

Guide to the Reader

NDA 21-213: MEVACOR OTC
Advisory Committee Background Information

Guide to the Reader

This document provides a comprehensive summary of the development program undertaken by Merck Research Laboratories in collaboration with Johnson&Johnson-Merck Consumer Pharmaceuticals to generate the New Drug Application (NDA) supporting nonprescription (over-the-counter or OTC) availability of the 10 mg dose of MEVACOR® (lovastatin) for reduction of total cholesterol (TC) and LDL-cholesterol (LDL-C) in people with mild to moderately elevated levels (TC between 200 and 240 mg/dL and LDL-C over 130 mg/dL). This summary reviews the large amount of information resulting from numerous clinical and consumer studies and extensive post-marketing safety experience from over 12 years of prescription use of the 10 mg to 80 mg dose range. All of the information contained within this summary is extracted directly from documents submitted to the FDA as part of the NDA. In some cases, material has been reordered or reformatted in order to consolidate the presentation.

Synopsis: The synopsis provided at the beginning distills the information further, and is intended to orient the reader to the key elements of the more detailed presentation that follows. Page annotations are provided which direct the reader to the sections of the main summary where the expanded information is located.

Introduction and Rationale: This section reviews the epidemiologic and clinical evidence supporting the conclusion that the target OTC population is at risk of developing coronary heart disease (CHD) and could benefit from safe and effective lipid lowering therapy. A table summarizing the main features of the studies that are referenced within this package is also provided.

Benefit of Lovastatin in an OTC Population: The design, analysis methods, and results of studies supporting the estimated primary prevention benefit of lovastatin 10 mg/day are summarized in terms of lipid modification and reduction in risk of CHD events.

Pharmacokinetics and Drug Metabolism: The pharmacokinetic properties of lovastatin are reviewed including an examination of the potential for drug interactions at the 10 mg dose.

Safety: The safety profile of lovastatin is examined from several perspectives: controlled long-term megatrials in over 15,000 patients at doses up to 80 mg/day, spontaneous adverse experience reports from prescription marketing, and experience in an OTC population. Special attention is focused on topics associated with the statin class and lipid lowering drugs in general including effects on liver, muscle and inadvertent use during pregnancy

Consumer Behavior: This section describes the proposed OTC labeling and consumer education and support program and provides results of clinical in-home use studies, label comprehension, and consumer surveys which demonstrate that consumer self-management of cholesterol is feasible and that the lipid lowering benefit can be achieved over the long term.

A list of references, denoted in the text by numbers within brackets [], follows the overall summary and conclusions. A copy of the current prescription labeling for MEVACOR tablets and the proposed OTC “Drug Facts” labeling text are appended along with copies of relevant publications.

Table of Contents

TABLE OF CONTENTS

	<u>PAGE</u>
Synopsis	S-1
1. Introduction	1
1.1 Rationale for Nonprescription Lovastatin	2
1.1.1 The Impact of Coronary Heart Disease	3
1.1.2 CHD Risk in Those Not Recommended for Prescription Treatment	3
1.1.3 Definition of the Nonprescription Lovastatin Treatment Population	5
1.1.4 Size of the OTC Eligible Population	5
1.1.5 Estimating CHD Risk Among the OTC Eligible Population	5
1.1.6 The Proven Benefit of Lowering Total Cholesterol	8
1.1.7 Rationale: Conclusions	9
1.2 Overview of Nonprescription Lovastatin Clinical Program	9
2. Benefit of Lovastatin in an OTC Population	11
2.1 Effect of Lovastatin on Lipids	12
2.1.1 Lipid Modifying Effect of Lovastatin 10 mg Daily	12
2.1.2 Comparison of Efficacy of Lovastatin 10 and 20 mg Daily	13
2.1.3 Attaining Desirable TC and LDL-C Levels With Lovastatin 10 and 20 mg	14
2.2 Effect of Treatment With Lovastatin on CHD Events in an OTC Eligible Population	16
2.2.1 Benefit of Lovastatin 20 to 40 mg in AFCAPS/TexCAPS	17
2.2.2 Estimate of CHD Risk Reduction With Lovastatin 10-mg Daily Regimen in an OTC-Eligible Population	19
2.3 Potential for Undertreatment in Higher Risk Populations	24
2.4 Rationale for Selecting 10-mg OTC Dose Regimen	25
2.5 Discussion	26
2.6 Benefit of Lovastatin 10 mg: Conclusions	26
3. Pharmacokinetics and Drug Metabolism	28
3.1 Background	28
3.2 In Vivo Analytical Methods	31
3.3 In Vitro and Nonclinical Data	31
3.4 Human Pharmacokinetics of Lovastatin	32
3.4.1 Disposition of ¹⁴ C-Lovastatin in Hypercholesterolemic Patients	32
3.4.2 Single Oral Dose Pharmacokinetics	33
3.4.3 Multiple Oral Dose Pharmacokinetics	33
3.4.4 Effect of Renal Impairment	35
3.4.5 Effect of Age and Gender	35
3.5 Pharmacokinetic Drug Interactions	35
3.5.1 Effect of Food	35

Nonprescription MEVACOR
FDA Advisory Committee Background Information

TABLE OF CONTENTS (CONT.)

	<u>PAGE</u>
3.5.2 Effect of Grapefruit Juice and other CYP3A4 Inhibitors	36
3.6 Human Pharmacology: Conclusions	38
4. Safety	40
4.1 Introduction	40
4.2 Experience with Marketed Prescription Drug—Overall	42
4.2.1 Postmarketing Studies	42
4.2.2 Spontaneous Reports During Marketed Use	46
4.3 Topics of Special Interest	50
4.3.1 Hepatobiliary Adverse Experiences	50
4.3.2 Myopathy	58
4.3.3 Exposure During Pregnancy	64
4.3.4 Drug-Drug Interactions	68
4.3.5 Drug-Disease Interactions	69
4.3.6 Drug Abuse and Overdose	72
4.4 Nonprescription Lovastatin Clinical Program Experience	73
4.4.1 Clinical Safety Data Collected	73
4.4.2 Overall Extent of Exposure of the Study Population	74
4.4.3 Demographics and Other Characteristics of the Study Population	75
4.4.4 Clinical Adverse Experiences	77
4.4.5 Drug-Demographic Interactions	86
4.5 Overall Safety Summary	88
4.6 Safety: Conclusions	88
5. Consumer Behavior	91
5.1 Introduction	91
5.2 Cholesterol Testing and Knowledge	92
5.2.1 Prevalence	92
5.2.2 The Desktop Cholesterol Analyzer	93
5.2.3 Cholesterol Recall Accuracy	94
5.3 Proposed Labeling System	95
5.3.1 Labeling System Aids Product Selection	96
5.3.2 Labeling System Encourages Interaction with Doctors	96
5.3.3 Labeling System and Compliance Program Promote Continued Use and Monitoring	97
5.4 Label Development and Testing Methods	97
5.5 Results: Product Selection	102
5.5.1 Product Selection Testing—Label 3 (Study 081)	102
5.5.2 Label Comprehension Testing—Label 4	105
5.6 Results: Product Use	109
5.6.1 Eating and Exercise Behavior	109
5.6.2 Persistence and Compliance Over the Long Term	110

Nonprescription MEVACOR
FDA Advisory Committee Background Information

.

TABLE OF CONTENTS (CONT.)

	<u>PAGE</u>
5.7 Interactions With Doctors	113
5.8 Summary	114
5.9 Consumer Behavior: Conclusions	115
6. Overall Summary and Conclusion	116
References	--

MEVACOR OTC™
SYNOPSIS

I. Rationale and Potential Benefit of Nonprescription Lovastatin (See Section 1. Introduction and Section 2. Benefit of Lovastatin in an OTC Population, pages 1 to 27)

Elevated cholesterol is one of the most common risk factors for coronary heart disease (CHD). The relationship between total cholesterol (TC) level and risk of CHD is strong and continuous with no evidence of a threshold. CHD endpoint studies in secondary and primary prevention show that lowering cholesterol lowers risk in a direct fashion. Despite therapeutic advances which have reduced the mortality rate of a CHD event in recent years, the disease remains prevalent and a leading cause of mortality and disability. Preventing the first CHD event also prevents the cascade of subsequent events which represent a substantial economic burden to our society.

Existing treatment guidelines reserve prescription treatment for lowering cholesterol to those individuals at highest risk. Yet, the large population with “average” or mildly elevated cholesterol (TC 200 to 240 mg/dL) contribute substantially to the total number of CHD events and associated burden of disease [7; 10]. A significant opportunity to reduce the burden of CHD in the nation lies in the prevention of the first CHD event in those who are at risk but not yet afflicted.

The benefit of lovastatin treatment in a primary prevention population with “average” cholesterol and moderate CHD risk was proven in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). AFCAPS/TexCAPS is the only study to specifically target generally healthy middle-aged and older men and women without CHD who had characteristics similar to those proposed as OTC eligible [3]. In AFCAPS/TexCAPS mean baseline TC (221 mg/dL) and LDL-C (150 mg/dL) were similar to the average levels in Americans of the same age and gender without cardiovascular disease, while baseline HDL-C (36 mg/dL for the men, 40 mg/dL for the women) was below average [1]. In addition to a low saturated fat, low cholesterol diet, AFCAPS/TexCAPS participants (N=6605) were randomized to receive placebo or lovastatin (20 mg with titration to 40 mg daily at Week 18 if LDL-C goal of 110 mg/dL was not achieved by Week 12). After an average follow-up of 5.2 years, lovastatin 20 to 40 mg daily reduced the incidence of first acute CHD events (defined as fatal or nonfatal myocardial infarction [MI], unstable angina or sudden death) by 37% (p=0.00008); MI by 40% (p=0.002); unstable angina by 32% (p=0.023); and coronary revascularization procedures by 33% (p=0.001) [3]. Based upon these data, lovastatin was approved by the FDA at all doses (10 to 80 mg) for the primary prevention of MI, unstable angina, and coronary revascularization.

I. Rationale and Potential Benefit of Nonprescription Lovastatin (Cont.)

Definition of the Nonprescription Lovastatin Treatment Population (p. 5)

The nonprescription lovastatin treatment-eligible population has been defined to complement current and projected future guidelines for CHD prevention by prescription treatment. The “OTC (over-the-counter) eligible” population is a generally healthy population without evidence of cardiovascular disease and with TC 200 to 240 mg/dL and LDL-C \geq 130 mg/dL. Age criteria for eligibility are also defined in the proposed nonprescription label (>40 years old for men and at least 1-year postmenopause for women), so that the target population would be at sufficient risk to achieve a meaningful benefit from treatment. While the standard risk factors of hypertension and diabetes are excluded because such people should be followed in a comprehensive health care setting, risk factors of smoking and low HDL-C, in addition to age, are included. Thus, the OTC-eligible population defined in this NDA approximates the group at moderate risk recommended by National Cholesterol Education Program Adult Treatment Panel II (NCEP ATP II) guidelines for lifestyle modification and frequent monitoring, but no pharmacologic treatment [2]. The use of nonprescription lovastatin allows individuals who are motivated to choose effective cholesterol modifying treatment to maintain good health while aging. Given that the size of this population is estimated to be 15.5 million men and women in the United States, use of nonprescription lovastatin provides a mechanism for treating the population more broadly to prevent the first CHD event in those at moderate risk.

Estimating the CHD Risk Among the OTC-Eligible Population (p. 5)

The degree of CHD risk in the OTC-eligible population, as defined above, has been estimated from subsets with these criteria in 3 large and independent databases, the Atherosclerosis Risk in Communities (ARIC) [4] and Framingham [29] epidemiologic study databases, and the placebo group of the AFCAPS/TexCAPS endpoint trial. Calculations of CHD risk in these 3 populations gave very consistent results in the range of 3% risk of myocardial infarction and nearly 6% risk of a CHD event over 5 years (i.e., just over 1% per year). From the OTC-eligible subset of the Framingham Heart Study where 20 years of follow-up data are available, the risk of a CHD event increases to 22% over 20 years, specifically 25% in men and 17% in women.

Benefit of Lovastatin in an OTC Population (p. 11)

Since 58% of the AFCAPS/TexCAPS cohort (N=3805) were eligible for OTC lovastatin use, a subgroup analysis was done to explore benefit using the definition developed for OTC eligibility. After an average follow-up of 5.2 years, lovastatin 20 to 40 mg daily reduced the incidence of first acute CHD events 44% ($p < 0.001$) in the OTC-eligible subgroup of AFCAPS/TexCAPS. This demonstrates that an OTC-eligible population is at sufficient risk to achieve a substantial benefit with lovastatin treatment.

I. Rationale and Potential Benefit of Nonprescription Lovastatin (Cont.)

The benefit of treating this population with the proposed nonprescription dose of lovastatin 10 mg daily has been defined first through characterizing the effect on lipid parameters in the OTC population and setting, and then by projecting CHD event reduction in the AFCAPS/TexCAPS trial (lovastatin 20 to 40 mg) to the lipid reduction measured with 10 mg. The 3 OTC studies which assessed efficacy of lovastatin 10 mg on lipid parameters in the OTC population included one standard design, placebo-controlled, clinic based study with a formal diet run-in phase (Study 075), and 2 use studies in a simulated “real world” OTC setting (Studies 076 and 079). Another placebo-controlled study of lovastatin 10 mg conducted previously during prescription development in a population with similar baseline lipid levels (Study 061) had results similar to those in the OTC placebo-controlled Study 075. A complete listing of the studies used in support of this application may be found in Table 4 (Section 1.2).

Effect of Lovastatin on Lipids (p. 12)

Based upon the studies in OTC populations, lovastatin 10 mg/day on average reduced TC 11%, LDL-C 18%, and TC/HDL-C 15%; HDL-C was increased 7%. Based upon lovastatin 20-mg pre-titration data from the OTC-eligible subgroup of AFCAPS/TexCAPS, lovastatin 20 mg daily reduced TC 17%, LDL-C 24% and TC/HDL-C 22%; HDL-C was increased 8%. The 20 mg regimen effect was similar in the 8,245-patient Expanded Clinical Evaluation of Lovastatin (EXCEL) study. EXCEL, a 12-month, randomized, parallel, double-blind, placebo-controlled study, compared placebo and lovastatin regimens ranging from 20 mg to 80 mg daily [6].

While the proposed OTC label program is not intended to provide for treatment to goal or dose titration, it is noteworthy that a substantial proportion of the OTC study participants reached desirable lipid levels with the 10-mg dose. NCEP ATP II guidelines define LDL-C <130 mg/dL as the goal for primary prevention; 69 to 75% of participants in the 3 OTC studies achieved this level. In fact, 17 to 26% of OTC study participants achieved LDL ≤100 mg/dL which is the goal defined for secondary prevention.

The dictum that each 1% reduction in TC results in an approximate 2% reduction in CHD events has been shown to be consistent in both primary and secondary prevention trials [8; 9; 30; 33; 35; 54]. The relationship was explored in the OTC-eligible subgroup of AFCAPS/TexCAPS treated with lovastatin. Each 1% reduction in TC resulted in a 2.78% reduction in the relative risk of a first acute CHD event. Similar relations were observed with LDL-C and TC/HDL-C ratio (2.34% and 2.81%, respectively).

I. Rationale and Potential Benefit of Nonprescription Lovastatin (Cont.)

Effect of Treatment With Lovastatin 10 mg on CHD Events in an OTC-Eligible Population (p. 16)

Data from the Lipid Research Clinics (LRC), Coronary Primary Prevention Trial (CPPT), the LRC Population Prevalence Study, and the Framingham Heart Study revealed that the TC/HDL-C ratio was a superior measure of risk for a first CHD event when compared with TC or LDL-C in men and women with no history of CHD [72].

Using the relation from the AFCAPS/TexCAPS OTC-eligible cohort for reduction in TC/HDL-C ratio and reduction in relative risk, and the average 10-mg effect on TC/HDL-C ratio, the relative risk reduction with the 10-mg dose was estimated to be 35%. This substantial risk reduction figure was translated into an estimation of the number of people needed to be treated with lovastatin 10 mg daily for 5 years to prevent one CHD event: approximately 55 people. The magnitude of the number needed to treat compares favorably to the benchmark of hypertension where it is commonly accepted practice to treat mild to moderate hypertension in individuals <65 years of age to prevent stroke. The number of such patients needed to be treated for 5 years to avoid one stroke is about 200 [53]. To further convey the impact of treatment with lovastatin 10 mg, these figures can be expressed as follows: for every 10,000 men and women taking lovastatin 10 mg for 5 years, an estimated 181 first acute CHD events would be prevented. This is about 4 times the number of events prevented (50 per 10,000 treated) in the hypertension treatment for stroke example.

Potential for Undertreatment in Higher Risk Populations (p. 24)

When evaluating the potential for under-treatment in higher risk populations it is important to consider the current NCEP ATP II guidelines for prevention and treatment of cardiovascular disease (CVD), the definition of OTC-eligible, and the unique aspects of the proposed consumer packaging of nonprescription lovastatin (see Section 5.). Men and women with existing CVD, very high lipid levels and major risk factors are a high priority for prescription treatment of high cholesterol and, therefore, are more likely to receive prescription treatment than those at moderate risk for CVD. Those currently receiving prescription treatment with some cost coverage would be unlikely to switch to nonprescription lovastatin due to increased cost. Those without access to prescription cholesterol treatment who purchase nonprescription lovastatin would receive the substantial benefit of lovastatin 10 mg daily treatment compared to no treatment or treatment with the currently available diverse consumer products with heart healthy claims. The simple OTC-eligibility exclusion criteria contained on the carton, TC >240 mg/dL and prior CVD, are readily understandable to the consumer and minimize misuse of the product by those with higher TC levels or preexisting CVD. The proposed package labeling also urges those with hypertension and diabetes to consult a physician

I. Rationale and Potential Benefit of Nonprescription Lovastatin (Cont.)

before using the product. Finally, the marketing of nonprescription lovastatin will be accompanied by a comprehensive education and support program that provides detailed information about cholesterol and other CVD risk factors, and was developed to encourage those with higher levels of risk to seek physician care. Thus it is expected that there will actually be a net increase in higher risk patients seeking physician care.

Rationale for Selecting 10-mg Dose Regimen (p. 25)

Effective use of nonprescription cholesterol-lowering medications requires life-long treatment; and the treatment target, CHD, is a disease that may remain asymptomatic for decades. Both the chronic treatment requirement and the asymptomatic nature of the disease represent a major paradigm shift from standard short-term OTC treatment targeted at specific symptoms. Selecting the lowest dose regimen with demonstrated efficacy is a conservative approach to launching a novel OTC program. The data summarized in this report support the conclusions that the potential benefit of the nonprescription lovastatin 10-mg regimen is clearly substantial. Lovastatin 10 mg daily favorably modifies lipids reducing TC 11%, LDL-C 18% and TC/HDL-C 15%, and increasing HDL-C 7%. With this regimen, approximately 70% of OTC eligible men and women can attain levels of LDL-C considered by NCEP to be desirable for high risk primary prevention patients. Finally, lovastatin 10 mg/day can reduce the risk of CHD by an estimated 35% in an OTC-eligible population. Given these data, lovastatin 10 mg daily is a highly effective dose, and most suitable for use in a new OTC class.

II. Safety of Lovastatin in Marketed Use and in Large Long-Term Trials (See Section 4. Safety, pages 40 to 90)

The benefits of nonprescription lovastatin 10 mg must be weighed against potential risks. The safety of lovastatin in doses up to 80 mg has been well-established in 12 years of extensive prescription use (estimated 24,000,000 patient years) and in two placebo-controlled megatrials totaling nearly 15,000 men and women treated chronically (AFCAPS/TexCAPS had an average of 5 years of follow-up, and EXCEL was a 12-month study) [3; 6]. In these controlled trials, the tolerability of the 20-mg daily dose was indistinguishable from that of placebo. When used by several hundred people up to 18 months in an OTC setting in this NDA program, the excellent safety profile of lovastatin 10 mg was confirmed. In the OTC studies, there were no drug-related serious adverse experiences or deaths.

Detailed review for this NDA of all available postmarketing adverse experience reports revealed no previously unsuspected toxicity, a wide margin of safety in overdose, and no suggestion of abuse potential. Three topics of special interest received a focused review in this summary: drug class related issues present for all statins related to liver, muscle, and use in pregnancy.

II. Safety of Lovastatin in Marketed Use and in Large Long-Term Trials (Cont.)

Liver (p. 50)

The primary site of action of lovastatin and other HMG-CoA reductase inhibitors (statins) is the liver. It is not surprising that these agents are associated with occasional increased hepatic transaminase levels. This tendency is also seen with the other classes of cholesterol-lowering agents. These elevations, characterized by minor elevations of ALT which are almost uniformly greater than AST, are usually not associated with elevations of alkaline phosphatase or bilirubin. This effect is dose related. Larger elevations in transaminase levels are infrequent. In the 8245-patient, 12-month EXCEL study, the incidence of 2 consecutive ALT elevations >3 x ULN was 0.1% for both the lovastatin 20-mg and placebo groups, 0.9% for the 40-mg groups and 1.5% for 80 mg group. Transaminase levels decreased after discontinuing study drug. Furthermore, in AFCAPS/TexCAPS, consecutive AST/ALT elevations >3 x ULN occurred in similar frequency in those receiving placebo and lovastatin 20 to 40 mg, and most elevations resolved without discontinuing medication.

Original concerns that minor increases in liver transaminases seen in some patients might have been indicative of a potential to cause more serious liver damage have proven to be unfounded with years of exposure with several statin drugs. There is little evidence that minor elevations of ALT are predictive of hepatotoxicity. For example, in the patients with 2- to 3-fold elevations of ALT during AFCAPS/TexCAPS, continuation of treatment was associated with a decrease in ALT in 72% of patients. This suggests that these small elevations in ALT are not indicative of significant liver injury. The ALT elevations are likely due to either increased ALT synthesis, decreased ALT clearance, or to enzyme leakage, thought to be related to destabilization of cellular membranes due to a change in lipid content. The fact that OTC users of the 10-mg dose would not be able to self-monitor LFTs and ascertain if they have an asymptomatic ALT elevation is not a clinical concern. These occasional asymptomatic elevations do not appear to be indicative of significant liver injury with lovastatin 20 to 40 mg/day. In fact, minor LFT elevations occur so frequently in the general population that LFT monitoring would result in numerous false positive signals.

Serious liver disease in lovastatin users appears to be very rare. The causal relationship between lovastatin and hepatitis or liver disease beyond asymptomatic increases in hepatic transaminases has not been established despite 24,000,000 patient years of prescription use. Spontaneous reports of liver failure or hepatitis in patients treated with lovastatin reflect a wide range of different hepatobiliary pathologies and are not suggestive of a single lovastatin-related pathogenesis. Individual reports are frequently confounded with concomitant medication and coexisting diseases. Despite the apparent minimal hepatotoxic potential of lovastatin 10 mg, the proposed nonprescription

II. Safety of Lovastatin in Marketed Use and in Large Long-Term Trials (Cont.)

lovastatin label takes a cautious approach. The back panel label and package insert contraindicate use in consumers with active liver disease, and advise consumers with a history of liver disease and consumers who are excessive alcohol users to consult their physician prior to using nonprescription lovastatin.

Muscle (p. 58)

Myopathy (defined as symptomatic creatine kinase [CK] elevations >10 x upper limit of normal [ULN]) is an adverse experience of interest associated with all statins. However, clinical study and marketed use experience indicate its occurrence is rare. Only 0.55 cases of rhabdomyolysis (severe myopathy) have been reported for every 100,000 patient-treatment years of lovastatin monotherapy worldwide. The risk of myopathy increases with dose; only 5 cases of myopathy (none of them considered to be rhabdomyolysis) have been reported at the 10-mg dose (720,000 patient years). Data from both EXCEL and AFCAPS/TexCAPS do not demonstrate a difference in the incidence of either myopathy or asymptomatic CK elevations >10 x ULN when placebo and lovastatin 20-mg treatment groups are compared [3; 6].

Interactions with certain drugs which could affect the risk of myopathy are known. Fibrates or niacin are independently associated with myopathy, and can interact pharmacodynamically with all statin drugs, apparently due to an effect on lipids rather than on specific inhibition of HMG-CoA reductase. In addition, lovastatin and some of the other statin drugs are metabolized by cytochrome P-450 3A4 (CYP3A4). Competitive inhibition by concomitant use of a few drugs similarly metabolized (e.g., cyclosporine, itraconazole, ketoconazole, erythromycin, clarithromycin, nefazodone and HIV protease inhibitors) can increase the statin activity and therefore the potential for myopathy. Clinical experience with marketed lovastatin at doses of 10 to 80 mg has shown that while the relative risk of myopathy may be increased by an interacting drug, the absolute risk is still extremely low, particularly with the 10-mg dose.

The symptoms of myopathy, sudden onset of unexplained muscle pain, muscle weakness or tenderness, can be recognized by patients and appear to resolve with drug discontinuation. A label warning to discontinue treatment and consult a physician if such symptoms occur can protect against serious clinical consequences. Furthermore, the label informs consumers to avoid medications that may interact with lovastatin. As fibrates and potent CYP3A4 inhibitors are available by prescription only, physicians and pharmacists have an opportunity to reinforce avoidance of concomitant medication use with medications such as lovastatin. Therefore, due to the very low incidence of myopathy, its symptomatic nature, and the information contained in the label, consumers should not be subject to appreciable risk when taking nonprescription lovastatin 10 mg.

II. Safety of Lovastatin in Marketed Use and in Large Long-Term Trials (Cont.)

Pregnancy (p. 64)

Use of lovastatin (and all statin drugs) during pregnancy has been contraindicated on the prescription label (Category X for use in pregnancy) because of the limited benefit of treatment for that time frame and concern about findings in rodent studies conducted at 40 to 80 times the human dose of lovastatin. Recent animal studies show that the fetal effects are caused indirectly by maternal toxicity associated with high doses rather than directly by fetal exposure to drug. A separate application has been submitted to FDA to remove the Pregnancy Category X status from the prescription label for lovastatin.

Postmarketing reports of inadvertent human exposure during pregnancy do not indicate an association between lovastatin use and any adverse outcome. Because of the limited benefit of treatment during pregnancy and the lower level of CHD risk in premenopausal women, nonprescription lovastatin will be indicated only for postmenopausal women, and will be contraindicated during pregnancy. However, should a premenopausal woman be inadvertently exposed to lovastatin during pregnancy, an adverse outcome related to the drug is very unlikely.

Safety Conclusion (p. 88)

The data reviewed indicate that lovastatin 10 mg can be safely marketed with appropriate labeling in the OTC environment for generally healthy individuals with mild to moderately elevated cholesterol. Because of the large margin of safety and the low dose proposed for nonprescription availability, consumers who make self-selection errors will not be subject to appreciable risk.

III. Feasibility of Consumer Self-Medication (See Section 5. Consumer Behavior, pages 91 to 115)

Data summarized above support the conclusions that the potential benefit of nonprescription lovastatin 10 mg in the proposed OTC-eligible population is substantial, that the excellent tolerability profile of the product permits its safe use according to OTC labeling, and that the benefit, therefore, outweighs the potential risk. The remaining question then, is whether or not consumers can appropriately self-medicate with the product such that the potential benefit can be achieved and the potential risk avoided. The OTC development program focused on 2 principal objectives: (1) the ability of consumers to correctly select whether or not to use the product according to the labeled criteria for eligibility and ineligibility, and (2) the performance of consumers in using the product appropriately over the long term.

Accessibility of Cholesterol Testing in the Community (p. 92)

In the past, information about one's lipid values could only be obtained through physician visits. Currently, access to cholesterol testing is rapidly becoming more widespread

III. Feasibility of Consumer Self-Medication (Cont.)

through community resources such as health fairs, employer wellness programs, and retail pharmacies using desktop cholesterol analyzers. Cholesterol testing in the study program was conducted using a reliable desktop analyzer which provides a full lipid profile on fingerstick blood (Cholestech LDX™). This same instrument was also used in the published ImPACT study showing that, with expanding use in community pharmacies, screening and monitoring of cholesterol is accessible to the public [67].

Nonprescription Lovastatin Label Education and Support System (p. 95)

Through an iterative process, the proposed MEVACOR™ OTC label was revised based on results of both comprehension tests and clinical use studies (see Figure 7). A comprehensive program of education and support was developed to guide consumer product selection and use. Extensive label reinforcement tools were included in the package carton, including a patient package circular, a video tape, and an informational brochure. A card and an incentive coupon to facilitate communication with the doctor and the toll-free product specialist, respectively, were also enclosed, as was an enrollment card for a compliance program. A complete set of the proposed packaging, label, and education and support materials are provided in the confidential package that accompanies this volume.

Label Comprehension and Product Selection (p. 102)

Label comprehension testing of the penultimate label iteration (Label 4) showed excellent comprehension of all key messages with the reinforcement tools further enhancing comprehension scores. Product selection behavior tested in a clinical use study (Study 081) showed that most consumers selected product correctly according to the label and that the reinforcement tools improved the selection decision. Communication with the product specialist at the toll-free service was a particularly effective reinforcement tool and was effective in encouraging people to call their doctors about cholesterol management.

Long-Term Consumer Self-Medication Behavior and Benefit (p. 109)

Evaluation of product use behavior in the MEVACOR™ OTC study program showed that consumers who are motivated to select the product do comprehend and comply with daily dosing and maintain or improve their eating and exercise habits while using the product. In a use study of 18-month duration (Study 076), about half of them remained on treatment at the end of 18 months, comparable to published reports on chronic prescription usage [17; 60]. This level of persistence was reflected in excellent sustained lipid changes over the 18 months, showing that the potential benefit of treatment with MEVACOR™ 10 mg OTC defined above can actually be achieved in those motivated consumers who persist with taking the product over the long term.

IV. Conclusion (See Section 6. Overall Summary and Conclusions, pages 116 to 117)

The prevalence and burden of CHD in this country merits a new approach to treating the population more broadly to prevent disease in those at moderate risk. Appropriate individuals who wish to improve their own long term CV health prospects should have open access to a proven safe and effective cholesterol lowering product. Lovastatin 10 mg produces substantial lipid changes in the defined OTC-eligible population which will result in meaningful clinical benefit in reduction of CHD events and their consequences. This proposal is reasonable because of the well-established tolerability of lovastatin, which has a wide margin of safety, and can be used safely according to labeling. The feasibility of self-management with MEVACOR™ OTC by the OTC-eligible population has been established through extensive testing. Consumers demonstrated their ability to select use of the product according to label criteria, to use it appropriately long-term, and to achieve sustained lipid modification. For motivated men and women in the OTC-eligible population, access to the nonprescription lovastatin treatment program, that includes drug therapy accompanied by information and support for appropriate product use and following a healthy lifestyle would provide an effective new option for lowering cholesterol and maintaining cardiovascular health. The resultant risk reduction provides a clear benefit to the individual, and extends a public health benefit over the participating OTC population at large.

1. Introduction

Elevated cholesterol is one of the most common risk factors associated with coronary heart disease events. In 1987, MEVACOR™¹ (lovastatin) was approved by the United States Food and Drug Administration as an adjunct to a diet restricted in saturated fat and cholesterol for lowering total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C). Since 1987, lovastatin has been marketed in doses of 10 to 80 mg, with the usual doses being 20 to 40 mg per day. The 10-mg dose has about 720,000 patient-treatment years of exposure. The safety of lovastatin has been established through the vast marketed use of the product. Total worldwide exposure to lovastatin is estimated to be 24 million patient-treatment years. In addition, the efficacy and safety of lovastatin has been characterized in two long-term, double-blind, placebo-controlled postapproval studies, Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS; N=6605) and Expanded Clinical Evaluation of Lovastatin (EXCEL; N=8245) study (approximately 15,000 men and women total) [3; 6]. In fact, based upon the proven benefit from AFCAPS/TexCAPS, lovastatin is approved at all doses for the primary prevention of myocardial infarction (MI), unstable angina, and coronary revascularization. Merck is now seeking marketing authorization for a 10 mg nonprescription dose of lovastatin.

This summary provides evidence supporting the approval of nonprescription lovastatin 10 mg in open-shelf distribution for the reduction of mild to moderately elevated cholesterol (total cholesterol: 200 to 240 mg/dL and LDL-cholesterol: \geq 130 mg/dL) in healthy individuals as an adjunct to a low-fat diet and exercise. In an NDA for a prescription drug, the key questions are “Is there proven benefit?” and “Are the potential safety risks worth the benefit of treatment?” In this nonprescription application, these two questions are appropriately considered in the context of a third question, “How well do people manage self-treatment of a condition without the direct supervision of a physician?”

The concept of chronic dosing to prevent disease on a nonprescription basis is not novel. Many consumers are dosing continuously with dietary supplements in an attempt to mitigate some of the effects of aging, including arthritis, cardiovascular disease, or osteoporosis. However, with the exception of supplements, most OTC products provide short-term treatment targeted at specific symptoms. Elevated cholesterol is asymptomatic, and its treatment is life-long; therefore, the success of a nonprescription treatment paradigm with cholesterol-lowering drugs depends on several factors. The

¹ MEVACOR is a trademark of Merck & Co., Inc., Whitehouse Station, New Jersey, U.S.A.

1. Introduction (Cont.)

product must be well tolerated and have proven benefit in a primary prevention cohort similar to the OTC target population. Consumers must know their cholesterol values before and during treatment, be able to select use of the product according to the labeling, know when to consult a doctor, and use the product on a continuous long-term basis.

The following sections assess the benefit and tolerability of lovastatin 10-mg treatment and present the unique and comprehensive product packaging that will facilitate proper use of the product and success of a nonprescription lovastatin treatment paradigm.

1.1 Rationale for Nonprescription Lovastatin

Epidemiological data on the prevalence of coronary heart disease (CHD) events and the growing burden of CHD on society indicate that there is an imperative need for broader and more effective risk factor modification, especially to reduce the impact of risk associated with total and LDL-C. The relationship between the level of cholesterol (total and LDL) and risk of CHD is continuous, graded, and strong, with no evidence of a threshold effect at either end of the cholesterol distribution [10]. Furthermore, a large body of evidence exists which demonstrates that interventions which lower cholesterol decreases the risk of atherothrombotic cardiovascular events for both primary and secondary prevention patients [8; 9; 30; 33; 35; 54; 64].

Based on the above, a nonprescription lovastatin treatment-eligible population has been defined to complement current guidelines for CHD prevention by prescription treatment. This “OTC-eligible” population is a generally healthy primary prevention (no evidence of CHD) population of middle-aged men and women (men >40 years old and postmenopausal women) with total cholesterol 200 to 240 mg/dL and LDL cholesterol \geq 130 mg/dL. These individuals are at moderate risk for CHD events, but are generally not recommended for pharmacological treatment to lower their elevated cholesterol by currently existing guidelines. For the motivated people in this population, access to the nonprescription lovastatin treatment program that would include drug therapy and information to maintain a healthy heart lifestyle would provide an effective new option for lowering cholesterol and reducing the risk of a first CHD event.

This section, 1.1 Rationale for Nonprescription Lovastatin, will establish the rationale for nonprescription lovastatin by describing the impact of CHD in the United States, defining the characteristics and size of the proposed population eligible for OTC treatment with lovastatin 10 mg, and estimating the CHD risk in the OTC-eligible subgroups of AFCAPS/TexCAPS and Framingham. The following section, 2. Benefit of Lovastatin in a Nonprescription Population, will quantify the efficacy and CHD risk reduction benefit of lovastatin 10 mg daily in an OTC-eligible population.

1.1.1 The Impact of Coronary Heart Disease

Despite significant reductions in the rate of coronary heart disease mortality in the last 20 years, cardiovascular disease remains a leading cause of mortality and morbidity in industrialized societies and accounts for significant utilization of health care resources. The occurrence of a major CHD event carries a poor prognosis. Within 6 years after a myocardial infarction (MI): 21 percent of men and 33 percent of women will have another heart attack; 7 percent of men and women will experience sudden death; and about 21 percent of men and 30 percent of women will be disabled with heart failure [25]. In 1996, CHD caused approximately 1 of every 4.9 deaths [25]. In 1999, it was estimated that 650,000 new MIs and 450,000 recurrent MIs would occur; about one third of these MIs would be fatal [25].

CHD is currently the leading cause of permanent premature disability in the U.S. work force [25]. As survival from acute CHD events is improved by new treatments and as a growing percentage of the United States and world populations are comprised of those who are middle aged and older, the detrimental effects of CHD morbidity in terms of resource utilization and quality of life are likely to grow. From 1979 to 1996 there has been an increase of about 30% in hospital admissions for CHD [25]. The Global Burden of Disease Study has projected that CHD, the fifth highest ranked cause of Disability-Adjusted Life-Years (DALYs) in 1990, will be the highest ranked cause by 2020. (DALYs are calculated as the sum of years of life lost due to premature death from an illness and years lived with disability, adjusted for severity, due to that illness.) [31; 32].

In summary, despite great strides in treatment of CHD, including the reduction of CHD mortality, CHD remains at epidemic proportions and presents a substantial burden to society. One of the approaches to combating this epidemic is prevention of the first event, thus, delaying or preventing morbidity associated with the first event and the cascade of subsequent CHD events. Primary prevention efforts may be enhanced by lowering the TC levels of a large segment of the U.S. population [36; 62]. Additionally, consumers who wish to reduce their own individual risk may do so by lowering their own lipid levels.

1.1.2 CHD Risk in Those Not Recommended for Prescription Treatment

Epidemiological observations have consistently demonstrated a continuous, strong, positive and independent relation between the incidence of CHD and total cholesterol (TC). The relation between CHD and TC holds across a wide range of concentrations including those considered normal or mildly elevated [7; 10]. The current National Cholesterol Education Program's (NCEP) Second Adult Treatment Panel (NCEP ATP II) Guidelines for the Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults reserve pharmacological intervention for primary prevention for

1.1.2 CHD Risk in Those Not Recommended for Prescription Treatment (Cont.)

those with the highest TC levels (TC >240 mg/dL). These guidelines do not recommend pharmacological lipid-lowering treatment in those with TC of 200 to 240 mg/dL unless they have an LDL-C of ≥160 mg/dL and additional risk factors that put them in the highest overall CHD risk stratum [2]. The NCEP ATP II pharmacological treatment guidelines are shown in Table 1.

Table 1

National Cholesterol Education Program Adult Treatment Panel II Pharmacological Treatment Guidelines for Patients Without Atherosclerotic Disease

Two or More Other [†] Risk Factors	LDL-Cholesterol (mg/dL)	
	Pharmacological Treatment Initiation Level	Treatment Goal
No	≥190	<160
Yes	≥160	<130

[†] Other risk factors for coronary heart disease (CHD) include: age (males: ≥45 years; females: ≥55 years or premature menopause without estrogen replacement therapy); family history of premature CHD; current cigarette smoking; hypertension; confirmed HDL-C <35 mg/dL and diabetes mellitus. Subtract one risk factor for HDL-C ≥60 mg/dL.

Despite the fact that TC levels 200 to 240 are not considered "high" [2], a sizable proportion of all CHD events occur in individuals with just such levels [36]. In the Multiple Risk Factor Intervention Trial (MRFIT) follow-up of screened men, 69% of CHD deaths in the first 16 years of follow-up were in those with TC between 182 to 264 mg/dL [13]. In the Framingham Heart Study, 40% of participants who developed a myocardial infarction had a TC between 200 to 250 mg/dL [15].

Because those with TC 200 to 240 mg/dL are at risk for CHD and because the NCEP ATP II Treatment Guidelines generally reserves prescription treatment for those at high risk, those with TC levels 200 to 240 mg/dL are a logical population for nonprescription lovastatin treatment. These guidelines are currently undergoing revision, but are not expected to lead to pharmacologic intervention at this level of risk.

1.1.3 Definition of the Nonprescription Lovastatin Treatment Population

The proposed nonprescription lovastatin package label targets lovastatin for use in primary prevention in a population that is, by definition, generally not recommended for treatment under NCEP ATP II guidelines. Specifically, the nonprescription lovastatin treatment population is defined as being men aged 40 and older, and postmenopausal women (at least 1 year past last menses), without CHD and with TC levels of 200 to 240 mg/dL and LDL-C levels of ≥ 130 mg/dL. Age criteria for eligibility are defined in the proposed nonprescription label because the incremental risk associated with increasing age begins at about 40 years of age for men and after menopause for women[73]. Those with a family history of cardiovascular disease, smoking, and low HDL-cholesterol are not advised against use, nor are women using estrogen replacement therapy. However, those with existing CHD, history of stroke, or the CHD risk factors of diabetes or hypertension are advised to consult a physician before using the product.

1.1.4 Size of the OTC Eligible Population

The number of people in the United States who are potentially eligible for nonprescription lovastatin treatment was estimated using data from the Third National Health and Nutrition Examination Survey (NHANES III), a population-based sample of the United States. The OTC eligible subset of NHANES III was defined by the following criteria: men aged >40 or postmenopausal women (surgical or natural) with TC 200 to 240 mg/dL, LDL-C >130 mg/dL, excluding those with self-reported cardiovascular disease (coronary, cerebrovascular, or peripheral vascular), self-reported diabetes, self-reported use of >1 antihypertensive medication (as a marker for moderate-to-severe hypertension) or use of lipid-lowering drugs. Using these criteria, there are approximately 15.5 million men and women potentially eligible to choose self-treatment with nonprescription lovastatin in the United States.

1.1.5 Estimating CHD Risk Among the OTC Eligible Population

Having established that the number of individuals who would meet the OTC-eligibility criteria is substantial, it is necessary to consider both the risk of CHD within this population as well as the ability to favorably modify the lipid profile with chronic treatment with lovastatin 10 mg.

To determine the risk of first CHD events in the proposed OTC eligible population, analyses were done based upon subgroups of large prospective observational and clinical trial cohorts with characteristics similar to the proposed nonprescription treatment-eligible population.

1.1.5.1 CHD Risk Estimates in OTC-Eligible Subgroups of ARIC and Framingham

CHD event rates may be approximated using data from two long-term, prospective, epidemiological databases: the Atherosclerosis Risk in Communities (ARIC) study [4], and the Framingham Heart Study [29].

The ARIC study is a prospective epidemiological study to examine the etiology of atherosclerosis and the variation in cardiovascular disease and its risk factors in 4 U.S. communities. The sample was designed to be representative of the U.S. population. The study cohort of over 16,000 persons underwent baseline evaluation by interview, physical examination, and laboratory assessment during 1986 through 1990. Re-evaluations were performed during 1990 through 1993, and 1994 through 1996 [4]. A subgroup of ARIC participants (N=2417) comparable to the nonprescription lovastatin treatment-eligible population was identified (men age 45 to 64, women age 55 to 64 at baseline, TC 200 to 240, LDL-C \geq 130; excluding cardiovascular disease, congestive heart failure, use of lipid-lowering medication, use of more than one antihypertensive medication, diabetes, >15 alcoholic beverages a week). In this subgroup, the observed rates of MI and CHD death were 0.4% per year for MI and 0.05% per year for CHD death over the 6 years of follow-up. Assuming a constant annual rate, it is estimated that over a 5-year period approximately 2% of nonprescription lovastatin treatment-eligible ARIC participants would have an MI and 0.25% would have a fatal CHD event. Other cardiovascular disease endpoints are not available from the ARIC database.

A subgroup of the original Framingham cohort and from the Framingham offspring cohort without cardiovascular disease was identified (N=5251). From these the OTC eligible were studied (men age \geq 40 and women age \geq 55 with TC 200 to 240, and LDL-C \geq 130, excluding those using lipid-lowering medication, those with diastolic BP \geq 100 and those with systolic BP \geq 160). The incidences of MI (fatal and nonfatal) and all CHD (MI + CHD death + coronary insufficiency + stable angina pectoris) were calculated (for men and women separately, as well as combined) and for each gender with stratification by age (<65 versus age \geq 65). For men and women, the 5-year event rates for first CHD event and first MI were 5.8 and 3.6%, respectively. Over 20 years, 22% of these people (25% of men and 17% of women) had a first CHD event.

1.1.5.2 CHD Risk in the OTC Eligible Subgroup of The Air Force/Texas Coronary Prevention Study AFCAPS/TexCAPS

The incidence of CHD was also estimated in an OTC-eligible subset of the Air Force/Texas Coronary Prevention Study (AFCAPS/TexCAPS) [1; 3]. AFCAPS/TexCAPS is the only study to specifically target healthy middle-aged and older men and women without CHD who had characteristics similar to those proposed as OTC eligible. The number (%) of AFCAPS/TexCAPS participants by baseline LDL-C and TC is presented in Table 2.

1.1.5.2 CHD Risk in the OTC Eligible Subgroup of The Air Force/Texas Coronary Prevention Study AFCAPS/TexCAPS (Cont.)

Table 2

Number (%) of AFCAPS/TexCAPS Participants by Baseline LDL-C and TC

Baseline LDL-C (NCEP ATP II Category)	Baseline TC (NCEP ATP II Category)		
	<200 (Desirable)	200 to 239 (Borderline-High)	≥240 [†] (High)
<130	495 (7%)	193 (3%)	3 (<1%)
≥130	596 (9%)	4092 (62%)[‡]	1226 (19%)

[†] Prescription treatment recommended if patient has:
 LDL-C ≥190 mg/dL;
 2 or more risk factors and LDL-C ≥160 mg/dL.
[‡] AFCAPS/TexCAPS participants meeting nonprescription lovastatin treatment-eligibility lipid criteria at baseline.

Among AFCAPS/TexCAPS participants, an OTC-eligible subset was identified by applying the nonprescription lovastatin treatment-eligibility criteria. Of the 4092 patients who met the lipid criteria for nonprescription lovastatin eligibility at baseline (TC 200-240 mg/dL and LDL-C ≥130 mg/dL), 287 (7.0%) were excluded from the subset due to diabetes (n=91; 2.2%) and/or use of multiple antihypertensive medications (n=212; 5.2%), leaving 3805 (57.6% of AFCAPS/TexCAPS participants). In this subset, 108 of 1921 participants randomized to placebo (5.6%) had a first acute CHD event (defined as fatal or nonfatal MI, unstable angina or sudden death). This rate was very similar to that of the overall study population (183 events in 3301 participants; 5.5%) [3].

1.1.5.3 CHD Risk is Similar in ARIC, Framingham and AFCAPS/TexCAPS OTC Eligible Subgroups

The estimates of CHD risk in the various OTC-eligible populations studied were remarkably consistent and clearly demonstrate that those who would qualify for OTC lovastatin treatment are at risk of CHD. (See Table 3)

1.1.5.3 CHD Risk is Similar in ARIC, Framingham and AFCAPS/TexCAPS OTC Eligible Subgroups (Cont.)

Table 3

Five-Year Risk of First CHD Event Among
 OTC Eligible Populations

Study Population/Type of Event [†]	% With Events Over 5 years
ARIC	
MI	2.0%
All CHD	Data not available
Framingham	
MI	3.6%
All CHD	5.8%
AFCAPS/TexCAPS	
MI	2.8%
Acute CHD	5.6%
[†] All CHD = MI + CHD death + coronary insufficiency + stable angina; Acute CHD = MI + CHD death + unstable angina.	

1.1.6 The Proven Benefit of Lowering Total Cholesterol

There is ample evidence from laboratory animal, genetic, epidemiological, and clinical studies confirming that elevated TC causes CHD, and that lowering TC will reduce the risk of CHD. Changes in TC levels correlate well with changes in CHD rates, and in the United States, approximately 30 to 40% of the reduction in CHD has been attributed to population-wide cholesterol reductions [71]. The epidemiological evidence shows that while the risk to the individual increases more steeply at levels above 200 mg/dL [12], risk of CHD is still seen with lower levels of TC, even when TC levels are well below 200 mg/dL [7; 9; 12].

AFCAPS/TexCAPS demonstrated that treatment with lovastatin 20 to 40 mg daily for primary prevention reduced the incidence of first acute CHD events by 37%, and the rate of fatal and nonfatal MI by 40% in men and women with average TC[3]. Of note, only 17% of AFCAPS/TexCAPS participants would have been recommended for lipid-lowering drug therapy according to NCEP ATP II guidelines based upon lipid values at study entry.

1.1.7 Rationale: Conclusions

The conclusions from this discussion of rationale for nonprescription lovastatin are:

- Despite significant reductions in the rate of CHD mortality, the detrimental effects of CHD morbidity continue to grow.
- Existing guidelines for cholesterol-lowering treatment conserve pharmacological treatment resources for those at highest risk for CHD.
- A substantial proportion of CHD events occur in men and women with average TC who are generally not recommended by existing guidelines for prescription cholesterol-lowering treatment.
- AFCAPS/TexCAPS has demonstrated that treatment with lovastatin for primary prevention benefits those with average cholesterol.
- A sizable OTC-eligible U.S. population has been identified to complement current guidelines for CHD prevention by prescription treatment.
- The observed 5-year risk of a first CHD event in OTC-eligible population subgroups of Framingham and AFCAPS/TexCAPS was 5.8 and 5.6%, respectively. The observed 5-year risk of MI in OTC-eligible subgroups of ARIC, AFCAPS/TexCAPS and Framingham was 2.0, 2.8 and 3.6%, respectively.
- For motivated men and women in the OTC-eligible population, access to the nonprescription lovastatin treatment program of drug therapy and extensive education and support would provide an effective new option for lowering cholesterol and maintaining cardiovascular health.

1.2 Overview of Nonprescription Lovastatin Clinical Program

As listed in Table 4, the following Merck sponsored clinical studies are included in this application for nonprescription use of lovastatin 10 mg: (1) Two pharmacokinetic studies (Protocol 078, lovastatin 40 mg; Protocol 082, lovastatin 10 mg and 40 mg); (2) Two double-blind placebo-controlled studies (Protocols 061 and 075); (3) Four open-label, clinical use studies (Protocols 076, 077, 079, 081); and (4) Two megatrials of lovastatin, EXCEL and AFCAPS/TexCAPS. The pharmacokinetic study Protocol 078 was not specifically conducted to support nonprescription lovastatin. Study Protocol 061 was conducted to support prescription lovastatin but the study population was similar to the OTC-eligible population. EXCEL was a one year safety study comparing placebo to lovastatin across the usual prescription dose range of 20 to 80 mg/day. AFCAPS/TexCAPS was a primary prevention endpoint trial with a sizable OTC-eligible subgroup (58% of total cohort).

1.2 Overview of Nonprescription Lovastatin Clinical Program (Cont.)

Table 4

All Clinical Drug Studies Supporting Nonprescription Lovastatin

Protocol Number	Study Description	Study Drug	Duration of Treatment	No. of Patients Treated
Phase I Clinical Pharmacology Studies				
078†	Open, single-dose, 4-period crossover: Effects of Grapefruit Juice on lovastatin and midazolam pharmacokinetics in healthy subjects	Lovastatin 40 mg or midazolam 2 mg or placebo	1 day (each)	16
082	Randomized, 2-period crossover pharmacokinetic study of 10- and 40-mg oral doses in healthy subjects	Lovastatin 10 mg Lovastatin 40 mg	10 days each x treatment	14
Phase III Double-Blind Studies				
061†	Randomized, placebo-controlled study in patients with TC 200-240 mg/dL and LDL-C 130-160 mg/dL (Prescription lovastatin study, containing OTC-appropriate patients)	Placebo run-in. Lovastatin 10 mg or Placebo	12 weeks	107 (24 placebo, 83 lovastatin)
075	Randomized, placebo-controlled study of lovastatin 10 mg in the treatment of moderate hypercholesterolemia following a trial of diet	Placebo run-in. Lovastatin 10 mg or Placebo	4 weeks run-in; 12 weeks treatment	210 (106 placebo, 104 lovastatin)
Phase III Open-Label Studies				
076	Patient self-selection of lovastatin 10 mg in the treatment of moderate hypercholesterolemia in an open-shelf, pharmacy setting (Use Study)	Lovastatin 10 mg	24 weeks (+12 mos. ext.)	722
077‡	Patient self-selection of lovastatin 10 mg in the treatment of moderate hypercholesterolemia in a worksite health center setting (Use Study)	Lovastatin 10 mg	24 weeks (terminated after 12 wk)	86
079	Restricted access study in the treatment of moderate hypercholesterolemia in a Storefront Setting (Use Study)	Lovastatin 10 mg	8 weeks (+ 4 months extension)	460
081	Patient self-selection of lovastatin 10 mg in the treatment of moderate hypercholesterolemia in Storefront, Open Shelf Setting (Use Study)	Lovastatin 10 mg	4 weeks (+ 2 months extension)	1144
Phase V Double-Blind Studies				
022†	Randomized, placebo-controlled study in men and women with TC 240-300 mg/dl [Expanded Clinical Evaluation of Lovastatin (EXCEL)]	Placebo run-in. Lovastatin 20 mg qd; or 20 mg bid; or 40 mg qd; or 40 mg bid; or Placebo	1 year	8245 (1650/group)
042†	Double-blind, placebo-controlled endpoint study in men and women with TC 180-264 mg/dL, LDL-C 130-180 mg/dL and HDL-C ≤45 (men) or ≤47 mg/dL (women) [Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)]	Placebo run-in. Lovastatin 20 mg with titration to 40 mg at Wk 18 if LDL-C>110 mg/dL; or Placebo	Average follow-up 5.2 years	6605 (3301 placebo, 3304 lovastatin)
† Study was conducted as part of the prescription lovastatin clinical program.				
‡ Early study termination due to poor enrollment.				

2. Benefit of Lovastatin in an OTC Population

The target OTC population and rationale for treatment for the prevention of CHD have been provided in Section 1.1. The benefit of treatment with lovastatin 10 mg daily in such an OTC population was explored using 3 different approaches:

- Observing the effect on lipid parameters associated with coronary heart disease (CHD) risk (i.e., TC, LDL-C, HDL-C and TC/HDL-C).
- Observing the percentage of OTC eligible men and women who attain desirable levels of TC and LDL-C as defined in National Cholesterol Education Program's Second Adult Treatment Panel (NCEP ATP II) guidelines.
- Estimating the effect on reduction of first acute CHD events (defined as fatal or nonfatal MI, unstable angina or sudden cardiac death) in the OTC-eligible population.

Data for these analyses came from 4 studies that specifically measured the lipid-modifying efficacy of the lovastatin 10-mg regimen: 2 double-blind, placebo-controlled trials (Studies 061 and 075), and 2 open-labeled trials (Studies 076 and 079). Studies 075, 076, and 079 were part of the nonprescription lovastatin clinical program, which evaluated lovastatin 10 mg in OTC-eligible individuals, and Study 061 evaluated the 10-mg regimen in a population with characteristics similar to that of the OTC population. For reference, the efficacy of the 20-mg daily regimen of lovastatin, the usual prescription starting dose, is also presented. The effects of the 20-mg regimen are based upon data from 2 large, double-blind, placebo-controlled clinical trials: AFCAPS/TexCAPS and EXCEL.

AFCAPS/TexCAPS data also provided the basis for FDA approval of all doses (10 to 80 mg) for the prescription MEVACOR™ indication to reduce the risk of myocardial infarction, unstable angina, and coronary revascularization procedures *in individuals without symptomatic cardiovascular disease, average to moderately elevated TC and LDL-C, and below average HDL-C*. AFCAPS/TexCAPS specifically targeted generally healthy middle-aged and older men and women without CHD who had characteristics similar to those proposed as OTC eligible [3]. Mean baseline TC (221 mg/dL) and LDL-C (150 mg/dL) were similar to the average levels in Americans of the same age and gender without cardiovascular disease, while baseline HDL-C (36 mg/dL for the men, 40 mg/dL for the women) was slightly below average [70]. In addition to a low saturated fat, low cholesterol diet, AFCAPS/TexCAPS participants were randomized to receive placebo or lovastatin (20 mg with titration to 40 mg daily at Week 18 if LDL-C goal of 110 mg/dL was not achieved by Week 12).

Finally, data from the EXCEL trial are presented. EXCEL was a 1-year double-blinded, placebo-controlled efficacy and safety trial in 8245 high-risk hypercholesterolemic patients randomized to receive various lovastatin dose regimens ranging from 20 to 80 mg daily [6].

2.1 Effect of Lovastatin on Lipids

Clinical trials demonstrated that lovastatin 10- to 80-mg daily regimens, approved for prescription use, favorably modify the atherogenic lipid profile by decreasing TC, LDL-C and the TC/HDL-C ratio in a dose-dependent manner. Lovastatin 10- to 80-mg daily regimens also increase HDL-C, a non-atherogenic and protective component of the lipid profile.

2.1.1 Lipid Modifying Effect of Lovastatin 10 mg Daily

Treatment with lovastatin 10 mg daily favorably modified lipid levels in OTC-eligible individuals (see Table 5). Data from 3 studies in the nonprescription lovastatin clinical program (075, 076 and 079) confirmed the efficacy that had been observed in the earlier placebo-controlled Study 061 from the prescription clinical program. In the 2 double-blind, placebo-controlled studies (061 and 075), treatment with lovastatin 10 mg daily produced statistically significant (p<0.001) reductions in TC, LDL-C and TC/HDL-C compared with diet alone (placebo group). In Study 075 the increase in HDL-C was also statistically significant (p<0.001) compared with diet alone (placebo).

Table 5

Effect of Lovastatin 10 mg on Lipid Levels
 Percent Change From Baseline

Study	061 (Double-blind, placebo- controlled)	075 (Double-blind, placebo- controlled)	076 (Open-label)	079 (Open-label)	Average Effect of Lovastatin 10-mg Regimen
Timing of Measurement	Week 12	Week 12	Week 8	Week 8	
N treated: Lovastatin 10 mg	83	104	722	460	
Mean % Change from Baseline (SD)	% (SD)	% (SD)	% (SD)	% (SD)	
➤ Total-C	-10.2† (10.8)	-11.4† (11.4)	-12.9 (11.1)	-10.4 (11.5)	-11%
➤ LDL-C	-15.2† (14.0)	-17.5† (15.7)	-21.7 (16.1)	-18.4 (15.3)	-18%
➤ HDL-C	7.2 (18.3)	6.7† (11.3)	6.9 (22.4)	5.4 (19.9)	7%
➤ TC/HDL Ratio	-15.0† (12.7)	-16.4† (11.8)	-15.4 (20.2)	-12.9 (15.9)	-15%
† Different than changes observed in those treated with placebo p<0.001.					

2.1.1 Lipid Modifying Effect of Lovastatin 10 mg Daily (Cont.)

Because the maximum effect of lovastatin upon the lipid profile is established after 4 to 6 weeks of treatment and maintained with continued therapy on a fixed regimen, data from studies with measurements after 6 weeks can be combined. When averaged, data from the 4 studies with lovastatin 10 mg daily demonstrate that treatment provides clinically meaningful reductions in atherogenic lipids such as TC and LDL-C, as well as beneficial effects upon HDL-C and TC/HDL-C ratio. Increasing HDL-C is important because low HDL-C (generally defined as <35 mg/dL) is associated with increased CHD risk and high HDL-C (generally defined as >65 mg/dL) is associated with decreased CHD risk.

2.1.2 Comparison of Efficacy of Lovastatin 10 and 20 mg Daily

Data for the lowest generally recommended prescription starting dose of lovastatin, 20 mg daily, is provided to benchmark the efficacy of the proposed 10-mg lovastatin nonprescription dose.

To characterize the effect of 20 mg daily, data are examined from 2 large clinical prescription trials, EXCEL and AFCAPS/TexCAPS [3; 6]. As noted previously, the population in AFCAPS/TexCAPS was similar to the U.S. OTC-eligible population. In fact, 58% of those participating in AFCAPS/TexCAPS met OTC-eligibility criteria. Data for the AFCAPS/TexCAPS OTC-eligible subgroup are presented to characterize the effect of lovastatin 20 mg. EXCEL is included as an independent confirmation of the lovastatin 20-mg dose effect in a non-OTC-eligible population.

Table 6 compares the average lipid modifying effect (% change from baseline) of lovastatin 10- and 20-mg daily regimens. Since a one-time titration from 20 mg to 40 mg daily was permitted at Week 18 in AFCAPS/TexCAPS, pre-titration lipid data from Week 18 were used to assess the efficacy of the 20-mg regimen. Because of a change in analysis methods over the course of the study, the 20-mg lipid efficacy data presented from AFCAPS/TexCAPS are for a group of OTC-eligible patients (N=1292) that had both baseline and Week 18 pre-titration lipid levels analyzed using the same methods.

As has been established, the effect of lovastatin on lipids is dose dependent. The magnitude of the dose response was expected based upon previously published dose-response analyses for HMG-CoA reductase inhibitors (statins) [68; 69]. Based on the published relationship between dose and effect seen in previous statin trials, it can be predicted that if the lovastatin 20-mg regimen reduced TC 17%, the 10-mg regimen would reduce TC 12% (an 11% reduction was observed); for LDL-C, if a 24% reduction were observed with the 20-mg regimen, the expected reduction with lovastatin 10 mg daily would be 17% (an 18% reduction was observed).

2.1.2 Comparison of Efficacy of Lovastatin 10 and 20 mg Daily (Cont.)

Table 6

Comparison of Effect of Lovastatin 10 and 20 mg on Lipid Levels
 Percent Change From Baseline

Population	Lovastatin Dose		
	10 mg Daily	20 mg Daily	
	Average Effect [†] Weeks 8-12	AFCAPS/TexCAPS OTC Eligible Week 18	EXCEL Week 48
N Treated with Lovastatin	1369	1292	1642
Mean % Change			
➤ Total-C	-11	-17	-17
➤ LDL-C (mg/dL)	-18	-24	-24
➤ HDL-C (mg/dL)	7	8	7
➤ TC/HDL Ratio	-15	-22	-21

[†] Averaged from Studies 061, 075, 076, 079, as shown on Table 5.

In summary, treatment with the 10- and 20-mg daily regimens resulted in clinically meaningful favorable changes to lipids associated with CHD risk. The effects seen in the OTC population are entirely consistent with those seen in prior studies for the 10- and 20-mg dose, and are therefore independent of baseline values over the range studied.

2.1.3 Attaining Desirable TC and LDL-C Levels With Lovastatin 10 and 20 mg

NCEP ATP II has defined the generally desirable level of TC as <200 mg/dL; the treatment goal for LDL-C in primary prevention (no evidence of CHD and with 2 or more CHD risk factors) is <130 mg/dL, and the treatment goal for LDL-C in secondary prevention (history of CHD or stroke) is ≤100 mg/dL [2]. The OTC eligible population is a primary prevention population that generally has, by the proposed definition, borderline-high TC (defined by NCEP ATP II as TC 200 to 240 mg/dL) and at least 1 CHD risk factor, namely age (men must be ≥40 years old and women must be postmenopausal). By the proposed OTC population definition, some individuals may have several risk factors (e.g., age, smoking, low HDL-C). While the proposed OTC label is not intended to address treatment to goal, it is of interest to note the degree to which the 10-mg dose lowered lipids to desirable levels in the OTC clinical studies.

2.1.3 Attaining Desirable TC and LDL-C Levels With Lovastatin 10 and 20 mg (Cont.)

Table 7 provides the percentage of men and women, with characteristics similar to those in the OTC eligible population, who reached desirable levels of TC and LDL-C. To characterize the effect of the 10-mg dose, data from the 3 OTC studies that collected lipid data (075, 076 and 079) were used. For comparison, lovastatin 20-mg data from the AFCAPS/TexCAPS OTC-eligible subgroup with Week 18 pre-titration data were used. The majority of individuals treated with 10-mg daily regimens attained desirable levels of TC (<200 mg/dL). The vast majority treated with 10 mg achieved the NCEP goal for primary prevention (68.8% to 75% had LDL-C <130 mg/dL). Notably, 17.4 to 25.7% of individuals treated with 10 mg also attained the goal targeted for secondary prevention (LDL-C ≤100 mg/dL), and this percentage was similar to the 21.5% observed with lovastatin 20 mg in AFCAPS/TexCAPS. These results indicate that permitting the use of lovastatin 10 mg daily in an OTC population would allow the majority of users to achieve desirable levels of these atherogenic lipids, even without dose titration.

Table 7

Response by Category of TC and LDL-C
 With Lovastatin 10- and 20-mg Regimens: Percent Achieving Goal

Regimen	Lovastatin 10 mg Daily			Lovastatin 20 mg Daily
Study (N Treated with Lovastatin)	075 (104)	076 (722)	079 (460)	AFCAPS/TexCAPS OTC eligible (1292) [†]
LDL-C Goal for Primary Prevention (<130 mg/dL)	75.0%	70.4%	68.8%	82.1%
LDL-C Goal for Secondary Prevention (≤100 mg/dL)	18.8%	25.7%	17.4%	21.5%
Desirable TC (<200 mg/dL)	44.3%	54.8%	55.3%	81.0%

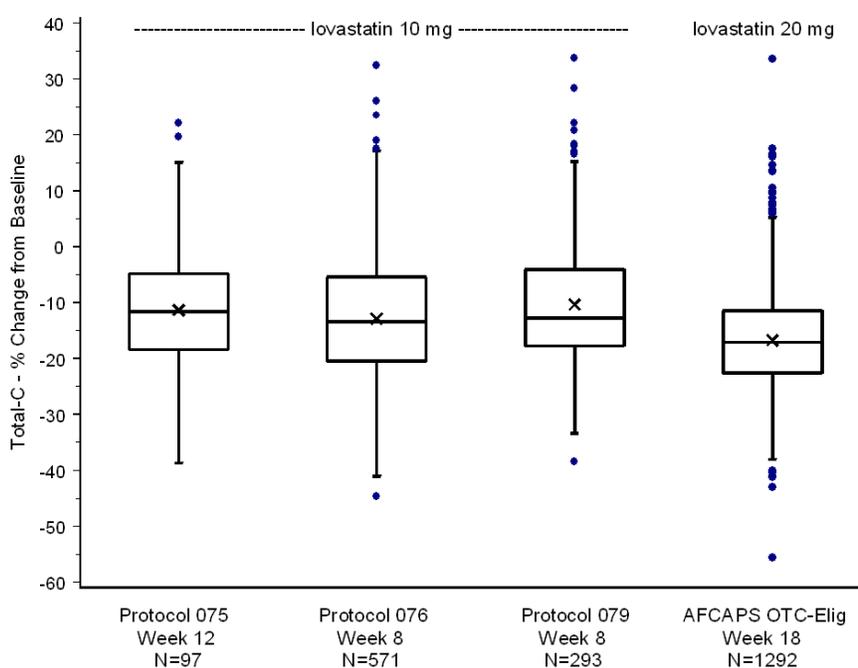
[†] Number in OTC eligible subgroup treated with lovastatin 20 mg was 1884; number with Week 18 data for pre-titration lipid analyses is 1292.

Figure 1 presents the range of total cholesterol reduction observed with both the lovastatin 10-mg regimen (in the nonprescription studies that measured lipids) and the 20 mg regimen (in pre-titration regimen from AFCAPS/TexCAPS). The horizontal line for each plot represents the median value for the study and the “X” represents the mean. The box represents the upper and lower boundaries of the 75th and 25th percentiles, respectively. The dots represent outliers. The effect of lovastatin 10 mg is relatively consistent across the nonprescription studies. Furthermore, though a dose response is evident when the effects of the 10- and 20-mg regimens are compared, there is considerable overlap in responses.

2.1.3 Attaining Desirable TC and LDL-C Levels With Lovastatin 10 and 20 mg (Cont.)

Figure 1

Total Cholesterol % Change From Baseline for OTC and AFCAPS Studies



2.2 Effect of Treatment With Lovastatin on CHD Events in an OTC Eligible Population

The benefit of lovastatin 20- to 40-mg daily treatment in reducing CHD events in a population with characteristics similar to the proposed OTC population was demonstrated in AFCAPS/TexCAPS. In this section, the overall AFCAPS/TexCAPS results and the benefits observed with lovastatin 20 to 40 mg daily in the large subgroup of participants that met OTC eligibility criteria at baseline are presented. Estimates of the benefit that would be expected, had 10 mg (and for comparison, 20-mg daily fixed dose) been used, are also presented.

2.2.1 Benefit of Lovastatin 20 to 40 mg in AFCAPS/TexCAPS

2.2.1.1 Overall Results of AFCAPS/TexCAPS

In AFCAPS/TexCAPS, lovastatin 20 to 40 mg daily reduced the incidence of first acute CHD events (defined as fatal or nonfatal MI, unstable angina or sudden death) 37% (p=0.00008); MI 40% (p=0.002); unstable angina 32% (p=0.023); coronary revascularization procedures 33% (p=0.001); and coronary and cardiovascular events 25% (p=0.006) and 25% (p=0.003), respectively after an average follow-up of 5.2 years [3].

2.2.1.2 Benefit of Lovastatin 20 to 40 mg Daily in the OTC-Eligible AFCAPS/TexCAPS Subgroup

A substantial subset (3805 of 6605, 58%) of the AFCAPS/TexCAPS population met the OTC eligibility criteria. In this OTC eligible subset, the benefit of treatment with lovastatin, beyond what could be achieved with diet alone, was assessed by calculating the relative risk reduction with lovastatin, compared to placebo. Event rates were estimated as crude rates (rate over the entire duration of the trial), and as 5-year rates using the Kaplan Meier method [38]. Relative risk estimates were derived by Cox regression models [37].

Over the duration of the trial, average follow-up 5.2 years, the crude rates for first acute CHD events (nonfatal MI, unstable angina, fatal CHD) were 5.6% (108/1921) and 3.2% (60/1884) for those in the OTC-eligible subgroup receiving placebo and lovastatin, respectively. The 5-year event rates estimated using the Kaplan-Meier method [38] are 5.3% and 3.0%, for those receiving placebo and lovastatin, respectively. In the OTC-eligible subgroup, treatment with lovastatin 20 to 40 mg daily resulted in a statistically significant risk reduction of 44% (95% confidence interval: 23 to 59%) compared to those treated with placebo (Table 8; data graphically displayed in Figure 2). The benefits observed in the OTC-eligible cohort are consistent with the overall results reported for the entire AFCAPS/TexCAPS cohort (see Table 8).

2.2.1.2 Benefit of Lovastatin 20 to 40 mg Daily in the OTC-Eligible AFCAPS/TexCAPS Subgroup (Cont.)

Table 8

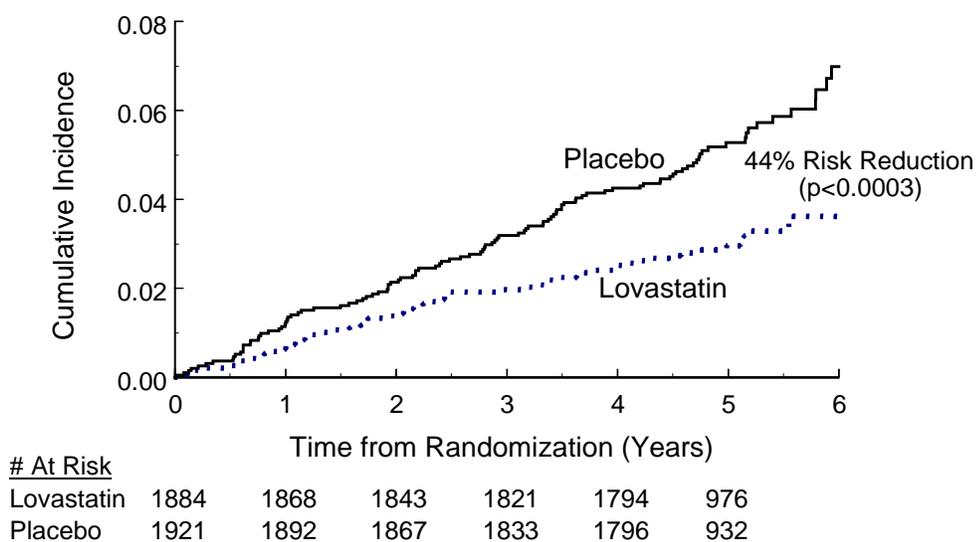
Comparison of First Acute CHD Event Relative Risk Reduction in the OTC-Eligible Subgroup and in the Overall AFCAPS/TexCAPS Population

Cohort Description	Events [†] /Patients (%)		5-Year K-M [‡] Event Rate (%)		Relative Risk Reduction (95% CI)	p-Value [§]
	Placebo	Lovastatin	Placebo	Lovastatin		
OTC Eligible	108/1921 (5.6)	60/1884 (3.2)	5.3	3.0	44.0% (23.3; 59.2)	.001
All Participants	183/3301 (5.5)	116/3304 (3.5)	5.2	3.3	37.3% (20.9; 50.3)	.001

[†] Nonfatal MI, Unstable Angina, Fatal CHD.
[‡] Estimated by Kaplan-Meier survival method.
[§] Between treatment group comparison

Figure 2

Cumulative Incidence of First Acute CHD Event for the AFCAPS/TexCAPS OTC-Eligible Participants by Treatment



2.2.2 Estimate of CHD Risk Reduction With Lovastatin 10-mg Daily Regimen in an OTC-Eligible Population

The availability of AFCAPS/TexCAPS data allows the benefit of lovastatin treatment to be explored in an OTC population. The effect of lovastatin 10 mg daily on the reduction of first acute CHD events was estimated using a 3 step process:

1. The efficacy of lovastatin 10 mg daily in modifying the atherogenic lipid profile was characterized (see Section 2.1.1 above).
2. The relation between CHD risk and changes in the atherogenic lipid lowering profile was estimated in the OTC-eligible subgroup of AFCAPS/TexCAPS treated with lovastatin.
3. Combining the characteristic changes in the atherogenic lipid profile from Step 1 and their estimated relation to CHD risk from Step 2, the impact of the lovastatin 10-mg daily regimen on relative risk of CHD and related measures (e.g., number needed to treat and number of events prevented) was estimated in an OTC population.

For comparison, the benefit of CHD risk reduction was estimated with a 20-mg fixed dose regimen, the usual prescription starting dose.

2.2.2.1 Association Between Reduction of Lipid Levels and CHD Events in AFCAPS/TexCAPS

Published meta-analyses of primary and secondary prevention trials support a decrease in the risk of CHD of approximately 2% for each 1% reduction in TC [8; 9; 30; 33; 35; 54]. In order to confirm that this relationship holds true at the lower end of the primary prevention risk spectrum, the association between reduction of atherogenic lipid levels with lovastatin and CHD reduction was investigated in the OTC-eligible subgroup of AFCAPS/TexCAPS treated with lovastatin.

The relationships between first acute CHD events and percent change in TC, LDL-C and the TC/LDL-C ratio from baseline to Year 1 were assessed by Cox proportional hazards regression models in the OTC-eligible subgroup of AFCAPS/TexCAPS treated with lovastatin[37]. All lipid measurements used in these analyses were measured at a lipid specialized laboratory. Only the first endpoint for an individual patient was included in the analysis. In addition, patients who experienced an event in their first year were excluded from the analysis of the relation between on-treatment lipid changes with first acute CHD events. In this way, Year 1 lipid data could be used to predict subsequent events. All other OTC-eligible lovastatin-treated participants with a Year 1 lipid measurement were included. Note that AFCAPS/TexCAPS participants who discontinued study medication were surveyed each year for endpoints; therefore, endpoint data were available for participants who discontinued after Year 1 but before study termination. Gender, study site, baseline lipid value and non-lipid CHD risk factors

2.2.2.1 Association Between Reduction of Lipid Levels and CHD Events in AFCAPS/TexCAPS (Cont.)

were also included in the model. Of the 1884 men and women who were OTC eligible and treated with lovastatin, 12.3% were excluded from this analyses because they had a first acute CHD event during the first year and/or did not have any lipid measurements at the Year 1 visit.

Table 9 shows the relation between reduction in TC, LDL-C, and TC/HDL-C, and CHD risk reduction in the OTC-eligible subgroup for AFCAPS/TexCAPS. Each 1% reduction in TC resulted in a 2.87% reduction in the relative risk of a first acute CHD event. Similar relations were observed with LDL-C and TC/HDL-C ratio (2.34% and 2.81%, respectively); however, only the TC/HDL-C ratio was statistically significant. This is not surprising since published data from AFCAPS/TexCAPS demonstrated that the relation between first CHD events and the baseline TC/HDL-C ratio was statistically significant while the relation with baseline TC and LDL-C was not [65]. Furthermore, when data from the Lipid Research Clinics (LRC), Coronary Primary Prevention Trial (CPPT), the LRC Population Prevalence Study and the Framingham Heart Study were reviewed, the TC/HDL-C ratio was found to be a superior measure of the risk for first CHD event when compared with either TC or LDL-C in men and women with no history of CHD [72].

Table 9

Relation of 1% Decrease in Lipid Component from Baseline to Year 1 in the Lovastatin Group and the Reduction in Relative Risk of a First Acute CHD Event in the OTC-Eligible Subgroup of AFCAPS/TexCAPS Treated With Lovastatin According to Cox Proportional Hazards Model[†]

Lipid Variable in Model	Regression Coefficient	Relative Risk Reduction		
		For Each Additional 1% Lipid Reduction	95% CI	p-Value
TC	0.028212	2.78%	(-0.51 to 5.96)	.0964
LDL-C	0.023672	2.34%	(-0.19 to 4.81)	.0699
TC/HDL-C	0.028537	2.81%	(0.93 to 4.66)	.0035

[†] Models also include gender, age, hypertension, family history of CHD, smoking status and baseline lipid value.

2.2.2.2 Methods for Estimating the Effect of Lovastatin 10-mg on CHD Risk Reduction

The lipid changes characteristic of the lovastatin 10-mg daily regimen were obtained from the 4 combined 10-mg studies in an OTC-like population; and changes characteristic of the lovastatin 20-mg daily regimen were obtained by using AFCAPS/TexCAPS Week 18 pre-titration data (see Section 2.1.1). The relative risk reduction was projected by applying the relation between the TC/HDL-C ratio and CHD risk (see Table 10) to the average TC/HDL-C reduction observed with lovastatin 10 and 20 mg daily (see Table 6). For comparison, data for TC and LDL-C are also presented.

The number of patients needed to treat to prevent one first acute CHD events was also calculated. The number needed to treat depends upon the time horizon of the analysis, the baseline event rate and the impact of treatment on the reduction in absolute risk. The time interval for the estimated number needed to treat was 5 years. The baseline risk was obtained from the Kaplan-Meier survival estimate at 5 years for OTC-eligible participants randomized to placebo in AFCAPS/TexCAPS [38]. By assuming the event rate over the 5-year period was constant, the 5-year risk of an event for patients on treatment with lovastatin was estimated from the projected reduction in the relative risk. The number needed to treat was then computed as the inverse of the difference in absolute risk between patients who receive lovastatin and those who do not. The number of events prevented per 10,000 treated was calculated by multiplying the absolute risk reduction by 10,000.

2.2.2.3 Impact of Treatment With Lovastatin 10 and 20 mg Daily on Relative Risk in the OTC-Eligible Population

The average percent change in lipids in OTC-eligible subgroups with lovastatin 10 mg daily (see Section 2.1.1) and the observed 20-mg data from AFCAPS/TexCAPS Week 18 were used to estimate the reduction in relative risk of a first CHD event (see Table 10). Based upon the statistically significant relation between TC/HDL-C ratio and risk reduction, the estimated relative risk reduction was 35% with the lovastatin 10-mg regimen. This result was consistent with results provided for comparison from TC and LDL-C analyses. As expected, a dose response was observed for each estimate of risk; however, substantial benefit is obtained at the 10-mg dose.

2.2.2.3 Impact of Treatment With Lovastatin 10 and 20 mg Daily on Relative Risk in the OTC-Eligible Population (Cont.)

Table 10

Impact of Treatment With Lovastatin 10 and 20 mg Daily on Observed Change (%) in Lipids and Estimated Relative Risk Reduction (%) of the First Acute CHD Event in an OTC-Eligible Population

Lipid Parameter	10 mg Daily Combined Study Data		20 mg Daily AFCAPS/TexCAPS Week 18 Pre-titration Subgroup	
	Lipid Reduction [†] (%)	Estimated Relative Risk Reduction (%)	Lipid Reduction [‡] (%)	Estimated Relative Risk Reduction (%)
TC / HDL-C	15	35	22	46
TC	11	27	17	38
LDL-C	18	35	24	44
[†] Data combined from Studies 061, 075, 076, 079 (N=1369), see Table 5. [‡] Data from OTC-eligible participants with 18-week lipid data (N=1292), see Table 6.				

The number of individuals needed to treat with lovastatin over 5 years with 10 and 20 mg daily to prevent 1 first acute CHD event is given in Table 11. Given the reduction in the TC/HDL-C ratio observed with 10 mg of lovastatin and the predicted reduction in CHD event rates for that regimen, about 55 people would need to be treated with lovastatin 10 mg daily for 5 years to prevent 1 CHD event². For comparison, Table 11 shows similar calculations based on the 20-mg lipid changes at Week 18 in the OTC-eligible subgroup of AFCAPS/TexCAPS. As expected, the dose-response pattern observed in CHD relative risk reduction is also reflected in the number needed to treat estimates.

² Following discussion with the FDA statistician, it is Merck's understanding that an alternative methodologic approach was used to calculate the number needed to treat; the results appear to be robust to alternative methods of assessment.

2.2.2.3 Impact of Treatment With Lovastatin 10 and 20 mg Daily on Relative Risk in the OTC-Eligible Population (Cont.)

Table 11

Estimated Number Needed to Treat for 5 Years With Lovastatin
10- and 20-mg Daily Regimens to Prevent 1 First Acute CHD Event in an
OTC-Eligible Population

Lipid Parameter	10 mg Daily Combined Study Data	20 mg Daily AFCAPS/TexCAPS Pre-Titration Subgroup
TC/HDL-C	55	41
TC	72	51
LDL-C	56	44

These calculations demonstrated treatment with lovastatin 10 mg daily is likely to have a clinically meaningful impact on reducing first acute CHD events (relative risk reduction estimated to be 35% based upon TC/HDL-C).

It is useful to benchmark the estimated benefit to hypertension which is another prevalent cardiovascular risk factor for which pharmacological treatment is widely accepted. Although treatment of hypertension is undertaken in a prescription setting, this does not diminish its use as a benchmark for purposes of judging the magnitude of the potential benefit in treating an asymptomatic, chronic condition such as borderline-high TC. The number of patients needed to treat for 5 years to avoid one stroke in persons <age 65 with mild to moderate hypertension is about 200 [53]. Therefore, the magnitude of the estimated benefits of treatment based upon the number needed to treat to prevent 1 event with nonprescription lovastatin 10 mg compares favorably with the estimated number needed to treat for the hypertension benchmark.

To further appreciate the impact that nonprescription lovastatin might have on CHD event reduction, one should consider that large numbers of people would be eligible for treatment. Based on the number needed to treat analyses, for every 10,000 men and women who use lovastatin 10 mg/day for 5 years, it is estimated that 181 first acute CHD events would be prevented, based upon the TC/HDL-C ratio analyses provided above. This is nearly 4 times the number of events targeted by the benchmark hypertension treatment for stroke strategy (See Table 12).

2.2.2.3 Impact of Treatment With Lovastatin 10 and 20 mg Daily on Relative Risk in the OTC-Eligible Population (Cont.)

Table 12

Estimated Number of Events Prevented if 10,000 Were Treated for 5 Years

Event	Medication	Number of Events Prevented/ 10,000 Treated
Stroke	Prescription Treatment for Mild-to-Moderate Hypertension in those ≤65 Years of Age	50
CHD	Nonprescription 10 mg Daily Lovastatin	181 [†]
CHD	Nonprescription 20 mg Daily Lovastatin	242 [†]

[†] Estimates for number of CHD events prevented were developed from data for TC/HDL-C reductions (see Table 11).

2.3 Potential for Undertreatment in Higher Risk Populations

When evaluating the potential for undertreatment in higher risk populations it is important to consider the current NCEP ATP II guidelines for prevention and treatment of cardiovascular disease, the definition of OTC-eligible, and the unique aspects of the proposed consumer packaging of nonprescription lovastatin.

As nonprescription lovastatin targets primary prevention, those who have had a prior cardiovascular event are not eligible, and the consumer packaging of the product directs such individuals to seek a physician for treatment. Similarly, high-risk primary prevention candidates (TC >240 mg/dL) who are generally recommended for prescription treatment by NCEP ATP II are not eligible for OTC treatment and are directed by the carton to seek medical advice for optimal control. The high-risk primary prevention exclusion criteria are TC >240 mg/dL, hypertension, and diabetes. The simple OTC-eligibility exclusion criteria contained on the carton, are readily understandable to the consumer and minimize misuse of the product.

Other nonlipid CHD risk factors identified by NCEP ATP II include: age ≥45 years for men or 55 years for women, family history of premature CHD, and current cigarette smoking. The comprehensive education and support program that accompanies the purchased product contains information about both lipid and nonlipid risk factors and was developed specifically to promote a healthy heart lifestyle. The comprehensive education and support program also includes a toll-free number for addressing consumer's questions including appropriate selection and use of the product.

2.3 Potential for Undertreatment in Higher Risk Populations (Cont.)

Misuse of the product should be minimized by the clear-cut definition of the target population, the simple algorithm for eligibility that uses information readily available to the consumer, and the comprehensive education and support program that encourages those at higher risk to seek physician care. Furthermore, those who are already on a prescription cholesterol reducer with some cost coverage have a financial incentive not to switch to purchasing nonprescription lovastatin. Consumers who made errors in selecting the product can obtain a full refund as an incentive to return the product and pursue appropriate medical advice. Those without access to prescription cholesterol treatment and have TC >240 mg/dL who use nonprescription lovastatin 10 mg would receive substantial benefit compared to no treatment. In summary, the use of nonprescription lovastatin allows individuals, who generally would not be recommended for treatment, to choose effective cholesterol modifying treatment and provides a mechanism for treating the population more broadly to prevent the first CHD event in those at moderate risk.

2.4 Rationale for Selecting 10-mg OTC Dose Regimen

Proven benefit to treatment and an acceptable safety profile are critical for approval of prescription medications. Lovastatin treatment has demonstrated proven benefit and an acceptable safety profile across the entire approved dose range of 10 to 80 mg/day (see Section 4.).

Effective use of cholesterol-lowering medications requires life-long treatment and, in primary prevention, the treatment target (CHD) can remain asymptomatic for decades. In the nonprescription setting, both the chronic treatment requirement and the asymptomatic nature of the disease represent a major paradigm shift from standard short-term OTC treatment targeted at specific, usually self-limiting, symptoms. Therefore, selecting the lowest dose regimen with demonstrated efficacy provides a conservative approach to launching a novel OTC program.

The data summarized in this section support the conclusions that the potential benefit of the nonprescription lovastatin 10-mg regimen is clearly substantial. Lovastatin 10 mg/day is the lowest approved prescription dose. Studies in OTC populations revealed that lovastatin favorably modifies lipids by reducing TC 11%, LDL-C 18% and TC/HDL-C 15% and increasing HDL-C 7%. As the OTC-eligible population is defined as having TC ≤240 mg/dL, LDL-C is expected to be ≤160 mg/dL for a majority of those who are OTC-eligible. With lovastatin 10 mg daily, approximately 70% of OTC eligible men and women can attain levels of LDL-C considered by NCEP to be desirable for high risk primary prevention patients (LDL-C <130 mg/dL). Furthermore, the risk of first CHD event is estimated to be reduced by 35% based upon reductions observed in the TC/HDL-C ratio with lovastatin 10 mg daily. Given these data, lovastatin 10 mg/day represents a conservative but effective and appropriate dose for introducing this new paradigm in OTC therapy.

2.5 Discussion

The benefit of treatment with lovastatin 10 mg daily in an OTC population was shown in each of the 3 different approaches used to assess efficacy. Lovastatin 10 mg favorably modified lipids associated with CHD risk: TC, LDL-C, HDL-C and TC/HDL-C. More importantly, nonprescription treatment with lovastatin 10 mg allowed the majority of those who are OTC-eligible to attain the desirable TC and LDL-C levels recommended for primary prevention by the NCEP ATP II. Furthermore lovastatin 10 mg was estimated to reduce the risk of CHD by up to 35% compared to dietary intervention alone. Comparisons between the lovastatin 10- and 20-mg regimens confirmed the dose response observed in other clinical trials across the entire lovastatin 10- to 80-mg daily range.

Currently, CHD is a leading cause of morbidity and mortality in the United States. As a significantly large percentage of the U.S. population ages, CHD related morbidity will increase. One of the approaches to combating CHD is prevention of the first event, thus, delaying or preventing morbidity associated with the first event and subsequent related CHD events. Primary prevention efforts may be enhanced by lowering the TC and LDL-C levels of the OTC population with lovastatin 10 mg daily. Access to nonprescription lovastatin would expand the options that are available to maintain cardiovascular health and, ultimately, to reduce the burden of CHD in the population that chooses to use it and the risk of CHD in the individual that chooses to use it.

2.6 Benefit of Lovastatin 10 mg: Conclusions

- It is possible to identify an OTC-eligible subgroup, from a population eligible for primary prevention, who would derive benefit from lovastatin treatment but for whom pharmacological treatment is not recommended by current or anticipated NCEP treatment guidelines.
- Treatment with lovastatin 10 mg daily in the OTC-eligible population produces clinically meaningful changes in lipids associated with CHD risk: TC, LDL-C, HDL-C and TC/HDL-C.
- Treatment with lovastatin 10 mg daily would allow the majority of OTC-eligible men and women to attain TC and LDL-C levels considered desirable by NCEP ATP II.
- The nonprescription lovastatin carton label may direct many higher cardiovascular risk patients to their physicians. Those who choose to self-medicate despite the label are likely to reduce their CHD risk, which is an improvement over no treatment.
- AFCAPS/TexCAPS demonstrated that lovastatin treatment reduces CHD events in OTC-eligible men and women.

2.6 Benefit of Lovastatin 10 mg: Conclusions (Cont.)

- Lovastatin 10 mg daily can reduce the burden of CHD risk in the OTC population by reducing the risk of a first CHD event by an estimated 35%, and is, therefore, an appropriate dose for OTC lovastatin.
- Lovastatin 10 mg daily in the OTC population can prevent many first CHD events and reduce the subsequent burden of CHD disease.
- An OTC-eligible individual who chooses to use nonprescription lovastatin 10 mg along with a healthier lifestyle over the long term can have a lower risk of CHD.

3. Pharmacokinetics and Drug Metabolism

3.1 Background

The majority of the information presented below is a review of material supplied for review in the original lovastatin marketing application, submitted for review in subsequent filings for lovastatin, or published after approval of the prescription lovastatin NDA. Only the information regarding the liquid chromatographic tandem mass spectrometric (LC/MS/MS) assay for lovastatin and its active β -hydroxyacid metabolite, L-154819, and the results of a multiple-dose study with 10- and 40-mg doses of lovastatin in healthy male subjects is submitted as “new information” in this current NDA. The 10-mg tablet of lovastatin proposed for the nonprescription market is the same composition, except for a slight change in coloring, as that currently marketed for prescription lovastatin.

Lovastatin is a lactone-pro-drug which, upon hydrolysis to the β -hydroxyacid (L-154819), is a potent inhibitor of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the primary step in the cholesterol synthetic pathway in the liver, the conversion of HMG-CoA to mevalonic acid.

Following oral administration, the drug is incompletely absorbed from the gastrointestinal tract, undergoes first-pass extraction in the liver, its primary site of action, and is extensively metabolized to both active and inactive metabolites. The parent lactone form is converted to the active β -hydroxyacid (L-154819) by esterases and by nonenzymatic hydrolysis. In addition to L-154819, 3 other downstream metabolites with HMG-CoA reductase inhibitory activity are detectable in the systemic circulation of man. Additionally, lovastatin and other lactones are present in plasma. These are not inhibitors of the enzyme but are detected following base hydrolysis to convert lactones to their corresponding β -hydroxyacids (see Figure 3). Given that several of these metabolites are active HMG-CoA reductase inhibitors, it is critical that drug equivalents (as β -hydroxyacids) are quantified in the general circulation since myopathy associated with these cholesterol-lowering agents may be associated with excessive inhibition of cholesterol synthesis in skeletal muscle. Measurement of drug equivalents (as β -hydroxyacids) may be accomplished with use of an enzyme inhibition assay which has as its basis the inhibition of HMG-CoA reductase.

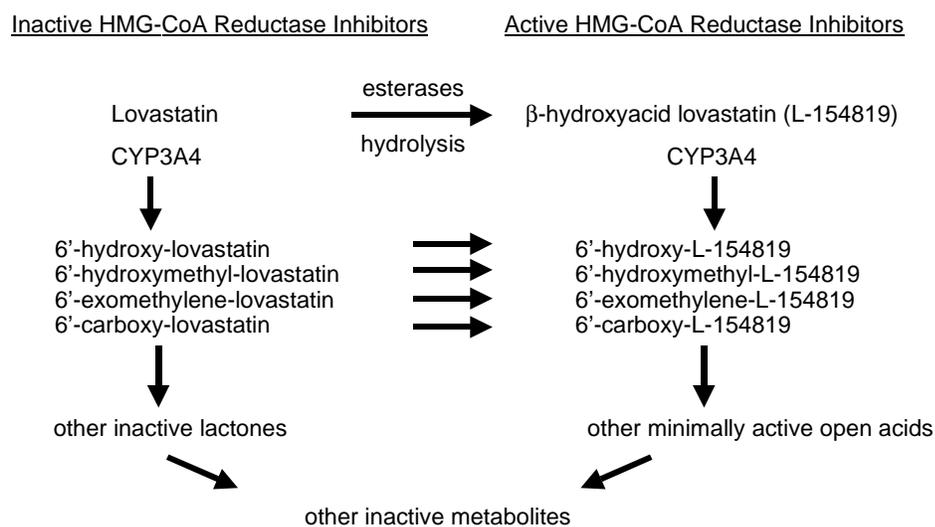
In addition, an LC/MS/MS analytical method has been recently developed to measure lovastatin and its active hydroxyacid metabolite in plasma and this assay was used to assay plasma samples from a multiple-dose study which compared 10- and 40-mg doses of lovastatin (Protocol 082) and an interaction study with lovastatin 40-mg and grapefruit juice (Protocol 078).

An overall summary of the plasma profile parameters for lovastatin-derived HMG-CoA reductase inhibitory activity from 5 definitive studies for lovastatin is presented in Table 13.

3.1 Background (Cont.)

Figure 3

Lovastatin Metabolism



3.1 **Background (Cont.)**

Table 13

Overall Summary of Plasma Profile Parameters for Lovastatin-Derived HMG-CoA Reductase Inhibitory Activity
 (Mean ± SD)

Study/Dosage Form	C _{max} (ng eq/mL)		T _{max} (h)		AUC ₂₄ (ng eq•hr/mL)		F [†] _{rel}	
	Active	Total	Active	Total	Active	Total	Active	Total
Dose-Proportionality/Food N=12								
3 x 20-mg CT	24.6±24.5	38.8±31.4	4.1±2.2	3.3±2.4	135±118	263±126	--	--
3 x 30-mg CT	26.4±24.8	47.4±31.2	3.0±1.1	3.2±1.8	227±231	425±299	1.04	1.00
3 x 40-mg CT	39.4±37.1	62.1±42.9	3.5±1.9	3.2±2.5	291±279	512±311	1.14	0.91
3 x 20-mg CT (w/food)	46.7±31.0	91.5±37.6	2.6±1.0	2.3±0.9	233±180	392±230	1.54	1.38
Multiple-Dose Kinetics, N=10								
4 x 20-mg CT—single dose	17.6±15.0	54.8±42.6	2.4±1.0	2.0±1.4	126±81.3	409±199		
4 x 20-mg CT—7 th dose	26.2±17.7	71.5±37.7	2.2±0.8	2.0±1.0	216±161	584±279		
Propranolol Interaction, N=12								
80-mg DFC	15.9±9.6	40.9±17.8	5.0±6.1	4.9±6.3	61.3±41.3	167±85.1		
Grapefruit Juice Interaction, N=15								
40-mg CT with water	22.0±9.0	40.2±21.4	3.8±1.8	3.5±1.9	139.9±46.1	227.7±64.6		
OTC Multiple-Dose, N=14								
10-mg CT Day 1	4.9±1.9	12.0±4.4	4.8±2.1	3.6±2.2	30.5±13.3	63.3±20.5		
10-mg CT Day 10	5.2±1.7	14.1±4.1	3.5±2.0	2.5±1.2	29.6±10.5	67.4±14.9		
40-mg CT Day 1	26.2±8.9	50.5±15.0	5.1±2.4	4.3±2.2	156±60.7	276±85.7		
40-mg CT Day 10	22.1±7.2	48.7±22.5	5.4±3.2	4.3±3.1	160±68.5	297±106		

3.2 In Vivo Analytical Methods

Three analytical methods have been used to quantify lovastatin, its active β -hydroxyacid metabolite L-154819, or the inhibitors of HMG-CoA reductase resulting from the administration of lovastatin. The first method quantifies lovastatin and L-154819, by high-performance liquid chromatography [HPLC] with UV detection. The second method also quantifies lovastatin and L-154819 by liquid chromatography with tandem mass spectrometric detection (LC/MS/MS). The third method quantifies the sum of L-154819 and other inhibitors in plasma (weighted by their respective inhibitory binding constants) by assessing the inhibition of HMG-CoA reductase activity [43]. Base hydrolysis of the plasma samples permits an assessment of latent inhibitors such as lovastatin and other lactone metabolites.

3.3 In Vitro and Nonclinical Data

The disposition of lovastatin has been studied in various animal species. Approximately 30% of an orally administered dose of lovastatin is absorbed in the mouse, rat, and dog. All species convert lovastatin to its β -hydroxyacid form, L-154819, as shown by its presence in their respective biological fluids. The reverse has also been shown in the rat and dog in that lovastatin can be found in biological fluids following the administration of L-154819. Lovastatin is hydrolyzed substantially faster in rodent plasma compared to dog or human plasma.

The formation of polar metabolites is much more extensive in rodents compared to the dog. This more extensive metabolism is reflected in a substantially smaller fraction of lovastatin and L-154819 being recovered in the bile of the rat and mouse compared to the dog. In addition, a taurine conjugate of L-154819 is found in rodents and not in the dog. It appears that oxidative pathways are relatively more important in rodents compared to the dog.

A metabolite, 6'-hydroxy-L-154819, which is approximately 70% as potent as L-154819, appears to be formed in all species studied, including man. In addition, another inhibitor has been found in the dog and rat and identified as the 6'-exomethylene metabolite [43]. These inhibitors are also present in human plasma or bile. Thus, dog and man are similar in that both seem to have the same inhibitory metabolites present in plasma or bile. Fewer inhibitors and less inhibitory activity, relative to inactive metabolites, are present in mouse plasma relative to dog plasma. More recent studies have documented that lovastatin and L-154819 metabolism is catalyzed by cytochrome P-450(CYP) 3A with no involvement of CYP2A1, CYP2C11, CYP2E1, CYP2B1/2, CYP1A1, or CYP1A2 [47; 48].

3.3 In Vitro and Nonclinical Data (Cont.)

The inhibition of CYP3A4 activity (as measured by testosterone 6 β -hydroxylation) by lovastatin was studied in an in vitro human liver microsomal system. The in vitro inhibition constant ($K_i = 7.7 \mu\text{M}$) is much higher than the clinically achievable plasma concentrations and, in particular, higher than the maximal plasma concentrations (C_{max}) of total HMG-CoA reductase inhibitory activity ($\sim 0.25 \mu\text{M}$) for lovastatin at its maximum approved prescription dose (80 mg). Thus, lovastatin at the proposed OTC dose would not inhibit the metabolism of other CYP3A4 substrates.

3.4 Human Pharmacokinetics of Lovastatin

3.4.1 Disposition of ^{14}C -Lovastatin in Hypercholesterolemic Patients

Following administration of intravenous and oral doses of ^{14}C -L-154819 (equivalent to 40-mg of lovastatin; 20 μCi) and ^{14}C -lovastatin (100 mg; 20 μCi), respectively, to 4 hypercholesterolemic patients, the urinary excretion of radioactivity averaged $\sim 10\%$ of the oral dose and $\sim 30\%$ of the intravenous dose. The remainder of the radioactivity was recovered in feces indicating that biliary excretion is an important route of excretion.

In plasma, the AUC for total HMG-CoA reductase inhibitory activity following the oral dose of ^{14}C -lovastatin accounted for $\sim 17\%$ of the AUC for radioactivity indicating the presence of inactive metabolites. No radioactivity was detected in red blood cells in either treatment. L-154819, itself, was cleared rapidly from plasma (plasma clearance = 640 mL/min) leading to a plasma half-life of 1.5 hours. Based on the AUC for total inhibitors and the AUC for L-154819 in this study, it was estimated that the bioavailability of L-154819 is $< 9\%$. This estimate is known to be high since inhibitors other than L-154819 contribute to the AUC of total inhibitors and the AUC of active inhibitors is about half that of total inhibitors.

The results of efforts to identify the human metabolites of lovastatin indicate that:

- Lovastatin and its corresponding β -hydroxyacid (L-154819) are present in human plasma; other metabolites are formed that exist as β -hydroxyacid: lactone pairs.
- The enzyme inhibitory profile of human plasma shows 3 major metabolites and L-154819; collectively, they account for $\sim 80\%$ of the total inhibitory activity of the unfractionated plasma.
- The inhibitory activity of each of these 3 metabolites is about 70% that of L-154819 based on comparisons with metabolites observed in the plasma and bile of dogs.
- The identity of these metabolites has been tentatively established as 6'-hydroxy-L-154819, 6'-hydroxymethyl-L-154819, and 6'-exomethylene-L-154819 [43].
- 6'-hydroxy-L-154819 undergoes an acid-catalyzed allylic rearrangement to the inactive 3'-hydroxy-L-154819 [44].

3.4.1 Disposition of 14C-Lovastatin in Hypercholesterolemic Patients (Cont.)

- The metabolites 6'-hydroxy-, 3'-hydroxy- 6'-hydroxymethyl-, and 6'-carboxy-L-154819 are present in human bile.
- The biotransformation of lovastatin and L-154819 is catalyzed by CYP3A4 [47; 48].

Finally, both lovastatin and L-154819 are highly bound to plasma proteins (>95%) over the concentration range of 0.5 to 50 µg of drug per mL of plasma.

3.4.2 Single Oral Dose Pharmacokinetics

Following single oral doses of 60, 90, and 120 mg of lovastatin administered to 12 healthy male volunteers, the plasma profile parameters for HMG-CoA reductase inhibitors indicate that the pharmacokinetics of lovastatin are linear over the 60- to 120-mg dose range. A plot of the observed mean inhibitor AUC values versus dose (Figure 4) also shows that the regression intercepts are close to zero, suggesting that linear kinetics prevail over the therapeutic dosage range.

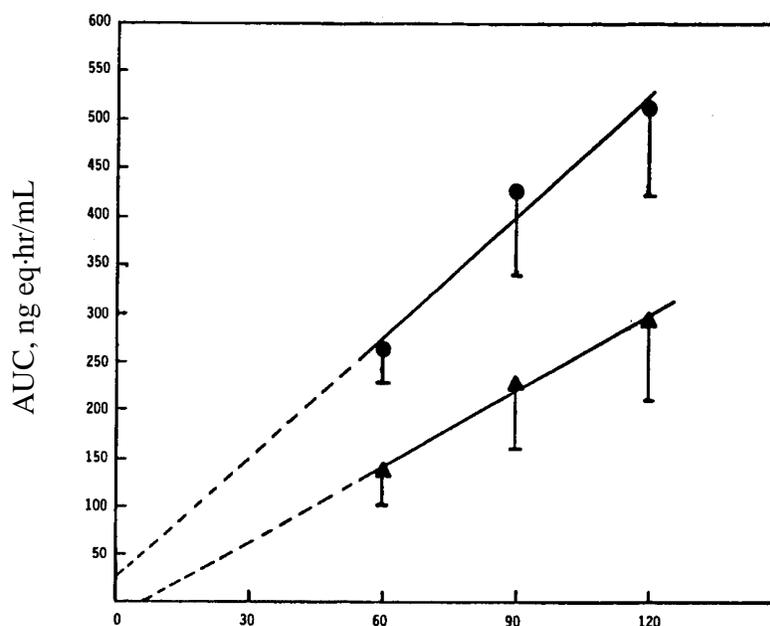
3.4.3 Multiple Oral Dose Pharmacokinetics

Once daily doses of lovastatin 80-mg were administered to 10 patients with primary hypercholesterolemia and the data indicated that steady state was obtained within 2 to 3 days. Mean AUC values for active and total inhibitors exhibited modest accumulation increasing by ~50% by the time steady state was attained.

3.4.3 Multiple Oral Dose Pharmacokinetics (Cont.)

Figure 4

Dose Versus Mean (SEM N=12) AUC₂₄ of Active (▲) and Total (●) Inhibitor Concentrations in Human Plasma Following Single Oral Doses of Lovastatin Administered as 3 x 20-, 3 x 30-, or 3 x 40-mg Tablets



The proposed nonprescription lovastatin dose is 10 mg taken once daily with the evening meal. Hence, a study was undertaken in healthy subjects (N=14) to investigate the multiple-dose pharmacokinetics of lovastatin, L-154819, and HMG-CoA reductase inhibitory activity following once-daily (x 10 days) evening doses of lovastatin 10 and 40 mg.

Plasma concentrations (AUC) of active or total HMG-CoA reductase inhibitory activity increased in approximately a linear fashion for the 10- and 40-mg doses of lovastatin administered in this study. Also there was very little accumulation (<10% of AUC) of inhibitory activity across the 10 days of dosing. The same was true for lovastatin and L-154819. Plasma concentrations of either chemical entity increased nearly in proportion to the dose of lovastatin administered and there was little, if any, accumulation over the 10 days of dosing.

3.4.3 Multiple Oral Dose Pharmacokinetics (Cont.)

Taken together with the data presented earlier for 60-, 90-, and 120-mg doses of lovastatin, these data indicate that the disposition of lovastatin is independent of dose across a 10- to 120-mg dose range as was inferred from the earlier data alone. This allows one to predict with confidence the effects of drug interactions, organ failure, and possibly other events on the plasma profiles of inhibitory activity following administration of lovastatin once a baseline has been established.

3.4.4 Effect of Renal Impairment

Six hypercholesterolemic patients with severe renal impairment (GFR=10 to 30 mL/min) and 7 healthy control subjects received a single oral 80-mg dose of ¹⁴C-lovastatin (100 µCi) so that the effect of renal impairment on lovastatin disposition would be evaluated. The urinary recovery of radioactivity decreased somewhat in patients with severe renal impairment (~10% vs. ~19% in healthy subjects) and the AUC for active or total inhibitors was 2-fold higher. Although the higher inhibitor levels expected from a 10-mg dose are clearly safe, it is recommended that nonprescription lovastatin should not be used in patients with renal insufficiency without consultation with a physician.

3.4.5 Effect of Age and Gender

The effects of age and gender on plasma HMG-CoA reductase inhibitory activity following multiple doses of lovastatin (80 mg) were investigated in 16 elderly (7 males and 9 females) and 18 young (9 males and 9 females) hypercholesterolemic patients [34]. Elderly subjects ranged in age from 70 to 79 years while young subjects ranged in age from 19 to 30 years. Following 80-mg doses of lovastatin given daily for 17 days, plasma concentrations of HMG-CoA reductase inhibitory activity were slightly higher (mean AUC 22 to 30% higher) in elderly females than in elderly males. The same was true for young females versus young males where mean AUC was 35 to 48% higher. These differences were not significant. Mean AUC for inhibitors was also higher (33 to 56%) in elderly versus young patients, but the only comparison reaching significance was that for total inhibitors in elderly versus young males. None of these differences indicated that dosage adjustments were necessary for elderly versus young patients or for female versus male patients.

3.5 Pharmacokinetic Drug Interactions

3.5.1 Effect of Food

Twelve healthy volunteers received a 60-mg dose of lovastatin while fasting and immediately following a standard test meal which was similar in fat content to the expected diet of patients being treated for hypercholesterolemia. In the nonfasting state, peak plasma concentrations of both active and total inhibitors occurred sooner and were higher than in the fasting state. On average, AUC values following the test meal were about 50% higher than those achieved under fasting conditions. It is recommended in product labeling that lovastatin be given with meals as in clinical studies of efficacy.

3.5.2 Effect of Grapefruit Juice and other CYP3A4 Inhibitors

Grapefruit Juice

Grapefruit juice has been shown to be an inhibitor of CYP3A4 and lovastatin is a substrate for CYP3A4. To investigate the effect of grapefruit juice on lovastatin, L-154819, and lovastatin-derived HMG-CoA reductase inhibitory activity profiles, sixteen healthy male subjects consumed 8 ounces of regular-strength grapefruit juice (12 ounces of concentrate diluted with 3 x 12 ounces of water) or water daily with breakfast for 4 days (juice with breakfast is common). In the evening of Day 3, each subject received a single 40-mg dose of lovastatin (it is recommended that lovastatin be taken after the evening meal). Midazolam, a sensitive probe for CYP3A4 inhibition, was included as a positive control in this study and subjects received a 2-mg oral solution dose of midazolam (prepared from commercially available VERSED™, Roche Laboratories [intravenous formulation]) 1 hour after the morning glass of grapefruit juice or water on Day 3.

Midazolam results exhibited the anticipated inhibition of CYP3A4-mediated metabolism by grapefruit juice as the mean plasma AUC for midazolam increased by 2.4-fold. On the other hand, grapefruit juice had a minimal effect on plasma profiles of lovastatin-derived HMG-CoA reductase inhibitory activity. Mean AUC and C_{max} for either active or total inhibitory activity increased by 30 to 42% in the presence of grapefruit juice. The effect of grapefruit juice on the pharmacokinetics of lovastatin and L-154819 was somewhat greater, but still relatively small. The mean AUC and C_{max} for lovastatin approximately doubled (94 to 128%) under the influence of grapefruit juice, a 3-fold greater increase than was noted for the range of metabolites with actual HMG-CoA reductase inhibitory activity. The plasma $t_{1/2}$ of lovastatin was not affected. The effect of grapefruit juice on L-154819 was less as mean AUC and C_{max} increased by 57% and 65%, respectively. These effects are small when compared to increases in lovastatin and L-154819 AUC (12 to 15 fold and 4 to 5 fold, respectively) reported when lovastatin was given with much higher amounts of grapefruit juice (200 mL of double-strength grapefruit juice (12 ounces of concentrate diluted with 12 ounces of water) 3 times daily for 2 days followed by 200 mL of double-strength grapefruit juice given with, and 0.5 and 1.5 hours after, an 80-mg morning dose of lovastatin)[45]. Unfortunately, the effect on HMG-CoA reductase inhibitors was not measured in that grapefruit juice study.

Other CYP3A4 Inhibitors

Several clinical drug-interaction pharmacokinetic studies assessing the effect of CYP3A4 inhibitors on lovastatin kinetics have been published since the original marketing application. However, most have only examined parent lovastatin rather than total inhibitor. Itraconazole increased lovastatin AUC 19-fold [46]. Oral erythromycin

3.5.2 Effect of Grapefruit Juice and other CYP3A4 Inhibitors (Cont.)

(500 mg P.O. t.i.d. for 7 days) was shown to increase the plasma AUC and C_{max} of lovastatin by 5.7-fold and 5.3-fold, respectively, following multiple oral dosing with lovastatin (40 mg P.O. q.d. for 7 days) in healthy subjects [49]. In kidney transplant patients, cyclosporine (2 to 6 mg/kg/day) led to a 20-fold elevation (versus historical values) in the plasma AUC of lovastatin (GC-MS) after multiple oral dosing with lovastatin (20 mg P.O. q.d. for 28 days) [50]. Diltiazem administration (120 mg SR P.O. b.i.d. for 2 weeks) resulted in a 3.6-fold and 4.3-fold increase in the plasma AUC and C_{max} of lovastatin, respectively, following a single oral dose of lovastatin 20 mg in healthy subjects [51]. Isradipine after multiple doses (5 mg P.O. b.i.d. for 5 days) had no significant effect on plasma concentrations of lovastatin or total HMG-CoA reductase inhibitors following multiple doses of lovastatin (20 mg P.O. q.d. for 5 days) in healthy subjects [52].

The Merck grapefruit juice study showed that the magnitude of pharmacokinetic effect of a CYP3A4 inhibitor on the plasma AUC of lovastatin (by chemical assay) is at least 3 times greater than that on the plasma AUC of active/total HMG-CoA reductase inhibitory activity (by enzymatic assay). The enzymatic assay results are more clinically relevant since the rare myopathies associated with HMG-CoA reductase inhibitors and other cholesterol-lowering drugs are believed to be the result of excessive inhibition of cholesterol synthesis in skeletal muscle and it is likely that all of the circulating active inhibitors of HMG-CoA reductase might cause or contribute to myopathy. Therefore, even in the presence of one of the most potent inhibitors of the CYP3A4 pathway (itraconazole), the systemic exposure to HMG-CoA reductase inhibitory activity in a patient on the 10-mg dose of lovastatin would be below the plasma exposure observed following 80-mg of lovastatin, the maximum approved prescription dose. Nonetheless, proposed labeling for nonprescription lovastatin warns against taking lovastatin with drugs that inhibit CYP3A4.

Summary

Daily morning consumption of regular-strength grapefruit juice with breakfast has a minimal effect on plasma concentrations of HMG-CoA reductase inhibitory activity (<50% increase in AUC or C_{max}) following a 40-mg evening dose of lovastatin. The effects on lovastatin and L-154819 plasma concentrations are somewhat greater (<2.3-fold increase in AUC or C_{max}), but small by comparison to effects noted with other more potent CYP3A4 inhibitors or unrealistic consumption of grapefruit juice. Based on its minimal effect on plasma concentrations of HMG-CoA reductase inhibitors following evening oral administration of lovastatin, daily consumption of moderate amounts of regular-strength grapefruit juice does not require adjustment of the lovastatin dose.

3.5.2 Effect of Grapefruit Juice and other CYP3A4 Inhibitors (Cont.)

In conclusion, the effects of other more potent CYP3A4 inhibitors on plasma concentrations of lovastatin derived HMG-CoA reductase inhibitory activity are greater than the effect of grapefruit juice. However, for patients taking the OTC dose of lovastatin (10 mg) the exposure to HMG-CoA reductase inhibitors would be no greater than that for patients taking the highest prescription dose of lovastatin (80 mg). This is fortuitous since the incidence of severe adverse experiences (such as myopathy including rhabdomyolysis) with lovastatin at any approved dose is low (<0.2%). Hence, the risk of severe adverse experiences with the OTC dose of lovastatin, even if inadvertently taken with a potent CYP3A4 inhibitor, is very low and far exceeded by the benefits realized from reduced cardiovascular risks. Nonetheless, proposed labeling for nonprescription lovastatin warns against taking lovastatin with drugs that potentially inhibit CYP3A4.

3.6 Human Pharmacology: Conclusions

- Lovastatin is an inactive lactone which, upon hydrolysis, is converted to the β -hydroxyacid, L-154819, which is an inhibitor of HMG-CoA reductase.
- Lovastatin and its β -hydroxyacid (L-154819) are highly bound (>95%) to human plasma proteins.
- Lovastatin is extensively metabolized to active and inactive metabolites including, L-154819, and 4 other lactone: β -hydroxyacid pairs, all of which account for ~80% of the total HMG-CoA reductase inhibitory activity observed in plasma.
- Lovastatin at the 10-mg dose is not an inhibitor of CYP3A4 ($K_i = 7.7 \mu\text{M}$) in humans at the recommended clinical doses.
- Biliary excretion is an important route of elimination for drug from the body.
- L-154819 is rapidly cleared from the body (total body clearance and $t_{1/2}$ averaged 639 mL/min and 1.5 hours, respectively).
- The systemic availability of L-154819 following an oral dose of lovastatin is less than 9% of the dose because of first-pass hepatic extraction.
- The plasma AUC of active and total HMG-CoA reductase activity is increased 2-fold in patients with severe renal impairment (GFR=10 to 30 mL/min). Nonprescription lovastatin should not be used in patients with renal insufficiency without consultation with a physician.
- When lovastatin is administered with food, as in clinical studies, the AUCs of active and total inhibitors are about 50% higher compared to administration in the fasting state. For maximum benefit, lovastatin, including nonprescription lovastatin, should be given with meals.

3.6 Human Pharmacology: Conclusions (Cont.)

- With lovastatin dosages of 10-, 40-, 60-, 90-, and 120-mg, peak concentrations are achieved in 3 to 5 hours and the AUC and C_{max} of both active and total HMG-CoA reductase inhibitory activity in plasma increase nearly proportionally with dose. With once-a-day dosage regimens of lovastatin (10-, 40-, or 80-mg) there is modest steady-state accumulation of active and total inhibitors in plasma (<10 to 50%). These data indicate that the pharmacokinetics of lovastatin are, in general, linear throughout the therapeutic dosage range.
- Even after coadministration with a potent inhibitor of CYP3A4 (such as itraconazole), the plasma exposure to active or total HMG-CoA reductase inhibitory activity in a patient on the 10-mg dose of lovastatin would be well below the plasma exposure observed following 80-mg of lovastatin, the maximum approved prescription dose.
- No dose adjustment is required during coadministration of nonprescription lovastatin with less potent inhibitors of CYP3A4, including calcium channel blockers and moderate daily consumption of regular-strength grapefruit juice.
- The proposed labeling should reduce the likelihood that potent CYP3A4 inhibitors will be used concomitantly with nonprescription lovastatin.

4. Safety

4.1 Introduction

This Safety Summary provides a comprehensive review of the extensive data available with prescription lovastatin (10 to 80 mg) as well as the safety data from the Nonprescription Lovastatin Clinical Program. Lovastatin has been marketed since 1987 as a prescription drug for the reduction of elevated cholesterol levels and is currently approved and marketed in 65 countries worldwide, including the United States. According to data from IMS Health, approximately 90 million prescriptions have been written worldwide for lovastatin during the past 10 years and 8,800,000,000 tablets have been distributed worldwide. Assuming 1 tablet was taken daily irrespective of dosage strength, there are 24 million patient-years of treatment experience with lovastatin. The usual recommended starting dose of prescription lovastatin is 20 mg daily (estimated 72% of usage; 17,280,000 patient-years) and the maximum recommended dose is 80 mg daily (estimated 3% of usage; 720,000 patient-years). The proposed nonprescription dose of 10 mg has been available by prescription and is estimated to account for approximately 720,000 patient-years of treatment (3% of total use).

Criteria for OTC Use

Merck believes that medications being considered for nonprescription status should meet the following criteria regarding safety:

- There should be a very low incidence of medically significant adverse reactions when used according to adequate warnings and directions.
- Circumstances in which use may be potentially unsafe can be anticipated and clearly warned against.
- The consumer should be able to identify adverse effects and determine when these effects may require professional care.
- There should be a large margin of safety and well-defined safety profile if used inappropriately or at higher doses.
- Collateral measures such as laboratory testing of hepatic transaminases should not be necessary for safe use of the product.
- There should be a low potential for abuse or misuse under conditions of wide availability.

The data in this Safety Summary show that lovastatin 10 mg meets each of the above criteria. There is a wealth of safety information available from clinical trials and spontaneous reports received during prescribed use of lovastatin 10 to 80 mg per day. These data go well beyond what is ordinarily submitted to support the approval of a prescription drug, and clearly establish the safety of doses above that proposed for nonprescription use.

4.1 Introduction (Cont.)

Support From Large, Long-Term Trials

The most comprehensive and informative data come from two large, placebo-controlled, published postmarketing trials of lovastatin: The Expanded Clinical Evaluation of Lovastatin [EXCEL (N=8245)] studied doses of 20 to 80 mg/day, and the Air Force, Texas Coronary Atherosclerosis Prevention Study [AFCAPS/TexCAPS (N=6605)] studied 20 to 40 mg/day. Together, these studies evaluated almost 15,000 participants over prolonged periods of treatment in a rigorous and placebo-controlled fashion. They provide strong evidence that lovastatin at doses of 20 mg and greater is generally well tolerated by a diverse patient population. The type and frequency of adverse experiences with lovastatin 20 mg was generally similar to placebo. This experience provides compelling evidence that the 10-mg dose of lovastatin will be safe and well tolerated when used as directed according to the nonprescription label and the education and support program provided to the consumer.

Spontaneous Adverse Experience Reports

Merck maintains a database of all adverse experiences spontaneously reported to the company during marketed use of its products. This Worldwide Adverse Experience System (WAES) offers the opportunity to monitor adverse experiences that have occurred during the very extensive marketed use of prescription lovastatin since 1987. This is a voluntary system and therefore data are often incomplete. However, the ability to monitor, even in a limited way, the large, uncontrolled population that has been exposed to lovastatin is a valuable tool to detect infrequent and previously unrecognized adverse experiences associated with the drug. Review of these data confirms that lovastatin is generally well tolerated outside of the clinical trial setting. A comprehensive review of the WAES data for this submission did not reveal any previously unrecognized adverse experiences of potential concern associated with lovastatin.

OTC Development Program

The Nonprescription Lovastatin Clinical Program included seven clinical trials of lovastatin 10 mg. The studies included: 2 Phase I clinical pharmacology studies, 1 Phase III double-blind, placebo-controlled study designed to obtain additional efficacy data on the 10-mg dose, and 4 Use Studies. The Use Studies were designed to assess how participants would self-select and self-medicate with a 10-mg daily dose of lovastatin in a nonprescription setting for periods of 3 to 18 months. To evaluate safety and tolerability, adverse experiences were collected. A control (placebo) group was not included in the Use Studies since the clinical and laboratory adverse experience profile of lovastatin 20 to 40 mg had previously been shown to be generally similar to that of placebo in EXCEL and AFCAPS/TexCAPS. Lovastatin 10 mg was well tolerated in the Nonprescription

4.1 Introduction (Cont.)

Lovastatin Clinical Studies. There were no serious drug-related adverse experiences in these studies. Equally important, the information presented in this summary confirms that even when label instructions are not followed with lovastatin 10-mg daily, the occurrence of a serious consequence is very unlikely.

Key Focus

Lovastatin, with its novel mechanism of action, was the first HMG-CoA reductase inhibitor approved in the United States. The original label reflected an appropriate level of caution based on some of the toxicology study findings at very high doses (e.g., hepatic transaminase elevations) and the relatively limited clinical experience. Long-term clinical studies and widespread use over the past 12 years provide new insights and allow the original findings to be placed in perspective. At the same time, the potential for lovastatin to be very rarely associated with myopathy was recognized during that widespread use. Based on the animal studies and clinical experience, there are 3 topics that need to be carefully addressed when considering suitability for nonprescription use of lovastatin 10 mg: the risk of hepatotoxicity, the risk of myopathy, and the risk with inadvertent use during pregnancy. These concerns are common to all statin-class drugs and in some cases may be related to lipid lowering rather than the statin class alone. This Safety Summary reviews each of these topics in separate sections and concludes that the risks are extremely low and can be managed with appropriate statements in the label.

4.2 Experience with Marketed Prescription Drug—Overall

4.2.1 Postmarketing Studies

4.2.1.1 Adverse Experiences From EXCEL

EXCEL was a randomized, double-blind, parallel, 48-week study. Lovastatin was compared with placebo in 8245 patients with hypercholesterolemia (TC 240 to 300 mg/dL and LDL-C >160 mg/dL). Patients with hypercholesterolemia were randomized into 5 similar groups (approximately 1650 per group) taking 1 of 4 dosage regimens of lovastatin (20 and 40 mg once daily, 20 and 40 mg twice daily), or placebo [6]. There was no dose titration during the study.

Clinical adverse experiences reported as possibly, probably, or definitely drug related occurring in $\geq 1.0\%$ in any one treatment group are presented in Table 14. The percentage of patients with serious clinical adverse experiences by body system are listed in Table 15. The safety profile of the lovastatin doses and placebo were comparable. None of the adverse experiences in Table 14 and Table 15 demonstrated a statistically significant increase in incidence with lovastatin treatment. EXCEL demonstrates the large margin of safety with lovastatin. Doses up to 8 times the proposed OTC dose were well tolerated when taken for approximately 1 year.

4.2.1.1 Adverse Experiences From EXCEL (Cont.)

Table 14

Percent of Patients With Specific Drug-Related[†] Clinical Adverse Experiences by Body System With an Incidence ≥1% in Any One Treatment Group
 EXCEL (48 Weeks)

	Lovastatin 20 mg q.p.m. [‡] (N=1642)	Lovastatin 40 mg q.p.m. [‡] (N=1645)	Lovastatin 20 mg b.i.d. [‡] (N=1646)	Lovastatin 40 mg b.i.d. [‡] (N=1649)	Placebo (N=1663)
	%	%	%	%	%
Number of patients with any drug-related adverse experiences	399 (24.3)	401 (24.4)	399 (24.2)	421 (25.5)	374 (22.5)
Number of patients without any drug-related adverse experience	1243 (75.7)	1244 (75.6)	1247 (75.8)	1228 (74.5)	1289 (77.5)
Body as a Whole/Site Unspecified					
Asthenia	1.7	1.4	1.5	1.2	1.4
Digestive System					
Abdominal pain	2.0	2.0	2.2	2.5	1.6
Constipation	2.0	3.2	3.2	3.5	1.9
Diarrhea	2.6	2.4	2.2	2.6	2.3
Dyspepsia	1.3	1.3	1.0	1.6	1.9
Flatulence	3.7	4.3	3.9	4.5	4.2
Nausea	1.9	2.5	2.2	2.2	2.5
Musculoskeletal System					
Muscle cramps	0.6	0.8	1.1	1.0	0.5
Myalgia	2.6	1.8	2.2	3.0	1.7
Nervous System and Psychiatric Disorders					
Dizziness	0.7	1.2	0.5	0.5	0.7
Headache	2.6	2.8	2.1	3.2	2.7
Skin and Skin Appendage					
Rash	0.8	1.0	1.2	1.3	0.7
Special Sense Disorders					
Blurred vision	1.1	0.9	0.9	1.2	0.8
[†] Determined by the investigator to be possibly, probably or definitely drug related. [‡] q.p.m. = once daily with evening meal; b.i.d. = twice daily. Although a patient may have had two or more drug-related adverse experiences, the patient is represented only once in the body system total.					

4.2.1.1 Adverse Experiences From EXCEL (Cont.)

Table 15

Number(%) of Patients With Serious Clinical Adverse Experiences by Body System
 EXCEL (48 Weeks)

	Lovastatin 20 q.p.m. [†] N=1642	Lovastatin 40 q.p.m. [†] N=1645	Lovastatin 20 b.i.d. [†] N=1646	Lovastatin 40 b.i.d. [†] N=1649	Placebo N=1663
	n (%)	n (%)	n (%)	n (%)	n (%)
Number of patients with a serious adverse experience	148 (9.0)	132 (8.0)	137 (8.3)	166 (10.1)	146 (8.8)
Number of patients without a serious adverse experience	1494 (91.0)	1513 (92.0)	1509 (91.7)	1483 (89.9)	1517 (91.2)
Body as a whole/site unspecified	23 (1.4)	29 (1.8)	30 (1.8)	37 (2.2)	27 (1.6)
Cardiovascular System	73 (4.4)	59 (3.6)	63 (3.8)	72 (4.4)	73 (4.4)
Digestive System	18 (1.1)	19 (1.2)	18 (1.1)	18 (1.1)	17 (1.0)
Endocrine System	2 (0.1)	0 (0.0)	0 (0.0)	2 (0.1)	0 (0.0)
Hematologic and Lymphatic System	1 (0.1)	1 (0.1)	0 (0.0)	1 (0.1)	4 (0.2)
Metabolic, Nutritional and Immune System	1 (0.1)	3 (0.2)	2 (0.1)	1 (0.1)	0 (0.0)
Musculoskeletal System	12 (0.7)	8 (0.5)	19 (1.2)	16 (1.0)	17 (1.0)
Nervous System and Psychiatric Disorders	9 (0.5)	8 (0.5)	8 (0.5)	14 (0.8)	7 (0.4)
Respiratory System	8 (0.5)	7 (0.4)	10 (0.6)	12 (0.7)	8 (0.5)
Skin and Skin Appendage	11 (0.7)	5 (0.3)	3 (0.2)	12 (0.7)	6 (0.4)
Special Sense Disorders	7 (0.4)	5 (0.3)	3 (0.2)	3 (0.2)	9 (0.5)
Urogenital System	18 (1.1)	24 (1.5)	21 (1.3)	26 (1.6)	14 (0.8)

[†] q.p.m. = once daily with evening meal; b.i.d. = twice daily.
 Although a patient may have had two or more serious adverse experiences, the patient is counted only once in the body system total.

4.2.1.2 Adverse Experiences From AFCAPS/TexCAPS

AFCAPS/TexCAPS was a randomized, double-blind, placebo-controlled study. The purpose was to evaluate lovastatin versus placebo in primary prevention of CHD in 6605 participants over a median duration of 5 years. The participants were predominately healthy men and women with average total cholesterol (TC) and low density lipoprotein cholesterol (LDL-C), below average high-density lipoprotein (HDL) cholesterol, and at least one CHD risk factor, namely age, ≥45 years for men and ≥55 years for women. The dose of lovastatin was initiated at 20 mg/day. The dose was increased to 40 mg daily at Week 18 if the patient's LDL-C level was >110 mg/dL.

4.2.1.2 Adverse Experiences From AFCAPS/TexCAPS (Cont.)

The profile of serious adverse experiences by body system is shown in Table 16. Adverse experiences are included irrespective of drug relationship. Participants are only counted once per category. The incidence of serious adverse experiences between treatment groups was compared using Fisher's exact test. The total number of participants experiencing any serious adverse experience was 1131 (34.2%) in the lovastatin group and 1126 (34.1%) in the placebo group (p=0.938). The cumulative incidence of serious adverse experiences in AFCAPS/TexCAPS was greater than in EXCEL, as would be expected given the 5 years of treatment.

As expected from the efficacy results, there were significantly fewer serious cardiovascular adverse experiences in the lovastatin group than the placebo group (260 versus 310; p=0.028). In the Nervous System and Psychiatric Disorders body system there were significantly more serious adverse experiences in those receiving lovastatin compared with placebo (62 versus 38; p=0.020); however, a treatment-group comparison of the types of disorders revealed no significant differences. The most frequently reported serious adverse experiences of the nervous system were falling (9 on lovastatin versus 7 on placebo), radiculopathy, lumbar (6 versus 4), and radiculopathy, cervical (4 versus 5). Fewer than 4 participants per treatment group experienced other types of serious adverse experiences of the nervous system.

Table 16

Number (%) of Participants With Specific Serious Clinical Adverse Experiences by Body System—AFCAPS/TexCAPS (Average 5 Years Follow-Up)

	Lovastatin (N=3304)		Placebo (N=3301)		Between- Group
	N	(%)	n	(%)	p-Value
Participants with any serious adverse experiences	1131	(34.2)	1126	(34.1)	0.938
Body as a Whole/Site Unspecified	169	(5.1)	179	(5.4)	0.582
Cardiovascular System	260	(7.9)	310	(9.4)	0.028
Digestive System	163	(4.9)	173	(5.2)	0.576
Endocrine System	82	(2.5)	88	(2.7)	0.642
Musculoskeletal System	153	(4.6)	147	(4.5)	0.768
Nervous System and Psychiatric Disorders	62	(1.9)	38	(1.2)	0.020
Respiratory System	85	(2.6)	89	(2.7)	0.759
Skin and Skin Appendage	265	(8.0)	243	(7.4)	0.332
Urogenital System	243	(7.4)	256	(7.8)	0.545

4.2.1.2 Adverse Experiences From AFCAPS/TexCAPS (Cont.)

Nonserious and serious adverse experiences that were determined by the investigator to be drug related were evaluated. There were no significant differences between lovastatin and placebo in the incidence of drug-related adverse experiences. The total number of participants experiencing any drug-related clinical or laboratory adverse experience was 577 (17.5%) in the lovastatin group and 525 (15.9%) in the placebo group (p=0.092).

Long-term, chronic use of lovastatin was well tolerated. There were no clinically important differences between lovastatin 20 and 40 mg daily and placebo in the number of participants experiencing confirmed clinically important elevations in CK (>10 x Upper Limit of Normal [ULN]) and hepatic transaminases (>3 x ULN). There were no clinically important differences between treatment groups in the incidences of fatal and nonfatal cancers.

4.2.1.3 Conclusions From EXCEL and AFCAPS/TexCAPS

Long-term, chronic use of lovastatin was generally well tolerated in both EXCEL and AFCAPS/TexCAPS participants. The safety profile of lovastatin 20 to 40 mg/day was comparable to that of placebo.

4.2.2 Spontaneous Reports During Marketed Use

Spontaneous reports provide some perspective on the frequency and potential relationship to lovastatin of serious adverse experiences in the general population. Spontaneous reports are those for which the reporting source is either a health care provider, a patient, a report in the literature, or a governmental agency. These spontaneous reports for lovastatin encompass prescription use across all doses. It is important to note that the spontaneous reporting system is a voluntary system. Therefore, despite attempts to obtain follow-up information, the data are not necessarily complete and may include reports with unsubstantiated diagnoses and incomplete information (e.g., total daily dose of lovastatin may not be reported). Drug relationship may not be determined in spontaneous reports. The number of reports needs to be viewed in the context of the extensive marketed experience with lovastatin (estimated 24,000,000 patient-treatment years). The estimated number of patient-treatment years is: 720,000 for 10 mg (3%), 17,280,000 for 20 mg (72%), 4,800,000 for 40 mg (20%), 480,000 for 60 mg (2%), and 720,000 for 80 mg (3%).

Spontaneous reports are divided into serious and nonserious adverse experiences. According to standard regulatory convention, a serious adverse experience is defined as one that: results in death, is life-threatening, results in a persistent or significant disability/incapacity, results in or prolongs hospitalization, is a congenital anomaly, is a cancer, or is the result of an overdose (accidental or intentional). Since April 1, 1998, the definition of a serious adverse experience was expanded to include any report of an "important medical event" (i.e., required medical intervention to prevent one of the aforementioned outcomes).

4.2.2.1 Serious Spontaneous Reports by Body System (WAES)

A total of 1989 spontaneous reports classified as serious were received as of 31-Dec-1999. The majority of reports originated from the United States. Table 17 displays the number of serious reports for each body system.

Five body systems had more than 240 serious spontaneous reports (approximate reporting rate of ≥ 1 per 100,000 patient-treatment-years [PTY]): musculoskeletal (543 [2.3 per 100,000 PTY]); body as a whole (379 [1.6 per 100,000 PTY]); hepatobiliary (331 [1.4 per 100,000 PTY]); cardiovascular (320 [1.3 per 100,000 PTY]); and eyes, ears, nose and throat (319 [1.3 per 100,000 PTY]). These five body systems are discussed in more detail below.

Musculoskeletal System

The most frequent serious adverse experiences are rhabdomyolysis (202 reports), myalgia (73 reports) and myositis (78 reports). Many of these reports are also counted in the Metabolism and Nutrition body system (if an elevated creatine kinase was reported). Warnings about the potential for myopathy are included in the prescription circulars for all HMG-CoA reductase inhibitors. See 4.3.2 for an in-depth discussion of myopathy.

Body as a Whole/Site Unspecified

The most frequently reported serious adverse experience in this body system was drug interaction (58 reports). The potential for drug-drug interactions is discussed in 4.3.4.

Hepatobiliary System

Within the hepatobiliary system, the majority of serious adverse experiences are classified under hepatitis (101 reports) or hepatic function abnormality (98 reports). See 4.3.1 for an in-depth discussion of elevations of LFTs and other hepatic adverse experiences.

Cardiovascular System

Within the cardiovascular system, there are 320 reports of serious adverse experiences. In general, the most frequently reported serious adverse experiences (congestive heart failure, myocardial infarction, cerebrovascular accident, and arrhythmia) reflect the underlying risk factors present in patients treated with lovastatin.

Eyes, Ears, Nose, and Throat

Within the Eyes, Ears, Nose and Throat system, the most frequently reported serious adverse experiences were related to the eye. The most frequently reported adverse experiences are cataracts and lenticular disorders, terms generally referring to the same diagnoses. The frequent reporting of these adverse experiences is likely a consequence of the recommendation of slit lamp examination of the lens which appeared as an initial

4.2.2.1 Serious Spontaneous Reports by Body System (WAES) (Cont.)

precaution in the product circular when the drug was marketed in 1987. The recommendation was made because lovastatin produced subcapsular lens opacities in dogs. However, these opacities occurred in dogs at extremely high plasma concentrations of lovastatin and extremely low cholesterol levels. Similar drug-related findings were not observed in humans in the preapproval trials.

The recommendation for slit lamp examination of the lens was subsequently removed from the product circular by the FDA in 1991 when evidence demonstrated the absence of clinical adverse effects on the lens. The evidence includes adverse experiences collected in long-term clinical studies with lovastatin, a report documenting an absence of effect on cholesterol concentrations in any region of the lens, and a lack of epidemiological association between cataracts and use of HMG-CoA reductase inhibitors [19; 20; 21]. To further investigate lens changes, a 2-year, randomized, double-blind, placebo-controlled clinical study (N=192) was conducted specifically to measure the cataractogenic potential of lovastatin 40 mg. The results show that there was no difference between lovastatin and placebo in the formation of cataracts or in visual function [18].

Table 17

Number of Serious Clinical Adverse Experiences Reported to WAES for Lovastatin by Body System (1987 Through Dec-1999)

Adverse Experience Term	(Total of 1989 Spontaneous Reports) Number of Reports [†]
Body as a Whole/Site Unspecified	379
Cardiovascular System	320
Digestive System	224
Endocrine System	36
Eyes, Ears, Nose, and Throat	319
Hematologic and Lymphatic System	140
Hepatobiliary System	331
Immune System	32
Metabolism and Nutrition	128
Musculoskeletal System	543
Nervous System	204
Psychiatric Disorder	53
Respiratory System	94
Skin and Skin Appendage	63
Urogenital System	204
[†] Reports with more than one adverse experience are counted in the body system pertaining to each adverse experience. Therefore, the sum of adverse experiences may be larger than the total number of reports.	

4.2.2.2 WAES Reports With Fatal Outcomes

From the time of market introduction to December 31, 1999, Merck received 130 reports in which a fatal outcome was reported in patients who had been exposed to lovastatin. This is not an alarming amount given the extensive usage in a patient population with cardiovascular disease. The 130 reports represent a reporting rate of 5.4 deaths per million patient-treatment-years of lovastatin. As would be expected in a large group of American adults, most of the deaths were attributed to cardiovascular events or cancer. Deaths due to acute liver disease or myopathy are discussed in 4.3.1 and 4.3.2, respectively.

Cardiovascular

There are 35 reports of patients who died from cardiovascular adverse experiences while taking or after taking lovastatin. These adverse experiences were often preexisting conditions or a consequence of risk factors cited in the patients' history. They reflect the population chosen for treatment with lovastatin, those with elevated cholesterol and CHD. In AFCAPS/TexCAPS, patients treated with lovastatin compared to placebo experienced a 37% lower incidence of the first major coronary event [3]. Based on this result and in view of the use of lovastatin throughout the years, there are no data to suggest a causal role of lovastatin in the exacerbation of a cardiovascular disease.

Cancer

Twenty-six patients have been reported to have died from a variety of cancers while or after taking lovastatin. Eleven of the patients were on lovastatin for ≤ 1 year before the diagnosis was made. Types of cancer included hepatobiliary, leukemia/lymphoma, pulmonary, prostate cancer, pancreatic cancer, angiosarcoma, adrenal cancer, metastatic cancer to the liver, primary cancer unknown, and melanoma. There is no pattern of reporting observed for any specific cancer. Considering 24 million patient-treatment years of lovastatin, this is a reporting rate of approximately 1 cancer death per one million patient-treatment-years. There are substantial data from postmarketing megatrials supporting the conclusion that HMG-CoA reductase inhibitors are not linked to an increased incidence of cancer in humans. In AFCAPS/TexCAPS there was no significant difference between treatment groups in incidence of fatal and nonfatal cancer [3]. A recent meta-analysis of 5 randomized controlled trials of HMG-CoA reductase inhibitors showed that active treatment was not significantly associated with change in non-cardiovascular mortality or cancer [64]. In view of the absence of predominance of any cancer type reported, the limited numbers of reported cases in WAES, and information from the published literature, there is no evidence lovastatin may induce or promote the development and progression of malignancies.

4.2.2.3 Conclusion From All Spontaneous Reports

Recent review of the WAES data does not reveal a new association between lovastatin and an adverse experience not currently included in the package circular. The spontaneous reports generally reflect the known side effects of the drug (myopathy and aminotransferase elevations), previous warnings within the product circular (lenticular disorders), or concomitant disease in the patient population (congestive heart failure, myocardial infarction).

4.3 Topics of Special Interest

4.3.1 Hepatobiliary Adverse Experiences

4.3.1.1 Introduction

The liver is the primary site of action for lovastatin. The prescription product circular of lovastatin recommends that liver function tests (LFTs) be performed before initiation of treatment, at 6 and 12 weeks after initiation of treatment or elevation in dose, and periodically thereafter (e.g., semi-annually) [63]. Therapy should be discontinued if there is a persistent increase in ALT or AST greater than 3 x ULN. This warning, which is similar for all drugs in this class, is based on findings from animal toxicology studies and the early clinical studies conducted with lovastatin. Lovastatin, the first HMG-CoA reductase inhibitor to be approved, showed an increase in ALT associated with treatment. Large clinical studies conducted postapproval and spontaneous reports received during marketed use provide reassurance that clinical hepatotoxicity associated with lovastatin is exceedingly rare. The postapproval data also indicate that routine monitoring of LFTs is an extremely low-yield procedure for identifying patients who might need to stop treatment to prevent serious liver injury, particularly at low doses of medication. These data have been reviewed by an independent consultant, Dr. Keith Tolman, Professor of Medicine and Director of Hepatology and Clinical Pharmacology at the University of Utah Medical School. Dr. Tolman concludes that there appears to be two types of hepatic abnormalities associated with the use of lovastatin: a dose-related asymptomatic ALT elevation that is not associated with clinically significant hepatic injury; and very rare hepatic reactions manifested primarily by hepatocellular or mixed injury. These hepatotoxic reactions may or may not be drug-related, and are so rare that LFT monitoring would not be useful in users of lovastatin 10 mg.

Because HMG-CoA reductase inhibitors may be associated with myopathy accompanied by elevated AST, this discussion will focus on ALT, which is more liver specific. When transaminases are elevated due to therapy with an HMG-CoA reductase inhibitor, in the absence of myopathy, ALT is almost invariably increased more than AST.

4.3.1.2 ALT Elevations in NDA Studies for Prescription Lovastatin

Chronic toxicology studies in rats and dogs demonstrated that exceedingly high doses of lovastatin (>180 mg/kg/day) caused elevations in ALT but were not associated with hepatocellular necrosis. Hepatic necrosis was noted in rabbits administered comparably high doses (100 to 200 mg/kg/day) of lovastatin. Rabbits are uniquely sensitive to HMG-CoA reductase inhibitors and quickly develop anorexia. The injury could be prevented by forcing adequate nutrition or co-administration of mevalonic acid suggesting that the hepatocellular injury was related to mevalonic acid depletion.

The Phase III clinical studies in support of the original NDA for prescription lovastatin compared lovastatin with active comparator agents rather than with placebo. Increased ALT was reported as a drug-related adverse experience in 3.1% of patients treated with lovastatin at 40 to 80 mg/day for up to 212 days, and this frequency was comparable to that seen with the comparator agents, cholestyramine (3.4%) and probucol (3.1%). Fifteen patients (1.5%) who received lovastatin had therapy discontinued or interrupted because of significant (>3 x ULN) increases of hepatic transaminases. One patient had a 10 x ULN increase in ALT, but in general the elevations were 3- to 6-fold. All 15 patients were asymptomatic. Nine of the 15 patients were taking more than 20 mg of lovastatin per day. The ALT elevations that necessitated discontinuation had not been preceded by smaller earlier elevations. Possible contributing factors to the elevated ALT levels were found in 8 of the patients (5 had preexisting ALT elevations, and 4 had self-reported heavy alcohol intake).

4.3.1.3 ALT Elevations in Postapproval Clinical Studies

EXCEL

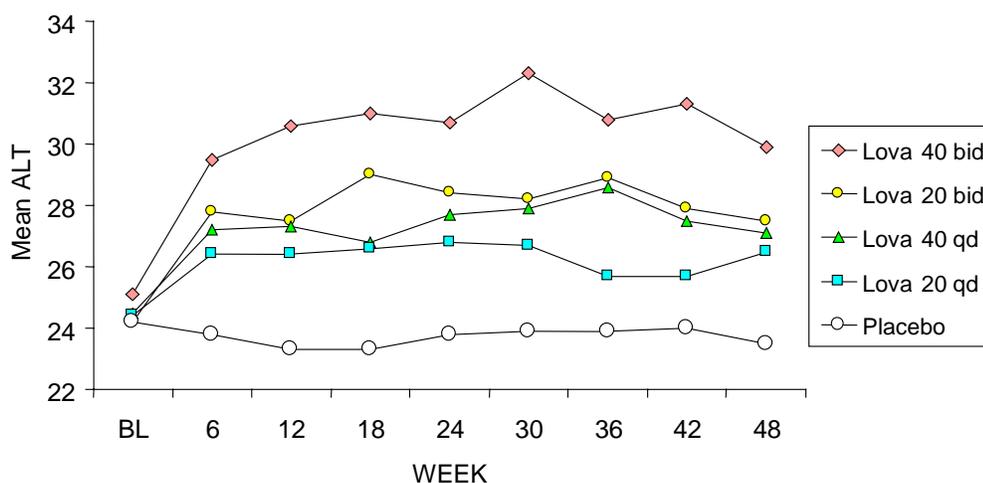
The 48-week EXCEL study excluded patients with preexisting elevations in hepatic transaminases. Throughout the 48 weeks of the study liver function tests were measured every 6 weeks. Preset guidelines required rapid re-testing of all those with ALT or AST values greater than 3 x ULN. Those with a confirmed elevation were discontinued from the study. Eighty-two percent of the placebo patients and 83% of the lovastatin patients completed 48 weeks of treatment.

Figure 5 presents the mean ALT by treatment group over the entire course of the study. There was a dose-related increase in mean ALT within the first 6 to 12 weeks, followed by a plateau. The increase in ALT with 20 mg was small (<3 U/L) and clinically insignificant. The increase occurred in the same time frame as the largest decrease in LDL-C, suggesting that the ALT change reflects the treatment-related alteration in cholesterol metabolism. The ALT elevations are likely due to either increased ALT synthesis, decreased ALT clearance, or to enzyme leakage, thought to be related to destabilization of cellular membranes due to a change in lipid content.

4.3.1.3 ALT Elevations in Postapproval Clinical Studies (Cont.)

Figure 5

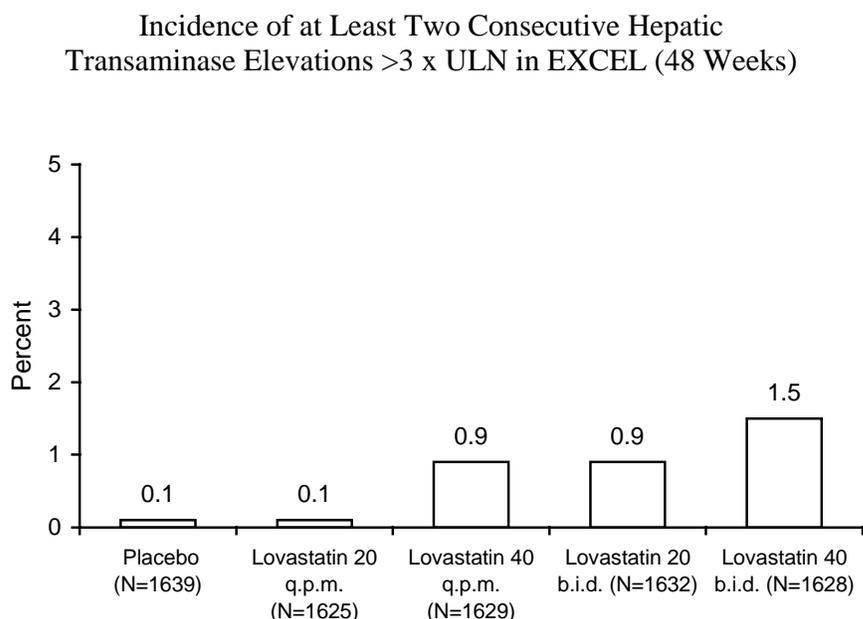
Mean ALT Elevations by Week—EXCEL (N=8245)



The crude rate of successively elevated ALT levels >3 x ULN in each of the 5 treatment groups is shown in Figure 6 and indicates a dose-proportional increase in incidence of 3 x ULN elevations of ALT ($p < 0.001$ for trend). It is noteworthy that there is no difference between placebo (0.1%) and the 20-mg daily dose of lovastatin (0.1%) suggesting that the incidence at 20 mg is extremely low. After discontinuation of study drug, hepatic transaminase levels decreased in 45 of the 47 patients who had confirmed ALT levels >3 x ULN. One of the other 2 patients was receiving placebo (level remained >3 x ULN), the other patient was receiving lovastatin 80 mg/day (unavailable for follow-up 13 weeks after discontinuation). There were no 10-fold elevations of ALT. Concomitant mild elevations in alkaline phosphatase were observed in 7 patients and one had a slight elevation of bilirubin. Four patients on lovastatin 80 mg/day had transient symptoms (nausea, abdominal pain, poor appetite, fatigue), but none was diagnosed by an investigator as having clinical hepatitis [6].

4.3.1.3 ALT Elevations in Postapproval Clinical Studies (Cont.)

Figure 6



AFCAPS/TexCAPS

The over 5-year AFCAPS/TexCAPS study also excluded those with preexisting elevated transaminase levels. Monitoring of ALT in this study closely followed recommendations established in the product circular, namely measurements were made prior to study entry and at 6-week intervals for the first year, and 6-month intervals thereafter. Over 50,000 transaminase measurements were made during the trial. Elevations of ALT >3 x ULN were rare and occurred with similar frequency in the lovastatin and placebo groups: 18 (0.6%) and 11 (0.4%) in those receiving lovastatin and placebo, respectively. Consecutive elevations >3 x ULN for ALT or AST were reported in 0.7% of participants who received lovastatin 20 mg daily and 0.4% who were titrated to lovastatin 40 mg daily. Only limited inferences can be drawn from examining data for the individual doses as comparisons by dose are of nonrandomized groups since titration was allowed.

4.3.1.3 ALT Elevations in Postapproval Clinical Studies (Cont.)

Of the 18 participants who were receiving lovastatin and had a confirmed ALT elevation of 3 x ULN, 14 either recovered on treatment or had a negative rechallenge (Table 18). One participant had chronic active hepatitis, one patient had fatty liver and hepatomegaly, and one participant had a positive rechallenge and was found to have concurrent cholelithiasis. Thus, in only 1 participant could lovastatin be reasonably deemed proximately related to the elevated ALT. Interestingly, the pattern was almost identical in the placebo-treated group, with 6 of the 11 participants having a negative rechallenge or recovering on treatment, 2 a positive rechallenge, and one found to have fatty liver.

Table 18

Outcome of ALT Elevations >3 x ULN in AFCAPS/TexCAPS (N=6605)
 Number of Patients by Treatment Group

Outcome	Lovastatin 20 to 40 mg (N=18)	Placebo (N=11)
	n	N
Negative rechallenge or resolved on treatment	14	6
Positive rechallenge	1	2
Discontinued treatment and had alternate diagnosis [†]	3	3

[†] Chronic active hepatitis, hepatitis A, fatty liver, cholelithiasis, or other medication.

There were 127 participants on lovastatin who had ALT elevations between 2 and 3 x ULN. These participants were continued on drug and followed (Table 19). In 91 participants (72%), subsequent ALT elevations decreased. In 18 (14%), the ALT remained in the 2 to 3 x ULN range. In the remaining 18 participants (14%), the ALT levels progressed to greater than 3 x ULN. The profile for placebo-treated patients was similar. Elevations between 2 and 3 x ULN were not predictive of progressive liver disease and thus not helpful as a monitoring tool.

4.3.1.3 ALT Elevations in Postapproval Clinical Studies (Cont.)

Table 19

Follow-Up of ALT Elevations Between 2 and 3 x ULN (40 IU/L)
 AFCAPS/TexCAPS (N=6605)

Subsequent Measurement	Number of Patients on Lovastatin (N=127)	Number of Patients on Placebo (N=91)
	n (%)	n (%)
Decreased Below 2 x ULN	91 (72)	64 (70)
Remained 2 to 3 x ULN	18 (14)	22 (24)
Increased to >3 x ULN	18 (14)	5 (5)

4.3.1.4 Spontaneous Reports During Marketed Use—WAES

Acute Liver Failure

There have been 5 reports of acute liver failure possibly related to lovastatin, or where lovastatin could not be excluded as causal, for a reporting rate of 1 in 4.8 million patient-treatment years. The 5 cases are summarized in Table 20. For perspective, the estimated background incidence of acute liver failure from all causes is 1/100,000-200,000 per year [61]. Therefore, there is no signal that lovastatin is associated with an increased risk of acute liver failure.

There were 13 WAES reports describing patients who died and had acute or chronic liver failure (0.54 reports per million patient-treatment-years). Four of the 13 patients had acute liver failure and a casual relationship with lovastatin could not be excluded; these patients are listed in Table 20. Two of the 13 patients had acute hepatitis and are included in the next section. Biopsies revealed that 1 of these 2 patients had granulomatous hepatitis, the other had autoimmune hepatitis with advanced micronodular cirrhosis. The remaining 7 patients had acute or chronic liver failure with a likely etiology other than lovastatin (e.g., primary biliary cirrhosis, hepatitis B, sepsis, chronic acetaminophen toxicity, overdose with multiple medications).

4.3.1.4 Spontaneous Reports During Marketed Use—WAESU (Cont.)

Table 20

Spontaneous Reports of Acute Liver Failure Possibly Related to Lovastatin
 WAES

Gender/ Age	Duration of Lovastatin Use	Lovastatin Dose (mg)	Relevant Medical History	Relevant Laboratory Results	Liver Biopsy	Autopsy Finding
F/63	7 months	Unknown	Polycystic kidney disease; nephrectomy; multiple transfusions; hepatitis B vaccine	Hepatitis A IgG+ Hepatitis B sAb+ Hepatitis B sAg and cAg negative	--	Fulminant liver failure; hemorrhagic fatty necrosis of pancreas
F/51	2 years	Unknown	--	--	--	Massive hepatic necrosis
M/75	7 months	20	CABG; nephrectomy; multiple transfusions	Hepatitis A, B, and C negative HIV ELISA [†] weakly positive	Submassive collapse, little evidence of regenerative activity	Massive and submassive hepatic necrosis
F/63	6 years	20	Cholelithiasis; cholecystectomy	--	Auto-immune hepatitis	Did not die.
F/53	2 months	Unknown	Coronary artery disease; diabetes mellitus	Hepatitis A, B, and C negative Smooth muscle Ab positive	Auto-immune chronic active hepatitis; early cirrhosis	Aspergillosis- multivisceral; intracerebral hemorrhage; fulminant hepatic necrosis

[†] Human Immunodeficiency Virus enzyme immunoassay.

Acute Hepatitis

There were 232 reports of “hepatitis” for a reporting rate of 9.7 cases per million patient-treatment years (this does not include the 5 reports of acute hepatic failure discussed above). In many of these cases, the only evidence of hepatitis was an elevated hepatic transaminase determination. The 232 reports exclude those labeled as Hepatitis A, B, or non-A, non-B. Most (177) of the reports were received before 1993, the first year that a sensitive test for Hepatitis C was widely available. The dose of lovastatin was known in 158 cases: ≥80 mg, 9 cases; 60 mg, 5 cases; 40 mg, 29 cases; 20 mg, 113 cases; and 10 mg, 2 cases. This does not suggest any relationship to dose as it parallels the known

4.3.1.4 Spontaneous Reports During Marketed Use—WAESU (Cont.)

utilization of lovastatin. Liver biopsies were available for 57 of the patients and are summarized in Table 21 (grouping was performed by outside expert hepatologist, Dr. Tolman). Of the remaining 175 reports of “hepatitis,” 67 had an elevated bilirubin in addition to increased hepatic transaminases. There was no pattern among the 232 cases indicative of a common pathogenesis. In some cases, the pattern of injury suggested a cholestatic reaction, in others there was predominantly hepatocellular damage, and in others a combination of the two. These data do not provide clear evidence that lovastatin is associated with any specific type of hepatotoxicity.

Table 21

Patients on Lovastatin With Pathologies Based Upon Liver Biopsies for “Hepatitis”
 WAES (Spontaneous Reports)

Hepatitis (N=36)		Other (N=21)	
Acute	6	Cholestatic	8
Chronic active	7	Fatty Liver	6
Chronic persistent	1	Cirrhosis	2
Chemical/toxic	5	Cholangitis	5
Autoimmune	3		
‘Nutritional’	1		
Granulomatous	8		
Inflammation	4		
Hypersensitivity	1		
TOTAL: 57			

4.3.1.5 Utility of Liver Function Test Monitoring

The medical appropriateness of periodic liver function testing to help prevent hepatic injury among users of lovastatin 10 mg may be evaluated by established criteria for judging the appropriateness of using a given test to screen for a specific disease. Any such test should be effective in reducing morbidity or mortality and sufficiently accurate to avoid large numbers of false-positive and false-negative results. Periodic liver function testing among users of lovastatin 10 mg cannot be justified by either of these two criteria. Extensive marketing experience shows that the serious hepatic injury with lovastatin use is extremely rare. It is by no means evident that these cases could have been prevented by periodic monitoring of transaminases.

4.3.1.5 Utility of Liver Function Test Monitoring (Cont.)

During the 5 years of AFCAPS/TexCAPS, over 50,000 ALT and AST tests were performed, but there were only 29 confirmed elevations >3 x ULN, 18 in the lovastatin group and 11 in the placebo group. Elevations >3 x ULN in ALT confirmed upon re-testing occurred in 0.4% of 3248 placebo recipients and in 0.6% of 3242 lovastatin recipients [3]. Confirmed elevations >10 x ULN occurred in 0.1% of the placebo recipients and 0.2% of the lovastatin recipients. In only one of the lovastatin patients and in two of the placebo patients was there a positive rechallenge.

These results, taken together, indicate that sustained elevations in ALT were very uncommon among lovastatin users at the doses tested (20 to 40 mg). Furthermore, the elevations were not predictive of progressive lovastatin-related liver disease. Hepatic transaminase elevations occur in association with numerous other conditions including viral hepatitis, alcohol use, obesity, and exercise. The comparable profile in placebo recipients indicates that the vast majority of hepatic transaminase elevations do not represent clinically significant hepatic injury that may be related to use of lovastatin.

4.3.1.6 Hepatobiliary Adverse Experiences: Conclusions

- Dose-proportional increases in hepatic transaminases (>3 x ULN) are observed with lovastatin; however, in studies of lovastatin 20 to 80 mg/day the incidence with 20 mg is no different than that observed with placebo.
- The spontaneous reporting rate for serious hepatic adverse experiences of heterogeneous pathology is extremely rare, on the order of 10 per million patient-treatment years of lovastatin, does not appear to be dose related, and the relationship to lovastatin is unclear in many of the reports.
- Routine monitoring of LFTs in users of nonprescription lovastatin could be expected to produce a high proportion of abnormal tests which are not indicative of any hepatotoxicity associated with lovastatin.
- Routine monitoring of LFTs will not reduce the extremely low risk of serious liver disease in people taking lovastatin 10 or 20 mg daily.

4.3.2 Myopathy

4.3.2.1 Introduction

Myopathy, including rhabdomyolysis, is associated with all HMG-CoA reductase inhibitors. Fortunately, clinical study and marketed experience indicate that myopathy is rare. In the context of therapy with an inhibitor of HMG-CoA reductase, the term myopathy has been defined as unexplained muscle pain or weakness accompanied with an elevated creatine kinase (CK) value >10 x upper limit of normal (ULN). Myopathy usually occurs within the first few weeks of treatment, or shortly after the introduction of

4.3.2.1 Introduction (Cont.)

an interacting drug. If myopathy occurs, therapy should be discontinued promptly, whereupon the patient usually recovers without sequelae. Physicians tend to use the term rhabdomyolysis when myopathy is severe and prompts hospitalization. Rhabdomyolysis may rarely, as a consequence of myoglobinuria, result in acute renal failure and death.

Myopathy is clearly a class effect, because it has been reported with all members of the statin class, and in rats the myopathic effects can be prevented by mevalonate, the product of the inhibited enzyme [56]. The risk of myopathy is dose related and increased by the concomitant use of fibrates, and to a lesser extent, nicotinic acid [5; 57; 59]. Both fibrates and niacin can cause myopathy when given alone [55; 58]. There is currently no explanation for why 3 classes of lipid-lowering drugs (HMG-CoA reductase inhibitors, fibrates, and niacin) that have quite different pharmacologic properties, can all cause myopathy. The mechanism by which any of these drugs cause myopathy is not understood. There is no evidence that fibrates or niacin inhibit plasma HMG-CoA reductase activity, so the interaction with these drugs appears to be an effect of lipid modification rather than specific inhibition of HMG-CoA reductase.

Lovastatin and some of the other HMG-CoA reductase inhibitors (statins) are metabolized by cytochrome P-450 3A4 (CYP3A4). Clinical experience has shown that the relative risk of myopathy with lovastatin is increased by concomitant use of those few drugs that substantially inhibit CYP3A4 (e.g., cyclosporine, itraconazole, ketoconazole, erythromycin, clarithromycin, and nefazodone), but the absolute risk is still very low[63]. Drug interactions are discussed further in 4.3.4.

4.3.2.2 Myopathy in Postapproval Clinical Studies

EXCEL

As noted earlier, EXCEL was a 48-week, placebo-controlled study using lovastatin doses of 20 mg to 80 mg/day. Myopathy, defined as muscle symptoms associated with an increase in CK to >10 x ULN, occurred in 5/6582 (0.08%) patients receiving treatment with lovastatin (4 patients receiving 80 mg [0.2%], 1 patient receiving 40 mg q.p.m. [0.1%], and none of the 1,642 patients receiving lovastatin 20 mg). The maximum CK levels in the five patients ranged from 1,991 to 10,300 IU/L. Clinical signs and symptoms occurred within 3 to 23 weeks after study entry. Two of the 5 patients continued to receive lovastatin and completed the study while their symptoms resolved and their CK levels returned to normal. CK levels for the 3 discontinued patients decreased to normal and symptoms resolved within 30 days of discontinuing lovastatin. None of the patients experienced myoglobinuria or acute renal failure.

4.3.2.2 Myopathy in Postapproval Clinical Studies (Cont.)

The incidence of muscle symptoms with any CK elevation above the ULN was similar in the groups receiving 20 or 40 mg of lovastatin per day and the placebo group (Table 22). As seen in Table 22, muscle symptoms, with or without any CK elevation, are relatively common in the population at large, and the majority are not drug-related.

Table 22

Incidence of Muscle Symptoms (With and Without Creatine Kinase Elevations) and Creatine Kinase Elevations (With or Without Muscle Symptoms) EXCEL (48 Weeks)

	Treatment Group				
	Lovastatin				Placebo N=1663
	20 mg q.p.m. N=1642	40 mg q.p.m. N=1645	20 mg b.i.d. N=1646	40 mg b.i.d. N=1649	
n (%)†	n (%)†	n (%)†	n (%)†	n (%)†	
Muscle symptoms with CK elevations					
CK >10 x ULN‡	0 (0.0)	1 (0.1)	0 (0.0)	4 (0.2)	0 (0.0)
Any CK elevation	35 (2.1)	17 (1.0)	26 (1.6)	58 (3.5)	27 (1.6)
Muscle symptoms without CK elevations	102 (6.2)	94 (5.7)	90 (5.5)	95 (5.8)	98 (5.9)
CK elevations with or without muscle symptoms					
CK >10 x ULN	3 (0.2)	3 (0.2)	3 (0.2)	8 (0.5)	7 (0.4)
Any CK elevation	473 (28.8)	491 (29.8)	525 (31.9)	572 (34.7)	480 (28.9)

† Percentages refer to patients randomized. ULN indicates upper limit of normal CK values (190 and 235 IU/L for women and men, respectively); q.p.m., once daily with the evening meal; and b.i.d. twice daily.
 ‡ Preplanned comparison; incidence was too low to test for trend with daily doses of lovastatin.

AFCAPS/TexCAPS

In this trial during which participants were taking lovastatin or placebo for over 5 years, CK elevations >10 x ULN were reported in 0.6% of the cohort: 21 receiving lovastatin 20 to 40 mg daily and 21 receiving placebo. Among the 3304 receiving lovastatin, the only case of symptomatic myopathy was one case of rhabdomyolysis. The episode of rhabdomyolysis occurred postoperatively following surgery for prostate cancer and was determined to be unrelated to treatment with lovastatin 20 mg (the participant restarted lovastatin without a recurrence of symptoms). Two cases of rhabdomyolysis were reported among the participants treated with placebo [3].

4.3.2.3 Spontaneous Reports of Myopathy During Marketed Use

The WAES database of postmarketing adverse experience reports was searched for all reports carrying a preferred term adverse experience code of rhabdomyolysis, myoglobinuria, myositis, polymyositis or muscle disorder (the specific term “myopathy” maps to the preferred term “muscle disorder”).

A total of 759 reports (serious and nonserious) with an adverse experience code of rhabdomyolysis, myoglobinuria, myositis, polymyositis or muscle disorder (including myopathy) were recorded. For the purposes of this analysis, the 759 reports will be considered to represent cases of drug-induced myopathy, which is conservative as some of these reports undoubtedly reflect underlying conditions not related to lovastatin. This represents a reporting rate of myopathy of approximately 3/100,000 patient-treatment years. Of the 759 reports of muscle adverse experiences, 262 (35%) included an adverse experience code of rhabdomyolysis or myoglobinuria and 497 (65%) included one or more of the 3 terms possibly indicative of less severe forms of myopathy (Table 23). Approximately 19% of the reports that included one of these 3 terms noted that the CK level was greater than 2000 U/L (>10 x ULN). Hospitalization was documented in 93 of the 497 reports (19%).

Table 23

**Spontaneous Reports of Rhabdomyolysis or Myopathy
 (WAES)**

	Rhabdomyolysis		Other Myopathy	
	Reports (N=262)	Deaths (n=20)	Reports (N=497)	Deaths (n=6)
Without concomitant medication indicated below	135	8	431	5
With concomitant medication [†] indicated below	127	12	66	1
Any CYP3A4 inhibitor	46	4	8	0
Cyclosporine	25	2	3	0
Erythromycin/clarithromycin	16	2	5	0
Itraconazole/ketoconazole	6	1	0	0
HIV protease inhibitor	1	0	0	0
Nefazodone	1	0	0	0
Niacin/nicotinic acid	28	3	25	1
Fibrates	69	6	36	0

[†] Patients may have been taking more than 1 concomitant medication.

4.3.2.3 Spontaneous Reports of Myopathy During Marketed Use (Cont.)

Rhabdomyolysis/Myoglobinuria

The 262 reports represent a reporting rate of rhabdomyolysis of 1.1/100,000 patient-treatment years. Information about concomitant medications is contained in 215 of the reports. Of the 262 reports of rhabdomyolysis, approximately half (48%) occurred in patients receiving concomitant medication with one or more drugs recognized to increase the risk of lovastatin-associated rhabdomyolysis. There were no reports of rhabdomyolysis in a patient taking an interacting medication in which the dose of lovastatin was 10 mg. This is especially noteworthy since the lovastatin prescription labeling recommends beginning therapy with 10 mg in patients taking cyclosporine, a potent inhibitor of CYP3A4.

In 135 (52%) of the 262 reports of rhabdomyolysis there was no mention of concomitant use of any medication known to increase the risk of lovastatin-associated rhabdomyolysis. These 135 reports represent a reporting rate of rhabdomyolysis in the absence of interacting medications of 0.55 per 100,000 total patient-treatment years. There were no reports of rhabdomyolysis in which the reported dose of lovastatin was 10 mg or less.

Myopathies Not Reported As Rhabdomyolysis

The 497 reports of myopathy without rhabdomyolysis included 66 (13%) in which concomitant medication with one or more drugs known to increase the risk of lovastatin-associated myopathy was noted. There were no reports involving a potentially interacting concomitant medication in which the total daily dose of lovastatin was 10 mg or less.

In 431 (87%) of the reports of myopathy without rhabdomyolysis, no concomitant medication with a drug known to increase the risk of lovastatin-associated myopathy was reported. These 431 cases included 5 reports (none fatal) in which total daily dose of lovastatin was 10 mg or less.

Relationship to Lovastatin Dose

The number of reports that specified a dose can be evaluated in the context of the estimated patient exposure. It is estimated that approximately 3% of patients on lovastatin received 10 mg daily, 72% received 20 mg, 20% received 40 mg, 2% received 60 mg, and 3% received ≥ 80 mg.

The risks of rhabdomyolysis and myopathy appear to be dose related. Although only an estimated 5% of all lovastatin users are taking more than 40 mg/day, approximately 28% of the rhabdomyolysis reports and 10% of the myopathy reports come from patients at

4.3.2.3 Spontaneous Reports of Myopathy During Marketed Use (Cont.)

that dose level. Table 24 shows the number of reported cases per 100,000 patient-treatment years for the different doses of lovastatin. The number of reported cases per 100,000 patient-treatment years was based on the number of reports of rhabdomyolysis or myopathy in patients without concomitant medications known to increase the risk of myopathy. The estimated patient-treatment years have not been adjusted downward to take these concomitant medications into account. Compared with the 20-mg dose, the number of reports of rhabdomyolysis per 100,000 patient-treatment years was approximately 10 times greater with doses ≥ 80 mg/day. The number of reports of myopathy per 100,000 patient-treatment years was approximately 3 times greater with doses ≥ 80 mg/day than with 20 mg/day. These data suggest that self-medicating patients who exceed the proposed nonprescription dose or inadvertently take a potentially interacting medication will not have a substantially greater absolute risk of myopathy.

Table 24

Reports of Rhabdomyolysis or Myopathy Per 100,000 Patient-Treatment Years
 by Total Daily Dose of Lovastatin
 (WAES)

	Total Daily Dose of Lovastatin				
	≤ 10 mg	20 mg	40 mg	60 mg	≥ 80 mg/day
Estimated Percent of Usage	3%	72%	20%	2%	3%
Estimated Patient Treatment Years (PTY)	720,000	17,280,000	4,800,000	480,000	720,000
Reported cases of Rhabdomyolysis for 100,000 PTY	0	.21	.67	1.4	2.9
Reported cases of Myopathy other than Rhabdomyolysis per 100,000 PTY	0.7	1.0	1.4	1.2	3.1

Deaths Due to Rhabdomyolysis or Myopathy

Twenty-six of the 759 rhabdomyolysis or myopathy reports (3%) had a fatal outcome (see Table 23). Four of the 20 patients who died after developing rhabdomyolysis were also taking a potent CYP3A4 inhibitor. Five of the patients who died had preexisting renal disease, 6 had diabetes, and 3 additional patients had both. No patient was known to be taking 10 mg.

4.3.2.3 Spontaneous Reports of Myopathy During Marketed Use (Cont.)

Potential for Myopathy: Conclusions

- The risk of myopathy or rhabdomyolysis is low and dose related.
 - In clinical trials, the incidence of myopathy in those receiving lovastatin 20 mg daily is similar to that reported for those taking placebo.
 - There have been no reported cases of rhabdomyolysis during marketed prescription use of lovastatin 10 mg daily.
- Myopathy is a rare symptomatic condition that can be recognized by patients with warnings provided in the nonprescription lovastatin label. The condition usually resolves after discontinuation of the drug.

4.3.3 Exposure During Pregnancy

4.3.3.1 Introduction

Inhibition of HMG-CoA reductase by lovastatin is competitive and incomplete, thus allowing for biologically necessary amounts of the enzymatic product, mevalonate, to be available for cholesterol synthesis. Thus, adverse reactions caused by loss of cholesterol for steroidogenesis and cell membrane formation would not be anticipated and have never been observed [39].

However, it is recommended that the prescription management of preexisting hypercholesterolemia should include discontinuation of lipid-lowering drugs before conception, because the safety profile of these drugs during pregnancy has not been determined in controlled studies[40], and discontinuation of lipid-lowering drugs for the relatively short duration of pregnancy should have little impact on long-term benefits of therapy for hypercholesterolemia. Further, the recommended OTC population is postmenopausal women. However, while it may be possible to suspend drug treatment during pregnancy, premenopausal women inappropriately taking lovastatin may be exposed early in the first trimester, prior to recognition of pregnancy.

When administered at high doses to pregnant rats and mice, lovastatin and/or its pharmacologically active metabolites were shown to be associated with the development of skeletal malformations in fetal offspring. Because of this, the theoretical possibility that the fetus could be deprived of cholesterol or other products of mevalonate, and the fact that discontinuation of lipid-lowering drugs for the relatively short duration of pregnancy was not expected to have any impact on the long-term benefits of therapy with these drugs, an FDA Pregnancy Category X was established for lovastatin [63] and all other statins subsequently approved in the United States despite lack of evidence for teratogenicity. More recent preclinical studies show that the fetal effects seen in rats are

4.3.3.1 Introduction (Cont.)

caused indirectly by maternal toxicity associated with the high doses of lovastatin used in the original animal studies, rather than a direct result of fetal exposure. For this reason, an application has been submitted to FDA to remove the pregnancy Category X status from prescription labeling from lovastatin.

4.3.3.2 Spontaneous Reports From Pregnancies During Marketed Use

An examination was conducted of all reports of use of lovastatin during pregnancy that were received by Merck, from December 1987 through December 1998 (the cutoff date for that analysis). The data obtained for these reports are not necessarily complete and may include unsubstantiated diagnoses and partial information. Attempts were made to follow-up all reports of exposure during pregnancy to identify the outcome of the pregnancy. Information is included in WAES whether the outcome is normal or abnormal, and regardless of the likelihood of a causal association. Although adverse pregnancy outcomes have been reported in pregnancies with lovastatin exposure, the reporting of these adverse experiences does not imply a causal association.

Reports in which pregnancy outcomes were known were categorized into one of the following outcomes: (a) congenital anomaly (occurrence of a structural defect in an embryo, fetus, stillborn or liveborn infant); (b) chromosomal abnormality; (c) spontaneous abortion (spontaneous miscarriage of conceptuses less than 20 weeks gestation from the first day of the last menstrual period [LMP]); (d) fetal death/stillbirth (non viability of conceptuses in pregnancies greater than or equal to 20 weeks gestation from LMP); and (e) live birth of a normal child.

Reports of exposure during pregnancy were classified as being prospective or retrospective. Prospective reports were all those for which notice of exposure was received prior to the outcome of the pregnancy being known. Retrospective reports were all those first received after the outcome of pregnancy was known. It is generally recognized that adverse pregnancy outcomes, particularly congenital anomalies, are likely to be disproportionately over-represented among retrospective reports [41]. Prospective reports, which are first submitted prior to any knowledge of pregnancy outcome, are less likely to be influenced by such reporting bias and more likely to reflect pregnancy outcomes in the exposed population as a whole. Thus, the incidence of pregnancy outcomes from prospective reports of lovastatin exposure during pregnancy can be compared to the incidence rates of pregnancy outcomes in the general population.

One hundred reports of exposure to lovastatin during pregnancy were received during the period of December 1987 to December 1998. The majority of these cases were reported as having first trimester exposure (0 to 13 weeks gestation).

4.3.3.2 Spontaneous Reports From Pregnancies During Marketed Use (Cont.)

Of the 100 lovastatin reports, 67 were prospective and 33 were retrospective. Among the 67 prospective reports, information on pregnancy outcome was obtained in 36 (54%), (Table 25). These outcomes included 2 elective terminations, 1 spontaneous abortion, 1 stillbirth resulting from an umbilical cord accident, and 32 normal live births. There were no prospective reports of congenital or chromosomal abnormalities. By definition, outcome data are available for all 33 retrospective reports (Table 25). These included 8 elective terminations, 2 spontaneous abortions, no still-births, and 23 live-births. There were 5 reports of congenital abnormalities: four reported in association with a live-birth and one in association with an elective abortion. There were no reports of chromosomal abnormalities.

Table 25

Summary of Reports of Exposure During Pregnancy to Lovastatin

Outcome	Prospective	Retrospective
Spontaneous abortion	1	2
Elective termination	2	8 [†]
Stillbirth	1 [‡]	0
Live birth	32	23 [§]
Unknown	31	0
Total	67	33
[†] Includes 1 congenital abnormality. [‡] Cord accident. [§] Includes 4 congenital abnormalities.		

Information received from postmarketing surveillance reports can be incomplete and neither the total number of adverse pregnancy outcomes (numerator) nor the total population of exposed pregnancies (denominator) can be estimated. However, if only prospectively reported cases of pregnancy exposures are considered, then these rates can be compared with those of the general population and the incidences of outcomes can be compared. Of the prospective reports 46% of the lovastatin cases were categorized as having an unknown outcome. Despite repeated attempts to obtain follow-up information, the outcomes of these pregnancies were not obtainable. However, given that adverse outcomes are more likely to be reported than good outcomes; some reassurance can be drawn from the absence of an excess incidence of adverse outcomes in these prospective reports. Furthermore, the retrospective reports of congenital anomalies consisted of a spectrum of unrelated malformations identified in fetuses and newborns. The anomalies appear to be unrelated by affected embryonic process or target organ, with no consistent pattern to suggest a common pathogenesis that could be attributed to lovastatin exposure.

4.3.3.2 Spontaneous Reports From Pregnancies During Marketed Use (Cont.)

Among prospectively reported cases, there were 32 live births and no congenital or chromosomal abnormalities in those which were exposed to lovastatin. In the United States approximately 3.9 per 100 live births are born with at least 1 congenital anomaly. Thus, although the numbers are small, the prospective reports provide no indication that exposure to lovastatin, at least in early pregnancy, is associated with a higher incidence of congenital or chromosomal abnormalities than in the general population. The incidence of spontaneous abortions and fetal deaths/still births among prospective reports of lovastatin exposed pregnancies also show no evidence of a higher incidence than that seen in the general population [42].

Among pregnancies that resulted in the live birth of a normal child, exposure to lovastatin occurred for similar or longer periods of time and for the same or higher doses of lovastatin than those pregnancies that resulted in adverse outcomes. These normal outcomes strengthen the possibility that the adverse pregnancy outcomes were more likely a reflection of the spontaneous background rates of adverse pregnancy outcomes in the general population, than due to lovastatin exposure.

4.3.3.3 Exposure During Pregnancy: Conclusions

- There is no apparent association between exposure to lovastatin during pregnancy and the occurrence of any adverse pregnancy outcomes. However, the number of reported cases with a known outcome is small. In view of the limited benefit of this drug in premenopausal women, nonprescription lovastatin will be indicated only for postmenopausal women and will be contraindicated in pregnancy. Should exposure in pregnancy nevertheless occur, treatment with lovastatin should be stopped.
- The lack of evidence for risk may provide some reassurance to women who are inadvertently exposed to lovastatin during pregnancy, and to the health care professionals responsible for their care.

4.3.4 Drug-Drug Interactions

Pharmacodynamic

Monotherapy with fibrates and, to a lesser extent, niacin, is occasionally associated with myopathy. Concomitant use of fibrates or niacin may increase the risk of myopathy in patients taking any of the HMG-CoA reductase inhibitors (statins). Gemfibrozil and niacin have not been shown to alter plasma levels of lovastatin. The increased risk of myopathy appears to be related to the additive lipid-lowering effect of these drugs. Fibrates, such as gemfibrozil, were the most commonly reported potentially-interacting drugs among the spontaneous reports of rhabdomyolysis in patients taking lovastatin (69 of 127 reports). There were 28 reports of rhabdomyolysis in patients taking niacin (mostly doses ≥ 1 gram/day).

Pharmacokinetic

Lovastatin is not known to affect the plasma concentration of any other drugs (see 3.5). Lovastatin is not an inhibitor of cytochrome P-450 3A4 (CYP3A4) in humans at the recommended clinical doses.

Many medications, including lovastatin, are metabolized by CYP3A4. CYP3A4 inhibitors have been shown to increase plasma concentrations of HMG-CoA reductase inhibitory activity in patients taking lovastatin. Potent inhibitors of CYP3A4 taken concomitantly with lovastatin have been reported to increase risk of myopathy. Table 33 (Section 4.3.2.3) provides a breakdown of the 46 spontaneous reports of rhabdomyolysis in patients also taking a potent CYP3A4 inhibitor. The largest number of reports involved cyclosporine (25), a drug taken by a relatively small number of patients. Thirteen of the 46 reports described patients taking 2 potent CYP3A4 inhibitors, or a potent CYP3A4 inhibitor and a fibrate or niacin. Five of the 6 patients taking an antifungal agent were also taking cyclosporine.

While spontaneous reports provide a signal of increased relative risk in patients taking lovastatin and a potent CYP3A4 inhibitor, AFCAPS/TexCAPS shows that the risk is actually quite low. In AFCAPS/TexCAPS, concomitant use of lovastatin and potent CYP3A4 inhibitors was not associated with increased frequencies of myopathy or myalgia (Table 26). There were 1046 patients who took 1 or more potent CYP3A4 inhibitors (erythromycin, clarithromycin, ketoconazole, itraconazole, nefazodone) during the study. The incidence of musculoskeletal adverse experiences in general, and myalgia in particular, were not significantly greater in patients taking potent inhibitors treated with lovastatin versus those receiving placebo. There were no cases of myopathy or rhabdomyolysis in the 535 patients taking lovastatin who also took a potent CYP3A4 inhibitor. AFCAPS/TexCAPS provides evidence that with lovastatin 20 to 40 mg daily, the frequency of muscle symptoms is not appreciably increased with concomitant use of potent inhibitors such as erythromycin.

4.3.4 Drug-Drug Interactions (Cont.)

Table 26

Adverse Experiences Following Concomitant Use of Potent CYP3A4 Inhibitors
 AFCAPS/TexCAPS (N=6605)

Adverse Experience	Lovastatin 20 to 40 mg (N=535 [†])		Placebo (N=511)	
	N	(%)	n	(%)
Any musculoskeletal AEs	406	(76)	386	(76)
Myalgia	35	(7)	44	(9)
Myopathy/Rhabdomyolysis	0	(0)	0	(0)

[†] Erythromycin (387), clarithromycin (107), ketoconazole (42), itraconazole (51).

4.3.4.1 Drug-Drug Interactions: Conclusions

- Other lipid-lowering agents (gemfibrozil and niacin) may increase the risk of myopathy through an unknown mechanism in patients taking any of the HMG-CoA reductase inhibitors.
- Concomitant treatment with potent CYP3A4 inhibitors may increase plasma HMG-CoA reductase inhibitory activity levels, and therefore may increase an individual's risk of myopathy. The risk of myopathy is very low with lovastatin 10 mg and 20 mg daily regimens, and would be expected to remain low even with concomitant use of a potent CYP3A4 inhibitor. Use of these drugs concomitantly with lovastatin is contraindicated on the nonprescription label.

4.3.5 Drug-Disease Interactions

The proposed nonprescription lovastatin label advises people with concurrent medical conditions such as hypertension and diabetes to consult their doctor before using lovastatin. Published clinical studies contain information about the safety of lovastatin when used by patients with common medical conditions such as hypertension and diabetes mellitus. Selected studies are discussed below.

Hypertension

Hypertension and hypercholesterolemia frequently coexist. The efficacy and safety of lovastatin in patients with hypertension were evaluated in a subgroup analysis of EXCEL [14]. There was no attenuation in the lipid-altering efficacy of lovastatin when administered in patients being treated concurrently with frequently administered

4.3.5 Drug-Disease Interactions (Cont.)

antihypertensive drugs. There appeared to be no clinically important deterioration in the safety and tolerability profiles of lovastatin when taken with these drugs. Lovastatin did not have a clinically important effect on blood pressure in the all-patients-treated analysis. The mean changes from baseline for blood pressure were similar in the lovastatin and placebo groups [6].

Diabetes Mellitus

The safety and tolerability of lovastatin in patients with diabetes mellitus has been examined in several studies [26]. Lovastatin was effective in reducing LDL-C and was generally well tolerated. Lovastatin did not have a clinically important effect on fasting glucose or hemoglobin A_{1c} [28].

Renal Disease

The prescription labeling for lovastatin advises that doses above 20 mg/day be used cautiously in patients with severe renal insufficiency (creatinine clearance <30 mL/min) [63]. This caution is based on the observation that cases of rhabdomyolysis have been reported in patients with severe renal impairment. Lovastatin is not known to directly affect renal function. In EXCEL, mean changes in serum creatinine were similar among the lovastatin and placebo groups. The effect of cholesterol-lowering therapy on the progression of diabetic nephropathy was studied in 34 patients with type II diabetes mellitus [27]. Changes in glomerular filtration rate over the 2-year study tended to be less in patients treated with lovastatin compared to those receiving placebo, supporting the position that lovastatin will not exacerbate underlying renal disease.

Liver Disease

Active liver disease tends to lower plasma cholesterol, and is itself a more urgent medical priority than reducing the need for lipid-lowering therapy. The prescription labeling for lovastatin states that active liver disease is a contraindication to treatment with the drug [63]. Clinical studies have not evaluated the safety of lovastatin in patients with active liver disease. However, there is no evidence that lovastatin exacerbates underlying liver disease. Additionally, there is no evidence that a history of liver disease that is no longer active poses any risk. As discussed in 4.3.1, the hepatotoxic potential of lovastatin in doses of 20 mg and below is negligible. Nevertheless, as a conservative measure, in the proposed nonprescription lovastatin product circular, consumers with active liver disease are directed not to use the product.

4.3.5 Drug-Disease Interactions (Cont.)

Thyroid Disease

In a small number of patients with serum cholesterol 200 to 240 mg/dL, the cholesterol elevation is due at least in part to other causes, principally subclinical hypothyroidism in women, and in a few patients, overt untreated hypothyroidism. Patients with hypothyroidism are frequently undiagnosed in the early stages of the disease, when they are asymptomatic with normal thyroxine but elevated thyroid-stimulating hormone levels, and may choose to take nonprescription lovastatin.

Hypothyroidism is thought to account for about 2% of all cases of hyperlipidemia [24]. A recent study [22] has investigated the relationship between subclinical hypothyroidism and hypercholesterolemia in a large patient population. Plasma samples were analyzed in a total of 1191 middle-aged patients. The overall prevalence of subclinical hypothyroidism was 1.9% in men and 7.6% in women. (For overt hypothyroidism, the prevalence was 0.5% in both men and women.) The patients were divided into 3 groups with total plasma cholesterol <5 mmol/L (194 mg/dL), 5 to 8 mmol/L (194 to 310 mg/dL), and >8 mmol/L (>310 mg/dL). In women the prevalence of subclinical hypothyroidism was 4.0% in the lowest, 8.5% in the middle, and 10.3% in the highest cholesterol stratum (p=0.02). In men, the mean prevalence was 1.8% and similar in the 3 groups. Thus, the issue seems to be largely confined to women, especially those with serum cholesterol levels far above the proposed nonprescription range. In women with subclinical hypothyroidism, the estimated effect is to cause an approximate 19 mg/dL increase [22; 23].

Treatment with nonprescription lovastatin will lower the elevated lipids, but correction of an underlying contributing cause, inadequate thyroid function leading to high thyroid-stimulating hormone levels, would clearly be preferable, at least as a first step. These patients should still benefit from the reduction in LDL-C that lovastatin 10 mg will provide, but a concern could be raised that treatment of hypercholesterolemia removes one of the signs of hypothyroidism, and therefore, reduces the probability of diagnosis and appropriate treatment with thyroid hormone replacement. However, because hypothyroidism is almost always diagnosed on the basis of symptoms that prompt consultation with a health care professional and thyroid function tests, rather than on the basis of mild to moderately elevated lipids, this concern seems more theoretical than real.

Whether or not a hypothyroid patient takes lovastatin, progression of the disease will produce symptoms that are likely to lead to medical consultation. It is not likely that correction of moderate hyperlipidemia, a nonspecific and relatively unimportant manifestation of hypothyroidism, will materially delay diagnosis, given the wide variety of symptoms—well known to most practitioners—that the disease causes. In addition, although evaluation of thyroid function should ideally be included before lipid-lowering

4.3.5 Drug-Disease Interactions (Cont.)

therapy is initiated, this is often not done in the absence of symptoms of thyroid hormone deprivation, especially in a primary care setting. Therefore, for all these reasons, the availability of nonprescription lovastatin is highly unlikely to constitute a significant barrier to the diagnosis and treatment of hypothyroidism. When the disease is diagnosed in a patient taking nonprescription lovastatin, the treating physician will likely request discontinuation of the product, so that the need for lipid-lowering therapy can be evaluated after restoration of the euthyroid state.

4.3.6 Drug Abuse and Overdose

The available data indicate that there is a wide margin of safety with lovastatin. In mice and rats, the acute LD₅₀ values were >20 grams/kg and >5 grams/kg, respectively. From postmarketing reports of overdoses, the largest dose, 5 to 6 grams of lovastatin, was taken by a subject who had no specific symptoms and who fully recovered. From all sources, including the published literature, there have been no known reports of overdosage with a fatal outcome involving lovastatin as the sole agent.

The American Association of Poison Control Centers (AAPCC) collects data from poison control centers in at least 34 states and the District of Columbia and tabulates this information. During the 10-year period 1988 to 1997, there were 6201 exposures to lovastatin reported, of which 3567 involved other agents in addition to lovastatin. The outcome was death in 2 cases, both of which involved lovastatin taken with other agents. Symptom data were collected for 1,631 exposures to lovastatin alone. Symptoms were distributed across a number of body systems and there was no specific pattern. The most common symptoms were nausea (0.8%), vomiting (0.8%), drowsiness (0.7%), and diarrhea (0.6%). There were 3 reports of increased AST/ALT (0.2%), 3 reports of muscle weakness (0.2%), and 1 report of rhabdomyolysis (0.1%).

High doses of lovastatin have been administered orally in a Phase I study in 88 patients with cancer [66]. The rationale was to attempt to achieve in patients drug concentrations associated with antiproliferative activity in laboratory studies. Patients were treated with 7-day courses of lovastatin given monthly at doses ranging from 2 to 45 mg/kg/day. Lovastatin given at a dose of 25 mg/kg/day for 7 consecutive days was well tolerated. Dose escalation was stopped at 45 mg/kg/day because of toxicity (myopathy).

There are no published reports describing recreational use of lovastatin. There are no WAES reports where lovastatin was the primary suspect agent that could be construed as evidence of drug abuse. Based on the drug's pharmacological properties and the extensive knowledge of the drug's clinical adverse experience profile, there is no information to suggest that the drug has the potential to be abused.

4.4 Nonprescription Lovastatin Clinical Program Experience

4.4.1 Clinical Safety Data Collected

Merck Research Laboratories (MRL) sponsored 7 clinical studies in support of the Nonprescription Lovastatin Clinical Program. These studies were conducted in the United States.

The primary safety data for the 10-mg dose are provided in 4 completed Phase III studies:

- One double-blind, placebo-controlled Efficacy Study (Protocol 075) was conducted to expand the efficacy and safety experience with a 10-mg dose of lovastatin in the treatment of elevated cholesterol.
- Three open-label Use Studies were conducted to evaluate how patients would self-select and self-medicate with a nonprescription dose of lovastatin when provided with drug and labeling instructions under minimal supervision by a health care professional: Pharmacy (Protocol 076), Restricted Access (Protocol 079), and Red Arrow (Protocol 081). Study extensions of 2 to 6 months duration were also conducted in the Use Studies, leading to a total of 18 months in Protocol 076.

An additional Use Study (Nurse Worksite Study [Protocol 077]) was initiated but was terminated prior to completion due to slow patient enrollment (86 patients enrolled of the planned 660). This was a 10-center open study conducted in worksite health centers by occupational health nurses. Since none of the 86 study patients reached the primary time point of interest (6 months), no data analyses were performed. Only 4 patients had any adverse experience; none was considered serious, and 3 were determined to be possibly related to the study drug (worsening of erectile dysfunction; heart racing; and chest tightness). These safety results had a negligible effect on the overall program's safety profile, and are not included in this summary.

For all investigational studies, an adverse experience was defined as any unfavorable and unintended change in structure or function of the body temporally associated with any use of the study drug, whether or not determined to be related to the use of the study drug. Clinical adverse experiences were collected through spontaneous, nonsolicited patient reporting in all studies. In the placebo-controlled Efficacy Study (Protocol 075), patients reported any adverse experience occurrences to a site investigator who was a physician. The severity of each adverse experience was rated as mild, moderate, or severe. An assessment of drug relationship (i.e., possibly, probably, definitely, probably not, or definitely not drug related) was made by the investigator.

In the open-label Phase III Use Studies (Protocols 076, 079, and 081), patients reported nonserious adverse experiences either directly to a site investigator who was a registered pharmacist or a registered nurse, or to a toll-free telephone support line staffed by a team of nurses and physicians, that was established for the Phase III clinical program. All

4.4.1 Clinical Safety Data Collected (Cont.)

serious adverse experiences were reported by the patient or the site investigator to the team of physicians available at the toll-free telephone support line. These physicians were responsible for collecting all serious adverse experience information, making assessments on serious adverse experience severity and drug relationship, and reporting that information to Merck. Physical examinations, vital signs, ECGs, and routine laboratory safety tests (including LFTs) were not performed in any of the Use studies.

Any adverse experiences that were determined to be possibly, probably, or definitely drug related by the investigator have been designated as “drug related” in tabulations in which drug-related adverse experiences are documented. The specific term reported on a case report form was mapped to a “preferred term” using the MRL Adverse Event Dictionary. This Safety Summary and the individual Clinical Study Reports present clinical adverse experience data using “preferred terms.”

4.4.2 Overall Extent of Exposure of the Study Population

Primary Study Period

A total of 2430 patients received lovastatin during the primary study periods in the 4 completed Phase III studies. Patients took lovastatin for durations ranging from 2 months to 6 months. Table 27 displays the distribution of patients exposed to lovastatin or placebo; the data are summarized by study and study period (primary or extension). Although some patients were screened more than once for a study, no patient was enrolled more than once in any of the studies.

Extension Study Periods

The clinical program included treatment extensions for the 3 Use studies. A subset (1240 patients) of the original primary study patients continued treatment with lovastatin 10 mg for up to a total of 18 months. The distribution of patients exposed to lovastatin 10 mg in a study extension is also provided in Table 27.

4.4.2 Overall Extent of Exposure of the Study Population (Cont.)

Table 27

Number of Patients With Exposure to Study Drug
 All Phase III Nonprescription Lovastatin Clinical Studies

Patients—Phase III	Primary Study Period		Extension Study Period [†]
	Lovastatin 10 mg	Placebo	Lovastatin 10 mg
Efficacy Study—Prot. 075			
Primary: duration up to 12 wk	104	106	
Pharmacy Use Study—Prot. 076			
Primary: duration up to 6 mos	722		
1 st Extension: duration up to 6 mos			465
2 nd Extension: duration up to 6 mos			389
Restricted Access Use—Study—Prot. 079			
Primary: duration up to 2 mos	460		
1 st Extension: duration up to 4 mos			263
Red Arrow Use Study—Prot. 081			
Primary: duration up to 1 mos	1144		
1 st Extension: duration up to 2 mos			512
TOTAL OF PATIENTS IN COMPLETED PHASE III STUDIES	2430	106	
Nurse Worksite Study—Prot. 077			
Primary: duration up to 12 wk	86		
TOTAL OF PATIENTS IN ALL PHASE III STUDIES[†]	2516	106	

[†] Includes patients in the Phase III terminated Nurse Worksite Study.
[‡] Patients participating in extensions were a subset of original patients, and their exposure was counted only once in the primary study period.

4.4.3 Demographics and Other Characteristics of the Study Population

4.4.3.1 Demographics

Demographic information on gender, age, and racial origin is summarized in Table 28 for patients in the Efficacy Study and the 3 Use Studies (primary and extension periods). It is important to note that placebo recipients served as controls for the double-blind Efficacy Study (Protocol 075) only. In the primary study periods, enrollment of men was more than twice that of women in the lovastatin treatment group: 1709 men (70.3%) and 658 women (27.1%). The placebo recipients in the Efficacy Study (Protocol 075) were more evenly distributed across gender, with 56 men (52.8%) and 50 women (47.2%).

4.4.3.1 Demographics (Cont.)

Despite efforts to proactively recruit patients from a wide socioeconomic background (through directed and multi-language study advertising), the majority of patients in Phase III primary studies were white, with 2074 (85.3%) of the lovastatin group and 96 (90.6%) of the placebo group reporting that racial origin. Ninety-five (3.9%) and 6 (5.7%) patients of the lovastatin and placebo groups, respectively, were black, and 69 (2.8%) and 2 (1.9%) of the patients in those respective treatment groups were of Hispanic origin.

Table 28

Baseline Demographic Characteristics by Treatment Group
 Phase III Nonprescription Lovastatin Clinical Program

	Primary Study Period		Extension Study Periods
	Lovastatin 10 mg (N=2430)		Placebo (N=106)
	Lovastatin 10 mg (N=1240)		Placebo (N=106)
	n (%)	n (%)	n (%)
Gender			
Male	1709 (70.3)	56 (52.8)	970 (78.2)
Female	658 (27.1)	50 (47.2)	270 (21.8)
Unknown [†]	63 (2.6)	0 (0.0)	
Age (years)			
<40	3 (0.1)	0 (0.0)	1 (<0.1)
≥40 and ≤44	145 (6.0)	2 (1.9)	71 (5.7)
≥45 and ≤49	365 (15.0)	13 (12.3)	214 (17.3)
≥50 and ≤54	368 (15.1)	20 (18.9)	190 (15.3)
≥55 and ≤59	476 (19.6)	25 (23.6)	264 (21.3)
≥60 and ≤64	424 (17.4)	18 (17.0)	225 (18.1)
≥65 and ≤69	308 (12.7)	18 (17.0)	154 (12.4)
≥70 and ≤74	144 (5.9)	6 (5.7)	77 (6.2)
≥75	104 (4.3)	4 (3.8)	44 (3.5)
Unknown [†]	93 (3.8)	0 (0.0)	
Mean ± SD	57.7±9.3	58.8±8.2	57.4±9.1
Median	57.0	58.0	57.0
Range	38 to 96	44 to 83	39 to 96
Racial Origin			
White	2074 (85.3)	96 (90.6)	1140 (92.0)
Black	95 (3.9)	6 (5.7)	35 (2.8)
Hispanic	69 (2.8)	2 (1.9)	28 (2.3)
Asian	47 (1.9)	1 (0.9)	20 (1.6)
Native American	7 (0.3)	1 (0.9)	1 (<0.1)
Other	7 (0.3)	0 (0.0)	2 (0.2)
Refused to Answer	131 (5.4)	0 (0.0)	14 (1.1)
Unknown [†]			

[†] Data not provided on case report forms (Protocol 081).

4.4.3.2 Secondary Diagnoses

The proposed nonprescription label directs patients with hypertension, diabetes, heart disease or stroke to consult a physician before using nonprescription lovastatin. Therefore, the Phase III Use Studies selected out most patients with these conditions, and therefore did not collect secondary diagnoses. Secondary diagnoses information is available on patients enrolled in the double-blind, placebo-controlled Efficacy Study (Protocol 075), but was not collected from patients in the other Phase III studies. The most frequently reported secondary diagnoses in Efficacy Study (Protocol 075) were arthritis (14.4 and 13.2% in the lovastatin and placebo groups, respectively), and hypertension (12.5 and 29.2% in the lovastatin and placebo groups, respectively).

4.4.3.3 Prior Therapies

Prior therapy information was not collected from patients in the Use Studies, but it is available on patients enrolled in the Efficacy Study (Protocol 075). The majority of patients in each treatment group did take medications prior to the study start (78.8 and 85.8% in the lovastatin and placebo groups, respectively). The most common prior therapies in each treatment group were vitamins and minerals (45.2 and 43.4% in the lovastatin and placebo groups, respectively), hormone replacement (29.8 and 28.3% in the lovastatin and placebo groups, respectively), and central nervous system drugs (28.8 and 34.0% in the lovastatin and placebo groups, respectively) which were primarily analgesics containing acetaminophen or aspirin.

4.4.3.4 Concomitant Therapies

Concomitant therapy information was not collected from patients in the Use Studies, but it is available for patients in the Efficacy Study (Protocol 075). One hundred seventy-seven patients (84.3%) took at least one concomitant therapy during the study. The most common concomitant therapies reported in each treatment group were vitamins and minerals, hormone replacement, and analgesics. In general, the profiles of concomitant therapies were similar to prior therapies with regard to numbers of patients as well as the types of drugs taken.

4.4.4 Clinical Adverse Experiences

Table 29 presents an overview of the clinical adverse experiences reported in the Phase III studies of the Nonprescription Lovastatin Clinical Program. In the Efficacy Study (Protocol 075), treatment groups were compared with respect to the overall incidence of adverse experiences, drug-related adverse experiences, serious adverse experiences, and adverse experiences that caused discontinuation. Tests of significance using Fisher's exact test were performed for these 4 endpoints; no significant differences between treatment groups were observed.

4.4.4 Clinical Adverse Experiences (Cont.)

Lovastatin was generally well tolerated in the Phase III studies. Seventeen lovastatin patients in the primary study period had adverse experiences that met the definition of serious, but none were considered drug-related. Two patients died of non-drug-related adverse experiences.

Table 29

Summary of Patients With Clinical Adverse Experiences
 in Primary, Pretreatment, Posttreatment and Extension Periods
 Phase III Nonprescription Lovastatin Clinical Program

	Phase III Use Studies (Protocols 076, 079 and 081)		Phase III Efficacy Study (Protocol 075)			
	Lovastatin 10 mg (N=2326)		Lovastatin 10 mg (N=104)		Placebo (N=106)	
Number of Patients [†]	N	(%)	n	(%)	n	(%)
Primary Study Period						
With one or more adverse experiences	588	(25.3)	39	(37.5)	37	(34.9)
With drug-related [‡] adverse experiences	405	(17.4)	6	(5.8)	11	(10.4)
With a fatal or nonfatal serious adverse experience	16	(0.7)	1	(1.0)	0	(0.0)
Who died	1	(0.04)	0	(0.0)	0	(0.0)
Discontinued due to an adverse experience	174	(7.5)	3	(2.9)	3	(2.8)
Discontinued due to a drug-related [‡] adverse experience	140	(6.0)	2	(1.9)	3	(2.8)
Discontinued due to a serious adverse experience	11	(0.5)	0	(0.0)	0	(0.0)
Pretreatment Period[§]						
With serious adverse experience	0	(0.0)	1	(1.0)	2	(1.9)
Posttreatment Period						
With serious adverse experience	1	(0.04)	0	(0.0)	0	(0.0)
Extension Period[¶]						
With fatal or nonfatal serious adverse experience	25		0		0	
Who died	1		0		0	
[†] Patients with adverse experiences may have been counted in more than 1 category. [‡] Determined by the investigator to be possibly, probably, or definitely drug related. [§] Pretreatment period refers to any patients with serious adverse experiences that occurred during the low-fat diet phase and placebo run-in phase of the pretreatment period in Efficacy Study (Protocol 075). One patient (BL10068) experienced a serious adverse experience during the placebo run-in phase, but was never randomized to study drug because he did not meet eligibility criteria. Posttreatment period refers to any patients with serious adverse experiences that occurred during the 2 weeks following discontinuation of study drug. [¶] Extension period refers to any patients with serious adverse experiences that occurred during the extension of study therapy period(s) in Protocols 076, 079, and 081. Percent is not calculated because the treatment group total "N" does not apply to extension period. One patient (AN 0062; 076-018) experienced 2 separate serious adverse experiences.						

4.4.4.1 Incidence of Clinical Adverse Experiences

The Nonprescription Lovastatin Clinical Program was not designed to provide comparative safety data versus placebo. As noted in Table 29, only 106 patients received placebo in the placebo-controlled Efficacy Study (Protocol 075). It would be inappropriate to compare the adverse experience profile of all patients who received lovastatin (n=2430) in the Phase III nonprescription studies to the profile of those who received placebo (n=106). Therefore, the tables in the remainder of this Safety Summary only present the adverse experience profile for patients who received lovastatin 10 mg in the Nonprescription Lovastatin Phase III Clinical Studies.

In the tabulations by body system, patients are counted more than once in the table if they had adverse experiences classified in more than one body system. However, patients are counted only once in the overall total and in a particular body system, even if they reported multiple occurrences of different adverse experiences within the same body system. Patients who reported multiple occurrences of the same adverse experience were counted only once for that particular adverse experience.

Table 30 summarizes the clinical adverse experiences by body system and individual adverse experience terms for all patients who received nonprescription lovastatin in a Phase III study. Only those adverse experiences that occurred in $\geq 1\%$ of the patients in the lovastatin treatment group are presented in this table. The most frequently reported adverse experiences were flatulence (3.5%) and headache (2.5%). There were no reports of hepatitis. Thirty-four patients (1.4%) reported muscle pain in the primary study phase, but there were no cases of myopathy or rhabdomyolysis with CK documented to be greater than 10 x ULN.

The incidence and variety of clinical adverse experiences that occurred in the Nonprescription Lovastatin Clinical Program shows that nonprescription lovastatin was generally well tolerated. There was no pattern to suggest that lovastatin 10 mg used without physician supervision would not be as well tolerated as the higher doses have been with physician supervision. Indeed, the adverse experience profile reported from lovastatin 10 mg recipients in the nonprescription clinical program is generally comparable to that of the placebo recipients in EXCEL.

4.4.4.1 Incidence of Clinical Adverse Experiences (Cont.)

Table 30

Number (%) of Patients With Specific Clinical Adverse Experiences by Body System With An Incidence $\geq 1\%$ —All Lovastatin Patients in Phase III Studies

	Primary Study Period (N=2430)		Extension Study Periods (N=1240 [†])	
	N	(%)	N	(%)
Patients with any adverse experiences	627	(25.8)	171	(13.8)
Body as a Whole/Site Unspecified	115	(4.7)	24	(1.9)
Pain, abdominal	43	(1.8)	8	(0.6)
Cardiovascular System[‡]	31	(1.3)	12	(1.0)
Digestive System	240	(9.9)	33	(2.7)
Constipation	33	(1.4)	3	(0.2)
Diarrhea	44	(1.8)	9	(0.7)
Flatulence	86	(3.5)	3	(0.2)
Musculoskeletal System	132	(5.4)	47	(3.8)
Myalgia	34	(1.4)	6	(0.5)
Nervous System and Psychiatric Disorders	133	(5.5)	21	(1.7)
Headache	60	(2.5)	4	(0.3)
Respiratory System	82	(3.4)	35	(2.8)
Infection, upper respiratory	28	(1.2)	10	(0.8)
Skin and Skin Appendage[‡]	53	(2.2)	14	(1.1)
Urogenital System[‡]	38	(1.6)	9	(0.7)
[†] Lovastatin patients in extension study periods were a subset of the original primary study period patients; no new patients were enrolled. [‡] All individual adverse experiences categorized in this body system have an incidence <1%. Although a patient may have had two or more adverse experiences, the patient is counted only once in the body system total and in "Patients with any adverse experience."				

4.4.4.2 Drug-Related Clinical Adverse Experiences

The incidences of clinical adverse experiences determined to be drug related (possibly, probably, or definitely) by the investigator are presented in Table 31. Overall, 411 lovastatin patients (16.9%) had drug-related clinical adverse experiences in Phase III studies. The most frequently reported drug-related adverse experience was flatulence (3.4%). The incidence of drug-related clinical adverse experiences in the Nonprescription Lovastatin Clinical Program was consistent with that reported in the prescription product circular.

4.4.4.2 Drug-Related Clinical Adverse Experiences (Cont.)

Table 31

Number (%) of Patients With Specific Drug-Related[†] Clinical Adverse Experiences by Body System With an Incidence ≥1% - All Lovastatin Patients in Phase III Studies

	Primary Study Period (N=2430)		Extension Study Periods (N=1240)	
	n	(%)	N	(%)
Patients with any drug-related [†] adverse Experiences	411	(16.9)	53	(4.3)
Body as a Whole/Site Unspecified	75	(3.1)	10	(0.8)
Pain, abdominal	29	(1.2)	4	(0.3)
Digestive System	190	(7.8)	15	(1.2)
Constipation	29	(1.2)	1	(0.1)
Diarrhea	33	(1.4)	6	(0.5)
Flatulence	82	(3.4)	3	(0.2)
Musculoskeletal System	73	(3.0)	17	(1.4)
Myalgia	29	(1.2)	4	(0.3)
Nervous System and Psychiatric Disorders	92	(3.8)	8	(0.6)
Headache	54	(2.2)	2	(0.2)
Skin and Skin Appendage[‡]	39	(1.6)	7	(0.6)
Urogenital System[‡]	16	(0.7)	1	(0.1)

[†] Determined by the investigator to be possibly, probably, or definitely drug related.
[‡] All individual adverse experiences categorized in this body system have an incidence <1%.
 Although a patient may have had two or more adverse experiences, the patient is counted only once in the body system total and in "Patients with any drug-related adverse experiences."

4.4.4.3 Serious Clinical Adverse Experiences

Merck has applied the following standard regulatory serious adverse experience definitions in the conduct of the clinical studies included in the Nonprescription Lovastatin Clinical Program. A serious adverse experience is any adverse experience occurring at any dose that: (1) results in death; (2) is life-threatening; (3) results in persistent or significant disability/incapacity; (4) is a congenital anomaly/birth defect in

4.4.4.3 Serious Clinical Adverse Experiences (Cont.)

the offspring of a patient taking the product; (5) is a cancer; (6) is the result of an overdose; or (7) is another important medical event that may jeopardize the patient and require medical/surgical intervention, based on appropriate medical judgment.

As of the 31-Dec-1999 Safety Update Report cutoff date, 46 patients who participated in any of the Nonprescription Lovastatin Clinical Studies reported serious adverse experiences during the pretreatment (low-fat diet and placebo run-in), primary, posttreatment, or extension study periods. Table 32 summarizes serious clinical adverse experiences by body system and individual adverse experience terms for the patients who received lovastatin in a Phase III study, in the primary, extension or 2-week posttreatment periods. This table does not include 3 patients who experienced a serious adverse event during the pretreatment/placebo run-in period of the Efficacy Study (Protocol 075).

There were no serious drug-related adverse experiences reported in any of the Nonprescription Lovastatin Clinical Studies. In most cases, the serious adverse experiences resolved spontaneously.

Deaths

Two patients experienced fatal adverse experiences:

- Allocation Number 2841 was a 45-year-old man who had been participating in Study 081 for approximately 3 weeks. On Day 22 he was struck by a vehicle driven by a drunk driver and was killed instantly. The investigator determined the patient's death to be not related to the study drug.
- Allocation Number 0004 was a 64-year-old man with hypertension who had been participating in Study 076 for approximately 7 months. On Day 227 he experienced an acute myocardial infarction at home and was unable to be resuscitated by medical personnel. The patient had a family history of sudden heart attacks (brother and uncle). The investigator determined the patient's death to be not related to the study drug. Although this patient was not a protocol violator based on the entrance criteria for the Pharmacy Study (Protocol 076), he would be considered ineligible for nonprescription lovastatin use based on proposed labeling criteria.

4.4.4.3 Serious Clinical Adverse Experiences (Cont.)

Table 32

Number (%) of Patients With Serious Clinical Adverse Experiences by Body System Occurring in ≥ 2 Patients—All Lovastatin Patients in Phase III Studies

	Primary Study Period		Extension Study Periods	
	Lovastatin Patients (N=2430)		Lovastatin Patients (N=1240 [†])	
	N	(%)	N	(%)
Patients with any serious adverse experience	18	(0.7)	25	(2.0)
Body as a Whole/Site Unspecified	7	(0.3)	4	(0.3)
Pain, chest	3	(0.1)	2	(0.2)
Syncope	1	(0.0)	1	(0.1)
Cardiovascular System	7	(0.3)	8	(0.6)
Atherosclerosis, coronary	3	(0.1)	2	(0.2)
Myocardial Infarction	2	(0.1)	2	(0.2)
Digestive System	4	(0.2)	5	(0.4)
Cholecystitis	2	(0.1)	1	(0.1)
Musculoskeletal System	1	(0.0)	2	(0.2)
Nervous System and Psychiatric Disorders	0	(0.0)	2	(0.2)
Respiratory System	2	(0.1)	1	(0.1)
Skin and Skin Appendage	1	(0.0)	2	(0.2)
Neoplasm, skin, malignant	1	(0.0)	2	(0.2)
Urogenital System	2	(0.1)	3	(0.2)
Neoplasm, breast, malignant	0	(0.0)	3	(0.2)
[†] Lovastatin patients in extension study periods were a subset of the original primary study period patients; no new patients were enrolled. Although a patient may have had two or more adverse experiences, the patient is counted only once in the body system total and in "Patients with any adverse experience." Note: This table does not include 3 patients with serious adverse events that occurred during a pretreatment/placebo run-in study phase.				

4.4.4.4 Discontinuations Due to Clinical Adverse Experiences

Table 33 displays the numbers of patients who discontinued from the study due to clinical adverse experiences during the primary study phase by treatment group and protocol. One hundred eighty of those patients who discontinued due to a clinical adverse experience did so during the primary study period. Eleven of these patients discontinued due to a serious adverse experience.

In addition, 1 patient who participated in the terminated Nurse Worksite Study (Protocol 077) discontinued due to a clinical adverse experience. This patient is not included in the data presented in Table 33.

Of those patients who discontinued during the primary study period, 145 discontinued due to a drug-related adverse experience.

Table 33

Number (%) of Patients Discontinued Due to Clinical Adverse Experiences Occurring During the Primary Study Period and Extension Study Periods by Treatment Group and Protocol

Treatment Group	Primary Study Period			Extension Study Periods				
	N	Number (%) Discontinued Due to a Clinical Adverse Experience	Number (%) Discontinued Due to a Drug-Related [†] Clinical Adverse Experience	N	Number (%) Discontinued Due to a Clinical Adverse Experience		Number (%) Discontinued Due to a Drug-Related [†] Clinical Adverse Experience	
Lovastatin: Efficacy Study	104	3 (2.9)	2 (1.9)	N/A	N/A	N/A	N/A	N/A
Use Studies	2326	174 (7.5)	140 (6.0)	1240	47 [‡]	(3.8)	33	(2.7)
Placebo: Efficacy Study	106	3 (2.8)	3 (2.8)	N/A	N/A	N/A	N/A	N/A

[†] Determined by the investigator to be possibly, probably or definitely drug related.
[‡] Includes 12 patients who had adverse experiences starting in the primary study period, but did not discontinue until the extension period.
 N/A Not Applicable. Protocol 075 did not conduct a treatment extension, and Protocols 076, 079 and 081 had no placebo recipients.
 Note: This table does not include 1 patient (AN 0013; 077-006) who discontinued from the terminated Nurse Worksite Protocol 077 due to a clinical adverse experience.

Table 34 provides a summary of the clinical adverse experiences by body system which caused study discontinuation. Only those adverse experiences occurring in ≥3 patients are included in this table. The most commonly occurring adverse experiences reported by lovastatin recipients leading to discontinuation (regardless of causality) were diarrhea (21), headache (20), myalgia (19), abdominal pain (19), and flatulence (16).

4.4.4.4 Discontinuations Due to Clinical Adverse Experiences (Cont.)

Table 34

Number (%) of Patients With Specific Clinical Adverse Experiences by Body System
 Occurring in ≥3 Patients—

All Discontinued Lovastatin Patients in Primary and Extension Study Periods

	Primary Period (N=2430)		Extension Periods (N=1240)	
	n	(%)	n	(%)
Patients who discontinued from study due to an adverse experience	177	(7.3)	47	(3.8)
Body as a Whole/Site Unspecified	44	(1.8)	10	(0.8)
Asthenia/fatigue	10	(0.4)	3	(0.2)
Distention, abdominal	5	(0.2)	2	(0.2)
Pain, abdominal	15	(0.6)	4	(0.3)
Pain, chest	12	(0.5)	0	(0.0)
Cardiovascular System	11	(0.5)	5	(0.4)
Atherosclerosis, coronary	2	(0.1)	1	(0.1)
Blood pressure increased	3	(0.1)	2	(0.2)
Myocardial infarction	2	(0.1)	2	(0.2)
Digestive System	61	(2.5)	9	(0.7)
Acid regurgitation	3	(0.1)	4	(0.3)
Anorexia	3	(0.1)	0	(0.0)
Constipation	11	(0.5)	1	(0.1)
Diarrhea	17	(0.7)	4	(0.3)
Dyspepsia	8	(0.3)	0	(0.0)
Flatulence	16	(0.7)	0	(0.0)
Nausea	6	(0.2)	3	(0.2)
Vomiting	3	(0.1)	0	(0.0)
Metabolic/Immune System[†]	1	(0.0)	3	(0.2)
Musculoskeletal System	37	(1.5)	11	(0.9)
Cramp, muscle	3	(0.1)	0	(0.0)
Myalgia	15	(0.6)	4	(0.3)
Pain, arm	1	(0.0)	2	(0.2)
Pain, elbow	2	(0.1)	1	(0.1)
Nervous System and Psychiatric Disorders	38	(1.6)	5	(0.4)
Dizziness	9	(0.4)	1	(0.1)
Headache	17	(0.7)	3	(0.2)
Paresthesia	4	(0.2)	0	(0.0)
Somnolence	3	(0.1)	0	(0.0)
Respiratory System[†]	9	(0.4)	2	(0.2)
Skin and Skin Appendage	23	(0.9)	5	(0.4)
Dermatitis	3	(0.1)	0	(0.0)
Pruritus	5	(0.2)	1	(0.1)
Rash	12	(0.5)	1	(0.1)
Special Sense Disorders[†]	4	(0.2)	1	(0.1)
Urogenital System	9	(0.4)	4	(0.3)
Impotence	4	(0.2)	3	(0.2)

[†] All individual adverse experiences categorized in this body system have an incidence <3 patients.

4.4.5 Drug-Demographic Interactions

4.4.5.1 Incidence of Clinical Adverse Experiences by Gender

The profile of clinical adverse experiences in the Nonprescription Lovastatin Phase III Clinical Program was examined separately for men and women. The ratio of men to women enrolled in the lovastatin treatment group was greater than 2.5 to 1, but the rate of adverse experiences was comparable across gender, with ~26% of men and ~29% of women reporting at least 1 adverse experience. Flatulence was the most commonly reported adverse experience (by 3.8% of men and 3.2% of women).

Of note, in EXCEL, 33% of patients were women (mean age 58 years). Overall, the tolerability profile of lovastatin was very favorable in both men and women.

4.4.5.2 Incidence of Clinical Adverse Experiences by Age

The profile of clinical adverse experiences in the primary study period for lovastatin patients was examined for patients younger than 65 years of age and patients 65 years and older. The ratio of lovastatin patients <65 years of age to those ≥65 years of age was greater than 3 to 1. Table 35 presents the adverse experiences by body system and age; individual adverse experiences that had an incidence ≥1% in either lovastatin group (<65 years of age or ≥65 years of age) are displayed. This table includes reported adverse experiences occurring in the primary study period without regard to causality. The overall incidence rate of adverse experiences was somewhat increased in the elderly subjects, with ~25% of lovastatin patients <65 years old, and ~33% of lovastatin patients ≥65 years old experiencing at least 1 adverse experience. Again, flatulence was the most frequently reported adverse experience (3.8% <65 years, and 3.4% ≥65 years) in the lovastatin treatment group.

Of note, in EXCEL, 1678 patients were 65 years of age or older. Lovastatin was generally well tolerated in the elderly. The incidence of nonserious adverse experiences or patients withdrawing from treatment due to adverse experiences did not appear to be age-related. There were no drug-related serious clinical adverse experiences in the elderly.

4.4.5.2 Incidence of Clinical Adverse Experiences by Age (Cont.)

Table 35

Number (%) of Patients With Specific Clinical Adverse Experiences
 With an Incidence $\geq 1\%$ by Body System and Age
 Lovastatin Patients in Primary Study Period of Phase III Studies

	Lovastatin [†]	
	<65 years (N=1781)	≥ 65 years (N=556)
	n (%)	n (%)
Patients with any adverse experience	439 (24.6)	185 (33.3)
Patients without an adverse experiences	1342 (75.4)	371 (66.7)
Body as a Whole/Site Unspecified	74 (4.2)	41 (7.4)
Asthenia/fatigue	7 (0.4)	11 (2.0)
Distention, abdominal	6 (0.3)	6 (1.1)
Pain, abdominal	29 (1.6)	14 (2.5)
Pain, chest	16 (0.9)	6 (1.1)
Cardiovascular System	19 (1.1)	12 (2.2)
Digestive System	166 (9.3)	73 (13.1)
Constipation	17 (1.0)	16 (2.9)
Diarrhea	33 (1.9)	11 (2.0)
Flatulence	67 (3.8)	19 (3.4)
Nausea	9 (0.5)	13 (2.3)
Musculoskeletal System	91 (5.1)	39 (7.0)
Myalgia	19 (1.1)	15 (2.7)
Nervous System and Psychiatric Disorders	99 (5.6)	34 (6.1)
Dizziness	12 (0.7)	9 (1.6)
Headache	48 (2.7)	12 (2.2)
Respiratory System	58 (3.3)	24 (4.3)
Infection, upper respiratory	22 (1.2)	6 (1.1)
Skin and Skin Appendage	36 (2.0)	17 (3.1)
Rash	14 (0.8)	7 (1.3)
Urogenital System	22 (1.2)	16 (2.9)
[†] Age not recorded for 93 of the total of 2430 lovastatin-treated patients. Only those body systems are listed in which at least 1% of lovastatin patients (either age group) had an adverse experience.		

4.4.5.3 Incidence of Clinical Adverse Experiences by Race

The profile of clinical adverse experiences in the Nonprescription Lovastatin Phase III Clinical Program was examined separately for white patients (~85% of lovastatin patients) and black patients (~4% of the lovastatin patients), the 2 largest racial groups in the clinical studies, comprising 89% of all Phase III lovastatin patients. Despite the disparity in group size, the actual rates of adverse experience occurrences for each of the 2 groups were relatively comparable. Once again, the most frequently reported adverse experience was flatulence, with 3.9% of the white lovastatin patients and 2.1% of the black lovastatin patients reporting this adverse experience.

Of note, in EXCEL, 459 of the 8,245 patients were black. The safety profile of lovastatin in black patients was generally favorable. There were no significant differences between racial groups in the incidence of drug-related adverse experiences and related discontinuations.

4.5 Overall Safety Summary

There is a wealth of safety information on lovastatin. Postmarketing monitoring of the population exposed to lovastatin over the last 12 years is reflected in the adverse experiences reported in WAES. Both serious and nonserious adverse experiences reported are consistent with the known effects of the drug and typical underlying disease states. They may also reflect previous warnings within the product circular (e.g., lenticular disorder) or concomitant disease in the patient population (e.g., congestive heart failure, myocardial infarction, pancreatitis). There are no new safety concerns. Serious adverse experiences attributable to lovastatin are very rare at the 10 and 20 mg doses. Additionally, the Nonprescription Lovastatin Clinical Program has shown that lovastatin 10 mg is generally well tolerated when used by patients who have self-selected according to a proposed label.

The data reviewed in this Safety Summary indicate that lovastatin 10 mg can be safely marketed with appropriate labeling in the OTC environment for generally healthy individuals with mild to moderately elevated cholesterol. There should be a very low incidence of medically significant adverse experiences (i.e., myopathy) when used according to the proposed warnings and directions. The label informs consumers to avoid medications that may interact with lovastatin, and to stop taking lovastatin and see a physician if they develop unexplained muscle pain, tenderness, or weakness. Because of the large margin of safety and the low dose proposed for nonprescription availability, consumers who make self-selection errors will not be subject to appreciable risk.

4.6 Safety: Conclusions

- Long term, chronic use of lovastatin at prescription doses of 10 to 80 mg daily is well tolerated. In controlled clinical trials, the safety profile of lovastatin 20 mg daily is comparable to that of placebo.

4.6 Safety: Conclusions (Cont.)

- Asymptomatic serum transaminase elevations are dose-dependent, and have not been proved to progress to clinical liver disease even when drug therapy is continued; the incidence of confirmed ALT elevations >3 x ULN is similar with lovastatin 20 mg daily and placebo. Clinically apparent liver disease (hepatitis, hepatic failure) associated with lovastatin use at any dose is very rare. Therefore, routine monitoring of liver function tests (LFTs) would not be of value in users of lovastatin 10 mg once daily.
- Although myopathy, and rhabdomyolysis in particular, may be considered the adverse experience of primary concern for the HMG-CoA reductase inhibitors, both clinical study experience and market-use experience indicate that their occurrence is rare. The risk of lovastatin-associated myopathy increases with increasing dose of lovastatin. In postmarketing experience over 12 years, only 5 cases of myopathy and no cases of rhabdomyolysis have been reported in association with use of the 10-mg dose. Myopathy is a symptomatic condition that can be recognized by patients and almost always resolves after drug discontinuation. Therefore, clinical consequences can be limited by a warning on the label to stop taking lovastatin and consult a physician if unexplained muscle pain, tenderness, or weakness occurs.
- Concomitant treatment with potent CYP3A4 inhibitors (cyclosporine, clarithromycin, itraconazole, ketoconazole, nefazodone, erythromycin and HIV protease inhibitors) may increase plasma HMG-CoA inhibitory activity levels, and therefore may increase the individual's risk of myopathy. Other lipid-lowering agents (gemfibrozil and niacin) may also increase the risk of myopathy through an unknown mechanism. However, the risk of myopathy is very low with the 10-mg dose of lovastatin, and would be expected to remain low in absolute terms even with concomitant use of a potent CYP3A4 inhibitor. Use of these drugs concomitantly with lovastatin is contraindicated on the nonprescription label.
- There is no indication of any association between exposure of lovastatin during pregnancy and the occurrence of any adverse pregnancy outcomes. In view of the limited benefits of this drug in premenopausal women, nonprescription lovastatin will be indicated only for postmenopausal women and will be contraindicated during pregnancy.
- Experience with prescription doses provides no evidence for an adverse effect of lovastatin on the course of hypertension, diabetes mellitus, or renal disease. Use is contraindicated in individuals with active liver disease and excessive alcohol use.

4.6 Safety: Conclusions (Cont.)

- When used for up to 18 months in an OTC setting to lower cholesterol, the excellent safety profile of lovastatin 10 mg once daily was consistent with that known from prescription usage.
- There are no clinically meaningful differences in the safety profile of lovastatin 10 mg and 20 mg once daily with regard to gender, age or race.
- Lovastatin 10 mg has a safety profile appropriate for use in the nonprescription setting.

5. Consumer Behavior

5.1 Introduction

Data summarized in the previous sections support the conclusions that the potential benefit of nonprescription lovastatin 10 mg in the proposed OTC-eligible population is substantial, that the excellent tolerability profile of the product permits its safe use according to OTC labeling, and that the benefit, therefore, outweighs the potential risk. This is particularly apparent when the potential benefit is prevention of first acute coronary heart disease events and the subsequent burden of disease, while the key potential risk entails very rare occurrence of myopathy which is recognizable, generally reversible, and manageable by labeling.

The remaining question then, is whether or not consumers can appropriately self-medicate with the product such that the potential benefit can be achieved and the potential risk avoided. The OTC development program focused on two principal objectives: (1) the ability of consumers to correctly select whether or not to use the product according to the labeled criteria for eligibility and ineligibility, and (2) the performance of consumers in using the product appropriately over the long-term.

In the OTC marketplace the product labeling system must serve as a guide to consumer self-management with the product, including product selection and use. The goal of the carton label is to provide sufficient information so that a consumer can make an appropriate purchase decision. It must effectively communicate who should or should not use the product, encourage communications with a doctor or other health care professional (especially under certain circumstances), describe how the product should be used, and communicate warnings relating to product use. After purchase, the consumer can make use of label reinforcement tools (e.g., package insert) or educational materials to expand upon or correct their initial understanding of the product's actions and use.

With the above goals in mind, the labeling development objectives in the nonprescription lovastatin program were 2-fold: (1) how to enable those people who would benefit from nonprescription cholesterol control to identify themselves while preventing ineligible people from taking nonprescription lovastatin 10 mg; and (2) how to encourage appropriate use of the product in order to achieve the maximum benefit.

To meet the first objective, the outside carton label must communicate the indication for use, and distinguish the criteria of those who are eligible from those who are ineligible. These messages must be sufficiently clear to the broad audience who might wish to purchase the product.

To meet the second objective, the labeling system must convey the correct use of the product, on a continuous daily basis, and in conjunction with measures such as cholesterol measurement and following a healthy lifestyle. Warnings need to be clear and sufficient to permit safe use of the product both initially and on a continued basis.

5.1 Introduction (Cont.)

Guidance on consulting a physician or other health care professional is necessary to reinforce the label messages for both selection and use, and encourage a collaborative approach to cholesterol management.

Thus, a comprehensive program of communication and support regarding self-management of cholesterol was developed. The feasibility of appropriate consumer product selection and self-medication with nonprescription lovastatin was then assessed by answering the following questions:

1. How will consumers know their lipid values before and during treatment?
2. After reviewing the label, will consumers select the product appropriately?
3. Will consumers understand the messages in the carton label and reinforcement tools?
4. Will consumers follow label directions when using the product initially and over the long term?
5. Does the nonprescription lovastatin proposed labeling system encourage collaboration with doctors?

To address these questions, a series of clinical use studies and consumer label comprehension studies were conducted with results summarized in this section. The key learnings from this development program led ultimately to the final proposed MEVACOR™ OTC label and accompanying education and support materials.

5.2 Cholesterol Testing and Knowledge

How will consumers know their lipid values before and during treatment? This is really a 3-part question: (1) are consumers currently getting their cholesterol tested, (2) how accessible is cholesterol testing in the community, and (3) how accurate are consumers' recall of their cholesterol test values?

5.2.1 Prevalence

The prevalence of cholesterol testing in the United States is high. A 1997 telephone survey of 1000 representative adults indicated that approximately three-quarters (72%) had been tested at some time, and one-half (48%) had been tested within the past year. This prevalence was even higher in the individuals who were in the OTC-eligible age range. In men over 40 years old, 89% had a test at some time, and 70% had a cholesterol test within the past year. In women past menopause, 93% had a test at some time, and 77% had a test within the past year.

5.2.1 Prevalence (Cont.)

In the past, information on one's lipid values could only be obtained through physician visits. Currently, access to cholesterol testing is rapidly becoming more widespread through community resources such as health fairs, employer wellness programs, and retail pharmacies using desktop cholesterol analyzers. It is expected that 4.5 million people will have their cholesterol tested in the year 2000 at health fairs and community screening events (an increase of 80% since 1997), and employee on-site screening has increased two-fold since 1997. Additionally, there are currently approximately 15,000 satellite cholesterol testing centers in communities, and 30 states allow patient-initiated testing without a doctor's order. In the nonprescription lovastatin development program, many participants expressed their interest in getting a cholesterol test as their next step in deciding to purchase the product. Awareness and interest in cholesterol in general is increasing, and is also reflected in the expanding use of diverse consumer products with healthy heart claims.

5.2.2 The Desktop Cholesterol Analyzer

There are several types of cholesterol analyzers in use in the community. The nonprescription lovastatin development program relied exclusively on the Cholestech LDX™ desktop analyzer for lipid measurements for the in-home use Studies 076, 079, and 081. This device was selected because it provides an accurate full lipid profile in 5 minutes from a fingerstick blood sample. It directly measures total cholesterol, triglycerides, and HDL-cholesterol, and calculates LDL-cholesterol from the Friedewald equation [11]. The Cholestech LDX™ analyzer has met NCEP performance requirements, and the correlation coefficients for lipid values compared to standardized enzymatic methods were in the range of 0.98 to 0.99 [16]. Currently, over 17,000 Cholestech LDX™ desktop analyzers have been sold. The increasing availability of cholesterol testing in the community will make it easier for consumers to have the cholesterol information they need in order to make an appropriate decision whether or not to purchase nonprescription lovastatin, and to monitor their progress during treatment.

5.2.2.1 Community Pharmacy-Based Monitoring Study

The feasibility of identifying elevated cholesterol and monitoring its treatment in a community setting was demonstrated in a study conducted by the American Pharmaceutical Association titled *Project ImPACT: Hyperlipidemia* (*ImPACT* is an acronym for Improve Persistence And Compliance with Therapy) [67]. The objective of this project was to demonstrate that pharmacists, in collaboration with patients and their physicians, could favorably impact patients' persistence and compliance with prescribed cholesterol-lowering medication.

5.2.2.1 Community Pharmacy-Based Monitoring Study (Cont.)

Twenty-six community-based ambulatory care pharmacies in the United States participated in the project. Each pharmacy used a Cholestech LDX™ analyzer to measure fasting lipid profiles, and all participating pharmacists attended a 2½-day training program at the project's inception on lipid testing and management. Patients were identified by their physicians, the participating pharmacists, or by self-referral. Where patients were not referred by their physicians, the physicians were contacted by the pharmacists, and were involved in patient management throughout the study. The pharmacists performed several key functions in this project. First, the pharmacist provided the patient with an initial consultation and lipid results from the Cholestech LDX™ analyzer. The pharmacist then collaborated with the patient's physician on developing an appropriate treatment plan and setting a treatment goal. The patient was asked to return to the pharmacy for follow-up visits every month for the first 3 months and then quarterly for the rest of the study. At these follow-up visits the pharmacist monitored patient progress, and communicated with the patient and physician about cholesterol results and progression toward the treatment goal.

A total of 574 patients were enrolled in the project, and 397 (69%) of these completed the 2-year study. In the 345 patients who were treated with lipid-lowering medication, compliance with drug therapy was 90%, and 62% of the patients reached their NCEP lipid goal. These results demonstrate that: (1) the resources already exist in the current community setting for identifying, treating, and monitoring elevated cholesterol; and (2) health care professionals such as pharmacists can facilitate communication between patients and doctors regarding their management of elevated cholesterol, and can provide support for consumers in their efforts to lower their risk of coronary heart disease (CHD).

5.2.3 Cholesterol Recall Accuracy

The accuracy of consumers reporting their own total cholesterol values was assessed as part of two in-home use studies (Study 076 and Study 079). In both studies combined, a total of 4829 consumers were asked to identify the numeric category that best described their cholesterol values and this recall was compared to the participant's actual cholesterol test performed at the study sites. In Study 079, 61% of the 1149 participants who self reported their total cholesterol within the OTC-eligible range (± 10 mg/dL) were correct when tested, 32% were above the OTC-eligible range and a small number (7%) had total cholesterol values below the range. Similar results were found in the Study 076, where 56% of the 1351 study participants who reported that their total cholesterol was within the range of 200 to 240 mg/dL were correct (± 10 mg/dL), 40% were above and 4% fell below.

5.2.3 Cholesterol Recall Accuracy (Cont.)

Study 076 also provided additional information on cholesterol self report in the numeric categories above 240 mg/dL and less than 200 mg/dL. An analysis of the recall data showed that 88% of participants who thought their cholesterol was >240 mg/dL (highest cholesterol numeric category) were in fact correct (defined as >230 mg/dL) based on their tested cholesterol values. For participants who placed their cholesterol in the lowest category (<200 mg/dL), 41% were found to have accurate recall of their cholesterol (defined as <210 mg/dL).

Thus, in Study 076 consumers' accuracy in reporting their own cholesterol numbers was excellent when these levels were high (above 240 mg/dL). The majority of people who thought their total cholesterol values were in the OTC-eligible range were correct; when they were incorrect, the levels were far more likely to be above than below the range. It is likely that in the OTC setting, patients will be able to readily obtain a new cholesterol test without having to rely on recall of previous test results.

5.3 Proposed Labeling System

The concept of chronic dosing to prevent disease on a nonprescription basis is not novel. Many consumers are self-medicating continuously with vitamins and minerals in an attempt to mitigate some of the effects of aging, specifically to prevent cardiovascular disease or osteoporosis. Elevated cholesterol is asymptomatic, and its treatment is life-long; therefore, the success of a nonprescription treatment paradigm with cholesterol-lowering drugs depends on several factors. Consumers must know their cholesterol values before and during treatment, be able to select use of the product according to the labeling, know when to consult a doctor, and use the product on a continuous basis long-term.

The nonprescription lovastatin 10-mg label system proposed in the NDA consists of the product carton back panel and the label reinforcement tools contained in the carton. The outside carton label guides interested consumers through the drug facts information in a stepwise process to help them determine if the product is right for them. The label reinforcement tools (postpurchase) emphasize product eligibility requirements and further instruct the consumer how to properly use the product. Samples of all the NDA label system components are provided in an accompanying volume, and consist of the following: (1) patient package insert, (2) informational booklet on cholesterol management and maintaining a healthy lifestyle, (3) short videotape (approximately 5 minutes) that reinforces key label messages, (4) coupon incentive to call a trained product specialist at a toll-free number, (5) doctor information card for facilitating communication, (6) enrollment card for a compliance program consisting of a free American Heart Association (AHA) cookbook and monthly motivational newsletters, and (7) wallet-sized reminder card that lists things to remember and provides a place for

5.3 Proposed Labeling System (Cont.)

tracking cholesterol values. The informational booklet and compliance program contain tips on maintaining a healthy lifestyle and managing CV risk factors such as smoking. All of these components have been fully developed and were tested in both label comprehension and clinical in-home use studies. It is envisioned that a full-service Internet web page, intended to answer questions and encourage appropriate use, will also be a part of the consumer support and label reinforcement program.

Prior to providing a comprehensive summary of the extensive label development program conducted in support of this application, it is worthwhile to summarize the final labeling system which resulted from this program, and is being proposed.

5.3.1 Labeling System Aids Product Selection

Since cholesterol test values are a surrogate for symptoms, the first thing the carton label instructs consumers is that they need a cholesterol test to determine if their total cholesterol is between 200 to 240 mg/dL and LDL cholesterol is greater than 130 mg/dL (see Section 1.1 for rationale behind these lipid eligibility criteria). Next, individuals must consider if their age is within the eligible range: men must be at least 40 years old, and women must be past menopause. The carton label then warns that individuals should not use the product or should talk to a doctor before use if they have any of the following conditions: history of coronary heart disease, stroke, diabetes, or hypertension; women who are pregnant, nursing, or of childbearing potential; liver disease or excessive alcohol use (more than 3 drinks on most days), allergy to lovastatin. Finally, the carton label warns against use by individuals who are taking any of several potentially interacting medications, specifically: erythromycin, clarithromycin, ketoconazole, itraconazole, nefazodone, cyclosporine, protease inhibitors, niacin (more than 500 mg daily), or other cholesterol lowering drugs.

5.3.2 Labeling System Encourages Interaction with Doctors

The nonprescription lovastatin labeling materials encourage consumer interaction with doctors during the processes of product selection and use. While appropriate individuals who meet label eligibility criteria are not required to consult with a doctor prior to using the product, they are encouraged to communicate with their doctor or health care professional about their use of the product. Furthermore, the carton label directs consumers with cholesterol above the OTC-eligible range or with higher cardiovascular (CV) risk to consult with a doctor before use. In addition, the label directs users of the product to immediately seek medical attention if unexplained muscle symptoms develop during product use. Finally, the label advises all consumers to inform their doctor about their use of the product, and to see their doctor for regular check-ups. Further support is available for purchasers of the product in the form of a unique toll-free telephone service to reinforce label messages. This service was piloted in use Study 079, and was fully

5.3.2 Labeling System Encourages Interaction with Doctors (Cont.)

tested as a postpurchase label reinforcement tool in use Study 081 (see below for details). In Study 081 a coupon was provided as an incentive to call the trained product specialists at a toll-free number for postpurchase review of the consumers' suitability for the product. An incentive would also be used with the marketed product to encourage calls to this telephone service.

5.3.3 Labeling System and Compliance Program Promote Continued Use and Monitoring

Consumers can not gauge the effectiveness of cholesterol lowering treatment by the resolution of symptoms, so they must get their cholesterol checked periodically to insure they are getting a response to treatment. The nonprescription lovastatin carton label and patient package insert direct consumers to get a cholesterol test after 8 weeks of treatment, and to consult with their doctor if their cholesterol has not gone down. Also, since the potential benefit of reduced coronary heart disease risk can only be achieved with continued treatment, consumers must be motivated to take the product over the long term. The carton label provides directions for taking one tablet with food every evening, and notes that the product must be taken on a continual basis in conjunction with eating a low-fat diet and exercising, or cholesterol values may go back up. These messages are reinforced in both the informational booklet on cholesterol and the compliance program motivational newsletters in a effort to encourage long-term use.

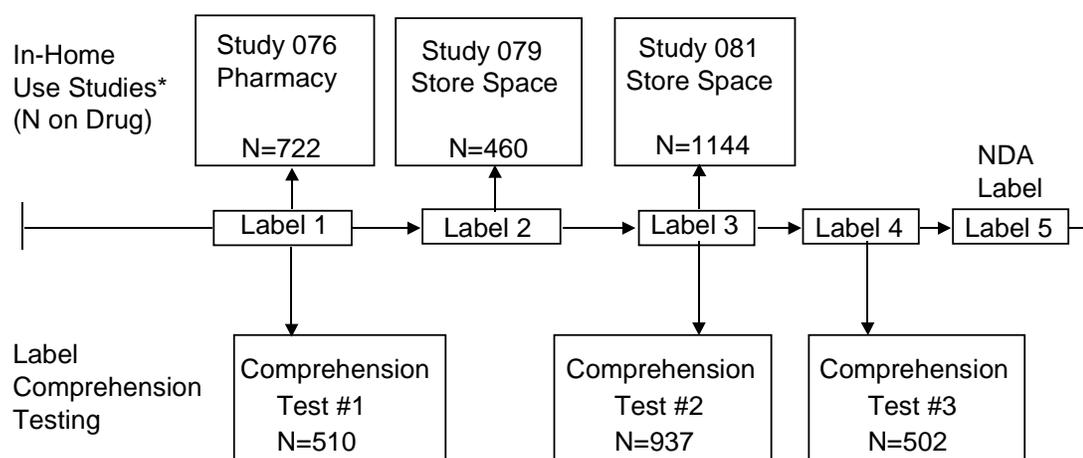
5.4 Label Development and Testing Methods

The history of label development for nonprescription lovastatin reflects the evolutionary development of the proposed OTC treatment paradigm. Each prototype label system was an iterative step toward the goal of labeling that is both easy to understand and effective in guiding consumers toward appropriate product selection and use in conjunction with a healthy lifestyle of low-fat diet and exercise. Figure 7 provides a visual overview of the label development activities which led to the proposed label in the NDA (Label 5). The nonprescription lovastatin development program included testing of the labeling for consumer understanding (label comprehension testing), and consumer behavior (clinical in-home use studies and companion consumer research surveys). In both the label comprehension and in-home use studies, the carton back panel label and carton contents were provided to study participants in a format that simulated a retail OTC product package (e.g., full-color graphics, proposed tradename, use of text, font, color and symbols as if a retail package). Results from these studies of consumer understanding and behavior will be discussed in reference to the feasibility questions listed at the beginning of this section.

5.4 Label Development and Testing Methods (Cont.)

Figure 7

Studies of Nonprescription Lovastatin Labeling



* Follow-up surveys also done on large subsets of participants to supplement key information from protocol.

Table 36 displays the components associated with each of the 5 carton labels and adjunctive support materials. During evolution of the label, the carton back panel underwent major modifications. The format of the first 2 labels was very similar to general OTC labeling in use in the marketplace at the time. Label 3 represented a significant change in format and content. Design features included a 2-part (flip-up) back panel to expand usable space for prominent display of label text, and colored symbols to point out important warning information. Label 4 was another significant change in design. The flip-up panel on Label 3 was found to be confusing to some consumers, and on Label 4 it was replaced by a single extended panel. The label format was reorganized and simplified for easier understanding. An “Easy Steps” approach was used to guide consumers through the product selection process, which was in the Drug Facts format required by the 1999 OTC Labeling Rule. The format of the NDA Label 5 is unchanged from Label 4, with minor refinements in text resulting from Label 4 comprehension testing.

5.4 Label Development and Testing Methods (Cont.)

Table 36

Nonprescription Lovastatin Labeling Component Development

Label	1	2	3	4	5
Where tested	Study 076	Study 079	Study 081	Label Comprehension	NDA Label
Carton back panel format	Standard OTC	Standard OTC	Flip-up with symbols	“Easy Steps,” Drug Facts	“Easy Steps,” Drug Facts
Reinforcement tools					
Package insert, informational booklet, compliance program	√	√	√	√	√
Toll-free telephone service					
For questions	√	√	√	√	√
Postpurchase label reinforcement			√	√	√
Videotape			√	√	√

Three clinical in-home use studies were conducted to test the first 3 versions of the label (each tested a separate version) by exploring aspects of consumer behavior in a variety of community-based settings and study designs to simulate the OTC real-world environment. These studies, Studies 076, 079, and 081, contributed useful information on consumer behavior, and are summarized in the sections that follow. Since no one study design and setting can answer all questions pertinent to consumer behavior, the discussion of consumer behavior results will draw from information collected in each of these studies. Table 37 shows an overview of the key information provided by each of the studies.

5.4 Label Development and Testing Methods (Cont.)

Table 37

Key Information From In-Home Use Studies

Information Collected	Study 076 Pharmacy	Study 079 Store Space	Study 081 Store Space
Cholesterol recall accuracy	√	√	
Product selection	√		√
Persistence for 18 months	√		
Dosing compliance	√	√	

Study 076 was placed in retail pharmacy settings in geographically and demographically diverse communities. The goals of the study, which used the first iteration of the carton label (Label 1), were to assess consumers' ability: to select product appropriately, to comply with continuous daily dosing, to persist with treatment over the long term (up to 18 months), and to achieve the benefit of cholesterol reduction in the OTC setting. The consumers' propensity to consult their personal physician was also examined. Physician interaction is encouraged in all labels, but is not a requirement for appropriate individuals who meet label eligibility criteria.

As Study 076 progressed, Study 079 was initiated to explore a novel restricted access distribution paradigm. This study piloted the process of pre-purchase eligibility assessment by a toll-free telephone service. Eligible participants were directed to study sites which were located in rented store space in shopping centers. This study was not designed to provide an opportunity for consumers to make product selection decisions or to persist on treatment long-term. However, learnings from the toll-free service were successfully applied postpurchase in the third study, Study 081.

Study 081 was conducted to evaluate the ability of consumers to select or reject product use appropriately when substantial additional reinforcement tools were added to the label system (Label 3). Although both Studies 076 and 081 provided product selection results, the results from Study 081 are considered more relevant since this study utilized a more advanced and fully-developed labeling system. Likewise, although both Studies 076 and 079 provide compliance information, the results from Study 076 are considered more relevant since this study had an 18-month treatment duration.

5.4 Label Development and Testing Methods (Cont.)

Table 38 lists the consumer research that was conducted in association with the in-home use studies. Studies 076 and 081 were accompanied by consumer research add-on questions at the conclusion of the last visit in each study (6 months and 1 month, respectively) to further understand each participant’s decision-making process and use of the product. Study 079 was followed by a survey on those consumers who were excluded due to higher risk of coronary heart disease. The results of the consumer research in Studies 076 and 079 which are pertinent to consumer behavior are discussed in the sections that follow.

Table 38

Consumer Research Surveys Associated with Clinical In-Home Use Studies

Information Collected	Study 076 Add-on Questions N=432	Study 079 Follow-up Survey N=402	Study 081 Add-on Questions N=826
Product selection			√
Continuous daily dosing	√		
Diet and exercise adherence	√		
Interaction with doctor	√	√	√

The information most relevant to the final proposed label system (Label 5) and how it drives appropriate product selection comes from Study 081, which is described in the next section.

Study 081 Design

Study 081 was an “all-comers”, open-label, observational in-home use study of consumers’ product selection decisions. Consumers were recruited through television, radio, and print advertising in 5 geographically dispersed major metropolitan areas: Chicago, Dallas, Houston, Minneapolis, and Washington DC. Advertising was designed to attract a healthy population of at least middle age who were concerned about lowering their cholesterol in a comprehensive healthy heart program. Study sites were located in community settings using rented space in shopping centers, and included sites placed in areas which would attract minority populations.

5.4 Label Development and Testing Methods (Cont.)

Consumers who responded to the advertising were given appointments to visit the study sites. At the first visit, participants were asked to read the product carton label, and to make an unaided decision whether or not to purchase the product based on their knowledge of their cholesterol levels, concomitant medications, and medical conditions. Participants who decided to purchase the product were then asked if any of the 4 safety warnings applied to them (current use of “Do Not Use” medications on the label, current liver disease, women of childbearing potential, allergy to lovastatin). Those who qualified were permitted to review and sign the informed consent form, purchase the product (\$15.00 for a one month supply), and go home with study drug in the OTC package with support materials. An appointment for the return visit to the study site was scheduled for 4 weeks. These participants had the opportunity to review and use the label reinforcement tools at home, one of which was the toll-free service which was available to reinforce the product eligibility criteria.

Participants who responded affirmatively to any of the safety warning questions were not permitted in this clinical trial to go home with study drug, but in-home review of the carton contents was simulated in a private area of the study site. These participants reviewed all of the label reinforcement tools including the videotape, but did not have the opportunity to contact the toll-free service from the study site. After this review, the participants made a second product selection decision at the study site but did not continue in the study.

5.5 Results: Product Selection

Do people understand the label and select product appropriately? Answers to this question are provided in the results of label comprehension testing on carton Label 4 (the last tested iteration prior to finalizing the draft label for the NDA), and in the results of consumer behavior testing of the preceding label version (Label 3) in Study 081.

5.5.1 Product Selection Testing—Label 3 (Study 081)

As noted above, actual consumer behavior regarding product selection was tested in the clinical in-home use Study 081 using carton Label 3 and label reinforcement tools. The purpose of the trial was to evaluate the ability of consumers to select or reject product use appropriately when substantial additional reinforcement tools were added to the label system. This was designed to be an “all-comer” trial in which all participants had the opportunity to make an initial purchase decision based on the product carton label, and all interested participants, whether eligible or not, were permitted to self-medicate except those who were subject to safety warnings. Interested participants were required to purchase the product. The study endpoints were the proportions of participants who made product selection errors after only reviewing the carton label, and after reviewing the carton label plus the label reinforcement tools.

5.5.1.1 Study 081 Product Selection Results

A total of 2416 participants responded to the advertising and came to the study sites where they reviewed the product outside carton label and made a product selection decision. Of the 2416 participants, 364 (15%) decided not to purchase the product because they were not interested, and 823 (34%) decided that they needed more information before deciding to purchase. This is analogous to interested consumers picking an OTC product off the shelf in a store, reviewing its label, and then half of them putting it back on the shelf. The carton label apparently caused many of the consumers to carefully consider their decision whether or not to purchase the product.

Prevalence of Label Exclusions in Participants With Medical History

Participants were asked to provide their medical history in order to assess the prevalence of label exclusions in the population, and to assess the correctness of the participant’s product selection decision. Of the 2416 participants who made a product selection decision, 2264 provided their medical history. The situations where consumers should decide not to purchase the product (provided on the carton label) are grouped for review of results into 4 label exclusion categories: (1) participants whose only reason for ineligibility was total cholesterol >240 mg/dL; (2) participants with conditions indicating higher CV risk, i.e., history of CHD, stroke, diabetes mellitus (DM), or hypertension (HTN); (3) participants subject to one or more of the 4 safety warnings; and (4) “other”, a heterogeneous group with a variety of exclusions. The reasons for ineligibility in the “other” group were: males less than 40 years old, total cholesterol <200 mg/dL, did not know total cholesterol value, past history of liver disease, and those consumers taking prescription or OTC cholesterol-lowering drugs or who did not know if they were taking cholesterol-lowering drugs. The prevalence of the carton label exclusions in the 2264 participants who provided medical history are displayed by category in Table 39.

Table 39

Study 081—Prevalence of Label Exclusions in Study Population

Label Exclusion Category	Prevalence in Study Population (N=2264)
Total cholesterol >240 mg/dL	381 (17%)
Higher CV risk (CHD, stroke, DM, HTN)*	262 (12%)
Safety warning*	120 (5%)
“Do Not Use” medications*	83 (4%)
Other*	604 (27%)
*Participants may have more than one exclusion	

5.5.1.1 Study 081 Product Selection Results (Cont.)

Correctness of Product Selection Decision in Participants With Medical History

Table 40 displays the percents of participants in each of the 4 label exclusion categories who made the correct product selection decision (decided not to purchase) after only reading the outside carton label, and again after reviewing both the carton label and label reinforcement tools contained in the package. In each of the label exclusion categories, the percentages of participants making the correct decision not to purchase the product increased after participants reviewed the label reinforcement tools.

Table 40

Study 081—Correctness of Product Selection Decision
 by Label Exclusion Category

Label Exclusion	N	Correct After Reading Carton Label (Outside)	Correct After Label Reinforcement Tools (Inside)
Total cholesterol >240 mg/dL only	381	54%	72% [†]
Higher CV risk (CHD, stroke, DM, HTN)	262	68%	83% [†]
Safety warning	120	68%	83%
“Do Not Use” medications	83	70%	83%
Other	604	70%	85% [†]

[†] Included toll-free service.

Toll-Free Label Reinforcement Service

The toll-free label reinforcement service was effective in influencing ineligible participants who purchased the product to reverse their initial product selection error. Approximately two-thirds (90 of 146, 62%) of ineligible participants who called the toll-free service subsequently stopped taking drug by their return visit (Week 4). In contrast, only about one-quarter (61 of 230, 26%) of ineligible participants who did not call the toll-free service subsequently stopped taking drug by Week 4. For comparison, the proportions of eligible participants who stopped taking drug by Week 4 was similar for those who called (9%) and those who did not call (11%). These results indicate that, in the ineligible people who went home with product, use of the toll-free service substantially improved the accuracy of the product selection process compared to the carton materials alone. Furthermore, these results suggest that the percentage of correct product selection decisions in the 120 participants subject to safety warnings could have been further improved if these participants had been able to contact the toll-free service while at the study site.

5.5.1.1 Study 081 Product Selection Results (Cont.)

Product Selection Decision: Conclusions

In summary, consumer behavior testing in Study 081 showed that, even with a still-evolving carton label (Label 3):

- Most consumers made an appropriate product selection decision
- The accuracy of the product selection decision was further improved when consumers reviewed the label reinforcement tools contained in the package
- The toll-free telephone label reinforcement service was highly effective as a label reinforcement tool.

These results support the conclusion that the nonprescription lovastatin 10 mg labeling system of communication, education and support effectively guides consumer product selection.

5.5.2 Label Comprehension Testing—Label 4

Testing of Label 3 revealed that many consumers failed to lift the flip-up back panel, and that the symbols and organization of the label elements may have unintentionally introduced misunderstanding of some of the key labeling messages. These learnings led to additional improvements in format and content which were incorporated into Label 4. (Label 4 is very similar to the final Label 5 proposed in this application.) Label comprehension testing on Label 4 was performed to evaluate how effectively key messages of the back panel label were communicated. In addition, the ability of label reinforcement tools to enhance communication of the key messages was evaluated. Finally, the results of this comprehension test were compared with the results of testing the earlier Label 3.

5.5.2.1 Methodology

Recruitment for comprehension testing was aimed at obtaining a representative sample of the U.S. population, not necessarily concerned or experienced regarding managing cholesterol. A “mall intercept” approach was used in 28 geographically and demographically dispersed shopping malls, where individuals walking in the malls were approached about participation in the test. The study population was augmented to insure a sufficient sampling of 2 subgroups: individuals subject to label safety warnings, and individuals with low literacy. The procedure was to have participants read the carton label and then answer questions. Then participants reviewed the internal contents of the product carton and answered additional questions. The carton and internal contents were visible to the participants for reference when responding to the questions. As a control measure, the questions included “false positives”, which were questions about items not mentioned in the labeling.

5.5.2.1 Methodology (Cont.)

The following label elements were identified as key messages to be tested:

1. What condition the product is for
2. Number of tablets to be taken on a daily basis
3. Appropriate menopausal status for product use (women)
4. Self-knowledge of total cholesterol level
5. Talk to a doctor before use if history of:
 - Heart disease
 - Stroke
 - Diabetes
6. Current or past history of hepatitis or liver disease
7. Pregnant, able to become pregnant, breast feeding
8. Certain “Do Not Use” medications

The success criterion for the key messages was to achieve correct comprehension by at least 80% of participants. For all other label elements of secondary importance, the goal was for the majority of participants to give correct answers.

5.5.2.2 Label 4 Comprehension Results

Results of the testing of the Label 4 system showed a high level of comprehension for all of the key messages. Some specific examples of the comprehension results are: (1) over 90% of people understood that they should know their cholesterol value before using the product, and (2) the dosing instructions and the message to inform a doctor about product use were understood by 96-99% of participants.

The label reinforcement tools were shown to further increase comprehension levels. Table 41 lists the situations where the label indicated a doctor should be consulted before product use, and the comprehension results after reading the carton label alone compared to results after reviewing the carton contents. For each element listed, comprehension improved after review of the label reinforcement tools.

5.5.2.2 Label 4 Comprehension Results (Cont.)

Table 41

Label 4 Comprehension Results
 Carton Label Alone Versus Carton Label Plus Reinforcement Tools

Ask a Doctor Before Use	% Correct (N=391)	
	After Carton Label	After Carton Label Plus Reinforcement Tools
Stroke	93	97
Heart disease	92	97
Diabetes	92	97
High blood pressure	90	95
Total cholesterol >240 mg/dL	70	87

Safety Warnings—“Do Not Use” Medications

An important specific goal of the nonprescription labeling system is to alert consumers about inappropriate use of nonprescription lovastatin 10 mg with concomitant medications that may increase the potential for a rare, usually reversible muscle adverse experience, as detailed in the Safety section of this document. The drugs known to interact pharmacokinetically or pharmacodynamically are specified on the carton back panel label and in the label reinforcement tools. Label 3 was less effective than desired in communicating the drug interaction warnings, and efforts were made to improve the comprehension of this section in Label 4. Table 42 compares the comprehension scores on drug interaction warnings between Label 3 and Label 4. Label 4 was successful in communicating the drug interaction warnings, and was statistically significantly better than Label 3 ($p \leq 0.050$). Table 42 also shows that comprehension of drug interaction warnings on Label 4 was further improved after review of the label reinforcement tools.

5.5.2.2 Label 4 Comprehension Results (Cont.)

Table 42

Label 4 Comprehension Results “Do Not Use” Medications
 Comparison to Label 3 and to Carton Label Plus Reinforcement Tools

	% Correct (After Carton Label)		% Correct (After Carton Label Plus Reinforcement Tools)
	Label 3 (N=406)	Label 4 (N=391)	Label 4 (N=391)
“Do Not Use” Medications			
Niacin ≥500 mg	64	90	96
Other cholesterol medications	74	88	98
Cyclosporine	58	81	91
Erythromycin	60	80	90

Label Comprehension of Product Selection Criteria: Conclusions

In summary, comprehension testing of Label 4 showed that

- Strong scores were achieved on key messages in the general population and the safety subgroup, and that low literacy subgroup scores were also acceptable (data not shown)
- Label 4 scored significantly better than Label 3 on comprehension of “Do Not Use” medication warnings
- Internal materials (label reinforcement tools) further improved comprehension.

Even though excellent label comprehension was achieved with Label 4, additional minor refinements were made to further enhance the final label submitted in the NDA (Label 5), which is provided in the materials accompanying this volume. These minor refinements included: reformatted liver disease and pregnancy warnings for increased prominence; strengthened drug interaction warning text; doctors and pharmacists added as individuals the consumer can contact to determine if they are taking a “Do Not Use” medication; and a caution to consumers with continuing medical conditions that they may need further medical care.

5.6 Results: Product Use

The next question this program addresses is: once a decision to self-treat has been made, do consumers follow the label directions when using the product initially and over the long term?

In response to this question, 3 areas of consumer behavior will be explored: (1) eating and exercise habits while on treatment with nonprescription lovastatin, (2) self-reported dosing patterns, and (3) persistence on treatment over the long term, and compliance with regular dosing (measured by tablet counts and lipid reduction). Results from Study 076 are most relevant to these topics since participants remained in the study for up to 18 months.

5.6.1 Eating and Exercise Behavior

An important issue for cholesterol management with nonprescription drugs is whether or not consumers will incorporate drug therapy together with adherence to a healthy lifestyle. While the nonprescription lovastatin clinical program did not attempt to verify the behavioral aspects of a healthy lifestyle, participants' self-reports of eating and exercise habits were collected in a follow-up survey in a subset of participants who completed 6 months of treatment in Study 076. The purpose was to find out if participants would substitute nonprescription lovastatin 10 mg for healthy eating and exercise habits. In Study 076, the pharmacists (who were the investigators) were instructed to provide no guidance or advice on lifestyle activities; participants had to rely solely on information in the labeling system (Label 1). The findings from the 403 participants in this survey are displayed in Table 43, and are very encouraging. Although the majority of participants said their eating and exercise habits had not changed, 40% indicated their eating habits improved, and 18% said their exercise habits improved. Very few indicated a worsening of either parameter.

Table 43

Self-Reported Eating and Exercise Habits in Study 076
Consumer Research Follow-up Survey (N=403)

	Better	No Change	Worse	Unknown
Eating habits	40%	51%	<1%	9%
Exercise habits	18%	76%	4%	2%

5.6.1 Eating and Exercise Behavior (Cont.)

The proposed nonprescription lovastatin program of communication, education, and support encourages healthy eating and exercise habits in conjunction with drug treatment in order to control cholesterol. In particular, the contents of the information booklet on cholesterol and the compliance program newsletters focus heavily on healthy eating and regular exercise. Consumers' understanding of these messages was tested in the label comprehension study of the Label 4 system. After reading just the carton back panel label, 86% of the 391 participants felt that eating right helps to control cholesterol and 85% felt that regular exercise helps to control cholesterol. These percentages increased to 96% and 95%, respectively, after participants reviewed the carton contents (label reinforcement tools).

These results suggest that consumers who use nonprescription lovastatin will maintain or improve their diet and exercise habits and not allow their lifestyle to deteriorate. This represents an opportunity to positively affect healthy lifestyle behavior in users of nonprescription lovastatin through the comprehensive communication, education, and support program that will be implemented.

5.6.2 Persistence and Compliance Over the Long Term

No drug can achieve its intended effect if it is not taken according to directions. The proposed nonprescription lovastatin labeling system provides clear dosing instructions on the carton: (1) one tablet with food every evening, and (2) continue dosing to avoid cholesterol going back up. These instructions are reinforced throughout the education and support materials. Comprehension testing of Label 4 showed a high level of understanding for both the number of tablets to be taken per dose and the number of tablets to be taken per day (99 and 96%, respectively).

In-home use Study 076 was a trial of 18-month treatment duration which provided a unique opportunity to observe consumer behavior regarding persistence and compliance in an OTC setting over the long term. (The duration of treatment in Study 076 was originally 6 months, but for those participants interested in continuing treatment, the duration was extended for 2 additional 6-month periods, for a total of 18 months.) It is important to remember that in order to observe consumer behavior in a simulated OTC environment, the pharmacist co-investigators were instructed not to remind or otherwise coach participants on the need to adhere to the dosing instructions. Therefore, the consumer behavior related to persistence and compliance evolves from the participants' self-motivation and from the support of the labeling system and the compliance program associated with the study. The compliance program was designed to further support a high level of persistence and compliance to therapy. Enrollees in the compliance program received a free AHA cookbook and up to 12 monthly newsletters. The newsletters focused on healthy eating, regular exercise, and the importance of continued dosing with nonprescription lovastatin. Approximately 75% of the participants enrolled in Study 076 voluntarily enrolled in the compliance program.

5.6.2.1 Long-Term Persistence

Persistence at 6, 12, and 18 months was defined in Study 076 as having taken any medication since the time drug was last dispensed. Another way to represent persistence is to observe the number of individuals remaining in the trial at 6-month intervals. Table 44 displays the persistence results observed using each of these definitions of persistence. Of the 722 participants who received study medication at the beginning of Study 076, 72% remained in the trial at 6 months, 57% remained in the trial at 12 months, and 49% remained in the trial at the end of 18 months.

Table 44

Study 076—Long-Term Persistence on Treatment

Time point	Persistence (N=722)	
	Participants Taking Any Drug in Last Interval N (%)	Participants Remaining in Trial N (%)
6 Months	504 (70%)	522 (72%)
12 Months	406 (56%)	414 (57%)
18 Months	321 (44%)	357 (49%)

The persistence rates in Study 076 were compared to those reported for prescription lovastatin in the published literature. One of the methods cited by authors for measuring persistence, assessment of prescription refills, is somewhat analogous to the definition used in Study 076 of participants remaining in the trial. In 2 studies using the prescription refill assessment of persistence [17; 60], persistence rates on lovastatin at one year were 64% and 50%, respectively. Thus, despite the study design features of Study 076 noted below which could have negatively influenced persistence, the 57% persistence rate at one year in the nonprescription setting compares favorably with the persistence rates reported for prescription treatment with lovastatin. The persistence results reported in Project ImPACT (69% at 2 years) indicate that an even higher level of persistence may be obtained in a community setting with a program providing optimal communication and support. Therefore, with the implementation of the full program that will accompany nonprescription lovastatin in the marketplace, and the accessibility of knowledgeable health care professionals such as pharmacists, it is reasonable to expect that the percent of consumers who persist on long-term therapy may approach that observed in Project ImPACT.

5.6.2.1 Long-Term Persistence (Cont.)

Several unique Study 076 design features might have contributed to the observed decline in persistence rates over time. First, interim study site appointments were not scheduled, i.e., participants were on their own to return when they needed a resupply of study medication. Second, the pharmacist-investigators were instructed not to influence participant behavior, including no encouragement of persistence or compliance. Third, since the reach of mass media advertising was sometimes quite far from the study locations, some participants had to travel long distances to reach the study sites. Finally, since the 6-month treatment extensions were added as the study progressed, participants had to make a decision to enroll multiple times. It is important to note that the observed decline in persistence includes participants who completed either a 6-month or 12-month treatment period and were eligible to continue (56 and 24 participants, respectively), but chose not to enroll in a further 6-month treatment extension. These study design features probably contributed to these participants' decisions not to continue.

5.6.2.2 Compliance

Table 45 displays the compliance results and reductions in LDL cholesterol at 6, 12, and 18 months of treatment. In patients who remained in the trial, compliance as a percent was calculated based on tablet counts over time for each 6-month interval. The participants who persisted on treatment exhibited a high degree of compliance throughout the study. As shown in Table 45, the proportions of participants who took 75 to 100% of their medication remained high (84 to 86%) throughout the 18-month treatment period.

The effect of treatment with cholesterol-lowering medication provides a unique, objective method of validating the compliance results obtained from tablet counts. In Study 076 the relationship between compliance and efficacy was explored using mean LDL-cholesterol reduction to represent efficacy. The results demonstrated that the excellent findings regarding compliance were confirmed by the objective measure of LDL-cholesterol reduction at each time point. As can be seen in Table 45, the clinically meaningful reductions in LDL-cholesterol observed at 6 months were maintained at 12 and 18 months.

5.6.2.2 Compliance (Cont.)

Table 45

Study 076—Long-Term Compliance and Lipid Results

Time Interval	Proportion of Compliant Participants [†]	Mean % Reduction in LDL Cholesterol at End of Interval
0 to 6 Months	84%	24%
6 to 12 Months	86%	20%
12 to 18 Months	86%	23%
[†] 75 to 100% compliant with dosing as determined by tablet counts over time.		

In summary, the results from Study 076 show that motivated consumers comply well with long-term daily dosing, and achieve clinically meaningful lipid changes. Thus, consumers have demonstrated that they can understand and will follow directions for long-term product use. This is not surprising, since motivated consumers have long been willing and able to take daily vitamin and mineral supplements on a continuous basis.

5.7 Interactions With Doctors

Another important question this program addresses is: does the nonprescription lovastatin labeling system encourage collaboration with doctors?

Two of the in-home use studies provide information on consumers' interaction with doctors. In Study 076 (Label 1), many participants took the initiative to contact their personal doctor about their use of nonprescription lovastatin: 30% of the participants reported that they spoke with their personal doctor between Visits 1 and 2 (the first 8 weeks of treatment), and 48% of the polled participants who completed 6 months of treatment had called their doctor about product use. These percents are most noteworthy in light of the following: (1) the label system used in Study 076 (Label 1) provided minimal advice regarding interaction with a doctor; and (2) participants on study drug had already been screened by the investigator (a pharmacist) and were judged to be eligible for product based on medical history and cholesterol test values.

Data on consumer behavior regarding consulting with their doctors were also collected in a consumer research telephone survey in follow-up to Study 079. In this study, consumers were screened for product eligibility by a toll-free service prior to visiting a study site. Participants who were excluded during the screening process due to their self-report of total cholesterol above the OTC-eligible range (some of whom also had higher

5.7 Interactions with Doctors (Cont.)

cardiovascular risk conditions such as existing CHD or diabetes) were instructed to call their doctors. Those who were excluded for reasons other than elevated cholesterol or higher CV risk were advised merely to follow a healthy lifestyle of low-fat diet and exercise. Approximately 5 to 6 months after participants' involvement in the clinical trial, a telephone interviewer asked a random subset of both these groups (202 of those advised to call their doctors, 200 of those not told to call) whether they had spoken with their doctors about cholesterol after their conversation with the study product specialist. Significantly more people (69% versus 51%, $p < 0.050$) who were advised by the product specialist to call their doctors about cholesterol management did so. It is also noteworthy that a majority (63%) contacted a physician without being recommended to do so. Thus, higher CV risk patients can be guided to seek a physician's advice by a labeling system that includes the advice of a product specialist at a toll-free label reinforcement service.

As previously noted, the proposed carton label directs consumers to consult with a doctor before use if the consumer is subject to "Talk to your doctor before use" warnings listed on the label, and if unexplained muscle symptoms develop during product use. Also, the label advises all consumers to inform their doctor about their use of the product, and to see their doctor for regular check-ups. Finally, consumers are advised to consult their doctor if their cholesterol does not go down after 8 weeks of product use. The label comprehension test of Label 4 showed that these messages were well understood. In addition to knowing when to consult a doctor before use, 96% of participants felt that a typical user of nonprescription lovastatin should talk to a doctor at some point.

Thus, the nonprescription lovastatin labeling system has been shown to encourage collaboration with doctors on cholesterol management, and responsible product promotion is likely to reinforce these messages. However, it should be noted that eligible consumers who know their cholesterol numbers need not consult a physician to safely use this product.

5.8 Summary

The data presented in this section demonstrate that consumer self-management of cholesterol in a nonprescription environment is feasible with the comprehensive nonprescription lovastatin program of communication, education, and support to the consumer. Furthermore, these results provide evidence that the benefit of reduced CHD risk with nonprescription lovastatin 10-mg treatment can be achieved through sustained lipid lowering in those consumers motivated to use the product continuously over the long term.

5.9 Consumer Behavior: Conclusions

- Cholesterol testing is increasingly available to the general public and is widely used.
- The nonprescription lovastatin labeling system effectively guides consumer product selection.
- The nonprescription lovastatin labeling system is well understood by consumers.
- Consumers maintain or improve eating and exercise habits while taking nonprescription lovastatin 10 mg in a nonprescription setting.
- A substantial segment of interested consumers comply well with long-term daily dosing with nonprescription lovastatin 10 mg, and achieve clinically meaningful lipid changes.
- The nonprescription lovastatin labeling system encourages collaboration with health care professionals.

6. Overall Summary and Conclusion

The approval of a nonprescription cholesterol reducing medication for the self-management of cholesterol represents an important shift in the approach to preventative medicine. Comprehensive information reviewing all pertinent issues regarding this proposal has been collected and summarized. These data support the conclusion that the time is right for a nonprescription form of MEVACOR™ which will become a substantial milestone in self care with impact on public health.

First, the target population defined in this proposal has been shown to be at sufficient risk of developing coronary heart disease and therefore warrant the option of treatment. The effectiveness of the product at the proposed 10-mg dose has been well characterized and is clinically meaningful. This is true both for the lipid modifications, as well as for the estimations of prevention of first acute CHD events and their sequelae which would be expected in the self-medicating population. Individuals who choose to invest in this treatment option would logically be self-motivated to persist on treatment. Long-term self treatment data collected in the MEVACOR™ OTC study program confirm this assertion. These data also confirm that a substantial reduction in LDL-C was sustained over the duration of treatment up to 18 months.

It is of utmost importance that a new nonprescription drug candidate have a well-established safety profile, and that any inherent potential risks be outweighed by the potential benefits of treatment. The vast clinical safety data on this widely used product attest to the fact that this criterion has been amply met by MEVACOR™ OTC. The product has a wide margin of safety. It is generally well-tolerated even at doses which are multiples of the proposed 10-mg dose. Even at the higher dose ranges, drug-related side effects of potential concern, particularly muscle related, are very rare. Furthermore, this type of rare event can be managed by effective consumer-friendly product labeling.

Finally, it has been demonstrated that an interested consumer can appropriately self-select and use such a product in a comprehensive OTC study program. The proposed labeling has evolved through repeated testing, both in terms of the standard comprehension testing, and also in novel clinical studies evaluating actual consumer behavior in using the product. The in-home use studies were designed to simulate real-world settings and allow participants to demonstrate their behavior with minimal artificial support or constraint. In this way, data have been generated which address critically important questions about how people will use the product in response to the labeling and innovative educational and support materials.

Data submitted in the NDA, and summarized in this volume, demonstrate that it is feasible to communicate sufficient information to consumers such that they will use the product appropriately. Through the development of this nonprescription product, a new type of consumer support program has been created and tested to reinforce label

6. Overall Summary and Conclusion (Cont.)

messages and ensure correct use over the long term. The results confirm that the label messages are well understood, that product selection decisions are thoughtful and generally correct, and that the label reinforcement tools further improve the appropriateness of decisions on product use. Additionally, this program has been shown to encourage collaboration with doctors in the management of cholesterol and to foster adherence to long-term treatment and a healthy lifestyle.

The time is right for this paradigm shift in nonprescription treatment as evidenced by several current trends. The public is increasingly aware of cholesterol as a risk factor and of the importance of a healthy lifestyle in maintaining cardiovascular health. In parallel, accurate cholesterol testing is becoming widely available to the consumer in diverse community-based settings. In addition, the public is expressing a growing interest in playing a role in health maintenance. This is evidenced by the rapid proliferation of consumer products with health claims which include cholesterol lowering and healthy heart benefits.

MEVACOR™ OTC can provide a substantial benefit in lowering cholesterol and preventing first heart attacks and their consequences. The magnitude of benefit defined clearly outweighs the potential risks, and the product can be labeled for safe and appropriate use. Therefore, approval of MEVACOR™ OTC will provide a valuable new treatment option to motivated Americans who desire access to a safe and effective product for maintaining cardiovascular health while aging.

Nonprescription MEVACOR™
FDA Advisory Committee Background Package

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Attachment 1
Outer Carton Back Panel

<p>Drug Facts</p>	<p>Purpose</p>
<p>Active ingredient (in each tablet) Lovastatin 10 mg.....Cholesterol Controller</p>	
<p>Use: MEVACOR® CC should be used to help lower total cholesterol which may lead to a healthier heart.</p>	
<p>Who should use MEVACOR CC:</p>	
<ul style="list-style-type: none"> Your total cholesterol is between 200–240 mg/dL AND your LDL ("bad") cholesterol is over 130 mg/dL, AND <ul style="list-style-type: none"> You are a woman past menopause (at least 1 year since last menstrual period) You are a man 40 years or older (men less than 40 years old, talk to your doctor before use) 	
<p>Warnings</p>	
<p>Allergy alert: Do NOT use if you are allergic to any of the ingredients in this drug.</p>	
<p>Liver disease: Do NOT use if you have hepatitis or other liver disease.</p>	
<p>Women: Do NOT use if you are pregnant, may become pregnant or are breast-feeding. Do NOT use unless you are past menopause.</p>	
<p>Do not use MEVACOR CC with the following medicines†:</p>	
<ul style="list-style-type: none"> erythromycin, or clarithromycin-Biaxin (for infections) other cholesterol-reducing drugs such as: <ul style="list-style-type: none"> niacin at daily doses of 500 mg or more, or gemfibrozil prescription statin drugs including: <ul style="list-style-type: none"> simvastatin-Zocor®, pravastatin-Pravachol, fluvastatin-Lescol, atorvastatin-Lipitor, cerivastatin-Baycol, or lovastatin-Mevacor®* 	
<ul style="list-style-type: none"> nefazodone-Serzone (for depression) cyclosporine (for immune suppression) protease inhibitors (for HIV/AIDS) 	
<p>Potentially serious side effects may occur when MEVACOR CC is used with these drugs. Seek immediate medical attention if you get unexplained muscle pain, tenderness, or weakness. If you are not sure if your medicine contains one of these drugs, call your doctor, pharmacist or 1-800-MEVACOR.</p>	
<p>Do not use MEVACOR CC unless directed by your doctor if you have a continuing medical condition including the following. You may need prescription strength cholesterol medicine or further medical care.</p>	
<ul style="list-style-type: none"> total cholesterol above 240 mg/dL (you may be at a greater risk for heart attack) heart disease, such as having had a heart attack or angina diabetes head a stroke high blood pressure 	
<p>Ask a doctor before use if you have 3 or more alcoholic drinks most days or had liver disease in the past.</p>	
<p>Keep out of reach of children. This product should not be given to children.</p>	
<p>In case of overdose, get medical help or contact a Poison Control Center right away.</p>	
<p>Directions</p>	
<ul style="list-style-type: none"> Take only one tablet with food every evening After about 8 weeks, you should have a cholesterol test <ul style="list-style-type: none"> if your cholesterol goes down, continue using MEVACOR CC along with eating a low-fat diet and exercising, or your cholesterol may go back up if your cholesterol does not go down, talk to your doctor You should tell your doctor that you are taking MEVACOR CC as part of a heart healthy program 	
<p>Inactive ingredients: cellulose, lactose, magnesium stearate, red ferric oxide, starch. Butylated hydroxyanisole (BHA) is added as a preservative.</p>	
<p>Questions? See inside package for additional information or call toll free 1–800–MEVACOR. If after buying this product you decide it is not right for you, return it for a full refund.</p>	

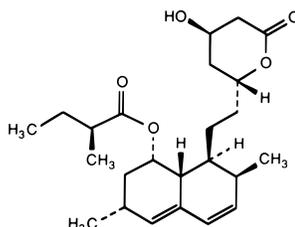
Attachment 2
Current MEVACOR Rx Label

TABLETS
MEVACOR®
 (LOVASTATIN)

DESCRIPTION

MEVACOR® (Lovastatin) is a cholesterol lowering agent isolated from a strain of *Aspergillus terreus*. After oral ingestion, lovastatin, which is an inactive lactone, is hydrolyzed to the corresponding β -hydroxyacid form. This is a principal metabolite and an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is an early and rate limiting step in the biosynthesis of cholesterol.

Lovastatin is [1S-[1 α (R*),3 α ,7 β ,8 β (2S*,4S*), 8 α β]]-1,2,3,7, 8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl 2-methylbutanoate. The empirical formula of lovastatin is C₂₄H₃₆O₅ and its molecular weight is 404.55. Its structural formula is:



Lovastatin is a white, nonhygroscopic crystalline powder that is insoluble in water and sparingly soluble in ethanol, methanol, and acetonitrile.

Tablets MEVACOR are supplied as 10 mg, 20 mg and 40 mg tablets for oral administration. In addition to the active ingredient lovastatin, each tablet contains the following inactive ingredients: cellulose, lactose, magnesium stearate, and starch. Butylated hydroxyanisole (BHA) is added as a preservative. Tablets MEVACOR 10 mg also contain red ferric oxide and yellow ferric oxide. Tablets MEVACOR 20 mg also contain FD&C Blue 2. Tablets MEVACOR 40 mg also contain D&C Yellow 10 and FD&C Blue 2.

CLINICAL PHARMACOLOGY

The involvement of low-density lipoprotein cholesterol (LDL-C) in atherogenesis has been well-documented in clinical and pathological studies, as well as in many animal experiments. Epidemiological and clinical studies have established that high LDL-C and low high-density lipoprotein cholesterol (HDL-C) are both associated with coronary heart disease. However, the risk of developing coronary heart disease is continuous and graded over the range of cholesterol levels and many coronary events do occur in patients with total cholesterol (total-C) and LDL-C in the lower end of this range.

MEVACOR has been shown to reduce both normal and elevated LDL-C concentrations. LDL is formed from very low-density lipoprotein (VLDL) and is catabolized predominantly by the high affinity LDL receptor. The mechanism of the LDL-lowering effect of MEVACOR may involve both reduction of VLDL-C concentration, and induction of the LDL receptor, leading to reduced production and/or increased catabolism of LDL-C. Apolipoprotein B also falls substantially during treatment with MEVACOR. Since each LDL particle contains one molecule of apolipoprotein B, and since little apolipoprotein B is found in other lipoproteins, this strongly suggests that MEVACOR does not merely cause cholesterol to be lost from LDL, but also reduces the concentration of circulating LDL particles. In addition, MEVACOR can produce increases of variable magnitude in HDL-C, and modestly reduces VLDL-C and plasma

triglycerides (TG) (see Tables I-III under *Clinical Studies*). The effects of MEVACOR on Lp(a), fibrinogen, and certain other independent biochemical risk markers for coronary heart disease are unknown.

MEVACOR is a specific inhibitor of HMG-CoA reductase, the enzyme which catalyzes the conversion of HMG-CoA to mevalonate. The conversion of HMG-CoA to mevalonate is an early step in the biosynthetic pathway for cholesterol.

Pharmacokinetics

Lovastatin is a lactone which is readily hydrolyzed *in vivo* to the corresponding β -hydroxyacid, a potent inhibitor of HMG-CoA reductase. Inhibition of HMG-CoA reductase is the basis for an assay in pharmacokinetic studies of the β -hydroxyacid metabolites (active inhibitors) and, following base hydrolysis, active plus latent inhibitors (total inhibitors) in plasma following administration of lovastatin.

Following an oral dose of ^{14}C -labeled lovastatin in man, 10% of the dose was excreted in urine and 83% in feces. The latter represents absorbed drug equivalents excreted in bile, as well as any unabsorbed drug. Plasma concentrations of total radioactivity (lovastatin plus ^{14}C -metabolites) peaked at 2 hours and declined rapidly to about 10% of peak by 24 hours postdose. Absorption of lovastatin, estimated relative to an intravenous reference dose, in each of four animal species tested, averaged about 30% of an oral dose. In animal studies, after oral dosing, lovastatin had high selectivity for the liver, where it achieved substantially higher concentrations than in non-target tissues. Lovastatin undergoes extensive first-pass extraction in the liver, its primary site of action, with subsequent excretion of drug equivalents in the bile. As a consequence of extensive hepatic extraction of lovastatin, the availability of drug to the general circulation is low and variable. In a single dose study in four hypercholesterolemic patients, it was estimated that less than 5% of an oral dose of lovastatin reaches the general circulation as active inhibitors. Following administration of lovastatin tablets the coefficient of variation, based on between-subject variability, was approximately 40% for the area under the curve (AUC) of total inhibitory activity in the general circulation.

Both lovastatin and its β -hydroxyacid metabolite are highly bound (>95%) to human plasma proteins. Animal studies demonstrated that lovastatin crosses the blood-brain and placental barriers.

The major active metabolites present in human plasma are the β -hydroxyacid of lovastatin, its 6'-hydroxy derivative, and two additional metabolites. Peak plasma concentrations of both active and total inhibitors were attained within 2 to 4 hours of dose administration. While the recommended therapeutic dose range is 10 to 80 mg/day, linearity of inhibitory activity in the general circulation was established by a single dose study employing lovastatin tablet dosages from 60 to as high as 120 mg. With a once-a-day dosing regimen, plasma concentrations of total inhibitors over a dosing interval achieved a steady state between the second and third days of therapy and were about 1.5 times those following a single dose. When lovastatin was given under fasting conditions, plasma concentrations of total inhibitors were on average about two-thirds those found when lovastatin was administered immediately after a standard test meal.

In a study of patients with severe renal insufficiency (creatinine clearance 10-30 mL/min), the plasma concentrations of total inhibitors after a single dose of lovastatin were approximately two-fold higher than those in healthy volunteers.

Clinical Studies

MEVACOR has been shown to be highly effective in reducing total-C and LDL-C in heterozygous familial and non-familial forms of primary hypercholesterolemia and in mixed hyperlipidemia. A marked response was seen within 2 weeks, and the maximum therapeutic response occurred within 4-6 weeks. The response was maintained during continuation of therapy. Single daily doses given in the evening were more effective than the same dose given in the morning, perhaps because cholesterol is synthesized mainly at night.

In multicenter, double-blind studies in patients with familial or non-familial hypercholesterolemia, MEVACOR, administered in doses ranging from 10 mg q.p.m. to 40 mg b.i.d., was compared to placebo. MEVACOR consistently and significantly decreased plasma total-C, LDL-C, total-C/HDL-C ratio and LDL-C/HDL-C ratio. In addition, MEVACOR produced increases of variable magnitude in HDL-C, and modestly decreased VLDL-C and plasma TG (see Tables I through III for dose response results).

The results of a study in patients with primary hypercholesterolemia are presented in Table I.

MEVACOR® (Lovastatin)

7825346

TABLE I
MEVACOR vs. Placebo
(Mean Percent Change from Baseline After 6 Weeks)

DOSAGE	N	TOTAL-C	LDL-C	HDL-C	LDL-C/ HDL-C	TOTAL-C/ HDL-C	TG.
Placebo	33	-2	-1	-1	0	+1	+9
MEVACOR							
10 mg q.p.m.	33	-16	-21	+5	-24	-19	-10
20 mg q.p.m.	33	-19	-27	+6	-30	-23	+9
10 mg b.i.d.	32	-19	-28	+8	-33	-25	-7
40 mg q.p.m.	33	-22	-31	+5	-33	-25	-8
20 mg b.i.d.	36	-24	-32	+2	-32	-24	-6

MEVACOR was compared to cholestyramine in a randomized open parallel study. The study was performed with patients with hypercholesterolemia who were at high risk of myocardial infarction. Summary results are presented in Table II.

TABLE II
MEVACOR vs. Cholestyramine
(Percent Change from Baseline After 12 Weeks)

TREATMENT	N	TOTAL-C (mean)	LDL-C (mean)	HDL-C (mean)	LDL-C/ HDL-C (mean)	TOTAL-C/ HDL-C (mean)	VLDL-C (median)	TG. (mean)
MEVACOR								
20 mg b.i.d.	85	-27	-32	+9	-36	-31	-34	-21
40 mg b.i.d.	88	-34	-42	+8	-44	-37	-31	-27
Cholestyramine								
12 g b.i.d.	88	-17	-23	+8	-27	-21	+2	+11

MEVACOR was studied in controlled trials in hypercholesterolemic patients with well-controlled non-insulin dependent diabetes mellitus with normal renal function. The effect of MEVACOR on lipids and lipoproteins and the safety profile of MEVACOR were similar to that demonstrated in studies in nondiabetics. MEVACOR had no clinically important effect on glycemic control or on the dose requirement of oral hypoglycemic agents.

Expanded Clinical Evaluation of Lovastatin (EXCEL) Study

MEVACOR was compared to placebo in 8,245 patients with hypercholesterolemia (total-C 240-300 mg/dL [6.2 mmol/L - 7.6 mmol/L], LDL-C >160 mg/dL [4.1 mmol/L]) in the randomized, double-blind, parallel, 48-week EXCEL study. All changes in the lipid measurements (Table III) in MEVACOR treated patients were dose-related and significantly different from placebo ($p \leq 0.001$). These results were sustained throughout the study.

TABLE III
MEVACOR vs. Placebo
(Percent Change from Baseline —
Average Values Between Weeks 12 and 48)

DOSAGE	N**	TOTAL-C (mean)	LDL-C (mean)	HDL-C (mean)	LDL-C/ HDL-C (mean)	TOTAL-C/ HDL-C (mean)	TG. (median)
Placebo	1663	+0.7	+0.4	+2.0	+0.2	+0.6	+4
MEVACOR							
20 mg q.p.m.	1642	-17	-24	+6.6	-27	-21	-10
40 mg q.p.m.	1645	-22	-30	+7.2	-34	-26	-14
20 mg b.i.d.	1646	-24	-34	+8.6	-38	-29	-16
40 mg b.i.d.	1649	-29	-40	+9.5	-44	-34	-19

**Patients enrolled

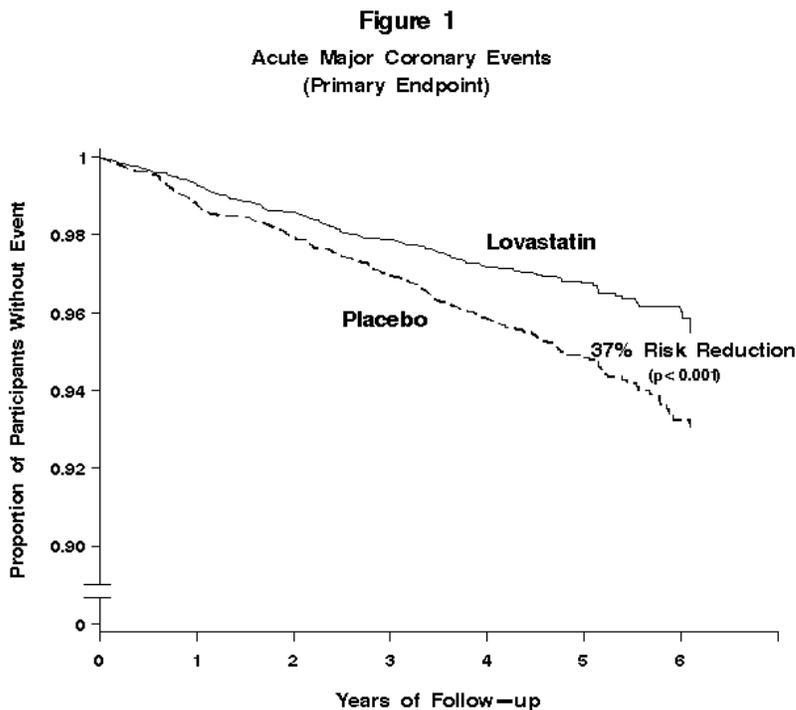
Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)

The Air Force / Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), a double-blind, randomized, placebo-controlled, primary prevention study, demonstrated that treatment with MEVACOR decreased the rate of acute major coronary events (composite endpoint of myocardial infarction, unstable angina, and sudden cardiac death) compared with placebo during a median of 5.1

years of follow-up. Participants were middle-aged and elderly men (ages 45-73) and women (ages 55-73) without symptomatic cardiovascular disease with average to moderately elevated total-C and LDL-C, below average HDL-C, and who were at high risk based on elevated total-C/HDL-C. In addition to age, 63% of the participants had at least one other risk factor (baseline HDL-C <35 mg/dL, hypertension, family history, smoking and diabetes).

AFCAPS/TexCAPS enrolled 6,605 participants (5,608 men, 997 women) based on the following lipid entry criteria: total-C range of 180-264 mg/dL, LDL-C range of 130-190 mg/dL, HDL-C of ≤ 45 mg/dL for men and ≤ 47 mg/dL for women, and TG of ≤ 400 mg/dL. Participants were treated with standard care, including diet, and either MEVACOR 20-40 mg daily (n= 3,304) or placebo (n= 3,301). Approximately 50% of the participants treated with MEVACOR were titrated to 40 mg daily when their LDL-C remained >110 mg/dL at the 20-mg starting dose.

MEVACOR reduced the risk of a first acute major coronary event, the primary efficacy endpoint, by 37% (MEVACOR 3.5%, placebo 5.5%; $p < 0.001$; Figure 1). A first acute major coronary event was defined as myocardial infarction (54 participants on MEVACOR, 94 on placebo) or unstable angina (54 vs. 80) or sudden cardiac death (8 vs. 9). Furthermore, among the secondary endpoints, MEVACOR reduced the risk of unstable angina by 32% (1.8 vs. 2.6%; $p = 0.023$), of myocardial infarction by 40% (1.7 vs. 2.9%; $p = 0.002$), and of undergoing coronary revascularization procedures (e.g., coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) by 33% (3.2 vs. 4.8%; $p = 0.001$). Trends in risk reduction associated with treatment with MEVACOR were consistent across men and women, smokers and non-smokers, hypertensives and non-hypertensives, and older and younger participants. Participants with ≥ 2 risk factors had risk reductions (RR) in both acute major coronary events (RR 43%) and coronary revascularization procedures (RR 37%). Because there were too few events among those participants with age as their only risk factor in this study, the effect of MEVACOR on outcomes could not be adequately assessed in this subgroup.



Atherosclerosis

In the Canadian Coronary Atherosclerosis Intervention Trial (CCAIT), the effect of therapy with lovastatin on coronary atherosclerosis was assessed by coronary angiography in hyperlipidemic patients. In the randomized, double-blind, controlled clinical trial, patients were treated with conventional measures (usually diet and 325 mg of aspirin every other day) and either lovastatin 20-80 mg daily or placebo.

Angiograms were evaluated at baseline and at two years by computerized quantitative coronary angiography (QCA). Lovastatin significantly slowed the progression of lesions as measured by the mean change per-patient in minimum lumen diameter (the primary endpoint) and percent diameter stenosis, and decreased the proportions of patients categorized with disease progression (33% vs. 50%) and with new lesions (16% vs. 32%).

In a similarly designed trial, the Monitored Atherosclerosis Regression Study (MARS), patients were treated with diet and either lovastatin 80 mg daily or placebo. No statistically significant difference between lovastatin and placebo was seen for the primary endpoint (mean change per patient in percent diameter stenosis of all lesions), or for most secondary QCA endpoints. Visual assessment by angiographers who formed a consensus opinion of overall angiographic change (Global Change Score) was also a secondary endpoint. By this endpoint, significant slowing of disease was seen, with regression in 23% of patients treated with lovastatin compared to 11% of placebo patients.

In the Familial Atherosclerosis Treatment Study (FATS), either lovastatin or niacin in combination with a bile acid sequestrant for 2.5 years in hyperlipidemic subjects significantly reduced the frequency of progression and increased the frequency of regression of coronary atherosclerotic lesions by QCA compared to diet and, in some cases, low-dose resin.

The effect of lovastatin on the progression of atherosclerosis in the coronary arteries has been corroborated by similar findings in another vasculature. In the Asymptomatic Carotid Artery Progression Study (ACAPS), the effect of therapy with lovastatin on carotid atherosclerosis was assessed by B-mode ultrasonography in hyperlipidemic patients with early carotid lesions and without known coronary heart disease at baseline. In this double-blind, controlled clinical trial, 919 patients were randomized in a 2 x 2 factorial design to placebo, lovastatin 10-40 mg daily and/or warfarin. Ultrasonograms of the carotid walls were used to determine the change per patient from baseline to three years in mean maximum intimal-medial thickness (IMT) of 12 measured segments. There was a significant regression of carotid lesions in patients receiving lovastatin alone compared to those receiving placebo alone ($p=0.001$). The predictive value of changes in IMT for stroke has not yet been established. In the lovastatin group there was a significant reduction in the number of patients with major cardiovascular events relative to the placebo group (5 vs. 14) and a significant reduction in all-cause mortality (1 vs. 8).

Eye

There was a high prevalence of baseline lenticular opacities in the patient population included in the early clinical trials with lovastatin. During these trials the appearance of new opacities was noted in both the lovastatin and placebo groups. There was no clinically significant change in visual acuity in the patients who had new opacities reported nor was any patient, including those with opacities noted at baseline, discontinued from therapy because of a decrease in visual acuity.

A three-year, double-blind, placebo-controlled study in hypercholesterolemic patients to assess the effect of lovastatin on the human lens demonstrated that there were no clinically or statistically significant differences between the lovastatin and placebo groups in the incidence, type or progression of lenticular opacities. There are no controlled clinical data assessing the lens available for treatment beyond three years.

INDICATIONS AND USAGE

Therapy with MEVACOR should be a component of multiple risk factor intervention in those individuals with dyslipidemia at risk for atherosclerotic vascular disease. MEVACOR should be used in addition to a diet restricted in saturated fat and cholesterol as part of a treatment strategy to lower total-C and LDL-C to target levels when the response to diet and other nonpharmacological measures alone has been inadequate to reduce risk.

Primary Prevention of Coronary Heart Disease

In individuals without symptomatic cardiovascular disease, average to moderately elevated total-C and LDL-C, and below average HDL-C, MEVACOR is indicated to reduce the risk of:

- Myocardial infarction
- Unstable angina
- Coronary revascularization procedures

(See CLINICAL PHARMACOLOGY, *Clinical Studies*.)

Coronary Heart Disease

MEVACOR is indicated to slow the progression of coronary atherosclerosis in patients with coronary heart disease as part of a treatment strategy to lower total-C and LDL-C to target levels.

Hypercholesterolemia

Therapy with lipid-altering agents should be a component of multiple risk factor intervention in those individuals at significantly increased risk for atherosclerotic vascular disease due to hypercholesterolemia. MEVACOR is indicated as an adjunct to diet for the reduction of elevated total-C and LDL-C levels in patients with primary hypercholesterolemia (Types IIa and IIb^{***}), when the response to diet restricted in saturated fat and cholesterol and to other nonpharmacological measures alone has been inadequate.

General Recommendations

Prior to initiating therapy with lovastatin, secondary causes for hypercholesterolemia (e.g., poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other drug therapy, alcoholism) should be excluded, and a lipid profile performed to measure total-C, HDL-C, and TG. For patients with TG less than 400 mg/dL (<4.5 mmol/L), LDL-C can be estimated using the following equation:

$$\text{LDL-C} = \text{total-C} - [0.2 \times (\text{TG}) + \text{HDL-C}]$$

For TG levels >400 mg/dL (>4.5 mmol/L), this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation. In hypertriglyceridemic patients, LDL-C may be low or normal despite elevated total-C. In such cases, MEVACOR is not indicated.

The National Cholesterol Education Program (NCEP) Treatment Guidelines are summarized below:

Definite Atherosclerotic Disease†	Two or More Other Risk Factors††	LDL-Cholesterol mg/dL (mmol/L)	
		Initiation Level	Goal
NO	NO	≥190 (≥4.9)	<160 (<4.1)
NO	YES	≥160 (≥4.1)	<130 (<3.4)
YES	YES or NO	≥130†† (≥3.4)	≤100 (≤2.6)

† Coronary heart disease or peripheral vascular disease (including symptomatic carotid artery disease).

†† Other risk factors for coronary heart disease (CHD) include: age (males: ≥45 years; females: ≥55 years or premature menopause without estrogen replacement therapy); family history of premature CHD; current cigarette smoking; hypertension; confirmed HDL-C <35 mg/dL (<0.91 mmol/L); and diabetes mellitus. Subtract one risk factor if HDL-C is ≥60 mg/dL (≥1.6 mmol/L).

††† In CHD patients with LDL-C levels 100-129 mg/dL, the physician should exercise clinical judgment in deciding whether to initiate drug treatment.

At the time of hospitalization for an acute coronary event, consideration can be given to initiating drug therapy at discharge if the LDL-C is ≥130 mg/dL (see NCEP Guidelines above).

Since the goal of treatment is to lower LDL-C, the NCEP recommends that LDL-C levels be used to initiate and assess treatment response. Only if LDL-C levels are not available, should the total-C be used to monitor therapy.

Although MEVACOR may be useful to reduce elevated LDL-C levels in patients with combined hypercholesterolemia and hypertriglyceridemia where hypercholesterolemia is the major abnormality (Type IIb hyperlipoproteinemia), it has not been studied in conditions where the major abnormality is elevation of chylomicrons, VLDL or IDL (i.e., hyperlipoproteinemia types I, III, IV, or V).^{***}

^{***} Classification of Hyperlipoproteinemias

Type	Lipoproteins elevated	Lipid Elevations	
		major	minor
I	chylomicrons	TG	↑→C
IIa	LDL	C	—
IIb	LDL, VLDL	C	TG
III (rare)	IDL	C/TG	—
IV	VLDL	TG	↑→C
V (rare)	chylomicrons, VLDL	TG	↑→C

IDL = intermediate-density lipoprotein.

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

Active liver disease or unexplained persistent elevations of serum transaminases (see WARNINGS).

Pregnancy and lactation. Atherosclerosis is a chronic process and the discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Moreover, cholesterol and other products of the cholesterol biosynthesis pathway are essential components for fetal development, including synthesis of steroids and cell membranes. Because of the ability of inhibitors of HMG-CoA reductase such as MEVACOR to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway, MEVACOR is contraindicated during pregnancy and in nursing mothers. **MEVACOR should be administered to women of childbearing age only when such patients are highly unlikely to conceive.** If the patient becomes pregnant while taking this drug, MEVACOR should be discontinued immediately and the patient should be apprised of the potential hazard to the fetus (see PRECAUTIONS, *Pregnancy*).

WARNINGS

Skeletal Muscle

Lovastatin and other inhibitors of HMG-CoA reductase occasionally cause myopathy, which is manifested as muscle pain or weakness associated with grossly elevated creatine kinase (> 10X the upper limit of normal [ULN]). **Rhabdomyolysis, with or without acute renal failure secondary to myoglobinuria, has been reported rarely and can occur at any time.** In the EXCEL study, there was one case of myopathy among 4933 patients randomized to lovastatin 20-40 mg daily for 48 weeks, and 4 among 1649 patients randomized to 80 mg daily. When drug treatment was interrupted or discontinued in these patients, muscle symptoms and creatine kinase (CK) increases promptly resolved. The risk of myopathy is increased by concomitant therapy with certain drugs, some of which were excluded by the EXCEL study design.

Myopathy caused by drug interactions.

The incidence and severity of myopathy are increased by concomitant administration of HMG-CoA reductase inhibitors with drugs that can cause myopathy when given alone, such as gemfibrozil and other fibrates, and lipid-lowering doses (≥ 1 g/day) of niacin (nicotinic acid).

In addition, the risk of myopathy appears to be increased by high levels of HMG-CoA reductase inhibitory activity in plasma. Lovastatin is metabolized by the cytochrome P450 isoform 3A4. Certain drugs which share this metabolic pathway can raise the plasma levels of lovastatin and may increase the risk of myopathy. These include cyclosporine, itraconazole, ketoconazole and other antifungal azoles, the macrolide antibiotics erythromycin and clarithromycin, HIV protease inhibitors, and the antidepressant nefazodone.

Reducing the risk of myopathy.

1. General measures. Patients starting therapy with lovastatin should be advised of the risk of myopathy, and told to report promptly unexplained muscle pain, tenderness or weakness. A creatine kinase (CK) level above 10X ULN in a patient with unexplained muscle symptoms indicates myopathy. **Lovastatin therapy should be discontinued if myopathy is diagnosed or suspected.** In most cases, when patients were promptly discontinued from treatment, muscle symptoms and CK increases resolved.

Of the patients with rhabdomyolysis, many had complicated medical histories. Some had preexisting renal insufficiency, usually as a consequence of long-standing diabetes. In such patients, dose escalation requires caution. Also, as there are no known adverse consequences of brief interruption of therapy, treatment with lovastatin should be stopped a few days before elective major surgery and when any major acute medical or surgical condition supervenes.

2. Measures to reduce the risk of myopathy caused by drug interactions (see above and PRECAUTIONS, *Drug Interactions*). Physicians contemplating combined therapy with lovastatin and any of the interacting drugs should weigh the potential benefits and risks, and should carefully monitor patients for any signs and symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic CK determinations may be considered in such situations, but there is no assurance that such monitoring will prevent myopathy.

The combined use of lovastatin with fibrates or niacin should be avoided unless the benefit of further alteration in lipid levels is likely to outweigh the increased risk of this drug combination. Combinations of fibrates or niacin with low doses of lovastatin have been used without myopathy in small, short-term clinical trials with careful monitoring. Addition of these drugs to lovastatin typically provides little additional reduction in LDL cholesterol, but further reductions of triglycerides and further increases in HDL cholesterol may be obtained. If one of these drugs must be used with lovastatin, clinical experience suggests that the risk of myopathy is less with niacin than with the fibrates.

In patients taking concomitant cyclosporine, fibrates or niacin, the dose of lovastatin should generally not exceed 20 mg (see DOSAGE AND ADMINISTRATION and DOSAGE AND ADMINISTRATION, *Concomitant Lipid-Lowering Therapy*), as the risk of myopathy increases substantially at higher doses. Interruption of lovastatin therapy during a course of treatment with a systemic antifungal azole or a macrolide antibiotic should be considered.

Liver Dysfunction

Persistent increases (to more than 3 times the upper limit of normal) in serum transaminases occurred in 1.9% of adult patients who received lovastatin for at least one year in early clinical trials (see ADVERSE REACTIONS). When the drug was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pretreatment levels. The increases usually appeared 3 to 12 months after the start of therapy with lovastatin, and were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity. In the EXCEL study (see CLINICAL PHARMACOLOGY, *Clinical Studies*), the incidence of persistent increases in serum transaminases over 48 weeks was 0.1% for placebo, 0.1% at 20 mg/day, 0.9% at 40 mg/day, and 1.5% at 80 mg/day in patients on lovastatin. However, in post-marketing experience with MEVACOR, symptomatic liver disease has been reported rarely at all dosages (see ADVERSE REACTIONS).

In AFCAPS/TexCAPS, the number of participants with consecutive elevations of either alanine aminotransferase (ALT) or aspartate aminotransferase (AST) (> 3 times the upper limit of normal), over a median of 5.1 years of follow-up, was not significantly different between the MEVACOR and placebo groups (18 [0.6%] vs. 11 [0.3%]). The starting dose of MEVACOR was 20 mg/day; 50% of the MEVACOR treated participants were titrated to 40 mg/day at Week 18. Of the 18 participants on MEVACOR with consecutive elevations of either ALT or AST, 11 (0.7%) elevations occurred in participants taking 20 mg/day, while 7 (0.4%) elevations occurred in participants titrated to 40 mg/day. Elevated transaminases resulted in discontinuation of 6 (0.2%) participants from therapy in the MEVACOR group (n=3,304) and 4 (0.1%) in the placebo group (n=3,301).

It is recommended that liver function tests be performed before the initiation of treatment, at 6 and 12 weeks after initiation of therapy or elevation in dose, and periodically thereafter (e.g., semiannually). Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality(ies) returns to normal. Should an increase in AST or ALT of three times the upper limit of normal or greater persist, withdrawal of therapy with MEVACOR is recommended.

The drug should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease. Active liver disease or unexplained transaminase elevations are contraindications to the use of lovastatin.

As with other lipid-lowering agents, moderate (less than three times the upper limit of normal) elevations of serum transaminases have been reported following therapy with MEVACOR (see ADVERSE REACTIONS). These changes appeared soon after initiation of therapy with MEVACOR, were often transient, were not accompanied by any symptoms and interruption of treatment was not required.

PRECAUTIONS

General

Lovastatin may elevate creatine phosphokinase and transaminase levels (see WARNINGS and ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with lovastatin.

Homozygous Familial Hypercholesterolemia

MEVACOR is less effective in patients with the rare homozygous familial hypercholesterolemia, possibly because these patients have no functional LDL receptors. MEVACOR appears to be more likely to raise serum transaminases (see ADVERSE REACTIONS) in these homozygous patients.

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7825346

Information for Patients

Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness (see WARNINGS, *Skeletal Muscle*).

Drug Interactions

Cyclosporine, Itraconazole, Ketoconazole, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin, Clarithromycin, HIV protease inhibitors, Nefazodone: see WARNINGS, *Skeletal Muscle*.

Coumarin Anticoagulants: In a small clinical trial in which lovastatin was administered to warfarin treated patients, no effect on prothrombin time was detected. However, another HMG-CoA reductase inhibitor has been found to produce a less than two seconds increase in prothrombin time in healthy volunteers receiving low doses of warfarin. Also, bleeding and/or increased prothrombin time have been reported in a few patients taking coumarin anticoagulants concomitantly with lovastatin. It is recommended that in patients taking anticoagulants, prothrombin time be determined before starting lovastatin and frequently enough during early therapy to insure that no significant alteration of prothrombin time occurs. Once a stable prothrombin time has been documented, prothrombin times can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of lovastatin is changed, the same procedure should be repeated. Lovastatin therapy has not been associated with bleeding or with changes in prothrombin time in patients not taking anticoagulants.

Antipyrine: Lovastatin had no effect on the pharmacokinetics of antipyrine or its metabolites. However, since lovastatin is metabolized by the cytochrome P450 isoform 3A4, this does not preclude an interaction with other drugs metabolized by the same isoform (see WARNINGS, *Skeletal Muscle*).

Propranolol: In normal volunteers, there was no clinically significant pharmacokinetic or pharmacodynamic interaction with concomitant administration of single doses of lovastatin and propranolol.

Digoxin: In patients with hypercholesterolemia, concomitant administration of lovastatin and digoxin resulted in no effect on digoxin plasma concentrations.

Oral Hypoglycemic Agents: In pharmacokinetic studies of MEVACOR in hypercholesterolemic non-insulin dependent diabetic patients, there was no drug interaction with glipizide or with chlorpropamide (see CLINICAL PHARMACOLOGY, *Clinical Studies*).

Endocrine Function

HMG-CoA reductase inhibitors interfere with cholesterol synthesis and as such might theoretically blunt adrenal and/or gonadal steroid production. Results of clinical trials with drugs in this class have been inconsistent with regard to drug effects on basal and reserve steroid levels. However, clinical studies have shown that lovastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve, and does not reduce basal plasma testosterone concentration. Another HMG-CoA reductase inhibitor has been shown to reduce the plasma testosterone response to HCG. In the same study, the mean testosterone response to HCG was slightly but not significantly reduced after treatment with lovastatin 40 mg daily for 16 weeks in 21 men. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of male patients. The effects, if any, on the pituitary-gonadal axis in pre-menopausal women are unknown. Patients treated with lovastatin who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may decrease the levels or activity of endogenous steroid hormones.

CNS Toxicity

Lovastatin produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). Vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis were also seen in dogs treated for 14 weeks at 180 mg/kg/day, a dose which resulted in a mean plasma drug level (C_{max}) similar to that seen with the 60 mg/kg/day dose.

CNS vascular lesions, characterized by perivascular hemorrhage and edema, mononuclear cell infiltration of perivascular spaces, perivascular fibrin deposits and necrosis of small vessels, were seen in dogs treated with lovastatin at a dose of 180 mg/kg/day, a dose which produced plasma drug levels (C_{max}) which were about 30 times higher than the mean values in humans taking 80 mg/day.

Similar optic nerve and CNS vascular lesions have been observed with other drugs of this class.

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7825346

Cataracts were seen in dogs treated for 11 and 28 weeks at 180 mg/kg/day and 1 year at 60 mg/kg/day.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 21-month carcinogenic study in mice, there was a statistically significant increase in the incidence of hepatocellular carcinomas and adenomas in both males and females at 500 mg/kg/day. This dose produced a total plasma drug exposure 3 to 4 times that of humans given the highest recommended dose of lovastatin (drug exposure was measured as total HMG-CoA reductase inhibitory activity in extracted plasma). Tumor increases were not seen at 20 and 100 mg/kg/day, doses that produced drug exposures of 0.3 to 2 times that of humans at the 80 mg/day dose. A statistically significant increase in pulmonary adenomas was seen in female mice at approximately 4 times the human drug exposure. (Although mice were given 300 times the human dose [HD] on a mg/kg body weight basis, plasma levels of total inhibitory activity were only 4 times higher in mice than in humans given 80 mg of MEVACOR.)

There was an increase in incidence of papilloma in the non-glandular mucosa of the stomach of mice beginning at exposures of 1 to 2 times that of humans. The glandular mucosa was not affected. The human stomach contains only glandular mucosa.

In a 24-month carcinogenicity study in rats, there was a positive dose response relationship for hepatocellular carcinogenicity in males at drug exposures between 2-7 times that of human exposure at 80 mg/day (doses in rats were 5, 30 and 180 mg/kg/day).

An increased incidence of thyroid neoplasms in rats appears to be a response that has been seen with other HMG-CoA reductase inhibitors.

A chemically similar drug in this class was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum drug concentration (as total inhibitory activity) after a 40 mg oral dose. Liver carcinomas were significantly increased in high dose females and mid- and high dose males, with a maximum incidence of 90 percent in males. The incidence of adenomas of the liver was significantly increased in mid- and high dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high dose males and females. Adenomas of the Harderian gland (a gland of the eye of rodents) were significantly higher in high dose mice than in controls.

No evidence of mutagenicity was observed in a microbial mutagen test using mutant strains of *Salmonella typhimurium* with or without rat or mouse liver metabolic activation. In addition, no evidence of damage to genetic material was noted in an *in vitro* alkaline elution assay using rat or mouse hepatocytes, a V-79 mammalian cell forward mutation study, an *in vitro* chromosome aberration study in CHO cells, or an *in vivo* chromosomal aberration assay in mouse bone marrow.

Drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration and giant cell formation were seen in dogs starting at 20 mg/kg/day. Similar findings were seen with another drug in this class. No drug-related effects on fertility were found in studies with lovastatin in rats. However, in studies with a similar drug in this class, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. No microscopic changes were observed in the testes from rats of either study. The clinical significance of these findings is unclear.

Pregnancy

Pregnancy Category X

See CONTRAINDICATIONS.

Safety in pregnant women has not been established.

Lovastatin has been shown to produce skeletal malformations at plasma levels 40 times the human exposure (for mouse fetus) and 80 times the human exposure (for rat fetus) based on mg/m² surface area (doses were 800 mg/kg/day). No drug-induced changes were seen in either species at multiples of 8 times (rat) or 4 times (mouse) based on surface area. No evidence of malformations was noted in rabbits at exposures up to 3 times the human exposure (dose of 15 mg/kg/day, highest tolerated dose).

Rare reports of congenital anomalies have been received following intrauterine exposure to HMG-CoA reductase inhibitors. In a review[†] of approximately 100 prospectively followed pregnancies in women exposed to MEVACOR or another structurally related HMG-CoA reductase inhibitor, the incidences of congenital anomalies, spontaneous abortions and fetal deaths/stillbirths did not exceed what would be expected in the general population. The number of cases is adequate only to exclude a 3 to 4-fold increase in congenital anomalies over the background incidence. In 89% of the prospectively followed pregnancies, drug treatment was initiated prior to pregnancy and was discontinued at some point in the first trimester when pregnancy was identified. As safety in pregnant women has not been established and there is no apparent benefit to therapy with MEVACOR during pregnancy (see CONTRAINDICATIONS), treatment should be immediately discontinued as soon as pregnancy is recognized. MEVACOR should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards.

Nursing Mothers

It is not known whether lovastatin is excreted in human milk. Because a small amount of another drug in this class is excreted in human breast milk and because of the potential for serious adverse reactions in nursing infants, women taking MEVACOR should not nurse their infants (see CONTRAINDICATIONS).

Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Because pediatric patients are not likely to benefit from cholesterol lowering for at least a decade and because experience with this drug is limited (no studies in subjects below the age of 20 years), treatment of pediatric patients with lovastatin is not recommended at this time.

ADVERSE REACTIONS

MEVACOR is generally well tolerated; adverse reactions usually have been mild and transient.

Phase III Clinical Studies

In Phase III controlled clinical studies involving 613 patients treated with MEVACOR, the adverse experience profile was similar to that shown below for the 8,245-patient EXCEL study (see *Expanded Clinical Evaluation of Lovastatin [EXCEL] Study*).

Persistent increases of serum transaminases have been noted (see WARNINGS, *Liver Dysfunction*). About 11% of patients had elevations of CK levels of at least twice the normal value on one or more occasions. The corresponding values for the control agent cholestyramine was 9 percent. This was attributable to the noncardiac fraction of CK. Large increases in CK have sometimes been reported (see WARNINGS, *Skeletal Muscle*).

Expanded Clinical Evaluation of Lovastatin (EXCEL) Study

MEVACOR was compared to placebo in 8,245 patients with hypercholesterolemia (total-C 240-300 mg/dL [6.2-7.8 mmol/L]) in the randomized, double-blind, parallel, 48-week EXCEL study. Clinical adverse experiences reported as possibly, probably or definitely drug-related in $\geq 1\%$ in any treatment group are shown in the table below. For no event was the incidence on drug and placebo statistically different.

[†] Manson, J.M., Freyssinges, C., Ducrocq, M.B., Stephenson, W.P., Postmarketing Surveillance of Lovastatin and Simvastatin Exposure During Pregnancy. *Reproductive Toxicology*. 10(6):439-446. 1996.

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	Placebo (N = 1663) %	MEVACOR 20 mg q.p.m. (N = 1642) %	MEVACOR 40 mg q.p.m. (N = 1645) %	MEVACOR 20 mg b.i.d. (N = 1646) %	MEVACOR 40 mg b.i.d. (N = 1649) %
<i>Body As a Whole</i>					
Asthenia	1.4	1.7	1.4	1.5	1.2
<i>Gastrointestinal</i>					
Abdominal pain	1.6	2.0	2.0	2.2	2.5
Constipation	1.9	2.0	3.2	3.2	3.5
Diarrhea	2.3	2.6	2.4	2.2	2.6
Dyspepsia	1.9	1.3	1.3	1.0	1.6
Flatulence	4.2	3.7	4.3	3.9	4.5
Nausea	2.5	1.9	2.5	2.2	2.2
<i>Musculoskeletal</i>					
Muscle cramps	0.5	0.6	0.8	1.1	1.0
Myalgia	1.7	2.6	1.8	2.2	3.0
<i>Nervous System/ Psychiatric</i>					
Dizziness	0.7	0.7	1.2	0.5	0.5
Headache	2.7	2.6	2.8	2.1	3.2
<i>Skin</i>					
Rash	0.7	0.8	1.0	1.2	1.3
<i>Special Senses</i>					
Blurred vision	0.8	1.1	0.9	0.9	1.2

Other clinical adverse experiences reported as possibly, probably or definitely drug-related in 0.5 to 1.0 percent of patients in any drug-treated group are listed below. In all these cases the incidence on drug and placebo was not statistically different. *Body as a Whole*: chest pain; *Gastrointestinal*: acid regurgitation, dry mouth, vomiting; *Musculoskeletal*: leg pain, shoulder pain, arthralgia; *Nervous System/Psychiatric*: insomnia, paresthesia; *Skin*: alopecia, pruritus; *Special Senses*: eye irritation.

In the EXCEL study (see CLINICAL PHARMACOLOGY, *Clinical Studies*), 4.6% of the patients treated up to 48 weeks were discontinued due to clinical or laboratory adverse experiences which were rated by the investigator as possibly, probably or definitely related to therapy with MEVACOR. The value for the placebo group was 2.5%.

Air Force / Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)

In AFCAPS/TexCAPS (see CLINICAL PHARMACOLOGY, *Clinical Studies*) involving 6,605 participants treated with 20-40 mg/day of MEVACOR (n=3,304) or placebo (n=3,301), the safety and tolerability profile of the group treated with MEVACOR was comparable to that of the group treated with placebo during a median of 5.1 years of follow-up. The adverse experiences reported in AFCAPS/TexCAPS were similar to those reported in EXCEL (see ADVERSE REACTIONS, *Expanded Clinical Evaluation of Lovastatin (EXCEL) Study*).

Concomitant Therapy

In controlled clinical studies in which lovastatin was administered concomitantly with cholestyramine, no adverse reactions peculiar to this concomitant treatment were observed. The adverse reactions that occurred were limited to those reported previously with lovastatin or cholestyramine. Other lipid-lowering agents were not administered concomitantly with lovastatin during controlled clinical studies. Preliminary data suggests that the addition of gemfibrozil to therapy with lovastatin is not associated with greater reduction in LDL-C than that achieved with lovastatin alone. In uncontrolled clinical studies, most of the patients who have developed myopathy were receiving concomitant therapy with cyclosporine, gemfibrozil or niacin (nicotinic acid) (see WARNINGS, *Skeletal Muscle*).

The following effects have been reported with drugs in this class. Not all the effects listed below have necessarily been associated with lovastatin therapy.

Skeletal: muscle cramps, myalgia, myopathy, rhabdomyolysis, arthralgias.

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, dizziness, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy, psychic disturbances, anxiety, insomnia, depression.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematosus-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia,

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7825346

positive ANA, ESR increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver; and rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma; anorexia, vomiting.

Skin: alopecia, pruritus. A variety of skin changes (e.g., nodules, discoloration, dryness of skin/mucous membranes, changes to hair/nails) have been reported.

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

Eye: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Abnormalities: elevated transaminases, alkaline phosphatase, γ -glutamyl transpeptidase, and bilirubin; thyroid function abnormalities.

OVERDOSAGE

After oral administration of MEVACOR to mice, the median lethal dose observed was $>15 \text{ g/m}^2$.

Five healthy human volunteers have received up to 200 mg of lovastatin as a single dose without clinically significant adverse experiences. A few cases of accidental overdosage have been reported; no patients had any specific symptoms, and all patients recovered without sequelae. The maximum dose taken was 5-6 g.

Until further experience is obtained, no specific treatment of overdosage with MEVACOR can be recommended.

The dialyzability of lovastatin and its metabolites in man is not known at present.

DOSAGE AND ADMINISTRATION

The patient should be placed on a standard cholesterol-lowering diet before receiving MEVACOR and should continue on this diet during treatment with MEVACOR (see NCEP Treatment Guidelines for details on dietary therapy). MEVACOR should be given with meals.

The usual recommended starting dose is 20 mg once a day given with the evening meal. The recommended dosing range is 10-80 mg/day in single or two divided doses; the maximum recommended dose is 80 mg/day. Doses should be individualized according to the recommended goal of therapy (see NCEP Guidelines and CLINICAL PHARMACOLOGY). Patients requiring reductions in LDL-C of 20% or more to achieve their goal (see INDICATIONS AND USAGE) should be started on 20 mg/day of MEVACOR. A starting dose of 10 mg may be considered for patients requiring smaller reductions. Adjustments should be made at intervals of 4 weeks or more.

In patients taking cyclosporine concomitantly with lovastatin (see WARNINGS, *Skeletal Muscle*), therapy should begin with 10 mg of MEVACOR and should not exceed 20 mg/day.

Cholesterol levels should be monitored periodically and consideration should be given to reducing the dosage of MEVACOR if cholesterol levels fall significantly below the targeted range.

Concomitant Lipid-Lowering Therapy

MEVACOR is effective alone or when used concomitantly with bile-acid sequestrants. Use of MEVACOR with fibrates or niacin should generally be avoided. However, if MEVACOR is used in combination with fibrates or niacin, the dose of MEVACOR should not exceed 20 mg (see WARNINGS, *Skeletal Muscle*).

Dosage in Patients with Renal Insufficiency

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A Symposium: Expanding the Impact of Statin Therapy: Would Patients Benefit from Broader Treatment and Access?

GUEST EDITOR:

Sidney C. Smith, Jr., MD
Professor of Medicine
Chief, Division of Cardiology
Director, Cardiovascular Center
University of North Carolina at Chapel Hill
Chapel Hill, North Carolina

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**A SYMPOSIUM:
EXPANDING THE IMPACT OF STATIN THERAPY:
WOULD PATIENTS BENEFIT FROM BROADER TREATMENT AND ACCESS?**

1E

Introduction

Sidney C. Smith, Jr.

3E

Bridging the Treatment Gap

Sidney C. Smith, Jr.

8E

**Insights on Treating an Over-the-Counter-Type Subgroup: Data from the Air Force/Texas
Coronary Atherosclerosis Prevention Study Population**

Antonio M. Gotto, Jr.

15E

Defining Patient Risks from Expanded Preventive Therapies

Keith G. Tolman

20E

Population Benefits of Cholesterol Reduction: Epidemiology, Economics, and Ethics

Thomas A. Pearson



Introduction

EXPANDING THE IMPACT OF STATIN THERAPY: WOULD PATIENTS BENEFIT FROM BROADER TREATMENT AND ACCESS?

Sidney C. Smith, Jr., MD

As one of the most prevalent and undertreated medical conditions in the United States today, elevated cholesterol is a known risk factor and the main culprit in cardiovascular disease (CVD). The American Heart Association estimates that >53 million people in the United States have high cholesterol levels and ≥ 1 of its related co-morbidities. With approximately 1 in 4 US citizens having CVD, it is the leading cause of death in the United States.¹

In the past 50 years, data from landmark epidemiologic studies, such as the Framingham Study² and the Multiple Risk Factor Intervention Trial (MRFIT),³ have proven the correlation between increased cholesterol levels and increased risk for coronary artery disease. With the development of statin drugs in the 1970s and 1980s, the aim of clinical trials has been to demonstrate the efficacy of drug treatment in reducing cholesterol levels, thereby reducing the risk of a CVD event.

Key treatment guidelines, such as those from the National Cholesterol Education Program (NCEP), have stratified patients according to risk, and have advocated for aggressive drug intervention in patients with high elevations of cholesterol who are at risk for CVD and related coronary events. To date, pivotal trials such as the Simvastatin Scandinavian Survival Study (4S),⁴ the West of Scotland Coronary Prevention Study (WOSCOPS),⁵ and the Cholesterol and Recurrent Events (CARE)⁶ study have proven the efficacy of statin drugs to reduce cardiovascular events in primary and secondary prevention.

According to the National Health and Nutrition Examination Surveys (NHANES), approximately 22 million people in the United States qualify for drug therapy for the treatment and management of hyper-

cholesterolemia.⁷ Although current treatment guidelines emphasize the need for management of hypercholesterolemia in high-risk patients, the NHANES data also indicate that only 5 million people are, in fact, being treated for elevated cholesterol. Making the picture even worse, data from the Framingham Study indicate that 35% of coronary incidents occur in low-risk patients who are ineligible for drug treatment under current treatment guidelines (i.e., patients with total cholesterol levels of 200–240 mg/dL).² These statistics point not only to the urgency of therapeutic intervention but to the need for treatment in an emerging treatment population—patients with moderate elevations of cholesterol.

Data from the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) reinforce the importance of drug intervention in this population. According to the results of this primary prevention study, treatment with lovastatin was asso-



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ciated with a 37% reduction in the relative risk for a first acute major coronary event.⁸ The AFCAPS/TexCAPS data highlight the therapeutic benefit for at-risk patients who are currently advised to manage their cholesterol through dietary means.

AQ:1

The articles in this supplement to *The American Journal of Cardiology* are based on presentations from a symposium in Atlanta sponsored by the School of Medicine of the University of North Carolina on November 6, 1999. In the first article, the importance of bridging the treatment gap is discussed. This is followed by a discussion on expanding preventive cholesterol therapy by Dr. Antonio M. Gotto, Jr. Based on data from the AFCAPS/TexCAPS study, the article focuses on the therapeutic benefits of statin treatment in an over-the-counter (OTC)-like population.

When considering expanding treatment to a broad population, the associated health risks must be taken into account. In his article, Dr. Keith G. Tolman outlines patient risks associated with expanded preventive therapies. Dr. Tolman also provides a comprehensive overview of hepatotoxicity and statin therapy. The article offers a compelling argument for the safety and tolerability of statin therapy, as well as the absence of a link between elevated liver function tests and hepatotoxicity.

Finally, Dr. Thomas A. Pearson examines the population benefits of expanding cholesterol treatment from epidemiologic, economic, and ethical points of view.

The panel of experts present at the symposium and contributing to this supplement are united in their

focus on the need for expanded treatment of hypercholesterolemia and on the potential benefits of offering OTC statin therapy for the management of this disorder. We hope that this supplement serves to enhance knowledge and understanding of the current treatment gap as well as the potential role and public-health benefit of statins in primary prevention.

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Bridging the Treatment Gap

Sidney C. Smith, Jr., MD

The leading cause of death and disability in the United States today is cardiovascular disease (CVD). The main risk factor, hypercholesterolemia, is grossly undertreated, although it is widely appreciated that lowering cholesterol levels is key to reducing the incidence of CVD. Cholesterol-lowering therapy decreases total mortality, cardiovascular events, the need for revascularization procedures, and hospitalization costs. A 25–35% reduction of low-density lipoprotein (LDL) indicates significant benefits with regard to morbidity and mortality. Unfortunately, most patients who are candidates for cholesterol-lowering treatment do not receive it. Wider use of lipid-lowering agents could, in fact, make a significant difference in patient outcomes. There is strong interest on the part of consumers in over-the-counter (OTC) cholesterol-lowering products that may help them

reduce their risk of developing heart disease and live healthier lives. Surveys estimate that half of all patients with high cholesterol would like to have an OTC statin product made available. Increased availability of cholesterol-lowering therapies as well as changes in physician prescribing practices could benefit a broad spectrum of the population that is currently untreated or undertreated. Current prescribing practices and guidelines have not resulted in widespread use of these therapies; therefore, outcomes for CVD prevention remains suboptimal. The proposed advantages of making statins available over-the-counter include their known efficacy, dose consistency, and proven safety profile. ©2000 by Excerpta Medica, Inc.

Am J Cardiol 2000;85:3E–7E

Cardiovascular disease (CVD) remains the leading cause of death and disability in the United States in both men and women.¹ Mortality data show that more people in the United States die from CVD than from any other illness. Nearly half a million men die from CVD each year and CVD is also the leading cause of death in women. In fact, more women than men die from CVD.

The main culprit in the high CVD mortality rate is coronary artery disease (CAD), the largest killer of men and women. The American Heart Association (AHA) estimates that nearly 14 million US citizens have a history of myocardial infarction and/or angina, the classic CAD symptoms. Approximately 1 million people have an acute myocardial infarction every year. In addition, by the time the average person reaches the age of 60, 1 in every 5 men and 1 in every 17 women will develop CAD.²

THE CARDIOVASCULAR DISEASE/ CORONARY ARTERY DISEASE (CVD/ CAD) TREATMENT GAP

The most startling fact in this epidemic is that most patients who have hypercholesterolemia, the main risk factor for CAD, and who are at risk for or have CAD, are undertreated or not treated and could clearly benefit from preventive strategies.

According to data from the National Health and Nutrition Examination Surveys (NHANES), there are 53.3 million adults with elevated cholesterol levels warranting intervention.³ Of these, approximately 22 million qualify for drug therapy based on current

management guidelines. However, only 5 million (roughly 20%) of these patients eligible for treatment are currently receiving drug therapy.⁴

The NHANES III indicates that 97 million adult US citizens have a total-cholesterol level >200 mg/dL. Of these, 38 million have a total cholesterol level >240 mg/dL⁴—levels that, according to the National Cholesterol Education Program (NCEP) guidelines, require treatment and management by a physician.

With nearly 60% of CAD costs hospital related, and \$50 billion per year spent on lost productivity, broadened primary-prevention initiatives appear to be the solution to closing the treatment gap, thereby controlling the CVD epidemic.

LOWERING SERUM CHOLESTEROL LEVELS: AN APPROACH TO CORONARY ARTERY DISEASE (CAD) MANAGEMENT

The healthcare community recognizes that reducing cholesterol levels is the optimal therapeutic strategy for controlling CAD. Landmark clinical trial data have demonstrated the importance of targeting low-density-lipoprotein (LDL) cholesterol levels when considering drug intervention. It is, however, necessary to assess global risk of CAD to determine to what degree interventional therapies should be pursued. As the following section will demonstrate, cholesterol-lowering therapy is associated with significant benefits, including decreases in total mortality, cardiovascular events, the need for revascularization procedures, and hospitalization costs.

BENEFITS OF LIPID-LOWERING THERAPIES

Several secondary-prevention trials have shown that lowering LDL cholesterol levels can reduce cardiovascular events in patients after myocardial infarction.

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tion. This was first shown in the Scandinavian Simvastatin Survival Study (4S)⁵ study in a high-risk population. The Cholesterol and Recurrent Events (CARE)⁶ trial and the Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID)⁷ study further supported the benefits in patients with average cholesterol levels (Figure 1). Interestingly, about one third of the patients in LIPID had unstable angina and also experienced a reduction in cardiovascular events.

Primary-prevention trials have also shown significant benefits both in a high-risk population in the West of Scotland Coronary Prevention Study Group (WOSCOPS)⁸ and in a low-risk population in the AFCAPS/TexCAPS trial⁹ (Figure 1). More than 80% of the individuals in the AFCAPS/TexCAPS study who did benefit from cholesterol-lowering therapies would not have qualified for these therapies under existing guidelines. The impressive results of the AFCAPS/TexCAPS study raise the important question of whether the NCEP treatment guidelines should be broadened.

CONTINUUM OF CORONARY ARTERY DISEASE (CAD) RISK IN LIPID TRIALS

In the secondary and primary-prevention studies cited earlier (Figure 1), the LDL cholesterol levels ranged from a high of about 190 mg/dL in the 4S trial to only 150 mg/dL in the AFCAPS/TexCAPS study. Overall, the relative risk reductions were 25–35%, corresponding to LDL cholesterol reductions of 25–35%. Absolute risk reductions ranged from 8.5% in the 4S trial among patients at higher risk due to high LDL cholesterol levels and a recent event, to approximately 2% in the lower-risk populations in the primary-prevention trials.

Findings on statins show that a 25–35% reduction of LDL cholesterol levels convey significant benefits with regard to cardiovascular morbidity and mortality. Further, a decrease in all-cause mortality has been shown in the secondary-prevention trials. Importantly, the secondary-prevention trials showed that benefits of treatment are not confined just to high-risk men. Therapeutic benefit was also observed in women, the elderly, and patients with diabetes. Data from the primary-prevention trials have demonstrated decreases in cardiovascular events and in cardiovascular mortality, however the primary-prevention trials were not powered to show reductions in total mortality.

LIPID-LOWERING THERAPIES: AN UNDER-APPRECIATED NECESSITY

Unfortunately, recent data reveal that most patients who are candidates for treatment do not receive lipid-lowering therapies. In the largest study evaluating implementation of lipid-lowering therapy to date, Sueta et al¹⁰ performed a retrospective chart audit on 58,890 adult outpatients with established CAD or congestive heart failure. Patient data were gathered from 140 medical practices in the United States, of which 75% were cardiology practices. Among the 48,586 patients with CAD, the majority (57%) did not have

LDL cholesterol levels documented in their charts, and only 11% were treated to their target LDL cholesterol goal (Figure 2). It was found that almost 90% of CAD patients were not being treated to goal with therapies that could make a significant difference in outcome. Based on this study, it is estimated that 90% of all patients in the United States are not being treated optimally with lipid-lowering therapies. Wider use of lipid-lowering agents could, in fact, make a significant difference in patient outcomes.

The use of lipid-lowering therapies in individuals with documented CAD varied with age and gender in the study by Sueta et al.¹⁰ The highest likelihood of receiving treatment was in the 50-year-old male, whose probability of being treated was about 50%. In patients older or younger than 50 years, the likelihood of treatment declined. Only 30% of individuals >75 years of age received any treatment at all. In the younger age group, women were less likely to be treated than men.

The implementation of primary-prevention strategies is also low, as was demonstrated by Pearson et al¹¹ in the recent Lipid Treatment Assessment Program (L-TAP) study involving 4,888 patients from 5 regions in the United States. The study found that 82% of patients with known CAD were not treated to their target LDL cholesterol goal of ≤ 100 mg/dL. Of those with ≥ 2 risk factors, 63% were not treated to the target goal of < 130 mg/dL, and 32% of the patients with < 2 risk factors did not achieve their target goal of < 160 mg/dL. Thus, there was a stepwise decrease in the application of important lipid-lowering therapies, with increasing severity of disease.

Data from the recent Heart and Estrogen/Progestin Replacement Study (HERS) indicate that $< 15\%$ of women with known CAD are treated to the current NCEP II LDL cholesterol goal of ≤ 100 mg/dL, and $< 40\%$ are treated to the previous NCEP I goal of ≤ 130 mg/dL.¹² It can thus be concluded that most individuals are not receiving adequate treatment overall, and those few who are receiving treatment are not being treated to goal.

CURRENT SELF-MEDICATION PRACTICES

The use of established medical therapies for CAD does not seem to reflect accurately the concern of the general public. Twenty-five percent of the adult population in the United States, 57–65 million people, are concerned about their cholesterol and would like to do something about it.¹³ Of those consumers who are very or somewhat concerned about their cholesterol, 49% use a nutraceutical product,¹⁴ such as vitamin E (17%), garlic (15%), niacin (8%), or other herbal preparations. Despite very little evidence of product efficacy, over-the-counter (OTC) medications directed toward prevention of CAD are the fastest growing segment of health products, with the majority of dollars spent on garlic supplements. In addition, 23% of individuals use low-dose aspirin. The HOPE trial showed little benefit of vitamin E,¹⁵ so aside from niacin, the OTC solutions available to the consumer

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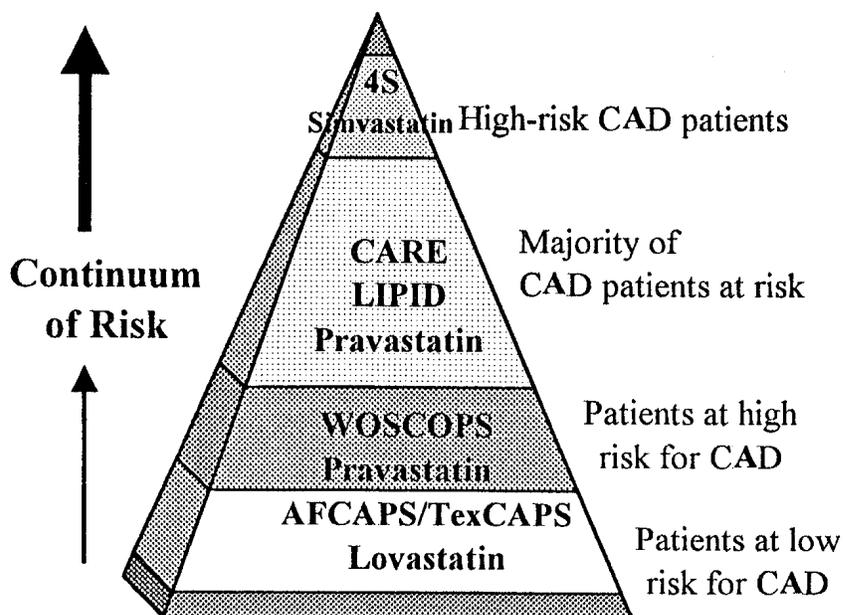


FIGURE 1. Continuum of risk in primary prevention trials. 4S = Scandinavian Simvastatin Survival Study; AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study; CAD = coronary artery disease.

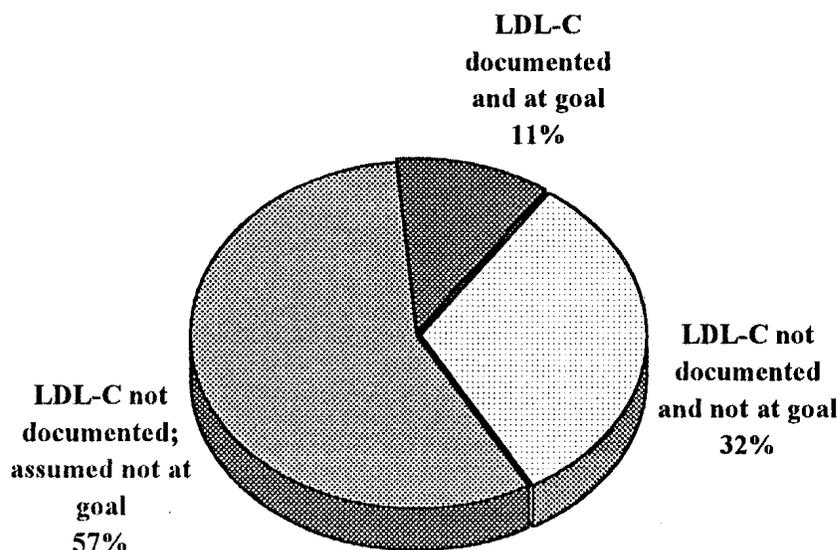


FIGURE 2. Percentage of coronary artery disease (CAD) patients on lipid-lowering drug therapy.¹⁰ LDL-C = low-density lipoprotein cholesterol.

are rather ineffective in lowering LDL cholesterol. Yet, consumers spend almost \$12 billion per year on self-medication to prevent CAD (Figure 3).¹⁶

Another OTC product, red yeast rice from China, is becoming increasingly popular as a result of claims that it promotes healthy cholesterol levels. Red yeast rice actually contains a low dose of lovastatin and is available to the general public without prescription. The public's response to red yeast rice suggests that

OTC statins could be a useful therapeutic option. The potential advantages of OTC statins over neutraceuticals include consistent dose, extensive clinical trials, and established safety.

The medical community has been closely following this controversial debate. Some healthcare providers believe that cholesterol-lowering drugs should always be taken under a doctor's supervision, while others profess lovastatin to be as safe as aspirin.

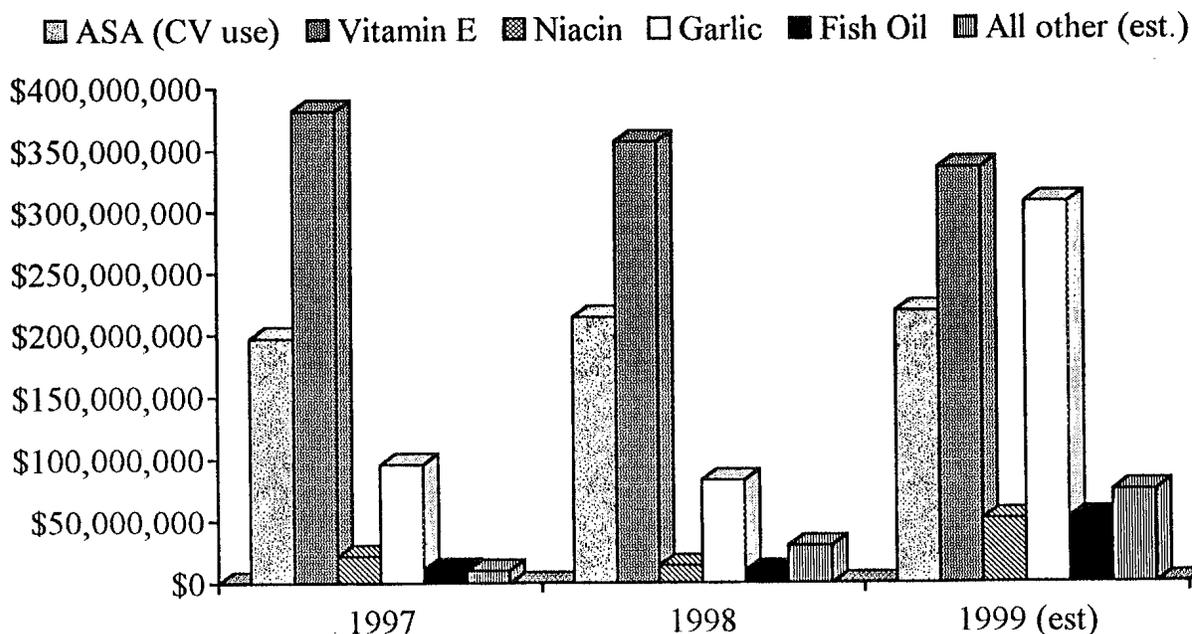


FIGURE 3. Annual dollar sales of heart-related supplements. ASA = acetylsalicylic acid (aspirin); CV = cardiovascular.

HIGH CONSUMER INTEREST IN OVER-THE-COUNTER (OTC) PRODUCTS

There is strong interest on the part of consumers in OTC products that may help them reduce their risk of developing heart disease and live healthier lives. Of those patients with high cholesterol, 50% in one survey indicated that they would like to have an OTC statin product made available.¹⁷ In the same survey, among those patients who are very or somewhat concerned about their cholesterol, >60% are interested in purchasing an OTC statin and >80% of consumers indicated that they would consult with their physician before using an OTC cholesterol reducer.

Interestingly, prescription brand statin manufacturers have been supporting direct-to-consumer educational advertising campaigns. Consumer advertising in the cholesterol arena seems to spur consumers to seek out the professional advice of their doctor. In a survey conducted from January to September 1998, during which time there was no special advertising campaign, general office visits increased by 2%. However, in the wake of heavy direct-to-consumer advertisement for cholesterol awareness and prescription statin therapies, there was a 19% increase in visits to physicians' offices.¹⁸

CONCLUSION

The available cholesterol-lowering therapies could be more beneficial if they were better utilized. Our current guidelines and prescribing practice have not resulted in widespread use of these important preventive therapies. Many consumers are using readily available OTC nutraceuticals for CAD prevention without substantiation of their benefits. There may be several advantages to making statins available OTC,

in light of their known efficacy, dose consistency, and proven safety profile confirmed in recent clinical trials. Issues that await further exploration include definition of appropriate dosage should statins be made available OTC, mechanisms by which an educational message about guidelines and cholesterol screening could be incorporated with OTC availability, and programs to expand patient-physician activities in CAD prevention.

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Insights on Treating an Over-the-Counter-Type Subgroup: Data from the Air Force/Texas Coronary Atherosclerosis Prevention Study Population

Antonio M. Gotto, Jr., MD, DPhil

The expansion of therapeutic options for management of dyslipidemia is a potentially valuable avenue for the optimal treatment of most patients at low-to-moderate risk for coronary artery disease (CAD). In primary prevention, this population is closely approximated by that of the landmark Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). In AFCAPS/TexCAPS, 6,605 men and women without evidence of CAD and with average total cholesterol (180–264 mg/dL) and low-density lipoprotein (LDL)-cholesterol (130–190 mg/dL) concentrations and low high-density lipoprotein (HDL)-cholesterol levels (≤ 45 mg/dL for men, ≤ 47 mg/dL for women) were treated with either lovastatin or placebo for a mean of 5.2 years. With few exceptions, the characteristics of the AFCAPS/TexCAPS cohort were similar to the profile of the majority of people in the United States and that of a potential over-

the-counter (OTC)-type subgroup. The dosage of lovastatin used was 20–40 mg/day, titrated to achieve an LDL-cholesterol target of ≤ 110 mg/dL. Treatment reduced the combined incidence of fatal and nonfatal myocardial infarction, unstable angina, and sudden cardiac death by 37% ($p < 0.001$). The risk for fatal and nonfatal heart attack was reduced by 40% ($p < 0.002$), and the need for coronary revascularization procedures was reduced by 33% ($p = 0.01$). Post hoc analysis of data from a subgroup of the AFCAPS/TexCAPS cohort resembling those in the general population who may benefit from OTC statins indicates similar benefits. The results have important implications for the identification and treatment of persons at risk for coronary disease.

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Although the positive epidemiologic association between cholesterol (total cholesterol and low-density lipoprotein [LDL] cholesterol) and increased risk for coronary artery disease (CAD) is well accepted, a substantial proportion of individuals who die from coronary disease do not have severely elevated cholesterol levels (Figure 1).¹ In fact, it is estimated that only 20% have total cholesterol levels > 240 mg/dL. Thus, there is a great deal of interest in the effects of lipid modification in patients with “average” cholesterol values.

The case has been made for secondary prevention using statin therapy in such patients, based on the findings of the Cholesterol and Recurrent Events (CARE)² and Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID)³ trials of pravastatin. The issue of primary prevention in this group, was addressed by the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS).⁴ In brief, AFCAPS/TexCAPS reported that a mean 5.2 years of treatment with lovastatin, 20–40 mg/day, in patients with average total cholesterol and LDL cholesterol, and below-average high-density lipoprotein

(HDL) cholesterol was associated with a 37% reduction in the relative risk for a first acute major coronary event (defined as fatal or nonfatal myocardial infarction, sudden cardiac death, or unstable angina). Because AFCAPS/TexCAPS targeted a relatively low-to-moderate risk population for intervention, the study's results may have broad applicability to the general US population. According to current guidelines, the majority of those eligible for treatment are currently undertreated for lipid disorders.⁵

Spurred by the substantial evidence of benefit, debate has turned to whether over-the-counter (OTC) availability of statins would represent a new avenue of reaching patients at risk for coronary disease. Within the AFCAPS/TexCAPS cohort, there was a subgroup of participants resembling those in the general population who may benefit from OTC statins.¹ The present report describes a post hoc analysis of data from this subgroup to estimate the possible benefit of treating an OTC-like population. We will also review the major demographic and safety findings observed in the overall AFCAPS/TexCAPS cohort.

DESIGN

The AFCAPS/TexCAPS design has been described in detail elsewhere.⁶ AFCAPS/TexCAPS was a primary-prevention study in 6,605 low-to-moderate risk subjects, with total cholesterol levels of 180–264 mg/dL and HDL cholesterol levels < 50 mg/dL. After

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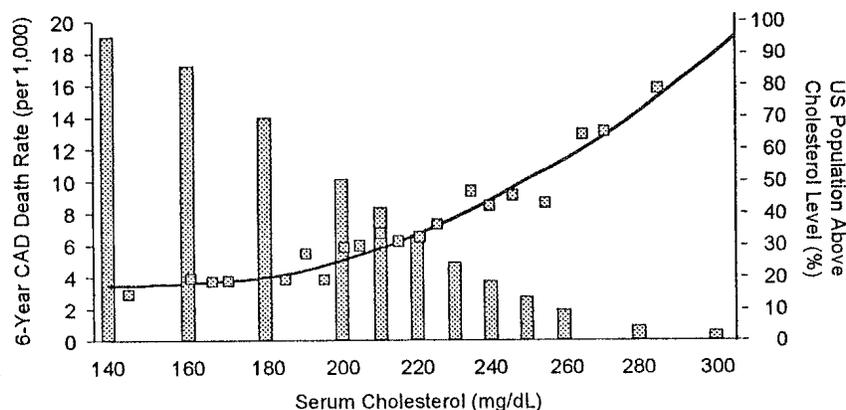


FIGURE 1. Distribution of total cholesterol and risk of coronary artery disease (CAD). (Adapted from *JAMA*¹¹ and *Arch Intern Med*.¹²)

TABLE I Number (%) of Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) Participants by Baseline Low-Density Lipoprotein Cholesterol (LDL-C) and Total Cholesterol (TC)

Baseline LDL-C	Baseline TC N (%)		
	<200 mg/dL	200–239 mg/dL	≥240 mg/dL
<130 mg/dL	495 (7%)	193 (3%)	3 (<1%)
≥130 mg/dL	596 (9%)	4,092 (62%)*	1,226 (19%)

*AFCAPS participants meeting nonprescription lovastatin lipid eligibility at baseline.

a 12-week run-in of the American Heart Association (AHA) Step I diet, participants were randomized to placebo or lovastatin 20 mg/day. The lipid goal of treatment was an LDL-cholesterol target of 110 mg/dL. If after a fixed period of time this target had not been reached, then the initial 20-mg dose of lovastatin was doubled to 40 mg (no further dose titration was performed after this point). Half of the subjects met titration requirements. It is important to note that at baseline only 17% of the overall AFCAPS/TexCAPS cohort would have qualified for drug treatment according to National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) II guidelines.⁴

Identifying an OTC-type subgroup: To model a potential OTC-type subgroup, only individuals with a total cholesterol level of 200–239 mg/dL and an LDL cholesterol level ≥130 mg/dL were considered. Very few in this group would have qualified for lipid-modifying drug treatment under current US guidelines, which reserve drug initiation in primary prevention to those with LDL cholesterol levels >190 mg/dL, or with LDL cholesterol levels of 160–190 mg/dL and ≥2 additional risk factors.

Table I shows the distribution of cholesterol risk groups in AFCAPS/TexCAPS participants according to total cholesterol and LDL cholesterol risk strata. Based on lipid criteria alone, 62% of the AFCAPS/TexCAPS cohort would meet the definition of OTC type. Of the 4,092 patients in this subgroup, 287 (7.0%) had diabetes or used multiple antihypertensive medications. Because these patients were felt to re-

quire regular monitoring by a physician, they were deemed unsuitable candidates for OTC lipid-modifying therapy and were excluded from the analysis. This left 3,805 patients, or 57.6% of all participants, for analysis. The percentage of nonprescription lovastatin-eligible patients randomized to lovastatin (n = 1,884; 49.5%) was similar to the percentage assigned to placebo (n = 1,921; 50.5%).

RESULTS

Because the identification of an OTC-type subgroup represents a post hoc analysis of the data, the most meaningful description of baseline data remains that of the overall cohort.

Baseline demographics: The lipid values of the overall cohort in AFCAPS/TexCAPS were compared (Figure 2) with the lipid values of the population comprising the 50th percentile of a referent population from the third National Health and Nutrition Examination Survey (NHANES III),⁷ the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT),⁸ the Helsinki Heart Study (HHS),⁹ and the West of Scotland Coronary Prevention Study (WOSCOPS).¹⁰ The NHANES III referent population was defined as men aged 45–73 years and women aged 55–73 years, without cardiovascular disease (n = 43.7 million). In AFCAPS/TexCAPS, the total-cholesterol and LDL cholesterol levels were lower than those of patients included in earlier primary-prevention studies.

Based on data from the trial's site at Wilford Hall,

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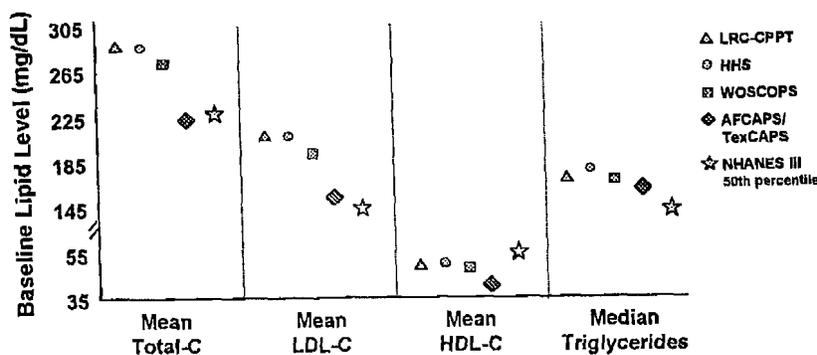


FIGURE 2. Primary-prevention studies and average lipid levels. AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study; HDL-C = high-density lipoprotein cholesterol; HHS = Helsinki Heart Study; LDL-C = low-density lipoprotein cholesterol; LRC-CPPT = Lipid Research Clinics Coronary Primary Prevention Trial; NHANES III = National Health and Nutrition Examination Survey III; Total-C = total cholesterol; WOSCOPS = West of Scotland Coronary Prevention Study. (Reprinted with permission from the American College of Cardiology, *J Am Coll Cardiol*.¹³)

Lipid Level	AFCAPS/TexCAPS (N = 6,605) (Average \pm SD, mg/dL)	NHANES Percentile*	US NHANES III Referent Population† (Mean \pm SD, mg/dL)
Mean Total-C	221 \pm 21	51	225 \pm 45
Mean LDL-C	150 \pm 17	60	142 \pm 37
Mean HDL-C	37 \pm 6	22	50 \pm 16
Median TG	158 \pm 76	63	140 \pm 120
Mean Total-C/HDL-C	6.1 \pm 1.1	81	4.9 \pm 2.1
Mean LDL-C/HDL-C	4.2 \pm 0.8	84	3.1 \pm 1.5

*Percentile ranks from United States NHANES III referent population for study population averages.
†Men aged 45-73 and women aged 55-73, without cardiovascular disease.
HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Total-C = total cholesterol; TG = triglycerides.

Lackland Air Force Base, San Antonio, Texas, baseline mean lipid levels in AFCAPS/TexCAPS were very similar to those in the NHANES III population. The total-cholesterol level in AFCAPS/TexCAPS was 221 mg/dL versus 225 mg/dL in NHANES III, and the LDL cholesterol level was 150 mg/dL versus 142 mg/dL (Table II). Only the baseline mean HDL cholesterol level in AFCAPS/TexCAPS (37 mg/dL) differed importantly (50 mg/dL) from the NHANES III referent population. However, AFCAPS/TexCAPS patients were deliberately selected to have relatively low HDL cholesterol levels, so this finding was expected.

In conjunction with the low HDL cholesterol levels, the AFCAPS/TexCAPS patients had slightly elevated triglyceride levels that were above the 50th percentile of the NHANES III referent population. Other baseline characteristics as compared with the NHANES III population are shown in Table III.

All participants had at least 1 common risk factor, which was age (males \geq 45 years, females \geq 55 years). The majority (66%) had \geq 2 risk factors. About 83% of the subjects would not have qualified for lipid-

modifying drug treatment, according to the current National Cholesterol Education Program (NCEP) guidelines. The distribution of risk factors was similar to the US referent population as represented by NHANES III (Table IV). However, as expected, the percentage of AFCAPS/TexCAPS participants with HDL cholesterol levels $<$ 35 mg/dL (35%) was higher than in NHANES III.

Lipid changes: The percent changes in cholesterol levels in the overall AFCAPS/TexCAPS cohort are shown in Figure 3. In the lovastatin-treated group, there was an 18% decrease in total cholesterol, a 25% decrease in LDL cholesterol, a 6% increase in HDL cholesterol, and a 15% decrease in triglycerides, compared with baseline levels. The total cholesterol/HDL cholesterol ratio decreased 22%, and the LDL cholesterol/HDL cholesterol ratio decreased 28%.

When analyzed according to OTC eligibility, the mean percent changes in LDL cholesterol levels from baseline at 1 year for these 3 groups were 25% for both the OTC-eligible subset and the non-OTC eligible. There was a similar increase in HDL cholesterol in both groups of approximately 6%.

	AFCAPS/TexCAPS	NHANES III
Sex (%)		
Women (n = 997)	15	42
Race (%)		
White	89	85
Hispanic	7	7
Black	3	8
Mean age (yr)	58 ± 7	60 ± 8
Men (range, 45–73)	57 ± 7	57 ± 8
Women (range, 55–73)	63 ± 5	64 ± 5
≥65 at randomization (%)	21	33

AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study.

Risk Factors	AFCAPS/TexCAPS	NHANES III
Hypertension	22%	15%
Active smoker	12%	26%
NIDDM	2%	4%
Family history	16%	9%
HDL-C <35 mg/dL	35%	13%

HDL-C = high-density lipoprotein cholesterol; NIDDM = non-insulin-dependent diabetes mellitus.

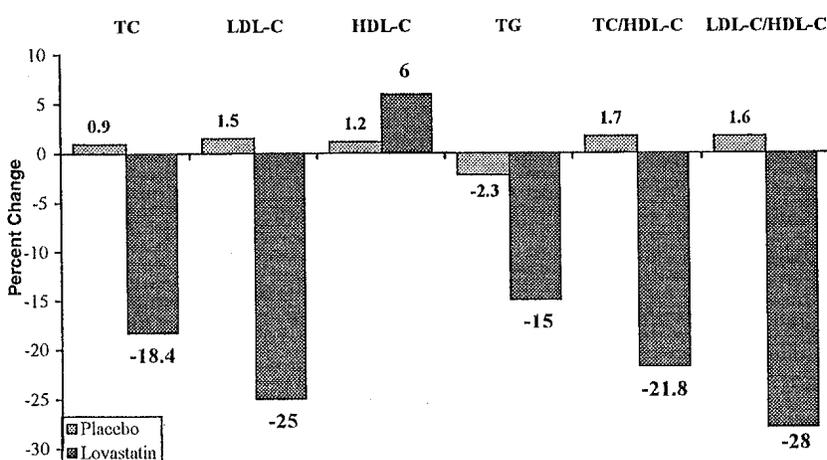


FIGURE 3. Percent change in lipids from baseline at year 1. For all lipid parameters, between group differences, and changes on lovastatin from baseline to year 1, $p < 0.001$. HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; TG = triglycerides. (Reprinted with permission from JAMA.⁴ Copyright 1998, American Medical Association.)

Primary endpoint (overall cohort): The primary endpoint in AFCAPS/TexCAPS was a composite of fatal or nonfatal myocardial infarction, sudden cardiac death, and unstable angina. Diagnosis of angina was based on the presence at hospitalization of typical clinical manifestations and was confirmed by either coronary angiography or the presence of reversible ST wave changes on exercise electrocardiogram. As shown in Figure 4, the cumulative incidence of the primary endpoint began to diverge between the 2

groups by the end of the first year of the trial. In the placebo group, 40 individuals had a primary endpoint event in the first year versus only 23 in the lovastatin group. By the end of the follow-up period, a 37% reduction in relative risk was observed with lovastatin treatment. Significant risk reductions were also seen in all secondary cardiovascular endpoints, including a 40% reduction in fatal and nonfatal myocardial infarction, a 32% reduction in unstable angina, a 25% reduction in all cardiovascular events, and a 25% reduc-

AQ: 2

Nonprescription Lovastatin Eligibility	Events/Patients (%)		5-Year Kaplan-Meier [†] Event Rate (%)		NNT [‡]	Events Avoided/10,000 treated (%) [§]	Relative Risk Reductions (95% CI)	P Value
	Placebo	Lovastatin	Placebo	Lovastatin				
Eligible	108/1,921 (5.6)	60/1,884 (3.2)	5.3	3.0	43	233	0.440 (0.233-0.592)	0.001
Not eligible	75/1,380 (5.4)	56/1,420 (3.9)	5.0	3.6	71	141	0.277 (-0.023-0.049)	0.067
Combined	183/3,301 (5.5)	116/3,304 (3.5)	5.2	3.3	54	185	0.373 (0.209-0.503)	0.001

CI = confidence interval; NNT = number needed to treat.
^{*}Nonfatal myocardial infarction, unstable angina, fatal coronary artery disease.
[†]Estimated by Kaplan-Meier survival method.
[‡]Number of patients needed to treat for the indicated time period to avoid 1 event = $\{1 / (\text{difference})\} \times 100$.
[§]Number of events avoided per 10,000 patients treated for the indicated time period = $(10,000 / \text{NNT})$.

tion in all coronary events. Need for revascularization procedures was also reduced by 33%.

Analysis of events according to lipid tertile and other risk factors (overall cohort): The data were analyzed across the tertiles of baseline LDL cholesterol or HDL cholesterol (Figure 5). The highest LDL cholesterol tertile in the placebo group had the highest baseline event rate, but there were no significant differences in event rates among the 3 tertiles in the treatment group. Lovastatin appeared to neutralize the excess risk associated with either a high LDL cholesterol or a low HDL cholesterol level. There was a benefit in all 3 tertiles of HDL cholesterol, but the greatest benefit was seen in those who had HDL cholesterol levels <40 mg/dL at baseline.

The higher risk associated with such risk factors as hypertension or cigarette smoking was reduced by lovastatin treatment to a level comparable with that of a placebo participant without risk factors. There was no heterogeneity between the subgroups. Men, women, those above and below the median age, patients who smoked, those with hypertension, and those with diabetes experienced relative risk reductions comparable with the benefits achieved by the overall cohort.

Treatment effects in the OTC-type subgroup: Among the OTC-eligible subset of AFCAPS/TexCAPS (Table 5), the primary endpoint event rates were 5.6% in the placebo group and 3.2% in the lovastatin group. The relative risk reductions were 44% (95% CI 23-59%) in the OTC-type subset and 28% (95% CI 2-49%) in the non-OTC-type subset. Therefore, the relative (44%) and absolute (~2%) risk reductions in the OTC-type subgroup were comparable with those observed in the overall cohort.

Safety and tolerability in AFCAPS/TexCAPS: Because the OTC analysis was not prespecified, the most meaningful description of safety data remains that of the overall cohort. The incidence of serious adverse events was 34% in both the placebo and the lovastatin groups. The rates of drug-related adverse events were 15.9% versus 17.5%, discontinuations due to adverse events were 13.6% versus 13.5%, and discontinuations due to drug-related adverse events were 2.1% versus 2.4% for the placebo and lovastatin groups, respectively.

Less than 1% of patients demonstrated liver elevations defined as alanine aminotransferase and aspartate aminotransferase >3 times the upper limit of normal. Creatinine kinase elevations >10 times the upper limit of normal were also seen in <1% of patients. There were no differences in liver enzyme elevations or creatinine kinase elevations between the placebo and the lovastatin groups.

The incidence of total mortality was not significantly different between the groups, with 77 deaths in the placebo group and 80 in the lovastatin group. There were too few cardiovascular deaths to perform statistical analysis, with 25 in the placebo group and 17 in the lovastatin group. The study was not powered to detect effects on mortality.

The incidence of fatal and nonfatal cancers, includ-

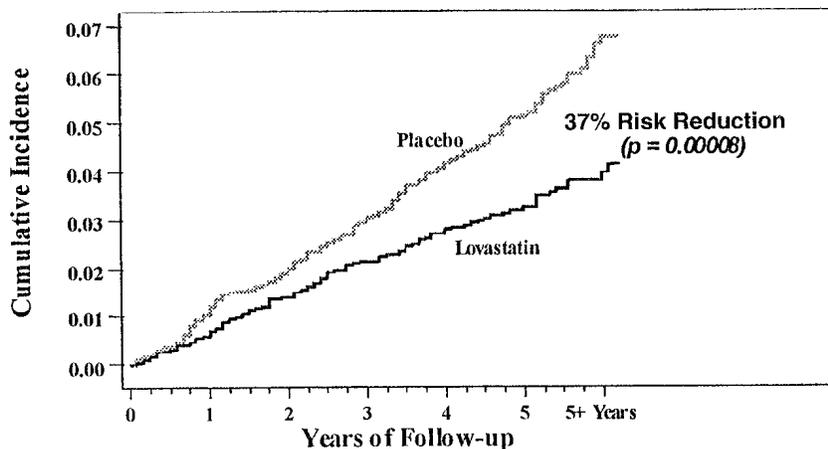
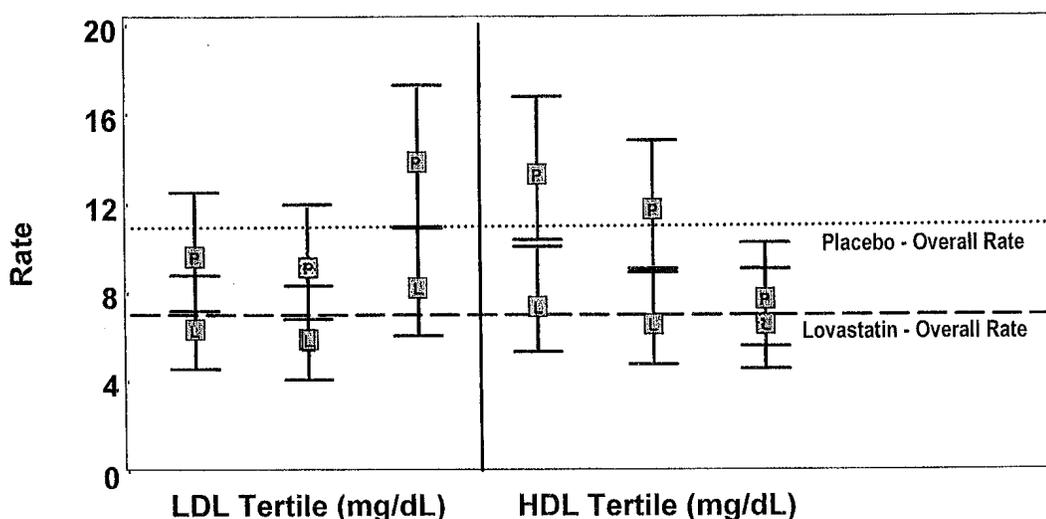


FIGURE 4. Primary endpoint: first acute major coronary event. (Reprinted with permission from JAMA.⁴ Copyright 1998, American Medical Association.)



Subgroup	LDL Tertile (mg/dL)			HDL Tertile (mg/dL)			* = Bottom Tertile ** = Top Tertile
	≤ 142*	143-156	≥ 157**	≤ 34*	35-39	≥ 40**	
N	2210	2196	2199	2115	2347	2143	
■ Lovastatin Events	37	33	46	40	41	35	
■ Placebo Events	54	52	77	71	68	44	

AQ: 6 FIGURE 5. Comparison of acute major coronary event rates: baseline lipid tertiles. HDL = high-density lipoproteins; LDL = low-density lipoproteins; Rate = rate of first primary endpoint event per 1,000 patient-years at risk. (Adapted with permission from JAMA.⁴ Copyright 1998, American Medical Association.)

ing prostate, melanoma, colon, lung, lymphoma, bladder, and breast cancer, was evaluated. There were no significant differences between treatment groups, with the exception of melanoma, for which there were significantly more cases in the placebo group (27) than in the lovastatin group (14). The difference may or may not be clinically relevant, but this finding is in accordance with other studies examining the anti-neoplastic effects of statins. There was no difference between the placebo group and the lovastatin group in overall fatal and nonfatal cancer during the 5 years of the trial.

CONCLUSIONS

In summary, a substantial number of people in the United States who are at risk for coronary disease may benefit from the availability of statin treatment. As shown by AFCAPS/TexCAPS, the benefit of treating such a population is a reduction in the relative risk for a first coronary event of at least 37%. Therefore, it is expected from this data that a projected OTC-type group would experience the benefits of therapy similar to those seen in higher-risk patients. There was no evidence of significant toxicity, nor was there any other significant reason not to give the drug to the

overall group. The remaining issues would be the relative cost of the drug, the ability of an individual to monitor his or her lipid levels, and the role of liver function testing and monitoring.

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Defining Patient Risks from Expanded Preventive Therapies

Keith G. Tolman, MD

In clinical trials, all lipid-lowering agents have been associated with mild, asymptomatic elevations of alanine aminotransferase (ALT) and aspartate aminotransferase enzymes. This, along with the fact that 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors are hepatotoxic in some animals, led the US Food and Drug Administration (FDA) to recommend monitoring of liver enzymes for all lipid-lowering agents, except the bile acid sequestrants. Because the drugs act by different mechanisms, ALT elevations may be a pharmacodynamic effect related to lipid lowering, rather than a direct effect of the drug. Animal studies support this assumption. ALT elevations of 3 times the upper limit of normal occur in <3% of patients in clinical trials of lipid-lowering drugs. The elevations are transient and often dose-related, and they usually revert to normal while continuing therapy and have never been associated with hepatotoxicity. Confounding factors include alcohol, acetamin-

ophen, and pre-existing liver disease, such as chronic hepatitis C and type II diabetes with fatty liver, which are both associated with mild, intermittent elevations of ALT. The more important issue is whether or not lipid-lowering agents are hepatotoxic. There are case reports of hepatotoxicity (cholestasis, jaundice, hepatitis, chronic active hepatitis, fatty liver, cirrhosis and acute liver failure) with all of the drugs, except cholestyramine. To date there are just 5 cases of documented liver failure linked to lovastatin. There is no evidence that monitoring reduces the rate of hepatotoxicity. Mild elevations of ALT that occur with many drugs, including HMG-CoA reductase inhibitors, do not predict hepatotoxicity. Liver enzyme elevations appear to be a class characteristic of lipid-lowering agents. Hepatotoxicity is a rare idiosyncratic reaction, occurring only with sustained released nicotinic acid. ©2000 by Excerpta Medica, Inc.

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Lipid-lowering drugs first became available in the mid-1950s, when nicotinic acid was found to lower cholesterol. The fibrinic acids and cholestyramine were discovered in the mid-1960s, and the statins followed in the late 1970s, starting with mevastatin extracted from penicillium, followed by lovastatin from aspergillum.¹ Gemfibrozil was approved in 1982. Lovastatin was the first statin made available for therapeutic use gaining approval in 1987, just 5 years after its discovery. Preclinical toxicology studies had revealed some hepatotoxicity in rabbits administered very high doses.² Clinical trials showed an apparent dose-related elevation in liver enzymes and thus lovastatin was approved with a recommendation to monitor for liver toxicity. Subsequently, all of the other lipid-lowering drugs also carried warnings for liver toxicity with recommendations for monitoring. Twelve years later, however, there is little evidence of hepatotoxicity with any of the lipid-lowering agents, with the exception of sustained-release nicotinic acid. Therefore, it is time to reexamine the issue of hepatotoxicity.

The statins are analogs of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. They are pro-drugs which competitively inhibit the HMG-CoA reductase enzyme. It is a class characteristic of all lipid-lowering drugs to elevate hepatic aminotransfer-

ase liver enzymes, but there is little evidence that they are hepatotoxic.

ANIMAL TOXICOLOGY STUDIES

Initial toxicology studies in animals suggested possible liver problems. Animal data on lovastatin demonstrated transient increases in alanine aminotransferase (ALT) in rats and dogs but no histologic evidence of liver disease.³ Possible mechanisms for the ALT elevations included increased ALT synthesis, decreased ALT clearance, and ALT leakage from hepatocytes whose membranes may have been altered by changes in lipid content. It was also noted that very high doses of lovastatin in rabbits caused hepatocellular necrosis. This could be reversed or prevented by giving mevalonate or by force-feeding the animals which became very malnourished during the study.² The relatively low levels of HMG-CoA in rabbits were thought to make them vulnerable to injury. Similar results were seen with high doses of simvastatin in guinea pigs, suggesting that depletion of mevalonate or a downstream metabolite might be related to toxicity.⁴

EVIDENCE OF ALANINE AMINOTRANSFERASE (ALT) ELEVATIONS WITH STATINS

Early studies with lovastatin revealed dose-related elevations in ALT starting at the 20-mg dose, escalating the concerns about liver problems.⁵ However, all of the lipid-lowering drugs show some evidence of elevated ALT levels. With atorvastatin, there was also a dose-related increase in the incidence of ALT elevations of 3 times the upper limit of normal (Table I).

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Similar results were seen with fluvastatin. Elevations tend to occur early and usually reverse themselves during therapy. In fact, all of the lipid-lowering agents, including the bile acid sequestrants, cause elevations in ALT. It appears that cholesterol lowering itself is associated with a release of ALT. Interestingly, the same phenomenon is seen with starvation and weight reduction surgery, both of which also cause decreases in cholesterol.⁶

Whether these ALT elevations are clinically relevant and actually reflect hepatotoxicity is questionable. Analysis of the percentage of patients with elevated ALT up to 3× the upper limit of normal with fluvastatin over time showed that these elevations appear to be transient.⁷ Interestingly, there was a gradual increase over time in the number of patients detected with mild elevations of ALT in the placebo group, whereas in the fluvastatin-treated group, the incidence decreased over time.

In the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), 127 of 6,605 patients treated with lovastatin experienced ALT elevations of 1.5–3.0 times the upper limit of normal.⁸ ALT subsequently returned to normal in 91 (72%) cases, stayed in the same range in 18 (14%), and gradually worsened in the remaining 18 (14%). The cases in which the ALT elevations worsened (11 placebo patients, 18 lovastatin patients) were reviewed to find an etiology. Of the 18 in the lovastatin group, 14 either recovered while still on treatment or had a negative rechallenge when they were restarted on the drug. Three of the patients had an alternative diagnosis: chronic active hepatitis, fatty liver, or another medication. None of these cases was thought to be drug-induced. One patient, who also had cholelithiasis, had a positive rechallenge and probably had drug-induced ALT elevations but has no evidence of liver disease. The pattern was similar in those patients receiving placebo. Thus, minor ALT elevations with the statins do not correlate with or predict hepatotoxicity, but rather reflect simple chemical changes in ALT or unmask underlying chronic liver disease.

ALAIINE AMINOTRANSFERASE (ALT) ELEVATIONS AMONG COMMONLY USED DRUGS

Various other drug classes are quite commonly associated with ALT elevations.⁹ For example, isoniazid is associated with a 10–20% incidence of ALT elevations, and sustained-released nicotinic acid with a 25–35% incidence.¹⁰ Borderline elevations of ≥ 1 liver function tests may occur in up to 15% of patients taking nonsteroidal anti-inflammatory drugs. Thus, asymptomatic aminotransferase elevations are common with many drugs and do not necessarily reflect hepatotoxicity.

PREVALENCE OF LIVER PROBLEMS IN THE POPULATION

Minor elevations of liver enzymes are common in the general population. Patients with these elevations are not always excluded from clinical trials of chole-

sterol reduction therapy. Thus, it is important to consider ALT elevations with lipid-lowering drugs in the context of the background incidence of liver problems. Surveys reveal that ALT elevations are common, as confirmed by the placebo incidence of 0.1–2% in most studies.¹¹ Analysis of several thousand patients with minor elevations of ALT showed that the most common causes are alcohol, hepatitis C, hepatitis B, various drugs, autoimmune hepatitis, and hemochromatosis.¹² In about 10% of cases, no obvious cause could be found in the patient's history. On further investigation, almost 40% of those patients had fatty liver, and about 10% had fibrosis.

There is a very high incidence of nonalcoholic steatohepatitis in obesity, dyslipidemia, and type II diabetes mellitus.¹³ These patients are characterized by minor, fluctuating elevations of ALT. They are predisposed to hypercholesterolemia and could have been included in studies. Heart failure can also cause minor elevations of ALT. Therefore, it is not surprising that there are many patients with minor, transient elevations of ALT. The issue is whether these patients also have hepatotoxicity.

Fatty liver is present in at least 32% of patients with type II diabetes.¹⁴ In some studies, the incidence is as high as 70%. Fatty liver may not be a benign condition in diabetics; some patients develop cirrhosis and ultimately hepatocellular carcinoma. Because these patients have hyperinsulinemia, those with elevated ALT and a fatty liver can be tested for insulin resistance before they become diabetic. Preliminary studies suggest that these patients can be treated with insulin enhancers, such as metformin and the new thiazolidinediones. The point, however, is that the inclusion of many such patients in studies involving lipid-lowering drugs could account for the high background incidence of elevated ALTs.

Finally, 1.6% of the population, or almost 4 million people, are infected with hepatitis C. Patients with hepatitis C are usually asymptomatic and commonly present with minor, fluctuating elevations of ALT. Although hepatitis C had not been recognized at the time many of the studies were conducted, it has been determined retrospectively that many of those patients had hepatitis C.

ARE THE LIPID-LOWERING DRUGS HEPATOTOXIC?

Information on the incidence of hepatotoxicity caused by lipid-lowering drugs is limited. With the exception of sustained-release nicotinic acid, these agents are generally not included in reviews of hepatotoxicity. Nevertheless, there are scattered reports of hepatotoxicity with all of the drugs, except cholestyramine.

Table II shows the liver abnormalities associated with cholesterol-lowering agents. There have been reports of jaundice, hepatocellular reactions, and cholestatic reactions with cholestipol; hepatomegaly with clofibrate; hepatocellular reactions, cholestasis, and 1 report of chronic active hepatitis with fenofibrate; and hepatocellular reactions with gemfibrozil. The statins

T2

TABLE I Percent Incidence* of Confirmed Alanine Aminotransferase Elevations of Three Times the Upper Limit of Normal

	Placebo	Drug Dose			
		10 mg	20 mg	40 mg	80 mg
Atorvastatin	—	0.2	0.2	0.6	2.3
Fluvastatin	—	—	0.2	1.5	2.7
Lovastatin	0.1	—	0.1	0.9	1.5

*Data from package inserts.

TABLE II Liver Abnormalities Reported Associated with Lipid-Lowering Agents

Drug	Elevated ALT/AST	Type of Hepatotoxicity	Monitoring Recommended
Bile acid sequestrants			
Cholestipol	Yes	J, HC, Chol	No
Cholestyramine	Yes	None	No
Fibric acid derivatives			
Clofibrate	Yes	Hepatomegaly	Yes
Fenofibrate	Yes	HC, Chol, CAH	Yes
Gemfibrozil	Yes	HC	Yes
HMG-CoA reductase inhibitors			
Atorvastatin	Yes	J, HC, Chol	Yes
Cerivastatin	Yes	HC	Yes
Fluvastatin	Yes	J, HC, Chol	Yes
Lovastatin	Yes	J, HC, Chol, ALF, CAH	Yes
Pravastatin	Yes	J, HC, Chol	Yes
Simvastatin	Yes	J, HC, Chol, ALF, CAH	Yes
Others			
Nicotinic acid	Yes	J, HC, Chol, ALF	Yes
Germander		J, HC, Chol	

ALF = acute liver failure; CAH = chronic active hepatitis; Chol = cholestatic; HC = hepatocellular (ie, hepatitis); J = jaundice.

have all been associated with reports of apparent hepatotoxic reactions.^{10,15-22} Many of these cases have not been verified, and the statins may not have been causally related. There are a few reports of acute liver failure with lovastatin and simvastatin. Clinically meaningful reactions are rare, with the exception of sustained-release nicotinic acid, which appears to be associated with a higher incidence of hepatotoxicity. A prospective study by McKenney et al¹⁰ revealed that 12 of 18 patients had to be withdrawn because of ALT elevations $>3 \times$ the upper limit of normal. Five of these patients also had symptoms of hepatic dysfunction. McKenney went so far as to suggest that sustained-release nicotinic acid should be restricted in its use. Interestingly, rapid release nicotinic acid is rarely associated with toxicity. There are, in fact, many patients who do not experience hepatotoxicity with rapid release nicotinic acid and subsequently have serious liver toxicity with the sustained release form of the drug.

We have had the opportunity to review in more detail all of the cases of lovastatin-associated acute liver disease in patients reported to Merck's Worldwide Adverse Database (WAES). In total, 232 cases were classified as acute hepatitis. There were 12 reports of possible acute liver failure. Of the 12 cases, 6

did not have acute liver failure. Of the remaining 6 cases, 4 had fulminant hepatic necrosis. One patient was diagnosed with autoimmune hepatitis, but at the time of diagnosis, it was impossible to distinguish between autoimmune hepatitis and chronic hepatitis C. Finally, the sixth patient had a metastatic tumor. Thus, there were 5 remaining cases of possible drug-induced acute liver failure after 24 million patient-years of experience with this drug (Table III). It has been estimated that only 10% of adverse reactions are spontaneously reported. If the number of reported cases is multiplied by 10 to correct for assumed underreporting, the corrected rate of acute liver failure with lovastatin is 2 per 1 million patients, while the background incidence in the population is 5 times that at 10 per 1 million. The corrected rate of hepatitis is 96 per 1 million patient-years, which is a small fraction of the background incidence of hepatitis in the general population. These data suggest that the risk of drug-induced liver injury with lovastatin is extremely low.

Biopsy data were available for 57 of the 232 cases of acute hepatitis that were reported (Table IV). No consistent pattern of injury is observed. Although multiple histologic patterns have been observed with hepatotoxicity of other drugs, it would be more common to see a fairly consistent histologic pattern.

TABLE III Reported Cases of Acute Liver Failure and Hepatitis with Lovastatin: 24 Million Patient-Years of Treatment

	n	Rate/10 ⁶ Patient-Years
Acute liver failure	5	0.2
Hepatitis	232	9.6

TABLE IV Liver Biopsy Results in Cases of Hepatitis on Lovastatin

Result	n
Hepatitis	36
Acute	6
Chronic active	7
Chronic persistent	1
Chemical/toxic	5
Autoimmune	3
"Nutritional"	1
Granulomatous	8
Inflammation	4
Hypersensitivity	1
Other	21
Cholestatic	7
Fatty liver	7
Cirrhosis	2
Cholangitis	5

Data from spontaneous reports to manufacturer.

TABLE V Comparative Incidence of Acute Liver Failure Among Various Drug Classes*

Drug Class	Per 10 ⁵
Background	0.5-1.0
Statins	0.2
NSAIDs	2.0
Thiazolidinediones	10
Bromfenac	100

NSAID = nonsteroidal anti-inflammatory drugs.
*Unpublished data presented in part at the US Food and Drug Administration Endocrinology and Metabolic Drugs Advisory Committee Meeting, April 22, 1999.

It is difficult to compare the incidence of liver failure among different drug classes. What little information is available comes from the FDA and is collected from the United Network for Organ Sharing (UNOS), the liver transplant registry (Table V). The background incidence of acute liver failure was very low at 0.5-1.0 per 100,000 individuals. The incidence with statins is 0.2 and with nonsteroidal anti-inflammatory drugs (NSAIDs) is 2.0. Statins and NSAIDs are the 2 major drug categories for which lipid monitoring is required, yet they are associated with virtually no liver toxicity. Compare this with the thiazolidinediones (e.g., troglitazone), with an incidence of acute liver failure of 10 per 100,000, and with bromfenac, with an incidence of 100 per 100,000. Hepatotoxicity has resulted in the withdrawal of both troglitazone and bromfenac by the FDA. It appears that although there are rare, apparently idiosyncratic hep-

atotoxic reactions with the statins, the incidence is very low.

ROLE OF MONITORING FOR HEPATOTOXICITY

Many of these reactions are cholestatic, are generally benign, and are easily detected because patients become symptomatic with pruritus or jaundice before serious liver injury. Monitoring is not needed because symptoms generally precede serious liver damage. Monitoring has proven useful to screen for chronic liver disease and for industrial hepatotoxicity. It has not proved predictive of acute hepatocellular reactions that progress rapidly to liver failure within only a few days of onset. Monitoring is recommended for all lipid-lowering drugs, but to date has not identified patients who are destined to have liver problems and historically has not been helpful.

CONCLUSION

Transient, minor, reversible elevations of ALT are characteristic of all the lipid-lowering agents. This appears to be a pharmacodynamic characteristic and is probably related to lowering of cholesterol levels. There are rare, idiosyncratic hepatotoxic reactions associated with all of the drugs, except cholestyramine. Only sustained-release nicotinic acid appears to have a significant incidence of hepatotoxicity.

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Population Benefits of Cholesterol Reduction: Epidemiology, Economics, and Ethics

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Cardiovascular disease mortality-rate reductions have slowed in the United States in the last decade, suggesting that additional strategies are needed to reduce rates further. Population-wide cholesterol reduction is a promising approach. Selection of a particular strategy is less an issue of efficacy, which has been proven through numerous studies, than it is an issue of epidemiology, economics, and ethics. These 3 imperatives constitute the foundation of renewed efforts to reduce the US population's cholesterol levels. Epidemiologic imperatives include risk reduction in low-to-moderate risk individuals, who comprise approximately 30% of the population and one third of incident cases of coronary disease. Any cholesterol-lowering strategy must address the challenge of reducing the incidence of coronary disease; to do otherwise will result in an increasing prevalence of

disease, with the attendant cost and disability burdens. Economic imperatives include the extension of preventive coverage to the low-to-moderate risk segment of the population, which currently is not included in any risk-reduction programs. Although cholesterol reduction with pharmacologic agents may not meet current standards for cost-effectiveness, over-the-counter (OTC) agents are under the rubric of individual, not societal, costs. Finally, current and proposed options for nonprescription cholesterol-lowering drugs raise a number of ethical issues such as beneficence, nonmaleficence, justice, and autonomy. Population-wide cholesterol reduction must be a mainstay for any strategy to reduce the burden of cardiovascular disease. ©2000 by Excerpta Medica, Inc. Am J Cardiol 2000;85:20E-23E

When discussing the issue of making prescription medications available over-the-counter (OTC), a population perspective becomes important. Over the past decade, the incidence of cardiovascular disease (CVD) has remained a major health concern, despite the medical community's success in reducing the mortality rate associated with it. In fact, data from the National Conference on Cardiovascular Disease Prevention show that although CVD mortality continues to decline, it decreased at a slower rate during the 1990s than during the previous 2 decades.¹ During those 2 decades, the yearly decline of CVD mortality was 2.6%, whereas the decline since 1990 has slowed considerably to about 1.5%. The mortality rates of specific CVDs, such as ischemic heart disease, have continued to decline for Caucasian men but less consistently among African-Americans, women, the poor, and those in certain geographic (often rural) areas. Moreover, it appears that stroke rates have stopped declining since 1990. Finally, congestive heart failure incidence, prevalence, and mortality are rapidly increasing as they have done for the last 25 years. The declines in cardiovascular morbidity and mortality appear to have reached a plateau.

POPULATION-WIDE CHOLESTEROL LOWERING CAN LOWER CARDIOVASCULAR DISEASE (CVD)

Evidence highlighting the strong international correlation between serum cholesterol levels and CVD supports population-wide cholesterol lowering as a strategy to reduce CVD rates further. Epidemiologic data have shown that populations with low serum cholesterol levels have low CVD rates, despite high levels of other risk factors. For example, in north Asia, countries such as China and Manchuria have very high rates of hypertension and smoking and relatively low rates of coronary disease because cholesterol levels are low. Populations with high serum cholesterol levels almost uniformly have high CVD rates. The Seven Countries Study showed a strong relation between serum cholesterol levels and rates of CVD.²

More compelling is the fact that changes in serum cholesterol levels correlate with changes in CVD rates. In some of the countries that have lowered their CVD rates most markedly, such as Finland and the United States, 30–40% of the reduction has been attributed to population-wide cholesterol reductions.³ Further, clinical studies, including serial angiographic studies and randomized controlled trials, in patients at varying degrees of risk, demonstrate that lowering cholesterol is related to lowering cardiovascular risk.⁴

ISSUES ASSOCIATED WITH POPULATION-WIDE CHOLESTEROL LOWERING

To evaluate the merits of OTC cholesterol agents as a means to effect population-wide cholesterol lowering, one must consider the clinical and economic

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benefits of their availability. To that end, there are 4 critical issues that need to be examined: efficacy, epidemiology, economics, and ethics.

Efficacy issues: In the past few decades, landmark trials such as the Simvastatin Scandinavian Survival Study (4S),⁵ the West of Scotland Coronary Prevention Study (WOSCOPS),⁶ and the Cholesterol and Recurrent Events (CARE) study⁷ have all proven the efficacy of cholesterol-lowering therapy in reducing CVD events and death in a variety of patients with hypercholesterolemia with and without CVD. As the efficacy of cholesterol lowering is no longer in doubt, the 3 issues that remain paramount in determining the value of OTC cholesterol therapy are epidemiology, economics, and ethics.

Epidemiologic issues: Traditionally, the treatment guidelines for cholesterol lowering have focused on the reduction of cholesterol levels in high-risk patients (i.e., patients with high levels of serum cholesterol). The guidelines have also emphasized the reduction in morbidity and mortality in patients in this category. However, data from the third National Health and Nutrition Examination Survey (NHANES III) highlight the benefits of cholesterol reduction in patients at moderate risk (i.e., the decreased incidence of CVD in patients with moderate cholesterol levels) and point to the epidemiologic imperative for cholesterol reduction in this segment of the population. Also important are the implications of the failure of medical practitioners to lower the incidence of CVD in this group. Statistics indicate that although mortality has been lowered, there is growing evidence that incidence has not been reduced.⁸ Finally, the clinical benefits of reduced serum lipids in CVD prevention in lower-risk patients are well established.

The NHANES III survey was conducted in the early 1990s and examined a random sample of US adults ages 20–74 years.⁹ Forty-one percent of the population had desirable cholesterol levels, with total cholesterol levels <200 mg/dL and high-density lipoprotein (HDL)-cholesterol levels >35 mg/dL (Table I). The corollary is that 59% of the population had less than desirable cholesterol levels. Twenty-nine percent of individuals had borderline-high cholesterol levels defined as total cholesterol levels of 200–239 mg/dL, and could be considered prime candidates for OTC therapy. Another 18% were at high risk, and about 7% had coronary artery disease (CAD), a percentage that is currently increasing and is very age-dependent. Therefore, about 30% of the US population were in the moderate-risk range. Of these, a sizeable proportion will develop CAD. It is important to emphasize that elevated cholesterol levels are one of many risk factors that contribute to CAD. For the purpose of the discussion in this article, the emphasis will be placed on 1 of the risk factors—elevated cholesterol levels.

Using the prevalence of cholesterol levels in NHANES III and the age-adjusted 10-year incidence rates of coronary disease as predicted from Framingham risk equations,¹⁰ one can estimate the expected number of CAD cases per 100 patients per 10 years by

cholesterol risk level in men and women aged ≥ 20 years without prior CAD (Table II). Approximately, one third of CAD cases occur in individuals from this moderate-risk group. For example, for every 10.5 men per 100 who develop CAD in a 10-year period, 3.6 would be from the moderate-risk group. Similarly, of the 5.2% of women expected to suffer a coronary event, 1.8% would be from the moderate-risk group. Therefore, this group is an obvious target to reduce the population burden for CVD.

Treating only high-risk individuals, particularly those who have already had a coronary event, reduces mortality without reducing the incidence of CAD. This approach will result in an increased prevalence of CAD, including increased morbidity and disability, with all of the attendant social costs as well as the cost of specialty medical care. There will also be an increase in population risk, resulting in a slower decline in cardiovascular disease mortality rates, as the prevalence of CAD cases and their attendant comorbidities accumulate in the population.

The clinical benefits of population-wide cholesterol reduction include reduced rates of sudden death and fatal myocardial infarction. Currently, 20% of individuals with a primary cardiovascular event do not have the opportunity for secondary preventive interventions because they present with a fatal manifestation of CVD.¹¹ The decreased disease prevalence due to population-wide cholesterol lowering will result in reduced costs of acute and chronic care. A reduced cholesterol level may also have a marked effect on the impact of other risk factors. Data from the Multiple Risk Factor Intervention Trial (MRFIT) study show that as cholesterol levels increase, there is a tremendous increase in risk in patients who are hypertensive, diabetic, or smokers.¹² In contrast, an individual who is neither hypertensive nor a smoker has a more modest increase in risk. Therefore, a population-wide decrease in cholesterol will also ameliorate the effects of other risk factors.

Not to be ignored are the benefits of the reduced atherosclerotic burden in individuals with CAD and their improved prognosis. When case fatality rates and prognosis improve, it is often attributed to secondary preventive interventions. However, shifting the population, for example, from an average of 3-vessel disease to 2- or 1-vessel disease (i.e., decreased atherosclerotic burden) because of population-wide risk factor reduction should also improve prognosis.

Economic issues: It is critical to consider the cost of population-wide cholesterol reduction, especially as the costs of healthcare spending approach 14–16% of the US gross national product. Population-wide cholesterol reduction will extend benefits, both clinical and cost-related, to a segment of the population not currently covered. It is important to consider both the cost of the disease prevented and the cost of treatments given, as well as the societal versus individual costs.

The World Bank's approach to eradication of a disease is simple and straightforward. It advocates finding an intervention that is 100% efficacious and

Risk Group	Prevalence (%)
Desirable (TC <200 mg/dL)	41
HDL ≥ 35 mg/dL	4
HDL <35 mg/dL	
Borderline (TC 200–239 mg/dL)	26
HDL ≥ 35 mg/dL	3
HDL <35 mg/dL	
High risk (TC ≥ 240 mg/dL)	18
CAD	7

CAD = coronary artery disease; HDL = high-density lipoprotein; TC = total cholesterol.

Risk Group	Prevalence (%) [*]	Age-Adjusted CAD Rates [†] (%)	CAD Cases per 100 Patients/10 Years (n)
Men			
TC <200 mg/dL	45	8.2	3.7
TC 200–239 mg/dL	30	12.0	3.6
TC ≥ 240 mg/dL	17	18.6	3.2
Women			
TC <200 mg/dL	45	3.1	1.3
TC 200–239 mg/dL	27	6.6	1.8
TC ≥ 240 mg/dL	20	10.3	2.1

CAD = coronary artery disease; TC = total cholesterol.
^{*}Percent of subjects from National Health and Nutrition Examination Survey III without CAD. Approximately 8% of the population has CAD.
[†]Incidence of CAD as predicted from Framingham risk equations.¹⁰

applying it to 100% of the population. For example, in the case of smallpox, vaccination has succeeded in eradicating the disease. In the case of cardiovascular diseases, there are 4 important patient groups to consider. The first group is comprised of individuals whose disease cannot be averted with known interventions, although about 60% of CVD cases are associated with known risk factors. The second group is comprised of patients in whom fatal CVD has been averted by current efforts, as evidenced by declining CVD mortality rates. The third group constitutes individuals whose CAD would be averted if our health system were more efficient and if current guidelines were adhered to. The fourth group is comprised of patients who would be treated if interventions were more cost-effective. Benefits could be extended to these patients, who account for as much as one third of the US population.

The expected costs of a population-wide clinical intervention include the cost of treatment plus the cost of any side effects and their monitoring.¹³ However, cost-savings can be realized when there is a decrease in morbidity as well as a reduction in coronary disease hospitalizations, revascularization procedures, and secondary preventive drugs. The cost of life extension should also be taken into account. Lastly, cost sources must be considered. Some individuals may personally want to bear the costs of treatment and side effects

because they cost less than the risks associated with an increased number of CVD events.

In the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPs), treatment of 1,000 individuals with lovastatin for 5 years was associated with 12 myocardial infarctions, 7 cases of unstable angina, and 17 revascularization procedures.¹⁴ The number of patients needed to treat to prevent an endpoint was less for men, smokers, and patients with hypertension or low HDL-cholesterol levels. Therefore, it is possible to identify subgroups within AFCAPS/TexCAPs that would be more cost-effective than average to treat. However, it is unlikely that treatment of such groups would be cost-effective by currently used criteria.¹⁵

Differences in the cost of therapy between individuals, changes in the cost of therapy over time, and the relative importance of quality-of-life benefits to the individual should also be examined. The balance between the cost of intervention versus the cost of no intervention always fluctuates.

The key issue in economic imperative for population-wide cholesterol reduction is societal versus individual costs. The current reticence to use cholesterol-lowering agents in low-risk groups is related to health-care plans' having to pay for cholesterol-lowering drugs that do not meet the current estimated criteria for cost-effectiveness. Individual costs, however,

are tied to the ethical considerations of population-wide cholesterol reduction.

Ethical issues: Discussion of the ethical imperative for population-wide cholesterol reduction involves the 4 main ethical principles of medicine: beneficence, nonmaleficence, justice, and autonomy. Beneficence is the desire to do good. In the case of cholesterol-reducing agents, clinical trial data certainly suggest that we can do "good" with these agents. Nonmaleficence is the commitment to "first do no harm." Cholesterol-lowering agents do appear very safe, without any real serious health risks. The third principle, justice, means equitable treatment for all patients. Although everyone should have equal access to cholesterol-reducing therapy, it is doubtful whether everyone actually does. The fourth principle, autonomy, pertains to patient choice. Patients, after receiving information and advice from their healthcare providers, should have the opportunity to elect the treatment of their choice.

NONPRESCRIPTION APPROACHES TO CHOLESTEROL LOWERING

Currently, there are a few nonprescription options that an individual with borderline-high cholesterol levels can use for cholesterol reduction. These include weight reduction through caloric restriction and exercise; low-fat, low-cholesterol diets; and high dietary fiber. In addition, individuals can try to lower their cholesterol with stanol ester-enriched foods, red rice yeast, and niacin, which are available OTC. However, whether these options satisfy the 4 ethical principles is debatable, since many of those therapies do not have long-term safety and efficacy data. Because the evidence for the efficacy of these options is limited, especially when compared with statins, the question remains: should OTC statins be an option?

CONCLUSION

The issues surrounding population-wide cholesterol lowering are no longer related solely to efficacy but are also connected to epidemiology, economics, and ethics. Approximately one third of the incidence of coronary artery disease involves individuals in the borderline-high total-cholesterol level range, a group

that might benefit from a population-wide CVD risk reduction strategy. The extension of cholesterol-lowering drug therapy to moderate-risk groups may not meet current standards of cost-effectiveness, but it must be kept in mind that the OTC costs would be individual, not societal. Finally, the right of an individual to treatment and the right to choose should be considered a matter of ethics.

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Attachment 4
AFCAPS/TexCAPS JAMA Publication

Original Contributions

Primary Prevention of Acute Coronary Events With Lovastatin in Men and Women With Average Cholesterol Levels

Results of AFCAPS/TexCAPS

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Context.—Although cholesterol-reducing treatment has been shown to reduce fatal and nonfatal coronary disease in patients with coronary heart disease (CHD), it is unknown whether benefit from the reduction of low-density lipoprotein cholesterol (LDL-C) in patients without CHD extends to individuals with average serum cholesterol levels, women, and older persons.

Objective.—To compare lovastatin with placebo for prevention of the first acute major coronary event in men and women without clinically evident atherosclerotic cardiovascular disease with average total cholesterol (TC) and LDL-C levels and below-average high-density lipoprotein cholesterol (HDL-C) levels.

Design.—A randomized, double-blind, placebo-controlled trial.

Setting.—Outpatient clinics in Texas.

Participants.—A total of 5608 men and 997 women with average TC and LDL-C and below-average HDL-C (as characterized by lipid percentiles for an age- and sex-matched cohort without cardiovascular disease from the National Health and Nutrition Examination Survey [NHANES] III). Mean (SD) TC level was 5.71 (0.54) mmol/L (221 [21] mg/dL) (51st percentile), mean (SD) LDL-C level was 3.89 (0.43) mmol/L (150 [17] mg/dL) (60th percentile), mean (SD) HDL-C level was 0.94 (0.14) mmol/L (36 [5] mg/dL) for men and 1.03 (0.14) mmol/L (40 [5] mg/dL) for women (25th and 16th percentiles, respectively), and median (SD) triglyceride levels were 1.78 (0.86) mmol/L (158 [76] mg/dL) (63rd percentile).

Intervention.—Lovastatin (20-40 mg daily) or placebo in addition to a low-saturated fat, low-cholesterol diet.

Main Outcome Measures.—First acute major coronary event defined as fatal or nonfatal myocardial infarction, unstable angina, or sudden cardiac death.

Results.—After an average follow-up of 5.2 years, lovastatin reduced the incidence of first acute major coronary events (183 vs 116 first events; relative risk [RR], 0.63; 95% confidence interval [CI], 0.50-0.79; $P < .001$), myocardial infarction (95 vs 57 myocardial infarctions; RR, 0.60; 95% CI, 0.43-0.83; $P = .002$), unstable angina (87 vs 60 first unstable angina events; RR, 0.68; 95% CI, 0.49-0.95; $P = .02$), coronary revascularization procedures (157 vs 106 procedures; RR, 0.67; 95% CI, 0.52-0.85; $P = .001$), coronary events (215 vs 163 coronary events; RR, 0.75; 95% CI, 0.61-0.92; $P = .006$), and cardiovascular events (255 vs 194 cardiovascular events; RR, 0.75; 95% CI, 0.62-0.91; $P = .003$). Lovastatin (20-40 mg daily) reduced LDL-C by 25% to 2.96 mmol/L (115 mg/dL) and increased HDL-C by 6% to 1.02 mmol/L (39 mg/dL). There were no clinically relevant differences in safety parameters between treatment groups.

Conclusions.—Lovastatin reduces the risk for the first acute major coronary event in men and women with average TC and LDL-C levels and below-average HDL-C levels. These findings support the inclusion of HDL-C in risk-factor assessment, confirm the benefit of LDL-C reduction to a target goal, and suggest the need for reassessment of the National Cholesterol Education Program guidelines regarding pharmacological intervention.

EPIDEMIOLOGICAL observations have demonstrated consistently a strong positive, continuous, independent, graded relation between plasma total cholesterol (TC) and the incidence of coronary heart disease (CHD). This relation covers a wide range of cholesterol concentrations, including those considered normal or mildly elevated.¹⁻³ In the Multiple Risk Factor Intervention Trial follow-up of screened men, 69% of deaths from CHD in the first 6 years of follow-up occurred in subjects with TC values between 4.71 and 6.83 mmol/L (182-264 mg/dL).⁴ In the first 16 years of the Framingham Heart Study, 40% of participants who developed a myocardial infarction had a TC level between 5.17 and 6.47 mmol/L (200-250 mg/dL).⁵

See also pp 1643 and 1659.

Large end point studies have demonstrated conclusively that effective cholesterol-lowering treatment can substantially reduce myocardial infarction and other coronary events. In the Scandinavian Simvastatin Survival Study

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the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor simvastatin reduced total mortality in patients with CHD by 30% because of a 42% reduction in deaths from CHD.⁵ Subsequently, pravastatin was shown to reduce fatal and nonfatal coronary events in patients with⁷ and without⁸ CHD. However, it is unknown whether benefit from reduction of low-density lipoprotein cholesterol (LDL-C) in patients without CHD (primary prevention) extends to individuals with average serum cholesterol levels, women, and older persons.

The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) targeted a cohort of generally healthy middle-aged and older men and women with average TC and LDL-C levels and with below-average high-density lipoprotein cholesterol (HDL-C) levels. The primary end point analysis was the incidence of first acute major coronary events, defined as fatal or nonfatal myocardial infarction, unstable angina, or sudden cardiac death. The inclusion of unstable angina was a unique feature of this study, and its inclusion as a primary end point reflects the increasing frequency of unstable angina as the initial presentation of CHD in the United States.⁹

METHODS

The design of the study has been described in detail previously.¹⁰ In summary, AFCAPS/TexCAPS was a randomized, double-blind, placebo-controlled primary prevention trial that included 6605 men and women and was conducted at 2 sites in Texas, Lackland Air Force Base in San Antonio ($n = 3737$) and University of North Texas Health Science Center in Fort Worth ($n = 2868$).

AFCAPS/TexCAPS was powered to investigate whether long-term lipid lowering with lovastatin would decrease the rate of first acute major coronary events compared with placebo during at least 5 years of follow-up in a cohort without clinical evidence of atherosclerotic cardiovascular disease and with average TC and LDL-C levels and below-average HDL-C levels. Unstable angina was prospectively defined and required new-onset exertional angina, accelerated or rest angina, or both, and at least 1 of the following: (1) electrocardiographic findings of at least 1-mm ST-segment changes and reversible defect on stress perfusion study, (2) angiographic findings of at least 90% epicardial vessel stenosis or at least 50% stenosis in the left main coronary artery (without exercise testing), or (3) at least 1-mm ST-segment changes with pain on electrocardiographic stress testing and/or rest electrocardiograph and evidence of at least 50% stenosis in a major epicardial vessel.

Secondary objectives were to investigate whether long-term treatment with lovastatin, compared with placebo, would decrease cardiovascular morbidity and mortality across the spectrum of clinical events by measuring the rates of 7 secondary end points, including 2 components of the primary end point. The secondary end points were (1) fatal or nonfatal coronary revascularization procedures, (2) unstable angina, (3) fatal or nonfatal myocardial infarction, (4) fatal or nonfatal cardiovascular events, (5) fatal or nonfatal coronary events, (6) cardiovascular mortality, and (7) CHD mortality.

The tertiary objectives were to investigate safety, that is, whether long-term treatment with lovastatin, compared with placebo, would result in similar rates of total mortality, noncardiovascular mortality (with subset analyses for unintentional or violent death and death from cancer), fatal and nonfatal cancer (excluding basal cell and squamous cell skin cancers), and discontinuation of medication because of adverse drug effects.

Participant Recruitment and Follow-up

Men aged 45 to 73 years and postmenopausal women aged 55 to 73 years who met the lipid entrance criteria and had no prior history, signs, or symptoms of definite myocardial infarction, angina, claudication, cerebrovascular accident, or transient ischemic attack were eligible for participation in the study. Lipid entry criteria (TC, 4.65-6.82 mmol/L [180-264 mg/dL]; LDL-C, 3.36-4.91 mmol/L [130-190 mg/dL]; HDL-C, ≤ 1.16 mmol/L [45 mg/dL] for men or ≤ 1.22 mmol/L [47 mg/dL] for women; and triglycerides, ≤ 4.52 mmol/L [400 mg/dL]) were to be met at both 4 and 2 weeks prior to randomization, with less than 15% difference in LDL-C values. In addition, participants with LDL-C values between 3.23 and 3.34 mmol/L (125-129 mg/dL) were included when the ratio of TC to HDL-C was more than 6.0. We excluded volunteers with uncontrolled hypertension, secondary hyperlipidemia, or type 1 or type 2 diabetes mellitus that was either managed with insulin or associated with a glycohemoglobin level of at least 10% (20% above the upper limit of normal). Additionally, volunteers were excluded if, according to the 1983 Metropolitan Life Insurance tables, they had a body weight of more than 50% greater than the desirable limit for height. All participants provided written informed consent.

The Data and Safety Monitoring Board and the institutional review boards of the 2 participating centers approved the consent form and protocol. The study was conducted under the supervision of a steering committee. Administrative, clinical, and data management was performed by a con-

tract research organization with staff at each site who were under the supervision of the clinical investigator. All personnel involved in participant care were blinded to treatment assignment and lipid levels.

Participants who met entrance criteria and completed a 12-week American Heart Association Step I diet run-in, including a 2-week placebo baseline run-in, were randomized to treatment with either lovastatin, 20 mg/d, or matching placebo. Participants in the lovastatin group were titrated to 40 mg/d if their LDL-C level was more than 2.84 mmol/L (110 mg/dL) at the 3-month study visit. The blind was maintained by titrating equal numbers of randomly selected placebo-group participants to 2 tablets daily. Throughout the trial, dietary reinforcement and other risk factor modification information was provided.

An extensive safety evaluation was performed prior to treatment, at 1 year, and at each subsequent year-end visit. Clinical visits were every 6 weeks for the first year. After 1 year, all randomized participants who continued the study drug were seen semiannually. Participants who discontinued use of the study drug were contacted on an annual basis for follow-up by questionnaire, which included an assessment of possible end point events and cancer occurrence. End point event information was compiled and adjudicated in the same manner for all participants, including those who had withdrawn from the study. An end point committee, blinded to treatment-group assignment and not involved in participant care, used prespecified criteria to adjudicate all end point events.

For analyses of changes in lipids, frozen serum samples obtained on the date of randomization before active treatment (day 1) and at the 1-year visit (post-treatment) were assayed at a specialized lipid laboratory at Johns Hopkins University, Baltimore, Md. This laboratory also analyzed lipids for the National Health and Nutrition Examination Survey (NHANES) III as noted by Sempos et al¹¹ (also P. S. Bachorik, PhD, unpublished data, 1997). The laboratory was standardized for lipid and lipoprotein measurements through the Centers for Disease Control and Prevention-National Heart, Lung, and Blood Institute Lipid Standardization Program.¹² All LDL-C values were calculated based on the Friedewald estimation.¹³

Statistical Analysis

The size of the sample was designed to provide 90% to 97% power to detect a 30% to 35% reduction in the number of participants with primary end point events by treatment with lovastatin. All analyses were performed on an inten-

tion-to-treat basis and all *P* values were 2-sided. A log-rank test, with study center and sex as stratification factors, was used to assess the effect of therapy on the rate of primary end point events. Analyses of relative reductions in risk resulting from lovastatin therapy were calculated using the Cox proportional hazards regression model that had study center and sex as stratification factors. The proportionality assumption was met for all Cox models. Cumulative incidence and interval estimates were calculated using the life-table method.

The effect of therapy on percent change in lipid parameters from baseline to 1 year was assessed using an analysis of variance model that included treatment, study center, and sex after first examining a model that also included the treatment-by-center and treatment-by-sex interaction effects. All participants with data at both baseline and 1 year were included.

The proportions of participants who discontinued therapy because of adverse events or had clinically important adverse events or laboratory abnormalities were compared between the 2 treatment groups using the Fisher exact test.

The trial was designed to continue until a total of 320 participants had experienced a first primary end point event or for a minimum of 5 years after the last participant was randomized, whichever occurred later. In addition to the final analysis, 2 interim analyses of the trial were planned for the points at which 120 and 240 participants, respectively, experienced the first primary end point event. A group sequential design was used with an early stopping rule, described previously,¹⁰ which preserved the type I error probability of .05. The critical values for finding statistical significance for 120, 240, and 320 participants with primary end points were .003, .016, and .044, respectively.

RESULTS

Early Termination for Efficacy

Following a review of the second interim analysis (data from 267 participants who had experienced a primary end point event), the Data and Safety Monitoring Board recommended that the trial be stopped early for efficacy. The voting members of the steering committee agreed unanimously on July 3, 1997, to accept the recommendation for early termination. The steering committee required that the participants and personnel continue to be blinded throughout the final visit of the study to provide unbiased assessment of all additional end point and safety information in the final analysis. End point status was determined for all but 1 active par-

ticipant within 3 months of the decision to stop the study (Figure 1).

Baseline Characteristics

Beginning May 30, 1990, and ending February 12, 1993, 6605 participants were randomized to treatment with lovastatin (2805 men and 499 women) or placebo (2803 men and 498 women). For comparison with the age- and sex-matched US population without clinical evidence of cardiovascular disease, the NHANES III percentile is presented for average baseline lipid levels.¹⁴ Baseline lipid levels were similar in both treatment groups; combined averages were as follows: mean (SD) TC, 5.71 (0.54) mmol/L (221 [21] mg/dL) (51st percentile); mean (SD) LDL-C, 3.89 (0.43) mmol/L (150 [17] mg/dL) (60th percentile); mean (SD) HDL-C, 0.94 (0.14) mmol/L (36 [5] mg/dL) for men and 1.03 (0.14) mmol/L (40 [5] mg/dL) for women (25th and 16th percentiles, respectively); and median (SD) triglycerides, 1.78 (0.86) mmol/L (158 [76] mg/dL) (63rd percentile). The 2 treatment groups were also balanced with respect to baseline demographics, risk factors, and medications (Table 1). A more detailed description of the baseline characteristics of the study cohort in comparison with the US NHANES III reference population is provided elsewhere.¹⁵

Adherence and Dropouts

The mean (SD) duration of follow-up was 5.2 (0.9) years (range, 0.2-7.2 years) for those treated with lovastatin and 5.2 (0.9) years (range, 0.1-7.2 years) in the placebo group. As assessed by pill counts, 99% of participants adhered to their study regimen for at least 75% of the time that they were receiving active treatment. Study drug regimens were maintained until trial termination by 2335 (71%) of the 3304 participants randomized to lovastatin and by 2081 (63%) of the 3301 randomized to placebo (Figure 1). Participants treated with placebo were more likely to be withdrawn from the study as a result of developing CHD or starting cholesterol-reducing medication (generally at the request of their primary care physician). The frequency of discontinuation for other reasons was similar between treatment groups.

Lipid Parameters

Lovastatin had a significant effect on changes in lipid levels from baseline (day 1) to posttreatment as assessed at 1 year ($P < .001$). Low-density lipoprotein cholesterol levels were reduced by 25%, TC levels were reduced by 18%, triglyceride levels were reduced by 15%, HDL-C levels were increased by 6%, and the ratios of TC to HDL-C and LDL-C to HDL-C were decreased by

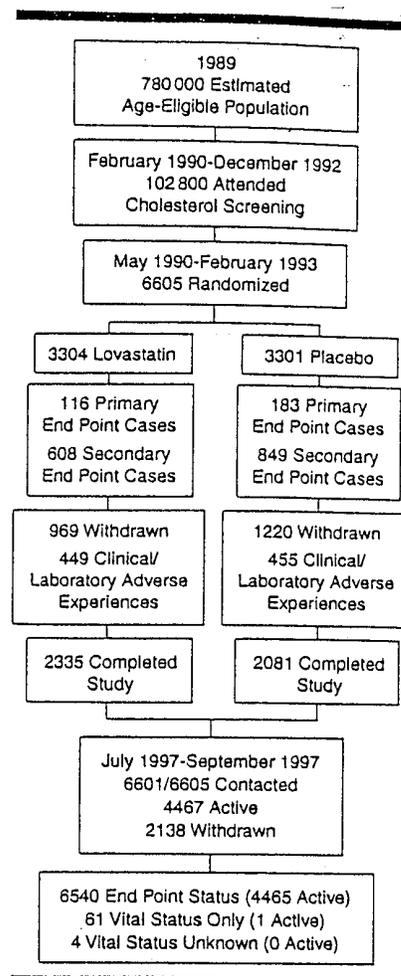


Figure 1.—Study chronology.

22% and 28%, respectively. By comparison, in the placebo group, there were small changes in lipid levels that were not clinically important (Figure 2). Treatment effects were similar in men and women (Table 2).

In the lovastatin group, 1657 participants (50%) were titrated from 20 mg/d to 40 mg/d, and of these, no participant was subsequently back-titrated. At 1 year, 1216 participants (42%) receiving lovastatin and 86 (3%) receiving placebo reached the study target for LDL-C values of no more than 2.84 mmol/L (110 mg/dL); 2334 participants (81%) receiving lovastatin and 350 (12%) receiving placebo reached an LDL-C level of 3.36 mmol/L (130 mg/dL) or less.

Efficacy End Points

Participants treated with lovastatin experienced a 37% lower incidence of the first acute major coronary event (primary end point defined as fatal or nonfatal myocardial infarction, unstable angina, or sudden cardiac death) than did those treated with placebo (Cox model 95% confidence interval, 21%-50%; $P < .001$).

Table 1.—Baseline Characteristics and Medications for Study Cohort by Treatment Group*

Baseline Characteristic	Placebo (N = 3301)	Lovastatin (N = 3304)
Men aged 45-73 y, No. (%)	2803 (85)	2805 (85)
Women aged 55-73 y, No. (%)	498 (15)	499 (15)
Age, mean (SD), y	58 (±7)	58 (±7)
Men	57 (±7)	58 (±7)
Women	63 (±5)	62 (±5)
≥65 y, No. (%)	701 (21)	715 (22)
Men	515 (18)	549 (20)
Women	186 (37)	166 (33)
Race, No. (%)		
White	2935 (89)	2925 (89)
Black	101 (3)	105 (3)
Hispanic	240 (7)	247 (7)
Weight, mean (SD), kg		
Men	86.4 (±11.36)	86.8 (±11.82)
Women	70.5 (±10.9)	70.9 (±10.9)
Body mass index, mean (SD), kg/m ²		
Men	27.0 (±3.0)	27.1 (±3.1)
Women	26.4 (±3.8)	26.4 (±3.5)
Blood pressure, mean (SD), mm Hg		
Systolic	138 (±17)	138 (±17)
Diastolic	78 (±10)	78 (±10)
Heart rate, mean (SD), beats/min	69 (±11)	69 (±11)
No. (%) who consume alcohol		
Men	1450 (52)	1366 (49)
Women	129 (26)	153 (31)
No. of drinks/wk, mean (SD)		
Men	5.9 (±6.3)	6.1 (±6.1)
Women	6.2 (±6.4)	6.3 (±6.2)
Women	3.0 (±3.5)	3.5 (±3.7)
NCEP CHD risk factors, No. (%)†		
Hypertension‡	729 (22)	719 (22)
Diabetes		
Non-insulin-treated diabetes	71 (2.0)	84 (3.0)
Non-insulin-treated diabetes or fasting blood glucose ≥6.99 mmol/L (126 mg/dL)	113 (3.4)	126 (3.8)
Current smoker	389 (12)	429 (13)
Family history of premature CHD	538 (16)	497 (15)
HDL-C <0.91 mmol/L (<35 mg/dL)	1146 (35)	1150 (35)
Medications, No. (%)		
Antihypertensives	695 (21.1)	661 (20.0)
ACE inhibitors	257 (7.8)	244 (7.4)
α-Blockers	67 (2.0)	68 (2.1)
β-Blockers	156 (4.7)	141 (4.3)
Calcium channel blockers	170 (5.1)	171 (5.2)
Diuretics	203 (6.1)	203 (6.1)
Estrogen with or without progestins§	137 (27.5)	155 (31.1)
Nonsteroidal anti-inflammatory drugs	445 (13.5)	494 (15.0)
Oral hypoglycemics	43 (1.3)	41 (1.2)
Thyroid replacement hormone	107 (3.2)	132 (4.0)
Aspirin	561 (17.0)	571 (17.3)

*NCEP indicates National Cholesterol Education Program; CHD, coronary heart disease; HDL-C, high-density lipoprotein cholesterol; and ACE, angiotensin-converting enzyme.

†All Air Force/Texas Coronary Atherosclerosis Prevention Study participants met National Cholesterol Education Panel criteria for age-related risk (age ≥45 years for men and ≥55 years for women).

‡Hypertension includes those reporting history of hypertension and/or those treated with antihypertensive agents for hypertension.

§Data are for women only.

A total of 116 participants treated with lovastatin compared with 183 in the placebo group had at least 1 primary end point event. Results of primary and secondary end point analyses are summarized in Table 3. Participants are counted only once within a specific end point analysis; however, a participant may be included in more than 1 analysis in Table 3 if they experienced different types of

end points, experienced an event that is comprised in more than 1 end point analysis (eg, the secondary end point, unstable angina, is also a component of the primary end point), or both.

Life-table plots (Figure 3) illustrate a difference between treatment groups beginning in the first year of treatment and continuing throughout the remainder of the study. These show the cumu-

lative incidence and the number of participants at risk. By treatment year, the average risk reduction in the primary end point (acute major coronary events) with lovastatin was 43% in the first year and 12%, 30%, 41%, and 49% in the second, third, fourth, and fifth years, respectively. These yearly rates were not statistically different from each other.

For the primary end point, the event rate for subjects receiving lovastatin averaged 7 per 1000 patient-years and was 37% less than the 11 per 1000 patient-years observed for the placebo group. These rates correspond to cumulative incidences of 4.0% and 6.8% for the lovastatin and placebo groups, respectively, during the study period ($P < .001$).

For secondary end points, treatment with lovastatin resulted in significant, consistent benefit compared with placebo, including 33% reduction in revascularizations ($P = .001$), 32% reduction in unstable angina ($P = .02$), and 40% reduction in the incidence of fatal or nonfatal myocardial infarction ($P = .002$). For coronary and cardiovascular events (total fatal or nonfatal), treatment with lovastatin resulted in significant ($P = .006$ and $P = .003$, respectively) reductions of 25% compared with placebo. The category of cardiovascular events included all atherosclerotic cardiovascular events, as specified by the end point definitions, including stable angina, thrombotic cerebrovascular accidents, transient ischemic attacks, and peripheral arterial vascular disorders. For the secondary end points fatal cardiovascular events and fatal CHD events, there were too few events to perform survival analysis based on prespecified criteria (Table 3).

Figure 4 summarizes the effect of treatment on the rate of the first primary end point event for predefined factors: sex, age (older defined as above the median by sex: >57 years for men and >62 years for women), history of hypertension, active cigarette smoking, family history of CHD, baseline LDL-C, and baseline HDL-C. Treatment group, as well as each of these factors, demonstrated a significant association with risk (eg, smoking was positively associated with first acute major coronary events). Baseline triglyceride level ($P = .98$) and history of diabetes ($P = .34$, 155 participants with diabetes) were not significant predictors of outcome. Within a factor, the numerical rate of first acute major coronary events was similar among those treated with lovastatin in the CHD positive-risk subgroup and those treated with placebo who did not have the CHD risk factor (eg, lovastatin-treated smokers had rates similar to placebo-treated nonsmokers).

The effect of treatment with lovastatin on the rate of first acute major coronary

Table 2.—Treatment Effects on Plasma Lipid Levels at 1 Year*

Lipid	Placebo, Mean or Median (SD)		Lovastatin, Mean or Median (SD)	
	mmol/L	mg/dL	mmol/L	mg/dL
Mean TC	5.90 (±0.72)	228 (±28)	4.75 (±0.62)	184 (±24)
Men	5.84 (±0.70)	226 (±27)	4.71 (±0.60)	182 (±23)
Women	6.20 (±0.75)	240 (±29)	4.97 (±0.65)	192 (±25)
Mean LDL-C	4.04 (±0.63)	156 (±25)	2.96 (±0.52)	115 (±20)
Men	4.02 (±0.63)	156 (±24)	2.96 (±0.51)	114 (±20)
Women	4.16 (±0.66)	161 (±26)	3.00 (±0.57)	116 (±22)
Median triglycerides	1.84 (±0.93)	163 (±82)	1.61 (±0.82)	143 (±73)
Men	1.82 (±0.90)	161 (±80)	1.59 (±0.79)	141 (±70)
Women	2.05 (±1.13)	181 (±100)	1.84 (±0.91)	163 (±81)
Mean HDL-C	0.97 (±0.20)	38 (±8)	1.02 (±0.21)	39 (±8)
Men	0.96 (±0.20)	37 (±8)	1.00 (±0.20)	39 (±8)
Women	1.05 (±0.21)	41 (±8)	1.11 (±0.21)	43 (±8)

*Data are for paired samples. Sample sizes are 2387-2495 for men and 420-439 for women. TC indicates total cholesterol; LDL-C, low-density lipoprotein cholesterol; and HDL-C, high-density lipoprotein cholesterol.

events was numerically greater in women than in men (46% vs 37% reduction in relative risk); however, the actual number of women who had a primary end point event was small (20 of 997), and there were no statistical differences in treatment effects between sexes. None of the subgroups differed significantly in treatment benefit (eg, treatment benefit was not different for participants with hypertension compared with participants without hypertension and benefit was not different for smokers compared with non-smokers, since none of the treatment-by-subgroup interactions were significant). There were no significant interactions between treatment and either LDL-C ($P = .99$) or HDL-C ($P = .16$) when evaluated as continuous variables in a model with the other associated covariates. No threshold to benefit was observed in LDL-C and HDL-C ranges studied.

In addition to the protocol-specified rates that considered time to the first event for withdrawn and active participants, we also analyzed the total number of events experienced by active and withdrawn participants including multiple events of the same type (eg, multiple myocardial infarctions experienced by a participant). There were 142 and 209 acute major coronary events in participants treated with lovastatin and placebo, respectively, with rates of 8 and 12 per 1000 patient-years, respectively. There were 137 and 195 coronary revascularizations (8 and 11 per 1000 patient-years) in participants treated with lovastatin and placebo, respectively. Combining acute major coronary events and coronary revascularizations, there were 279 and 404 (16 and 23 per 1000 patient-years) in the lovastatin and placebo groups, respectively. If 1000 men and women were treated with lovastatin for 5 years, approximately 19 acute major coronary events (12 myocardial infarctions and 7 presentations of unstable an-

gina) and 17 coronary revascularizations could be prevented.

Tolerability and Safety

Overall, treatment with lovastatin was well tolerated. Mortality and incidence of fatal and nonfatal cancer (tertiary end points to assess safety) did not demonstrate any difference between treatment groups. The overall mortality rate was similar in each group, with 80 deaths among participants treated with lovastatin and 77 deaths among participants treated with placebo (4.6 and 4.4 per 1000 patient-years in participants treated with lovastatin and placebo, respectively). The majority of deaths had noncardiovascular causes. There were 17 deaths from cardiovascular causes among participants treated with lovastatin and 25 in the placebo group (1.0 and 1.4 per 1000 patient-years in lovastatin and placebo groups, respectively) and 63 deaths from noncardiovascular causes among participants treated with lovastatin and 52 in the placebo group (3.6 and 3.0 per 1000 patient-years among participants treated with lovastatin and placebo, respectively). There were 4 deaths from trauma, 3 in the placebo group and 1 in the lovastatin group.

The overall incidence of fatal and nonfatal cancer, excluding nonmelanoma skin cancers, was 15.1 and 15.6 per 1000 patient-years (252 and 259 cases) among participants treated with lovastatin and placebo, respectively. The most frequently reported tertiary end point cancers are summarized in Table 4. The number of participants reporting nonmelanoma skin cancers, predominantly diagnoses of basal cell and squamous cell cancers, was 250 (7.6%) in the lovastatin group and 243 (7.4%) in the placebo group.

The number of participants with any adverse experience that led to discontinuation was 449 (13.6%) in the group treated with lovastatin and 445 (13.8%) in the pla-

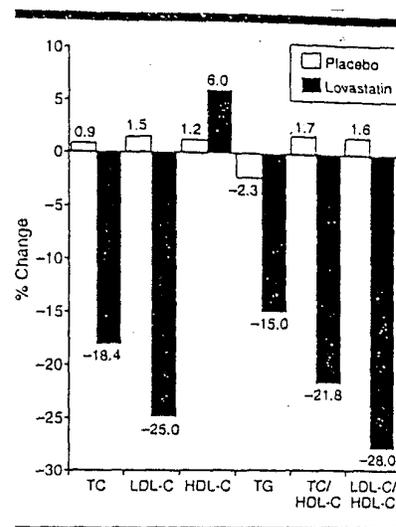


Figure 2.—Comparison of percent change in lipid parameters from baseline to 1 year by treatment group. All differences between treatment groups were significant ($P < .001$). TC indicates total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; and TG, triglycerides.

cebo group. Both treatment groups had similar numbers of adverse experiences that were considered serious (ie, life-threatening, causing death or a permanent disability, resulting in or prolonging hospitalization, or diagnosis of any cancer), 1131 (34.2%) and 1126 (34.1%) in the groups treated with lovastatin and placebo, respectively. One participant from each treatment group was unblinded after discontinuation of the study drug and before the end of the study. A placebo-treated patient, who discontinued therapy because of idiopathic hepatitis, was unblinded because a primary care physician advised beginning lipid-reducing treatment. Another participant was unblinded when he developed study drug-related Stevens-Johnson syndrome after approximately 9 months of treatment with lovastatin. Following appropriate treatment and within 2 weeks of discontinuing lovastatin use, this participant recovered. No other lovastatin-related, life-threatening, serious, adverse experiences were reported.

Consecutive elevations of more than 3 times the upper limit of normal in either aspartate aminotransferase (AST) or alanine aminotransferase (ALT) were rare, and the incidence was similar in both treatment groups (18 [0.6%] of 3242 participants and 11 [0.3%] of 3248 receiving lovastatin and placebo, respectively). (Not all participants had postrandomization tests.) Examining these elevations by final dose for those who were titrated also revealed no significant trends. Consecutive elevations of more than 3 times the upper limit of the normal range in

Table 3.—Efficacy End Points*

End Points	Placebo (N = 3301)		Lovastatin (N = 3304)		Relative Risk (95% CI)†	P Value‡
	n	Rate§	n	Rate§		
Primary end point: acute major coronary events defined as fatal or nonfatal myocardial infarction, unstable angina, or sudden cardiac death	183	10.9	116	6.8	0.63 (0.50-0.79)	<.001
Secondary end points						
Revascularizations	157	9.3	106	6.2	0.67 (0.52-0.85)	.001
Unstable angina	87	5.1	60	3.5	0.68 (0.49-0.95)	.02
Fatal and nonfatal myocardial infarction	95	5.6	57	3.3	0.60 (0.43-0.83)	.002
Fatal and nonfatal cardiovascular events	255	15.3	194	11.5	0.75 (0.62-0.91)	.003
Fatal and nonfatal coronary events	215	12.8	163	9.6	0.75 (0.61-0.92)	.006
Fatal cardiovascular events	25	1.4	17	1.0
Fatal CHD events	15	0.9	11	0.6

*CI indicates confidence interval; CHD, coronary heart disease; and ellipses, too few for survival analysis.
 †To calculate risk reduction, subtract relative risk from 1. Relative risk and confidence interval calculated with Cox proportional hazards model.

‡P value calculated with log-rank test and adjusted for the interim analysis for the primary end point only. P values for secondary end points are unadjusted.

§Rate per 1000 patient-years.

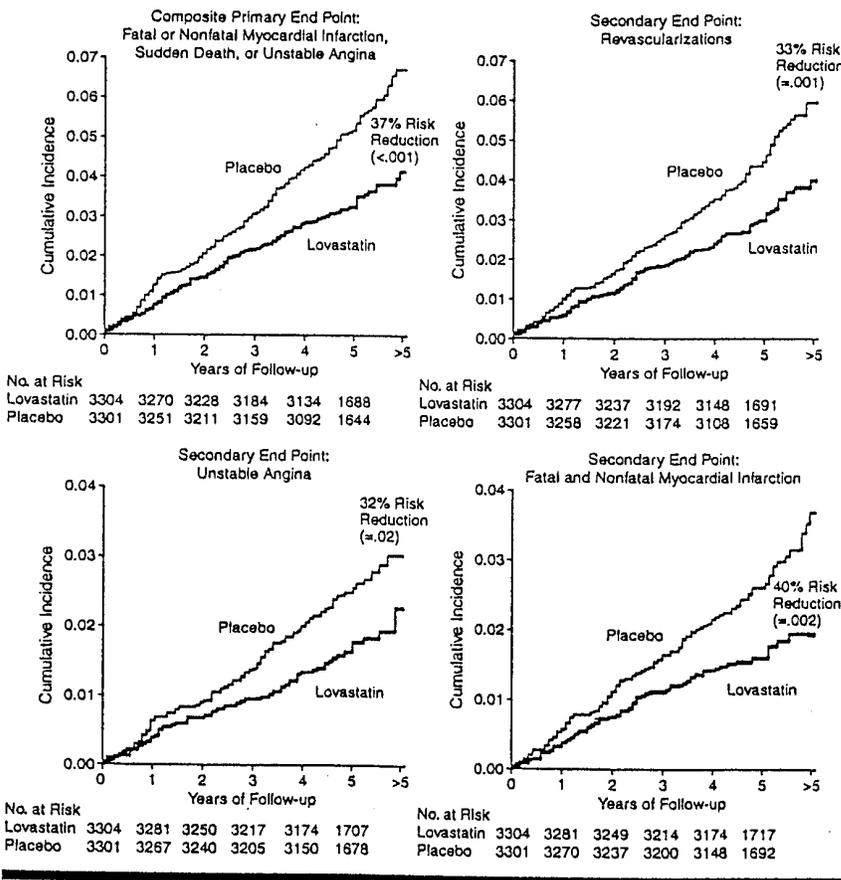


Figure 3.—Cumulative incidence of primary end points (composite of fatal and nonfatal myocardial infarction, sudden death, and unstable angina) and secondary end points (fatal and nonfatal myocardial infarction, unstable angina, and coronary revascularizations) by treatment group.

either AST or ALT were reported in 11 (0.7%) of 1585 participants and 7 (0.4%) of 1657 receiving lovastatin, 20 mg/d, and lovastatin, 40 mg/d, respectively. (Unlike the other comparisons of randomized treatment groups, the dose comparisons are of nonrandomized groups.)

The number of participants with any drug-attributable AST elevation above the upper limit of normal was similar between treatment groups (33 [1.0%] and 34 [1.0%] in the groups treated with lovastatin and placebo, respectively); however, the number with any ALT drug-

related elevations was significantly ($P = .003$) higher in the group treated with lovastatin (110 [3.3%] and 70 [2.1%] for lovastatin and placebo, respectively). The percentage of participants reporting myalgia leading to discontinuation was 0.3% for both treatment groups.

Creatine kinase (CK) elevations greater than 10 times the upper limit of normal were rare, and the incidence was similar in both treatment groups (11 [0.7%] of 1586, 10 [0.6%] of 1657, and 21 [0.6%] of 3248 receiving lovastatin, 20 mg/d, lovastatin, 40 mg/d, and placebo, respectively). (Denominators are participants having postrandomization tests; unlike the other comparisons of randomized treatment groups, the dose comparisons are of nonrandomized groups.) There were no cases of myopathy (defined as muscle symptoms accompanied with CK elevations >10 times the upper limit of normal). There were 3 cases of rhabdomyolysis; 2 cases occurred in placebo-treated participants, and 1 case occurred in a participant treated with lovastatin following surgery for prostate cancer.

COMMENT

In AFCAPS/TexCAPS, treatment with lovastatin resulted in a 37% reduction ($P < .001$) in the risk for first acute major coronary events, defined as fatal or nonfatal myocardial infarction, unstable angina, or sudden cardiac death. The study was originally powered to detect a 30% difference between the treatment groups after 320 participants had experienced a primary event; however, the benefit after the second interim analysis (with 267 participants experiencing an event) was of such magnitude that the predefined conditions for stopping the study were met. The differences between the 2 treatment groups appeared as early as 1 year (40 participants with events in the placebo group vs 23 treated with lovastatin).

Analysis of secondary end points confirmed that the composite primary end point was representative of its components: lovastatin therapy significantly reduced the risk for fatal or nonfatal myocardial infarction by 40% and unstable angina by 32%. Risk reduction with lovastatin across the spectrum of cardiovascular events was further confirmed by a 33% risk reduction in the need for revascularizations ($P = .001$) and 25% risk reductions in both total cardiovascular and total coronary events ($P \leq .006$). The number of deaths in AFCAPS/TexCAPS was low (157 total deaths; 42 cardiovascular deaths, of which 26 were CHD deaths), and as predicted,¹⁰ the study was not adequately powered to detect treatment differences in the low frequency end points of cardiovascular mortality and CHD mortality.

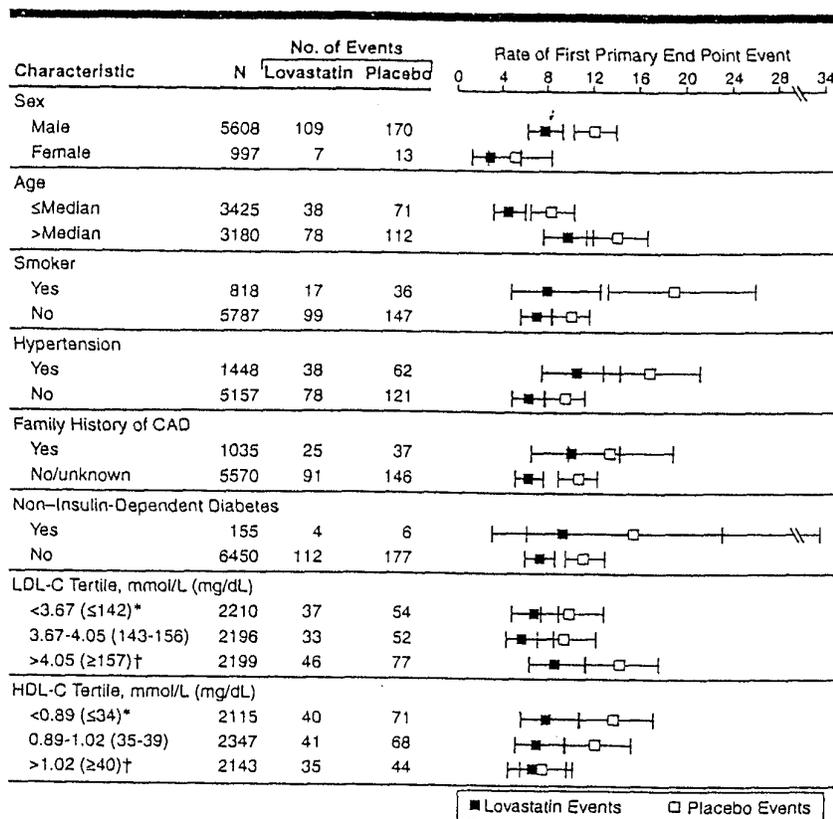


Figure 4.—Comparison of primary end point event rates (per 1000 patient-years at risk) and 95% confidence intervals by treatment within demographic and risk factor subgroups at baseline. CAD indicates coronary artery disease; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; asterisks, bottom tertile; and daggers, top tertile.

Primary end point risk reduction with lovastatin was apparent across all baseline LDL-C tertiles with no threshold to benefit observed across baseline LDL-C levels (range, 2.33-6.08 mmol/L [90-235 mg/dL]). Benefit was also apparent within subgroups, including women, men older than the median age (>57 years), women older than the median age (>62 years), and for participants with additional CHD risk factors. As observed in secondary prevention trials,^{6,7} female AFCAPS/TextCAPS participants responded to treatment as well as, if not better than, male participants. Lovastatin appeared to attenuate (Figure 4) the risk conferred by sex, age, family history, hypertension, smoking, LDL-C levels, and below-average HDL-C levels.

AFCAPS/TextCAPS is, to our knowledge, the first primary prevention trial to demonstrate risk reduction from lipid modification in generally healthy men and women without clinical evidence of cardiovascular disease and with average TC and LDL-C levels and below-average HDL-C levels. The baseline means for TC and LDL-C (5.71 mmol/L [221 mg/dL] and 3.89 mmol/L [150 mg/dL], respectively) are similar to the average levels for age- and

sex-matched individuals without cardiovascular disease in NHANES III.¹⁴ Mean baseline HDL-C values (0.94 mmol/L [36 mg/dL] for men and 1.03 mmol/L [40 mg/dL] for women) were below the average for the NHANES III reference population; however, the HDL-C range for the cohort is 0.47 to 1.58 mmol/L (18-61 mg/dL). Only 17% of AFCAPS/TextCAPS participants would have met current National Cholesterol Education Program (NCEP) guidelines for drug therapy (TC, ≥ 6.21 mmol/L [240 mg/dL]; LDL-C, ≥ 4.14 mmol/L [160 mg/dL]; and 2 or more risk factors) and 32% would not have a fasting lipid profile measurement by current NCEP guidelines (TC, < 6.21 mmol/L [240 mg/dL] without 2 or more risk factors).¹⁶

Earlier primary CHD prevention studies included only middle-aged men with very high TC and LDL-C concentrations.^{8,17,18} In the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT),¹⁷ the upper age limit was 59 years (mean age, 47.8 years), and the mean TC, LDL-C, and HDL-C concentrations at baseline (prior to diet therapy) were 7.55 mmol/L (292 mg/dL), 5.59 mmol/L (216 mg/dL),

Table 4.—Treatment Group Comparison of Participants With Cancer

Cancer	Placebo (N = 3301)	Lovastatin (N = 3304)	P Value*
All fatal and nonfatal most frequently reported	259	252	.75
Prostate	108	109	>.99
Melanoma	27	14	.04
Colon	20	25	.55
Lung	17	22	.52
Lymphoma	11	12	>.99
Bladder	11	12	>.99
Breast	9	13	.52

*P values are for between-treatment-group differences.

and 1.16 mmol/L (45 mg/dL), respectively. In the Helsinki Heart Study,¹⁸ the upper age limit was 55 years (mean age, 47.3 years), and the mean baseline lipid values for TC, LDL-C, and HDL-C were 6.98 mmol/L (270 mg/dL), 4.86 mmol/L (188 mg/dL), and 1.22 mmol/L (47 mg/dL), respectively. Likewise, the West of Scotland Coronary Prevention Study (WOSCOPS)⁸ was limited to middle-aged men; the upper age limit was 64 years (mean age, 55.2 years) and the mean baseline lipid values for TC, LDL-C, and HDL-C were 7.03 mmol/L (272 mg/dL), 4.97 mmol/L (192 mg/dL), and 1.14 mmol/L (44 mg/dL), respectively. All of these trials reported statistically significant reductions in the primary end point of the combined incidence of nonfatal myocardial infarction and CHD death; the risk reductions were 19% in LRC-CPPT,¹⁷ 34% in the Helsinki Heart Study,¹⁸ and 31% in WOSCOPS.⁸ Extrapolation of the results of these 3 trials of middle-aged men with moderate-to-severe hypercholesterolemia to the general population with lower TC and LDL-C levels, to women, and to older individuals has remained a matter of debate.¹⁹

Results from AFCAPS/TextCAPS are consistent with findings from previous primary prevention trials with high-risk cohorts^{8,17,18}; however, treatment with lovastatin in AFCAPS/TextCAPS extends the benefit to a lower-risk segment of the general population. In contrast with earlier studies, the AFCAPS/TextCAPS cohort included Hispanics, African Americans, and older persons (baseline mean age, 58.2 years; upper limit, 73 years; 21% older than 65 years).¹⁵ The AFCAPS/TextCAPS trial is also the first large-scale primary prevention trial of LDL-C reduction to include a substantial number of women (997 of the 6605 participants randomized). The cohort was also generally healthy, with only 12% active smokers, 22% with hypertension, and 2% with diabetes.

Inclusion of unstable angina in the primary end point analysis resulted from the observations that hospital admissions for diagnostic and surgical intervention fol-

lowing unstable angina were increasing while myocardial infarction, as the cause for initial presentation, was decreasing.⁹ AFCAPS/TexCAPS data indicate that approximately equal numbers of patients initially present with unstable angina and nonfatal myocardial infarction.

The issue of safety and drug tolerance is particularly important in primary prevention, where the risks of long-term drug therapy must be considered in the context of achievable benefit. AFCAPS/TexCAPS provides long-term safety data on a cohort treated up to 7 years with lovastatin. The withdrawal rate was comparable to that seen in other primary prevention trials,^{3,18} and frequency of withdrawal for adverse experiences was similar in the treatment groups.

The results confirm and, by longer treatment duration, extend those from the Expanded Clinical Evaluation of Lovastatin (EXCEL) trial,²⁰ in which 8245 participants were studied for 1 year using regimens representative of the entire lovastatin dosage range. Both EXCEL and AFCAPS/TexCAPS demonstrated no cases of lovastatin-induced myopathy, no significant differences between treatment with lovastatin, 20 mg/d, and placebo in the number of participants experiencing clinically important elevations in transaminase concentrations (>3 times the upper limit of normal) and CK elevations (10 times the upper limit of normal). Furthermore, AFCAPS/TexCAPS provides reassuring data about long-term treatment with

lovastatin, cancer rates, and traumatic deaths, and confirms the safety shown in other large long-term studies with simvastatin and pravastatin.^{6,8}

The AFCAPS/TexCAPS results indicate that cholesterol reduction with lovastatin for men and women with average TC and LDL-C levels could potentially improve quality of life by extending CHD event-free survival and conserving invasive treatments. The economic impact of treatment requires resource utilization analyses that consider the cost of long-term treatment, hospitalization, and the cost of diagnostic and therapeutic intervention.

These findings support and extend the recommendations of the NCEP to include HDL-C in addition to TC in initial risk-factor assessment, target LDL-C reduction as the primary goal of therapy, and, if necessary, titrate treatment to achieve an LDL-C goal level. The benefit seen in all subgroups and across all tertiles of LDL-C in AFCAPS/TexCAPS occurred with 25% LDL-C reduction and suggests that treatment with lovastatin could be considered in asymptomatic participants at relatively low risk for CHD and with average TC and LDL-C levels (>3.36 mmol/L [130 mg/dL]) and below-average HDL-C levels (<1.29 mmol/L [50 mg/dL]).

AFCAPS/TexCAPS demonstrates that lovastatin, 20 to 40 mg/d, can reduce the risk for first acute major coronary events in men and women with average or mildly elevated TC and LDL-C levels

and below-average HDL-C levels. Using NHANES III survey data,¹⁴ approximately 8 million Americans without documented cardiovascular disease meet the age and lipid criteria of AFCAPS/TexCAPS. Assuming that only 17% of the reference population would qualify for drug treatment by current NCEP guidelines, we estimate that 6 million Americans currently not recommended for drug treatment may benefit from LDL-C reduction with lovastatin. These results support the inclusion of HDL-C measurement in initial risk-factor assessment and suggest reassessment of NCEP guidelines regarding pharmacological intervention.

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Attachment 5
EXCEL Arch Intern Med Publication

Expanded Clinical Evaluation of Lovastatin (EXCEL) Study Results

I. Efficacy in Modifying Plasma Lipoproteins and Adverse Event Profile in 8245 Patients With Moderate Hypercholesterolemia

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• In the Expanded Clinical Evaluation of Lovastatin (EXCEL) Study, a multicenter, double-blind, diet- and placebo-controlled trial, we evaluated the efficacy and safety of lovastatin in 8245 patients with moderate hypercholesterolemia. Patients were randomly assigned to receive placebo or lovastatin at a dosage of 20 mg once daily, 40 mg once daily, 20 mg twice daily, or 40 mg twice daily for 48 weeks. Lovastatin produced sustained, dose-related ($P < .001$) changes as follows (for dosages of 20 to 80 mg/d): decreased low-density lipoprotein-cholesterol level (24% to 40%), increased high-density lipoprotein-cholesterol level (6.6% to 9.5%), decreased total cholesterol level (17% to 29%), and decreased triglyceride level (10% to 19%). The National Cholesterol Education Program's low-density lipoprotein-cholesterol level goal of less than 4.14 mmol/L (160 mg/dL) was achieved by 80% to 96% of patients, while the less than 3.36 mmol/L (130 mg/dL) goal was achieved by 38% to 83% of patients. The difference between lovastatin and placebo in the incidence of clinical adverse experiences requiring discontinuation was small, ranging from 1.2% at 20 mg twice daily to 1.9% at 80 mg/d. Successive transaminase level elevations greater than three times the upper limit of normal were observed in 0.1% of patients receiving placebo and 20 mg/d of lovastatin, increasing to 0.9% in those receiving 40 mg/d and 1.5% in those receiving 80 mg/d of lovastatin ($P < .001$ for trend). Myopathy, defined as muscle symptoms with a creatine kinase elevation greater than 10 times the upper limit of normal, was found in only one patient (0.1%) receiving 40 mg once daily and four patients (0.2%) receiving 80 mg/d of lovastatin. Thus, lovastatin, when added after an adequate trial of a prudent diet, is a highly effective and generally well-tolerated treatment for patients with moderate hypercholesterolemia.

(*Arch Intern Med.* 1991;151:43-49)

Lovastatin, a potent and highly effective inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase, suppresses hepatic cholesterol synthesis¹ and upregulates the number of hepatic low-density lipoprotein (LDL) receptors.² The increase in the receptor-mediated removal of LDL from plasma accounts for the large reductions in LDL-cholesterol level achieved with lovastatin. Studies of the efficacy of lo-

statin in modifying plasma lipid and lipoprotein level have primarily involved patients with heterozygous familial or other severe forms of hypercholesterolemia,^{3,4} many of whom required a dose of 80 mg/d during extended treatment.⁵

In early short-term clinical trials (<6 months), lovastatin was well tolerated, with few adverse effects attributable to the drug.^{3,4} During extended, uncontrolled, open-label, and compassionate-use studies, elevations in serum transaminase levels greater than three times the upper limit of normal (ULN) were reported in 1.9% of adult patients who received lovastatin for at least 1 year.⁶ Myopathy, arbitrarily defined as elevations in serum creatine kinase (CK) level greater than 10 times the ULN with associated muscle symptoms, was reported in 0.5% of patients, the majority of whom were concomitantly receiving cyclosporine, gemfibrozil, or niacin.⁶

The present study was undertaken to evaluate further the efficacy of lovastatin in patients with moderate hypercholesterolemia and to define the relationship, if any, among treatment, dose, and duration of treatment for adverse effects. Special emphasis was placed on abnormal serum transaminase levels, muscle symptoms associated with CK level elevations, and abnormalities of the human lens. The ophthalmologic findings from this study, presented in separate reports,^{10,11} show no detectable effect of lovastatin on the lens after 48 weeks of treatment.

To obtain a sample typical of the majority of patients likely to be treated with a cholesterol-lowering drug, patients selected for enrollment had moderate hypercholesterolemia (total cholesterol level, <7.76 mmol/L [<300 mg/dL]). Treatment groups were large to permit sensitive comparisons for events of low frequency, while the maintenance of a parallel placebo group and fixed doses of lovastatin for the 48-week study facilitated assessment of treatment effects related to dose and duration of treatment.

PATIENTS AND METHODS

The methods and design of this study have been previously described in detail.¹²

Patient Selection

Investigators from 362 clinical sites in the continental United States participated in this multicenter study. Patients with primary hypercholesterolemia who were 18 to 70 years old were considered for enrollment. Fasting plasma lipid and lipoprotein level entry criteria were total cholesterol level between 6.21 and 7.76 mmol/L (240 to 300 mg/dL), LDL-cholesterol level of 4.14 mmol/L (160 mg/dL) or higher, and triglyceride levels lower than 3.95 mmol/L (350 mg/dL). Women with childbearing potential were excluded, as were patients who had impaired hepatic or renal function, unstable medical conditions, and diabetes mellitus requiring insulin or oral hypoglycemic

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From the Lipid Research Clinic, Oklahoma Medical Research Foundation, Oklahoma City (Dr Bradford); Merck Sharp & Dohme Research Laboratories, West Point, Pa (Drs Shear, Chremos, and Gould, Mr Hesney, and Ms Langendorfer); Lipid and Arteriosclerosis Prevention Clinic, University of Kansas, Kansas City (Dr Dujovne); Clinical Research International Inc, Research Triangle Park, NC (Ms Downton and Drs Higgins and Hurley); Department of Pediatrics, Louisiana State University Medical Center, New Orleans (Dr Franklin); Department of Medicine, State University of New York Health Science Center at Syracuse (Dr Nash); Department of Medicine, Baylor College of Medicine, Houston, Tex (Dr Pool); and Center for Aging, University of Alabama at Birmingham (Dr Schnaper).

Reprint requests to the Lipid Research Clinic, Oklahoma Medical Research Foundation, 825 Northeast 13th St, Oklahoma City, OK 73104 (Dr Bradford).

therapy. All patients gave written informed consent following approval of the protocol by the appropriate institutional review board.

Experimental Design

The protocol excluded concomitant use of other lipid-modifying agents. Lipid and lipoprotein measurements were obtained after at least 4 weeks on an American Heart Association Step I or more restrictive diet and 2 weeks before scheduled randomization. Patients who met the entry criteria were randomly assigned to one of five parallel treatment groups: placebo or 20 mg of lovastatin with the evening meal, 40 mg of lovastatin every evening, 20 mg of lovastatin with the morning and evening meals, or 40 mg of lovastatin twice daily. Patients, investigators, and study staff were "blinded" to treatment group assignment. Patients were to continue on their prerandomization lipid-lowering diet and to take study medication for 48 weeks. Return visits were scheduled every 6 weeks for clinical and laboratory assessments. Laboratory tests were performed by SmithKline Beecham Laboratories (Clinical Trials Division, Van Nuys, Calif). Based on responses to a general query and self-reports, changes in a patient's health status that occurred after randomization were recorded and considered adverse experiences; investigators blindly rated the suspected causal relationship of the adverse experience to the study drug.

Lipid (total cholesterol and triglyceride) and lipoprotein (LDL-cholesterol and high-density lipoprotein [HDL]-cholesterol) levels were determined by standard methods¹² every 12 weeks after randomization. Blood samples were collected by venipuncture while the patients, who had fasted overnight, were seated. The central laboratory met the standardization criteria of the Centers for Disease Control, Atlanta, Ga, for total and HDL-cholesterol analyses. Results from split-sample analyses indicated that triglyceride determinations were overestimated by 12% (mean) and that the calculated mean for LDL-cholesterol was underestimated by 2%. This measurement bias was inconsequential for treatment comparisons and changes relative to baseline.

The laboratory safety panel, which was scheduled every 6 weeks after randomization, included measurements for serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), CK, creatinine, total bilirubin, alkaline phosphatase, and fasting glucose. Hematologic determinations included measurements of hemoglobin, hematocrit, white blood cell count with differential count, and platelet count. Preset criteria were used for retesting and withdrawal of patients who had elevated ALT, AST, or CK levels.¹²

Statistical Methods

All data management and statistical analyses were performed by the coordinating center (Clinical Research International Inc, Research Triangle Park, NC).

Efficacy Analyses

The trial was designed to address several specific questions concerning the efficacy of lovastatin in modifying plasma lipid and lipoprotein levels: (1) Does therapy with 20 mg once daily of lovastatin differ from that with placebo? (2) Does therapy with 40 mg once daily of lovastatin differ from that with 20 mg twice daily? (3) Do higher total daily dosages (20 mg vs 40 mg vs 80 mg) of lovastatin progressively increase its efficacy?¹²

The percentage change from baseline for each lipid and lipoprotein determination was used to test for treatment group differences. A patient's baseline value was the mean of two prerandomization measurements, and the mean of up to four measurements was used to determine postrandomization levels. The results reported herein are for all patients randomized, but similar results were obtained when analyses were performed with the use of only those patients (approximately 83%) who met the protocol requirements. Between 1452 (88%) and 1497 (90%) patients in each treatment group had both a baseline and at least one LDL-cholesterol postrandomization value.

Patients withdrawn from the trial for adverse clinical experiences or lack of therapeutic effect and those who had no postrandomization

lipid value were included in the analysis by the assignment of rank scores.¹³ An analysis of variance on ranks (ranking without regard to investigator or treatment) was used with investigator and treatment group as model effects. $P < .05$ was considered statistically significant.

As an additional description of LDL-cholesterol level response, the proportion of patients who achieved the National Cholesterol Education Program (NCEP) target levels at week 48 is presented. The NCEP guidelines set LDL-cholesterol level treatment goals for two subgroups of patients with high-risk LDL-cholesterol levels: those who have coronary heart disease (CHD) or at least two other CHD risk factors (LDL-cholesterol level, < 3.36 mmol/L [< 130 mg/dL]) and those without CHD and less than two other CHD risk factors (LDL-cholesterol level, < 4.14 mmol/L [< 160 mg/dL]).¹⁴

Safety Analyses

All patients randomized were also included in safety analyses. All information collected was included, and missing data were not imputed. Hypothesis testing was performed to determine statistically significant ($P < .05$) differences among treatment groups in the incidence of the primary end points: confirmed (two successive) transaminase level elevations (ALT or AST) that were greater than three times the ULN and muscle symptoms (myalgia or muscle weakness) with a CK level elevation greater than 10 times the ULN. These cutpoints were selected to permit direct comparison with earlier studies of lovastatin and, for AST and ALT, to reflect conventions proposed for the evaluation of hepatotoxicity.¹⁵ Actuarial life-table methods were applied to calculate treatment group incidences with the use of cumulative survival functions,¹⁶ which were compared among treatment groups by a trend test application¹⁷ of the log-rank method.¹⁸ The trend tests compared the placebo group and the groups receiving daily doses of lovastatin of 20 mg, 40 mg (groups receiving 40 mg every evening and 20 mg twice daily combined), and 80 mg.

Variation in the occurrence of common ($> 1\%$ in any group) clinical adverse experiences among treatment groups beyond that expected by chance alone was evaluated with the use of 95% confidence intervals. Due to the many different kinds of adverse experiences reported, we identified instances where the range of the proportion of patients in each group who were affected by an adverse experience exceeded the 95th percentile of the range that would be expected assuming homogeneity of adverse experiences among treatment groups (ie, binomial samples with a common rate parameter generated by the parent distribution with parameters $n = 1650$, the approximate sample size in each treatment group, and p , the proportion of all patients who had the adverse experience).¹⁹ Each adverse experience for which the range in proportions expected among treatment groups exceeded the 95% confidence interval was then inspected for patterns suggestive of a treatment effect, ie, higher proportions of affected individuals in the lovastatin groups compared with the placebo group.

RESULTS

Patient Characteristics at Baseline, Compliance, and Study Completion

A total of 8245 patients were randomized to treatment. The treatment groups were of similar size, with 1642 to 1663 patients in each of the five groups. Patient characteristics evaluated at baseline and reported in detail elsewhere¹² were very similar among treatment groups. The study cohort (age range, 21 to 75 years; mean ages, 54 years for men and 58 years for women) was predominantly (92%) white, and 59% were men. Eighteen percent reported smoking cigarettes, 17% were at least 30% overweight, 14% had an HDL-cholesterol level less than 0.90 mmol/L (35 mg/dL), 62% had CHD or at least two of the CHD risk factors (in addition to a high level of LDL-cholesterol) specified by the NCEP guidelines,¹⁴ 40% had hypertension, and 29% had CHD. The mean plasma lipid

Table 1.—Change From Baseline in Plasma Lipid and Lipoprotein Levels*

Variable	Treatment Group				
	Placebo	Lovastatin			
		20 mg qpm	40 mg qpm	20 mg bid	40 mg bid
LDL-cholesterol	+0.4 (11)	-24 (11)	-30 (11)	-34 (11)	-40 (11)
HDL-cholesterol	+2.0 (12)	+6.6 (13)	+7.2 (13)	+8.6 (13)	+9.5 (13)
Total cholesterol	+0.7 (8)	-17 (8)	-22 (8)	-24 (8)	-29 (9)
LDL-cholesterol/ HDL-cholesterol ratio	+0.2 (16)	-27 (14)	-34 (14)	-38 (13)	-44 (13)
Total cholesterol/ HDL-cholesterol ratio	+0.6 (13)	-21 (12)	-26 (12)	-29 (11)	-34 (11)
Triglycerides†	+3.6	-10	-14	-16	-19

*Values are percent change from baseline (SD). LDL indicates low-density lipoprotein; HDL, high-density lipoprotein. Statistically significant differences for all lipid/lipoprotein variables are as follows: placebo vs 20 mg once daily with the evening meal (qpm) ($P < .001$); 40 mg qpm vs 20 mg with the morning and evening meals (bid) ($P < .017$ or less); trend with increasing daily dose, 20 mg vs 40 mg (40 mg qpm and 20 mg bid combined) vs 80 mg ($P < .001$).

†Median triglyceride values are presented; all others are mean values. The first and third quartile values for triglycerides were, respectively (-13, +21) for placebo, (-23, +6) for 20 mg qpm, (-28, +1) for 40 mg qpm, (-28, -1) for 20 mg bid, and (-32, -5) for 40 mg bid.

and lipoprotein levels measured at baseline (after at least 4 weeks of diet) included a total cholesterol level of 6.67 mmol/L (258 mg/dL), an LDL-cholesterol level of 4.65 mmol/L (180 mg/dL), and an HDL-cholesterol level of 1.16 mmol/L (45 mg/dL). The median triglyceride level was 1.75 mmol/L (155 mg/dL).

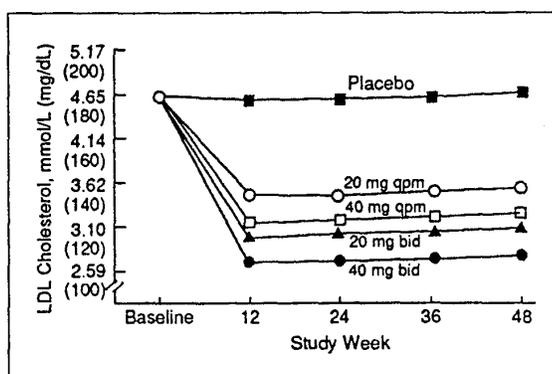
Self-reported compliance with the prescribed study medication regimen was high throughout the 48-week treatment period and similar among placebo and lovastatin treatment groups. Less than 3% of patients in each group reported that they failed to take study medication for 3 consecutive days within the 14 days preceding a lipid level determination. The proportion of patients who reported full or partial (half the time or longer) adherence to the study diet was similar among placebo and lovastatin treatment groups but declined from a level of 83% at baseline to approximately 75% at week 48.

From 1352 (82%) to 1394 (85%) patients in each treatment group completed 48 weeks of treatment. Patient withdrawals from the study were due to adverse experiences (6% in the placebo group and from 7% of those who received 20 mg/d of lovastatin to 9% who received 80 mg/d of lovastatin), protocol deviations (3% in each group), and other reasons (including patient choice, private physician recommendation, fear of having been assigned to receive placebo, and patient relocation; 6% in the placebo group, and 3% to 4% in the lovastatin treatment groups, suggesting that blinding may not have been fully maintained throughout the study). Unavailability for follow-up was rare and similar among groups, ranging from 2% to 3% of patients in each group.

Lipid and Lipoprotein Levels

Lipid and lipoprotein levels are summarized in Table 1. The mean percent changes from baseline showed statistically significant ($P < .001$) differences in response between the placebo group and the group receiving 20 mg/d lovastatin for all measurements. A significant ($P < .001$) dose-related trend was observed for each lipid and lipoprotein determination when responses to lovastatin were compared for dosages from 20 mg/d to 40 mg/d to 80 mg/d. Lovastatin at a dosage of 40 mg every evening also differed significantly ($P < .017$ or lower) from the 20 mg twice daily dosage in its effect on all lipid and lipoprotein measurements.

LDL-Cholesterol Level.—Lovastatin at a dosage of 20 mg/d lowered the LDL-cholesterol level by 24%. At each higher dosage level, incremental reductions were observed (up to 40% at 80 mg/d), indicating a dose-dependent response.



Mean low-density lipoprotein (LDL)-cholesterol levels during the 48-week treatment period. Statistically significant differences were found between placebo and 20 mg once daily with the evening meal, 20 vs 40 vs 80 mg/d, and 40 mg every evening (qpm) vs 20 mg twice daily with the morning and evening meals (bid) (Table 1).

The response level observed at week 12 was essentially maintained throughout the 48-week treatment period (Figure). This relatively stable response pattern was also observed with total cholesterol and triglyceride levels.

According to the NCEP guidelines, for the subgroup of patients with an LDL-cholesterol level goal of less than 4.14 mmol/L (<160 mg/dL) (589 to 632 patients in each treatment group), 80% of those given 20 mg/d of lovastatin reached the NCEP target; this percentage increased modestly with higher doses to 96% of patients receiving 80 mg/d of lovastatin. For the patient subgroup with an NCEP target of less than 3.36 mmol/L, 38% of those receiving 20 mg/d of lovastatin reached this goal; this percentage rose substantially to 83% of those patients receiving 80 mg/d of lovastatin. The mean percent decrease in the LDL-cholesterol level produced by lovastatin was similar for these two subgroups at each dosage level.

HDL-Cholesterol Level.—Lovastatin raised the HDL-cholesterol level a mean of 6.6% at the 20-mg/d dosage and 9.5% at the 80 mg/d dosage. The substantial and dose-dependent response observed at week 12 was maintained throughout the 48-week treatment period.

Triglyceride Level.—Lovastatin produced substantial, dose-dependent decrements in triglyceride level, with median decreases ranging from 10% at the 20-mg/d dosage to 19% at the 80-mg/d dosage.

Table 2.—Incidence of Serum Transaminase Level Elevations*

Elevation	Treatment Group, No. (%)				
	Placebo	Lovastatin			
		20 mg qpm	40 mg qpm	20 mg bid	40 mg bid
>3 times ULN					
Successive†	2 (0.1)	2 (0.1)	12 (0.9)	11 (0.9)	20 (1.5)
Single	15 (1.2)	10 (0.8)	22 (1.9)	21 (1.8)	42 (3.2)
>2 times ULN					
Successive	7 (0.5)	6 (0.5)	17 (1.3)	21 (1.7)	42 (3.0)
Single	28 (2.2)	28 (2.1)	44 (3.7)	54 (4.1)	81 (6.1)

*Incidence is calculated by life-table estimate of an elevation in either alanine aminotransferase or aspartate aminotransferase level at the specified level within 48 weeks of treatment. ULN indicates upper limit of normal (50 and 65 U/L for aspartate aminotransferase [ages <66 and ≥66 years, respectively] and 55 U/L for alanine aminotransferase). Successive elevations are those confirmed by repeated testing.

† $P < .001$ for trend with increasing daily doses of lovastatin; other levels of increase were not tested. Included are 10 patients with elevations not considered drug related by investigators: 20 mg once daily with the evening meal (qpm) ($n = 1$), 40 mg qpm ($n = 5$), 20 mg with the morning and evening meals (bid) ($n = 3$), and 40 mg bid ($n = 1$) (see text for explanation).

Safety Analyses

Liver Function Tests.—The incidence of serum transaminase level elevations of potential clinical importance is shown in Table 2. Successive serum transaminase level elevations greater than three times the ULN were found in two (0.1%) patients receiving placebo and two (0.1%) patients receiving 20 mg/d of lovastatin. The incidence increased to 0.9% in each of the 40 mg every evening and 20 mg twice daily lovastatin groups and to 1.5% in the 80-mg/d lovastatin group ($P < .001$ for trend with increasing dose).

Among the 47 patients with two successive elevations greater than three times the ULN, 32 had an elevated ALT level only, 14 had elevated ALT and AST levels, and one had an elevated AST level only. Six (13%) of the 47 patients experienced their first elevation greater than three times the ULN within the first 90 days of the study (one, zero, two, one, and two patients for the placebo, 20-mg/d, 40-mg every evening, 20-mg twice daily, and 80-mg/d lovastatin groups, respectively). Thereafter, the first elevations occurred sporadically over time.

Intercurrent illness and medications other than the study drug were considered by investigators to be responsible for or to be contributing to the transaminase level elevation in 10 of the 47 patients (zero, one, five, three, and one patient for the placebo, 20-mg/d, 40-mg every evening, 20-mg twice daily, and 80-mg/d lovastatin groups, respectively). Among the 37 patients without identified factors, four (all in the 80-mg/d lovastatin group) had transient symptoms, including nausea and abdominal pain (one patient), poor appetite (one patient), and fatigue (two patients). Seven of the 37 patients had concomitant mild elevations (above the ULN) in the alkaline phosphatase level, and one patient had a slightly elevated total bilirubin level. No patient was diagnosed by an investigator as having clinical hepatitis. The mean maximum AST level was 205 U/L (range, 76 to 706 U/L) and the mean maximum ALT level was 403 U/L (range, 170 to 1356 U/L).

After discontinuation of the study drug, transaminase levels decreased in 45 of the 47 patients. The ALT level returned to within normal limits in 29 patients after a mean of 7 weeks after discontinuation. In the remaining 16 patients whose transaminase levels decreased, within a mean of 11 weeks after discontinuation, ALT levels were less than 1.5 times the ULN in 11 patients, 1.5 to two times the ULN in four patients, and two to three times the ULN in one patient. The two patients whose levels remained greater than three times the ULN included a patient receiving placebo and another

receiving 80 mg/d of lovastatin whose ALT level had decreased but who was unavailable for follow-up 13 weeks after discontinuation (last recorded ALT value, 371 U/L).

The incidences of single transaminase level elevations greater than three times the ULN and single and successive elevations greater than two times the ULN were no higher in the patients receiving 20 mg/d of lovastatin than in the placebo group; these incidences rose progressively in the groups receiving 40 and 80 mg/d of lovastatin (Table 2). For patients who completed 48 weeks of treatment, the mean changes from baseline in transaminase levels were as follows (values are expressed in units per liter for ALT/AST): $-0.5/+3.2$ for the placebo group, $+2.2/+4.6$ for the 20-mg/d lovastatin group, $+3.0/+5.0$ for the 40-mg of lovastatin every evening group, $+3.3/+5.3$ for the 20-mg of lovastatin twice daily group, and $+5.0/+5.7$ for the 80-mg/d lovastatin group. Corresponding values for alkaline phosphatase levels (in units per liter) were $+5$ for the placebo group; $+3$ for 20-mg/d, 40-mg every evening, and 20-mg twice daily of lovastatin groups; and $+2$ for 80-mg/d lovastatin group.

CK Level/Muscle Symptoms.—Muscle symptoms with a CK level elevation greater than 10 times the ULN were observed in only five patients: one (0.1%) receiving 40 mg of lovastatin every evening and four (0.2%) receiving 80 mg/d of lovastatin (Table 3). While the incidence was higher in the group receiving 80 mg/d, it was too low to permit a meaningful statistical test of treatment effect. Four of the five patients were women; none experienced myoglobinuria or acute renal failure. The five cases occurred between 3 and 23 weeks of the start of drug therapy, with maximum CK levels ranging from 2000 to 10 300 U/L. Two of the five patients continued to receive lovastatin and completed the study while their muscle symptoms resolved and their CK levels returned to normal. In these two patients, symptoms consisted of abdominal muscle pain in one patient (not considered to be drug related by the investigator; 40 mg every evening lovastatin group) and persistent generalized muscle soreness that had been chronic before entry into the study in the second patient (80-mg/d lovastatin group). In the three patients who were withdrawn from the study, symptoms consisted of muscle weakness for 8 days in one patient; abdominal and chest pain, nausea, muscle weakness, and fatigue with concurrent acute cholecystitis (leading to hospitalization) in one patient; and pain in the upper portion of the chest and the anterior aspect of the neck along with esophageal spasm, which led to hospitalization, in the third patient. The CK levels for these three patients decreased to normal and symptoms resolved within 30 days of

Table 3.—Incidence of Muscle Symptoms With and Without Creatine Kinase (CK) Elevations*

	Treatment Group, No. (%)				
	Placebo	Lovastatin			
		20 mg qpm	40 mg qpm	20 mg bid	40 mg bid
Muscle symptoms with CK elevation					
CK >10 times ULN†	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	4 (0.2)
Any CK elevation	27 (1.6)	35 (2.1)	17 (1.0)	26 (1.6)	58 (3.5)
Muscle symptoms with no CK elevation	98 (5.9)	102 (6.2)	94 (5.7)	90 (5.5)	95 (5.8)
CK elevation with or without muscle symptoms					
CK >10 times ULN	7 (0.4)	3 (0.2)	3 (0.2)	3 (0.2)	8 (0.5)
Any CK elevation	480 (28.9)	473 (28.8)	491 (29.8)	525 (31.9)	572 (34.7)

*Percentage refers to patients randomized. ULN indicates upper limit of normal (190 and 235 U/L for women and men, respectively, for CK); qpm, once daily with the evening meal; and bid, with the morning and evening meals.

†Preplanned comparison; incidence was too low to test for trend with daily doses of lovastatin.

Table 4.—Clinical Adverse Experiences Involving Greater Than 1% of Patients and Occurring With a Range in Frequency That Exceeded the 95% Confidence Interval*

Clinical Adverse Experience	Treatment Group, No. (%)				
	Placebo	Lovastatin			
		20 mg qpm	40 mg qpm	20 mg bid	40 mg bid
Constipation	78 (4.7)	72 (4.4)	102 (6.2)	126 (7.7)	97 (5.9)
Palpitation	38 (2.3)	24 (1.5)	46 (2.8)	34 (2.1)	19 (1.2)
Sprains and strains	20 (1.2)	13 (0.8)	6 (0.4)	9 (0.5)	10 (0.6)
Tooth disorder, not otherwise specified	7 (0.4)	11 (0.7)	6 (0.4)	5 (0.3)	20 (1.2)
Myocardial infarction	18 (1.1)	14 (0.9)	3 (0.2)	15 (0.9)	15 (0.9)
Sleep disorder†	11 (0.7)	4 (0.2)	18 (1.1)	15 (0.9)	11 (0.7)
Eye inflammation	8 (0.5)	16 (1.0)	18 (1.1)	2 (0.1)	5 (0.3)

*Percentage refers to patients randomized. qpm indicates once daily with the evening meal; and bid, with the morning and evening meals. A pattern of occurrence suggestive of a treatment effect is present only for constipation.

†Nonspecific complaints, excluding insomnia.

discontinuation of lovastatin.

The incidence of muscle symptoms with any CK level elevation above the ULN was similar among the placebo group (1.6%) and the 20-mg/d (2.1%), 40-mg every evening (1.0%), and 20-mg twice daily (1.6%) lovastatin groups. The incidence for the 80-mg/d lovastatin group was 3.5% (Table 3). Muscle symptoms with no CK level elevation occurred with similar frequency in the placebo group (5.9%) and all lovastatin groups (range, 5.5% to 6.2% of patients). Any CK level elevation above the ULN (with or without muscle symptoms) during the 48-week treatment period was observed in 29% of patients receiving placebo, 29% of patients receiving 20 mg/d of lovastatin, and up to 35% of patients receiving 80 mg/d of lovastatin.

Other Clinical Adverse Experiences.—Ninety-two specific types of clinical adverse experiences occurred in more than 1% of patients in any treatment group. The range in incidences of seven adverse experiences was outside the 95% confidence interval (Table 4). Constipation, which occurred in 4.7% of patients receiving placebo and from 4.2% to 7.7% of patients receiving lovastatin, was the only one of these seven adverse experiences whose pattern of occurrence suggested a treatment-related effect. The other six adverse experiences, which did not suggest an effect of lovastatin, were myocardial infarction, palpitation, tooth disorder, sprains and strains, sleep complaints (excluding insomnia), and eye inflammation. Insomnia occurred with similar frequency in the placebo group (2.6%) and lovastatin groups (range, 2.1% to 3.3%).

Serious clinical adverse experiences as defined by the Food

and Drug Administration (which include any hospitalization, severe or permanent disability, or cancer regardless of cause) occurred in 8.8% of patients in the placebo group and in 8.0% (40 mg every evening) to 10.1% (80 mg/d) of patients in the lovastatin groups. No significant variation was found in the incidence of the following serious clinical adverse experiences (percentage of patients in the placebo group and the 20-mg/d, 40-mg every evening, 20-mg twice daily, and 80-mg/d lovastatin groups, respectively): death due to CHD or nonfatal myocardial infarction (1.2, 1.1, 0.3, 1.2, 1.2), cancer (0.7, 1.1, 1.2, 0.5, 1.1), and deaths due to all causes (0.2, 0.5, 0.3, 0.6, 0.5). Of the 36 deaths, 31 were attributed to ischemic heart disease or arrhythmia, two to postsurgical pulmonary embolism, one to hemorrhagic stroke, one to ruptured abdominal aortic aneurysm, one to viral pneumonia, and none to accidental causes.

The incidence of clinical adverse experiences (any change in health status) resulting in study discontinuation was 5.1% in the placebo group and ranged from 6.3% (20 mg twice daily) to 7.0% (80 mg/d) in the lovastatin groups. The range in incidence of adverse experiences considered to be drug related and resulting in study discontinuation was outside the 95% confidence interval (2.1% in the placebo group and 3.6% [20 mg/d] to 4.0% [40 mg every evening] of patients in the lovastatin groups).

Other Serum Chemistry and Hematologic Determinations.—Mean levels of change from baseline for patients who completed the 48 weeks of treatment were similar among placebo and lovastatin groups for fasting glucose level, serum

creatinine level, hemoglobin level, total white blood cell count, and differential cell count (data not shown). Platelet count increased by a mean (\pm SD) of $8 \pm 44 \times 10^9/L$ in the placebo group, while the mean change ranged from an increase of $5 \pm 47 \times 10^9/L$ to a decrease of $2 \pm 43 \times 10^9/L$ in the lovastatin groups. One patient (placebo group) was withdrawn from the study as a result of a decreased platelet count.

Blood Pressure, Pulse, and Weight.—Mean (\pm SD) changes from baseline to the end of therapy for systolic blood pressure were similar for the placebo group (-0.6 ± 16 mm Hg) and the lovastatin groups (range, -1.3 ± 16 to -0.2 ± 15 mm Hg). For diastolic blood pressure, the mean decreases tended to be slightly higher in the lovastatin groups (range, -0.7 ± 10 to -0.4 ± 10 mm Hg) than in the placebo group (0.0 ± 10 mm Hg). Mean increases in pulse were 0.7 ± 10 per minute in the placebo group and ranged from 0.0 to 0.8 ± 10 in the lovastatin groups. Mean (\pm SD) weight gain tended to be slightly greater in the lovastatin groups (each group, 0.7 ± 4 kg) than in the placebo group (0.3 ± 4 kg).

COMMENT

Lovastatin administered for 48 weeks produced clinically important changes in all lipid and lipoprotein levels measured in this study. Mean percent decreases in LDL-cholesterol level ranged from 24% to 40% for the groups receiving 20 mg/d to 80 mg/d of lovastatin. The HDL-cholesterol level increased from 6.6% to 9.5%, triglyceride levels decreased from 10% to 19%, and the ratio of LDL-cholesterol to HDL-cholesterol decreased by 27% to 44%. These changes were stable over time, dose dependent, and statistically significant. All dosage levels of lovastatin tested were generally well tolerated; the rate of discontinuation due to clinical adverse experiences was only 1.2% to 1.9% higher than that for placebo for groups receiving 20 mg/d to 80 mg/d of lovastatin.

The percentage changes in lipid and lipoprotein levels reported herein in patients with moderate hypercholesterolemia are very similar to those reported in earlier studies of patients with more severe hypercholesterolemia.^{3,6} Moreover, due to their lower baseline cholesterol levels, a substantial proportion of patients with moderate hypercholesterolemia can achieve an adequate therapeutic response with lovastatin therapy and diet alone. With respect to the achievement of NCEP treatment goals¹⁴ for lowering LDL-cholesterol level in individual patients, a measure that to our knowledge has not been applied previously in a large trial, we observed that 80% of the lower-risk subgroup given 20 mg of lovastatin daily achieved their LDL-cholesterol level target of less than 4.14 mmol/L (<160 mg/dL). Thus, to achieve their goal, only one fifth of patients with moderate hypercholesterolemia who do not have CHD or at least two other CHD risk factors would need higher doses of lovastatin or a second drug to lower the LDL-cholesterol level. Some of these lower-risk patients at baseline did not exceed the LDL-cholesterol level threshold (4.91 mmol/L [190 mg/dL]) requiring drug treatment according to the NCEP guidelines,¹⁴ reflecting the fact that this protocol was implemented before the release of these guidelines. For the higher-risk subgroup with a lower LDL-cholesterol level goal (<3.36 mmol/L [<130 mg/dL]), we found that 38% of those receiving 20 mg of lovastatin daily reached their target; this percentage increased progressively with each higher dosage level, up to 83% of those receiving the 80 mg/d. Consequently, a greater proportion of the higher-risk patients may require larger doses of lovastatin and, in

some instances, the addition of a second drug to reach LDL-cholesterol levels recommended by the NCEP guidelines. Alternatively, if diet fails to produce the desired lowering of the LDL-cholesterol level, a bile acid sequestrant could be added as the initial drug in patients who require pharmacologic intervention and lovastatin given as an additional drug as needed to achieve the NCEP goal for LDL-cholesterol level lowering.

Lovastatin at a dosage of 20 mg twice daily produced a significantly ($P < .001$) greater reduction in LDL-cholesterol level than did the 40-mg every evening dosage (34% vs 30%). In assessing the clinical significance of this finding, consideration in individual patients should also be given to the compliance implications of these two regimens (twice daily vs once daily).

The incidences of confirmed transaminase elevations greater than three times the ULN for the 40 mg/d and 80 mg/d dosages (0.9% and 1.5%, respectively) were both lower than previously reported.¹⁹ A trend for dose-dependent increments in the frequency of abnormal transaminase levels at lower elevations, eg, greater than two times the ULN, was also apparent and has been noted previously.^{3,6} Many of the abnormal transaminase levels observed in this study were transient. The source of the enzyme elevations is most likely the liver, as 46 of the 47 patients with confirmed elevations reached a level greater than three times the ULN due to their ALT level, while only 15 did so as a result of their AST level. Successive transaminase elevations greater than three times the ULN were infrequent in the first 12 weeks of therapy. A clear temporal relationship between these elevations and treatment duration did not develop. The elevations in transaminase levels confirm the need to monitor patients during the first year of therapy.²⁰

Transaminase level elevations occur with other lipid-altering compounds, such as niacin, gemfibrozil, and clofibrate.²¹ While the transaminase level changes observed in the present study were clearly related to the lovastatin dose, the precise mechanism for this effect is unclear. Animal studies have shown that hepatic changes can be prevented with coadministration of mevalonic acid, the product of the enzyme inhibited by lovastatin.²²

A definitive characterization of a drug-induced myopathic syndrome was not evident in this study. Creatine kinase level elevations above the ULN occurred in more than one quarter of patients, with similar frequency in the placebo and lovastatin treatment groups. The incidence of muscle symptoms combined with a CK level elevation was similar in the placebo group and the groups receiving 20 mg/d and 40 mg/d of lovastatin (1% to 2% of patients), and was only slightly higher in the group receiving 80 mg/d of lovastatin (3.5%). Only five patients receiving lovastatin (one at 40 mg every evening and four at 80 mg/d) exhibited muscle symptoms with a CK level elevation greater than 10 times ULN; in two of these patients, the symptoms and CK level elevations resolved with continued lovastatin therapy. Patients with clinically significant renal insufficiency or those receiving concomitant therapy with gemfibrozil, niacin, or cyclosporine were excluded by protocol, thereby eliminating factors known to be associated with an increased risk of development of severe myopathy.²⁰ The mechanism responsible for this myopathy is not understood, although presumably it may be the result of complex interactions associated with drugs administered concomitantly and, in some instances, underlying disease.^{19,23}

The range in incidences of seven of the 92 different types of common clinical adverse experiences observed in this study was outside the expected 95% confidence interval, about five of which would be expected by chance alone. Further inspection indicated that constipation was the only symptom for which the frequency pattern among treatment groups might be associated with lovastatin treatment. Even so, the maximum increase in incidence above placebo was less than 3%, which is much lower than that seen with bile acid sequestrants.²¹ Insomnia has been attributed to lovastatin administration in one study,²⁴ but this association was not confirmed in another.²⁵ Based on self-reporting, we also found no evidence to support such an association. Although a decrease in coronary events was not observed after 48 weeks of treatment, none was expected until at least 2 years of therapy had been completed.^{26,27} We found no evidence of a previously reported early increase in coronary events.²⁸ The tendency toward a slight mean increase in weight (0.4 kg relative to placebo) found in the present study in patients in the lovastatin groups has also been noted in previous studies.^{5,29}

While lovastatin was effective and generally well tolerated at all dosages studied, the favorable efficacy and safety profile of lovastatin at 20 mg/d is particularly noteworthy, as approximately two thirds of patients in the United States are prescribed this dosage.³⁰ Clinically important lipid and lipoprotein level changes were observed with this dose, while the incidence of adverse events, including transaminase and CK level elevations with muscle symptoms, was virtually indistinguishable from that of the placebo group. The favorable efficacy and safety profile of lovastatin, particularly that

observed at lower dosage levels, might encourage the premature use of lovastatin before diet therapy has been given an adequate trial according to the NCEP guidelines.¹⁴ More clinical adverse experiences were found in association with higher dosages of lovastatin. Still, even at 80 mg/d, the frequency of these adverse experiences was low. This favorable efficacy and safety profile may be the result of extensive first-pass extraction of lovastatin by the liver, with less than 5% of the orally administered drug appearing in the general circulation as active metabolites.³¹

In summary, lovastatin produced substantial, dose-related reductions in LDL-cholesterol, total cholesterol, and triglycerides levels as well as noteworthy dose-related increases in HDL-cholesterol level. The lipid and lipoprotein level changes were stable over time. The incidence of adverse events of potential clinical importance was very low, and previously unreported adverse experiences related to lovastatin treatment were not evident. Based on the very favorable changes in the lipoprotein profile and the low incidence of adverse effects, we conclude that lovastatin, when added after an adequate trial of a prudent diet, is a highly effective and generally well-tolerated drug for the treatment of patients with moderate hypercholesterolemia.

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