REVIEW ARTICLE

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Comparative Tolerability of the HMG-CoA Reductase Inhibitors

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Abstract

The availability of the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors has revolutionised the treatment of lipid abnormalities in patients at risk for the development of coronary atherosclerosis. The relatively widespread experience with HMG-CoA therapy has allowed a clear picture to emerge concerning the relative tolerability of these agents. While HMG-CoA reductase inhibitors have been shown to decrease complications from atherosclerosis and to improve total mortality, concern has been raised as to the long term safety of these agents. They came under close scrutiny in early trials because ocular complications had been seen with older inhibitors of cholesterol synthesis. However, extensive evaluation demonstrated no significant adverse alteration of ophthalmological function by the HMG-CoA reductase inhibitors.

Extensive experience with the potential adverse effect of the HMG-CoA reductase inhibitors on hepatic function has accumulated. The effect on hepatic function for the various HMG-CoA reductase inhibitors is roughly dose-related and 1 to 3% of patients experience an increase in hepatic enzyme levels. The majority of liver abnormalities occur within the first 3 months of therapy and require monitoring. Rhabdomyolysis is an uncommon syndrome and occurs in approximately 0.1% of patients who receive HMG-CoA reductase inhibitor monotherapy. However, the incidence is increased when HMG-CoA reductase inhibitors are used in combination with agents that share a common metabolic path.

The role of the cytochrome P450 (CYP) enzyme system in drug-drug interactions involving HMG-CoA reductase inhibitors has been extensively studied. Atorvastatin, cerivastatin, lovastatin and simvastatin are predominantly metabolised by the CYP3A4 isozyme. Fluvastatin has several metabolic pathways which involve the CYP enzyme system. Pravastatin is not significantly metabolised by this enzyme and thus has theoretical advantage in combination therapy. The major interactions with HMG-CoA reductase inhibitors in combination therapy involving rhabdomyolysis include fibric acid derivatives, erythromycin, cyclosporin and fluconazole.

Additional concern has been raised relative to overzealous lowering of cholesterol which could occur due to the potency of therapy with these agents. Currently, there is no evidence from clinical trials of an increase in cardiovascular or total mortality associated with potent low density lipoprotein reduction. However, a threshold effect had been inferred by retrospective analysis of the Cholesterol and Recurrent Events study utilising pravastatin and the role of aggressive lipid therapy is currently being addressed in several large scale trials.

The therapy of dyslipidaemia prior to the advent of the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors was limited to agents with predominant effects on very low density lipoprotein and mild-to-moderate alteration of low density lipoprotein (LDL) [fibrates], or to compounds such as the bile acid sequestrants and nicotinic acid whose use was complicated by poor patient compliance. The early clinical trials that analysed the impact of hypolipidaemic therapy (Helsinki Heart Study,[1] Lipid Research Clinics Coronary Primary Prevention Trial[2]) revealed a statistically significant but quantitatively minimal effect on cardiovascular mortality, which appeared to be balanced by an increase in noncardiovascular death rates.

The development of the HMG-CoA reductase inhibitors, which are clinically highly efficacious in lowering plasma LDL levels and are proven to be effective in trials with clinical end-points, has revolutionised preventive cardiology. HMG-CoA reductase inhibitor therapy has proven to be efficacious in clinical studies in which treatment was given to patients with either normal or elevated cholesterol levels in both primary and secondary prevention trials. Adequately powered trials [the Scandinavian Simvastatin Survival Study (4S)[3] and the Long Term Intervention with Pravastatin in Ischaemic Disease (LIPID) trials][4] have demonstrated both a decrease in cardiovascular mortality and an improvement in all-cause mortality with HMG-CoA reductase inhibitor therapy. To date, the adverse effects of HMG-CoA reductase inhibitor therapy have been minimal and are clearly outweighed by the beneficial reduction in both total and cardiovascular mortality, indicative of a positive benefit-risk relationship with these agents. This review focuses on the potential adverse effects of the HMG-CoA reductase inhibitors, either as monotherapy or in combination with drugs that may interfere with their metabolism.

1. Adverse Effects of the HMG-CoA Reductase Inhibitors

1.1 Ocular Effects

Agents that interrupt the biosynthetic pathway of cholesterol late in the synthetic process – well beyond the HMG-CoA reductase step – have been shown to cause lens opacities in experimental animals and humans. HMG-CoA reductase inhibitors, with their partial inhibitory activity against HMG-CoA reductase (the early rate-limiting enzyme in cholesterol synthesis), have been intensely scrutinised for potential adverse effects on lens opacity and cataract formation. Concern has arisen that lipophilic agents may penetrate the lens to a greater extent than compounds that are preferentially carried within the plasma compartment, and thus may demonstrate a higher potential for the induction of cataracts due to either excessive cholesterol reduction or tissue accumulation. Gerson et al.[5] performed *ex vivo* studies utilising lenses explanted from experimental animals and grown in tissue culture to compare the effects of hydrophilic and lipophilic HMG-CoA reductase inhibitors.[5] The incorporation within the lens of radiolabelled [^{14}C]acetate into cholesterol could be altered by high concentrations of HMG-CoA reductase inhibitors. The dose-response curve for the hydrophilic agent pravastatin was 2 orders of magnitude to the right of those for the relatively lipophilic agents simvastatin and lovastatin, resulting in a 100-fold decrease in the inhibition of cholesterol synthesis in the lens. This selective alteration in cholesterol synthesis within the tissue was thought to be due to the inability of pravastatin to enter the intact lens, and raised the possibility that hydrophilic agents may have less potential for the generation of cataracts or opacities when compared with compounds characterised by a higher degree of lipophilicity and tissue penetration.

However, no clear relationship between the formation of cataracts and either the extent of cholesterol lowering or the mechanism or extent of reduction in cholesterol synthesis has been clearly delineated. Experimental animals exposed to extremely high doses of HMG-CoA reductase inhibitors demonstrated low drug concentrations within the lens proper (<500 ng/g), and a statistically significant association could not be determined between the concentration of drug within the lens and the degree of cataract formation. Furthermore, no significant differences could be determined in the cholesterol content or sterol composition within the lens proper when analysing tissue that was either normal or affected by cataract formation. The very high doses of the various HMG-CoA reductase inhibitors used in the *in vitro* trials have been hypothesised to expose the lens to the agent via the aqueous humour, with the potential for enhanced concentrations in the outer cortical region of the lens where cholesterol synthesis is critical and any reduction may result in the development of opacities. HMG-CoA reductase inhibitors of different chemical structures and penetrative capabilities were administered, establishing that the induced changes in the lens appeared to be a function of the biochemical mechanism of this class of drugs rather than the toxic effect of a specific drug. Additionally, the doses used were far in excess of the ranges utilised in the normal treatment of humans with dyslipidaemia.[5]

These experimental data raised the question of the potential induction of drug-associated lens opacities and resulted in intense scrutiny of HMG-CoA reductase inhibitors in early clinical trials. Laties et al.[6] evaluated the 8245 participants of the Expanded Clinical Evaluation of Lovastatin (EXCEL) trial using biomicroscopic lens examination.[6] The EXCEL study was a double-blind, placebo-controlled, parallel-group trial that evaluated dyslipidaemic patients who received either placebo or the lipophilic agent lovastatin at 20, 40 or 80 mg/day. Visual acuity assessments and slit-lamp examinations were performed over the 48-week trial period, and no statistically significant differences in corneal opacity were observed between the various dosages of lovastatin when compared with placebo therapy. Additionally, no significant changes were found among the groups for alteration of visual acuity, progression in pre-existing lens opacity, rate of cataract extraction

or any spontaneously reported adverse ophthalmological effect.

Several smaller studies have examined the potential risk of lens toxicity in patients receiving simvastatin. Lundh and Nilsson[7] evaluated 29 patients with elevated levels of LDL and compared them with an age- and gender-matched group of patients with a normal lipid profile over a 24-month trial period of HMG-CoA reductase inhibitor therapy. Baseline ophthalmological examination revealed similar nuclear and cortical lens opacities and number of vacuoles in the treatment and control groups. The dyslipidaemic patients were treated with the lipophilic agent simvastatin, and there was no clinically demonstrable deleterious impact of HMG-CoA reductase inhibitor therapy on the ophthalmological parameters relative to placebo.

Schmidt et al.[8] also studied the potential effects of simvastatin in 45 patients with primary dyslipidaemia. The end-point of the trial was the ophthalmological determination of lens opacity by Scheimphflug photography; in addition, a complete ophthalmological examination was also performed at 6-month intervals over the 24-month period of the trial. No clinically significant differences were determined following treatment with simvastatin when compared with the control group who did not receive simvastatin.

Harris et al.[9] performed a detailed ophthalmological evaluation of simvastatin in 621 dyslipidaemic patients who were randomised to receive placebo or simvastatin 20mg or 40 mg/day. The participants were free from cataracts at the beginning of the study and were evaluated at 6 and 18 months using a detailed ophthalmological examination. The refractive condition of the eye and mean ocular pressure were not altered by simvastatin therapy. Tests using the Oxford grading system for a number of clinical measures of cataract formation were performed and no clear differences were determined between the treatment and control groups. The grading system evaluated posterior subcapsular cataracts, white scatter, morphological features (e.g. fibre folds or focal dots within the lens) and the presence of cortical spokes. In addition, Scheimphflug slit-lamp image photography and retro-illumination analysis of the percentage of cataracts within a defined region of the lens were performed at each visit. The effect of simvastatin therapy on ophthalmological parameters could not be differentiated from placebo.

The lack of demonstrable ophthalmological toxicity with the initial HMG-CoA reductase inhibitors (pravastatin, lovastatin and simvastatin) resulted in the US Food and Drug Administration eliminating the requirement for intermittent ophthalmological examinations to be performed on a routine basis in patients receiving HMG-CoA reductase inhibitors.

1.2 Central Nervous System Effects

Therapy with HMG-CoA reductase inhibitors has the potential to alter a number of CNS parameters, including sleep and cognition. The possibility that the different HMG-CoA reductase inhibitors could cause distinctive alterations in sleep patterns was first reported by Schaefer[10] in an observational trial in which patients self-reported disturbances in sleep. A total of 18% of patients who received lovastatin noted disturbances in the duration of sleep compared with no changes in sleep patterns in patients receiving pravastatin. The HMG-CoA reductase inhibitors vary in their transfer across the blood-brain barrier,[11] which is presumably at least partially related to the variations in the hydrophilic characteristics of the agents.

Early studies that attempted to examine the potential adverse CNS effects of HMG-CoA reductase inhibitors were hampered by design problems (e.g. they were retrospective or nonblinded) but were compatible with the possibility that lipophilic HMG-CoA reductase inhibitors may adversely affect brain activity with secondary effects on cognition and sleep. However, quantitative and subjective measurements of the effects of HMG-CoA reductase inhibitor therapy in healthy volunteers have not clearly delineated any alteration of brain activity when the various agents were compared with placebo.

Pravastatin and simvastatin were compared with placebo in a double-blind, randomised, crossover study in healthy volunteers.[12] The volunteers were administered placebo or 40 mg/day of either sim-

vastatin or pravastatin (which are not equipotent doses), and a variety of parameters were monitored. Electroencephalograph (EEG) evoked potentials and power spectral analysis, as well as biochemical measurements (e.g. creatine kinase and aminotransferases), were obtained and a number of questionnaires analysing subjective responses for a variety of potential neurological variables were completed by the participants. HMG-CoA reductase inhibitor therapy significantly lowered cholesterol without the induction of significant adverse effects in muscle or hepatic function. Additionally, no significant differences in hydrophilic or lipophilic HMG-CoA reductase inhibitor therapy could be demonstrated when compared with placebo. EEG evoked potentials, depression scores, mood, sleep and cognitive performance were not adversely affected by hypolipidaemic therapy in the 1-month trial.

Several studies using polysomnographic techniques have also been performed. Partinen et al.[13] compared lovastatin and pravastatin in dyslipidaemic patients who were characterised by primary hypercholesterolaemia. The individuals participating in the trial provided subjective sleep assessments during the crossover study, and polysomnographic recordings were obtained. Patients were evaluated for sleep deficiency, percentage rapid eye movement sleep, wake time during sleep, total wake time and entries to waking. Pravastatin and lovastatin did not show marked differences from placebo, although the mean change in the group randomised to lovastatin was towards improved sleep.[13] Lipophilic HMG-CoA reductase inhibitors may also be differentiated by their relative partition coefficients: simvastatin is more lipophilic than lovastatin. Simvastatin was compared with pravastatin in a double-blind, placebo-controlled, crossover study using polysomnographic techniques, but the analysis could not demonstrate a statistically significant difference between pravastatin and simvastatin.[14]

The large-scale clinical trials are hampered by the potential lack of reporting accuracy in sleep disturbances. However, the EXCEL trial evaluated various dosages of lovastatin in a 48-week trial period and could not convincingly demonstrate alterations in sleep performance with the various administration regimens relative to placebo.[15] The bulk of the clinical data thus does not support significant sleep abnormalities associated with HMG-CoA reductase inhibitor therapy when intergroup or placebo comparisons are made.

Daytime cognitive performance has also been evaluated with HMG-CoA reductase inhibitor therapy because of the potential for agents that accumulate in the CNS to have adverse effects, either through causing a primary abnormality or secondary to cumulative alterations in sleep patterns. In a study by Kostis et al.,[16] a fixed dosage of lovastatin 40 mg/day was compared with pravastatin 40 mg/day in a 6-week, double-blind, randomised, placebo-controlled, crossover study using a 3-way Latin square design in patients characterised by a predominant elevation in LDL levels and normal triglyceride levels (Fredrickson Class IIA). Sleep patterns were analysed by measuring sleep efficiency, rapid eye movement, density and activity time in each sleep stage, total sleep time and latency. Cognitive performance was also evaluated. Lovastatin and pravastatin treatments were associated with the expected alteration of lipid parameters when compared with placebo, but neither agent caused changes in either cognition or sleep parameters.

Gengo et al.[17] evaluated the effects of treatment with fixed dosages of pravastatin 40 mg/day and lovastatin 40 mg/day on daytime cognitive function in a double-blind, placebo-controlled, crossover study in 36 patients with primary hypercholesterolaemia. A number of mental performance tests were performed at baseline and at 2 and 4 weeks, including digit symbol substitution, auditory vigilance, selective reminding, word call, choice reaction time and visual analogue rating scales. Treatment with lovastatin and pravastatin was not shown to cause adverse effects on cognition, and the drugs could not be differentiated from each other.

In summary, HMG-CoA reductase inhibitors appear to cause few, if any, changes in sleep and cognition patterns when compared with placebo, and

the theoretical concerns about the potential alteration of CNS function do not appear to be warranted.

1.3 Hepatic Effects

Drugs that undergo metabolism within the liver have the potential to adversely affect hepatic function by inducing either cholestatic changes or elevations of aminotransferase levels. The HMG-CoA reductase inhibitors vary in their degree of hepatic concentration because of their different lipophilic characteristics and partition coefficients within the tissue compartment. However, the degree of hepatic dysfunction associated with the various HMG-CoA reductase inhibitors appears to be similar when analysed in clinical trials and safety studies. Significant hepatic toxicity has been arbitrarily defined as an elevation in ALT and AST levels greater than 3 times normal on 2 successive measurements.

1.3.1 Lovastatin

There is extensive safety data relating to the potential hepatic toxicity of lovastatin. The Lovastatin Study Groups evaluated 745 patients with significant dyslipidaemia despite dietary therapy and documented the prevalence of abnormal hepatic function associated with lovastatin therapy over a mean trial duration of 5.2 years.[18] The average age of the cohort was 50 years and 42% had a history of coronary atherosclerosis. The trial was designed to increase the dosage of lovastatin to 80 mg/day, which was achieved by 77% of the patients. 58% of the patients took other lipid-lowering agents, including bile acid sequestrants. A total of 10 patients discontinued the study because of asymptomatic but significant elevations in aminotransferase values, and their hepatic function tests reverted to normal following discontinuation of the drug.

Tobert[19] reviewed the accumulated data for the long term adverse effects of lovastatin therapy and reported an incidence of significant and persistent increase in aminotransferase levels of 1.9%, which was reversible with discontinuation of therapy.

The EXCEL study was a very large scale trial evaluating the effects of various doses of lovastatin compared with placebo in 8245 patients.[17] The incidence of aminotransferase abnormalities in the group receiving lovastatin was similar to that for placebo (0.1%) when lovastatin was administered at 20 mg/day. Patients randomised to receive lovastatin 40 mg/day had a 0.9% incidence of increased aminotransferases compared with 1.5% in the group receiving 80 mg/day. The trend for increased hepatic abnormalities was statistically significant, but the absolute differences were small, indicating a generally acceptable level of adverse events involving elevated aminotransferase levels despite achieving the maximal recommended dosage levels for lovastatin treatment.

1.3.2 Simvastatin

Simvastatin has an increased potency per milligram compared with the other first generation HMG-CoA reductase inhibitors. It has been studied in an analysis of data from approximately 2400 patients involved in controlled clinical trials and their open extensions (mean follow-up 1 year).[20] The trial analysis involved a predominantly male population with an average age of 50 years. The trials used increasing dosages of simvastatin titrated to 40 mg/day. Persistent elevations of aminotransferase levels were observed in 1% of this cohort; these increases were asymptomatic and not associated with clinically apparent episodes of hepatitis. Molgaard et al.[21] reported a 3-year study of the use of simvastatin alone or in combination with a bile acid resin in hypercholesterolaemic patients. Similarly, this study did not demonstrate sustained elevations in levels of alkaline phosphatase or aminotransferases.[21]

1.3.3 Atorvastatin

Atorvastatin was recently released as a synthetic and highly lipophilic agent with a long half-life because of its concentration within hepatic tissue. Black et al.[22] reviewed the safety profile of atorvastatin using pooled data from 21 completed and 23 ongoing studies involving a total of 4271 participants. Atorvastatin was used at dosages ranging from 10 to 80 mg/day and treatment periods ranging from 4 months to more than 2 years in the combined cohorts. Atorvastatin has been demonstrated to have a similar safety profile to the other HMG-CoA reductase inhibitors, with fewer than 2% of the total number of patients being removed from the tri-

als because of drug-attributable adverse effects. A total of 0.7% of patients receiving atorvastatin had confirmed aminotransferase elevations greater than 3 times the upper limit of normal, which generally occurred within the first 4 months of treatment.

Dart et al.[23] reported on a comparison of efficacy and safety in 177 patients who were randomised to receive either atorvastatin or simvastatin at various dosages. Patients were followed both for efficacy and safety variables, and neither atorvastatin nor simvastatin was associated with clinically important elevations in circulating aminotransferase levels. Davidson et al.[24] reported a similar study of a comparison of atorvastatin and lovastatin in 1049 patients who were randomised to receive either atorvastatin 10 mg/day or lovastatin 20 mg/day versus a control group who received dietary therapy and placebo.[24] After a 4-week period, the group randomised to diet plus placebo was also randomised to receive either lovastatin or atorvastatin. The safety profile evaluated changes in aminotransferase levels and demonstrated no clinically significant difference between atorvastatin or lovastatin.

1.3.4 Cerivastatin

Cerivastatin is a highly potent synthetic HMG-CoA reductase inhibitor that is used in microgram doses. Stein[25] reported the results of clinical studies of this compound in over 2700 patients, of whom 1000 were treated for up to 1 year. The safety data for cerivastatin were compiled using dosages of 0.02 to 0.4 mg/day and compared with dietary therapy or other HMG-CoA reductase inhibitors. Fewer than 1% of patients who received cerivastatin 0.4 mg/day or less were shown to have statistically significant increases in aminotransferase levels. Davignon et al.[26] reviewed the phase II and III clinical trials that compared cerivastatin with either placebo or lovastatin, simvastatin and pravastatin. The adverse effect profile for all of the HMG-CoA reductase inhibitors evaluated was similar and, specifically, there were no clinically significant increases in hepatic enzyme levels when the different agents and regimens were compared.

1.3.5 Fluvastatin

Fluvastatin is another synthetic HMG-CoA reductase inhibitor for which there is considerable safety experience. Jokubaitis[27] reported the clinical experience with over 1800 patients receiving fluvastatin for dyslipidaemia for over 1 year, which demonstrated that the frequency of aminotransferase level elevations and discontinuation rates were similar to those for other HMG-CoA reductase inhibitors.[27]

Fluvastatin was also evaluated in a retrospective analysis utilising data from controlled clinical trials involving 1815 patients who were treated with a dosage of at least 20 mg/day and compared with placebo.[28] Patients were stratified as high or low risk for cardiovascular events by tabulation of the presence and severity of hypertension, obesity or glucose intolerance. There were 837 high risk patients, and fluvastatin was not associated with a persistent elevation of hepatic enzyme levels in this group. No significant changes were seen in the low risk group.

Banga et al.[29] reported the findings of a 1-year trial in 381 patients with primary hypercholesterolaemia who were randomised to receive fluvastatin 10 to 40 mg/day.[29] The most frequently reported adverse effect was abdominal pain, but significant biochemical abnormalities involving liver enzymes were rare and comparable to those in trials involving other HMG-CoA reductase inhibitors.

1.3.6 Pravastatin

Pravastatin has a long history of clinical use in a wide variety of patient subsets, including those with diabetes, the elderly, heart transplant recipients and children with severe genetic lipid abnormalities. Knipscheer et al.[30] reported on a series of 72 children with heterozygous familial hypercholesterolaemia who were treated for a 12-week period with pravastatin in a placebo-controlled study. The trial utilised 3 different dosage ranges of pravastatin and demonstrated that the incidence of adverse events was minimal and equally distributed throughout the 3 treatment groups.

Patients with primary hypercholesterolaemia were treated in another 3-year study of pravastatin

in 61 patients with either type IIA or type IIB hyperlipidaemia who had been stabilised on a low cholesterol diet prior to randomisation.[31] Patients were allocated to receive pravastatin 20 or 40 mg/day with upwards titration permitted. The adverse event profile was minimal and only 8 patients receiving pravastatin withdrew because of drug-related toxicity. The adverse events included abnormal liver function, although an acute elevation of aminotransferase levels occurred in only 1 patient receiving pravastatin.

Pravastatin has also been evaluated in elderly patients, defined as those over 65 years of age, in a 96-week study reported by Santinga et al.[32] Pravastatin was effective in this patient cohort, which consisted of 142 individuals with an age range at onset of 64 to 90 years and who had failed to achieve lipid normalisation despite dietary therapy. Pravastatin was well tolerated and efficacious in this elderly population, and the incidence of adverse events, including abnormal liver function, was essentially equal to that of the placebo.

Patients with diabetes have been presumed to be at increased risk for induced hepatic abnormalities secondary to fatty infiltration of the liver and the use of multiple drug regimens with the potential for interactions and secondary toxicity.[33] Pravastatin has been studied in patients with type 2 (non–insulin-dependent) diabetes mellitus in a cohort of 325 patients who were also dyslipidaemic.[34] Pravastatin demonstrated hypolipidaemic efficacy in the patients with diabetes, and the adverse events involving liver functions were similar to those in the group randomised to placebo.

Pravastatin has also been studied in comparative trials involving nicotinic acid, pravastatin or a statin-fibrate combination. Davignon et al.[35] studied a group of 158 patients with type IIA or type IIB hypercholesterolaemia who were randomised to receive placebo, nicotinic acid or pravastatin during an 8-week trial, which was followed by an 88-week intervention period which allowed the addition of other lipid-lowering agents. The group that was initially randomised to nicotinic acid had a statistically significant increase in aminotransferase levels, whereas patients receiving either pravastatin or placebo could not be differentiated with regard to liver function abnormalities.

Stalenhoef et al.[36] evaluated the efficacy and safety of increasing dosages of pravastatin in a double-blind study using simvastatin as a comparative agent.[36] Simvastatin appeared to be more potent than pravastatin in improving the lipid profile; however, the safety analysis showed only mild hepatic abnormalities that did not differ between the treatment groups.

Pravastatin has also been studied in 245 African-American individuals with primary hypercholesterolaemia who had been treated with an American Heart Association type I diet.[37] The patients were randomised either to pravastatin or placebo and were followed for changes in lipid profile and adverse events. The placebo and pravastatin groups had no patients who demonstrated an increase in aminotransferase levels above 3 times the upper limit of normal, and both groups had high compliance rates.

The combination of pravastatin and fibrates has been advocated for the management of carefully selected patients with significant mixed dyslipidaemia because of the frequent inability of either a statin or a fibrate, when used as monotherapy, to completely normalise the lipid profile. Pravastatin has been studied with gemfibrozil alone and in combination for the treatment of hypercholesterolaemia in 290 ambulatory patients who were not optimally managed with monotherapy.[38] The combination of these 2 drugs was associated with elevations of creatine kinase without significant clinical myopathy, but there were no significant elevations of aminotransferase levels, confirming the hepatic tolerability of combination therapy with pravastatin.

1.3.7 Overview

The use of HMG-Coa reductase inhibitors is associated with mild elevations of circulating aminotransferase levels in approximately 1 to 3% of patients receiving these agents when the abnormality is defined as 2 successive readings above 3 times the upper limit of normal (table I). Clinical trial evidence has demonstrated that the alterations of

Table I. Abnormal liver function tests (LFTs)[a] in major clinical trials of HMG-CoA reductase inhibitors. In none of the trials was the incidence of abnormal LFTs in the active group significantly different from that in the placebo group

Trial	Drug	Proportion of patients in study group with abnormal LFTs (%)
AFCAPS/TexCAPS[39]	Lovastatin	0.6
CARE[40]	Pravastatin	3.1
LIPID[4]	Pravastatin	2.1
WOSCOPS[41]	Pravastatin	1.2
4S[3]	Simvastatin	0.9

a Defined as aminotransferase levels >3 times upper limit of normal.

AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study; **CARE** = Cholesterol and Recurrent Events; **LIPID** = Long Term Intervention with Pravastatin in Ischaemic Disease; **WOSCOPS** = West of Scotland Coronary Primary Prevention Study; **4S** = Scandinavian Simvastatin Survival Study.

hepatic function associated with HMG-CoA reductase inhibitors appears to be dose-related but generally reversible as the agent is discontinued. Niacin has been associated with fulminant hepatic failure, which is in contrast to the experience with HMG-CoA reductase inhibitors.[42] The use of HMG-CoA reductase inhibitors may be associated with mild elevations of aminotransferase levels but has not been definitely correlated with severe morbidity involving alteration of hepatic function, emphasising the advantageous risk-benefit ratio of the HMG-CoA reductase inhibitors.

1.4 Muscular Effects

Rhabdomyolysis is an uncommon syndrome associated with a number of underlying aetiologies, including toxic, metabolic, inflammatory, infectious, traumatic and drug-induced causes.[43] The syndrome is characterised by acute, severe muscle destruction associated with myoglobinuria and the potential for renal failure. Myoglobin is released in copious quantities from the muscle, causing a colour change in the urine rather than the serum. Confirmatory testing for myoglobin requires a specific immunoassay. Rhabdomyolysis may also cause acute renal failure via direct toxic effects on the tubular epithelial cells or by introducing intratubular cast formation, which is complicated by associated hypovolaemia or acidosis. Myoglobin may additionally inhibit the production of nitric oxide and trigger diffuse intrarenal vasoconstriction and ischaemia in individuals with borderline renal hypoperfusion.

The incidence of rhabdomyolysis of any cause may be increased in patients with underlying metabolic myopathies, which may be determined by an evaluation of muscle histopathology with subsequent determinations of enzyme activity, including phosphorylase, phosphofructokinase, carnitine palmitoyltransferase and myoadenylate deaminase. Lofberg et al.[44] demonstrated enzyme defects in 23% of patients with recurrent rhabdomyolysis, which emphasises the potential problems in administering drugs with rare but clearly demonstrable rates of toxicity in patients with a prior history of muscular abnormalities.

The precise mechanism of HMG-CoA reductase inhibitor-induced myotoxicity is not known. However, Flint et al.[45] studied the possible underlying mechanisms using *in vitro* preparations and demonstrated that myotoxicity, as demonstrated in this experimental setting, was related to HMG-CoA reductase inhibitor-induced depletion of metabolic intermediates, including mevalonate, farnesol and geranylgeraniol. Supplementation of the compounds depleted by HMG-CoA reductase inhibitor therapy ameliorated the toxic effects of these drugs. Several intermediate proteins are required for the post-translational modification by isoprenylation of a number of essential regulatory proteins in mammalian cells. Pravastatin and lovastatin were demonstrated to exert their toxic effects on myocytes through a decreased rate of post-translational modification of the regulatory proteins by geranylgeraniol.

In vitro studies have shown that the various HMG-CoA reductase inhibitors have differing effects in striated muscle cells, such as the mouse C2-C12 myoblast, when the effects of various concentrations of HMG-CoA reductase inhibitors on cholesterol synthetic capacity and viability are studied.[46] Pravastatin 200 μmol/L had little effect on cellular cholesterol levels as compared with the reduction

(>90%) in myoblast cholesterol induced by lovastatin 25 μmol/L. Additionally, simvastatin and lovastatin, but not pravastatin, decreased the viability of the myoblast by nearly 50% at concentrations ranging between 1 and 5 μmol/L, and caused a decrease in viability of approximately 90% in the 10 to 15 μmol/L dose range.

The HMG-CoA reductase inhibitors have also been demonstrated to have lethal effects on cultured L6 myoblasts derived from rabbits. Simvastatin was demonstrated to decrease the isoprenylation of Ras proteins and induce a significant translocation of Ras from the membrane fraction into the cytosol. Inhibitors of phosphatidylinositol 3-kinase activity also caused cellular death with morphological changes similar to those induced by simvastatin.[47]

It has been shown that plasma coenzyme Q (ubiquinone) was lowered in 20 hyperlipidaemic patients who were treated with simvastatin, with resultant lower circulating levels of coenzyme Q and a lower coenzyme Q : cholesterol ratio when compared with healthy controls. Watts et al.[48] postulated that this metabolic alteration may be clinically important and is potentially related to the myotoxic effects of HMG-CoA reductase inhibitors. De Pinieux et al.[49] studied the effect of HMG-CoA reductase inhibitors on circulating levels of ubiquinone and the blood lactate : pyruvate ratio in dyslipidaemic patients who received either fibrates, HMG-CoA reductase inhibitors or placebo. The lactate : pyruvate ratio was used as a test for mitochondrial dysfunction. HMG-CoA reductase inhibitors appeared to increase the lactate : pyruvate ratio when compared with placebo recipients or healthy controls. The lactate : pyruvate ratio was not statistically different between patients randomised to receive fibric acid therapy or placebo. Additionally, ubiquinone serum levels were decreased in patients who received HMG-CoA reductase inhibitors, leading to the conclusion that the alterations in circulating levels of lactate and pyruvate were compatible with mitochondrial dysfunction.

Laaksonen et al.,[50] however, examined the hypothesis that intracellular coenzyme Q deficiency in the mitochondria of myocytes could disturb normal cellular respiration and result in cell death and rhabdomyolysis. Simvastatin was administered at a dosage of 20 mg/day for a 6-month period to 19 hypercholesterolaemic patients who consented to undergo muscle biopsy. Muscle high-energy phosphate and ubiquinone levels were assayed but were found to be no different from baseline or healthy control values, which did not support the hypothesis that altered isoprenoid synthesis or energy generation in muscle cells is a significant clinical factor following simvastatin therapy at normal dosages in humans.

Despite the *in vitro* evidence of HMG-CoA reductase inhibitor–related muscular toxicity, the rate of clinically apparent rhabdomyolysis (defined as a compatible clinical syndrome and creatine kinase elevation in excess of 1000 IU/L) has been, fortunately, rare in patients in large-scale trials. The average incidence approximates to 0.5%, indicating the relative tolerability of the HMG-CoA reductase inhibitors in the normal clinical setting (fig. 1).

1.5 Relationship Between Low Cholesterol Levels and Mortality

A number of epidemiological studies have demonstrated a J-shaped relationship between cholesterol levels and mortality, which began a debate on the potential causal relationship between hypocholesterolaemia and mortality. The controversy increased after early intervention trials of hypolipidaemic therapy did not show an increase in total survival despite statistically significant reductions in cardiovascular morbidity and mortality, implying an adverse effect of overzealous lipid lowering.

Epidemiological studies are generally unable to determine if the relationship between low cholesterol and increased mortality is of a causal nature or secondary to confounding variables. The Honolulu Heart Study demonstrated a J-shaped relationship when quintiles of cholesterol level were compared with total mortality rates, implicating an association between low cholesterol and increased adverse events.[51] However, a re-analysis of the Honolulu Heart Study demonstrated that the excess mortality in the lower cholesterol quintiles was limited to

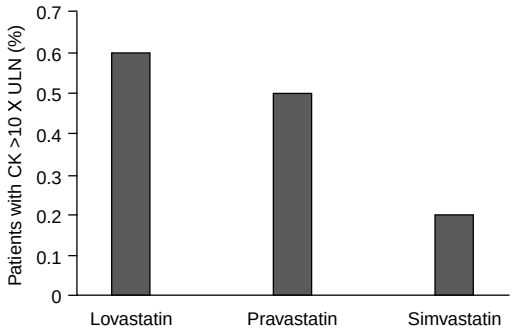

Fig. 1. Incidence of elevation of creatine kinase (CK) levels in major clinical trials of lovastatin (AFCAPS/TexCAPS[39]), pravastatin (CARE[40]) and simvastatin (4S[3]). Clinically significant elevations in muscle enzyme levels were documented in <1% of recipients of HMG-CoA reductase inhibitors in these clinical trials. **AFCAPS/TexCAPS** = Air Force/Texas Coronary Atherosclerosis Prevention Study; **CARE** = Cholesterol and Recurrent Events; **ULN** = upper limit of normal; **4S** = Scandinavian Simvastatin Survival Study.

patients with confounding health problems such as heavy alcohol consumption, smoking, pre-existent cirrhosis or a variety of intestinal diseases (fig. 2).[52] The long term follow-up of patients in the Framingham Heart Study who were free from malignancy or cardiovascular disease at the initial evaluation demonstrated a positive association between total mortality and cardiovascular mortality when correlated with cholesterol levels.[53] This did not support the hypothesis that low cholesterol levels resulted in an increase in mortality.[53]

Clinical trials had not addressed the potential risks or benefits of aggressive lipid lowering until the recent Post Coronary Artery Bypass Graft (Post-CABG) trial[54] and the AVERT (Atorvastatin Versus Revascularisation Treatments) study.[55] The Post-CABG trial evaluated the potential benefits of aggressive lipid lowering in addition to low dose anticoagulation therapy in an angiographic study involving 1351 patients who had undergone prior saphenous vein bypass graft and whose LDL levels ranged between 130 and 175 mg/dl.[54] A two-by-two factorial design was used to assign patients to either aggressive or moderate therapy with lovastatin for an average duration of 4.3 years. Aggressive therapy resulted in a reduction in mean LDL-cholesterol (LDL-C) level to 93 to 97 mg/dl, while the group randomised to a more moderate approach had a range of LDL levels from 132 to 136 mg/dl. The primary angiographic end-point was the mean percentage per patient of grafts with a decrease of at least 0.6mm in luminal diameter. Best results were achieved by aggressive use of lovastatin. Safety surveillance documented no excess of adverse effects in the group receiving aggressive therapy.

The AVERT trial was an 18-month, multicentre, non-blind, randomised, parallel, comparative trial in patients with stable coronary artery disease who had at least 1 vessel with >50% stenosis.[55] Patients were randomised to receive atorvastatin 80 mg/day or balloon angioplasty plus usual care, which included lipid-lowering therapy. A total of 73% of the patients in the usual care group received hypolipidaemic therapy, of whom the vast majority received HMG-CoA reductase inhibitor treatment. Atorvastatin 80 mg/day was used in the aggressive therapy group and resulted in a 46% reduction in LDL-C level from baseline values. The primary end-point was the composite occurrence of ischaemic events, which were defined as cardiac death, cardiac arrest, nonfatal myocardial infarction, cerebrovascular accident or hospitalisation for unstable angina or revascularisation procedures. Safety parameters were followed and the adverse events in

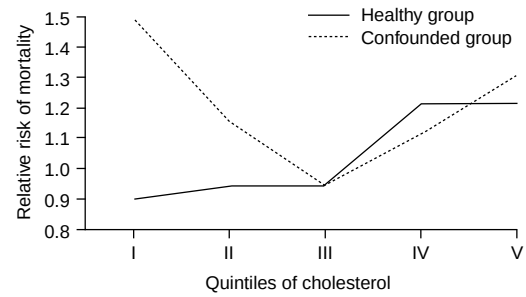

Fig. 2. Relative risk of mortality in the Honolulu Heart Study.[51] Excess risk was eliminated when controlled for confounding factors.[52]

both groups were similar. Four patients in the atorvastatin group had aminotransferase levels greater than 3 times the upper limit of normal on 2 separate occasions. No patients had clinically apparent rhabdomyolysis (creatine kinase levels greater than 10 times the upper limit of normal accompanied by compatible symptoms).

The recent lipid-lowering trials using clinical or angiographic end-points support the hypothesis that in patients with significant risk for events as determined by the presence of pre-existing atherosclerosis, an aggressive approach to hyperlipidaemic therapy is justified and does not appear to be associated with major short term adverse events. An analysis of the 5 major HMG-CoA reductase inhibitor trials with clinical end-points [4S,[3] the Cholesterol and Recurrent Events (CARE) study,[40] the West of Scotland Coronary Primary Prevention Study (WOSCOPS),[41] the LIPID study[4] and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)[39]] also did not demonstrate increases in violent behaviour, suicides or malignancy (table II).

Table II. Fatal and nonfatal malignancies in clinical trials of HMG-CoA reductase inhibitors. In none of the trials was the number of malignancies in the active group significantly different from that in the placebo group

Trial	No. of patients	No. of malignancies	
		active group	placebo group
AFCAPS/TexCAPS[39]	5608	252	259
CARE[40]	4159	171	161
LIPID[4]	9014	403	399
WOSCOPS[41]	6595	116	106
4S[3]	4444	35	33

AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study; **CARE** = Cholesterol and Recurrent Events; **LIPID** = Long Term Intervention with Pravastatin in Ischaemic Disease; **WOSCOPS** = West of Scotland Coronary Primary Prevention Study; **4S** = Scandinavian Simvastatin Survival Study.

1.6 Drug Interactions

Considerable interest has been generated in the role of the cytochrome P450 (CYP) enzyme system in drug-drug interactions involving HMG-CoA reductase inhibitors. Drug metabolism may be classified into 2 major categories: phase I and phase II reactions. Phase I reactions convert the parent drug into a more hydrophilic compound by reduction, oxidation or hydrolysis. Phase II reactions involve the conjugation of the drug to a different chemical group such as acetate, sulfate or glucuronate. Phase I and phase II reactions may occur concurrently, and a phase I reaction followed by conjugation is common in the hepatic handling of a number of drugs.

The CYP enzyme system, which catalyses Phase I reactions, is frequently involved in drug interactions. The CYP system has a number of isoenzymes. The coadministration of 2 CYP substrates that are metabolised by the same isoenzyme will result in the potential for an interaction. Whether such an interaction occurs is determined by the relative binding affinity of the 2 compounds, but may result in increased circulating concentrations of one or both of the drugs. In addition, coadministered drugs may be inhibitors of the isoenzyme and interfere with the normal metabolism of a drug, with a secondary and potentially toxic elevation in blood concentrations.

CYP3A4 is the most abundant isoenzyme in humans, with localisation predominantly in the liver and small intestine. CYP3A4 is intimately involved in the metabolism of HMG-CoA reductase inhibitors (table III). Lovastatin, simvastatin and atorvastatin are predominantly metabolised by this isoenzyme, and it represents one of the two major pathways for cerivastatin metabolism. Pravastatin is metabolised by multiple pathways, of which the CYP3A4 isoenzyme provides a quantitatively minimal effect. Fluvastatin is predominantly metabolised by CYP2C9 and CYP2D6; the former is also the isoenzyme responsible for the metabolism of warfarin.

The CYP3A subfamily accounts for approximately 60% of the total CYP activity in hepatic tissue and 70% of total activity within the gastrointestinal tract. The CYP3A4 isoenzyme is responsible for the metabolism of a large number of pharmaceutical compounds, including the azole antifungal agents, calcium antagonists, immunosuppressive agents, macrolide antibacterials, HIV protease in-

hibitors and certain antihistamines (table IV). Compounds metabolised by this isoenzyme may also act as inhibitors (mibefradil, ketoconazole, itraconazole, erythromycin, diltiazem and cyclosporin). The ingestion of grapefruit juice has also been shown to decrease the activity of CYP3A4 in the gastrointestinal tract, which may result in increases in the concentrations of a number of substrates with significant intestinal first-pass metabolism. CYP3A4 may be irreversibly inactivated by several potent inhibitors, such as mibefradil (which has now been removed from the marketplace because of toxic drug interactions). Inducers of the enzyme system are less common but include rifampicin (rifampin) and dexamethasone; coadministration of inducers can cause lower than expected drug concentrations.

The plasma concentrations of HMG-CoA reductase inhibitors that are primarily metabolised by CYP3A4 may be considerably increased when coadministered with a potent inhibitor. Simvastatin, atorvastatin, lovastatin and cerivastatin are primarily metabolised by the 3A4 isoenzyme and thus, theoretically, may be at higher risk for interactions. A secondary shunt pathway (CYP2C8) is available for cerivastatin, which reduces the potential adverse effects of isolated inhibition of the 3A4 isoenzyme. Atorvastatin is predominantly metabolised by the 3A4 isoenzyme, but the 2 primary metabolites of this compound have HMG-CoA reductase inhibition activity equal to that of the parent drug, which may result in a diminution of the effect of a coadministered CYP3A4 inhibitor.

From a pharmacological point of view, the apparent effect of a CYP3A4 inhibitor on HMG-CoA reductase inhibitor concentrations depends not only on the metabolic pathways involved but also on the assay used to quantify the drug interaction. The total amount of active inhibitor can be measured by an assay that measures the total inhibition of HMG-CoA reductase activity. However, assay of the total inhibitory activity determines both the active and latent lactone forms of simvastatin or lovastatin, which may thus lead to overestimation of the physiologically relevant concentration of these agents. The use of an assay that measures enzyme inhibition is more clinically relevant than the quantification of both the active and inactive forms of the HMG-CoA reductase inhibitors. The correct selection of the assay for measuring the clinical effects of HMG-CoA reductase inhibitors and their potential interactions with CYP3A4 inhibitors remains controversial.

The question of which specific assay to use is especially relevant in the delineation of the potential role of HMG-CoA reductase inhibitor therapy in the precipitation of muscle toxicity. Rhabdomyolysis has been demonstrated to be associated with a high concentration of HMG-CoA reductase inhibitor in plasma when total HMG-CoA reductase inhibitory activity is measured. Such high concentrations may be idiosyncratic or secondary to the concomitant use of an interacting drug such as a CYP3A4 inhibitor. This may be the mechanism by which HMG-CoA reductase inhibitors are associated with muscular toxicity, but the exact mechanism has not been clearly elucidated and is probably more complex than previously considered.

The presence of alternative pathways for the metabolism of an administered HMG-CoA reductase inhibitor may also be of clinical importance. Cerivastatin is metabolised by CYP3A4, but it also

Table III. Cytochrome P450 (CYP) isoenzymes responsible for metabolism of HMG-CoA reductase inhibitors

Isoenzyme	Drug
CYP3A4	Atorvastatin
	Cerivastatin
	Lovastatin
	Simvastatin
CYP2C8	Cerivastatin
CYP2C9 and 2D6	Fluvastatin
Multiple pathways	Pravastatin

Table IV. Examples of inhibitors and inducers of cytochrome P450 3A4

Inhibitors	Inducers
Calcium antagonists	Barbiturates
Cyclosporin	Phenytoin
Erythromycin	Primidone
Grapefruit juice	Rifampicin (rifampin)
Ketoconazole	Troglitazone

has available a secondary alternative pathway for metabolism (CYP2C8). Coadministration of cerivastatin with a CYP3A4 inhibitor may not lead to elevated and possibly toxic concentrations. Similarly, fluvastatin, which is metabolised by a different enzyme system (CYP2C9 and 2D6), may also be coadministered with a CYP3A4 inhibitor.

Despite the potential problems associated with drug interactions, clinical trials and large-scale safety studies have demonstrated a markedly low rate of clinically evident drug interactions even when HMG-CoA reductase inhibitors are coadministered with agents that theoretically pose risks of adverse clinical events. The database involving simvastatin, which has been used in more than 20 million patients who were followed with postmarketing surveillance, has been analysed. A total of 275 patients with myopathy were documented, which translates into an incidence of 1 in 70 000 patients. Postmarketing surveys may be limited by the possibility that the true number of adverse events is underestimated, but the low rate of toxic effects is supported by the analysis of the large-scale clinical trials. The postmarketing studies determined that the coadministration of HMG-CoA reductase inhibitors and agents with significant CYP3A4 inhibitory capacity increases the risk of myopathy by 16-fold. The CYP3A4 inhibitor most commonly coadministered with simvastatin that cause myopathy was cyclosporin, but no excess myopathy was reported with the more commonly prescribed calcium antagonists despite the potential for interaction.[56]

2. Trial Overview

The best estimation of the risk-benefit ratio in comparative toxicity of HMG-CoA reductase inhibitors can be obtained from the closely monitored, large-scale clinical intervention trials that have firmly established the benefits of HMG-CoA reductase inhibitor monotherapy for primary prevention in individuals with both normal (AFCAPS/TexCAPS[39]) and elevated (WOSCOPS[41]) cholesterol levels. Additionally, HMG-CoA reductase inhibitor monotherapy has reduced the number of clinical events in secondary prevention in patients with both relatively normal (CARE[40] and LIPID[4]) and elevated (4S[3]) cholesterol levels.

2.1 Primary Prevention

2.1.1 Normal Cholesterol Levels

The use of pharmacological therapy in individuals with a relatively normal cholesterol level as an attempt to decrease the primary advent of cardiac events has been controversial because of a presumed adverse risk-benefit relationship of drug therapy in a relatively low risk population. The AFCAPS/TexCAPS trial compared lovastatin with placebo in an attempt to decrease the rate of the first major coronary event in men and women who had no clinically evident atherosclerotic disease and normal total and LDL cholesterol levels.[39] The AFCAPS/TexCAPS trial was a large study of 5608 men and 997 women, half of whom received lovastatin 20 to 40 mg/day in a blinded, placebo-controlled fashion. The trial was stopped prematurely because of a 37% reduction by lovastatin in the composite primary end-point, which included fatal and nonfatal myocardial infarction, sudden death or unstable angina. Additionally, there were benefits in the lovastatin-related reductions in the rates of revascularisation procedures. Patients were followed for safety parameters as well as clinical end-points. Elevation of creatine kinase levels to greater than 10 times the upper limit of normal were rare, with an incidence similar in both the treatment and control groups. In the analysis, creatine kinase level elevations were stratified according to lovastatin dosage. Of the participants who received lovastatin 20 mg/day, 0.7% had elevations of creatine kinase. The group randomised to lovastatin 40 mg/day had creatine kinase elevations at an incidence of 0.6%. Both of these rates were similar to that in the placebo group. There was a total of 3 patients with rhabdomyolysis, 2 of whom were in the placebo group.

Consecutive elevations of more than 3 times the upper limit of normal for the aminotransferase levels were also rare and the incidence was equal in both lovastatin groups. A total of 0.6% of the 3242 individuals receiving lovastatin demonstrated abnor-

mal liver values, which was similar to the rate in the placebo group (0.3% of 3248).

2.1.2 Elevated Cholesterol Levels

WOSCOPS was a large-scale trial involving 6595 men with elevated cholesterol levels (272 ± 23 mg/dl) who were randomised to receive pravastatin 40 mg/day or placebo over a 4.9-year follow-up period.[41] Pravastatin therapy resulted in the expected significant reductions in total and LDL-C levels, which were correlated with a 31% reduction in death and nonfatal myocardial infarction. A total of 4 patients were demonstrated to have asymptomatic elevations of creatine kinase levels greater than 10 times the upper limit of normal, 3 of whom received pravastatin. Elevations in aminotransferase levels were also rare (42 pravastatin recipients and 32 placebo recipients, not statistically significant).

2.2 Secondary Prevention

2.2.1 Normal Cholesterol Levels

The CARE[40] and LIPID[4] trials evaluated patients with known coronary heart disease and relatively normal cholesterol levels. The CARE study was a landmark trial that analysed patients following a myocardial infarction whose total cholesterol levels averaged 208 mg/dl.[40] The 4159 patients were randomised to receive either pravastatin 40 mg/day or placebo over a 5-year trial period. The primary end-point was fatal or nonfatal myocardial infarction. Pravastatin therapy resulted in a 24% reduction in risk of the primary end-point and also reduced the frequency of stroke and need for revascularisation. Safety analysis of the CARE database revealed that 74 patients in the placebo group discontinued therapy compared with 45 patients who were randomised to receive pravastatin. Liver function tests were analysed and the aminotransferase elevations were not statistically significantly different between the groups receiving pravastatin or placebo (66 *vs* 73, respectively). Creatine kinase levels were also monitored and 4 patients in the placebo group were documented to have myositis compared with none in the pravastatin arm.

The LIPID trial was a double-blind, randomised study involving 9014 patients who had had either a myocardial infarction or who had a history of hospitalisation for unstable angina. These patients were randomised to receive either pravastatin 40 mg/day or dietary therapy.[4] The primary end-point was mortality from coronary heart disease, for which pravastatin therapy resulted in a relative risk reduction of 24%. Additionally, total mortality was improved in the intervention group, with a 22% reduction in relative risk achieved by pravastatin. A number of safety parameters were analysed and there was no significant increase in the number of adverse events that were ultimately attributed to the administration of pravastatin. Hepatic function tests revealed elevated aminotransferase levels in 2.1% of patients in the pravastatin arm compared with 1.9% in the dietary group. Creatine kinase levels were also measured and myopathy was documented in 8 patients receiving pravastatin compared with 10 patients receiving dietary therapy, emphasising the significantly favourable risk-benefit ratio in secondary prevention even with relatively normal cholesterol levels.

2.2.2 Elevated Cholesterol Levels

The 4S was the first large-scale HMG-CoA reductase inhibitor trial to demonstrate an improvement in cardiovascular and total mortality by using HMG-CoA reductase inhibitor therapy.[3] The 4S group tested the lipid hypothesis in 4444 patients who had had either a prior myocardial infarction or had angina. The 4S cohort was relatively high risk when stratified by total cholesterol level (mean level 264 mg/dl). Simvastatin therapy significantly reduced total and LDL cholesterol level, which translated into a relative risk of death in the simvastatin group of 0.70. Cardiovascular deaths were markedly decreased with simvastatin, and the 4S trial was the first major HMG-CoA reductase inhibitor trial to show improvements in total mortality coupled with documented benefits in a number of subgroups, including men, women and the elderly.

Adverse experiences were monitored, and a total of 6% of patients in both groups discontinued the study medication. Rhabdomyolysis was demonstrated in 1 woman taking simvastatin 20 mg/day, which resolved with the discontinuation of ther-

apy. An increase in creatine kinase level to more than 10 times the upper limit of normal occurred in 1 patient randomised to dietary therapy and 6 patients in the placebo group, but the increased level was not maintained in repeat analysis and was not associated with a clinical syndrome suggestive of myositis. Tests for liver function abnormalities demonstrated an elevation of aminotransferase levels to more than 3 times the upper limit of normal in 23 patients in the placebo group and 20 patients in the simvastatin therapy group.

In summary, the data from the clinical trials demonstrate an overwhelmingly favourable risk-benefit ratio for HMG-CoA reductase inhibitor therapy across a number of subgroups, emphasising the benefits of agents that allow aggressive lipid lowering.

3. Conclusions

HMG-CoA reductase inhibitors have revolutionised the ability of the clinician to intervene in patients with dyslipidaemia and effectively alter their lipid profiles. The 6 currently available HMG-CoA reductase inhibitors have been intensively scrutinised in both preclinical and clinical trials as to their safety profiles and risk-benefit ratios. Current data suggest that these drugs are both highly efficacious and relatively similar in their adverse effect profiles, and the results of the clinical trials justify an aggressive approach to patients with dyslipidaemia.

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