of the US population.[34] Indeed, the recent NCEP ATP III guidelines provide definitive criteria for the diagnosis of the metabolic syndrome.[34] Future trials may thus focus on the therapeutic effects of statins, fibrates and other agents in individuals with the metabolic syndrome, from the perspective of both cardiovascular risk and the development of type 2 diabetes.

3. High Density Lipoprotein, Triglyceride and Other Lipid Subfractions: Impact on Cardiovascular Disease

Although high LDL-C is undoubtedly a causal risk factor for CHD, LDL-C alone is insufficient to fully evaluate cardiovascular risk.[35] The role of triglyceride (TG) and HDL-C levels in determining vascular risk has been demonstrated by the PROCAM and Veterans Affairs High-density lipoprotein Intervention Trial (VA-HIT) studies.[17,36] Within each LDL-C subgroup, the risk of myocardial infarction increased with increasing TG levels and reduced HDL-C levels, an effect that was most pronounced in individuals with lower LDL-C levels.

The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) further illustrated the importance of HDL-C in predicting CHD risk in individuals with average LDL-C levels. In this study, individuals with low HDL-C and average LDL-C levels disproportionately benefited from statin therapy.[37] HDL apolipoprotein (apo)A-I kinetic studies have shown that statin treatment can increase apoA-I production but the evidence is not conclusive,[38] with cholesterol depletion in hepatocytes resulting in selective upregulation of the SRB-I receptor, facilitating the removal of HDL_2, which may account for the overcatabolism. Oversynthesis may be related to an effect on peroxisome proliferator-activated receptor α (PPARα) and increased apoA-I synthesis.[39] Statins have also been shown to produce modest reductions in cholesteryl ester transfer protein (CETP) activity;[40] since reduced CETP activity may be associated with increased HDL levels,[41] this effect may partly account for the modest effects of statins on increasing HDL. However, the precise mechanisms by which statins modify HDL-C and how individual statins may differ in this regard are still uncertain.

Although evidence accumulates to support plasma TG as a CHD risk factor, the effects of TG reduction on CHD outcome are unclear. Indeed, the NCEP ATP III guidelines recommend that correction of hypertriglyceridaemia (>1.6 mmol/L) should be considered only following the treatment of LDL-C and HDL-C to target.[34]

The influence of statins on CHD risk reduction in hypertriglyceridaemic patients also remains contentious. Statins exert TG-lowering effects via several different mechanisms: (i) by increasing expression of LDL receptors; (ii) increasing the clearance of TG-containing lipoproteins; and (iii) inducing activation of PPARα, which may decrease hepatic transcription of apolipoprotein C-III, thus altering the composition of TG-containing lipoproteins such that their catabolism is enhanced.[42] These effects may be particularly important in the management of dyslipidaemia in patients with type 2 diabetes, where

the primary defect is excess generation of TG-rich lipoprotein particles.[43]

A focus on LDL-C alone may incompletely identify patients at risk and it is also conceivable that some patients may benefit from therapy that does not have LDL-C reduction as a primary effect. Both the VA-HIT and Bezafibrate Infarction Prevention (BIP)[36,44] studies indicate that hypertriglyceridaemic patients with low HDL-C may benefit from fibrate therapy. In VA-HIT, a 22% reduction in coronary events over 5 years was seen in men with coronary disease and baseline levels of LDL-C <3.6 mmol/L, plasma TG <3.3 mmol/L and HDL-C <1 mmol/L. This risk reduction was associated with no change in LDL-C and, average reduction in TG of 31% and increase in HDL-C of 6%. Furthermore, in the Diabetes Atherosclerosis Intervention Study (DAIS), of 731 patients with type 2 diabetes, a 29% reduction in plasma TG and a 6% increase in HDL-C following therapy were associated with a significant reduction in atherosclerotic disease progression.[45] The ongoing FIELD study will attempt to address the issues of treating HDL-C and plasma TG in patients with type 2 diabetes. This is a 4-year primary prevention study using micronised fenofibrate in patients with type 2 diabetes and LDL-C inclusion criterion of <3 mmol/L and primary endpoint of cardiovascular events.[32]

The NCEP ATP III guidelines recommend the use of non-HDL-C as a secondary goal of lipid lowering after achieving target LDL-C levels.[19] Because of its simple calculation, non-HDL-C measurement is readily available in clinical practice with no additional cost. Since it circumvents TG measurement, it avoids the potential limitations of TG as a CHD risk marker and directly reflects the cholesterol content of all proatherogenic lipoprotein particles, that is, very low density lipoprotein (VLDL), intermediate density lipoprotein (IDL), LDL and even lipoprotein (a). Furthermore, since its derivation does not require a fasting sample, it avoids potential interindividual variability due to postprandial lipid changes. A routine calculated LDL-C could not circumvent many of these limitations, since its accurate estimation via the Friedwald equation requires plasma TG <4.5 mmol/L. Indeed, the results of the strong heart study, supported by data from the Systolic Hypertension in the Elderly Program (SHEP) and Lipid Research Clinics (LRC) studies,[46-48] support the utility of non-HDL-C as a superior predictor of CHD risk both in diabetic and nondiabetic individuals.

It is clear that accurate risk assessment requires the assessment of multiple lipid parameters. Optimal risk reduction and lipid-regulating therapy may require either monotherapy or combination therapy, thus resulting in the development of a targeted strategy using a variety of agents. The precedent for such an approach has been set in the evolution of pharmacotherapy in hypertension.

4. Inflammation, Coronary Heart Disease and Lipid-Lowering Therapy

Compelling evidence for the importance of inflammation in atherosclerotic disease has evolved in parallel from both clinical and experimental studies.[49] Indeed, accumulating data indicate that insights gained from the link between inflammation and atherosclerosis may yield prognostic information of potential clinical value.

A variety of studies have demonstrated that inflammation, as measured by C-reactive protein (CRP) levels, may be an important cardiovascular risk factor.[50] These studies have included elderly as well as middle-aged subjects and have shown consistency for the development of first-ever myocardial infarction, stroke or symptomatic peripheral vascular disease.[50] Indeed, in a recent study of 27 939 women followed for 8 years for vascular events, CRP level was a stronger independent predictor of cardiovascular events than LDL-C.[51] Furthermore, in the Cholesterol and Recurrent Events (CARE) study the magnitude of risk reduction attributable to pravastatin therapy was greater among individuals with evidence of enhanced inflammation,[52] while lovastatin therapy in the AFCAPS/TexCAPS trial produced the greatest benefit in subjects with elevated CRP levels irrespective of LDL-C.[53]

Various models linking lipid metabolism and inflammation to atherosclerosis have been developed. According to the LDL oxidation hypothesis, LDL-C particles retained in the intima, partly by proteoglycan binding, undergo oxidative modification, producing modified lipoprotein particles that can in-

duce the expression of a variety of inflammatory mediators in macrophages and the vessel wall.[54] The apoprotein components of such lipoprotein particles may also be proinflammatory as a consequence of inciting T-cell responses and activating the antigen-specific limb of the immune response.

Other lipid parameters, particularly TG-enriched VLDL and IDL particles, both directly and following oxidative modification, may activate inflammatory factors such as various matrix metalloproteinases and nuclear factor-kappa B (NFκB), which is a key factor in the synthesis and release of inflammatory cytokines.[55] HDL particles may have anti-inflammatory effects partly as a result of reverse cholesterol transport from the vessel wall but also the transport of antioxidant enzymes such as platelet-activating factor acetylhydrolase and paraoxonase, which can break down oxidised lipids, thus neutralising their proinflammatory potential.[56]

Experimental and clinical outcome data support the concept that statins, in addition to LDL-lowering properties, exhibit anti-inflammatory effects. Both pravastatin and cerivastatin have been shown to reduce macrophage content in atherosclerotic plaques,[57] whereas simvastatin, fluvastatin and atorvastatin reduce intimal inflammation and suppress the expression of tissue factor, adhesion molecules and matrix metalloproteinases.[57]

Statin therapy may thus contribute to atherosclerotic plaque stability by both reducing plaque size and modifying its physicochemical properties. Changes in plaque size associated with LDL-C reduction occur over an extended period and are often minimal. The acute coronary syndrome (ACS) is related to thrombosis superimposed on an unstable atherosclerotic lesion. The clinical benefits of early statin therapy on cardiovascular outcome in ACS as illustrated by the MIRACL study may thus be related to anti-inflammatory rather than lipid-lowering effects of statins. Indeed, growing evidence indicates that inflammation as measured by CRP predicts an unfavourable outcome in ACS, independent of any other factors.[58]

Other lipid-lowering therapies also exert potentially important anti-inflammatory properties, independent of lipid-lowering effects. PPARs are transcription factors belonging to the nuclear receptor superfamily, which are widely expressed on a variety of tissues including atherosclerotic tissue and inflammatory cells.[42,59] To date, three different PPAR subtypes have been identified: PPARα, PPARβ/δ and PPARγ. Fibrates are synthetic PPARα agonists, whereas the thiazolidinedione (TZD) class of insulin-sensitising drugs, which also have multiple effects on lipid metabolism, are synthetic PPARγ agonists.[42] Recent data have demonstrated that fenofibrate, via its PPARα agonist properties, may exert anti-inflammatory effects by repressing cytokine-induced activation of a number of inflammatory genes such as *VCAM-1*, *COX-2* and *IL-6* by negatively interfering with NF-κB transcriptional activity.[60,61]

A variety of studies have established the role for PPARγ in modulating inflammatory responses,[62,63] with data accumulating to support the potential anti-inflammatory effects of the TZDs. Both *in vitro* and animal studies have demonstrated that TZD therapy, including rosiglitazone, pioglitazone and troglitazone; inhibits tissue factor and inflammatory cytokine expression as well as macrophage activation.[64-66]

The clinical application of the potential anti-inflammatory properties of both fibrates and TZDs on atherosclerotic vascular disease remains to be evaluated. However, in various animal models and in post-coronary stent studies, TZD therapy may attenuate atherosclerotic disease progression and improve plaque stability,[67-69] effects which may be partly attributable to anti-inflammatory mechanisms.

The true clinical utility of measuring inflammation and the potential benefits of agents with anti-inflammatory effects remain unclear. At present CRP estimation may be used to provide additional information on cardiovascular risk and provide supportive evidence for the initiation of risk factor modification in individuals previously considered at low risk, that is, those with low LDL-C levels but elevated CRP levels. Recent recommendations from the American Heart Association define a CRP level >3 mg/dL as representing high relative risk.[70] The results of ongoing large-scale randomised studies are, however, awaited to assess the wider clinical application of inflammation and its treatment.

5. Therapeutic Advances in Lipid-Lowering Therapy

5.1 Advances in Statin Therapy

Despite development of novel approaches to cholesterol reduction, statin therapy remains the mainstay of cholesterol-lowering therapy. The ideal statin should exhibit potent enzyme inhibition, preferential action and distribution in the liver, optimal pharmacokinetics (including duration of action on HMG-CoA and upregulation of LDL-receptors), good safety profile and low potential for drug interactions. Rosuvastatin, launched in the UK in the spring of 2003, is an enantiomeric synthetic compound, which is relatively hydrophilic and is a significantly more potent inhibitor of HMG-CoA reductase activity than the five currently available statins.[71,72] Rosuvastatin appears to be actively absorbed into hepatocytes by a high-affinity uptake process and has a terminal half-life of approximately 20 hours. Rosuvastatin is metabolised by the cytochrome P450 (CYP) enzyme system via the isoenzymes CYP2C9 and CYP2C19, with little or no metabolism by the CYP3A4 isoenzyme. Since many other drugs (netaglinide, cyclosporin, azole antifungals)[73] primarily undergo CYP3A4 metabolism, rosouvastatin may demonstrate a reduced potential for drug interactions. The relative hydrophilicity of rosouvastatin may also influence its safety profile, since hydrophilicity may be a factor in determining a reduced myotoxic potential. Pravastatin has similar hydrophilicity to rosuvastatin and has the lowest reported incidence of statin myotoxicity.[73] In clinical studies evaluating a dose range of between 5 and 80mg, reductions in total cholesterol of 31% up to 46%, LDL-C of 40% up to 69% and plasma TG of 10% up to 22% have been observed, with increases in HDL-C levels of up to 13% having been noted[74-76] (table II). Rosuvastatin is licensed for use in the 10–40 mg/day dosage range, and an extensive outcome study programme is under way to investigate its effects on atherosclerosis and cardiovascular disease.

Another recently developed statin, which is in late stages of clinical development, is pitavastatin. This compound is currently in phase III clinical trials, with initial data demonstrating that pitavastatin 8mg lowered LDL-C by 68% and plasma TG by 30% while raising HDL-C up to 15%.[77]

Table II. Percentage change in lipid parameters from baseline after 6 weeks' treatment with rosuvastatin across the dose range 5–80mg (licensed dose range for rosuvastatin is 10–40 mg/day)

Parameter	5mg	10mg	20mg	40mg	80mg
Triglycerides	−18	−37	−37	−40	−40
LDL-C	−28	−40	−34	−55	−69
Non-HDL-C	−27	−45	−42	−47	−51
HDL-C	−4	+6	+18	+15	+10
ApoB/apoA-I	−20	−36	−36	−40	−45
Non-HDL-C/HDL-C	−28	−48	−50	−53	−55

apo = apolipoprotein; **HDL-C** = high-density lipoprotein-cholesterol; **LDL-C** = low-density lipoprotein-cholesterol.

5.2 Cholesterol Absorption Inhibitors

In clinical practice there can be considerable variation in response to statin therapy. This may be related to a variety of factors, including poor compliance, with up to 30% of patients discontinuing statins.[78] Concomitant drug therapy is another potential cause of variability in response. The CYP3A4 or CYP2C9 pathways metabolise all statins, other than pravastatin. Drugs that inhibit or induce these pathways can affect plasma statin levels and thus clinical response. In clinical trial conditions, where such factors are minimised, a considerable interindividual variability in LDL-C-lowering effect remains, appearing largely independent of the drug and dose used.[78] Furthermore, diminishing responses over periods of up to 1 year have been noted in response to both simvastatin and pravastatin;[73] flagging compliance may certainly have a role in this observation but a compensatory increase in HMG-CoA reductase activity rather than induction of CYP may also play a role in loss of statin efficacy. One important factor influencing statin response is genetic variability in cholesterol absorption. Subgroup analysis of the Scandinavian Simvastatin Survival Study (4S) divided participants into quartiles according to serum cholestanol-cholesterol ratio,[79] cholestanol being an index of intestinal cholesterol absorption. The reduction in cholesterol in response to simvastatin was significantly lower in subjects in the highest cholestanol-cholesterol quartile, that is, high cholesterol absorbers and low synthesisers. Further studies using

mavalonate turnover as an index of cholesterol synthesis have also demonstrated that low basal rate of cholesterol synthesis and high absorption are associated with a poor response to statins.[79]

Subgroup analysis from the 4S study also demonstrated that as well as influencing the response to simvastatin therapy, baseline cholestanol-cholesterol ratio was an important determinant of CHD risk reduction.[80,81] Individuals with the highest baseline cholestanol-cholesterol ratio (high absorbers, low synthesisers of cholesterol) demonstrated significantly less reduction in CHD events than those in the lowest quartile (low absorbers, high synthesisers) [table III].

The most likely explanation for these observations is that downregulation of HMG-CoA reductase resulting from increased intestinal cholesterol absorption was responsible for the suboptimal response to simvastatin. The fact that this phenomenon was seen in the context of a controlled trial suggests that it may be genetically determined rather than as a results of dietary or compliance factors.

Therefore, one potential approach to improving the LDL-C response to statin therapy is to inhibit intestinal cholesterol absorption, resulting in upregulation of HMG-CoA reductase expression.

Naturally occurring cholesterol absorption inhibitors include phytosterols and phytostanols, which compete with cholesterol for incorporation into mixed micelles and produce modest LDL-C reductions. The sterol and stanol esters of fatty acids render them more lipid soluble and more effective agents in the bowel as inhibitors of cholesterol absorption. Phytostanol consumption over a range of 0.8–3.2 g/day has been shown to produce a dose-dependent reduction in LDL-C of 1.7–8.7%.[82]

Several studies have now demonstrated enhanced LDL-C-lowering effects of statins when cholesterol absorption inhibitors are given concomitantly (table IV). The effects of combination therapy appear additive, resulting in decrements in LDL-C ranging from 10 to 20% compared with statin therapy alone, which in many cases is similar to or greater than that achieved by doubling the dose of statin.

The first synthetic cholesterol absorption inhibitor, ezetimibe, has been approved for use both in the US and Germany, either as monotherapy or in combination with statins, and is also progressing through the mutual recognition process in the EU. Ezetimibe selectively inhibits dietary and biliary cholesterol absorption at the brush border of the intestinal epithelium without affecting the absorption of TG or fat-soluble vitamins.[83] It localises in the intestine and undergoes enterohepatic circulation, thus delivering drug to the intestinal site of action.[84] Ezetimibe thus reduces overall cholesterol delivery to the liver; secondarily inducing increased expression of LDL receptors, resulting in increased removal of LDL-C from the plasma. Ezetimibe is rapidly absorbed and extensively metabolised by glucuronidation, with plasma concentration-time profiles of both conjugated and unconjugated drug exhibiting multiple peaks, indicating enterohepatic circulation.[85]

Human dose-ranging studies suggest that much of the LDL-C-lowering effect of ezetimibe is present at a 1mg dose, with an optimal effect thus far identified with the 10mg dose.[86] In pooled efficacy analyses involving 329 patients (table V), the 5 and 10 mg/day dosages reduced LDL-C by 15.7 and 18.5%, respectively, while increasing HDL-C by 2.9 and 3.5%, with no change in plasma TG levels.[87] The degree of LDL-C reduction was directly related to dose, with 67.8% of patients in the 10 mg/day group experiencing a reduction in LDL-C of greater than 15% as compared with 54% in the 5 mg/day group.[87] Ezetimibe 10 mg/day has also been shown to reduce chylomicron cholesterol content by up to 69%,[88] potentially reducing the atherogenic potential of chylomicron remnants. Ezetimibe has been

Table III. Distribution of coronary heart disease (CHD) events in the Scandinavian Simvastatin Survival Study (4S) study based on cholestanol-cholesterol ratio (C : CR) at baseline (prior to simvastatin treatment)

	C : CR <107 mmol/lmol	C : CR 107–126 mmol/lmol	C : CR 127–148 mmol/lmol	C : CR >148 mmol/lmol
Placebo (n = 434)	37	39	36	32
Simvastatin (n = 434)	22	24	31	38
Relative risk of CHD	0.62[a]	0.66	0.75	1.17[a]

a $p < 0.01$, CHD events in lowest C : CR quartile vs CHD events in the highest quartile following simvastatin therapy.

Table IV. Combined effects of plant-derived and pharmacological cholesterol absorption inhibitors and statin therapy

Study design	Patients (no.)	Methods	Results of combined therapy
Open, uncontrolled	Postmenopausal, coronary heart disease (132)	Simvastatin 10–20mg + stanol 3g over 12w	16% additional ↓ in LDL-C levels vs simvastatin alone
Open, uncontrolled	Familial hypercholesterolaemia (12)	Simvastatin 20–40mg + stanol ester 2.2g over 6w	20% additional ↓ in LDL-C levels vs simvastatin alone
Randomised, double-blind, placebo-controlled	Hypercholesterolaemia (167)	Statin + stanol ester 3g over 8w	10% additional ↓ in LDL-C levels vs statin alone
Randomised, double-blind, placebo-controlled	Hypercholesterolaemia (23)	Simvastatin + ezetimibe 10mg over 2w	17% additional ↓ in LDL-C levels vs simvastatin alone

LDL-C = low-density lipoprotein cholesterol; **w** = weeks; ↓ indicates decrease.

shown to significantly reduce the extent of aortic atherosclerosis in apoE-deficient knockout mice, with reductions of 80 and 71% observed in animals fed, respectively, with atherogenic and low-fat diets.[89]

In a multicentre study known as the Add-on study, ezetimibe, when combined with continuing statin therapy, produced an additional 20% reduction in LDL-C.[90,91] Most of this response was seen within 2 weeks of commencing combination therapy, with the additive reduction being consistent across all statins.

In coadministration studies with atorvastatin and simvastatin, ezetimibe resulted in additional reductions in plasma TG of 9% and increase in HDL-C of 3 and 2%, respectively.[91]

In studies of up to 12 weeks' duration ezetimibe has an adverse event profile similar to that of placebo.[91] Since ezetimibe undergoes metabolism by glucuronidation, it has no significant effects on the bioavailability of various drugs including, warfarin, digoxin, oral contraceptives, sulphonylureas, statins and fenofibrate.

Cholesterol, along with fat-soluble vitamins and other lipids, once incorporated into micelles, is absorbed by enterocytes via a mechanism that is not completely understood. It is subsequently esterified by acyl coA-cholesterol acyltransferase (ACAT) and packaged into chylomicrons, which enter the mesenteric lymph and ultimately the plasma. Hydrolysis of chylomicrons by a glycerol ester hydrolase results in the production of chylomicron remnants, which may induce endothelial dysfunction and promote atherogenesis. Blocking the intestinal absorption of cholesterol may thus reduce cholesterol content of chylomicrons and so reduce plaque formation. If hepatic clearance of lipoproteins is increased by upregulation of LDL receptors as a consequence of statin therapy, removal of chylomicron remnants from the plasma will also be enhanced. As well as potentiating the LDL-C-lowering effects of statins and diminishing the clinical variability in response to statin therapy, combination statin and ezetimibe therapy may produce significant additional reductions in CHD risk.

5.3 Acyl-Coenzyme A-Cholesterol Acyltransferase Inhibitors

ACAT catalyses the formation of intracellular cholesterol esters from free cholesterol[90] and has two subtypes ACAT 1 and 2. ACAT 1 is primarily found in the vascular wall, with ACAT 2 being located in the intestinal mucosa and hepatocytes. Inhibition of ACAT 1 may reduce cholesterol accumulation within macrophages and thus reduce foam cell formation, while inhibition of ACAT 2 may affect cholesterol absorption.[92] Several ACAT inhibitors have been shown to reduce lipid levels and to have antiatherogenic effects in animals, reducing plaque size and progression. However, many of these developed agents are poorly absorbed and to date only avisimibe has progressed to human studies, having reached phase II/III trials. In the largest published study to date, involving 130 men, no significant changes in total cholesterol, LDL-C, HDL-C or apoB were seen in comparison with placebo.[93] In contrast, VLDL was reduced across the avisimibe dosage range of 50, 125, 250 and 500 mg/day by 26, 20, 21 and 30% and TG by 22, 17, 16 and 23%, respectively (table V). This was an 8-week placebo-controlled study and across the four doses used avisimibe was well tolerated with no clinical or biochemical abnormalities noted.

Although in animal studies avisimibe has been shown to reduce LDL-C and apoB levels, in humans it appears to be primarily a TG-lowering agent, with apparent optimal effects at the lowest dosage of 50 mg/day. The long-term potential clinical benefits of avisimibe on lipid levels and human atherosclerosis require further study.

5.4 Microsomal Triglyceride Transfer Protein Inhibitors

Microsomal triglyceride transfer protein (MTP) is an important factor in the assembly of VLDL, which is a precursor of LDL. Defects of the MTP gene cause abetalipoproteinaemia, in which VLDL and chylomicron production is impaired,[94] resulting in low plasma levels of TG and LDL-C.[95] MTP inhibition may thus have therapeutic potential for reducing atherogenic lipoproteins in humans.

In animal studies reductions in total cholesterol and plasma TG of 89 and 81%, respectively, have been achieved with MTP inhibitor therapy.[96] However, human trials have yet to be reported, with initial evidence not being encouraging, as the most advanced of these agents (BMS 201038) has been found to cause fat infiltration and liver enzyme elevation.[97]

5.5 Cholesteryl Ester Transfer Protein Inhibition

Cholesteryl ester transfer protein (CETP) is an enzyme that facilitates the transfer of cholesteryl esters from HDL to apoB-containing lipoproteins in exchange for TG.[98] CETP inhibition may be an effective means by which to raise plasma HDL. This concept is derived from several lines of evidence. Patients with CETP gene mutations have elevated HDL-C levels;[97] population studies have demonstrated associations between CETP mutations, reduced CETP activity and increased HDL-C levels,[98,99] and sustained CETP inhibition in animals has been shown to increase HDL-C levels and reduce atherosclerosis.[100]

The most advanced CETP inhibitor in development, JTT-705, has been shown in animal studies to increase HDL-C levels, decrease non-HDL-C and reduce aortic atherosclerosis by up to 70%.[101]

In a human study 198 individuals were treated over a 4-week period with placebo, low-dose JTT-705 (300 mg/day), medium-dose (600 mg/day) or high-dose (900 mg/day).[102] Among the treatment groups there was a dose-dependent increase in HDL-C, reaching a plateau after only 1-week of treatment. Relative to placebo, HDL-C increased by 15% in the low-dose group, 26% in the medium-dose group and 34% in the high-dose group. Reductions in LDL-C were also seen in the low- (3.5%), medium- (5.5%) and high-dose (7.4%) groups, but only the high-dose group achieved statistical significance. JTT-705 appeared to be well tolerated and exhibited a safety profile similar to placebo. Only five participants (2.5%) discontinued because of adverse events, three of whom were in the high-dose group. These data thus support the concept that

Table V. Summary of clinical trial evidence of the effects of new therapies on plasma lipids in humans; all data from placebo-controlled, randomised, double-blind studies

Drug	Condition	Dose (mg/day)	Duration (w)	LDL-C (% change)	HDL-C (% change)	TG (% change)	Comments
Ezetimibe	Hyperlipidaemia	0.25	12	−9.9	0	0	LDL-C reduced in dose-dependent manner, with all doses having similar tolerability to placebo
		1	12	−14.0	0	0	
		5	12	−15.7	+2.9	−1.0	
		10	12	−18.5	+3.5	−6.0	
Avasimibe	Combined hyperlipidaemia and low HDL-C	50	8	+4.0	+2.0	−22.0	Main effect on TG, with maximum reduction of 23% ($p < 0.05$). Effects independent of dose
		125	8	+9.0	+2.0	−17.0	
		250	8	+5.0	+1.0	−16.0	
		500	8	+4.0	−2.0	−23.0	
JTT-705, cholesteryl ester transfer protein inhibitor	Normolipidaemic	300	4	−4.9	+15.5	0	All doses increased HDL-C; only the 900 mg/day dosage significantly reduced LDL-C
		600	4	−5.4	+26.4	−5.9	
		900	4	−7.4	+34.5	−11.1	

HDL-C = high-density lipoprotein cholesterol; **LDL-C** = low-density lipoprotein cholesterol; **TG** = triglycerides; **w** = weeks.

CETP inhibition may represent a promising new mechanism for elevating HDL levels. However, further clinical studies are required to evaluate both the safety and efficacy of this approach.

5.6 ATP-Binding Cassette Transporter A1 (Liver X Receptor) Agonists

Reverse cholesterol transport appears to be a major mechanism by which HDL may protect against atherosclerosis. Mutations in the ATP-binding cassette transporter A1 (ABCA1) gene result in Tangier disease, a rare disorder characterised by very low HDL-C levels and aberrant cellular cholesterol efflux. ABCA1 mediates the efflux of phospholipids and cholesterol to apolipoprotein receptors, the initial step in reverse cholesterol transport, thus playing a critical role in HDL metabolism.[103]

No therapeutic agents targeting ABCA1 have been tested in humans. Circumstantial evidence for the concept that overexpression of ABCA1 may have clinical benefit comes from animal studies in which mice overexpressing the human ABCA1 gene in liver and macrophages demonstrated a 183% increase in HDL-C, a 47% decrease in non-HDL-C and 36% decrease in apoB-containing lipoproteins.[103] These changes were associated with a 65% reduction in aortic atherosclerosis.

The liver X receptor (LXR)/retinoid X receptor promoter element, which is activated by oxysterols, has been shown to enhance transcription of ABCA1.[104] Recent animal and *in vitro* data with synthetic LXR agonists have shown significant upregulation of ABCA1 expression with increases of up to 60%.[105] Unfortunately, TG levels were also raised and since LXR agonists may modulate the expression of many genes, extensive analyses of these agents is required before they can be used in clinical practice.

5.7 Bile Acid Transport Inhibitors

These agents include both bile acid-binding agents such as cholestyramine and specific inhibitors of ileal bile acid transport thought to be mediated by a specific Na^+/bile acid transporter (IBAT inhibitors). Approximately 2–5g of bile acids are constantly recycled from the liver to the gut, with relatively small stool excretion. Blocking the reuptake process substantially increases the amount of faecal bile acid loss. Replenishment of this supply by the liver occurs by conversion of cholesterol to bile, resulting in depletion of hepatocyte cholesterol and upregulation of LDL receptors.

Cholestyramine proved effective in cholesterol and cardiovascular risk reduction in early studies[106] but is poorly tolerated. A new bile acid sequestrant, colesvelam, has recently been launched,[107] being effective at a dose of 625mg four to six times daily. It is too early to make any judgements on tolerability and acceptance in clinical practice. IBAT inhibitors result in more complete blockade of bile acid reuptake and should be more effective than bile acid-binding agents, which work by competitive inhibition. IBAT inhibitors such as S-8921 are undergoing clinical evaluation and have the potential to produce significant LDL-C reductions.

6. Conclusions

The most recent treatment guidelines advocate lower target LDL-C levels in larger numbers of patients, while epidemiological and clinical trial evidence accumulates to support the hypothesis that lower is indeed better. The HDL-C issue remains contentious, since statin studies have failed to demonstrate a significant correlation between change in HDL-C and change in event rate; furthermore, in statin studies there is a trend for HDL-C to disappear as a risk factor in individuals receiving statins. However, epidemiological data such as PROCAM, as well as intervention studies such as AFCAPS/Tex CAPS, VA-HIT and BIP, indicate that a significant proportion of patients may benefit from LDL-C reduction as well as TG reduction and raising HDL-C. Direct comparative studies of statins and HDL-C-raising drugs such as fibrates are thus required, while the benefits of aggressive lipid intervention are being further studied in a number of large clinical endpoint trials.

The advent of more potent statins may have a significant impact on our approach to cholesterol lowering, while a number of agents that reduce cholesterol by non-HMG-CoA reductase mechanisms are under development, including cholesterol absorption inhibitors and agents that alter arterial cholesterol storage. The use of statins in combination with such agents or with dietary factors influ-

encing cholesterol absorption may indicate the directions in which new, evolutionary strategies to optimise lipid-regulating therapy may proceed.

Expiry of the patent of simvastatin in April 2003 will result in production and marketing of generic versions of the drug, which should have significant cost implications. With considerable evidence supporting the long-term safety profile of statins, these agents, once off patent, may be suitable candidates for over-the-counter distribution. Such a strategy is being actively considered in both the US and UK, and may represent a 'safe' and cost-effective method of getting more people who could potentially gain benefit from cholesterol reduction on to statin therapy, thus meeting an important public health goal.

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