Risk-benefit and Cost-effectiveness Assessments of the statins

Ijeoma Nneka OKONKWO

Master of Philosophy

SCHOOL OF LIFE AND HEALTH SCIENCES

ASTON UNIVERSITY

September 2003

DEDICATION

TO ALMIGHTY GOD FOR HIS BLESSSINGS AND GRACE THROUGHOUT THIS PERIOD,

TO MY FAMILY FOR THEIR SUPPORT AND LOVE

MUM, DAD AND MY BROTHERS AND SISTER

ACKNOWLEDGEMENTS

I would like to thank my supervisor, Professor Alain Li Wan Po for his guidance and help throughout the period of this project.

My thanks and gratitude to my parents and my brothers and sister for their financial and moral support, without whom I could not have done this.

Thanks also to my colleagues Zoriah Aziz, Lubna Uppal, Yingxin Xu, and others who encouraged me, right from the beginning of the course through it, and were always there to give advice and help.

Special thanks to Emeka, for your prayers, love and understanding, and for being there for me always.

All glory to God for seeing me through, for making this possible, to Him be all honour and praise forever, Amen.

CONTENTS

ABBREVIATIONS

ADEs: adverse drug events

AERS: adverse events reporting system

ALT: alanine transaminase

AP: angina pectoris

ARF: acute renal failure

AST: aspartate transaminase

ATP: adult treatment panel

BCOHTA: British Columbia office of health technology assessment

CCOHTA: Canadian coordinating office for health technology assessment

CE: cost-effectiveness

CHD: coronary heart disease

CK: creatine kinase

EBM: evidence-based medicine

FDA: food and drug administration

HDL-C: high density lipoprotein cholesterol

IDL: intermediate density cholesterol

IHD: ischaemic heart disease

LDL-C: low density lipoprotein cholesterol

LRC CPPT: lipid research clinics coronary primary prevention trials

MI: myocardial infarction

NCEP: national cholesterol education programme

NICE: National institute of clinical excellence

QALY: quality adjusted life years

RBA: risk-benefit assessment

RCTs: randomized controlled trials

RD: risk difference

SGOP: serum glutamic oxaloacetic transaminase

SGPT: serum glutamic pyruvic transaminase

TC: total cholesterol

TG: triglycerides

ULN: upper limit of normal

VLDL-C: very low density lipoprotein cholesterol

YOLS: years of life saved

`SUMMARY

Risk-benefit and cost-effectiveness assessments of the statins

IJEOMA NNEKA OKONKWO

Master of Philosophy.

Objective: To undertake a risk-benefit assessment of the statins with particular emphasis on determining whether serious adverse drug events associated with cerivastatin could have been predicted from its clinical trials and to report on sources of heterogeneity of cost-effective estimates in economic evaluations of the statins.

Methods: Randomized controlled trials (RCTs) of cerivastatin and economic evaluations of the statins were retrieved by systematic searches of databases, historical searches, and writing to manufacturers and other authors of published searches of databases, and writing to manufacturers and other authors of published reports. The adverse events data reported (myalgia, increased CK levels greater than ten times the ULN, ALT levels greater than three times the ULN) in the RCTs were pooled using risk difference meta-analysis. The economic evaluation studies were assessed qualitatively.

Results: The results from the meta-analyses showed that the adverse drug events profile of cerivastatin could not have been deduced from the clinical trials. There were no significant differences in the rates of adverse events occurrences between cerivastatin

and placebo or active comparators largely as a result of inadequate power of RCTs detecting differences in low event rates. Observational studies and commentaries however suggest a much higher incidence of cerivastatin-associated rhabdomyolysis. Assessments of the economic evaluations showed disparities in the CE estimates arrived at by the different studies depending on the various factors. A wide discrepancy in the CE estimates in different studies was observed even when considering primary and secondary prevention alike.

Conclusion: Randomized controlled trials, as currently undertaken, are not sensitive enough for clear definition of adverse drug event profiles. Although efforts should be made to improve the quality of clinical trials by increasing trial periods, involving patients that mirror the types of patients likely to be on the test drug in real life, and older patients, who seem to be at a higher risk of suffering from statin induced adverse events, observational studies would still be required. CE estimates from economic evaluations vary according to the model used. Cost of treating adverse events should be incorporated when conducting economic evaluations as such costs have been shown to be quite substantial.

CHAPTER 1

INTRODUCTION

1.1 Coronary Heart Disease

The heart needs a constant supply of oxygen and nutrients, and the blood in the coronary arteries carries these to it. When the coronary arteries are narrowed or clogged and cannot supply enough blood to the heart, the result is coronary heart disease (CHD). Narrowing or blockade of the coronary arteries is usually a result of deposition on the walls of the vessels of cholesterol or fat (atherosclerosis), and this deposition is aggravated by abnormally high blood levels of cholesterol (hypercholesterolaemia). Symptoms of CHD are chest pain (angina) or shortness of breath resulting when not enough oxygen carrying blood gets to the heart. The person may feel a tightness, heaviness, pressure or squeezing, usually behind the breastbone. If the blood supply to any portion of the heart is completely cut off by a total blockade of a coronary artery, a heart attack results. Coronary heart disease is the leading causes of death in most developed countries of the world for both men and women (Carlson et al, 2001).

CHD is caused by a group of factors (risk factors), and they can either be non-modifiable (age, sex, family history, genetics), or modifiable (obesity, inappropriate dietary intake, physical inactivity, diabetes mellitus, hypertension, cigarette smoking and hypercholesterolaemia). When combined, these factors interact with each other increasing the risk for CHD.

Attention has been focused on treating the modifiable risk factors and particularly on hypercholesterolaemia to prevent CHD morbidity and mortality.

The presence of established CHD or prior myocardial infarction (MI) increases the risk of MI five to seven times that seen in men and women without CHD, and low-density lipoprotein cholesterol is a significant predictor of subsequent morbidity and mortality (NCEP, 1994).

1.1.1 Hypercholesterolaemia

Hypercholesterolaemia is a lipid disorder that occurs when plasma levels of cholesterol are abnormally high (usually >160mg/dL). This may result in atherosclerosis causing narrowing of the arteries and therefore may lead to a CHD event. Hypercholesterolaemia is a chronic condition that often requires life-long treatment. Studies have demonstrated that elevated cholesterol levels are an independent and significant risk factor for CHD (The expert panel, 1988; Pekannen et al, 1990). Data from studies such as the Framingham study (Castelli et al, 1992) and others show that the risk of developing CHD is related to the degree of cholesterol and low-density lipoprotein cholesterol (LDL-C) elevation. The Multiple Risk Factor Intervention Trial (MRFIT, 1982) showed a powerful relationship between cholesterol and CHD with a flat curve up to a cholesterol level of 5.2mmol/L, but with a gradual increase in CHD mortality rate to 6.5mmol/L, and above this, the mortality rate showed a steep increase. In the Framingham Heart Study (Castelli et al, 1992), there was no strict cut off points between

cholesterol levels that were safe and those that were at high risk of CHD, as the relationship between cholesterol and CHD was continuous. Hypercholesterolaemia is additive to other nonlipid risk factors for CHD as age, cigarette smoking, hypertension and diabetes.

1.1.2 Cholesterol

Cholesterol is a waxy fat-like substance that occurs naturally in all parts of the body, which the body needs to function normally. It is one of the major lipids of importance in human metabolism. Lipids are a heterogeneous group of compounds that have in common the property of solubility in organic solvents and insolubility in water (Dodson & Barnet, 1999). Other lipids of importance are triglycerides and phospholipids. The body uses cholesterol to produce vitamin D, bile acids that help to digest fat and many hormones. Only a little amount of cholesterol in the blood is needed to meet these needs and where there is excess, hypercholesterolaemia results which gives rise to atherosclerosis and increased risk for CHD.

Lipids are insoluble in water and therefore they form large complex structures with a protein (apolipoprotein) in order to become water-soluble and be transported in plasma. These proteins in combination with cholesterol, triglycerides and phospholipids are known as lipoproteins. Lipoproteins are classified as high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), intermediate density lipoproteins (IDL), very low-density lipoprotein cholesterol (VLDL), and chylomicrons. LDL-C is

the main cholesterol carrying lipoprotein with up to approximately 70% of total plasma cholesterol (Dodson, Barnet, 1999); HDL-C accounts for 20% of total plasma cholesterol. The main triglycerides-carrying lipoproteins are chylomicrons and VLDLs (Feher and Richmond, 1997).

1.1.3 Synthesis of cholesterol

The body mostly synthesizes cholesterol, although a little is absorbed from the diet. Cholesterol is synthesized in many tissues but the liver is the main site of synthesis in man. Cholesterol is transported to the tissues after synthesis as endogenous lipid in VLDL, which is eventually converted to LDL, and this LDL, rich in cholesterol, may either be removed from circulation by its receptors located mainly in the liver, adrenal glands and adipose tissues, or taken up into peripheral tissues. This process of uptake into peripheral tissues is fundamental to the process of atherogenesis and has led to LDL being termed the "atherogenic lipoprotein" (Dodson & Barnet, 1999).

Although increased serum levels of cholesterol have been directly linked to the risk of CHD, it is low-density lipoprotein (LDL) cholesterol that is more closely associated with the risk and extent of disease.

1.1.4 Classification of Hyperlipidaemia

Hyperlipidaemia can be classified as either primary or secondary.

Primary hyperlipidaemia is usually genetic/hereditary, and patients with this type will usually require medication and intensive intervention to prevent morbidity associated with the condition. Primary hyperlipidaemia is further classified into types I to V by WHO/Fredrickson (available at www.gpnotebook.co.uk) as follows:

Table 1.1: Classification of primary hyperlipidaemias

Type	Elevated particles	Associated clinical disorder	Serum TC	Serum TG
I	Chylomicrons	Lipoprotein lipase deficiency, Apolipoprotein C-II deficiency	N	++
IIa	LDL	Familial hypercholesterolaemia Polygenic hypercholesterolaemia, Nephrosis, hypothyroidism, Familial combined hyperlipidaemia	++	N
IIb	LDL, VLDL	familial combined hyperlipidaemia	++	+
III	IDL	Dysbetalipoproteinaemia	+	+
IV	VLDL	familial hypertriglyceridaemia, Familial combined hyperlipidaemia, Sporadic hypertriglyceridaemia, Diabetes	N+	++
V	VLDL	diabetes	+	++

IDL= intermediate density lipoproteins; LDL= low density lipoproteins; TC =total cholesterol; TG= triglycerides; VLDL= very low density lipoproteins; + = increased; + + = greatly increased; N= normal; N+= normal or increased

The most common inherited/familial hyperlipidaemia is familial hypercholesterolaemia.

Secondary hyperlipidaemias are common and account for about 40% of the total prevalence of lipid abnormalities. The most common causes of secondary hyperlipidaemias include obesity, diabetes mellitus, excessive alcohol consumption, thyroid, renal and liver disease, iatrogenic e.g. thiazide diuretics, beta-blockers, steroids and oral contraceptives (Dodson & Barnet, 1999)

Recently, blood lipid disorders in type 2 diabetes have been subject to clinical interest, and it has been shown that dyslipidaemia is common in type 2 diabetes. The characteristics of type 2 diabetic dyslipidaemia are high triglyceride levels (TG) and a low HDL-C point, with little or no difference in TC and LDL-C levels (Carlson et al, 2001).

1.1.5 Epidemiology

CHD is a common cause of death in many countries of the world. In the UK, CHD is a major cause of morbidity and mortality, accounting for about one quarter of all deaths in 1996: 28% among men and 18% among women (Rayner et al, 1998). CHD accounts for the deaths of 31% of men and women aged 45-65 years (Ebrahim et al, 1999). In the 1998 Health Survey for England, it was found that men and women had similar mean cholesterol of 5.5mmol/L and 5.6mmol/L respectively (desirable levels < 5.17mmol/L), with mean cholesterol increasing with age, the proportion rising steeply with age in both

sexes to age 54 years, then plateaus among men at around 20-25% but continues to increase in women to around 45%. (Evans & Primatesta, 1999). The increase is most notable among women so that levels become substantially higher than men's from age 60. In Ireland, in 1988, the CHD mortality rate for men and women was 260 per 100,000 population, the figure nearly four times the rate in France -67 per 100,000 population (Coronary heart disease: an epidemiological overview, 1994).

In Canada, Ischaemic heart disease (IHD) accounted for 22% of total deaths and 38% of hospital admissions in 1992 (Heart and Stroke Foundation, 1995). The risk of death from CHD increases with age in both men and women, but women have a lower risk than men for all age groups except after the age of 75 years when the risk is higher (Perras and Baladi, 1997).

Total cholesterol (TC) and LDL-C levels increase throughout life in men and women. Among subjects in the 1991 Heart Survey for England in 1986/87, the mean TC concentration was 5.8mmol/L for both men and women, increasing with age. Mean serum cholesterol concentration was 5.7mmol/L in both sexes among subjects who were aged 18-64 years and were not taking lipid lowering drugs. (Coronary heart disease: an epidemiological overview, 1994). By estimates, approximately 45% of all CHD cases among men are attributable to increased cholesterol levels and 47% of all female CHD, and the proportion (of CHD cases of men attributed to increased cholesterol levels) ranged from 20% in men aged 16-24 years to 52% in men aged 55-64 years (McPherson et al, 2002).

In Canada, between 1986 and 1990, the prevalence of hyperlipoproteinaemia was determined by a survey of 9 provinces, which included a total of 16,924 participants aged 18-74 years. Of this population, 46% had a TC level above 5.2mmol/L, 15% had an LDL-C level greater than 4.1mmol/L, 15%, a TG level above 2.3mmol/L, and 8% a HDL-C level less than 0.9mmol/L threshold values after which the risk increases (Connelly et al, 1992).

Figures from the United States Health and Nutrition Exam Survey, 1988-1991, and ATP guidelines, 40% of all adults aged 20-74 years would require fasting lipoprotein analysis and 29% would be candidates for dietary therapy.

1.2 Pharmacological Interventions

The National Cholesterol Education Program (NCEP) has given guidelines for the control and treatment of hypercholesterolaemia. The report of the NCEP adult treatment panel (ATP) III has classified LDL-C levels as follows:

<2.6mmol/L is optimal, 2.6-3.3mmol/L-near or above optimal, 3.36-4.1mmol/L-borderline high, 4.13-4.9mmol/L-high, and >4.9mmol/L-very high (Expert panel, 2001). In this report, the NCEP updated existing recommendations for the clinical management of high blood cholesterol. A new lower goal of LDL-C was established in ATP II to be <2.6mmol/L.

Lowering blood cholesterol levels is the target of any intervention, with the aim of preventing a first coronary event (primary intervention), or a subsequent one (secondary prevention).

1.2.1 Primary prevention

Primary prevention offers the greatest opportunity for reducing the burden of CHD. Primary prevention aims at maintaining cholesterol levels of patients that have no history of CHD, but have a moderately high LDL-C level and two or more risk factors for CHD. Such patients have a lower risk than secondary prevention patients of experiencing or dying from a coronary event. The clinical approach to primary prevention is founded on the public health approach that calls for lifestyle changes including reduced intakes of saturated fats, increased physical activity, and weight control. Primary prevention trials (Lipid research clinics program, 1984; Frick, 1987; Shepherd et al, 1995) showed a significant decrease in coronary events (fatal and nonfatal CHD combined), fatal CHD and overall mortality were slightly, but not significantly reduced. The NCEP ATP I guidelines for management of high blood cholesterol levels outlined a strategy for primary prevention of CHD in individuals with high levels of LDL-C (>4.13mmol/L) or those with borderline levels (3.59-4.1mmol/L) and multiple risk factors (2+). The third report of the NCEP (ATP III) now calls for yet more intensive LDL-C lowering in certain groups of people: It focuses on primary prevention in persons with multiple risk factors, many of whom have a relatively high risk for CHD and will benefit from more intensive lowering of LDL-C. One aim of

primary prevention is to reduce long-term risk (>10 years), as well as short-term risk (<10 years) (Expert panel, 2001).

1.2.2 Secondary prevention

Secondary prevention deals with patients who have a history of CHD, and therapy here is to prevent further occurrence of a cardiac event. Secondary prevention trials (4S 1994, Sacks et al, 1996) have shown that cholesterol lowering in patients with established CHD reduces total morbidity and mortality. In the ATP III report, the NCEP updated existing recommendations for the clinical management of high blood cholesterol. ATP II had earlier affirmed the importance of intensive management of LDL-C in persons with established CHD, and set a new lower LDL-C goal of < 2.6mmol/L for these patients. (Expert panel, 2001). Most patients with CHD will need LDL-lowering drug therapy.

1.2.3 Therapy

The major aim of treatment of hypercholesterolaemia is to reduce the atherosclerotic process and the incidence of clinical vascular disease. Studies have been carried out that show that dietary and drug treatment interventions for cholesterol reduction can reduce the risk of CHD and cause regression of existing atherosclerotic lesions. (Holme 1990, Brown et al, 1990).

1.2.4 Diet

Dietary intervention is usually the first choice of therapy considered. Diet is considered the cornerstone for most forms of hyperlipidemias. Diets high in saturated fats, cholesterol and excessive caloric intake all can result in high cholesterol levels and increase the risk of CHD. The NCEP ATP II have a recommended dietary approach (Therapeutic Lifestyle Changes Diet TLC), and these diets have the goal of reducing total fat intake to less than 30% of calories, reducing saturated fat intake while increasing polysaturated and monosaturated fats, reducing cholesterol consumption, and keeping daily caloric intake at levels required to reach and maintain ideal weight, and also to provide carbohydrate and protein at appropriate ratios for a balanced diet. (Table 1.1) Patients who require dietary treatment are usually given dietary counseling to enable them maintain the diet plan, as this requires them to change how they and their families prepare and eat food. Increased consumption of fruits and vegetables is encouraged. Patients however have to be compliant with their diets. Dietary interventions should be given at least a 3- 6-month trial period before determining the effectiveness of cholesterol lowering. Drug therapy is initiated if an adequate trial of diet therapy does not achieve the required therapeutic goal. Diet alone can reduce cholesterol levels by 5% (Langford & Kendall, 2001), therefore the majority of patients will need drug therapy usually with a statin.

Table 1.2: Nutrient composition of the TLC diet (taken from the NCEP executive summary, 2001

Nutrient	Recommended Intake
Saturated fat	<7% of total calories
Polyunsaturated fat	Up to 10% of total calories
Monounsaturated fat	Up to 20% of total calories
Total fat	25-35% of total calories
Carbohydrate	50-60% of total calories
Fiber	20-30g/d
Protein	Approximately 15% of total calories
Cholesterol	<200mg/d
Total calories	Balance energy intake and expenditure to maintain desirable body weight/prevent weight gain

1.2.5 Drug therapy

NCEP recognizes five major classes of drugs for the treatment of hypercholesterolaemia:

- Bile acid sequesterants, e.g. cholestyramine
- Nicotinic acid (niacin)
- Fibric acid derivatives, e.g. gemfibrozil,
- HMG-CoA reductase inhibitors, and

- Estrogen replacement therapy, although this last option is not popular at all.

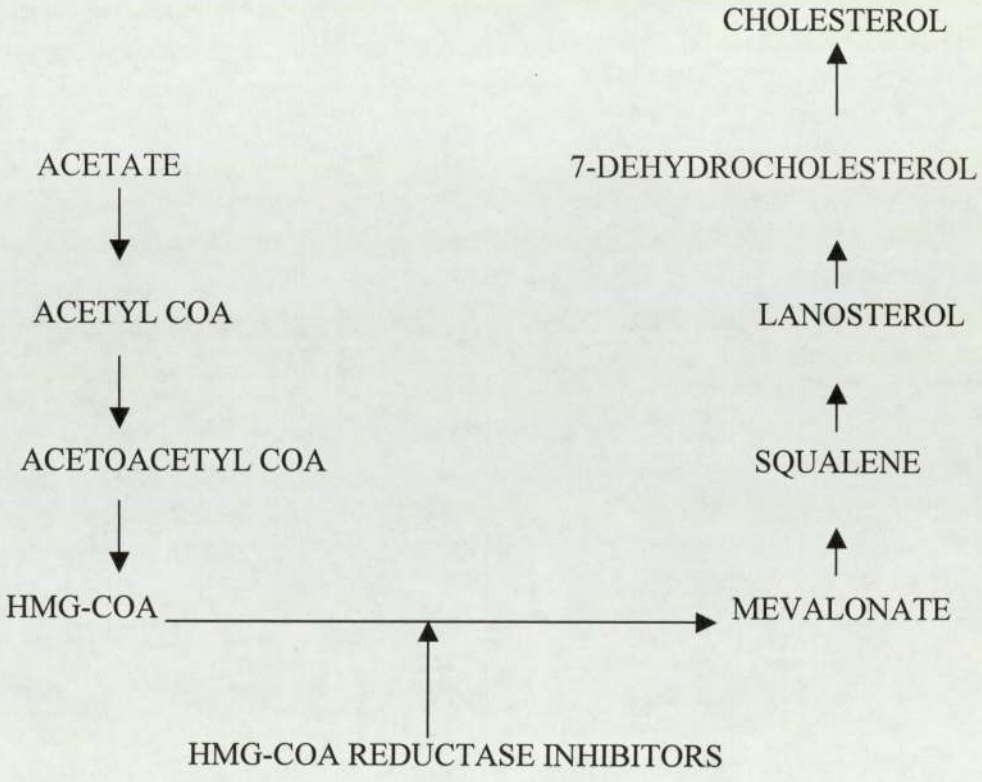
All these classes of drugs have been shown to reduce cholesterol levels by various percentages in clinical trials (Committee of principal investigators-WHO 1978, Frick, 1987; Lipid research clinics program, 1984). The bile acid sequesterants (cholestyramine) and nicotinic acid (niacin) are not as popular due to lack of or reduced compliance caused by adverse reactions. The fibric acid derivatives are more effective in lowering triglyceride (TG) levels and are not as effective as the statins in lowering LDL-C levels. Of all these pharmacological agents that have been used for cholesterol reduction, the statins have been shown to be the most effective drugs for the treatment of primary hypercholesterolaemia and their use has grown at a fast pace over the last decade, mainly because their marked effectiveness has been difficult to resist.

1.3 Statins

The first statin (lovastatin) was introduced in 1987 for cholesterol reduction and since then the statins have been shown to be more effective in reduction of LDL-C levels significantly more than other agents used. Studies using statins have significantly reduced the incidence of myocardial infarction (MI) and death from cardiovascular causes in men with moderate hypercholesterolaemia and no history of MI (Shepherd et al, 1995), and significantly reduced all-cause mortality especially from CHD in men and women with hypercholesterolaemia and angina pectoris (AP) or previous MI (4S, 1994).

The mechanism of action of the statins is by inhibiting the enzyme HMG-Co A reductase, which prevents the formation of mevalonate, the rate-limiting step in cholesterol synthesis. This inhibition leads to a reduction of plasma level of cholesterol, which in turn causes an up regulation in LDL-cholesterol receptors, and hence a clearance of cholesterol from the plasma. This inhibition of HMG-CoA reductase by statins has become the most common pharmacological method of cholesterol reduction in both the United States and Europe due to the excellent tolerability, efficacy, and safety (Stein et al, 1997).

Figure 1.1 Cholesterol synthesis and inhibitory action of HMG-CoA reductase inhibitors.



Members of this class of drugs include lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, and cerivastatin. Among these statins, lovastatin, simvastatin and pravastatin are compounds of microbial origin and therefore enantiomerically pure. Lovastatin and simvastatin are prodrugs and are metabolized in vivo to their active forms. Fluvastatin, atorvastatin and cerivastatin are all synthetic agents. Fluvastatin, which was the first synthetic statin, is a racemic compound. Fluvastatin, pravastatin and atorvastatin are all active in their open ring forms. These five statins are therapeutically used in a dose range between 10 and 80mg per day. Cerivastatin is the newest member of this group of agents, and as a sodium salt, is present in the active, open ring form. Cerivastatin was approved for marketing in 1997.

The statins are absorbed after oral administration, ranging from between 30% (lovastatin) and 98% (cerivastatin and fluvastatin). Food generally does not affect drug absorption, but for lovastatin (increases absorption) and pravastatin (decreases absorption). The plasma half-lives range between 1.1 hours to 30 hours. All are lipophilic except for pravastatin and fluvastatin, which are hydrophilic. Excretion is through hepatic cytochrome P450 enzymes, CYP3A4 for all except pravastatin (sulfation), and fluvastatin (CYP2C9). Cerivastatin has a dual excretion pathway, CYP3A4 and CYP2C8.

1.3.1 Efficacy

Research on cholesterol lowering has been going on for more than a decade now. Data from clinical trials (4S 1994,Shepherd et al, 1995; Sacks et al, 1996) have shown the value of statins in attenuating the risk of coronary artery disease. Reductions in low-density lipoprotein (LDL) cholesterol levels elicited by the statins have steeply decreased coronary event rates in the settings of primary and secondary prevention (Jacobson, 2000). This has led to a widespread use of statins.

Until recently, the statins had been proven through many clinical trials (4S 1994, Shepherd et al, 1995; Sacks et al, 1996) to be efficacious, well tolerated and safe. Systematic reviews (Ross et al, 1999; LaRosa JC et al, 1999; Kong et al, 1997) have also been carried out on statins, which attest to their efficacy and tolerability. The recent withdrawal of cerivastatin casts a shadow on the risk profile on the statins as a class.

1.3.2 Adverse drug reactions

The statins as with many other pharmacological agents are associated with a number of adverse effects. A few of these effects include headaches, gastrointestinal disturbances, dyspepsia, sleeping disturbances, myalgia, and central nervous system disturbances (Steiner et al, 1991, Hsu et al, 1995). Rare occurrences (<1%) of myopathy (unexplained muscle weakness or soreness), occasionally leading to myogolbinemia secondary to rhabdomyolysis, have been associated with HMG-CoA reductase inhibition (Garnett,

1995). Other adverse events observed are increased serum liver enzymes (aspartate transaminase and alanine transaminase) and creatine kinase (CK).

1.3.3 Drug interactions with statins

Drug interactions occur when the pharmacokinetics or pharmacodynamics of one drug is altered by another. Many drug interactions have been seen in the use of statins, some of which are minor and do not affect the activity of the drug. Other more serious interactions exist and are usually due to inhibition of cytochrome P450 (CYP) 3A4, the main site of biotransformation of most of the statin drugs. Due to differences in statin physico-chemical and pharmacokinetic properties however, some important differences in their interaction potential are evident (Corsini et al, 1999). Generally statins as a class are known to have drug interactions with other lipid-lowering drugs as fibrates and nicotinic acid, cyclosporin A, warfarin, macrolides, and antifungal imidazoles, which lead to or cause an increase in serum levels of the statin and may lead to skeletal muscle toxicity and rhabdomyolysis (Paoletti et al, 2002).

1.4 Evidence-based medicine (EBM)

The evidence base for preventing acute coronary syndromes with statin therapy has become one of the most formidable of any aspect of clinical medicine over the past twenty years (Velasco, 1999). Through advances in pharmaceutical research it has

become evident that the statins are the pharmacological agents of choice in the lowering of cholesterol levels as a prevention of coronary heart disease.

Evidence-based practice involves finding and interpreting the best evidence available to answer specific clinical questions and making decisions based on reliable evidence. Sackett et al have described evidence-based medicine as " the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients"(Sackett et al, 1996). The concept of evidence-based medicine grew from the need to apply the evidence derived from clinical trials to everyday practice as an approach to clinical problem solving and to improve on patients' care and treatment.

Making clinical decisions requires the optimal use of current available resources to improve patients' outcome. Clinicians and all healthcare professionals often encounter difficulties in making decisions about diagnosis and treatment of patients and often rely on other sources of information. These usually include textbooks, reviews and reports of research procedures. These sources may be outdated, or based on personal views, and may be biased. Furthermore, there are so many reports being published in biomedical journals that it is virtually impossible for the clinician to locate and identify those of importance to them and on time too. Moreover, clinical usefulness of many research findings in treatment studies is usually limited by their external validity and the applicability of outcome measures used in such studies to real-life clinical practice (Geddes et al, 1996). Evidence-based practice therefore becomes increasingly important as it involves the critical and systematic evaluation/appraisal of available evidence for its

validity and usefulness, the results of which are applied in clinical practice. This results in clinicians having the best available evidence to base their decision-making concerning their patients and their medications on.

1.4.1 Advantages and disadvantages of Evidence-based medicine

Evidence-based medicine (EBM) is very advantageous because it provides interventions that are backed by the most up to date evidence, ensuring that patients receive optimum treatment. EBM is a tool of self-learning that helps practitioners keep up to date with current practices and information throughout their career. EBM is also used by decision makers to make better use of limited medical resources through the systematic evaluation of clinical effectiveness and cost-effectiveness.

EBM is disadvantageous because it requires a lot of substantial investment of time and effort to acquire the necessary skills needed for EBM and evidence.

1.4.2 Limitations of EBM

EBM so far still depends largely on results of clinical trials, which unfortunately leave a lot to be desired such as better quality trials that include a greater number of patients and improved reporting of trials outcomes. High quality trials have yet to be undertaken, and only interventions that are common, or those that require a treatment or intervention that

has a commercial application are usually undertaken cause clinical trials are expensive and non-commercial research funds are scarce.

Evidence-based medicine comprises mainly of systematic reviews/meta-analysis, economic analysis, risk-benefit assessments, and decision analysis.

1.4.3 Systematic reviews

A systematic review or overview is a method used to summarize research evidence. Systematic reviews are usually carried out when there is a clinical/therapeutic question that needs to be answered e.g. why was cerivastatin therapy resulting in rhabdomyolysis in a number of patients when it was proven from clinical trials to be relatively safe? The objective of a systematic review is to evaluate studies that address the question of interest comprehensively and systematically.

A systematic review is carried out in a number of steps:

1. There has to be a definite/appropriate therapeutic question. The objectives of the review have to be clearly defined. Outcomes have to be valid and appropriate.
2. Literature search: all relevant literature is carefully searched for all studies carried out on the intervention, or topic under investigation.
3. Assessment of eligibility of studies for inclusion, study quality and reported findings. Here the assessment usually involves two researchers.
4. Analyzing the data: the findings from all the studies that have met with the inclusion criteria have to be aggregated to produce a result. Sometimes this

analysis is qualitative but is usually quantitative. Quantitative assessment of the data is carried out by meta-analysis.

5. Interpreting the results: the evidence should be summarized and discussed clearly to put the results in context. Any uncertainty around any quantitative estimates of effects should be pointed out.

A systematic review may allow estimation of efficacy of treatment, side effects of a treatment and comparison of treatments

1.4.4 Meta-analysis

A meta-analysis is a statistical technique for systematically combining the findings from independent studies, and is most often used to assess the clinical effectiveness of healthcare interventions, by combining data from two or more randomized control trials. Its validity depends on the quality of the systematic review on which it is based (Davies, Crombie, 2001).

A good meta-analysis aims for complete coverage of all relevant studies, looks for the presence of heterogeneity, and explores the robustness of the main findings using sensitivity analysis (Davies, Crombie, 2001).

Outcome conversions are used in a meta-analysis because outcomes in original studies are often diverse and so have to be converted into a common index to be integratable. Two types of data index can be used normally: (i) continuous data e.g. mean difference

(Clare et al, 1993), effect size (Hedges, 1981) and (ii) binary or dichotomous data e.g. odds ratio, rate ratio or rate difference (Zhang, 1994). Rate difference is the outcome conversion to be used in this review.

-Rate/risk difference

Here the difference in the event rates between the treatment and control/placebo groups is the parameter of interest.

Risk is a word that is fundamental to evidence-based medicine. Risk is the chance, or probability of having a specific event, and can be of a good or bad event. The risk of an event can be expressed by dividing the number with the event by the total number of people, e.g. of 120 men taking a statin for the treatment of hypercholesterolemia, 20 had myalgia after 8 weeks. The risk of developing myalgia was 20/120=0.2 approximately. Assuming 80 patients were taking placebo and 3 of them developed myalgia, then the risk of developing myalgia in the control group will be 3/80=0.04 approximately.

Risk difference is the risk in the treated (experimental) group minus the risk in the control/placebo group.

$RD = Ri - Ro$

Where

- RD represents the risk or rate difference
- Ri represents the risk or rate in the experimental group, and
- Ro represents the risk or rate in the placebo/control group.

RD =0.2 - 0.04

RD =0.16

If the risk difference is 0, then the experimental intervention has an identical effect as the control, if greater than 0, it increases the risk, and if less than 0, it reduces the risk of the event. Risk difference provides an estimate of excess risk on an absolute scale, i.e. the number of additional cases expected per so many exposures.

Confidence intervals (95%) associated with estimates of a rate difference can be calculated as follows:

CI = RD ± 1.96 SE (RD), where

CI = confidence interval

RD = risk difference

SE = standard error

1.4.5 Economic analysis

Economic analysis seeks to identify and to make explicit one set of criteria that may be useful in deciding among different uses for scarce resources. Economic evaluation has been defined (Drummond et al, 1997) as the comparative analysis of alternate courses of action in terms of both their costs and consequences. An economic evaluation aims to identify, measure, value and compare the costs and consequences of the alternatives being considered, and thus economic evaluations are always comparative in nature.

Four major analytical techniques are commonly used for pharmacoeconomic assessment of healthcare interventions: cost-minimization analysis, cost-effectiveness analysis, cost-utility analysis and cost-benefit analysis (Freund & Dittus, 1992). These four techniques all consider cost in the same way and have one basic key difference: how the consequences are measured and valued.

-Cost-minimization analysis (CMA)

Cost-minimization analysis assumes that the two treatments being compared have similar levels of effectiveness and thus the efficiency evaluation is then essentially a search for the least cost alternative.

-Cost-effectiveness analysis (CEA)

CEA is one of the techniques of economic evaluation designed to compare the costs and benefits of a healthcare intervention to assess whether it is worth doing (Phillips, Thompson, 2001). The aim of CEA is to maximize the level of benefits i.e. health effects, relative to the resources available. CEA measures consequences on a single scale, e.g. the number of life years gained where life saving interventions are considered. In the economic evaluation of cardiovascular disease interventions, a specific form of cost-effectiveness analysis- cost per year of life saved (YOLS) is the most commonly used.

-Cost utility analysis

Utility refers to the value or worth of a specific level of health status. Analyses that employ utilities as a measure of the value of programme effects are termed cost utility analyses (CUA). CUA is a type of CEA where the consequences are measured as quality adjusted life years (QALY). Results of CUA are expressed in terms of cost per QALY gained by undertaking one programme instead of another.

-Cost benefit analysis (CBA)

CBA measures both the costs and consequence in money terms. CBA measures all consequences in monetary units using contingent valuation or willingness to pay methods (Drummond et al, 1997). The method is useful when there are a wide range of diverse outcomes associated with the treatments being evaluated. Results are expressed in terms of whether the monetary value of benefits outweighs the costs.

1.4.6 Risk-benefit assessments

Risk-benefit assessments (RBA) measure the risks and benefits of different therapeutic interventions with a view to determine whether the benefits of the intervention are more than the risks associated with the intervention and vice versa. In effect risk-benefit assessments compare the efficacy of a given intervention with its adverse events profile. Medical practitioners are used to making risk/benefit comparisons of some sort prior to

prescribing any medication, because all pharmacological interventions have some risks associated with their use, and to be able to do this the practitioner /prescriber must have easy access to the data. On a larger scale, RBAs are conducted in systematic reviews for the purpose of keeping the medical practitioners and clinicians up to date with the risk-benefit profiles of the different medications they prescribe on daily basis.

Collecting evidence of efficacy and adverse effects of the given intervention is of major importance. It is easy enough to obtain the efficacy data of a drug, as this is clearly reported in clinical trials carried out on the drug. Clinical trials are carried out primarily to determine/prove the efficacy of the given drug under investigation as well as the adverse event profile. However, as clinical trials are expensive to run, and are also run for a limited time-frame, adverse events are either not detected or the trial period is too short to determine the seriousness of those reported, or the number of patients involved in the trials is limited. So in carrying out a risk-benefit assessment of a given intervention, relying on the results of clinical trials alone for adverse events data will not yield enough data for the study.

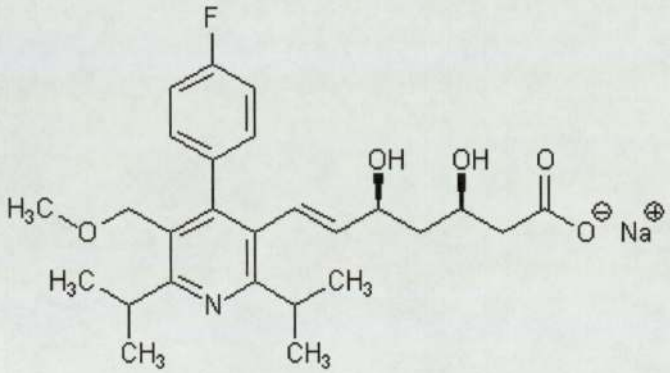
The majority of adverse event records of drugs are usually obtained from post-marketing surveillance. Herein lies the importance of post-marketing surveillance. Most potentially dangerous adverse events profiles of drugs are detected by this surveillance system as can be seen for example in the case of cerivastatin. It is important then that health care professionals have easy and up to date access to such adverse drug reaction reports.

Post-marketing surveillance of marketed medications is achieved primarily through MedWatch, the FDA's safety information and adverse-event reporting programme. MedWatch was introduced in 1993 (Kessler, 1993) by the FDA to encourage health care professionals to report any serious adverse effects suspected to be related to drug therapy. Other sources of data of adverse drug reactions are observational studies such as case studies, cohort studies and case reports.

This study is an evidence-based assessment of cerivastatin with respect to its ability to cause rhabdomyolysis more than the other drugs in its class.

1.5 Cerivastatin and rhabdomyolysis

1.5.1 Cerivastatin



Cerivastatin Sodium

Figure 1.2. Structure of Cerivastatin sodium.

Cerivastatin is an entirely synthetic and enantiomerically pure pyridine derivative. Unlike the other statins that are therapeutically active in milligram doses, cerivastatin has been shown to be active in microgram doses (Stein et al, 1997). Its inhibitory activity is 100 times that of lovastatin and is stereospecific since only the (+)-enantiomer will inhibit the enzyme HMG-CoA reductase (Bischoff et al, 1997). The Food and Drug Administration (FDA) approved Cerivastatin for marketing in 1997.

Cerivastatin has been shown to have a variety of pharmacodynamic effects in animals and in vitro studies. Preclinical studies carried out in animals in vitro have shown that cerivastatin has a high affinity for HMG-CoA reductase, and that it inhibits hepatic cholesterol synthesis at concentrations approximately 100 times lower than those required by lovastatin (Bischoff et al, 1997). The demethylated (M1) and hydroxylated (M23) metabolites of cerivastatin were found to possess inhibitory activity similar to the parent compound.

Continuing research showed that the antihyperlipidemic activity of cerivastatin is not entirely due to its inhibition of HMG-CoA reductase. A preliminary report from an in vitro study showed cerivastatin-mediated reduction of monocyte adhesion to vascular endothelium (a critical step in the development of atherosclerosis) (Yoshida et al, 1999). Cerivastatin, lovastatin and simvastatin increased the fibrinolytic potential of human umbilical vein smooth muscle cells in vitro by increasing their production of tissue plasminogen activator inhibitor-1(Wiesbauer et al, 2000).

Cerivastatin has been shown to improve endothelial functions in individuals who have impaired endothelium-dependent vasodilation. This impairment is important in the pathogenesis of atherosclerosis and acute coronary syndromes in patients with hypercholesterolemia. In a double-blind study, (John et al, 2000), 35 patients were randomized to treatment with cerivastatin 0.4mg/day or placebo, and endothelium-dependent increases in forearm blood flow were markedly and statistically significantly greater in patients receiving cerivastatin than placebo.

Cerivastatin undergoes almost complete GI absorption after oral administration, undergoes moderate first-pass metabolism and has a high hepatic selectivity. Cerivastatin has an absolute bioavailability of 60%; more than 80% of an administered dose is absorbed within 6 hours, with an absorption half-life of 1-2hours. Its maximum plasma concentration is attained after 2-3 hours, and is highly bound to plasma proteins (>99%), predominantly to albumin but also to alpha1-acid glycoprotein, and has a volume of distribution of approximately 0.3L/kg at steady state (Plosker et al, 2000). Cerivastatin exhibits linear pharmacokinetics.

Metabolism of cerivastatin occurs in a two way process; benzylic methyl ether demethylation, yielding metabolite M1, and stereoselective hydroxylation of a methyl group yielding metabolite M23. Cerivastatin has been shown to have a dual metabolic pathway, utilizing the isoenzymes P450 (CYP) 2C8 and 3A4 (Muck, 1998), to yield active metabolites which contribute 20-25% of the total activity of each dose of the drug, and this dual metabolic pathway is thought to be part of the reason for the drug's

desirable tolerability and safety profile. Plasma elimination half-life after oral administration is 2-3 hours. Approximately 70% of each dose of cerivastatin is excreted in faeces. Intact cerivastatin accounts for less than 2% of the originally administered dose. Cerivastatin has no enzyme inhibitory or inducing activity. The pharmacokinetic characteristics of cerivastatin are not affected by advanced age, gender, or ethnicity. (Plosker et al, 2000).

The safety, tolerability and pharmacokinetics of cerivastatin were studied in 48 young and elderly male volunteers in a randomized, double-blind, placebo-controlled study (Mazzu et al, 1997). The results indicated that age did not affect the pharmacokinetics of cerivastatin in male subjects.

In a randomized, double-blind, placebo- controlled trial, cerivastatin was studied in 49 healthy volunteers who were randomized into treatment groups as age-matched, male-female pairs. The pharmacokinetics of cerivastatin were predictable and similar in males and females (Stein et al, 1997).

Cerivastatin was withdrawn from the market in August 2001. The withdrawal was due to reported cases of drug-induced rhabdomyolysis, which led to the death of a number of patients (Tuffs, 2001).

1.5.2 Rhabdomyolysis

Rhabdomyolysis is a clinical and biochemical syndrome that results from injury to the sarcolemma of skeletal muscle and the subsequent release of skeletal muscle contents into systemic circulation. (Poels & Gabreels, 1993; Dayer-Berenson, 1994). There are a large number of causes of rhabdomyolysis, a number occurring in healthy individuals as a result of various causes such as excessive exercise, bacterial and viral infections, toxins and drugs. Some cases are attributed to hereditary metabolic abnormalities or structural abnormalities of the skeletal muscle cell (Poels & Gabreels, 1993). Hypothyroidism may predispose one to drug-induced myopathy, which may eventually result in rhabdomyolysis (Tomlinson, 2001).

Clinical presentations include muscular signs and symptoms, which present as pain, weakness, and tenderness. Non-specific symptoms include fatigue, fever, tachycardia, nausea, and dark red colored urine that results from excretion of myoglobin. Muscle components released into the systemic circulation include creatine kinase (CK), creatinine, potassium, uric acid, myoglobin, calcium, and phosphate, among others (Omar et al, 2001). This results in myogolbinemia and possibly myoglobinuria.

There are three major complications of rhabdomyolysis; acute renal failure secondary to myoglobinuria, cardiac arrest or arrhythmias due to hyperkalemia and hypocalcaemia, and compartment syndrome, which results from muscle swelling and subsequent

compression of nerves and blood vessels (Poels & Gabreels, 1993). Rhabdomyolysis can lead to renal failure and death.

Diagnosis is made primarily from measurements of serum CK (an enzyme present in skeletal muscle). CK is composed of either M- or B- subunits. Each is encoded by a unique gene and associate to form three isoenzymic forms: BB, MB and MM. These isoenzymes are all found in different tissues in humans: CK-BB is predominantly found in brain tissue, CK-MB in heart muscles, and CK-MM in skeletal and heart muscle. CK-MM (skeletal and cardiac isoenzymes of CK) is raised in rhabdomyolysis. It is the most sensitive indicator of damage to muscles, and measuring serum concentrations can help determine both the extent and timing of the damage to muscles (Omar et al, 2001). The CK level begins to rise 2-12 hours after muscle injury, peaks in 1-3 days and declines within 3-5days. Concentration of serum CK is considered significantly elevated when it is at least 10 times the upper limit of normal. Estimation of myoglobin in serum and urine is also useful in diagnosis, particularly in the early stages. Myoglobin is filtered by the kidney and appears in the urine when plasma concentrations exceed 1.5mg/dL (Poels et al, 1993), and this gives the urine a dark red brown color. Myoglobin has a short half-life and is rapidly cleared by renal excretion and metabolism to bilirubin. Therefore serum levels return to normal in about 6-8hours following cessation of muscle injury (Larbi et al, 1998). Due to its rapid clearance, absence of myoblobinemia does not exclude the diagnosis of rhabdomyolysis. Other biochemical findings include hyperkalaemia, increased anion gap, and levels of other muscle enzymes as lactic dehydrogenase (LDH), aminotransferase, blood urea nitrogen (BUN), creatinine,

carbonic anhydrase III, serum aldolase, uric acid, potassium and phosphorus. Concentrations of calcium are initially low but increase as calcium is released from the damaged muscle cells.

The mainstay of treatment here is to essentially correct hypotension, dehydration, and to prevent complications such as acute renal failure (ARF), and cardiac arrhythmias. Therapy involves removal of causative agents where known e.g. drugs or infection (Omar et al, 2001). Large quantities of fluids should be administered to maintain adequate hydration and urinary output. Diuretics are given to improve diuresis, thereby flushing out blocked renal tubules; mannitol is commonly used for this. Alkalinization of the urine may be necessary to prevent myoglobin from dissociating to its nephrotoxic metabolites, ferrihemate and globin (Dhawan et al, 1997). In the occurrence of acute renal failure, dialysis may be required. Potassium levels should be monitored carefully to prevent cardiac complications and may need to be treated. This can be achieved using sodium bicarbonate, glucose and insulin. Calcium infusion is not advised as this may enhance the deposition of calcium in damaged muscle and lead to further damage (Zieger et al, 1990). Rhabdomyolysis has excellent prognosis once discovered in the early stages. It is important to correct the hyperkalaemia and renal function early and adequately to prevent fatal outcomes.

Rare cases of rhabdomyolysis have been associated with statin therapy generally, but over the last year, were seen more with cerivastatin therapy, either used alone or in combination with other drugs. The mechanism by which statins cause myopathy and

rhabdomyolysis is not yet known. There are currently two theories that have been suggested. The first suggests an alteration in the stability of cell membrane permeability of the myocyte as a result of decreased cholesterol synthesis (Jones, 2000). The second proposes decreases in mitochondrial concentrations of ubiquinone (a vitamin-like fat-soluble nutrient), which facilitates electron transplant, thus causing disturbances in cellular energy production and subsequent cell death. (Shetty, 98; Christians, 98, Bliznakov, 2002).

The withdrawal of cerivastatin from the market on August 8, 2001 was as a result of several cases of deaths due to rhabdomyolysis as a presumed consequence of high dose cerivastatin, especially in combination with another cholesterol lowering drug, gemfibrozil (Tuffs, 2001). This withdrawal has further increased the need for better surveillance of drugs and medical products especially of adverse events profiles and questions the reliability of clinical trials for elucidating the adverse events profile of drugs.

1.6 Objectives

The present study was undertaken:

1. To undertake a risk-benefit assessment of the statins with particular emphasis on determining whether serious adverse drug events associated with cerivastatin could have been predicted from its clinical trials.

2. To determine the possible sources of heterogeneity in cost-effectiveness estimates in cost-effectiveness studies of the statins.

CHAPTER 2

RISK-BENEFIT ASSESSMENT OF CERIVASTATIN

2.1 INTRODUCTION

Since their introduction in the 1980s, the statins have become important agents for the prevention of CHD, because of their proven effectiveness in lowering cholesterol levels and preventing cardiovascular morbidity and mortality (4S, CARE, WOSCOPS, AFCAPS). Until recently, the available evidence suggested that the marketed statins exerted their beneficial effects with relatively little toxicity. With the introduction of a number of similar drugs, in-use experience suggested that both their benefits and risk appeared to be well-defined class-effects. The newer statins were granted marketing authorization on the basis of cholesterol-lowering effects rather than on the basis of their effects on clinical outcomes. Cerivastatin was introduced in 1997 as the sixth and most potent HMG-CoA reductase inhibitor for lowering lipid levels in patients with coronary heart disease or those at high risk for CHD. The statin was subsequently withdrawn from sale worldwide in August 2001(Weber, 2001), due to several deaths resulting from the complications of severe rhabdomyolysis. The withdrawal of cerivastatin raised concerns about the safety of the other statins. Staffa, showed that the rate of reporting of fatal rhabdomyolysis with cerivastatin was many-fold greater than with other statins on the United States market (Staffa et al, 2002). Differences in potency, lipophilicity and

bioavailability of cerivastatin relative to the others have been suggested as possible reasons for the higher incidence of rhabdomyolysis (Davidson, 2002).

We report on a systematic review of controlled trials of cerivastatin, prior to its withdrawal in 2001, to determine whether the evidence available then suggested that it was an unusual statin with respect to risk-benefit profile, particularly in relation to rhabdomyolysis. Observation studies, case reports and commentaries, leading to and subsequent to its withdrawal, are also reviewed to identify issues relevant to the risk-benefit profiling of cerivastatin.

2.2 METHODS

This work was performed according to the QUORUM (Quality of Reporting of Meta-analysis) recommendations for improving the quality of meta-analysis of randomized controlled trials (Moher et al, 1999)

2.2.1 LITERATURE SEARCH:

Retrieval of studies

Reports of randomized controlled trials of cerivastatin were identified through a systematic search of the following:

(i) Electronic searches of Medline database through the Biomed website. The

database was searched from 1983 till October 2001. Other databases searched were Ingenta, Idealibrary, and Science direct.

(ii) Historical searches through the reference list of all retrieved studies, reports, and books.

(iii) Writing to the authors of relevant studies for retrieval.

(iv) The Cochrane database was searched to identify systematic reviews and relevant studies.

Food and Drug Administration (FDA) website was searched extensively for literature on the subject. The websites of organizations (CCOHTA, BCOHTA, NICE) undertaking health technology assessments were also searched to obtain any health technology assessments carried out on lipid lowering agents.

All relevant studies were identified using the following subject headings:

- Cerivastatin/statins/HMG-CoA reductase inhibitors
- Randomized clinical trials/case reports
- Rhabdomyolysis/myopathy/adverse events
- Rhabdomyolysis and biochemical features
- Rhabdomyolysis and statins

These were then combined to retrieve the relevant papers. The searches were limited to studies conducted in human subjects.

2.2.2 Selection criteria

For a study to be included in the systematic review, it had to be a randomized controlled trial, but the target population of patients in the trials was unlimited. For pooling of results the stated primary outcome of intervention must be reduction of LDL cholesterol, with intervention duration of at least 4 weeks with or without a follow up period, and data on mortality or morbidity were available. There were no language limitations. No age or sex restrictions were applied. Primary outcomes of interest for the meta-analysis were increases in enzyme levels- AST and ALT above three times the upper limit of normal, CK levels ten times the upper limit of normal, myalgia, back pain, leg pain and pain. Abstracts were not included in the study.

2.2.3 Data extraction

Data extraction was carried out by myself with cross validation by my supervisor. Data extracted from the trials include trial characteristics such as (1) first author's name, year of publication, (2) study design (double-blind, parallel, multicentre), (3) number of participants, (4) age range, mean age of patients, number of patients in each treatment group, (5) type and dosage of statin drug, (6) length of trial. Also extracted was the reported adverse events recorded in the trials (myalgia, back pain, leg pain, pain, elevated levels of aspartame transaminases (AST) and alanine transaminases (ALT) greater than three times the upper limit of normal (ULN), and creatine kinase CK more

that ten times ULN.

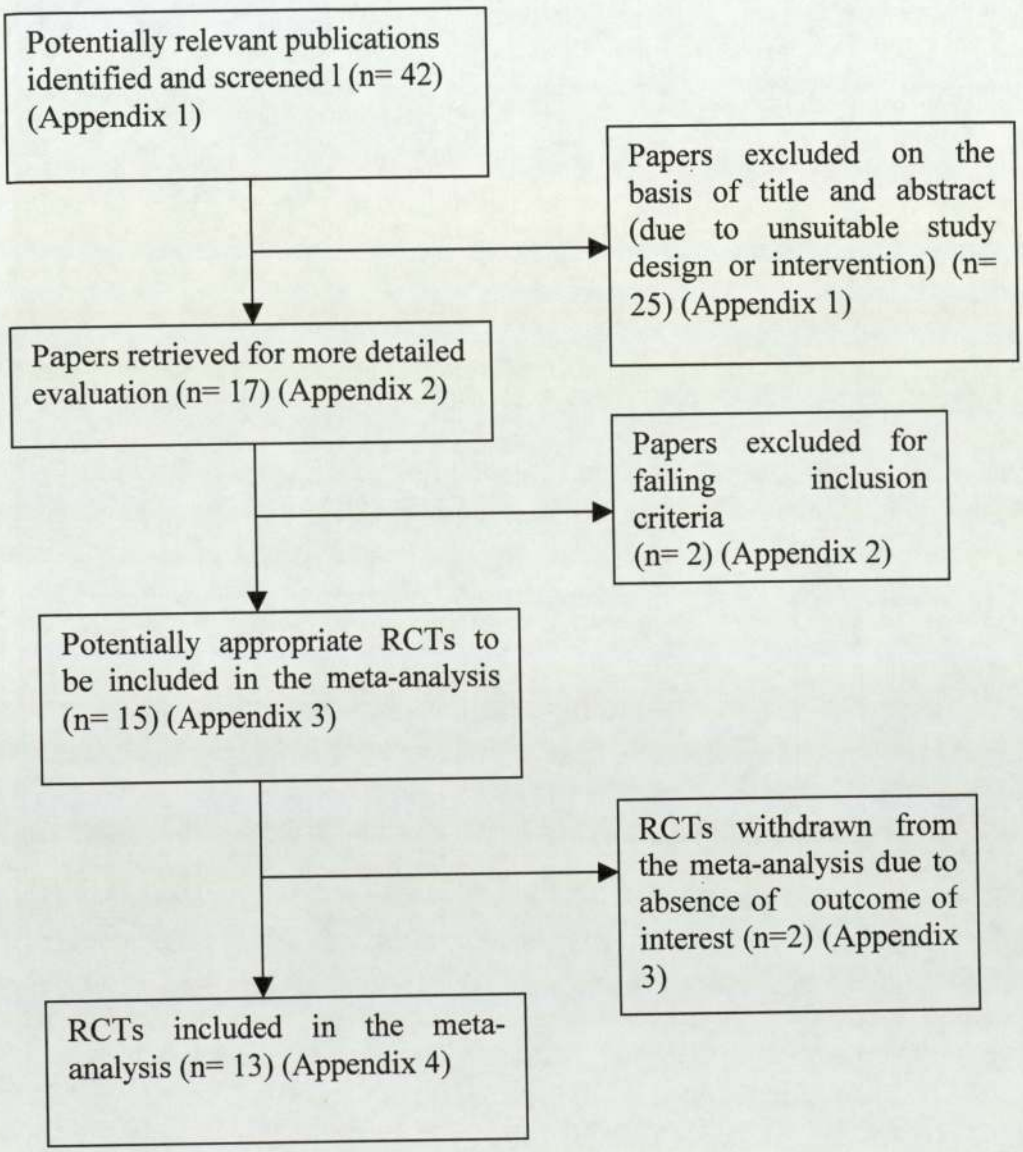
2.2.4 Outcome conversions and statistical analysis

Differences in the rate of occurrence of adverse events in patients receiving cerivastatin relative to placebo or control drug were estimated. Homogeneity of effect was tested using Cochran's Q statistic (Cochran, 1954) at a significant level of 0.1. If no heterogeneity was observed, a fixed-effects model (Mantel, 1959) was used; otherwise DerSimonian and Laird's random effects model (DerSimonian, 1986) was used. Risk differences were estimated for myalgia, back pain, leg pain, pain, increased CPK levels above 10 times ULN, and increases of AST and ALT levels above 3 times ULN. For most of the outcomes, the low event rates necessitated the use of exact methods.

Case-reports and commentaries were assessed qualitatively.

2.3 RESULTS

Figure 2.1: Meta-analysis flow diagram



2.3.1 General characteristics of the RCTs

13 RCTs met the inclusion criteria, out of which 10 were double-blind RCTs (Betteridge 99, Farnier 98, Hanefeld 99, Insull 2000, Leiter 99, Ose 99, Rubinstein 99, Stein 97, Stein 99, Tao 2000), one was a prospective, randomized, open-label, blinded end point study (Hunninghake et al, 2001), one a randomized, open-label, parallel-group, optional dose-titration study (McPherson et al, 2001), and the last was a long term comparative trial (Sasaki et al, 1998). All the trials were undertaken between 1997 and 2001 among male and female patients with age ranging from 18 to 80 years (females generally had to be postmenopausal or surgically sterilized, or had to use birth control measures approved by the investigator). LDL-C levels for inclusion in all the trials ranged from >4.13mmol/L to >6.46mmol/L in the trials including patients with severe hypercholesterolemia, or >130mg/dl in the presence of definite coronary artery disease (CAD), or two or more of the following risk factors: CAD, family history of CAD, cigarette smoking, hypertension, low levels of blood HDL-C (<1.5mmol/L), or severe obesity. Triglyceride (TG) levels were generally between <3.9mmol/L to <4.5mmol/L, but for one trial that was in the range 2.24-5.6mmol/L (Farnier, 1998).

Characteristics of the RCTs are outlined in Table 2.1. Tables 2.2 and 2.3 show the patients demographics. Efficacy results can be found in appendix 5. Number of patient withdrawals and deaths are shown in Appendix 6.

The 13 trials that were included are Betteridge and colleagues (1999), Farnier and colleagues (1998), Hanefeld and colleagues (1999), Hunninghake and colleagues (2001),

Insull and colleagues (2000), Leiter and colleagues (1999), McPherson and colleagues (2001), Ose and colleagues (1999), Rubinstein and colleagues (1999), Sasaki and colleagues (1998), Stein and colleagues (1997), Stein and colleagues (1999), and Tao and colleagues (2000).

Betteridge and colleagues (1999)

The study was of 12 weeks, with an extension period of 88 weeks. Male and female patients with uncomplicated primary hypercholesterolemia, aged between 21 and 75 years were recruited. A total of 63 centers in 12 countries participated in the study. The primary outcome of interest was percentage reduction in LDL-C at week 12. There was no significant intergroup differences in age, sex, alcohol consumption, smoking or duration of family history of hyperlipidemia. At conclusion of week 12, 894 patients were valid for efficacy analysis, 153, 146, 156 and 154 on cerivastatin 0.025mg, 0.05mg, 0.1mg and 0.2mg respectively, 138 on simvastatin 20mg, and 147 on placebo. Percentage changes in LDL-C were –2% (placebo), -12.5% (0.025mg), -16.6% (0.05mg), -24.7% (0.1mg), -30.6% (0.2mg), -40.3% (simvastatin 20mg) (Appendix 5). A total of 172 patients were transferred from placebo to cerivastatin 0.025mg at the end of 12 weeks.

1158 patients were valid for 12-week safety analysis. A total of 175 patients were transferred from placebo to cerivastatin 0.025mg at the end of the 12-week period and 1141 patients were valid for the 52 and 100-week safety analysis. Common adverse

events (Table 2.4) (>2.5% of any treatment group over the 12 week, 52 week and 100 weeks) occurred with a higher incidence for cerivastatin than for placebo. Five deaths occurred during the 100 week study: three were due to suspected or confirmed concomitant consequences of ischaemic heart disease and two to complications of malignancy. None was thought to be related to exposure to study drug. A total of 79 patients experienced 93 adverse events leading to withdrawal during the study. The overall incidence of patients withdrawing because of adverse events was 6.6% for cerivastatin and 8.6% for simvastatin.

Adverse events reported are shown in Tables 2.4 and 2.5.

Farnier and colleagues (1998)

The study lasted 16 weeks with an extension phase of 36 weeks. Male and postmenopausal or surgically sterilized female patients aged 10-80 years with mixed hyperlipidemia were included in the study. Of the 751 patients randomized to double blind treatment, 166 received 0.1mg cerivastatin, 171 received 0.2mg cerivastatin, 175 received 0.3mg cerivastatin, 160 received 1,200mg gemfibrozil, and 79 received placebo. Primary efficacy criterion was the change from baseline in measured LDL-C after 16 weeks of treatment. A total of 592 patients were eligible for efficacy analysis at the end of 16 weeks. LDL-C levels had been decreased in patients valid for efficacy by 15.1%, 23%, and 24%, with 0.1, 0.2 and 0.3mg cerivastatin, respectively, compared with reductions of 7.5% with gemfibrozil and <1% in the placebo group. The significant reductions in LDL-C that occurred in the first 16 weeks were sustained in the subsequent

36-week, non-placebo controlled phase. Most common adverse events reported are gastrointestinal disturbances (Table 2.4). The incidence of abnormal CPK levels > 3 x ULN and abnormal AST and ALT > 2 x ULN were very low over the whole 52 week treatment period. Number of patients with CPK levels > 10 x ULN and AST and ALT levels above 3 x ULN is shown in Table 2.5.

Hanefeld and colleagues (1999)

Male and female (post menopausal or surgically sterilized) patients aged 18-75 years with primary hypercholesterolemia were recruited for the study. The trial involved 24 centers in five European countries. A total of 351 patients were randomized to treatment; 71 patients to placebo, 140 patients to the 0.3mg cerivastatin dose, and 138 patients to the 0.4mg cerivastatin dose. Patients were randomized to cerivastatin 0.3mg, 0.4mg and placebo for a total of 8 weeks. Primary outcome of interest was the relative reduction in LDL-C at week 8. Both cerivastatin treatment groups showed a marked mean reduction in LDL-C concentrations when compared with baseline, and this was maintained until the end of the treatment period. Mean decreases in LDL-C concentration of 35.8 ± 1.0% with 0.4mg, and 32.5± 1.0% with 0.3mg dose, were highly significant ($P < 0.0001$) compared with placebo (increase of 0.2 ± 1.4%). One patient withdrew during treatment due to a serious adverse event: deterioration of established concomitant arthritis of the left lower limb (0.4mg dose), and this was not considered to be related to the study medication. One patient died (0.3mg) 2 days after end of treatment, patient had

underlying atherosclerotic disease and the possible relationship to the study drug was assessed as 'remote'. Overall incidence of adverse events was low, with only a few occurring in more than 2.5% of patients in any treatment group. Back pain and headache were the only adverse events that had a higher incidence with both cerivastatin groups than with placebo and where the incidence increased with the higher cerivastatin dose. CPK, AST and ALT concentrations revealed no clinically significant changes with cerivastatin treatment compared with placebo. (Table 2.5)

Hunninghake and colleagues (2001)

Twelve sites in the United States enrolled patients in this study. Men and women aged 18-80 years with dyslipidemia were enrolled. Women of childbearing age had to use a suitable method of contraception approved by the investigator. A total of 215 patients were randomized to receive treatment (137 men and 78 women). 108 patients received Atorvastatin10mg and 107 patients received cerivastatin 0.3mg. Patients were randomized for a total of six weeks on cerivastatin 0.3mg and atorvastatin 10mg. Primary outcome of interest was percentage reduction in LDL-C from baseline to week 6. Both treatment groups had significant decreases in LDL-C from baseline at week 6, with the atorvastatin- induced reduction (37.7%) being significantly greater (<0.0001) than that with cerivastatin (30.2%).

Over the 6-week study period, patients randomized to cerivastatin reported a greater number of adverse events than patients randomized to atorvastatin. The proportion of patients having adverse events considered to be associated with treatment was

significantly greater ($p < 0.05$) for the cerivastatin (14%) than for the atorvastatin (5%) groups. In both groups, most adverse events were mild or moderate in nature. 4 patients experienced a severe adverse event: two in each group. No patients had AST or ALT level greater that 3 x ULN in both treatment groups, 3 patients (2 on cerivastatin and 1 on atorvastatin) had CPK level of 3 times the ULN.

Insull and colleagues (2000)

Ambulatory men or women (not of child-bearing potential) aged 18-75 years with documented primary hypercholesterolemia were eligible. The study was conducted at 59 centers in the USA and Canada. A total of 1170 patients were randomized to double blind treatment: 199 to placebo, 195 to cerivastatin 0.4mg, and 776 to cerivastatin 0.8mg. 1102 (94%) patients completed the 8-week study. This was an 8-week study with primary outcome being the change in baseline LDL-C at end of week 8. Cerivastatin 0.8mg reduced mean LDL-C by 41.8% from baseline ($P < 0.0001$ versus placebo), compared with 35.6% ($P < 0.0001$ versus placebo) for cerivastatin 0.4mg. Near maximum reduction in LDL-C levels was achieved after 4 weeks of treatment with both cerivastatin doses. In the total efficacy population, cerivastatin 0.8mg brought more patients to NCEP goal than cerivastatin 0.4mg. Both doses were well tolerated with most adverse events judged mild in intensity by the study investigators. Adverse events were responsible for premature withdrawals of a total of 39 patients: 1.5% in the placebo group, 3.1% in the 0.4mg cerivastatin group, and 3.9% in the 0.8mg cerivastatin group (Appendix 6). A total of 22 patients had serious adverse events: 1% in the placebo, 2.1%

in the 0.4mg dose and 2.1% in the 0.8mgh dose. Incidence of significant transaminase and CPK abnormalities was generally similar across treatment groups. 12 patient on cerivastatin (both doses) experienced CPK levels > 10 x ULN (Table 2.5). 12 patients in both cerivastatin groups had a SGOT level 3 x ULN, and 9 patients had SGPT levels 3 x ULN (Table 2.5).

Leiter and colleagues (1999)

Three Canadian centers participated in this 32-week study, with extension phase of 72 weeks. The study included male and female patients aged 18-75 years with documented primary hypercholesterolemia. Women were surgically sterile or one year postmenopausal. A total of 596 patients were enrolled in the short-term phase, of which 387 were randomly assigned to study treatment. 260 patients were randomly assigned to receive cerivastatin (0.05-0.3mg) and 127 patients received simvastatin (5-40mg) (Table 2.3). 153 patients participated in the long-term extension phase, of which 94 and 59 patients received cerivastatin and simvastatin respectively. The primary outcome was percentage change in LDL-C from baseline. Both drugs had a marked onset of action within the first 2 weeks with further decreases in LDL-C observed up to the end of the first 32 weeks of study. Overall, 89% of patients treated to cerivastatin responded to treatment (15% drop in LDL-C level), as did 93% of patents on simvastatin.

A total of 385 patients were included in the safety analysis at week 32. Overall a similar percentage of patients experienced adverse events in the two treatment groups during the

short-term phase (76% cerivastatin and 73% simvastatin). The most common adverse events are reported in Table 2.4. Serious adverse events occurred in only 15 (5.8%) and 5 (3.9%) patients in the cerivastatin and simvastatin groups respectively during the first 32 weeks of treatment. Premature withdrawal due to adverse events occurred in 10 (7.9%) simvastatin-treated patients in the short-term phase compared with 14 (5.4%) of those on cerivastatin. Only 9.1% of withdrawals in patients on cerivastatin were considered to be due to study treatment while in the simvastatin group 52% of withdrawals were attributed to the drug. Incidence of alterations in laboratory parameters was similar in the two treatment groups during the first 32 weeks and over the entire 104 weeks. Significant increases in CPK, AST and ALT levels were rare in both treatment groups (Table 2.5)

McPherson and colleagues (2001)

This was a 52-week study. 48 centers in Canada participated in the study. Patients aged 18-75 years with documented primary hypercholesterolemia who did not respond adequately to dietary intervention were enrolled. A total of 654 patients were enrolled at the 48 centers. 417 patients out of these were randomized to receive treatment. 209 received cerivastatin 0.1-0.4mg, and 208 to pravastatin 10-40mg (Table 2.3). The primary outcome of interest was percentage LDL-C reduction by more than 20%. Efficacy outcome was similar in the 2 groups; with 74.2% of cerivastatin patients and 74% of pravastatin patients achieving an LDL-C decrease ≥ 20% at endpoint relative to baseline. The 2 treatments were deemed equivalent with respect to efficacy. Incidence of

treatment-emergent adverse events was similar between both groups (73.6% cerivastatin, 74.9% pravastatin). Majority of adverse events included headache, nausea, pain etc (Table 2.4). Nine patients in the cerivastatin group experienced serious adverse events, none of which were considered related to study medication. 13 in the pravastatin group experienced serious adverse events, 2 of which were considered possibly related to study medication. 12 patients in the cerivastatin group and 7 patients in the pravastatin group withdrew from the study due to an adverse event. Alterations in laboratory parameters were similar; 4 patients in each group had a CK level more than 3 x ULN in both groups, and 2 patients on cerivastatin and one on pravastatin withdrew due to elevated CK levels. One patient each in both groups discontinued therapy due to myalgia.

Ose and colleagues (1999)

Men and women (of non-child bearing potential) aged 18-75 years with documented primary hypercholesterolemia were recruited for the study, which took place in 24 centers in Europe. 492 patients were randomized to treatment. 332 patients were on 0.4mg dose of cerivastatin, and 162 patients on 0.2mg cerivastatin. The study was a 28-week study, and the primary outcome of interest was percentage change in LDL-C from baseline at week 24. Maximum treatment effect was observed after 4 weeks of active treatment and sustained until week 24. Patients had significantly greater percentage decrease in LDL-C in the 0.4mg dose (-38.3±0.7%) than in the 0.2mg dose (-31.8±1.0%). Overall incidence on adverse events was 65.5% (217/332) in the

cerivastatin 0.4mg group and 60.5% (98/162) in the cerivastatin 0.2mg group. Most common adverse events outlined in Table 2.4. Increased CK, AST and ALT plasma levels occurred in both the 0.2mg and 0.4mg groups. No patient in either group had CK levels greater than 10 x ULN. 2 patients had AST levels > 3x ULN, 1 patient had ALT level greater than 3x ULN in the 0.4mg group. No patients had AST or ALT levels greater than 3x ULN in the 0.2mg group. Table 2.5.

Rubinstein and colleagues (1999)

This was a 12-week study, and was conducted in 11 medical centers in Israel and South Africa, in type II diabetic patients with hypercholesterolemia. Men and women aged 30-80 years were enrolled. Eligible patients were randomly assigned to groups to receive cerivastatin 0.1mg (107) patients, or 0.3mg (107 patients), or placebo (51 patients) for 12 weeks. Primary outcome parameter was the percentage reduction in LDL-C at week 12. At the end of the study, LDL-C concentrations were decreased by 20.2% and 33.8%in the patients treated with cerivastatin 0.1mg and 0.3mg respectively. There was a 15% reduction in LDL-C in 69% and 91% of the cerivastatin 0.1mg and 0.3mg groups, respectively. An adverse event of any kind was reported in 45% of the placebo treated patients and similar cases in the two treatment groups. Common adverse events that occurred included upper respiratory tract infection, and flu-like syndrome (Table 2.4). Five patients withdrew from the study due to adverse events: two patients in the placebo group, two patients in the cerivastatin 0.1mg group, and one patient in the 0.3mg group.

Sasaki and colleagues (1998)

Male and female patients, aged 20-64 who had severe primary hypercholesterolemia (TC ≥ 6.7mmol/L) were enrolled. Seventy-three patients at 12 medical institutions in Japan participated in the study. Cerivastatin was administered at a dose of 0.15mg (n=33), and 0.3mg (n=40) for the first 12 weeks. Flexible dosing was adopted for the next 36-six weeks (extension period). Study duration was 48weeks in all. Primary outcome was the percentage reduction in LDL-C. In both groups, serum LDL-C decreased significantly at week 4 and remained significantly lower than baseline thereafter. Percentage reductions in LDL-C were significantly greater (P=0.002, LDL-C 33.4% and P=0.03, LDL-C 35.0% respectively) in the 0.3mg group than in the 0.15mg group. Adverse events were observed in one patient in each group. Abnormal laboratory values were observed in 7 patients in the 0.15mg group and 9 patients in the 0.3mg group (Table 2.5).

Stein and colleagues (1997)

Men or women aged 21-65 years with primary poly- and monogenic hypercholesterolemia were enrolled in the study. The study was carried out at 13 lipid clinics in the U.S. 319 patients were randomized to double-blind treatment, out of which 308 were included in the efficacy analysis. 89 patients were assigned to 0.1mg cerivastatin taken twice daily, 88 patients to 0.2mg taken in the evening with meals, 86 patients to 0.2mg taken once at bedtime, and 45 patients to placebo. All 319 patients

were included in the safety analysis. This was a 4-week study and the primary outcome was the percentage change in LDL-C. All three active treatment groups showed substantial and highly significant reductions from baseline to endpoint in lipid parameters. The percentage change in LDL-C for the two once-daily cerivastatin 0.2mg groups was significantly greater than the 0.1mg twice-daily group. Maximum response was seen in the third week of therapy. Common treatment-emergent events in all groups included headache, rhinitis, and pharyngitis (Table 2.4). Two patients withdrew from the study as a result of adverse events. No deaths were recorded. No CK elevation was either consistent or associated with clinical symptoms of muscle pain. No SGOT or SGPT levels of 3 x ULN was recorded (Table 2.5).

Stein and colleagues (1999)

This study was conducted at 2 sites in the United States. Adults, including postmenopausal women aged 18-75 years with primary hypercholesterolemia were eligible for the study. On the whole, 41 patients were randomized to 0.8mg cerivastatin (n=28) or placebo (n=13). This was a 4-week study and the primary outcome was percentage change in LDL-C at week 4. LDL-C was reduced by 44.0 ± 2.0% in cerivastatin-treated patients, compared with an increase of 1.2 ± 2.8% in those on placebo. A maximum effect was seen by 21 days and LDL-C remained stable at this reduced level through to day 28. One adverse event was reported by 18 of 28 patients (64%) given 0.8mg cerivastatin and by 7 of 13 patients given placebo. All of the adverse events were classified as being mild or moderate in intensity and all but 3 resolved by

the end of the study. Elevations in AST and ALT > 3xULN and CK > 10 x ULN were not observed in any patients.

Tao and colleagues (2000)

This study was conducted in three centers in China. Men and postmenopausal women aged 18-75 years with primary hypercholesterolemia were eligible. 470 patients were randomized to receive cerivastatin 0.1mg (n=119), 0.2mg (n=117), 0.3mg (n=116) or placebo (n=118). This was an 8-week study, with a 16-week extension phase, and the primary outcome was the percentage change in LDL-C from baseline to the end of week 8. Cerivastatin 0.1mg, 0.2mg, and 0.3mg produced a dose-dependent, statistically significant decrease in LDL-C, compared with placebo. The most common adverse events are shown in Table 2.4. Adverse events were generally mild, transient and not treatment limiting. In all, 6 (1.3%) patients withdrew due to treatment-emergent adverse events. No patient had a CPK level> 10 x ULN, one patient (0.3mg group) had AST and ALT elevations > 3 x ULN (Table 2.5).

Table 2.1 Summary of study characteristics

Study	Study design	Intervention	Treatment daily Dose (mg)	Treatment period	Entry criteria	Primary endpoint
Betteridge, 99	Multicentre DB randomized trial	Cerivastatin Simvastatin Placebo	0.025 0.05 0.1 0.2 20	4 wks diet 6 wks SB placebo 12wks DB 88wks extension	LDL-C ≥ 4.13 or LDL-C≥ 3.36mmol/L with CHD or with ≥ 2 risk factors TG≤ 3.9 Aged 21-75 years	% reduction in LDL-C at week 12
Farnier, 98	Multicentre DB randomized trial	Cerivastatin Gemfibrozil Placebo	0.1 0.2 0.3 1,200	4wks diet 6wks SB placebo 16wks DB 36wks extension	LDL-C ≥ 4.13 TG 2.24-5.6mmol/L Aged 18-80years	% reduction in LDL-C
Hanefeld, 99	Multicentre DB randomized trial	Cerivastatin Placebo	0.3 0.4	4wks diet 6wks SB placebo 8wks DB	LDL-C ≥ 4.9 or ≥ 4.13 with one or more risk factors TG ≤ 3.9mmol/L Aged 18-75	% reduction in LDL-C
Hunninghake, 2001	Prospective randomized open label study	Cerivastatin Atorvastatin	0.3 10	8wks screening/diet phase 6wks randomization	LDL-C ≥ 4.13 TG ≤ 4.5 Aged 18-80	% reduction in LDL-C
Insull, 2000	Pivotal multicentre DB placebo-controlled study	Cerivastatin Placebo	0.4 0.8	4wks diet 6wks SB placebo 8wks DB 52wks extension	LDL-C ≥ 4.13 or LDL-C ≥ 3.36+ CHD or with ≥2 risk factors TG ≤ 4.5 Aged 18-75years	Change in baseline in LDL-C at week 8
Leiter, 99	Multicentre DB randomized parallel group study	Cerivastatin Simvastatin	0.05-0.3 5-40	4wks diet 6wks SB placebo 32wks DB 72wks extension	LDL-C ≥ 4.13 TG ≤ 3.9 FR score ≤15 Aged 18-75 years	% change in LDL-C
McPherson, 2001	Multicentre randomized open label parallel group dose titration study	Cerivastatin Pravastatin	0.1-0.4 10-40	4 - 8wks diet 52wks randomization	LDL-C ≥ 4.13 TG≤ 4.5 Aged 18-75	% LDL-C reduction by ≥ 20%

Summary of study characteristics continued

Study	Study design	Intervention	Treatment daily dose (mg)	Treatment period	Entry criteria	Primary endpoint
Ose, 99	Multinational DB randomized parallel group study	Cerivastatin	0.2 0.4	4wks diet 6wks SB placebo 24wks DB	LDL-C ≥ 4.13 or LDL-C ≥ 3.36+ CHD or with ≥2 risk factors Aged 18-75	% change in LDL-C at week 24
Rubinstein, 99	Multinational multicentre DB randomizes study	Cerivastatin Placebo	0.1 0.3	4wks diet 6wks SB placebo 12wks DB	LDL-C ≥ 3.36+ diabetes TG ≥ 4.5 Aged 30-80 years	% reduction in LDL-C
Sasaki, 98	Long term comparative trial	Cerivastatin	0.15 0.3	4wks lead in with placebo 12wks randomization 36 wks extension	TC ≥ 6.7 TG ≤ 4.5 Aged 20-64	% reduction in LDL-c
Stein, 97	Multicentre DB randomized parallel group study	Cerivastatin	0.1 b.d 0.2 even 0.2 bed	4wks diet 6wks SB placebo 4wks DB	LDL-C >4.13 and < 6.46 TG ≤ 3.9 Aged 21-65	% change in LDL-C
Stein, 99	DB randomized parallel group study	Cerivastatin Placebo	0.8	4wks diet 2wks SB placebo 4wks DB	LDL-C ≥ 4.13 or LDL-C ≥ 3.36+ CHD or with ≥2 risk factors TG ≥ 4.5 Aged 18-75	% change in LDL-C at week 4
Tao, 2000	Multicentre DB randomized placebo controlled study	Cerivastatin Placebo	0.1 0.2 0.3	4wks diet 5wks SB placebo 8wks DB 16wks extension	LDL-C ≥ 4.13 or LDL-C ≥ 3.36+ CHD or with ≥2 risk factors TG ≤ 3.9 Aged 18-75 years	% change in LDL-C at week 8

SB- single blind, DB- double blind, TG- triglyceride, LDL-C- low-density lipoprotein cholesterol, CHD- coronary heart disease, TC- total cholesterol, FR- food rating

Patient demographics

Table 2.2: Mean age of patients in the cerivastatin RCTs

Trial	Age range	Cer (mg) 0.025	Cer (mg) 0.05	Cer (mg) 0.1	Cer (mg) 0.15	Cer (mg) 0.2	Cer (mg) 0.3	Cer (mg) 0.4	Cer (mg) 0.8	Sim	Ator	Pra	Gem	Placebo
Betteridge, 99	21-75	**55.8**	**53.7**	**53.9**	-	**53.8**	-	-	-	**55.0**	-	-	-	**55.0**
Farnier, 98	18-80	-	-	**53.9**	-	**53.6**	**53.8**	-	-	-	-	-	**53.6**	**54.6**
Hanefeld, 99	18-75	-	-	-	-	-	**55**	**56**	-	-	-	-	-	**55**
Hunninghake, 2001	18-80	-	-	-	-	-	**54.3**	-	-	-	**56.5**	-	-	-
Insull, 2000	18-75	-	-	-	-	-	-	**57.3**	**57.2**	-	-	-	-	**55.7**
Leiter, 99	18-75	-	-	-	-	-	**51.2**	-	-	**53.7**	-	-	-	-
McPherson, 2001	18-75	-	-	-	-	-	-	**54.4**	-	-	-	**53.5**	-	-
Ose, 99	18-75	-	-	-	-	**57.7**	-	**56.6**	-	-	-	-	-	-
Rubinstein, 99	30-80	-	-	**59.6**	-	-	**58.9**	-	-	-	-	-	-	**58.8**
Sasaki, 98	20-64	-	-	-	**56.3**	-	**55.3**	-	-	-	-	-	-	-
Stein, 97	18-75	-	-	-	-	-	-	-	**54.5**	-	-	-	-	**51.0**
Stein, 99	21-65	-	-	**50.7**	-	**53.1** 52.8	-	-	-	-	-	-	-	**53.9**
Tao, 2000	18-75	-	-	**57.8**	-	**60.0**	**59.3**	-	-	-	-	-	-	**60.6**

Cer- Cerivastatin, and different doses used in the different trials
Ato- Atorvastatin
Pra- Pravastatin
Sim- Simvastatin
Gem-Gemfibrozil
*- Mean age for patients in 0.2mg with dinner, and 0.2mg at bedtime groups respectively

Table 2.3: Number of patients in each dosage group

Trial	Cer (mg) 0.025	Cer (mg) 0.05	Cer (mg) 0.1	Cer (mg) 0.15	Cer (mg) 0.2	Cer (mg) 0.3	Cer (mg) 0.4	Cer (mg) 0.8	Sim	Ator	Prav	Gem	Placebo
Betteridge, 99	163	162	158	-	168	-	-	-	154	-	-	-	161
Farnier, 98	-	-	166	-	171	175	-	-	-	-	-	160	79
Hanefeld, 99	-	-	-	-	-	140	138	-	-	-	-	-	71
Hunninghake, 2001	-	-	-	-	-	107	-	-	-	108	-	-	-
Insull, 2000	-	-	-	-	-	-	195	776	-	-	-	-	199
Leiter, 99	-	-	-	-	-	260	-	-	127	-	-	-	-
McPherson, 2001	-	-	-	-	-	-	209	-	-	-	208	-	-
Ose, 99	-	-		-	162	-	332	-	-	-	-	-	-
Rubinstein, 99	-	-	101	-	-	106	-	-	-	-	-	-	45
Sasaki, 98	-	-	-	33	-	40	-	-	-	-	-	-	-
Stein, 97	-	-	92	-	92, * 89	-	-	-	-	-	-	-	46
Stein, 99	-	-	-	-	-	-	-	28	-	-	-	-	13
Tao, 2000	-	-	119	-	117	116	-	-	-	-	-	-	118

Cer- Cerivastatin, and different doses used in the different trials
Ato- Atorvastatin
Pra- Pravastatin
Sim- Simvastatin
Gem-Gemfibrozil
*- Number of patients in the 0.2mg does taken in the evening and at bedtime respectively

2.3.2 Adverse event reports

All the trials attempted to record all adverse reaction observed throughout the trial period, and all changes in enzyme levels especially of aspartate transaminase (AST), alanine transaminase (ALT), and creatine phosphokinase (CPK), and in some cases serum glutamic- oxaloacetic transaminase (SGOT), and serum glutamate pyruvate transaminase (SGPT).

Most frequent adverse events reported in the RCT's collectively were headache, dyspepsia, myalgia, rhinitis, abdominal pain, pharyngitis, diarrhea, angina pectoris, pain, back pain, and various others. Summary of these are listed in Table 2.4

There were increases in laboratory parameters (AST, ALT, CPK, SGOT, SGPT) in most of the trials but these were mostly said to be insignificant, or comparable to placebo, or not due to test drug.

A summary of the changes in enzyme levels and number of patients is recorded in Table 2.5.

Table 2.4: Most frequent adverse events reported in the RCTs

Study/Trial	Pain	Others
Betteridge, 99	Back pain, myalgia	A.P, dyspepsia, insomnia, rash, somnolence, nausea, URTI, headache, constipation, bronchitis, flu syndrome.
Farnier, 98	Back pain, myalgia	Dyspepsia, diarrhea, constipation, asthenia, A.P
Hanefeld, 99	Back pain, arthralgia, abdominal pain	Diarrhea, sore throat, leukopenia, infection, accidental injury, headache, Rhinitis, URTI.
Hunninghake, 2001	----------	Constipation, diarrhea, dyspepsia, flatulence, bloating
Insull, 2000	Myalgia, leg pain, arthralgia, back pain, abdominal pain.	Headache, pharyngitis, rhinitis, asthenia, accidental injury, diarrhea, dyspepsia, rash, sinusitis, flu, nausea, flatulence, dizziness
Leiter, 99	Back pain, myalgia	----------
McPherson, 2001	Myalgia, pain, abdominal pain, chest pain	Headache, nausea, dizziness, diarrhea, cystitis, joint disorder, dyspepsia, amblyopia.
Ose, 99	Abdominal pain, myalgia.	Arrhythmia, blurred vision, diarrhea, insomnia, joint stiffness, psoriasis, sinusitis, skin eruptions, headache, lethargy, dysuria, impotence, nausea.
Rubinstein, 99	Abdominal pain, chest pain.	URTI, flu-like syndrome, rash, transient ischaemic attack.
Sasaki, 98	----------	Flushing, general malaise.
Stein, 97	Chest pain, arthralgia.	Rhinitis, headache, pharyngitis, flu syndrome, sinusitis, insomnia.
Stein, 99	Back pain, arthralgia.	Headache, pharyngitis, rash.
Tao, 2000	Abdominal pain, back pain, chest pain.	Ventricular extrasystoles, dry mouth, dizziness, cough, pharyngitis, Rhinitis, urinary tract infection, palpitations, hyperglycemia, hypaesthia, insomnia, neoplasm.

AP- angina pectoris
URTI- upper respiratory tract infection.

Table2.5: Changes in liver enzyme levels and CK in the RCTs.

Study	Number randomized to cerivastatin	Number with CPK >10x ULN or myalgia/pain	Number with AST/SGOT > 3x ULN	Number with ALT/SGPT >3x ULN	Number randomized to comparator	Number with CPK >10xULN	Number with AST/SGOT >3x ULN	Number with ALT/SGPT >3x ULN
Betteridge, 99	Complicated design and reporting. Evaluated patients shown as denominator.	2/649 (CK↑) 12/780 (myalgia) 76(back pain) 42(pain)	1(AST↑)	3(ALT↑)	(Placebo)	1/161(CK↑) 2/192(myalgia) 4(back pain)	1(AST↑)	0(ALT↑)
					(Simvastatin)	0/154 (CK↑) 5/186(Myalgia) 18(Back pain) 5(pain)	0(AST↑)	0(ALT↑)
Farnier, 98	512	0(CK↑) 3(Myalgia)	0(AST↑)	0(ALT↑)	160(gemfibrozil)	0(CK↑) 1(Myalgia)	0(AST↑)	0(ALT↑)
					79(placebo)	0(CK↑) 2(Back pain)	0	0
Hanefeld, 99	278	0(CK↑)	0(AST↑)	0(ALT↑)	71(placebo)	0(CK↑) 1(Back pain)	0(AST↑)	0(ALT↑)
Hunninghake, 2001	107	0(CK↑)	0(AST↑0	0(ALT↑)	108(atorvastatin)	0(CK↑)	0(AST↑)	0(ALT↑
Insull, 2000	971	12(CK↑) 26(Myalgia) 26(Back pain) 26(Leg pain)	12(SGOT↑)	9(SGPT↑)	199(placebo)	0(CK↑) 7(Myalgia) 11(Back pain) 4(Leg pain)	0(SGOT↑)	0(SGPT↑)
Leiter, 99	260	2(CK↑) 8(Myalgia) 19(Back pain)	3(AST↑)	3(ALT↑)	127(simvastatin)	0(CK↑) 8(Myalgia) 5(Back pain)	0(AST↑)	1(ALT↑)
McPherson, 2001	209	2(CK↑) 1(Myalgia) 3(pain)	0(AST↑)	0(ALT↑)	208(pravastatin)	1(CK↑) 1(Myalgia) 1(Pain)	0(AST↑)	0(ALT↑)
Ose, 99	332	0(CK↑) 1(Myalgia)	2(AST↑)	1(ALT↑)	162	0(CK↑)	0(AST↑)	0(ALT↑)
Rubinstein, 99	214	0(CK↑)	0(AST↑)	0(ALT↑)	51(placebo)	0(CK↑)	0(AST↑)	0(ALT↑)
Sasaki, 98		7(CK↑not defined)	Not defined	Not defined	33	3(CK↑not defined	Not defined	Not defined
Stein, 97	174	0(CK↑) 5(Arthralgia)	0(SGOT↑)	0(SGPT↑)	45	0(CK↑)	0(SGOT↑)	0(SGPT↑)
Stein, 99	28	0(CK↑) 2(Back pain)	0(AST↑)	0(ALT↑)	13(placebo)	0(CK↑) 1(Back pain))	0(AST↑)	0(ALT↑)
Tao, 2000	352	0(CK↑)	1(AST↑)	1(ALT↑)	118Placebo)	0	0(AST↑)	0(ALT↑)

2.4 Meta-analysis

2.4.1 Elevation of ALT 3x > ULN

Cerivastatin versus placebo

Cerivastatin was compared to placebo in seven randomized controlled trials (Betteridge 99, Farnier 98, Hanefeld 99, Insull 2000, Rubinstein 99, Stein 99, and Tao 2000). The frequencies of ALT elevations are shown in Table 2.6. There were generally few cases of elevations of ALT. The rates were homogeneously low (Q statistic 8.04; p = 0.24) and there was no statistically significant difference in the rates of ALT elevation between the placebo and cerivastatin groups (Chi squared test; 0.83; p = 0.36) with a pooled estimate of difference of 0.0022 (95%= -0.0025-0.0069). The results are illustrated in Figure 2.2

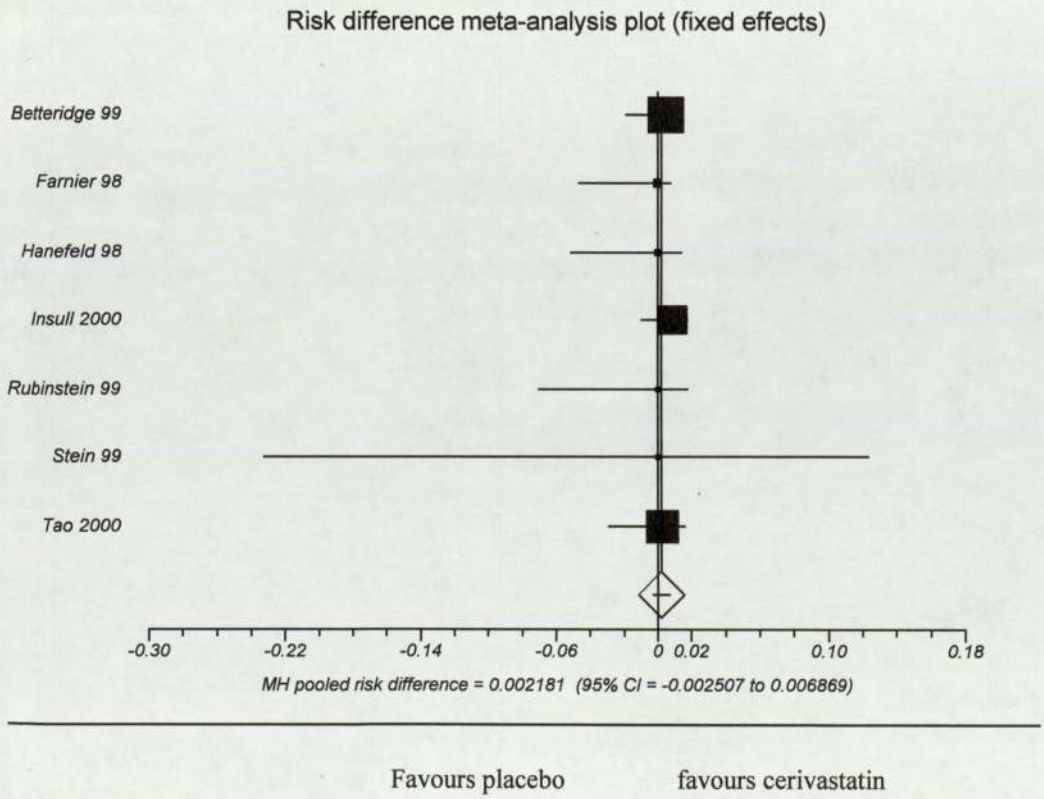
Table 2.6: Number of patients reporting ALT/SGPT elevations 3xULN: test vs. placebo

Trial	n cerivastatin	N ALT/SGPT	n placebo	N ALT/SGPT
Betteridge 99	649	3	161	0
Farnier 98	512	0	79	0
Hanefeld 98	278	0	71	0
Insull 2000	971	9	199	0
Rubinstein 99	214	0	51	0
Stein 99	28	0	13	0
Tao 2000	352	1	118	0

Table 2.7: Risk difference meta-analysis: cerivastatin vs placebo

Stratum	Risk difference	95% CI (Miettinen)		M-H Weight	
1	0.004622	-0.018731	0.01351	141052.347265	Betteridge 99
2	0	-0.046446	0.00746	12573.114737	Farnier 98
* 2	-0.005275	-0.022755	0.012204	12573.114737	[Haldane approx.]
3	0	-0.051468	0.013668	9785.438591	Hanefeld 98
* 3	-0.005152	-0.024966	0.014661	9785.438591	[Haldane approx.]
4	0.009269	-0.009715	0.017526	105740.195311	Insull 2000
5	0	-0.070293	0.0177	5156.6393	Rubinstein 99
* 5	-0.00729	-0.034584	0.020004	5156.6393	[Haldane approx.]
6	0	-0.232472	0.123288	328.494356	Stein 99
* 6	-0.018473	-0.126612	0.089667	328.494356	[Haldane approx.]
7	0.002841	-0.028776	0.015938	124257.002849	Tao 2000

Figure 2.2: Meta-analysis of the rates of difference of ALT elevations observed in randomized controlled trials of cerivastatin versus placebo.



Cerivastatin versus active comparator

Active comparators for cerivastatin in randomized controlled trials have included simvastatin (Betteridge 1999 and Leiter 1999), pravastatin (McPherson, 2001), atorvastatin (Hunninghake 2001,) and gemfibrozil (Farnier 98). The incidence of ALT elevations greater than three times the upper limit of normal (> 3x ULN) was low in all the published trials and the frequencies were too low for robust comparisons (Table 2.8)

Table 2.8: Number of patients reporting ALT/SGPT elevations 3xULN: test vs. comparator

Trial	n cerivastatin	N ALT/SGPT	Comparator	n comparator	N ALT/SGPT
Betteridge 99	649	3	Simvastatin	154	0
Farnier 98	512	0	Gemfibrozil	160	0
Hunninghake 2001	107	0	Atorvastatin	108	0
Leiter 99	260	3	Simvastatin	127	1
McPherson 2001	209	0	Pravastatin	208	0
Ose 99	332	1	Cerivastatin	162	0
Sasaki 98	40	1	Cerivastatin	33	2
Stein 97	174	0	Cerivastatin	45	0

Ose 99 cerivastatin 0.2mg vs. 0.4mg
Sasaki 98 cerivastatin 0.15mg vs. 0.3mg
Stein 97 cerivastatin 0.1mg vs. 0.2mg

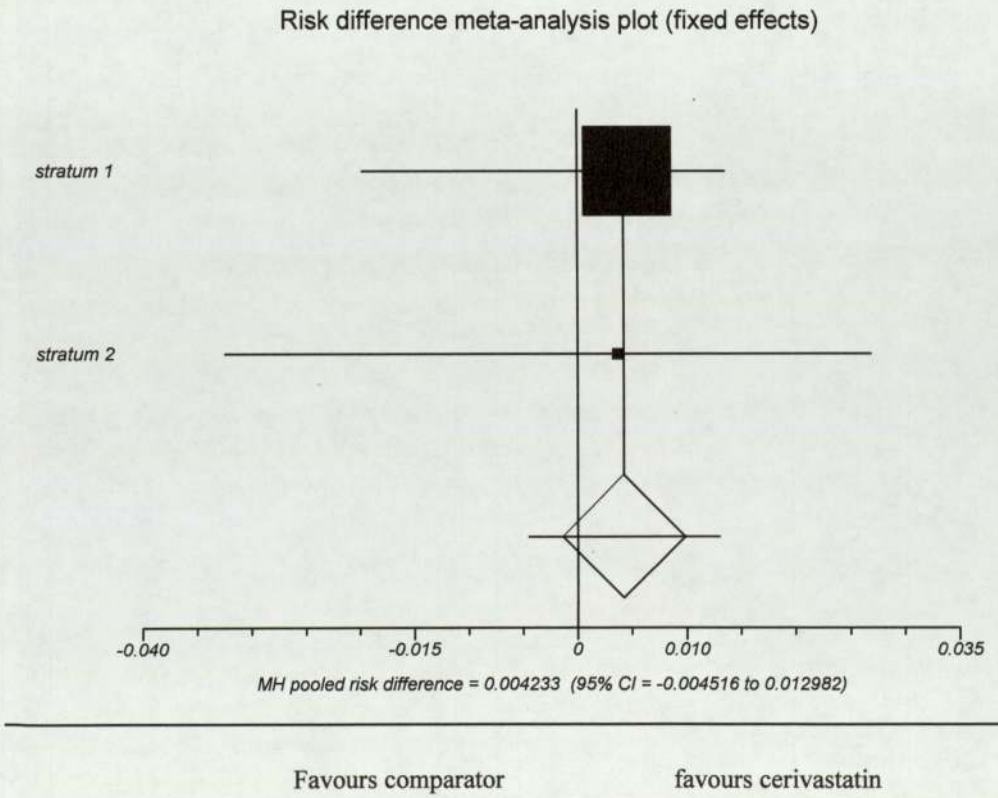
Simvastatin was compared to cerivastatin in two trials. There was no significant heterogeneity in the results of the two trials (Q statistic 0.024; p = 0.88) and the fixed

effect model estimate of the difference in the rates of ALT elevation showed no difference for the two statins (Chi-Squared statistic 0.90; p = 0.343). The pooled estimate of rate of ALT elevation (3x > ULN) was 0.0042 (95%CI= -0.0045-0.013). This is shown graphically in Figure 2.3.

Table 2.9: Cerivastatin versus simvastatin: risk difference meta-analysis

Stratum	Risk difference	95% CI (Miettinen)	M-H Weight	
1	0.004622	-0.019767 0.01351	141052.347265	stratum1 Betteridge
2	0.003664	-0.032425 0.026869	9489.595432	stratum 2 Leiter

Figure 2.3: Meta-analysis of the difference in the rates of ALT elevation in randomized controlled trials comparing cerivastatin with simvastatin.



Cerivastatin dose effect

There was no significant difference in the rate of ALT elevation in the trials comparing different doses of cerivastatin (Table 2.8).

2.4.2 Myalgia

Cerivastatin versus placebo

The frequencies of occurrence of myalgia in the trials comparing cerivastatin with placebo are shown in Table 2.10. The cases of myalgia were few, and the rates were homogeneously low (Q statistic 6.62; p=0.36). There was no statistically significant difference between the placebo and cerivastatin groups (Chi squared test =0.16; p=0.68) with a pooled estimate of difference of 0.002023 (95% CI= -0.011818 to 0.007772). The results are illustrated in Figure 2.4.

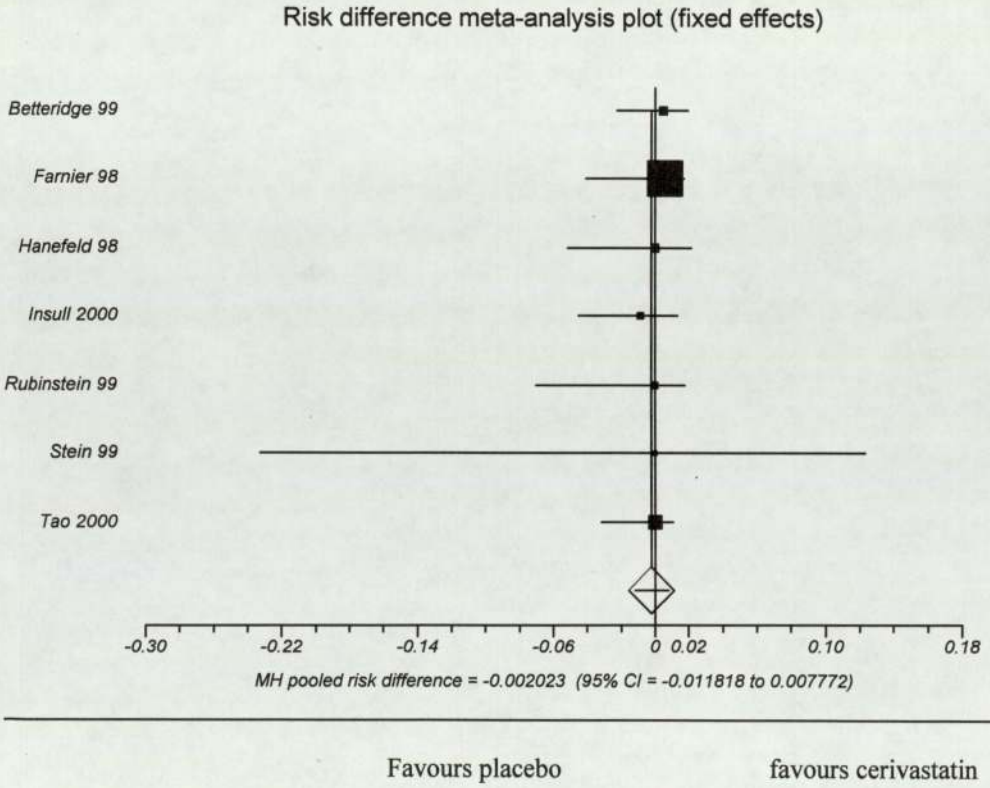
Table 2.10: Number of patients reporting myalgia: test vs. placebo

Trial	n cerivastatin	N myalgia	n placebo	N myalgia
Betteridge 99	780	12	192	2
Farnier 98	512	3	79	0
Hanefeld 98	278	0	71	0
Insull 2000	971	26	199	7
Rubinstein 99	214	0	51	0
Stein 99	28	0	13	0
Tao 2000	352	0	118	0

Table 2.11: Rate differences observed with cerivastatin and placebo

Stratum	Risk difference	95% CI (Miettinen)		M-H Weight	
1	0.004968	-0.022389	0.019058	13678.2526	Betteridge 99
2	0.005859	-0.040624	0.017098	87896.351015	Farnier 98
3	0	-0.051524	0.021209	8981.317583	Hanefeld 98
* 3	-0.0042	-0.024832	0.01653	8981.317583	[Haldane approx.]
4	-0.0084	-0.044977	0.013558	5066.286126	Insull 2000
5	0	-0.070293	0.0177	5156.6393	Rubinstein 99
* 5	-0.0073	-0.034584	0.020004	5156.6393	[Haldane approx.]
6	0	-0.232472	0.123288	328.494356	Stein 99
* 6	-0.018	-0.126612	0.089667	328.494356	[Haldane approx.]
7	0	-0.031593	0.010818	25531.857474	Tao 2000
* 7	-0.0028	-0.015051	0.009481	25531.857474	[Haldane approx.]

Figure 2.4: Meta-analysis of the difference in the rates of myalgia in randomized controlled trials comparing cerivastatin with placebo



Cerivastatin versus active comparators

The observed frequencies of myalgia occurrence are shown in Table 2.12. Estimations of the rates show little difference between the rates observed with cerivastatin and the comparators (Table 2.12). Because of the heterogeneity of the results, there were no pooled values for Q statistic and Chi Square. The pooled estimate of risk difference was 0.0876 (95% CI = -0.02235 to 0.00283). The results are illustrated in Figure 2.5.

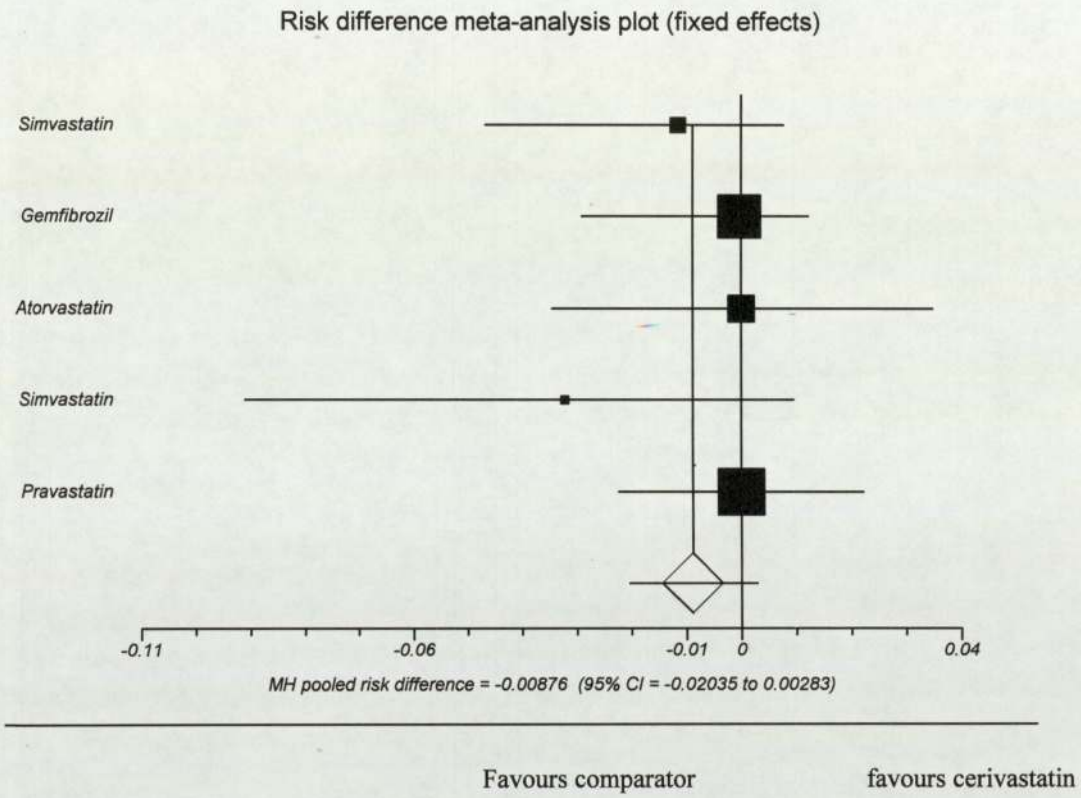
Table 2.12: Number of patients reporting myalgia: test vs. comparator

Trial	n cerivastatin	N myalgia	Comparator	n comparator	N myalgia
Betteridge 99	780	12	Simvastatin	186	5
Farnier 98	512	3	Gemfibrozil	160	1
Hunninghake 2001	107	0	Atorvastatin	108	0
Leiter 99	260	8	Simvastatin	127	8
McPherson 2001	209	1	Pravastatin	208	1
Ose 99	332	1	Cerivastatin	162	0
Sasaki 97	40	0	Cerivastatin	33	0
Stein 97	174	0	Cerivastatin	45	0

Table 2.13: Rate differences observed between cerivastatin and active comparators

Stratum	Risk difference	95% CI (Miettinen)		M-H Weight	
1	-0.011497	-0.046631	0.007597	6247.62943	Simvastatin-Betteridge 99
2	-0.000391	-0.028941	0.012156	19922.145869	Gemfibrozil- Farnier 98
3	0	-0.034502	0.034814	11826.001195	Atorvastatin-Hunninghake
* 3	0.000042	-0.017981	0.018066	11826.001195	[Haldane approx.]
4	-0.032223	-0.091053	0.009479	1725.748527	Simvastatin- Leiter 99
5	-0.000023	-0.022371	0.022227	21840.502421	Pravastatin- McPherson

Figure 2.5: Meta-analysis of the difference in the rates of myalgia in randomized controlled trials comparing cerivastatin with active comparators



2.4.3 CPK elevation

Cerivastatin versus active comparator

The observed rates of elevation of CPK are shown in Table 2.14

Table 2.14: Observed number of patients reporting elevation of CPK

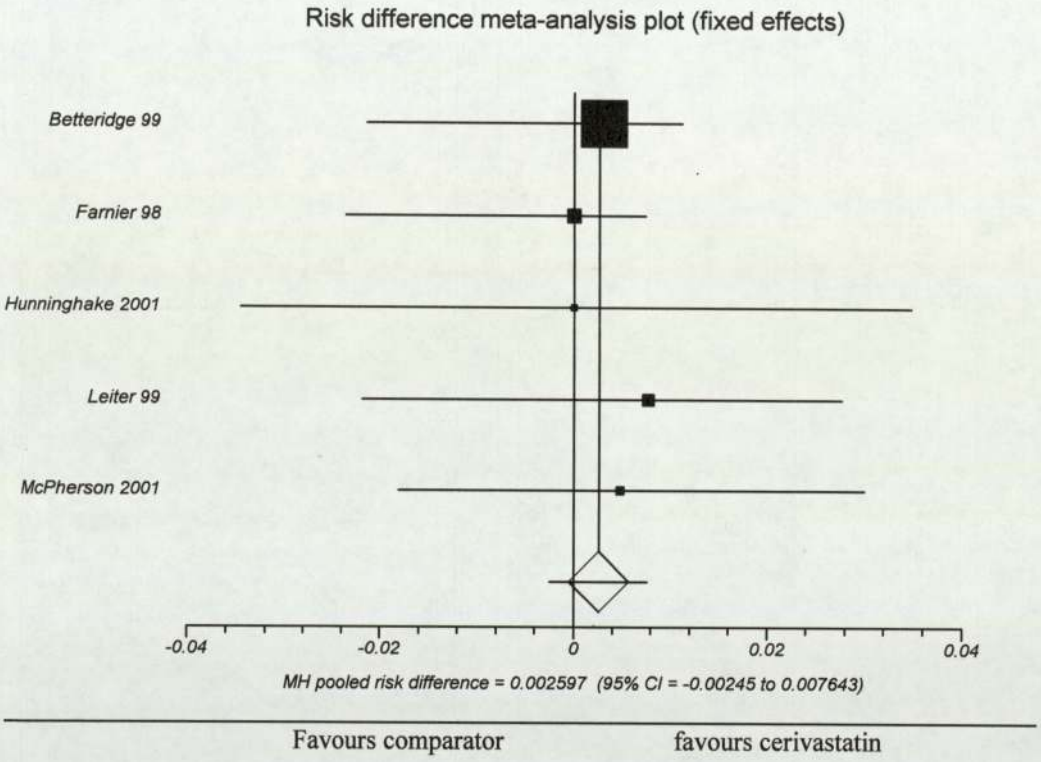
Trial	n cerivastatin	N CPK	Comparator	n comparator	N CPK
Betteridge 99	649	2	Simvastatin	154	0
Farnier 98	512	0	Gemfibrozil	160	0
Hunninghake	107	0	Atorvastatin	108	0
Leiter 99	260	2	Simvastatin	127	0
McPherson	209	2	Pravastatin	208	1

Estimation of the rates show no difference between the rates observed with cerivastatin and the comparators as a group (as shown in Table 2.15). The rates were homogeneously low (Q statistic ("non-combinability" for risk difference) = 2.137741 (df = 4) p = 0.7104). The pooled estimate (Greenland-Robins) of risk difference was 0.002597 (Approximate 95% CI= -0.00245 to 0.007643), with no statistically significant difference in the rates of CPK elevation between cerivastatin and the comparators (Chi-square for pooled risk difference = 1.017129, df=1, p=0.3132).

Table 2.15: Rate differences observed with cerivastatin and the comparators

Stratum	Risk difference	95% CI (Miettinen)		M-H Weight	
1	0.003082	-0.0213	0.011174	211251.506182	Betteridge 99
2	0	-0.02348	0.007458	47331.581708	Farnier 98
* 2	-0.002131	-0.01114	0.006878	47331.581708	[Haldane approx.]
3	0	-0.034502	0.034814	11826.001195	Hunninghake 2001
* 3	0.000042	-0.017981	0.018066	11826.001195	[Haldane approx.]
4	0.007692	-0.021817	0.027648	34062.015504	Leiter 99
5	0.004762	-0.018016	0.029949	14630.336022	McPherson 2001

Figure 2.6: Meta-analysis of the difference in the rates of CPK elevation in randomized controlled trials comparing cerivastatin with active comparator



2.5 Observational studies and commentaries

Case reports were identified and retrieved. No case-controlled studies or cohort studies were obtained. Reports of statistical reviews carried out by the FDA on clinical trials of cerivastatin and labelling changes made over the years were also retrieved.

2.5.1 Case reports

A number of case reports were identified during a literature search of cases of rhabdomyolysis due to cerivastatin therapy (Table 2.16). They are 28 cases in all, 13 (46.4%) patients on combination therapy with gemfibrozil, 1(3.7%) with niacin, and 14 (50%) monotherapy with cerivastatin. 1 patient on monotherapy was on the 0.1mg dose, 1 on 0.3mg, 11 patients on the 0.4mg dose, 1 on 0.8mg dose. Patients' ages ranged from 46-82 years, 14 cases occurred in women and 14 in men. Four patients had renal impairment. One patient was taking cyclosporin, which is known to increase the risk for myopathy and rhabdomyolysis when used in combination with a statin, and two were on levothyroxine, indicating the presence of hypothyroidism, which could predispose one to myopathy. The patients' CK level ranged from 7,768U/L to 180,160U/L, ALT levels ranged from 95U/L to 1,094U/L and AST levels ranged from461U/L to 2,183U/L, though not all ALT and AST levels were reported. One death was reported in the 11 cases reported by Ravnan.

Table 2.16: Case reports of patients who developed rhabdomyolysis due to cerivastatin therapy.

Author	Age	Ethnicity	Sex	Medical history	Statin mg	Co.D mg	Other drugs	SCr mg/dl	CP K U/L	AST U/L	ALT U/L	Pt outcome
Alexandridis, 2000	75	-	F	Severe combined Hyperlipidemia	Cer 0.6	Gem 600	Felodipine, metoprolol	0.8	46,000	1,950	780	recovered
Barki, 2002	76	-	M	Hypercholesterolemia	Cer 0.4	-	Ibuprofen		92,050	-	1363	recovered
Bruno-Joyce, 2001	82	White	M	Hyperlipidemia, CAD with angina, prostrate cancer,osteoarthritis, and MI	Cer 0.4	Gem 600	Propranolol, aspirin.	1.5	60,000	949	307	recovered
Feeney, 2002	64	White	M	CAD, MI, hypertension, hypercholesterolemia, prostrate cancer.	Cer 0.8		Diltiazem, lisinopril/ hydrochlorthiazide, metoprolol , cyproterone acetate, diclofenac/ misoprostol	6.9	41,000	-	-	recovered
Gemici, 2001	77		F	Hypercholesterolemia	Cer 0.3			7.4	8,900	2,066	1,049	recovered
Hamilton-Craig, 2001	-	-	M	Combined hyperlipidemia	Cer 0.3	Gem 600	Diltiazem, aspirin	-	30,000	1827	1,089	recovered
Hamilton-Craig, 2001	63	-	F	Combined hyperlipidemia	Cer 0.4	Gem 600	-	-	14,500	352	191	recovered

Author	Age	Ethnicity	Sex	Medical history	Statin mg	Co.D mg	Other drugs	SCr mg/dl	CP K U/L	AST U/L	ALT U/L	Pt outcome
Hyman, 2002	61	Black	F	D.M, asthma, peptic ulcer, hypertension, gastric ulcer, psychological treatment diverticula and hysterectomy.	Cer 0.4		Azithromycin, risperidone, Vit E, conjugated estrogen, amantadine, naproxen, flubicasone (inhalation), quetiapine, lanoprazole, trezadone,albuterol salmeterol.		30,916	-	-	-
Hyman, 2002	47	Hispanic	M	Smoker, unstable acute MI, and hypertension.	Cer 0.4		Quinapril, nitroglycerin, aspirin, clopidogrel, ranitidine, metroprlol.		48,580	-	-	-
Hyman, 2002	62	Black	F	Hypertension, intermediate coronary syndrome and atherosclerosis.	Cer 0.4		Ferrous sulphate, captopril, ibuprofen.		26,150	-	-	-
Hyman, 2002	46	Black	M	Hypertension, asthma, intermediate coronary syndrome.	Cer 0.4		Lanoprazole, celecoxib, felodipine, albuterol, atenolol, cyclobenzaprine, sublingual nitroglycerin, HCTZ.		8,410	-	-	-
Hyman, 2002	56	Hispanic	F	Hypertension, D.M, hypothyroidism, cellulitis, CVA.	Cer 0.4		Insulin 70/30, aspirin, felodipine, clopidogrel, lanoprazole, HCTZ, quinapril, levothyroxine.		34,420	-	-	-

Author	Age	Ethnicity	Sex	Medical history	Statin mg	Co.D mg	Other drugs	SCr mg/dl	CP K U/L	AST U/L	ALT U/L	Pt outcome
Hyman, 2002	72	Black	M	Stent-CVA, hypertension, colon polyps, carotid stenosis prostatectomy.	Cer 0.4		Enteric-coated aspirin, clopidgrel, famotidine, propoxyphene/acetamino-phen, amlodipine, insulin, HCTZ		30,000	-	-	-
Marinella, 2002	48		M	D.M, hyperlipidemia, hypertension	Cer 0.4	Gem 600	Glyburide, metformin, furosemide, metoprolol, terazosin, candesartan.	4.1	111,850	2134	628	recovered
Pogson, 99	74		F	Severe coronary disease, D.M, hyperlipidemia	Cer 0.3	Gem 600	Aspirin , allopurinol, iron supplements, hydrochlorthiazide , metformin , glyburide .	4.3	16,094	-	-	recovered
Ravnan, 2002	74		F	Hypertension	Cer 0.4		Captopril, aspirin, felodipine, atenolol, chlorthalidone	5.3	46,923	687	-	-
Ravnan, 2002	74		M	-	Cer 0.8	Niacin 1g	Naproxen, atenolol	8.7	95,711	1387	363	-
Ravnan, 2002	72		M	D.M	Cer 0.4	Gem 600	Enalapril, hydrochlorthiazide-triamterene	4.1	65,102	1219	782	-
Ravnan, 2002	65		F	-	Cer 0.8	Gem 600	Cholestyramine, naproxen,	6.2	348,000	2183	1075	-
Ravnan, 2002	65		F	-	Cer 0.8	Gem 600	Cholestyramine, naproxen, propoxyphene, hydrocodone-acetaminophen	6.2	348,000	2183	1075	-

Author	Age	Ethnicity	Sex	Medical history	Statin mg	Co.D mg	Other drugs	SCr mg/dl	CP K U/L	AST U/L	ALT U/L	Pt outcome
Ravnan, 2002	63		M	-	Cer 0.4	Gem 600	Fosinopril, aspirin, furosemide, amiodarone.	1.3	71,460	1696	640	-
Ravnan, 2002	75		F	-	Cer 0.4		Etodolac, aspirin, levothyroxine	5.8	75,600	-	-	-
Ravnan, 2002	59		M	D.M, renal impairment	Cer 0.4	Gem 600	Felodipine, verapamil, aspirin, insulin	1.9	180,160	1579	777	-
Ravnan, 2002	68		M	D.M, renal impairment	Cer 0.4		Benazepril, clopidogrel, Atenolol, aspirin	3.5	12,685	609	638	-
Ravnan, 2002	55		F	Renal impairment	Cer 0.4		Benazepril, amitriptyline, nitroglycerin, clopidogrel, hydrochlorthiazide-triamterene	8.3	257,373	461	240	-
Ravnan, 2002	59		M	D.M	Cer 0.8	Gem 600	Amlodipine, glyburide, cyclobenzaprine, tramadol	0.7	36,606	797	302	-
Ravnan, 2002	75		F	D.M	Cer 0.4	Gem 600	Nifedipine, atenolol, aspirin, glipizide	2.3	7,768	153	95	-
Rodriguez, 2000	52		F	renal failure secondary to polycystic kidney disease, hypercholesterolemia.	Cer 0.1		Prednisone, mycophenolate, ranitidine, cyclosporin.	1	12,615	709	828	recovered

CAD- coronary artery disease, DM- Diabetes mellitus, HCTZ- Hydrochlorothiazide, MI- Myocardial infarction, DM- Diabetes mellitus CVA- cerebrovascular accident, Co D. - Co administered drug, SCr- serum creatinine

2.6 FDA reports

Searches of the FDA website identified statistical reviews carried out by the FDA on reports of clinical trial submitted by the company, supporting the safety and efficacy profile of cerivastatin. The reviews carried out by the FDA concluded that cerivastatin was efficacious and safe. No significant adverse events were identified in the trials. Full accounts of the reviews are reported in Appendix 7. However, since first licensing, labelling changes were made twice to the warning and contraindication sections of the cerivastatin product label, first in December 1999 and then later in May 2001.

2.7 Discussion

In this study, meta-analysis of thirteen randomized controlled trials of cerivastatin show no significant differences in the rates of adverse events occurrence between cerivastatin and placebo or active comparator. Pooled results of rate differences in adverse events between cerivastatin and active comparators/placebo indicate that there was no significant difference in the occurrence of adverse events between the various groups. The incidence of the adverse events CPK elevation > 10xULN and ALT elevation >3xULN, and myalgia was not significantly greater with cerivastatin than with active comparators or placebo, as can be seen in the meta-analysis graphs (Figures 2.2 to 2.6). Little or no data was available on AST elevation > 3x ULN, back pain, leg pain, and pain (Table 2.5). Controlled clinical trials probably markedly underestimate the risk of myopathy to the wider cerivastatin target population, because patients with

confounding illnesses such as hypertension, diabetes, and those with altered renal function, and the elderly, are excluded from the trials.

Observational studies and commentaries however suggest a much higher incidence of cerivastatin-associated rhabdomyolysis. Staffa et al (2002) showed from their review of reports in the Adverse Events Reporting System of the FDA that the rate of fatal rhabdomyolysis associated with cerivastatin therapy was 16-80 times as high as the rates for any other statin. Another study reviewing statin-associated myopathy (Thompson et al, 2003) identified 3339 cases of statin-associated rhabdomyolysis in their review of the Qscan FDA database from January 1, 1990 through March 31, 2002. Cerivastatin was the most commonly implicated statin, with 57% of all the cases being attributed to it. The case reports retrieved which are shown in Table 2.16 outline a number of patients with reported rhabdomyolysis due to cerivastatin therapy. Many of the patients had predisposing factors for rhabdomyolysis; 12 were taking cerivastatin in combination with gemfibrozil, 4 had renal impairment, 2 were on levothyroxine therapy, suggesting the presence of hypothyroidism, 1 was on Azithromycin, and 1 was also taking cyclosporin. Most of the drugs taken concomitantly with cerivastatin by these patients (gemfibrozil, cyclosporin, macrolides antibiotics) are known to interact with the statins and increase their serum concentrations. Conditions such as hypothyroidism have been shown to predispose patients on statin therapy to rhabdomyolysis. Some of the patients were on the higher doses of cerivastatin, 0.4-0.8mg, often in combination of gemfibrozil. Many more reports were submitted to the FDA's AERS over the period cerivastatin was being marketed. Such reports lead to the

rising concerns about the increased number of patients suffering from rhabdomyolysis due to cerivastatin therapy, and lead eventually to its recall. Although changes were made to the cerivastatin product label, first to include a contraindication of concomitant use of cerivastatin and gemfibrozil, and secondly, to include a warning that the starting dose of cerivastatin should be 0.4mg, and that starting therapy with doses above this increased the risk of rhabdomyolysis, the number of patients reporting the adverse event did not fall. Cases of rhabdomyolysis continued to be reported, probably due to the fact that although the first new prescribing information (contraindication of concurrent therapy with gemfibrozil) was issued in 1999, it was not published in the Physicians' Desk Reference (PDR) until 2001 (Weaver, 2002). The withdrawal of cerivastatin heightened awareness for the safety of statins and combination therapy, but one thing that had been learnt from the cerivastatin episode is that a wide safety margin is not a statin class effect.

2.8 Limitations of the study

Meta-analysis has become a useful tool for studying the effects of treatment across a number of trials. Meta-analyses however are also subject to bias, most especially publication bias. This mainly arises from exclusion from the study of unpublished studies, which may have negative results, non-exhaustive searches, language restrictions and too rigid or too lax inclusion/exclusion criteria. To avoid such problems, exhaustive literature searches were conducted, and no language restrictions were applied. The company marketing cerivastatin was also contacted requesting

reports of all clinical trials conducted on cerivastatin up to its withdrawal. Various authors were also contacted with a request for other studies. However not all clinical trials of cerivastatin were included in this meta-analysis. One trial was an abstract and in Chinese and was not included. Others did not report the outcomes of interest. There were no unpublished reports included in this meta-analysis as none was found.

2.9 Conclusion

Myopathy and rhabdomyolysis could not have been predicted as major adverse effects of cerivastatin from its clinical trials. The clinical trials reported a low incidence of adverse events relative to placebo or other statins. This is a reflection of the fact that rhabdomyolysis is a rare adverse event. Moreover the trials were of short duration and included small numbers of patients. The severity of this adverse event was picked up not from the clinical trials of cerivastatin, but from observational data through reports made by various parties to the FDA's Postmarketing surveillance system, the AERS. The cerivastatin tragedy has made it obvious once again that more care should be taken with drugs and adverse events associated with them. As clinical trials are not sufficient for providing the reassurance necessary on the long-term safety of drugs, the onus lies on health professionals and manufacturers to make better use of the spontaneous adverse reaction reports.

CHAPTER 3

Cost-effectiveness Analysis: Sources of heterogeneity in published cost-effectiveness estimates: the statins as a case example.

3.1 INTRODUCTION

Economic evaluations involve the identification, measurement, and valuation of costs and outcomes, and then comparison of the costs (inputs) and benefits (outcomes) of two or more alternative treatments or activities (Economic evaluations). Four different types of economic evaluations are often used depending on how benefits to the individual are measured and valued: cost-minimization, cost-effectiveness, cost-utility, and cost-benefit evaluations. Economic evaluations differ according to their scope and intent and can adopt a broad societal perspective or have a very narrow focus. Economic evaluations have now gained greater acceptance as a tool for decision-making in health care over the last two decades (Elixhauser 1993, 1998).

Several large-scale long-term clinical trials of the statins have demonstrated their effectiveness in lowering cholesterol levels and thereby reducing the risk of coronary heart disease (4S, CARE, WOSCOPS). These drugs are expensive, and as a result, many analyses have focused on the cost-effectiveness of these agents. Different parties have carried out economic evaluations of the statins, and come up with different cost-effectiveness estimates.

The objective of this study is to review published economic evaluations of the statins to identify sources of heterogeneity, which could significantly alter estimates of cost-effectiveness.

3.2 Methods

3.2.1 Literature search

Economic assessments of the statins were identified through a search of Medline database from 1990 to 2003, searches through the reference lists of retrieved studies, and writing to authors/libraries to retrieve other reports.

Published studies were identified using the following subject heading:

- Statins/HMG Co A reductase inhibitors/cerivastatin
- Economic evaluations/ cost effectiveness studies.

These were then combined to retrieve relevant papers. The searches were limited to English language.

3.2.2 Data extraction

Hard copies of the identified reports were retrieved and abstracted to identify the type of economic assessment undertaken, the method of costing, the quantification of outcome,

source of effectiveness data, the perspective adopted, the assumptions made and the estimates obtained.

3.3 Results

3.3.1 Characteristics of CEAs of statins

18 economic evaluations of statins were identified (Table 3.1). These studies were carried out between 1991and 2003. One study (Ganz, 2000) considered the statins as a class while the rest evaluated the cost effectiveness of specific statins. Of these 18 studies, two were cost-utility analyses (QALY) (Ganz, 2000, Prosser, 2000), one was a cost-minimization analysis (McPherson, 2001), and the rest were cost-effectiveness studies with Year of Life Saved (YOLS) as the measure of benefit. Five of the studies dealt with secondary prevention (Elliott, 99; Grover, 99; Maclaine, 2001; Ganz, 2000; and Johannesson, 97), six with primary prevention (Hamilton, 95; Martens, 94; Cobos, 99; Hillman, 99; McPherson, 2001 and Spearman, 97), and seven with both (Ebrahim, 99; Goldman, 91; Huse, 98; Pharaoh, 96; Pickin, 99; Russell, 2001; and Prosser, 2000) (Figure 4.1). The models used for each study varied from Markov model, to Life table method, CHD policy model and others.

Characteristics of the studies are shown in Table 3.1 and 3.2.

Tables 3.3, 3.4 and 3.5 outline the estimate CE for primary and secondary prevention in men and women.

Table 3.6 outlines the studies that included cerivastatin in the economic analysis, both for primary prevention and secondary prevention.

Table 3.1: Characteristics of CEAs of statins

Study	Study type	Statin studied					
		Ato	Cer	Flu	Lov	Pra	Sim
Cobos, 99	Cost-effectiveness			*	*	*	*
Ebrahim, 99	Cost-effectiveness	*				*	*
Elliott, 99	Cost-effectiveness	*	*	*	*	*	*
Ganz, 2000	Cost utility						
Goldman, 91	Cost effectiveness				*		
Grover, 99	Cost effectiveness						*
Hamilton, 95	Cost effectiveness				*		
Hillman, 99	Cost effectiveness	*		*	*	*	*
Huse, 98	Cost effectiveness	*		*	*	*	*
Johannesson, 97							*
Maclaine, 2001	Cost effectiveness	*	*	*		*	*
Martens, 94	Cost effectiveness			*	*	*	*
McPherson, 2001	Cost minimization		*			*	
Pharaoh, 96	Cost effectiveness						*
Pickin, 99	Cost effectiveness					*	*
Prosser, 2000	Cost utility						*
Russell, 2001	Cost effectiveness	*		*	*	*	*
Spearman, 97	Cost effectiveness			*	*	*	*

Ato-atorvastatin
Cer-cerivastatin
Flu-fluvastatin
Lov-lovastatin
Pra-pravastatin
Sim-simvastatin

Table 3.2: Characteristics of the CEAs: outcomes, analytical method, source of data etc.

Study	Outcome	Sponsorship	Source of effectiveness data	Analytical method
Ganz, 2000	Cost/QALY	Brigham and women's hospital and Harvard Med School	CARE trial	Markov model
Prosser, 2000	Cost/QALY	Government	4S, WOSCOPS, REGRESS, KAPS	CHD policy model
Ebrahim, 99	Cost/YOLS	Not declared	Not clear	Life table method
Elliott, 99	Cost/YOLS	Not declared	Published review (Kellick et al, 1997)	Modified Markov model
Goldman, 91	Cost/YOLS	Henry J Kaiser Family Foundation; and Agency for Health care Policy and Research, Rockville	Clinical trials of lovastatin	CHD policy method
Grover, 99	Cost/YOLS	Not declared	4S trial of Simvastatin	CVD life expectancy model
Hamilton, 95	Cost/YOLS	Government/Industry	EXCEL (Lovastatin trial, 1991)	CHD prevention model
Huse, 98	Cost/YOLS	Not declared	Data from approved US Food and Drug Administration product labelling	Markov model
Johannesson, 97	Cost/YOLS	Industry	4S trial of Simvastatin	Markov model
Martens, 94	Cost/YOLS	Industry	Clinical trials of the four statins studied	Mathematic model of CHD morbidity, mortality and treatment costs
Pharaoh, 96	Cost/YOLS	None	Not clear	Life table method
Pickin, 99	Cost/YOLS	not declared	4S, WOSCOPS	Life table method
Russell, 2001	Cost/YOLS	Industry	The CURVES study	Markov model
Cobos, 99	Cost/LDL-C reduction	not declared	Meta-analysis (Kong et al 97, Delea et al)	Stochastic simulation model
Hillman, 99	Cost/LDL-C reduction	Industry	Meta analysis of efficacy trials published between Jan 1985 and Jan 1997	Population based treat to target analysis
Spearman, 97	Cost/LDL-C reduction	not declared	Prudential health care, North Texas	Prospective, randomized balance cohort design
Maclaine, 2001	Cost/LDL-C reduction (to < 3mmol/L)	not declared	Meta analysis (Hillman, 99), RCT of Simvastatin (Ose, 98), Published study of Cerivastatin (Stein, 99)	Lipid lowering cost effectiveness model
McPherson, 2001	Cost/ LDL-C reduction (by > 20%)	Industry	Clinical trial	Cost-minimization

Table 3.3: Estimate CE ratios for primary prevention in men: base case values

		Estimate CE (Men)					
Study	**Perspective**	**Atorvastatin**	**Cerivastatin**	**Fluvastatin**	**Lovastatin**	**Pravastatin**	**Simvastatin**
Cost/YOLS							
Ebrahim, 97	-	£4,889				£12,767	£10,452
Goldman, 91	-				<$40,000		
Hamilton, 95	Societal				Cn$20,882		
Huse, 98	Third party payer	$44,036		$56,492	$77,908	$63,076	$52,813
Martens, 94	-			Cn$38,000	Cn$53,000	Cn$56,200	Cn$48,300
Pharaoh, 96	-						£136,000
Pickin, 99	-					£12,000	£8,200
Russell, 2001	Healthcare payer	Cn$23,774		Cn$34,647	Cn$31,619	Cn$42,420	Cn£33,558
Cost/QALY							
Prosser, 2000	Societal						$54,000-$420,000
Cost/%LDL reduction							
Cobos, 99 (based on Delea et)	Societal *			233,804 PTA	279,778 PTA	270,880 PTA	245,084PTA
	Public-finance			184,616 PTA	223, 584 PTA	218,449 PTA	194,950 PTA
Cobos 99 (based on Kong et al)	Societal **			266,481 PTA	271,428 PTA	369,364 PTA	298,419 PTA
	Public-finance			214,462 PTA	217,686 PTA	302,705 PTA	239,385 PTA
Hillman, 99	Third party payer	$17.02-$19.5 (34-39)		$19.00-$22.80 (20-24)	$31.48-$35.42 (24-27)	$30.58-$40.78 (18-24)	$24.71-$28.37 #(27-31)
Spearman, 97	Managed care organization			$8.6 (7.78-9.56)	$21.74 19.09-25.00)	$23.59 (20.56-227.34)	$19.93 (16.75-24.11)
	Patient			$13.29(12.01-14.78)	$30.29(26.51-34.95)	$33.24(28.95-38.56)	$27.82(23.33-33.75)
Cost/LDL reduction by 20%							
McPherson, 2001	-		$1224			$1452	

Cn$- Canadian dollars*- Results obtained from a Meta- analysis by Delea et al, **- Results obtained from a Meta- analysis by Kong et al, PTA- Pesetas

Table 3.4:Estimate CE for secondary prevention in men: base case values

Study	Perspective	Estimate CE (Men)					
		Atorvastatin	Cerivastatin	Fluvastatin	Lovastatin	Pravastatin	Simvastatin
Cost/YOLS							
Ebrahim, 99	-	£2,188				£7,721	£6,096
Elliott, 99	-	$5,421	$6,158	$5,790	$15,073	$8,575	$9,232
Goldman, 91	-				<$20,000		
Grover, 99	Third party payer						$5,424-$9548
Johannesson, 97	-						$3,800-$27,400
Huse, 98	Third party payer	$15,190		$20,150	$27,389	$22,490	$18,509
Pharaoh, 96	-						£32,000
Pickin, 99	-					£7,400	
Russell, 2001	Healthcare payer	Cn$16,898		Cn$25,065	Cn$22,807	Cn$30,998	Cn$24,251
Cost/QALY							
Ganz, 2000	Societal					$18,800*	
Prosser, 2000	Societal						<$50,000
Cost/LDL reduction to <3mmol/L							
Maclaine, 2001	Healthcare system	£383	£383	£820		£1,213	£431

Table 3.5: Estimate CE for primary and secondary prevention in women: base case values

Study	Perspective	Estimate CE					
		Atorvastatin	Cerivastatin	Fluvastatin	Lovastatin	Pravastatin	Simvastatin
Primary prevention Cost/YOLS							
Goldman, 91	-				>$50,000		
Hamilton, 95	Societal				Cn$36,627		
Huse, 98	Third party payer	$277,322		£345,875	$468,115	$382,790	$325,976
Russell, 2001		Cn$84,101		Cn$113,601	Cn$108,154	Cn$141,109	Cn$114,128
Cost/QALY							
Prosser, 2000	Societal						$62,000-$1,400 000
Secondary prevention Cost/YOLS							
Grover, 99	Third party payer						$8,389-$13,747
Huse, 98	Third party payer	$34,859		$45,737	$62,062	$50,905	£42,170
Russell, 2001		Cn$55,295		Cn$74,972	Cn$71,585	Cn$94,001	Cn$75,603
Cost/QALY							
Prosser, 2000	Societal						<$50,000

Table 3.6: Studies that included cerivastatin in the cost-effectiveness analysis: base case values

Study	Study type	Estimate CE					
		Cerivastatin	**Atorvastatin**	**Fluvastatin**	**Lovastatin**	**Pravastatin**	**Simvastatin**
Elliott, 99	Cost effectiveness (Cost/YOLS)	$6,158	$5,421	$5,790	$15,073	$8,575	$9,232
Maclaine, 2001	Cost effectiveness (Cost/LDL reduction)	£501	£383	£820		£1,213	£431
McPherson, 2001	Cost minimization Cost/LDL reduction by >20%)	$1,224				$1,452	

As the economic evaluations were carried out in different countries and hence reported estimates in different currencies, all were converted to the United States Dollar with exchange rates as of Tuesday the 4th of March 2003. The following tables show the converted CE estimates for primary and secondary prevention in men and women.

Table 3.7: Estimate CE ratios for primary prevention in men: all estimates converted to US dollars: base case values

Study	Perspective	Atorvastatin	Cerivastatin	Fluvastatin	Lovastatin	Pravastatin	Simvastatin
Cost/YOLS							
Ebrahim, 97	-	7,729				20,190	16,541
Goldman, 91	-				<40,000		
Hamilton, 95	Societal				14,064		
Huse, 98	Third party payer	44,036		56,492	77,908	63,076	52,813
Martens, 94	-			25,578	35,697	37,857	32,538
Pharaoh, 96	-						215,251
Pickin, 99	-					18,979	12,979
Russell, 2001	Healthcare payer	16,003		23,323	21,297	28,575	22,607
Cost/QALY							
Prosser, 2000	Societal						54,000-420,000
Cost/LDL reduction by ≤ 25%							
Cobos, 99 (based on Delea et al)	Societal*			1,533	1,834	1,775	1,607
	Public-finance			1,210	1,465	1,432	1,278
Cobos 99 (based on Kong et al)	Societal **			1,747	1,779	2,421	1,957
	Public-finance			1,406	1,427	1,984	1,569
Cost/%LDL-C reduction							
Hillman, 99	Third party payer	17.02-19.5		19.00-22.80	31.48-35.42	30.58-40.78	24.71-28.37
Spearman, 97	Managed care organization			8.6 (7.78-9.56)	21.74 (19.09-25.00)	23.59 (20.56-227.34)	19.93 (16.75-24.11)
	Patient			13.29(12.01-14.78)	30.29 (26.51-34.95)	33.24 (28.95-38.56)	27.82 (23.33-33.75)
Cost/LDL reduction by >20%							
McPherson, 2001	-		1224			1452	

*- Results obtained from a Meta- analysis by Delea et al, **- Results obtained from a Meta- analysis by Kong et al, PTA- Pesetas

Table 3.8:Estimate CE for secondary prevention in men: all estimates converted to US dollars: base case values

Study	Perspective	Estimate CE (Men)					
		Atorvastatin	Cerivastatin	Fluvastatin	Lovastatin	Pravastatin	Simvastatin
Cost/YOLS							
Ebrahim, 99	-	3,460				12,214	9,644
Elliott, 99	-	5,421	6,158	5,790	15,073	8,575	9,232
Goldman, 91	-				<20,000		
Grover, 99	Third party payer						5,424-9,548
Johannesson, 97	-						3,800-27,400
Huse, 98	Third party payer	15,190		20,150	27,389	22,490	18,509
Pharaoh, 96	-						50,625
Pickin, 99	-					11,706	
Russell, 2001	Healthcare payer	11,363		16,857	15,341	20,855	16,314
Cost/QALY							
Ganz, 2000	Societal					18,800*	
Prosser, 2000	Societal						<50,000
Cost/LDL reduction to <3mmol/L							
Maclaine, 2001	Healthcare system	606	793	1,297		1,919	682

Table 3.9: Estimate CE for primary and secondary prevention in women: all estimates converted to US dollars: base case values

Study	Perspective	Estimate CE					
		Atorvastatin	Cerivastatin	Fluvastatin	Lovastatin	Pravastatin	Simvastatin
Primary prevention Cost/YOLS							
Goldman, 91	-				>50,000		
Hamilton, 95	Societal				24,783		
Huse, 98	Third party payer	277,322		345,875	468,115	382,790	325,976
Russell, 2001		59,909		76,870	73,182	95,483	77,228
Cost/QALY							
Prosser, 2000	Societal						62,000-1,400 000
Secondary prevention Cost/YOLS							
Grover, 99	Third party payer						8,389-13,747
Huse, 98	Third party payer	34,859		45,737	62,062	50,905	42,170
Russell, 2001		37,478		50,814	48,520	63,713	51,245
Cost/QALY							
Prosser, 2000	Societal						<50,000

Table 3.10: Studies that included cerivastatin in the cost-effectiveness analysis: base case values

US Dollars

Study	Study type	Estimate CE					
		Cerivastatin	Atorvastatin	Fluvastatin	Lovastatin	Pravastatin	Simvastatin
Elliott, 99	Cost effectiveness (Cost/YOLS)	$6,158	$5,421	$5,790	$15,073	$8,575	$9,232
Maclaine, 2001	Cost effectiveness (Cost/LDL reduction)	$606	$793	$1,297	$1,919		$682
McPherson, 2001	Cost minimization Cost/LDL reduction by >20%)	$1,224				$1,452	

3.4 Discussion

Sources of heterogeneity identified in the cost-effectiveness studies were:

3.4.1 Type of prevention

Cost-effectiveness estimates vary depending on whether therapy is for primary or secondary prevention. Generally, therapy is more cost-effective for secondary prevention of coronary heart disease because a prior cardiovascular event is a positive predictor of a second event. Therefore for a patient who already has had a coronary event, cholesterol-lowering therapy should improve the cost-effectiveness of effective preventative strategies. For a patient who has never had a coronary event, the cost-effectiveness of cholesterol lowering therapy may not be favourable and will depend relatively more on other risk factors such as age and the presence of diseases such as diabetes.

That preventative strategies are more effective for secondary prophylaxis than for primary prevention is demonstrated by within study comparisons such as those of Ebrahim (1997). Thus the reported cost per life year saved for primary prevention was estimated to be £4889 compared to £ 2188 for secondary prevention. Similarly Huse (1998) reported a cost-effectiveness estimate of $44036 for primary prevention and $15190 for secondary prevention.

One disconcerting aspect when comparing the cost-effectiveness estimates across studies is the wide discrepancy between studies as is well illustrated by the Ebrahim (1997) and Huse (1997) studies. Although both studies investigated both primary and secondary prevention using the YOLS measure, the estimates from the two studies differed several-fold for both primary and secondary prevention. Primary prevention with atorvastatin was estimated by Ebrahim to cost $7,729/YOLS while that estimated by Huse was $44,036/YOLS (Table 3.7), and secondary prevention estimates were $3,460/YOLS for Ebrahim and $15,190/YOLS for Huse using atorvastatin (Table 3.8).

3.4.2 Cost-effectiveness measure used

Different cost-effectiveness measures are used in economic evaluations ranging from cost per year of life saved (YOLS), cost per quality adjusted life years (QALY), to cost per percentage change in LDL-C levels, and cost per percentage change in LDL-C levels to a specific target. The various economic evaluations reviewed in this study used any one of these outcome measures. As expected cost per QALY and cost per YOLS were higher than cost per LDL-C reduction. In the primary prevention table for men Table 3.7, CE estimate for simvastatin ranged between $12,979 and $52,813 for the cost per YOLS measures, and between $19.93 and $1,957 for the cost per LDL-C reduction measures. The same goes for all the other statins in the studies. A study carried out by Morris et all in 1999 showed that different outcome measures in economic evaluations lead to varying cost-effectiveness estimates (Morris, 1999). Morris and Godber examined the extent to which the relative cost-effectiveness of

cholesterol-modifying agents varied depending on the cost-effectiveness measured used. The main outcome measures used in the study were cost per 1% reduction in LDL-C level; incremental cost per life year gained; least-cost agent achieving the LDL-C reduction required to meet the target level of 160mg/dl; incremental cost per life year-gained of agents reaching the target LDL-C level of 160mg/dl relative to no therapy; incremental cost per life year gained of agents achieving the target LDL-C levels of 160mg/dl relative to the least-cost agent reaching the target. Open-ended measures were found to be of little use to healthcare decision makers in the real world because they fail to take into account the magnitude of LDL-C reduction required. The recommendation of the study was that incremental cost per year of life gained in reaching a predefined LDL-C target be used to measure cost-effectiveness in cholesterol-modifying pharmacotherapy.

3.4.3 Inclusion criteria/patient characteristics

3.4.3.1 Age group

Cost-effectiveness of cholesterol modifying pharmacotherapy greatly varies depending on the age groups and risk factors of the patients. One study (Hamilton, 95) concluded that treatment with a statin (lovastatin) appeared to be cost-effective for high risk men of all ages ($20,882 to $50,079), high risk women aged 50-70 ($36,627 to $43,127), and low risk men aged 40-60 ($46,571 to $48,214), but that treatment was not cost-effective for low risk men younger than 35 years and low risk women younger than 45

years. Cost-effectiveness of statins varies widely by age and sex and is sensitive to the presence of non-lipid CHD factors. Some of the studies measured cost-effectiveness according to selected patient characteristics. Prosser et al (2000) showed that primary prevention with a statin compared with diet therapy was $54 000 to $1,400,000 per QALY, but that as expected the estimates varied depending on the age group and risk factors of the patients concerned. Cost-effectiveness ratios for the base-case analysis started at $150,000 per QALY for women 65 to 74 years of age and increased to $730,000 per QALY for women 35 to 44 years of age. Cost-effectiveness ratios become more favourable as age increases. Elliott et al (Elliott, 1999) showed the different cost-effectiveness ratios for different ages of patients involved in the study. Patients aged 40 had CE estimates ranging from $6,646 to$18,480 while patients aged 70 ranged from $4,787 to $13,311(Elliott, 1999).

3.4.3.2 Risk factors

Cost-effectiveness of treatment strategies varies significantly depending on cholesterol levels and risk factors of patients. Cost-effectiveness ratios vary differentially with individual risk factors, and generally become more favorable with increasing number of risk factors. Certain risk factors (diastolic blood pressure and HDL-C levels) have a greater impact on cost-effectiveness than others. Higher diastolic blood pressure and lower HDL-C levels favour CE ratios. CE ratios for women are higher than that for men, as seem from the studies in the tables above. For men with LDL-C levels of 4.1mmol/L (160mg/dL) or greater, primary prevention ranged from $130,000 per

QALY to $260,000 per QALY (Prosser, 2000). One study (Huse, 98) showed different CE estimates of five different statins for primary prevention for patients with no risk factors and those with three risk factors (hypertension, smoking and diabetes mellitus), and secondary prevention for patients with no risk factors and those with one or other risk factor (diabetes mellitus). For primary prevention with no risk factors, CE estimates ranged from $44,036 to $77,908 for age 45 and from $31,544 to $58,356 at age 65. When risk factors were taken into consideration the CE estimates ranged from $13,064 to $25,653 at age 45 and from $8,313 to $18,862 at age 65. The same scenario was observed in secondary prevention. With no risk factors CE estimates ranged from $15,190 to $27,389 at age 45 and from $11,846 to $21,474 at age 65 (Huse, 98). Increases in the LDL-C levels of these patients resulted in reduced CE estimates.

3.4.3.3 Study perspective

The perspective taken in the study will affect the cost-effectiveness estimates arrived at. Taking a narrow healthcare trust perspective is likely to generate some useful data, but such results would not be as useful as those obtained from adopting a societal perspective. Providers of health care may be interested in the detailed costs and consequences for their own organization, to determine if a new therapy is more cost-effective than the present one being used (Health care payer/provider perspective). Economic evaluations that take on a health payer perspective could determine the mix of interventions that would maximize health outcomes within its limited budget, and this would normally not maximize the welfare of the society within resources available.

Adopting a societal perspective takes into account alternative uses for resources outside the healthcare sector, and may yield greater welfare to society. Using alternative perspectives would probably result in different cost-effectiveness ratios along with different cost-effectiveness thresholds for each perspective, e.g. higher income persons may be willing to pay more than others, whereas managed-care organizations may insist on cost saving. Different perspectives adopted determine the costs considered. The following table shows costs considered by some of the different perspectives.

Table 3.11: Perspectives of economic analysis and costs considered

Perspective	**Costs of primary interest**
Societal	All medical and nonmedical costs: • Hospitalization • Long-term care • Home care • Social welfare services Productivity losses (indirect costs) Intangible costs
Third party payer	Charges that pertain to reimbursement of providers average, not marginal costs
Health care provider	Variable costs that influence the expenses of providing health care
Patient	Costs that affect out-of-pocket payments Lost wages (indirect costs)
Employer	All insurable direct costs Lost wages (indirect costs)

Source: Luce BR, Elixhauser A: standards for socio-economic evaluation of health care products and services. Springer-Verlag Berlin Heidelberg New York. 1990

The cost-effectiveness estimates in the Tables above all show the base case estimates. Under different conditions (age groups, risk factors, LDL-C levels, primary or secondary prevention), these CE estimates vary across the studies. Using the study by Ebrahim et al, 1999, as a case example, the cost-effectiveness of the statins for lipid-lowering therapy was estimated both for primary and secondary prevention, with baseline risk presented as total and CHD mortality. Primary prevention cost-effectiveness was measured at a 0.5% level of total mortality per year, and secondary prevention at 3% total mortality per year. The results showed the gross cost per life-year gained (not including any NHS savings), and the net cost per life-year gained (taking into account potential savings due to avoiding CHD events and associated costs of treatment and hospitalisation). CE estimates for secondary prevention in this study compared favourably with other interventions provided by the NHS. Cost per life-year gained increased when people with lower risk were offered treatment.

3.5 Conclusion

Cost-effectiveness evaluations are used for decision making in health care, helping the healthcare industry meet the challenge of providing the best quality care with the most efficient use of resources. These evaluations therefore have to be of good quality to be useful to the health care system. As has been observed above, different economic evaluations for cholesterol-lowering pharmacotherapy with the statins have resulted in various different CE estimates, depending on the different factors discussed. The wide discrepancies in the CE estimates in different studies even when considering primary and secondary prevention alike are a source of concern. The one explanation could be

the different countries where these evaluations are carried out, different centers and costs of the various drug and physician visits, laboratory tests, in the different countries and the costs taken into consideration.

CHAPTER 4

Integrating effectiveness and cost data

Cost-effectiveness evaluation is undertaken to help decision-making with respect to whether an effective treatment is worth paying for. In Chapter 2, the problems associated with effectiveness data derived from randomised controlled trials demonstrate that such data are incomplete. In particular, it was shown that the adverse effects of treatments are poorly estimated by randomised controlled trials. Adverse effects of cerivastatin, which were severe enough to lead to its withdrawal were not identified reliably in those trials and even with the benefit of hindsight, the rates of rhabdomyolysis (a serious adverse effect that led to withdrawal of cerivastatin) and surrogate measures for this adverse effect (muscle pain, elevation of enzyme levels) were not estimated reliably. Given that the incidences of those adverse events were low, the small number of patients involved in the various trials do not provide adequate power to detect clinically meaningful differences between different statins. For example, in the trial by Insull et all (2000), out of a total of 971 patients on cerivastatin, 0.4mg and 0.8mg, the number of patients reported to have elevated CK levels above 10 times ULN was 12, which is a mere 1.2% of the population. The number of patients reporting myalgia was 26 (2.6%), still a negligible number. A similar scenario is seen with the study reported by Leiter et al (1999), with respect to CK elevation greater than 10 x ULN. Only 2 out of 260 (0.8%) patients were affected, and 8/260 (3%) patients developed myalgia. The same goes for the other adverse events like muscle pain.

Deriving data required for economic evaluations from clinical trials is a common practice. Unfortunately, clinical trials differ from regular practice in a number of ways, including the fact that clinical trials are often performed on selected patients, often use specialist settings using up to date medical equipment, adhere to strict treatment protocols, and involve great effort to ensure that both patients and clinicians comply with therapy. The scenario in clinical trials do not portray the real life practice of drug therapy. There may be significant differences between what happens in clinical trials and what actually happens in reality. Clinical trials tend to concentrate on efficacy rather than effectiveness (Morris, 1997). This one flaw therefore makes data from clinical trials questionable/incomplete for cost-effectiveness analyses.

The cost-effectiveness studies surveyed in Chapter 3 showed wide disparity in the cost-effectiveness estimates arrived at. None of the studies incorporated important adverse outcomes, probably because estimates of both the frequency and the cost of their management are ill defined. It is argued that cost-effectiveness models, which do not take account of adverse effects, are not sufficiently robust for informing policy decisions. Yet none of the studies reviewed here took full account of the adverse events suffered by the patients and therefore, of the cost of managing them. Costs that are taken into consideration in most economic evaluations include cost of intervention, which ranges from cost of medication, to cost of physician visits, and cost of laboratory tests. Indirect costs include days lost to hospital visits and visits for laboratory tests. There could be an argument that the cost effectiveness estimates arrived at in such studies are not reliable. Including the costs of managing adverse effects may or may not make a substantial difference to the cost-effectiveness estimates. However, as seen from Chapter 2, adverse drug reactions can really be a problem. Many patients

suffering adverse reactions may have to take further measures to counteract these effects, all adding to the cost of taking the agent being evaluated. The costs of treating adverse events arise as a direct consequence of taking the drug in question and should therefore not be ignored. Having said that, being able to estimate exactly those costs is problematic. Recent estimates suggest that such costs can be considerable. For example, in the United States, studies were conducted to estimate the cost of adverse events in hospitalised patients. One study (Johnson, 1995) estimated the cost of drug morbidity and mortality at more than $136 billion a year. Another (Bates, 1997) found that an adverse drug event (ADE) was associated with $2595 of additional costs to the hospital for all ADEs, and for preventable ADEs, the figure was almost twice as high. These studies concluded that the costs of ADEs are substantial. Annual additional costs associated with all ADEs in a large tertiary care hospital were $5.6 million (Bates, 1997). These estimates did not include cost of injuries to patients, malpractice costs, or the costs of less serious medication errors or admissions related to ADEs.

The wide discrepancy in the cost-effectiveness estimates reported, even when only beneficial outcomes are taken into account, highlights the limitations of those estimates. The figures from CE estimates in Chapter 3 show the discrepancies in the cost-effectiveness estimates for different statins used for secondary prevention in male patients for example. Estimated cost-effectiveness of simvastatin for secondary prevention in men ranged between $682 and $50,625. A study in 1997 showed that different cost-effectiveness measures used in economic evaluations lead to varying cost-effectiveness estimates in Canada (Morris and Godber, 1997). The study evaluated the effect of using different cost-effectiveness measures in the economic evaluation of cholesterol-modifying pharmacotherapy. Main outcome measures studied are cost per

1% reduction in LDL-C level; incremental cost per life-year gained; least-cost agent achieving the LDL-C reduction required to meet the target level of 160mg/dl; incremental cost per life year gained of agents reaching the target LDL-C level relative to no therapy; incremental cost per life-year gained of agents achieving the target LDL-C of 160mg/dl relative to the least-cost agent reaching the target. Cost-effectiveness estimates varied depending on many different factors as discussed in Chapter 3. Thus, while fluvastatin was more cost-effective than atorvastatin, based on the cost of reaching a target level of 160mg/dl, when pre-treatment LDL-C level was in the range 190-220 mg/dl, the reverse was true when the level was in the range 220 to 245 mg/dl. When the measure was incremental cost per life-year gained relative to no therapy, fluvastatin was always better than atorvastatin (Morris and Godber, 1999). When the comparator was the least-cost agent able to lead to a target LDC-L level of 160mg/dl, atorvastatin was more cost-effective than fluvastatin except in the pre-treatment LDL-C range of 190-205 mg/dl.

A study by Jefferson et al (2002) reviewed the quality of systematic reviews of economic evaluations in healthcare. They found consistent evidence of serious methodological flaws in a significant number of economic evaluations. Lack of clear description of methods, lack of explanation and justification for the framework and approach used, lack of clear descriptions of methods used to define effectiveness, benefits and resource and cost estimates, and low-quality estimates of effectiveness for the interventions evaluated were the most frequent flaws.

In the process of integrating cost and effectiveness data for cost-effectiveness evaluations, all possible areas should be taken into account. All areas that could add to

the cost of therapy with the drug, both direct and indirect costs, should be well incorporated. Effectiveness data should take into account the adverse events profile of the drug.

One way of ensuring that clinical trials reflect reality more closely is by undertaking clinical trials using a naturalistic protocol. The aim of this type of clinical trial is to evaluate the effectiveness or cost-effectiveness of a given intervention under real-world conditions. These naturalistic trials involve patients typical of the normal caseload and the therapy of interest is compared with current care, under settings and physicians that are fairly representative of the target population. Moreover, the trial protocol should be flexible. However such trials have their shortcomings too as they provide data for the settings in which they are conducted and generalisability becomes a problem. Economic modelling allows exploration of the impact of alternative settings and may reduce the uncertainty but as with any predictions, their reliability depends on the precision with which parameter estimates are measured.

Economic evaluations are tools for decision making in healthcare. Drugs that have passed the effectiveness, efficacy and tolerability test are then subject to cost-effectiveness studies. There is a serious problem when a drug is highly efficacious but is extremely expensive, that the health care system is not able to utilize it for patients in their communities. Economic evaluations are carried out for the purpose of comparing alternative therapies to ensure the most cost-effective agents are used for patients' therapies. The different economic evaluations reviewed in chapter 3 show the varying estimates arrived at by different studies. Secondary prevention using statin therapy has been proven to be cost-effective. Primary prevention however depends more on the

patients and risk factors they have. Costs of treating adverse drug events were not included in the evaluations. Including such data may or may not alter the estimates arrived at. Until now, effectiveness data for economic evaluations are usually derived from clinical trials. As effectiveness encompasses efficacy and safety, the effectiveness data derived from clinical trials may not be reliable, as most trials do not adequately expose the long-term adverse events profile of the drug under trial, and are conducted under specially designed conditions which do not always portray real life conditions. Generating data for economic evaluations from economic models is another approach. However their reliability depends on the precision with which parameter estimates are measured.

Efforts should concentrate on improving the quality of clinical trials, by including as diverse a population of patients as possible (older patients, those that have the sort of ailments and complications that are commonly seen in real life situations), and if possible increase the number of patients enrolled into these trials as well as trial period. This will improve the quality of effectiveness data derived. In its pre-approval database, cerivastatin 0.8mg had an overall myopathy of 1.3% and 5.6% in elderly women (Davidson, 2002). The FDA acknowledged this was a signal cerivastatin was more myotoxic than other statins and that the elderly population represents a group at higher risk for safety problems, and are often not included in significant numbers in a pre-approval regulatory submission. Package inserts and changes to the prescribing information of drugs alone are not enough to prevent serious drug interactions and adverse drug reactions.

Collecting effectiveness and cost data for a given intervention is vital for the conduct of economic evaluations of any given intervention. It is imperative that efforts are made to get data as reliable as possible. How best to do this is still the subject of much debate and research.

Improvements in the quality of clinical trials may ensure that data for economic evaluations are more reliable/complete, and will improve decision-making concerning choice of health care for patients. These are areas that need to be visited by manufacturers and regulatory bodies as well as clinicians and other healthcare professionals.

Appendix 1

List of the 42 studies identified from initial search.

Betteridge DJ. International multicentre comparison of cerivastatin with placebo and simvastatin for the treatment of patients with primary hypercholesterolemia. Int J Clin Prac 1999; 53 (4): 243-250

Bischoff H, Angerbauer R, Boberg M, et al. Preclinical review of cerivastatin sodium-a step forward in HMG-Co A reduction inhibition. Atherosclerosis 1998; 139 (suppl 1): S7-S13

Bischoff H, Allen H, Heller MD. Preclinical and clinical pharmacology of cerivastatin. Am J Cardiol 1998; 82 (4) suppl 2: 18J-25J

Bischoff H, Angerbauer R, Bender J, et al. Cerivastatin: pharmacology of a novel synthetic and highly active HMG-Co A reductase inhibitor. Atherosclerosis 1997; 135 (1): 119-130

Davignon J, Hanefeld M, Nakaya N, et al. Clinical efficacy and safety of cerivastatin: summary of pivotal phase IIb/III studies. Am J Cardiol 1998; 82 (4) suppl 2: 32J-39J

Deighan CJ, Caslake MJ, McConnell M, et al. Comparative effects of cerivastatin and fenofibrate on the atherogenic lipoprotein phenotype in proteinuric renal disease. J Am Sco Nephrol 2001; 12 (2): 341-348

Farnier M, Cerivastatin study group. Cerivastatin in the treatment of mixed hyperlipidemia: the RIGHT Study. Am J Cardiol 1998: 82: 47J-51J

Garcia P, Errasti FJ, Lavilla B, et al. Effects of cerivastatin in dyslipidemia and other cardiovascular risk factors after renal transplantation. Transplantation proceedings 2002; 34: 401-402

Hanefeld M, Deslypere JP, Ose L, et al. Efficacy and safety of 0.3mg and 0.4mg cerivastatin once daily in patients with primary hypercholesterolemia: a multicentre, randomized, double-blind, placebo-controlled study. J Int Med Res 1999; 27: 115-120

Hunninghake DB. Clinical efficacy of cerivastatin: phase IIa dose-ranging and dose-scheduling studies. Am J Cardiol 1998; 82 (4) suppl 2: 26J-31J

Hunninghake D, Insull W, Knopp R, et al. Comparison of the efficacy of atorvastatin versus cerivastatin in primary hypercholesterolemia. Am J Cardiol 2001; 88: 635-639.

Insull W, Isaacsohn J, Kwiterovich P, et al. Efficacy and safety of cerivastatin 0.8mg in patients with hypercholesterolemia: the pivotal placebo-controlled clinical trial. J Int Med Res 2000; 28: 47-68

Isaacsohn J, Zinny M, Mazzu A, et al. Influence of gender on the pharmacokinetics, safety, and tolerability of cerivastatin. Eur J Clin Pharmacol 2001; 56 (12): 897-903

Kaneeider NC, Reinisch CM, Dunzendorfer S, et al. Induction of apoptosis and inhibition of migration of inflammatory and vascular wall cells by cerivastatin. Atherosclerosis 2001; 158 (1): 223-33

Kantola T, Kivisto KT, Neuvonen PJ. Effects of itraconazole on cerivastatin pharmacokinetics. Eur J Clin Pharmacol 1999; 54 (11): 851-855.

Keane WF, Brenner BM, Mazzu A, Agro A. The CHORUS (Cerivastatin in Heart Outcomes in Renal Disease: Understanding Survival) protocol: a double-blind, placebo-controlled trial with esrd. Am J Kidney Dis 2001; 37 (Suppl 2): S48-53

Leiter LA, Hanna K, Canadian Cerivastatin Study Group. Efficacy and safety of cerivastatin in primary hypercholesterolemia: a long-term comparative titration study with simvastatin. Can J Cardiol 1999; 15 (5): 545-555

Mabuchi H, Kiozumi J, Kajinami K. Clinical efficacy and safety of cerivastatin in the treatment of heterozygous familial hypercholesterolemia. Am J Cardiol 1998; 82: 52J-55J

Mazzu A, Lettieri J, Kiaser L, et al. influence of age on the safety, tolerability, and pharmacokinetics of the nivel HMG-Co A reductase inhibitor cerivastatin in healthy male volunteers. J Clin Pharmacol 19989; 38 (8): 715-719

McPherson R, Hanna K, Agro A, et al. Cerivastatin versus branded pravastatin in the treatment of primary hypercholesterolemia in primary care practice in Canada> a one year, open label, randomized, comparative study of efficacy, safety, and cost-effectiveness. Clin Therapeutics 2001; 23 (9): 1492-1507.

Muck W, Frey R, Unger S, Voith B. Pharmacokinetics of cerivastatin when administered under fasted and fed conditions in the morning or evening. Int J Clin Pharmacol Ther 2000; 38 (6): 298-303

Muck W, Neal DA, Boix, et al. Tacrolimus/cerivastatin interaction study in liver transplant recipients. Br J Clin Pharmacol 2001; 52 (2): 213-215

Muck W, Ochmann K, Mazzu A, Lettiri J. Biopharmaceutical profile of cerivastatin: a novel HMG-Co A reductase inhibitor. J Int Med Res 1999; 27 (3): 107-114

Muck W, Ochmann K, Rohde G, et al. Influence of erythromycin pre- and co-treatment on single dose pharmacokinetics of the HMF-Co A reductase inhibitor cerivastatin. Eur J Clin Pharmacol 1998; 53 (6): 469-473.

Muck W, Ritter W, Ochmann K, et al. absolute and relative bioavailability of the HMG-Co A reductase inhibitor cerivastatin. Int J Clin Pharmacol Ther 1997; 35 (6): 255-260.

Ose L, Luurila O, Eriksson J, et al. efficacy and safety of cerivastatin 0.2mg and 0.4mg, in patients with primary hypercholesterolemia: a multinational, randomized, double-blind study. Curr Med Res Opin 1999; 15 (3): 228-240

Ose L, Olavi L, Eriksson J, et al. Cerivastatin and gender effect: sub-analysis of results from multinational, randomized, double blind study. Curr Med Res Opin 2000; 16 (2): 80-87

Renders L, Mayer-Kander I, Koch C, et al. Efficacy and drug interactions of the new HMG-Co A reductase inhibitors cerivastatin and atorvastatin in CsA-treated renal transplant recipients. Nephrol Dial Transplant 2001; 16: 141-146

Ridker PM, Rifai N, Lowenthal MD. Rapid reduction in C-reactive protein with cerivastatin among 785 patients with primary hypercholesterolemia Circulation 2002; 103: 1191-1193.

Rubinstein A, Maritz FJ, Soule SG, et al. Efficacy and safety of cerivastatin for type 2 diabetes and hypercholesterolemia. J Cardio Risk 1999; 6: 399-403.

Sachse R, Ochmann K, Rhode G, Muck W. The effect of omeprazole pre- and co-treatment on cerivastatin absorption and metabolism in man. Int J Clin Pharmacol Ther 1998; 36 (10): 517-520

Sasaki J, Arakawa K,Yamamoto K, et al. A long term comparative trial of cerivastatin sodium, a new HMG-Co A reductase inhibitor, in patients with primary hypercholesterolemia. Clin Therapeutics 1998; 20 (3): 539-548.

Schall R, Muller FO, Hundt HK, et al. No pharmacokinetic or pharmacodynamic interaction between rivastatin and warfarin. Clin Pharmacol 1995; 35 (3): 306-13

Stein E. Cerivastatin in primary hyperlipidemia- a multicenter analysis of efficacy and safety. Atherosclerosis 1998; 139 (suppl 1): 15-22

Stein E, Schopen U, Catagay M. A pooled efficacy analysis of cerivastatin in the treatment of primary hypercholesterolemia. Clin Drug Invest 1999; 18: 433-444

Stein E, Sprecher D, Allenby KS, et al. Cerivastatin, a new potent synthetic HMG-Co A reductase inhibitor: effect of 0.2mg daily in subjects with primary hypercholesterolemia. J Cardiovasc Pharmacol Ther 1997; 2 (1): 7-16

Stein E, Isacsohn J, Stoltz R, et al. Pharmacodynamics, safety, tolerability, and pharmacokinetics of the 0.8mg dose of cerivastatin in patients with primary hypercholesterolemia. Am J Cardiol 1999; 83: 1433-1436.

Tao P, Wu X, Yu X, et al. efficacy and safety of cerivastatin 0.1mg, 0.2mg and 0.3mg in Chinese patients with primary hypercholesterolemia: a multicentre, randomized, double-blind, placebo-controlled study.

Tomita N, Morishila R, Ogihara T. Ongoing clinical trials by vascular statin, cerivastatin. Nippon Rinsho 2001; 59 (suppl 3): 477-482.

Tsunekawa T, Hayashi T, Kano H, et al. Cerivastatin, a hydroxymethylglutaryl coenzyme a reductase inhibitor, improves endothelial function in elderly diabetic patients within three days. Circulation 2001; 104 (4): 376-379

Vincent L, Chen W, Hong L, et al. Inhibition of endothelial cell migration by cerivastatin, an HMG-Co A reductase inhibitor: contribution to its anti-angiogenic effect. FEBS Letters 2001; 495: 159-166

Yu WC, Chen CH, Tsao HM, Ding YA. A randomized, double blind comparison of cerivastatin and lovastatin treatment of primary hypercholesterolemia. Zhonghua Yi Xue Za Zhi (Taipei) 2002; 65 (6): 260-267

Papers excluded on the basis of title and abstract (due to lack of suitability of study design or intervention) (n= 25)

1 Bischoff H, Angerbauer R, Boberg M, et al. Preclinical review of cerivastatin sodium-a step forward in HMG-Co A reduction inhibition. Atherosclerosis 1998; 139 (suppl 1): S7-S13

2 Bischoff H, Allen H, Heller MD. Preclinical and clinical pharmacology of cerivastatin. Am J Cardiol 1998; 82 (4) suppl 2: 18J-25J

3 Bischoff H, Angerbauer R, Bender J, et al. Cerivastatin: pharmacology of a novel synthetic and highly active HMG-Co A reductase inhibitor. Atherosclerosis 1997; 135 (1): 119-130

4 Davignon J, Hanefeld M, Nakaya N, et al. Clinical efficacy and safety of cerivastatin: summary of pivotal phase IIb/III studies. Am J Cardiol 1998; 82 (4) suppl 2: 32J-39J

5 Deighan CJ, Caslake MJ, McConnell M, et al. Comparative effects of cerivastatin and fenofibrate on the atherogenic lipoprotein phenotype in proteinuric renal disease. J Am Sco Nephrol 2001; 12 (2): 341-348

6 Garcia P, Errasti FJ, Lavilla B, et al. Effects of cerivastatin in dyslipidemia and other cardiovascular risk factors after renal transplantation. Transplantation proceedings 2002; 34: 401-402

7 Hunninghake DB. Clinical efficacy of cerivastatin: phase IIa dose-ranging and dose-scheduling studies. Am J Cardiol 1998; 82 (4) suppl 2: 26J-31J

8 Isaacsohn J, Zinny M, Mazzu A, et al. Influence of gender on the pharmacokinetics, safety, and tolerability of cerivastatin. Eur J Clin Pharmacol 2001; 56 (12): 897-903

9 Kaneeider NC, Reinisch CM, Dunzendorfer S, et al. Induction of apoptosis and inhibition of migration of inflammatory and vascular wall cells by cerivastatin. Atherosclerosis 2001; 158 (1): 223-33

10 Kantola T, Kivisto KT, Neuvonen PJ. Effects of itraconazole on cerivastatin pharmacokinetics. Eur J Clin Pharmacol 1999; 54 (11): 851-855.

11 Mabuchi H, Kiozumi J, Kajinami K. Clinical efficacy and safety of cerivastatin in the treatment of heterozygous familial hypercholesterolemia. Am J Cardiol 1998; 82: 52J-55J

12 Mazzu A, Lettieri J, Kiaser L, et al. Influence of age on the safety, tolerability, and pharmacokinetics of the novel HMG-Co A reductase inhibitor cerivastatin in healthy male volunteers. J Clin Pharmacol 19989; 38 (8): 715-719

13 Muck W, Frey R, Unger S, Voith B. Pharmacokinetics of cerivastatin when administered under fasted and fed conditions in the morning or evening. Int J Clin Pharmacol Ther 2000; 38 (6): 298-303

14 Muck W, Neal DA, Boix, et al. Tacrolimus/cerivastatin interaction study in liver transplant recipients. Br J Clin Pharmacol 2001; 52 (2): 213-215

15 Muck W, Ochmann K, Mazzu A, Lettiri J. Biopharmaceutical profile of cerivastatin: a novel HMG-Co A reductase inhibitor. J Int Med Res 1999; 27 (3): 107-114

16 Muck W, Ochmann K, Rohde G, et al. Influence of erythromycin pre- and co-treatment on single dose pharmacokinetics of the HMF-Co A reductase inhibitor cerivastatin. Eur J Clin Pharmacol 1998; 53 (6): 469-473.

17 Muck W, Ritter W, Ochmann K, et al. absolute and relative bioavailability of the HMG-Co A reductase inhibitor cerivastatin. Int J Clin Pharmacol Ther 1997; 35 (6): 255-260.

18 Ose L, Olavi L, Eriksson J, et al. Cerivastatin and gender effect: sub-analysis of results from multinational, randomized, double blind study. Curr Med Res Opin 2000; 16 (2): 80-87

19 Sachse R, Ochmann K, Rhode G, Muck W. the effect of omeprazole pre- and co-treatment on cerivastatin absorption and metabolism in man. Int J Clin Pharmacol Ther 1998; 36 (10): 517-520

20 Schall R, Muller FO, Hundt HK, et al. No pharmacokinetic or pharmacodynamic interaction between rivastatin and warfarin. Clin Pharmacol 1995; 35 (3): 306-13

21 Stein E. Cerivastatin in primary hyperlipidemia- a multicenter analysis of efficacy and safety. Atherosclerosis 1998; 139 (suppl 1): 15-22

22 Stein E, Schopen U, Catagay M. A pooled efficacy analysis of cerivastatin in the treatment of primary hypercholesterolemia. Clin Drug Invest 1999; 18: 433-444

23 Tomita N, Morishila R, Ogihara T. Ongoing clinical trials by vascular statin, cerivastatin. Nippon Rinsho 2001; 59 (suppl 3): 477-482.

24 Tsunekawa T, Hayashi T, Kano H, et al. Cerivastatin, a hydroxymethylglutaryl coenzyme a reductase inhibitor, improves endothelial function in elderly diabetic patients within three days. Circulation 2001; 104 (4): 376-379

25 Vincent L, Chen W, Hong L, et al. Inhibition of endothelial cell migration by cerivastatin, an HMG-Co A reductase inhibitor: contribution to its anti-angiogenic effect. FEBS Letters 2001; 495: 159-166

Appendix 2

Papers retrieved for more detailed evaluation

1 Betteridge DJ. International multicentre comparison of cerivastatin with placebo and simvastatin for the treatment of patients with primary hypercholesterolemia. Int J Clin Prac 1999; 53 (4): 243-250

2 Farnier M, Cerivastatin study group. Cerivastatin in the treatment of mixed hyperlipidemia: the RIGHT Study. Am J Cardiol 1998: 82: 47J-51J

3 Hanefeld M, Deslypere JP, Ose L, et al. Efficacy and safety of 0.3mg and 0.4mg cerivastatin once daily in patients with primary hypercholesterolemia: a multicentre, randomized, double-blind, placebo-controlled study. J Int Med Res 1999; 27: 115-120

4 Hunninghake D, Insull W, Knopp R, et al. Comparison of the efficacy of atorvastatin versus cerivastatin in primary hypercholesterolemia. Am J Cardiol 2001; 88: 635-639.

5 Insull W, Isaacsohn J, Kwiterovich P, et al. Efficacy and safety of cerivastatin 0.8mg in patients with hypercholesterolemia: the pivotal placebo-controlled clinical trial. J Int Med Res 2000; 28: 47-68

6 Keane WF, Brenner BM, Mazzu A, Agro A. The CHORUS (Cerivastatin in Heart Outcomes in Renal Disease: Understanding Survival) protocol: a double-blind, placebo-controlled trial with esrd. Am J Kidney Dis 2001; 37 (Suppl 2): S48-53

7 Leiter LA, Hanna K, Canadian Cerivastatin Study Group. Efficacy and safety of cerivastatin in primary hypercholesterolemia: a long-term comparative titration study with simvastatin. Can J Cardiol 1999; 15 (5): 545-555

8 McPherson R, Hanna K, Agro A, et al. cerivastatin versus branded pravastatin in the treatment of primary hypercholesterolemia in primary care practice in Canada> a one year, open label, randomized, comparative study of efficacy, safety, and cost-effectiveness. Clin Therapeutics 2001; 23 (9): 1492-1507.

9 Ose L, Luurila O, Eriksson J, et al. Efficacy and safety of cerivastatin 0.2mg and 0.4mg, in patients with primary hypercholesterolemia: a multinational, randomized, double-blind study. Curr Med Res Opin 1999; 15 (3): 228-240

10 Renders L, Mayer-Kander I, Koch C, et al. Efficacy and drug interactions of the new HMG-Co A reductase inhibitors cerivastatin and atorvastatin in CsA-treated renal transplant recipients. Nephrol Dial Transplant 2001; 16: 141-146

11 Ridker PM, Rifai N, Lowenthal MD. Rapid reduction in C-reactive protein with cerivastatin among 785 patients with primary hypercholesterolemia Circulation 2002; 103: 1191-1193.

12 Rubinstein A, Maritz FJ, Soule SG, et al. Efficacy and safety of cerivastatin for type 2 diabetes and hypercholesterolemia. J Cardio Risk 1999; 6: 399-403.

13 Sasaki J, Arakawa K,Yamamoto K, et al. a long term comparative trial of cerivastatin sodium, a new HMG-Co A reductase inhibitor, in patients with primary hypercholesterolemia. Clin Therapeutics 1998; 20 (3): 539-548.

14 Stein E, Sprecher D, Allenby KS, et al. Cerivastatin, a new potent synthetic HMG-Co A reductase inhibitor: effect of 0.2mg daily in subjects with primary hypercholesterolemia. J Cardiovasc Pharmacol Ther 1997; 2 (1): 7-16

15 Stein E, Isaacsohn J, Stoltz R, et al. Pharmacodynamics, safety, tolerability, and pharmacokinetics of the 0.8mg dose of cerivastatin in patients with primary hypercholesterolemia. Am J Cardiol 1999; 83: 1433-1436.

16 Tao P, Wu X, Yu X, et al. efficacy and safety of cerivastatin 0.1mg, 0.2mg and 0.3mg in Chinese patients with primary hypercholesterolemia: a multicentre, randomized, double-blind, placebo-controlled study.

17 Yu WC, Chen CH, Tsao HM, Ding YA. A randomized, double blind comparison of cerivastatin and lovastatin treatment of primary hypercholesterolemia. Zhonghua Yi Xue Za Zhi (Taipei) 2002; 65 (6): 260-267

Papers excluded for clearly not fulfilling inclusion criteria

Keane WF, Brenner BM, Mazzu A, Agro A. The CHORUS (Cerivastatin in Heart Outcomes in Renal Disease: Understanding Survival) protocol: a double-blind, placebo-controlled trial with esrd. Am J Kidney Dis 2001; 37 (Suppl 2): S48-53 - abstract

Yu WC, Chen CH, Tsao HM, Ding YA. A randomized, double blind comparison of cerivastatin and lovastatin treatment of primary hypercholesterolemia. Zhonghua Yi Xue Za Zhi (Taipei) 2002; 65 (6): 260-267-abstract

Appendix 3

Potentially appropriate RCTs to be included in the meta-analysis n=15

1 Betteridge DJ. International multicentre comparison of cerivastatin with placebo and simvastatin for the treatment of patients with primary hypercholesterolemia. Int J Clin Prac 1999; 53 (4): 243-250

2 Farnier M, Cerivastatin study group. Cerivastatin in the treatment of mixed hyperlipidemia: the RIGHT Study. Am J Cardiol 1998: 82: 47J-51J

3 Hanefeld M, Deslypere JP, Ose L, et al. Efficacy and safety of 0.3mg and 0.4mg cerivastatin once daily in patients with primary hypercholesterolemia: a multicentre, randomized, double-blind, placebo-controlled study. J Int Med Res 1999; 27: 115-120

4 Hunninghake D, Insull W, Knopp R, et al. Comparison of the efficacy of atorvastatin versus cerivastatin in primary hypercholesterolemia. Am J Cardiol 2001; 88: 635-639.

5 Insull W, Isaacsohn J, Kwiterovich P, et al. Efficacy and safety of cerivastatin 0.8mg in patients with hypercholesterolemia: the pivotal placebo-controlled clinical trial. J Int Med Res 2000; 28: 47-68

6 Leiter LA, Hanna K, Canadian Cerivastatin Study Group. Efficacy and safety of cerivastatin in primary hypercholesterolemia: a long-term comparative titration study with simvastatin. Can J Cardiol 1999; 15 (5): 545-555

7 McPherson R, Hanna K, Agro A, et al. cerivastatin versus branded pravastatin in the treatment of primary hypercholesterolemia in primary care practice in Canada> a one year, open label, randomized, comparative study of efficacy, safety, and cost-effectiveness. Clin Therapeutics 2001; 23 (9): 1492-1507.

8 Ose L, Luurila O, Eriksson J, et al. efficacy and safety of cerivastatin 0.2mg and 0.4mg, in patients with primary hypercholesterolemia: a multinational, randomized, double-blind study. Curr Med Res Opin 1999; 15 (3): 228-240

9 Renders L, Mayer-Kander I, Koch C, et al. Efficacy and drug interactions of the new HMG-Co A reductase inhibitors cerivastatin and atorvastatin in CsA-treated renal transplant recipients. Nephrol Dial Transplant 2001; 16: 141-146

10 Ridker PM, Rifai N, Lowenthal MD. Rapid reduction in C-reactive protein with cerivastatin among 785 patients with primary hypercholesterolemia Circulation 2002; 103: 1191-1193.

11 Rubinstein A, Maritz FJ, Soule SG, et al. Efficacy and safety of cerivastatin for type 2 diabetes and hypercholesterolemia. J Cardio Risk 1999; 6: 399-403.

12 Sasaki J, Arakawa K,Yamamoto K, et al. a long term comparative trial of cerivastatin sodium, a new HMG-Co A reductase inhibitor, in patients with primary hypercholesterolemia. Clin Therapeutics 1998; 20 (3): 539-548.

13 Stein E, Sprecher D, Allenby KS, et al. Cerivastatin, a new potent synthetic HMG-Co A reductase inhibitor: effect of 0.2mg daily in subjects with primary hypercholesterolemia. J Cardiovasc Pharmacol Ther 1997; 2 (1): 7-16

14 Stein E, Isacsohn J, Stoltz R, et al. Pharmacodynamics, safety, tolerability, and pharmacokinetics of the 0.8mg dose of cerivastatin in patients with primary hypercholesterolemia. Am J Cardiol 1999; 83: 1433-1436.

15 Tao P, Wu X, Yu X, et al. Efficacy and safety of cerivastatin 0.1mg, 0.2mg and 0.3mg in Chinese patients with primary hypercholesterolemia: a multicentre, randomized, double-blind, placebo-controlled study.

RCTs withdrawn from the meta-analysis due to absence of outcome of interest n=2

1 Renders L, Mayer-Kander I, Koch C, et al. Efficacy and drug interactions of the new HMG-Co A reductase inhibitors cerivastatin and atorvastatin in CsA-treated renal transplant recipients. Nephrol Dial Transplant 2001; 16: 141-146- outcome measured efficacy and drug interactions

2 Ridker PM, Rifai N, Lowenthal MD. Rapid reduction in C-reactive protein with cerivastatin among 785 patients with primary hypercholesterolemia Circulation 2002; 103: 1191-1193- outcome measured reduction in C-Reactive protein.

Appendix 4

RCTs included in the meta-analysis n= 13

1 Betteridge DJ. International multicentre comparison of cerivastatin with placebo and simvastatin for the treatment of patients with primary hypercholesterolemia. Int J Clin Prac 1999; 53 (4): 243-250

2 Farnier M, Cerivastatin study group. Cerivastatin in the treatment of mixed hyperlipidemia: the RIGHT Study. Am J Cardiol 1998: 82: 47J-51J

3 Hanefeld M, Deslypere JP, Ose L, et al. Efficacy and safety of 0.3mg and 0.4mg cerivastatin once daily in patients with primary hypercholesterolemia: a multicentre, randomized, double-blind, placebo-controlled study. J Int Med Res 1999; 27: 115-120

4 Hunninghake D, Insull W, Knopp R, et al. Comparison of the efficacy of atorvastatin versus cerivastatin in primary hypercholesterolemia. Am J Cardiol 2001; 88: 635-639.

5 Insull W, Isaacsohn J, Kwiterovich P, et al. Efficacy and safety of cerivastatin 0.8mg in patients with hypercholesterolemia: the pivotal placebo-controlled clinical trial. J Int Med Res 2000; 28: 47-68

6 Leiter LA, Hanna K, Canadian Cerivastatin Study Group. Efficacy and safety of cerivastatin in primary hypercholesterolemia: a long-term comparative titration study with simvastatin. Can J Cardiol 1999; 15 (5): 545-555

7 McPherson R, Hanna K, Agro A, et al. cerivastatin versus branded pravastatin in the treatment of primary hypercholesterolemia in primary care practice in Canada> a one year, open label, randomized, comparative study of efficacy, safety, and cost-effectiveness. Clin Therapeutics 2001; 23 (9): 1492-1507.

8 Ose L, Luurila O, Eriksson J, et al. efficacy and safety of cerivastatin 0.2mg and 0.4mg, in patients with primary hypercholesterolemia: a multinational, randomized, double-blind study. Curr Med Res Opin 1999; 15 (3): 228-240

9 Rubinstein A, Maritz FJ, Soule SG, et al. Efficacy and safety of cerivastatin for type 2 diabetes and hypercholesterolemia. J Cardio Risk 1999; 6: 399-403.

10 Sasaki J, Arakawa K,Yamamoto K, et al. a long term comparative trial of cerivastatin sodium, a new HMG-Co A reductase inhibitor, in patients with primary hypercholesterolemia. Clin Therapeutics 1998; 20 (3): 539-548.

11 Stein E, Sprecher D, Allenby KS, et al. Cerivastatin, a new potent synthetic HMG-Co A reductase inhibitor: effect of 0.2mg daily in subjects with primary hypercholesterolemia. J Cardiovasc Pharmacol Ther 1997; 2 (1): 7-16

12 Stein E, Isacsohn J, Stoltz R, et al. Pharmacodynamics, safety, tolerability, and pharmacokinetics of the 0.8mg dose of cerivastatin in patients with primary hypercholesterolemia. Am J Cardiol 1999; 83: 1433-1436.

13 Tao P, Wu X, Yu X, et al. Efficacy and safety of cerivastatin 0.1mg, 0.2mg and 0.3mg in Chinese patients with primary hypercholesterolemia: a multicentre, randomized, double-blind, placebo-controlled study . J Clin Res. 2000; 3:29-40.

Appendix 5

Efficacy results of the randomized controlled trials of cerivastatin

Trial	Drugs (mg)		LDL-C reduction (%)	HDL-C increase (%)	TG reduction (%)	TC reduction (%)
Betteridge, 99	Cerivastatin	0.025	-11.5	0.2	-0.2	-8.8
		0.05	-15.5	1.4	-5.7	-11.9
		0.1	-23.6	3.7	-10.4	-17.8
		0.2	-29.1	3.2	-10.9	-21.8
	Simvastatin	20	-38.3	5.2	-12.8	-18.2
	Placebo		-0.3	-1.1	5.7	-0.5
Farnier, 998	Cerivastatin	0.1	-15.1	9.7	-14.8	-14.1
		0.2	-23.0	10.1	-11.7	-18.5
		0.3	-24.2	11.3	-20.3	-19.8
	Gemfibrozil	1,200	-7.5	13.3	-50.3	-12.6
	Placebo		-0.6	4.8	2.1	1.2
Hanefeld, 99	Cerivastatin	0.3	-32.5	5.8	-17.3	-24.3
		0.4	-35.8	4.1	-14.8	-26.8
	Placebo		0.2	-0.3	8.4	0.6
Hunninghake, 2001	Cerivastatin	0.3	-30.3	4.3	-12.5	-22.2
	Atorvastatin	10	-37.7	6.8	-17.5	-27.5
Insull, 2000	Cerivastatin	0.4	-35.6	7.9	-13.7	-25.0
		0.8	-41.8	8.7	-18.4	-29.9
	Placebo		0.2	2.8	-1.9	0.9
Leiter, 99	Cerivastatin	0.05-0.3	-22.5	8.78	-8.79	-15.86
	Simvastatin	5-40	-31.75	10.95	-9.49	-22.49

Trial	Drugs (mg)		LDL-C reduction (%)	HDL-C increase (%)	TG reduction (%)	TC reduction (%)
McPherson, 2001	Cerivastatin	0.1-0.4	-29.8	3.8	-1.7	-20.7
	Pravastatin	10-40	-27.5	2.2	-0.4	-19.2
Ose, 99	Cerivastatin	0.2	-30.32	7.4	-11.5	-20.6
		0.4	-37.9	8.1	-11.1	-25.6
Rubinstein, 99	Cerivastatin	0.1	-20.2	5.7	-3.9	-13.7
		0.3	-33.8	6.2	-12.3	-23.5
	Placebo		0.6	3.1	4.5	1.5
Sasaki, 98	Cerivastatin	0.15	-31.2	3.3	3.9	-21.6
		0.3	-33.6	11.4	-7.3	-24.4
Stein, 97	Cerivastatin	0.1	-25.7	5.3	-11.6	-18.9
		0.2(even)	-29.4	2.3	-11.6	-21.9
		0.2 (bed)	-30.4	3.2	-10.9	-22.1
	Placebo		1.4	-1.2	-3.1	-0.01
Stein, 99	Cerivastatin	0.8	-44.0	3.2	-11.2	-30.8
	Placebo		1.2	-1.2	15.9	1.4
Tao, 2000	Cerivastatin	0.1	-21.0	8.7	-8.8	-15.8
		0.2	-26.5	8.5	-10.8	-18.7
		0.3	-28	7.8	-11.7	-21.7
	Placebo		0.2	3.4	6.6	1.3

Appendix 6: Number of withdrawals and deaths recorded in the randomized controlled trials of cerivastatin

Trial	Drugs (mg)	n(%)Withdrawals	Reason for withdrawals	nDeaths
Betteridge, 99	Cerivastatin 0.025-0.2 Simvastatin 20 Placebo	51(6.6%) 13 (8.6%) -	Adverse events	5
Farnier, 98	Cerivastatin 0.1-0.3 Gemfibrozil 1,200 Placebo	- - -	-	- - -
Hanefeld, 99	Cerivastatin 0.3 0.4 Placebo	- 1 -	Deterioration of established concomitant arthritis of the left lower limb	1 - -
Hunninghake, 2001	Cerivastatin 0.3 Atorvastatin 10	- -	-	- -
Insull, 2000	Cerivastatin 0.4 0.8 Placebo	6 30 3	CPK elevation-, AST and ALT elevation-, myalgia-, leg cramps (0.4mg), elevated CPK, Elevated ASTand ALT, myalgia, leg cramps, skin disorders, dizziness etc (0.8mg), and duodenal ulcer, dyspepsia, back pain, and arthralgia (placebo).	- - -
Leiter, 99	Cerivastatin 0.05-0.3 Simvastatin 5-40	14 10	Adverse events. 9.1% of withdrawals in cerivastatin group attributed to study treatment, 52% in simvastatin group attributed to treatment.	- -
Sasaki, 97	Cerivastatin 0.15 0.3	- -	-	- -
Stein, 97	Cerivastatin 0.1 bd 0.2 even 0.2 bed	1 1 -	Arm pain-0.1mg, skin rash and itching-0.2mg evening.	- - -
Stein, 99	Cerivastatin 0.8 Placebo	- -	-	- -
Tao, 2000	Cerivastatin 0.1 0.2 0.3 Placebo	2 1 3 -	Facial oedema, accidental injury-0.1mg, abdominal pain-0.2mg, abnormal liver tests, arthralgia and surgery-0.3mg.	- - - -

Appendix 7: Regulatory Authority- Food and Drug Administration (FDA) reports

The food and drug administration carried out statistical reviews on cerivastatin prior to approval of the drug for marketing and also post market reviews. The reviews and reports are outlined here in the order in which they were done starting from the first application by Bayer for marketing of their drug, Baycol (cerivastatin sodium), to its withdrawal from the markets in August 2001.

June 1996

Bayer Corporation Pharmaceutical Division presented the results of 10 completed controlled clinical trials so as to establish the efficacy of cerivastatin for the treatment of hypercholesterolemia in the proposed dose range of 0.05- 0.3mg. Based on this application, FDA carried out a statistical review and evaluation of the clinical studies presented.

The review was divided into three main sections; section I, review of the pilot studies (studies 109 and 110), section II, the review of the pivotal studies (studies 120, 124 and 132) and section III, review of other studies (studies 111, 123, 126, 139 and 149).

The studies in section I were dose-response studies conducted early in the phase III program, both multicenter, with 6 parallel treatment arms. 207 patients (study 109), and 196 patients (study 110), were randomized to treatment. There were 6 dropouts in each

of the studies, in study 109, 4 were due to adverse events, and in study 110, 3 were due to an adverse event. (Table 3.10)

Table 1: Patient disposition for studies 109 and 110

	Placebo	**0.025mg**	**0.05mg**	**0.1mg**	**0.2mg**	**Active control**
Study 109(D9-012)						
No. randomized	35	35	34	37	33	33
No. dropouts	1	2	0	0	1	2
ITT	34	35	34	37	33	32
Study 110						
No. randomized	34	32	35	31	33	31
No. dropouts	3	1	1	1	0	0
ITT	34	32	35	31	33	31

Table 2: Patients that withdrew from therapy due to adverse events.

Study	**Length (wks)**	**Myalgia n (mg)**	**Abd pain n (mg)**	**↑CPK n (mg)**	**↑SGPT n (mg)**	**Insomnia n (mg)**
109 (D91-012)	4	1(0.025)	-	1(0.025)	2(0.2)	-
110	4	-	1(Placebo)	-	1(0.05)	1(placebo)

Abd- abdominal

The studies in section II were defined as phase 3 pivotal trials. The primary objective of the trials was to show that each dose of cerivastatin significantly reduced LDL-C compared to placebo. In study 120, about 5-8% of patients dropped out, in study 124 and 132 the rate was slightly higher, 10-15%, and the primary reason for this was adverse drug events. In the three trials, a total of 6 cerivastatin-treated patients withdrew due to abnormal liver function test results.

Table 3: Summary of designs for the studies in section II

Study	Treatment/dose	Treatment periods	Entry criteria	Primary endpoint
120	CER 0.025 0.05 0.1 0.2 SIM 40 PLA	4 wks diet 6wks SB pla+diet 12wks DB 88wks extension	LDL-C>160mg/dl or LDL-C >130mg/dl with CHD or>2RF's, TG<350mg/dl, Age 21-75	% reduction in LDL-C at week12 (valid case analysis)
124 (D91-031)	CER 0.05 0.1 0.2 0.3 LOVA 40 PLA	4wks diet, 6wks SB pla+diet, 24wks DB, 72wks extension.	LDL-C>160mg/dl, TG<350mg/dl, FR<15, Age 18-75	% reduction in LDL-C at endpoint (valid visits only).
132	CER 0.1 0.2 0.3 GEM 1200 PLA	4wks diet, 6wks SB pla+diet, 16wks DB, 88wks extension.	LDL-C>155 and <190mg/dl, TG <500mg/dl, Age 18-80.	% reduction in LDL-C at end point (valid visits only)

DB- double blind
SB- single blind
RF- risk factor
FR- food rating score

The third section of the review had 5 trials (Table 3.12). Total number of withdrawals was 28 (Table 3.13). There were no recorded withdrawals from trials 123 and 239.

Table 4: Summaries of studies in section III

Study	Treatment/dose	No of pts	Treatment period	Entry criteria	Withdrawals due to adverse events
111 (D91-016)	CE R 0.1 bd 0.2even. 0.2 bed PLA	92 92 89 46	4 wks diet 6wks SB diet+placebo 4wks DB	FR<15,LDLC>160mg/dl and <250mg/dl, TG <350mg/dl	2pts arm pain (0.1mg), rash (0.2mg bed)
123 (D92-010)	CER 0.3 PLA	23 12	No run in period, no AHAP diet, 4wks DB	_____	_____
126	CER 0.05-0.3 SIM 5-40	260 127	4wks diet, 6wks SB diet+placebo, 32 wks DB	LDL-C>160mg/dl, TG<350mg/dl, FR<15	10 (Sim) 14 (Cer)
139	CER 0.2 0.3 PLA	18 18 18	4wks diet, 6wks SB diet+placebo, 6wks DB	Genotyped heterozygous familial hypercholesterolemia, LDL-C>194mg/dl, TC>292mg/dl, TG<350mg/dl, close relation or pt has xanthomatosis.	_____
149	CER 0.3 0.4 PLA	140 138 71	4wks diet, 6wks SB diet +placebo, 8 wks DB	LDL-C >190mg/dl, LDL-C>160mg/dl+1or more RF (family history of CHD, obese, smoker), TG <350mg/dl.	2(1 in 0.3mg dose, 1 in 0.4 mg dose)

SB- single blind
TC- total cholesterol
TG- triglyceride
RF- risk factor

June 1997

FDA approved cerivastatin for marketing following reviews of the trials presented by Bayer.

May 1999

Approval of new supplemental dose (0.4mg) of cerivastatin by FDA. No statistical review was carried out.

December 1999

Bayer Corporation changed the baycol prescribing information to include a contraindication with gemfibrozil. "The combined use of cerivastatin and gemfibrozil is contraindicated due to a risk for rhabdomyolysis and concurrent use should not occur under any circumstances."

July 2000

The FDA carried out a second statistical review when an application was submitted for approval of a higher dose (0.8mg) of cerivastatin for marketing. Here the sponsor submitted a 52 week randomized trial (D97-008) in support of the higher dose. Cerivastatin 0.8mg was compared to 0.4mg and placebo/pravastatin 40mg. The primary objective of the trial was to compare the safety and efficacy of cerivastatin 0.8mg and placebo after 8 weeks of treatment. The reviewer conducted statistical analyses of 3 laboratory parameters: AST, ALT, and CPK. Throughout the double-blind period, 24 weeks, percentage of patients with AST, and ALT values greater than the upper limit of normal (ULN) increased over time in the 0.8mg dose but not in the 0.4mg dose. Tables 3.13 and 3.14 show the number of patients that had increases of AST, ALT, and CPK levels 5, and 10 times the ULN.

Table 5: No of patients with AST and ALT elevations >3xULN at anytime on treatment.

Week	Placebo (n=198)	0.4mg (n=194)	0.8mg (n=774)
AST			
8	0	2	10
24	1	2	12
52	2	2	14
ALT			
8	0	1	8
24	1	2	11
52	1	2	13

Table 6: No of patients with CPK elevations >5x ULN and >10x ULN at anytime on treatment.

Week	Placebo/pravastatin (n=198)	0.4mg (n=193)	0.8mg (n=770)
8			
>5xULN	2	6	20
>10xULN	0	2	10
24			
>5xULN	2	7	25
>10xULN	0	3	13
52			
>5xULN	5	8	35
>10xULN	1	3	15

May 2000

In response to a consult request from Mary Parks, M.D, Medical Officer in the Division of Endocrine and Metabolic Drug Products, the FDA issued a memorandum. The M.D was concerned because of the desire of some pharmaceutical companies to seek nonprescription status for their HMG-CoA reductase inhibitors despite their association with liver failure, and had requested a meeting with the Agency to discuss the possibility of nonprescription designation for their statins, despite reservations from the Agency about the marketing of cholesterol-lowering agents in the OTC setting.

For the memorandum, cases were defined as "liver failure" if the reporter stated a diagnosis of liver failure or if the patient underwent a liver transplantation.

The Adverse Event Reporting System (AERS) database was searched to determine the number of potential cases of statin-induced liver failure. A total of 90 cases were found in the database, and of the 90, only 62 of them were in accordance with the case definition of liver failure associated with the use of statins. Among the 62 cases, 38 (61%) resulted in death, 6 patients received liver transplant and 5 out of the 6 survived. Table 3.15 shows the different statins and the number of cases identified with each.

Table 7: Liver failure cases associated with each statin

Drug	n Liver failure	n Fatal	n Nonfatal
Atorvastatin	13	8	5
Cerivastatin	3	1	2
Fluvastatin	3	2	1
Lovastatin	18	9	9
Pravastatin	13	8	5
Simvastatin	12	10	2
Total no of cases	62		

May 2001

Bayer submitted an application for changes to be made/effected to the warnings, dosage and administration, and patient information about baycol sections of the package insert. The changes included warnings that starting therapy above 0.4mg dose increased the risk of myopathy and rhabdomyolysis, and that the starting dose of baycol was 0.4mg once daily in the evening regardless of previous lipid therapy.

August 2001

Bayer Corporation discontinued the marketing and distribution of all dosage strengths of baycol.

REFERENCES

Alexandridis G, Pappas G, Elisaf MS. Rhabdomyolysis due to combination therapy with cerivastatin and gemfibrozil. Am J Med. 2000; 109:261

Bakri R, Wang J, Wierzbicki AS, Goldsmith D. Cerivastatin monotherapy-induced muscle weakness, rhabdomyolysis and acute renal failure. Int J Cardiol. 2002; 1: 1-3.

Bates DW, Spell N, Cullen DJ, et al. The costs of adverse drug events in hospitalized patients. JAMA 1997; 277: 307-311.

Beetham R. Biochemical investigation of suspected rhabdomyolysis. Ann Clin Biochem. 2000; 37: 581-587

Betteridge DJ, for International Cerivastatin Study Group, University College, London Medical School, London. International multicentre comparison of cerivastatin with placebo and simvastatin for the treatment of patients with primary hypercholesterolemia. Int J Clin Pract. 1999; 54(4): 243-250.

Bischoff H, Angerbauer R, Bender J, Bischoff E et al. Cerivastatin: pharmacology of a novel synthetic and highly active HMG-Co A reductase inhibitor. Atherosclerosis 1997; 135: 119-130

Bjerre LM, LeLorier J. Do statins cause cancer? A meta-analysis of large randomized clinical trials. Am J Med. 2001; 110:716-723.

Blauw GJ, Lagaay MA, Smelt AHM et al. Stroke, statins, and cholesterol: a meta-analysis of randomized, placebo-controlled, double blind trials with HMG-CoA reductase inhibitors. Stroke 1997; 28: 946-950.

Bliznakov EG. Lipid-lowering drugs (statins), cholesterol, and coenzyme Q10. The Baycol case- a modern Pandora's box. Biomed Pharmacother 2002; 56: 56-59

Brown G, Albers JJ, Fisher LD, et al. Regression of coronary artery disease as a result of intensive lipid-lowering therapy on men with high levels of apolipoprotein B. N Eng J Med. 1990; 232:1289-1298.

Bruno-Joyce J, Dugas JM, MacCausland OE. Cerivastatin and gemfibrozil-associated rhabdomyolysis. Ann Pharmacotherapy. 2001; 35:1016-1019.

Bucher HC, Griffith LE, Guyatt GH. Systematic review on the risk and benefit of different cholesterol-lowering interventions. Arterioscler Thromb Vasc Biol. 1999; 19: 187-195.

Carlson LA, Gotto AM, Illinworth DR. Current hyperlipidemia. Science press limited, Second edition, 2001.

Castelli WP, Anderson K, Wilson PW, Levy D. Lipids and risk of coronary heart disease. The Framingham Study. Ann Epidemiology 1992; 2 (1-2): 23-8

Chaiyakunapruk N, Boudreau D, Ramsey SD. Pharmaco-economic impact of HMG-Co A reductase inhibitors in type 2 diabetes. J Cardiovasc Risk. 2000; 8:127-132.

Christians U, Wolfgang J, Floren LC. Metabolism and drug interactions of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors in transplant patients: are the statins mechanistically similar? Pharmacol Ther 1998; 80: 1-34.

Chung KC, Pomerantz K, Harrison B. Cost of cerivastatin in cost-effectiveness study. Am J Health Syst Pharm. 2000; 57:1712

Clare M, Sacks F, Rosner B. Does fish oil lower blood pressure? Circulation 1993; 88: 523-533

Cobos A, Jovell AJ, Garcia-Altes A, et al. Which statin is most efficient for the treatment of hypercholesterolemia? A cost-effectiveness analysis. Clin Therapeutics. 1999; 21(11): 1924-1936.

Cochran WG. The combination of estimates from different experiments. Biometrics 1954; 10: 101-129.

Committee of Principal Investigators (WHO). A co-operative trial in the primary prevention of ischaemic heart disease using clofibrate. B Heart J 1978; 40: 1069-1118.

Connelly PW, Maclean DR, Horlick L, O'Connor B, Petrasovits A, Little JA. Plasma lipids and lipoproteins and the prevalence of risk factors for Coronary heart disease in Canadian adults. Canadian Heart Health surveys Grp. Canadian Med Association J 1992; 146 (11): 1977-1987.

Coronary heart disease. Coronary heart disease, an epidemiological overview. Dept of Health, London. The Stationary Office. 1994

Corsini A, Bellosta S, Baetta R et al. New insights into the pharmacodynamic and pharmacokinetic properties of statins. Pharmacol Ther 1999; 84: 413-428.

Crouse III JR, Byington RP, Furberg CD. HMG-Co A reductase inhibitor therapy and stroke risk reduction: an analysis of clinical trials data. Atherosclerosis. 1998; 138:11-24.

Crouse III JR, Byington RP, Hoen HM, et al. Reductase inhibitor monotherapy and stroke prevention. Arch. Int Med. 1997; 157:1305-1310.

Davidson M H. Combination therapy for dyslipidemia: safety and regulatory considerations. Am J Cardiol 2002; 90 (suppl): 50K-60K

Davidson M.H. Strategies to improve adult treatment panel III guideline adherence and patient compliance. Am J Cardiol. 2002; 89(suppl): 8C-22C.

Davies HUW, Crombie IK. What is meta-analysis? Available at http://www.evidence-based-medicine.co.uk

Davignon J, Hanefeld M, Nakaya N, et al. Clinical efficacy and safety of cerivastatin: summary of pivotal phase IIb/III studies. Am J Cardiol. 1998; 82:32J-39J.

Dayer-Berenson, L. Rhabdomyolysis: a comprehensive guide. ANNA J. 1994; 21:15-18.

DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled Clinical Trials 1986; 7: 177-188.

Dhawan R, Jyothinagaram MG, Schwartz AB. Pathogenesis and management of rhabdomyolysis. Medical Monograph Series, Continuing Medical Education. 1997; 7(2).

Di Mascio R, Marchioli R, Tognoni G. Cholesterol reduction and stroke occurrence: an overview of randomized clinical trials. Cerebrovasc Disease. 2000; 10(2): 84-92.

Dodson PM, Barnet AH. Lipids in primary care. The Medical Publishing Group. 1999. First Edition.

Drummond MF, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes. Oxford University Press. Second Edition, 1997

Dujovne CA. Side effects of statins: Hepatitis versus "Transaminitis"- Myositis versus "CPKitis". Am J Cardiol 2002; 89:1411-1413.

Economic evaluations available at
http://www.who.int/substance_abuse/PDFfiles/economicevaluation.pdf.

Ebrahim S, Davey Smith G, McCabe C, Payne N, Pickin M, Sheldon TA, et al. What role for statins? A review and economic model. Health Tech Assess1999; 3 (19).

Eilxhauser A. Health care cost-benefit analysis and cost-effectiveness analysis from1979-1990: a bibliography. Med Care 1993; 31: JS1-JS10

Elixhauser A, Halpem M, Schmier J et al. Health care cost-benefit analysis and cost-effectiveness analysis from 1991-1996: am update. Med Care 1998; 36: MS1-MS145.

Elliott WJ, Weir DR. Comparative cost-effectiveness of HMG-Co A reductase inhibitors in secondary prevention of acute myocardial infarction. Am J Health-Syst Pharm. 1999; 56:1726-1732.

Evans B, Primatesta P (eds) 1999: Health Survey for England 1998. London. The Stationary Office

Expert panel on detection, evaluation, and treatment of high blood cholesterol in adults. Executive summary of the third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adults Treatment Panel). JAMA. 2001; 285:2486-2497.

Farmer JA. Economic implications of lipid-lowering trials: current considerations in selecting a statin. Am J Cardiol. 1998; 82:26M-31M.

Farnier M, The Cerivastatin Study Group. Cerivastatin in the treatment of mixed hyperlipidemia: the RIGHT Study. Am J Cardiol. 1998; 82:47J-51J.

Feher MD, Richmond W. Lipids and lipid disorders. Mosby International Limited. 1997 Second Edition.

Freund D, Dittus R. Principles of pharmacoeconomic evaluation of drug therapy. Pharmacoeconomics 1992; 1(1): 20-32.

Frick MH, Helsinki Heart Study. Primary prevention trial with gemfibrozil in middle aged men with dyslipidemia. N Eng J Med 1987; 317: 1237-1245

Ganz DA, Kuntz KA, Jacobson GA, et al. Cost-effectiveness of 3-methyl-3-hydroxyglutaryl coenzyme A reductase inhibitor therapy in older patients with myocardial infarction. Ann Intern Med. 2000; 132:780-787.

Garnett WR. Interactions with hydroxymethylglutaryl coenzyme A reductase inhibitors. Am J Health Syst Pharm 1995; 52: 1639-1645

Geddes JR, Game D, Jenkins NE, et al. What proportion of primary psychiatric interventions are based on randomized evidence? Qual Health Care 1996; 5 (4): 215-217

Gemici G, Toprak A, Oktay A. Rhabdomyolysis due to cerivastatin monotherapy. Am J Med. 2001; 110(9): 742.

Goldman L, Weinstein MC, Goldman PA, et al. Cost-effectiveness of HMG-Co A reductase inhibition for primary and secondary prevention of coronary heart disease. JAMA. 1991; 265(9): 1145-1151.

Gould LA, Rossouw MD, Santanello NC, et al. Cholesterol reduction yields clinical benefit: a new look at old data. Circulation. 1995; 91(8): 2274-2282.

Grover SA, Coupal L, Paquet S, et al. Cost-effectiveness of hydroxy-3-methylglutaryl coenzyme A reductase inhibitors in the secondary prevention of cardiovascular disease. Arch Int Med. 1999; 159:593-600.

Hamilton-Craig I. Statin-fibrate combination therapy. Aus Prescriber. 2001; 24(5): 109.

Hamilton VH, Racicot F, Zowall H, et al. The cost-effectiveness of HMG-Co A reductase inhibitors to prevent coronary heart disease: estimating the benefits of increasing HDL-C. JAMA. 1995; 273:1032-1038.

Hanefeld M, Deslypere JP, Ose L, et al. Efficacy and safety of 0.3mg and 0.4mg cerivastatin once daily in patients with hypercholesterolemia: a multicentre, randomized, double-blind, placebo-controlled study. J Int Med Research. 1999; 27:115-129.

Hargreaves IP, Heales S. Statins and myopathy. Lancet. 2002; 359:711-712.

Hay JW, Yu WM, Ashraf T. Pharmacoeconomics of lipid-lowering agents for primary and secondary prevention of coronary artery disease. Pharmacoeconomics. 1999; 15(1): 47-74.

Hayem G. Statins and muscle: what price glory? Joint Bone Spine. 2002; 69:249-251.

Heart and Stroke Foundation of Canada. Heart disease and stroke in Canada, Ottawa, ON. Heart and Stroke Foundation of Canada, 1995

Hebert PR, Gaziano MJ, Chan KS, et al. Cholesterol lowering with statin drugs, risk of stroke, and total mortality: an overview of randomized trials. JAMA. 1997; 278(4): 313-321.

Hedges LV. Distribution theory for glass's estimator of effect size and related estimators. J Edu Stat 1981; 6: 107-128

Hilleman DE, Phillips JO, Mohiuddin MD, et al. A population-based treat-to-target pharmacoeconomic analysis of hmg-coa reductase inhibitors in hypercholesterolemia. Clin Thera. 1999; 21(3): 536-562.

Hodel C. Myopathy and rhabdomyolysis with lipid-lowering drugs. Toxicology Letters. 2002; 128:159-168.

Holme I. An analysis of randomized trials evaluating the effect of cholesterol reduction on total mortality and coronary heart disease incidence. Circulation. 1990; 82:1916-1924.

Hsu I, Spinler, SA, Johnson NE. Comparative evaluation of the safety and efficacy of HMG-Co A reductase inhibitor monotherapy in the treatment of primary hypercholesterolemia. Ann Pharmacotherapy. 1995; 29:743-759.

Hunninghake D, Insull W, Knopp R, et al. Comparison of the efficacy of atorvastatin versus cerivastatin in primary hypercholesterolemia. Am J Cardiol. 2001; 88:635-639.

Huse DM, Russell MW, Miller JD, et al. Cost-effectiveness of statins. Am J Cardiol. 1998; 82:1357-1363.

Insull W, Issachsohn J, Kwiterovich P, et al. Efficacy and safety of cerivastatin 0.8mg in patients with hypercholesterolemia: the pivotal placebo-controlled clinical trial. J Int Med Res. 2000; 28:47-68.

Jacobson TA. Cost-effectiveness of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor therapy in the managed care era. Am J Cardiol. 1996; 78(suppl6A): 32-41.

Jacobson TA. "The lower the better" in Hypercholesterolemia Therapy: A reliable clinical guidance? Ann Int Med 2000; 133: 549-554.

Jacobson TA, Schein JR, Williamson A, et al. Maximizing the cost-effectiveness of lipid-lowering therapy. Arch Intern Med. 1998; 158:1977-1989.

Jefferson T, Demicheli V, Vale L. Quality of systematic reviews of economic evaluations in health care. JAMA 2002; 287 (21): 2809-2818

Johannsson M, Jonsson B, Kjekshus J, et al. Cost effectiveness of simvastatin treatment to lower cholesterol levels in patients with coronary heart disease. N Eng J Med 1997; 336: 322-336.

John S, Jacobi J, Delles C, et al. Rapid improvement of endothelial function after lipid-lowering therapy with cerivastatin within two weeks (abstract) Am J Coll Cardiol 2000; 35 (Suppl A): 256A

Johnson JA, Bootman JL. Drug related morbidity and mortality: a cost of illness model. Arch Int Med 1995; 155: 1949-1956.

Jolain B, Pettitt D. Letters to the editor. Clin Thera. 1995; 17(3): 572-580.

Jones PH. Hyperlipoproteinemias. In: Rakel RE, ed. Conn's current therapy 2000. Philadelphia: WB Saunders, 2000:578-584.

Kessler DA. Introducing MedWatch: a new approach to reporting medication and device adverse effects and product problems. JAMA 1993; 269: 2765-2768

Kong SX, Crawford SY, Gandhi SK, et al. Efficacy of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors in the treatment of patients with hypercholesterolemia: a meta-analysis of clinical trials. Clin Thera. 1997; 19(4): 778-797.

Langford NJ, Kendall, MJ. Rhabdomyolysis with HMG-CoA reductase inhibitors: a class effect? J Clin Pharm. Thera. 2001; 26(6): 391-395.

Larbi EB. Drug-induced rhabdomyolysis. Ann Saudi Med. 1998,18(6): 525-530.

LaRosa JC, He J, Vupputuri S. Effects of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. JAMA. 1999; 282(24): 2340-2346.

Lee JA, Maddix DS. Rhabdomyolysis secondary to a drug interaction between simvastatin and clarithromycin. Ann Pharmacotherapy. 2001; 35:26-31.

Leiter LA, Hanna K, et al. Efficacy and safety of cerivastatin in primary hypercholesterolemia: a long-term comparative titration study with simvastatin. Can J Cardiol. 1999; 15(5): 545-555.

Lipid Research Clinics Program. The lipid research clinical coronary primary prevention trial results I: Reduction in incidence of coronary heart disease. JAMA 1984; 251: 351-364.

Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J National Cancer Institute 1959; 22: 719-748.

Marinella MA. Rhabdomyolysis and anuric myoglobinuric renal failure associated with cerivastatin and gemfibrozil. Hospital Physician July, 2002:38-42.

Martens LL, Guibert R. Cost-effectiveness analysis of lipid-modifying therapy in Canada: comparison of HMG-CoA reductase inhibitors in the primary prevention of coronary heart disease. Clin Thera. 1994; 16(6): 1052-1062.

Massy ZA, Ma JZ, Louis TA, et al. Lipid-lowering therapy in patients with renal disease. Kidney Int. 1995; 48(1): 188-198.

Mazzu A, Lettieri J, Hogan C, et al. A multiple dose study of the safety and pharmacokinetics of cerivastatin in young and elderly male volunteers (abstract). Atherosclerosis 1997; 130 Suppl: S29

McClellan KJ, Wiseman LR, McTavish D. Cerivastatin. Drugs. 1998; 55(3): 415-420.

McPherson K, Britton A, Causer L. Coronary heart disease: estimating the impact of changes in risk factors.2002. National Health Forum. The Stationary office

McPherson R, Hanna K, Agro A, et al. Cerivastatin versus branded pravastatin in the treatment of primary hypercholesterolemia in primary care in Canada: a one year, open-label, randomized, comparative study of efficacy, safety, and cost-effectiveness. Clin Thera. 2001; 23(9): 1492-1506.

Memorandum on Safety review available at http://www.fda.gov/ohrms/dockets/ac/00/backgrd/3622b1_pm_safety_review.pdf

Moher D, Cook DJ, Eastwood S, et al. Improving the quality of reports of meta-analysis of randomized controlled trials: the QUORUM statement. Lancet. 1999; 354: 1896-1900.

Morris S. A comparison of economic modeling and clinical trials in the economic evaluation of cholesterol-modifying pharmacotherapy. Health Econs. 1997; 6:589-601.

Morris S, Godbar E. Choice of cost-effectiveness measure in the economic evaluation of cholesterol-modifying pharmacotherapy. Pharmacoeconomics. 1999; 16 (2): 193-205

Muck W, Unger S, Kawano K, et al. Inter-ethnic comparisons of the pharmacokinetics of the HMG-Co A reductase inhibitor cerivastatin. Br J Clin Pharmacol 1998; 45: 583-590

Muldoon MF, Manuck SB, Mendelsohn AB, et al. Cholesterol reduction and non-illness mortality: meta-analysis of randomized clinical trials. BMJ. 2001; 322:11-15.

Multiple risk factor intervention trial research group. Multiple risk factor intervention trial: Risk factor changes and mortality results. JAMA 1982: 248 (12): 1465-1477

National Cholesterol Education Programme (NCEP). Second report of the NCEP expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult treatment panel II. Circulation 1994; 89: 1329-1445

Omar MA, Wilson JP. FDA adverse event reports on statin-associated rhabdomyolysis. Ann Pharmacotherapy. 2002; 36:288-295.

Omar MA, Wilson JP, Cox TS. Rhabdomyolysis and HMG-CoA reductase inhibitors. Ann Pharmacotherapy. 2001; 35:1096-1107.

Ose L, Luurila O, Eriksson J et al. Efficacy and safety of cerivastatin 0.2mg and 0.4mg, in patients with primary hypercholesterolemia: a multinational, randomized, double-blind study. Curr Med Res Opin. 1999; 15(3): 228-240.

Paoletti R, Corsini A, Bellosta S. Pharmacological interactions of statins. Atherosclerosis suppl. 2002; 3 (1): 35-40

Pekannen J et al. Ten-year mortality from cardiovascular disease in relation cholesterol level among men with and without pre-existing cardiovascular disease. N Eng J Med 1990; 322: 1700-1707

Perras C, Baladi J. HMG-CoA reductase inhibitors. A review of published clinical trials and pharmacoeconomic evaluations. CCOHTA. 1997; 5:E

Perreault S, Levinton C, Le Lorier J. Efficacy and cost of hmg-co a reductase inhibitors in the treatment of patients with primary hyperlipidemia. Can J Clin Pharm. 2000; 7(3): 144-154.

Pharoah PDP, Hollingworth W. Cost effectiveness of lowering cholesterol concentration with statins in patients with and without pre-existing coronary heart disease: life table method applied to health authority population. BMJ. 1996; 312:1443-1448.

Phillips C, Thompson G. What is cost-effectiveness? Available at http://www.evidence-based-medicine.co.uk

Pickin DM, McCabe CJ, Ramsay LE, et al. Cost effectiveness of HMG-Co A reductase inhibitor (statin) treatment related to the risk of coronary heart disease and cost of drug treatment. Heart. 1999; 82:325-332.

Pignone M, Phillips C, Murlow C. Use of lipid lowering drugs for primary prevention of coronary heart disease: meta-analysis of randomized trials. BMJ. 2000; 321:983-986.

Plosker GL, Dunn CJ, Figgitt DP. Cerivastatin. A review of its pharmacological properties and therapeutic efficacy in the management of hypercholesterolemia. Drugs. 2000; 60(5): 1179-1206.

Poels PJ, Gabreels FJ. Rhabdomyolysis: a review of the literature. Clin Neurol Neurosurg. 1993; 95:175-192.

Pogson GW, Kindred LH, Carper BG. Rhabdomyolysis and renal failure associated with cerivastatin-gemfibrozil combination therapy. Am J Cardiol. 1999; 83(7): 1146.

Ravnan SL, Locke C, Yee WP, Haase K. Cerivastatin-induced rhabdomyolysis: 11 case reports. Pharmacotherapy 2002; 22(4): 533-537.

Rayner M, Mockford C, Boaz A. Coronary heart disease statistics. 1998 edition, London. British Heart Foundation 1998.

Reckless JPD. Cost-effectiveness of statins. Curr Opin Lipidology. 2000; 11:351-356.

Rodriguez ML, Mora C, Navarro JF. Cerivastatin-induced rhabdomyolysis. Ann Intern Med. 2000; 132(7): 598.

Ross SD, Allen IE, Connelly JE, et al. Clinical outcomes in statin treatment trials: a meta-analysis. Arch Int Med. 1999; 159:1793-1802.

Rossouw JE. Lipid-lowering interventions in angiographic trials. Am J Cardiol. 1995; 76:86C-92C.

Rubinstein A, Maritz FJ, Soule SG, et al. Efficacy and safety of cerivastatin for type 2 diabetes and hypercholesterolemia. J Cardiovasc Risk. 1999; 6:399-403.

Russell MW, Huse DM, Miller JD, et al. Cost effectiveness of HMG-Co A reductase inhibition in Canada. Can J Clin Pharmacol. 2001;8(1): 9-16.

Sackett DL, Rosenberg WMC, Muir Gray JA, et al. Evidence-based medicine: What it is and what it isn't. BMJ. 1996; 312:71-72.

Sacks FM, Pfeffer MA, Moye LA et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial Investigators Eng J Med1996; 335: 1001-1009

Sasaki J, Arakawa K, Yamamoto K, et al. A long-term trial of cerivastatin sodium, a new HMG-CoA reductase inhibitor, in patients with primary hypercholesterolemia. Clin Therapeutics. 1997; 20(3): 539-548.

Savoie I, Wright JM, Bassett K. Lipid lowering therapy. BCOHTA 1998; 98:4J

Scandinavian Simvastatin survival study group. Randomizes trial of cholesterol lowering in 4,444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet. 1994; 344:1383-1389.

Shepherd J. Economics of lipid lowering in primary prevention: lessons from the west of Scotland Coronary Prevention Study. Am J Cardiol. 2001; 87(suppl): 19B-22B.

Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. N Eng J Med. 1995; 333:1301-1307.

Shetty HGM, Rooutledge PA, Davies DM. Disorders of muscle, bone, and connective tissues. In: Davies DM, Ferner RE, De Glanville H, eds. Davies textbook of adverse drug reactions. London: Chapman and Hall, 1998: 541-543.

Spearman ME, Summers K, Moore V, et al. Cost-effectiveness of initial therapy with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors to treat hypercholesterolemia in a primary care setting of a managed-care organization. Clin Therapeutics. 1997; 19(3): 582-602.

Staffa JA, Chang J, Green L, et al. Cerivastatin and reports of fatal rhabdomyolysis. N Eng J Med. 2002; 346(7): 539-540.

Statistical review Application number 020740: Centre for drug evaluation and research available at
http://www.fda.gov/cder/foi/nda/97/020740ap_baycol_statrP1.pdf

Statistical review, application number:020740/S002. Centre for drug evaluation and research available at
http://www.fda.gov/cder/foi/nda/99/20-740S002_Baycol_statr.pdf

Statistical review, application number 20-740/S008/S013 available at
http://www.fda.gov/cder/foi/nda/2000/20-740S008_Baycol_statr.pdf

Stein E. Cerivastatin in primary hypercholesterolemia- a multicenter analysis of efficacy and safety. Atherosclerosis. 1998; 139(suppl): S15-S22.

Stein E, Isaacsohn J, Stoltz R, et al. Pharmacodynamics, safety, tolerability, and pharmacokinetics of the 0.8mg dose of cerivastatin in patients with primary hypercholesterolemia. Am J Cardiol. 1999; 83:1433-1436.

Stein E, Sprecher D, Allenby KS, et al. Cerivastatin, a new, potent, synthetic HMG-Co A reductase inhibitor: effect of 0.2mg daily dose in subjects with primary hypercholesterolemia. J Cardiovasc Pharmacol Ther. 1997; 2(1): 7-16.

Steiner A, Weisser B, Vetter WA. Comparative review of the adverse effects of treatments for hyperlipidemia. Drug Safety. 1991; 6:118-130.

Szucs TD. Pharmaco-economic aspects of lipid-lowering therapy: is it worth the price? European Heart Journal. 1998; 19(M): M22-M28.

Talbert RL. Hyperlipidemia. Pharmacotherapy: A pathophysiological approach. Appleton and Lange, 3rd edition 1997.

Tao P, Wu XS, Yu XJ, et al. Efficacy and safety of cerivastatin 0.1mg, 0.2mg, and 0.3mg in Chinese patients with primary hypercholesterolemia: a multicentre, randomized, double-blind, placebo-controlled study. J Clin Res. 2000; 3:29-40.

The Expert Panel. Report of the National Cholesterol Education Program expert panel on detection, evaluation, and treatment of high blood cholesterol in adults. Arch Int Med 1988; 148: 36-69

Thompson PD, Clarkson P, Karas RH. Statin-associated Myopathy. JAMA 2003; 289 (13): 1681-1690.

Tomlinson B, Lan IW. Combination therapy with cerivastatin and gemfibrozil causing rhabdomyolysis: is the interaction predictable? Am J Med. 2001; 110(8): 669.

Tuffs A. Bayer faces shake up after Lipobay withdrawn: news extra. BMJ. 2001; 323:828.

Velasco JA. After 4S, CARE, and LIPID--- is evidence-based medicine being practiced? Atherosclerosis. 1999; 147(suppl 1): S39-S44.

Warshaesky S, Packard D, Marks SJ, et al. Efficacy of 3-hydroxy-3-methylglytaryl coenzyme A reductase inhibitors for prevention of stroke. J Gen Int Med 1999; 14(12): 763-774.

Weaver SJ, Doering PL. Cerivastatin and the dissemination of adverse event information. Ann Pharmacotherapy. 2002; 36:1099-1103.

Weber W. Drug firm withdraws statin from the market. Lancet 2001; 358: 568

Weise WJ. Fatal rhabdomyolysis associated with simvastatin in a renal transplant patient. Am J Med. 200; 108:351.

Wiesbauer F, Kaun C, Bodlaj G, et al. HMG-Co A reductase inhibitors affect the fibrinolytic system of human vascular smooth muscle cells in vitro (abstract) J Am Coll Cardiol 2000; 35 (Suppl A): 311A

Yamamichi N, Koba Y, Kasai T. Rhabdomyolysis due to antihyperlipidemic drugs: a case report and indicative risk factors. Eur Heart J Int Med. 2001; 12:384-385.

Yan L, Lan F, Wang Z, et al. Statins and myotoxicity. Trends Pharmacological Sciences 2003; 24 (3): 113-114.

Yoshida M, Gerszten RE, Rosenzweig A et al. HMG-Co A reductase inhibitor-induced reduction of monocyte adhesion to vascular endothelium involves small GTP binding protein Rho dependent mechanism (abstract). Circulation 1999; 100 (Suppl): I-693

Zachoval R, Gerbes AL, Schwandt P, et al. Short-term effects of statin therapy in patients with hyperlipoproteinemia after liver transplantation: results of a randomized cross-over trial. J Hepatology. 2001; 35: 86-91.

Zhang WY, Li Wan Po A. Effectiveness of topically applied capsaicin: a meta-analysis. Eur J Clin Pharmacology 1994; 46 (6): 517-522

Ziegler O, Droulin P. Safety, tolerability, and efficacy of simvastatin and fenofibrate- a multicenter study. Simvastatin-fenofibrate study group. Cardiology 1990; 77 (suppl): 50-57