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REVIEW ARTICLE

Drugs 2004; 64 (11): 1181-1196
0012-6667/04/0011-1181/$24.00/0

Medical Lipid-Regulating Therapy

Current Evidence, Ongoing Trials and Future Developments

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Contents

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

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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[28]	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[26]	600	Atorvastatin 80mg or pravastatin 40mg	Calcium content of coronary arteries by EBCT
REVERSAL[25]	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

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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

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