

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER: 19-766/S040**

**CORRESPONDENCE**



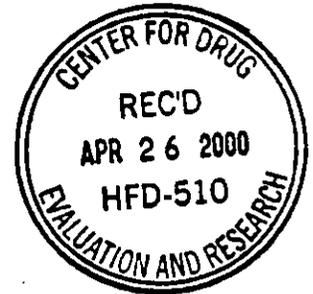
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April 25, 2000  
(Via Federal Express)



Andrew S.T. Haffer, Pharm.D.  
Regulatory Review Officer  
Division of Drug Marketing,  
Advertising and Communications  
Food and Drug Administration  
HFD-40, Room 17B-20  
5600 Fishers Lane  
Rockville, MD 20857



Re: NDA 19-766  
ZOCOR® (simvastatin)

**Press Release – 40 mg alternate starting dose**

Dear Dr. Haffer:

It is our understanding that Merck's supplemental New Drug Application for a change to the labeling of Zocor may be approved as early as this Friday. The supplement provides for a 40 mg alternative starting dose for Zocor in patients requiring a large reduction in LDL-C. Attached for DDMAC review and comment is a proposed press release (ZOCNEWS00(2)) announcing the approval (Attachment 1). A copy of the reference cited in the press release, with pertinent sections underlined and bracketed, is included as Attachment 2. To facilitate your review, Merck has also attached the following documents:

Attachment 3: a reprint describing the ongoing Heart Protection Study that was included in the supplement and is mentioned on page 2 of the press release. (MRC/BHF Heart Protection Study of cholesterol-lowering therapy and of antioxidant vitamin supplementation in a wide range of patients at increased risk of coronary heart disease death: early safety and efficacy experience. *European Heart Journal* (1999) 20, 725-741.)

Attachment 4: the draft label and cover letter Merck submitted to the FDA Review Division on June 30, 1999.

Attachment 5: the Worldwide Clinical Summary document that was included in the SNDA submission.

Dr. Andrew Haffer  
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Merck would like to issue the press release upon approval of the supplement and appreciates your prompt attention to this matter. Please contact me at (215) 652-3476 if you have any questions.

Sincerely,



Ellen R. Westrick.  
Executive Director  
Office of Medical/Legal

APPEARS THIS WAY  
ON ORIGINAL

Attachments (1-5)

Cc: Ms. Margaret Simoneau  
Project Manager  
Division of Metabolic and Endocrine Drug Products  
HFD-510, Room 14B04

APPEARS THIS WAY  
ON ORIGINAL

3 Page(s) Redacted

Draft

RELEASE

# Treatment Patterns and Distribution of Low-Density Lipoprotein Cholesterol Levels in Treatment-Eligible United States Adults

Thomas J. Hoerger, PhD, Mohan V. Bala, PhD, Jeremy W. Bray, MS,  
Timothy C. Wilcosky, PhD, and John LaRosa, MD

To estimate the fraction of United States (U.S.) adults who are eligible for treatment to reduce elevated low-density lipoprotein (LDL) cholesterol levels based on Adult Treatment Panel II (ATP II) guidelines and the percent reduction in LDL cholesterol required by those who qualify for treatment, we analyzed data on 7,423 respondents to Phase 2 of the Third National Health and Nutrition Examination Survey (NHANES III) administered between 1991 and 1994. Approximately 28% of the U.S. adult population aged  $\geq 20$  years is eligible for treatment based on ATP II guidelines. Eighty-two percent of adults with coronary heart disease are not at their target LDL cholesterol level of 100 mg/dl. Of those eligible for treatment, 65% report that they receive no treatment. Overall, 40% of people who qualify for drug

therapy require an LDL cholesterol reduction of  $> 30\%$  to meet their ATP II treatment goal. Approximately 75% of those with coronary heart disease who qualify for drug therapy require an LDL cholesterol reduction of  $> 30\%$ . Although elevated LDL cholesterol levels can be treated, prevalence rates in the U.S. adult population remain high. Several recent studies indicate that a considerable percentage of people treated with drug therapy do not reach their treatment goals. The findings in this study provide at least a partial explanation for why many patients receiving therapy do not reach their treatment goals: they require a larger reduction in LDL cholesterol than many therapies can provide. ©1998 by Excerpta Medica, Inc.

(Am J Cardiol 1998;82:61-65)

In this study, we use recently obtained data from Phase 2 of the third National Health and Nutrition Examination Survey (NHANES III) to address the following questions: (1) What fraction of the United States (U.S.) adult population aged  $\geq 20$  years is eligible for treatment to lower low-density lipoprotein (LDL) cholesterol based on the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel or ATP II) guidelines? (2) What fraction of the eligible population reports that it receives treatment? (3) What is the percent reduction in LDL cholesterol required by those who qualify for drug intervention to reach their LDL cholesterol goals as prescribed by ATP II? We believe that answers to these questions will provide important information regarding current lipid management, which in turn can assist in developing effective intervention strategies to attain the goals outlined by ATP II.

## METHODS

The analyses in this study are based on data from Phase 2 of the NHANES III survey, which was conducted from 1991 to 1994. NHANES III is the seventh

in a series of national surveys started in 1960 and was conducted from October 1988 to October 1994. NHANES III sampled 39,695 persons aged  $\geq 20$  months, of whom 31,311 (79%) completed both the survey questionnaire and a physical examination. Phase 2 of NHANES III was conducted from September 1991 to October 1994. In Phase 2, 15,427 persons completed both the survey and the physical examination, of whom 8,588 were aged  $\geq 20$  years.<sup>1</sup>

One of the goals of the NHANES III survey is to estimate the national prevalence of diseases and risk factors. Thus, patients were asked about history of diseases, such as systemic hypertension, diabetes mellitus, and heart attack, as well as about risk factors, such as current and past cigarette use. The NHANES III survey also measured total cholesterol, high-density lipoprotein cholesterol, and serum triglycerides for all examinees  $\geq 4$  years.

The NHANES III Phase 2 data were recently released publicly. In estimating the prevalence of elevated LDL cholesterol levels, it is important to use the most recent data available because cholesterol screening and treatment patterns have been changing rapidly. For example, the ATP II recommendations were released in 1993, coinciding with the NHANES III Phase 2 survey period of 1991 to 1994. Furthermore, cholesterol-lowering drug therapy has also changed rapidly with the introduction of new statin drugs. Thus, results from the NHANES III Phase 2 data will further enhance our understanding of current lipid levels and management.

In our analysis, we used NHANES III Phase 2 data to determine the fraction of the population aged  $\geq 20$

From Research Triangle Institute, Research Triangle Park, North Carolina; Centocor, Inc., Malvern, Pennsylvania; and Tulane University Medical Center, New Orleans, Louisiana. This study was supported in part by Parke-Davis and Pfizer, Inc. Manuscript received December 5, 1997; revised manuscript received and accepted February 11, 1998.

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**TABLE I** Coronary Heart Disease Risk Groups Based on Adult Treatment Panel II Treatment Recommendations

Coronary Heart Disease Risk Group	LDL Cholesterol to Initiate Diet (mg/dl)	LDL Cholesterol to Initiate Drug (mg/dl)	LDL Cholesterol Goal (mg/dl)
Without coronary heart disease and with <2 risk factors*	≥160	≥190	<160
Without coronary heart disease and with ≥2 risk factors*	≥130	≥160	<130
With coronary heart disease	>100	≥130	≤100

\*Positive risk factors for coronary heart disease include age (≥45 for men; ≥55 or premature menopause for women), family history of premature coronary heart disease, current cigarette smoking, hypertension, low high-density lipoprotein cholesterol (<35 mg/dl), and diabetes mellitus. High high-density lipoprotein cholesterol (≥60 mg/dl) is a negative risk factor.

Source: Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults: Summary of the second report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel II). JAMA. 1993;269:3015-3023.

**TABLE II** Percentage of U.S. Adults\* Who Qualify for Treatment Under Adult Treatment Panel II Guidelines

	Quality for Treatment		
	Dietary Therapy Alone (%)	Drug Therapy <sup>†</sup> (%)	Total (%)
All	16.4	11.8	28.2
Race			
White	17.2	11.8	29.0
Black	12.4	12.1	24.5
Race/ethnicity			
Mexican-American	10.8	7.4	18.2
Non-Hispanic black	12.5	12.2	24.7
Non-Hispanic white	17.7	11.8	29.5
Men (age)	17.6	12.8	30.3
20-44	11.5	7.2	18.7
45-54	26.9	22.1	48.9
55-64	26.3	21.1	47.4
65-74	26.0	19.7	45.7
75+	25.1	18.5	43.6
Women (age)	15.3	10.8	26.1
20-44	9.3	2.8	12.2
45-54	17.9	10.2	28.1
55-64	26.4	24.3	50.7
65-74	26.5	27.3	53.8
75+	23.7	29.1	52.8

\*≥20 years.

<sup>†</sup>Subjects who qualify for drug therapy also qualify for dietary therapy.

years eligible for treatment according to the ATP II guidelines. ATP II treatment recommendations are listed in Table I.<sup>2</sup> Within this analysis, a person is considered eligible for treatment if he/she belongs to 1 of the following 3 risk groups: (1) has coronary heart disease and an LDL cholesterol level >100 mg/dl; (2) does not have coronary heart disease, has ≥2 risk factors, and an LDL cholesterol level ≥130 mg/dl; or (3) does not have coronary heart disease, has <2 risk factors, and has an LDL cholesterol level ≥160 mg/dl. Even though ATP II recommends a treatment target LDL cholesterol level of 160 mg/dl for people without coronary heart disease and <2 risk factors, the guidelines also state that an LDL cholesterol level of <130 mg/dl is considered desirable for everyone without coronary heart disease.

The LDL cholesterol level for each individual was calculated from their total cholesterol, high-density lipoprotein cholesterol, and triglycerides based on the following formula: LDL cholesterol = total cholesterol - high-density lipoprotein cholesterol - (triglycerides/5).

This formula, known as the Friedewald equation, was used by the NHANES III to calculate LDL levels for respondents who fasted. To increase sample size, we also applied this formula to nonfasting respondents. Because the formula is not accurate for triglyceride levels >400 mg/dl, we excluded subjects with triglyceride levels >400 mg/dl from our analysis (269 observations excluded). We defined the presence of coronary heart disease as a positive response to the Rose Questionnaire for angina pectoris or a positive response to the question: Has a doctor ever told you that you had a heart attack? Family history of premature coronary heart disease was based on respondents

reporting that a first-degree blood relative had a heart attack before age 50. Current cigarette use was defined as a positive response to the question: Do you smoke cigarettes now? We classified respondents as hypertensive if they reported being told by a physician ≥2 times that they had high blood pressure, had been told to take antihypertensive medication, or had ≥2 observed blood pressure readings ≥140/90 mm Hg (systolic ≥140 or diastolic ≥90 mm Hg). We defined the presence of diabetes mellitus as a positive response to the question: Have you ever been told by a doctor that you have diabetes or sugar diabetes?

Diagnosis of high cholesterol was defined as a positive response to the question: Have you ever been told by a health professional that you have high cholesterol? We defined those currently eating fewer high-fat or high-cholesterol foods, controlling weight or losing weight, or exercising on the advice of a health professional to be under dietary therapy. Anybody taking prescribed medicine to lower cholesterol was defined as being under drug therapy.

Following the recommendation of the NHANES III Phase 2 public use file documentation, we excluded 38 subjects with unreliable interviews. We excluded 269 persons with triglyceride levels >400 mg/dl, 350 with missing triglyceride levels, and 29 with missing high-density lipoprotein levels. Finally, we excluded 479 subjects with missing information on risk factors needed to classify treatment eligibility, yielding a total analysis sample of 7,423 persons. All estimates were weighted by the examination sample weights contained in the NHANES III Phase 2 public use file to produce nationally representative estimates for the period 1991 to 1994. Given the relatively high response rate for NHANES III as a whole and the

**TABLE III U.S. Population by Coronary Heart Disease Risk Group: Number and Percentage Not Meeting Goals**

	Coronary Heart Disease Risk Group		
	Without Coronary Heart Disease		With Coronary Heart Disease (treatment goal $\leq$ 100 mg/dl)
	<2 Risk Factors (treatment goal <160 mg/dl)	$\geq$ 2 Risk Factors (treatment goal <130 mg/dl)	
Estimated number in risk group (millions)	121.1	48.7	10.2
Not meeting treatment goals			
Estimated number (millions)	15.7	26.6	8.4
Percentage of risk group	12.9%	54.6%	82.5%
Qualify for dietary therapy alone			
Estimated number (millions)	11.0	15.6	2.9
Percentage of risk group	9.1%	32.1%	28.3%
Qualify for drug therapy*			
Estimated number (millions)	4.7	11.0	5.5
Percentage of risk group	3.8%	22.6%	54.2%
Not meeting desirable level of 130 mg/dl			
Estimated number (millions)	44.6	26.6	NA
Percentage of risk group	36.8%	54.6%	NA

\*People who qualify for drug therapy also qualify for dietary therapy.  
NA = not applicable.

surveys nationally representative sampling frame, we are confident that our results are nationally representative. All results were calculated using SAS 6.11<sup>3</sup> statistical software.

## RESULTS

**Prevalence in the U.S. adult population:** In Table II, we show the percentage of U.S. adults who qualify for intervention under the ATP II guidelines by race, ethnicity, sex, and age. Overall, 28.2% (50.7 million people) of Americans aged  $\geq$ 20 are eligible for treatment based on observed LDL cholesterol levels; 16.4% (29.5 million) qualify for dietary therapy alone, and 11.8% (21.2 million) qualify for drug therapy. About 24% of blacks are eligible for treatment, compared with 29% of whites, and about 30% of males are eligible for treatment versus about 26% of females.

Table III shows the estimated number and percentage of U.S. adults aged  $\geq$ 20 who are not meeting ATP II treatment goals as well as desired LDL cholesterol levels of <130 mg/dl by coronary heart disease risk group. The treatment goal differs from the desired level only for people without coronary heart disease and <2 risk factors. Of those with coronary heart disease, 82.5% are not meeting ATP II treatment goals, and 54.2% qualify for drug therapy. Among U.S. adults without coronary heart disease and with  $\geq$ 2 risk factors, 54.6% are not meeting ATP II treatment goals, and 22.6% qualify for drug therapy. About 37% of U.S. adults without coronary heart disease and with <2 risk factors are not at the desirable LDL cholesterol level of <130 mg/dl, and 12.9% are not meeting the ATP II treatment goals. About 4% of people in this risk group qualify for drug therapy. If we examine adults without coronary heart disease as a

group, 41.9% (71.2 of 169.9 million) are not meeting their desirable LDL cholesterol level of <130 mg/dl. Of those who qualify for drug therapy, 78% (16.5 of 21.2 million) have coronary heart disease or at least 2 coronary heart disease risk factors.

**Treatment of elevated low-density lipoprotein cholesterol levels:** Table IV shows the estimated number and percentage of the U.S. adult population qualifying for treatment who report that they are receiving dietary and drug therapy to lower their LDL cholesterol by risk group and treatment eligibility. Among those eligible for treatment based on observed LDL cholesterol levels, 29.0% report that they receive dietary therapy only, and 6.1% report that they receive drug therapy. Sixty-five percent report that they receive no treatment. The percentage of persons who report that they receive dietary therapy alone is actually highest for those with no coronary heart disease and <2 risk factors. Among patients

with coronary heart disease who are eligible for treatment, 29.0% report that they receive dietary therapy only, and 12.7% report that they receive drug therapy. Thus, even in this high-risk subgroup, more than half of the respondents report that they do not receive any treatment to lower their LDL cholesterol levels.

**Low-density cholesterol reduction required:** In Table V, we examine the percent reduction in LDL cholesterol required by people qualifying for drug therapy according to the ATP II guidelines based on observed LDL cholesterol levels. Of all people qualifying for drug therapy, 40.4% (an estimated 8.5 million people) require a reduction in LDL cholesterol levels of >30% to reach their treatment goal. Among those with coronary heart disease who qualify for drug therapy, 74.8% required a reduction in LDL cholesterol of >30%. Those without coronary heart disease who are eligible for drug treatment are less likely to require >30% reductions in LDL cholesterol to meet ATP II treatment goals; however, 55.4% of the people in this group require a reduction of >30% to reach the desirable LDL cholesterol level of  $\leq$ 130 mg/dl.

## DISCUSSION

NHANES III Phase 2 data provide the latest source of information on the distribution of LDL cholesterol levels in U.S. adults. Based on this nationally representative sample, >28% of U.S. adults and >82% of U.S. adults with coronary heart disease are eligible for treatment based on ATP II guidelines. The relation between elevated LDL cholesterol levels and increased coronary heart disease morbidity and mortality has been well established.<sup>4-8</sup> Because coronary heart disease results in about 500,000 deaths annually in the U.S., elevated LDL cholesterol levels are a

**TABLE IV Treatment-Eligible Population Receiving Therapy by Risk Group and Treatment Eligibility**

	No Coronary Heart Disease									
	<2 Risk Factors			≥2 Risk Factors			Coronary Heart Disease			All Treatment Eligible
	Diet Eligible	Drug Eligible	All Eligibles	Diet Eligible	Drug Eligible	All Eligibles	Diet Eligible	Drug Eligible	All Eligibles	
Estimated number (million)	11.0	4.7	15.7	15.6	11.0	26.6	2.9	5.5	8.4	50.7
Receiving dietary therapy										
Estimated number (million)	3.3	1.9	5.2	3.7	3.3	7.0	0.7	1.8	2.4	14.7
Percentage	30.0%	41.3%	33.3%	23.5%	30.5%	26.4%	23.6%	31.8%	29.0%	29.0%
Receiving drug therapy										
Estimated number (million)	0.4	0.1	0.5	1.0	0.5	1.6	0.3	0.8	1.1	3.1
Percentage	3.3%	2.2%	2.9%	6.7%	4.7%	5.9%	9.6%	14.3%	12.7%	6.1%
Receiving no treatment										
Estimated number (million)	7.4	2.6	10.0	11.0	7.1	18.0	1.9	3.0	4.9	33.0
Percentage	66.8%	56.5%	63.7%	69.8%	64.9%	67.8%	66.8%	53.9%	58.3%	65.0%

**TABLE V Reduction in Low-Density Lipoprotein Cholesterol Required to Meet Adult Treatment Panel II Treatment Goal or Desired Level for Those Who Qualify for Drug Treatment**

	Coronary Heart Disease Risk Group				
	Without Coronary Heart Disease			Coronary Heart Disease—to Reach Treatment Goal and Desired Level ≤100 mg/dl	All to Reach Treatment Goal
	With <2 Risk Factors to Reach Treatment Goal <160 mg/dl	With ≥2 Risk Factors to Reach Treatment Goal <130 mg/dl	All to Reach Desired Level of <130 mg/dl		
Estimated number in risk group who qualify for drug therapy (millions)	4.7	11.0	15.7	5.5	21.2
Require >30% reduction					
Estimated number (millions)	0.4	4.0	8.7	4.1	8.5
Percentage	9.1%	36.5%	55.4%	74.8%	40.4%

public health problem that requires serious attention, and prompt diagnosis and effective treatment of elevated LDL cholesterol levels may substantially reduce coronary heart disease mortality as well as reduce related health care expenditures.

Our findings indicate that most U.S. adults eligible for cholesterol-lowering therapy report that they do not receive treatment. Only about 35% of treatment-eligible persons report that they receive dietary or drug therapy. Even among patients with coronary heart disease who are eligible for drug therapy, over half report that they receive no therapy. In NHANES, treatment prevalence is self-reported by patients and no attempt was made to confirm treatment by reviewing medical records. Still, these results suggest that many patients with elevated LDL levels remain untreated.

For those who are treated, recent research casts doubt on the ability of dietary therapy to produce sizable reductions in LDL cholesterol, particularly if the therapy is not accompanied by intensive counseling.<sup>9,10</sup> Among drug therapies, bile acid sequestrants are expected to reduce LDL cholesterol by 15% to

20%, and 3-hydroxy-3methylglutaryl coenzyme A reductase inhibitors are expected to reduce LDL cholesterol by 20% to 60% depending on the agent and dose chosen.<sup>11</sup> However, a number of recent studies indicate that, even when drug therapy is prescribed, a considerable percentage of people treated do not reach their target LDL cholesterol levels. Less than half of patients with LDL cholesterol >160 mg/dl achieved target lipid levels.<sup>12</sup> Among those with heart disease, only 30% of patients achieved ATP II goals after treatment with fluvastatin at 20 mg,<sup>13</sup> and only 24% of patients reached their goals after treatment with 3-hydroxy-3methylglutaryl coenzyme A reductase inhibitors.<sup>14</sup> In a 2.5-year study, 70% of patients with coronary heart disease and baseline LDL cholesterol levels >130 mg/dl needed combination therapy to reach ATP II goals.<sup>15</sup> Another study found that only 38% of patients currently undergoing treatment for hypercholesterolemia were meeting their ATP II treatment goal.<sup>16</sup>

Our results show that a large percentage of people who qualify for drug treatment require substantial reductions in LDL cholesterol levels. Forty percent of

all persons who qualify for drug treatment require at least a 30% reduction in LDL cholesterol; nearly 75% of those with coronary heart disease who qualify for drug treatment need at least a 30% reduction in LDL cholesterol. For a patient group often treated with drugs, middle-aged men aged 45 to 64 years with coronary heart disease, 80% of the population eligible for drug treatment requires at least a 30% reduction in LDL cholesterol. Thus, our findings provide at least a partial explanation for why many individuals receiving therapy do not reach their treatment goals; they require a larger reduction in LDL cholesterol than many therapies can provide.

**Acknowledgment:** Sharon Barrell, Debra Bost, and Judy Cannada provided assistance in preparing the manuscript and Berna Demiralp provided programing assistance. Mohan V. Bala was employed by Research Triangle Institute at the time this article was written.

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European Heart Journal (1999) 20, 725-741

Article No. euhj.1998.1350, available online at <http://www.idealibrary.com> on IDEAL

## MRC/BHF Heart Protection Study of cholesterol-lowering therapy and of antioxidant vitamin supplementation in a wide range of patients at increased risk of coronary heart disease death: early safety and efficacy experience

MRC/BHF Heart Protection Study Collaborative Group\*

**Aims** In observational studies, prolonged lower blood total cholesterol levels — down at least to  $3 \text{ mmol} \cdot \text{l}^{-1}$  — are associated with lower risks of coronary heart disease. Cholesterol-lowering therapy may, therefore, be worthwhile for individuals at high risk of coronary heart disease events irrespective of their presenting cholesterol levels. Observational studies also suggest that increased dietary intake of antioxidant vitamins may be associated with lower risks of coronary heart disease. The present randomized trial aims to assess reliably the effects on mortality and major morbidity of cholesterol-lowering therapy and of antioxidant vitamin supplementation in a wide range of different categories of high-risk patients.

**Methods and Results** Men and women aged 40 to 80 years were eligible provided they were considered to be at elevated risk of coronary heart disease death because of past history of myocardial infarction or other coronary heart disease, occlusive disease of non-coronary arteries, diabetes mellitus or treated hypertension; had baseline blood total cholesterol of  $3.5 \text{ mmol} \cdot \text{l}^{-1}$  or greater; and no clear indications for, or contraindications to, either of the study treatments. Eligible patients who completed a pre-randomization run-in phase on active treatment were randomly allocated to receive simvastatin (40 mg daily) or matching placebo tablets and, in a  $2 \times 2$  factorial design, antioxidant vitamins (600 mg vitamin E, 250 mg vitamin C and 20 mg beta-carotene daily) or matching placebo capsules. Follow-up visits after randomization are scheduled at 4, 8 and 12 months, and then 6-monthly, for at least 5 years.

Between July 1994 and May 1997, 15 454 men and 5082 women were randomized, with 9515 aged over 65 years at entry. Diagnostic criteria overlapped, with 8510 (41%) having had myocardial infarction (most of whom were either female, or elderly or with low blood cholesterol), 4869 (24%) some other history of coronary heart disease, 3288 (16%) cerebrovascular disease, 6748 (33%) peripheral vascular disease, 5963 (29%) diabetes mellitus (of whom 3985 had no history of coronary heart disease) and 8455

(41%) treated hypertension. Baseline non-fasting total cholesterol levels were less than  $5.5 \text{ mmol} \cdot \text{l}^{-1}$  in 7882 (38%) participants, and LDL (low density lipoprotein) cholesterol less than  $3.0 \text{ mmol} \cdot \text{l}^{-1}$  in 6888 (34%).

During a mean follow-up of 25 months (range: 13 to 47 months), no significant differences had been observed between the treatment groups in the numbers of patients with muscle symptoms, other possible side-effects leading to termination of study treatment, or elevated liver and muscle enzymes. After 30 months of follow-up, 81% of randomized patients remained compliant with taking their study simvastatin or placebo tablets, and allocation to simvastatin produced average reductions in non-fasting blood total and LDL cholesterol of about  $1.5$ – $1.6 \text{ mmol} \cdot \text{l}^{-1}$  and  $1.1$ – $1.2 \text{ mmol} \cdot \text{l}^{-1}$  respectively. Eighty-seven per cent of patients remained compliant with taking their vitamin or placebo capsules, and allocation to the vitamin supplement produced an average increase in plasma vitamin E levels of about  $18 \text{ mg} \cdot \text{l}^{-1}$ . Based on this initial follow-up period, the estimated annual rate of non-fatal myocardial infarction or fatal coronary heart disease is 2.4%, annual stroke rate is 1.3%, and annual all-cause mortality rate is 2.2%.

**Conclusion** The Heart Protection Study is large, it has included a wide range of patients at high risk of vascular events, and the treatment regimens being studied are well-tolerated and produce substantial effects on blood lipid and vitamin levels. The study should, therefore, provide reliable evidence about the effects of cholesterol-lowering therapy and of antioxidant vitamin supplements on all-cause or cause-specific mortality and major morbidity in a range of different categories of individuals for whom uncertainty remains about the balance of benefits and risks of these treatments.

(*Eur Heart J* 1999; 20: 725-741)

**Key Words:** Randomized trial, cholesterol-lowering, simvastatin, antioxidant vitamins, coronary heart disease.

## Introduction

### *Reliable assessment of the effects of lowering blood cholesterol*

**Blood cholesterol and coronary heart disease associations**  
There is general agreement that, for people in Europe or North America with above-average levels, blood cholesterol is an important cause of coronary heart disease, and evidence is emerging that it may also be an important cause of coronary heart disease even for those with average or below-average levels<sup>(1-4)</sup>. For, when populations in prospective observational studies are divided into groups on the basis of their usual cholesterol level, there is a steady progression of coronary heart disease rates between one group and the next. Widespread surveys in rural China have revealed mean total cholesterol levels of about 3 mmol.l<sup>-1</sup> in many areas, with some communities having mean levels as low as 2 mmol.l<sup>-1</sup> and mean coronary heart disease death certification rates in middle age that are only about 5% of those in Britain<sup>(5)</sup>. Prospective studies in Asian populations show that the positive relationship between coronary heart disease risk and blood total cholesterol continues down at least to 3 mmol.l<sup>-1</sup> (i.e. well below the range commonly seen in Western populations), without any evidence of a 'threshold' in this range below which a lower blood cholesterol is not associated with a lower risk<sup>(6,7)</sup>. Overall in these observational studies, the continuous relationship between coronary heart disease risk plotted on a doubling scale and blood cholesterol level is roughly linear. This implies that the *proportional* reduction in coronary heart disease risk associated with a particular prolonged *absolute* cholesterol difference may be similar throughout the range, at least above about 3 mmol.l<sup>-1</sup>. So, for example, a prolonged difference of about 1 mmol.l<sup>-1</sup> in blood cholesterol might correspond to about 50% less coronary heart disease, irrespective of the baseline cholesterol level. It also suggests that a greater absolute cholesterol difference would be associated with a correspondingly greater proportional reduction in risk throughout this range.

### *Effects of lowering blood cholesterol*

Randomized trials are more relevant than observational studies in assessing how rapidly the coronary heart disease avoidance that is associated epidemiologically with a prolonged cholesterol difference can be achieved by treatments that lower blood cholesterol. Earlier randomized controlled trials of drugs or diets involved an average blood cholesterol difference of only about 10%, and this was maintained for an average of only about 4

years<sup>(8)</sup>. Overall, the results of those trials indicated that, within just a few years of lowering cholesterol by a small amount in middle age, the reduction in coronary heart disease was at least half as great as that expected from a long-term difference in cholesterol of the same magnitude<sup>(9-10)</sup>. Some observational studies have found low cholesterol to be associated with increased rates of death from certain non-coronary causes (e.g. cancer, chronic respiratory disease, trauma, haemorrhagic stroke)<sup>(9)</sup>. It is unclear, however, whether these inverse associations are causal, or due to some form of confounding (with certain diseases or habits causing both death and lower cholesterol<sup>(11)</sup>) or, indeed, due to chance. Randomized evidence is not subject to such biases, but even in combination the early trials were far too small for reliable detection of plausible effects of a relatively small reduction in cholesterol on all-cause mortality or specific non-coronary causes of death<sup>(9,12)</sup>.

By contrast with the cholesterol-lowering drugs and diets studied in those earlier trials, the HMG CoA reductase inhibitors ('statins': such as atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, and simvastatin) can produce substantial lowering of blood total and low density lipoprotein (LDL) cholesterol (i.e. 1 to 2 mmol.l<sup>-1</sup>) and triglyceride (0.5 mmol.l<sup>-1</sup>), along with small increases in high density lipoprotein (HDL) cholesterol<sup>(13-17)</sup>. Recently, the results from some randomized trials of the effects of statin therapy on coronary heart disease morbidity and mortality have become available<sup>(18-19)</sup>. As would be expected from the observational studies, the larger blood cholesterol reductions produced by the statins in those trials appeared to result in larger reductions in coronary heart disease. Typically, an average reduction in blood cholesterol of about 1 mmol.l<sup>-1</sup> maintained for about 5 years produced a reduction in non-fatal myocardial infarction and fatal coronary heart disease (i.e. total coronary heart disease) of about one-quarter, which is about half the effect associated epidemiologically with a prolonged 1 mmol.l<sup>-1</sup> difference in blood cholesterol levels among middle-aged individuals, and the reductions in coronary heart disease appeared to be somewhat greater in trials with larger cholesterol reductions. But, even after these studies, there is still only limited evidence about the effects of cholesterol-lowering therapy on mortality in many particular types of patient (e.g. among those who have not had a myocardial infarction, and among those who are female, elderly or with below-average cholesterol levels). Moreover, although these recent trials have not indicated any excess of non-coronary deaths or major morbidity (e.g. cancer incidence) with cholesterol-lowering therapy<sup>(18-19)</sup>, even in aggregate they were not large enough<sup>(20-22)</sup> to rule out the sort of excesses (i.e. about 15 to 20%) in cause-specific mortality, or cancers of particular sites, that some reviewers have suggested might be produced<sup>(23-26)</sup>.

Hence, the present, much larger, MRC/BHF Heart Protection Study aims to help resolve many of the remaining uncertainties as to the magnitude of any benefits of cholesterol-lowering therapy on survival in a

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\*Collaborators and participating centres are listed at the end of the report.

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wide range of different types of patient at elevated risk of coronary heart disease, and as to whether any adverse effects on cause-specific mortality or morbidity outweigh any benefits in particular types of patient. To do this, more than 20 000 such patients have been randomly allocated to receive 40 mg daily simvastatin or matching placebo for at least 5 years, with the aim of achieving an average cholesterol difference during the trial of about  $1.5 \text{ mmol.l}^{-1}$ .

### *Reliable assessment of the effects of antioxidant vitamin supplementation*

*Antioxidant vitamins and coronary heart disease associations*  
LDL cholesterol may be rendered atherogenic by oxidative modification that allows it to be accumulated by macrophages in the artery walls<sup>[27,28]</sup>, and in animal studies antioxidants have been shown to slow the progression of atherosclerosis<sup>[29-31]</sup>. Vitamin E is the major antioxidant in LDL particles, and LDL does not become oxidatively modified *in vitro* until the associated vitamin E is first degraded<sup>[32,33]</sup>. Supplementation of vitamin E substantially prolongs the resistance of LDL to oxidative damage<sup>[33,34]</sup>, and may have other potentially protective effects<sup>[35-38]</sup>. Beta-carotene, which can also function as a fat-soluble antioxidant in certain physiological circumstances, is carried with vitamin E in the fatty cores of the LDL particles. Vitamin C is the major water-soluble antioxidant in the plasma, and it has been shown *in vitro* to regenerate oxidized vitamin E<sup>[39,40]</sup>. In some epidemiological studies, dietary intake and plasma levels of antioxidant vitamins were inversely associated with coronary heart disease incidence<sup>[41-45]</sup> and plasma levels of autoantibodies to oxidized LDL and the degree of LDL susceptibility to oxidative damage were associated with atherosclerosis<sup>[46,47]</sup>. Increased dietary consumption of antioxidant vitamins has also been found to be inversely associated with cancer incidence<sup>[48]</sup>. Consequently, several reports<sup>[22,49,50]</sup> have called for large-scale intervention trials of dietary antioxidants (in particular, vitamins E and C) among high-risk individuals. But, even though there are many reasons to be hopeful, any protective effects may be only moderate. Hence, if several trials of limited statistical power are undertaken then some may produce favourable results and some may fail to do so.

#### *Effects of antioxidant vitamin supplementation*

Results are currently available from only one large randomized trial of vitamin E, in which 6 years of a low daily dose of vitamin E (50 mg daily) was not shown to have protective effects<sup>[51,52]</sup>. On the other hand, promising results on non-fatal myocardial infarction have been reported from a relatively small trial of about 18 months of 400-800 IU daily vitamin E<sup>[53]</sup>; but there were few cardiovascular events in that study, no apparent effects on cardiac or other mortality, and some quite striking imbalances at baseline between the treatment

groups, and so the evidence of benefit is weak. Despite suggestions from observational studies that people who eat more fruit and vegetables containing beta-carotene have lower risks of certain types of cancer and cardiovascular disease, the results thus far from large trials of beta-carotene (with or without the addition of vitamin A) have been unpromising<sup>[54,55]</sup>. Hence, much more evidence is needed from large-scale randomized trials about the effects on cardiovascular events and mortality of prolonged supplementation with antioxidant vitamins.

The Heart Protection Study aims to obtain reliable evidence about the effects of antioxidant vitamins by having randomized high-risk individuals not only to simvastatin vs placebo but also to antioxidant vitamin supplementation vs placebo in a '2 x 2 factorial' design. The antioxidant vitamin regimen being studied (600 mg of vitamin E, 250 mg of vitamin C and 20 mg of beta carotene daily) is within the range considered likely to be safe and potentially effective<sup>[56]</sup>. The factorial design allows all patients to contribute fully to assessment of the separate effects of cholesterol-lowering therapy and of antioxidant supplementation, without any material increase in sample size beyond that required for a study that only assessed one or other treatment<sup>[57]</sup>. Such a study design will also provide some information about the combined effects of cholesterol-lowering therapy and of antioxidant supplementation.

### *Plan of investigation*

To avoid the uncertainties of interpretation that have affected the results of many previous prevention trials, the Heart Protection Study was designed to be really large, to involve a substantial cholesterol reduction and substantial antioxidant supplementation, and to include a wide range of patients at substantial risk of death within 5 years both from coronary heart disease and from other causes.

#### *Eligibility: many different categories of patient at increased risk of coronary heart disease death*

Patients with a history of myocardial infarction or other coronary heart disease, occlusive disease of non-coronary arteries, diabetes or treated hypertension are all at increased risk of death from coronary heart disease, irrespective of their cholesterol level. Hence, a heterogeneous mixture of such patients is deliberately being studied (see Fig. 1: 'Eligibility for the MRC/BHF Heart Protection Study'). For the reasons given in the Introduction, patients with baseline cholesterol levels down to  $3.5 \text{ mmol.l}^{-1}$  were eligible provided that they were considered on the basis of other factors to be at substantial 5-year risk of coronary heart disease death. Along with those smaller statin trials which have

- (1) Male or female aged about 40 to 80 years
- (2) High risk of coronary heart disease death over the next 5 years:
  - (i) Coronary disease: definite or probable clinical diagnosis of myocardial infarction, unstable angina, stable angina, PTCA or CABG;
  - (ii) Occlusive disease of non-coronary arteries: clinical, angiographic or ultrasound diagnosis of carotid artery stenosis (e.g. transient ischaemic attack or non-disabling stroke not thought to be haemorrhagic), carotid endarterectomy, leg artery stenosis (e.g. intermittent claudication) or surgery;
  - (iii) Diabetes mellitus: clinical diagnosis of insulin-dependent or non-insulin-dependent diabetes; or
  - (iv) Treated hypertension: use of antihypertensive drug therapy in male aged 65 years or over (in order to be at sufficiently high risk of vascular events).
- (3) No clear indications for the study treatments: the patient is not already taking HMG CoA reductase inhibitors or high-dose vitamin E supplements, and neither the patient nor the patient's doctor considers there to be any definite need to do so.
- (4) No clear contraindications to the study treatments:
  - (i) baseline plasma cholesterol:  $<3.5 \text{ mmol} \cdot \text{l}^{-1}$ ;
  - (ii) chronic liver disease (La. cirrhosis or hepatitis) or abnormal liver function (La. alanine transaminase  $>1.5 \times$  upper limit of normal);
  - (iii) severe renal disease or evidence of renal impairment (La. creatinine  $>2 \times$  upper limit of normal);
  - (iv) inflammatory muscle disease (such as dermatomyositis or polymyositis) or creatine kinase  $>3 \times$  upper limit of normal;
  - (v) concurrent treatment with cyclosporin (or a condition likely to result in organ transplantation and the need for cyclosporin);
  - (vi) concurrent treatment with fibrates or high-dose niacin. (P.S. Patients on cholesterol-lowering diets or drugs — other than HMG CoA reductase inhibitors, fibrates or high-dose niacin — could still be entered in the study); or
  - (vii) child-bearing potential (La. pre-menopausal women who is not sterilized or using a reliable method of contraception).
- (5) No other predominant medical problem:
  - (i) severe heart failure or some importantly life-threatening condition other than vascular disease (such as very severe chronic airways disease or any cancer other than non-melanoma skin cancer);
  - (ii) psychiatric disorder, senility or physical disability (such as severely disabling stroke); or
  - (iii) recent history of alcohol or drug abuse.

Figure 1 Eligibility for the MRC/BHF Heart Protection Study.

likewise included patients with below-average baseline levels of total cholesterol<sup>[21]</sup>, the Heart Protection Study should involve sufficiently large numbers of high-risk patients with low total cholesterol levels (e.g. 3.5 to 5.2  $\text{mmol} \cdot \text{l}^{-1}$ ) for the effects on coronary heart disease incidence to be assessed separately in this subgroup. No upper limit of cholesterol for inclusion was imposed in the study since it was considered likely that there would be patients (such as those who have not previously had a myocardial infarction, women or the elderly) in whom many clinicians would be substantially uncertain as to the benefits of lowering even an elevated cholesterol. But, all patients in whom statin therapy was considered by their own doctor to be clearly indicated (or clearly contraindicated) because of their cholesterol levels, or any other reason, were not to be randomized.

*Sample size: several thousand individuals in each of several different high-risk categories*

Previous studies in patients with coronary heart disease, diabetes mellitus, carotid stenosis and peripheral vascular disease<sup>[20,28-31]</sup> had indicated that the 5-year control group rate of fatal coronary heart disease in the study population might be about 9%, with a further 5-6% dying from non-cardiac causes; and similar rates were

also indicated in treated hypertensives who were both male and aged over 65<sup>[34]</sup>. It was anticipated, therefore, that among 20 000 such patients there would be about 1500 coronary heart disease deaths, plus similar numbers of non-fatal myocardial infarctions, during 5 years of follow-up. If so, and if cholesterol-lowering therapy reduced 5-year coronary heart disease mortality by about 25%, and all-cause mortality by 15-20%, then a study of this size should have an excellent chance of demonstrating such effects at convincing levels of statistical significance (La.  $>90\%$  power at  $2P < 0.01$ ). Moreover, for the antioxidant comparison, an apparent reduction of just 10% in the incidence of coronary heart disease (e.g. 1500 with a coronary heart disease event among controls vs 1350 among those allocated vitamins) would yield a high degree of statistical significance ( $2P = 0.003$ ).

In any particular category of such high-risk patients, randomization of several thousand patients should also allow reliable assessment of a reduction of a quarter in fatal coronary heart disease. The study therefore sought to randomize large enough numbers in each of a wide range of different categories for sufficiently powerful analyses of the effects on coronary heart disease within each of the different pre-existing disease categories studied (e.g. coronary disease; occlusive disease of non-coronary arteries; diabetes mellitus; and treated hypertension) and of several other major subgroups (including

women, those aged 65–80-years at entry, and those with baseline cholesterol of 3.5–5.2 mmol.l<sup>-1</sup>). Among the 20 000 randomized patients there would also be expected to be over 1000 deaths from causes other than coronary heart disease and over 1000 new cancers during the scheduled follow-up. If so, the study should help assess the effects of the treatments not just on all-cause mortality but also on particular non-coronary causes of death and on the incidence of particular types of cancer. But, the best evidence on such questions for cholesterol-lowering will most probably be provided by consideration of this study's results along with those from the other main trials in a prospectively planned collaborative meta-analysis<sup>[27]</sup>.

### Planned comparisons of outcome

For cholesterol-lowering therapy, the primary comparisons in the Heart Protection Study are to involve log-rank analyses<sup>[27]</sup> of all-cause mortality, of coronary heart disease mortality (ICD 410–414 in the 9th International Classification of Diseases), and of all mortality from causes other than coronary heart disease during the scheduled treatment period among all those allocated active-simvastatin vs all those allocated placebo-simvastatin (i.e. 'intention-to-treat' analyses). For the antioxidant vitamin supplementation, the primary comparisons are to involve log-rank analyses of total coronary heart disease and of fatal coronary heart disease during the scheduled treatment period among all those allocated active-vitamins vs all those allocated placebo-vitamins. (No allowance will be made for multiple hypothesis testing in the primary comparisons of each of the study treatments.)

Secondary comparisons are to be made of the effects of allocation to cholesterol-lowering therapy on ten specific non-coronary causes of death: (i) haemorrhagic stroke (ICD 430–432), (ii) other strokes (433–438), (iii) other vascular (390–459 excluding coronary heart disease or stroke), (iv) neoplastic (140–239), (v) respiratory (460–519), (vi) hepatic (570–576), (vii) renal (580–593), (viii) other medical causes (rest of 000–799), (ix) suicide (950–959), and (x) other non-medical causes. (In interpreting these results, allowance is to be made for multiple hypothesis testing, for the effects observed on relevant non-fatal events, and, particularly, for evidence from other studies<sup>[21]</sup>.) Secondary comparisons are also to be made of the effects of cholesterol-lowering therapy allocation and of vitamin allocation on (i) total coronary heart disease rates in the first two years and in the later years of scheduled treatment, to see if any protective effect increases with time; on (ii) cause-specific mortality rates (i.e. deaths from coronary heart disease and deaths from non-coronary causes, as defined above) not only during the scheduled treatment period but in long-term follow-up thereafter, to see if any benefits or hazards persist; and on (iii) total (i.e. fatal and non-fatal) stroke. Other pre-specified secondary comparisons of the effects of cholesterol-lowering therapy allocation and

of vitamin allocation on fatal coronary heart disease and on total coronary heart disease are to be made in the following different circumstances:

- (i) in different categories of pre-existing disease (i.e. in those with coronary disease; and, in the absence of coronary disease, in those with occlusive disease of non-coronary arteries and in those with diabetes mellitus);
- (ii) in various pre-specified categories of patient (men and women; age  $\leq$  and  $>$ 65 years at entry; diastolic blood pressure  $\leq$  and  $>$ 90 mmHg at entry; screening cholesterol level  $\leq$  5.2, 5.3–6.0, 6.1–7.0, 7.1–7.8,  $>$ 7.8 mmol.l<sup>-1</sup>; screening LDL-cholesterol, HDL-cholesterol and vitamin levels subdivided into 3 similar-sized groups; smokers and non-smokers);
- (iii) in the presence and the absence of the other study treatment; and
- (iv) among patients subdivided with respect to the size of the reduction in blood cholesterol and the size of the increase in vitamin levels; respectively, during the pre-randomization run-in period (see below).

Tests for heterogeneity of the proportional effects observed in subgroups, or tests for trend if patient categories can be arranged in some meaningful order, are to be used (with allowance for multiple comparisons and consideration of evidence from other studies) to determine whether the effects in specific subcategories are clearly different from the overall effects<sup>[25]</sup>. Comparisons are also to be made of the effects of cholesterol-lowering therapy allocation on total non-coronary mortality in the five groups of baseline cholesterol (as defined above), and of the effects of each of the study treatments on the incidence of site-specific cancers, of confirmed cerebral haemorrhages, of vascular procedures (i.e. CABG, PTCA), of hospitalizations for various causes, and of days spent in hospital for coronary heart disease and other cardiovascular events. Many other analyses will also be performed and presented, in the context of evidence from other studies, with due allowance made for their exploratory (and, perhaps, data-dependent) nature<sup>[27]</sup>.

### Interim analyses: role of the independent Data Monitoring Committee and the Steering Committee

During the study, interim analyses of mortality and of any other information that is available on major events (including serious adverse experiences), along with any other analyses that the committee request, are supplied regularly (and at least annually), in strict confidence, to the chairman of the independent Data Monitoring Committee. In the light of these analyses and the results of any other relevant trials, the Data Monitoring Committee is to advise the Steering Committee if, in their view, the randomized comparisons in the Heart

Protection Study have provided both (a) 'proof beyond reasonable doubt'<sup>\*</sup> that for all, or for some specific types, of patient in the study, use of either treatment is clearly indicated or clearly contraindicated in terms of a net difference in all-cause mortality, and (b) evidence that might reasonably be expected to influence materially the patient management of many clinicians who are already aware of any other available trial results. The Steering Committee can then decide whether to modify the study or to seek extra data. Unless this happens, the Steering Committee, the collaborators, the funding agencies and the central administrative staff (except those who supply the confidential analyses) will remain ignorant of the interim results on mortality and major morbidity.

## Results

### *Invitation of potentially eligible patients to screening clinics*

Medical collaborators from 69 U.K. hospitals appointed senior nurses to run the study clinics and obtained local ethics committee approval. With the permission of their relevant consultant colleagues, records of patient discharges and of special wards or clinics were used to identify potentially eligible candidates for the study. The coordinating centre used this information to seek agreement, in the name of the local collaborator, from general practitioners to invite patients to the local study clinic. These invitations involved over-sampling of particular types of patient to help ensure that sufficient numbers in each of various categories (i.e. type of prior disease; female; older; but not cholesterol level since this was not known prior to screening) were recruited to allow direct assessment of the study treatments in each category. In total, the coordinating centre invited 130 873 patients to attend screening clinics at the 69 collaborating hospitals.

### *Screening clinic visit (at - 2 months of study)*

63 603 patients attended the study screening clinics, where the specially trained study nurse completed a brief questionnaire about past medical history, current treatment, and other factors relevant to eligibility and coronary heart disease risk. Height, weight and blood pressure were recorded, and the study inclusion and exclusion criteria checked. A non-fasting blood sample was taken into heparinised vacutainers, with an immediate preliminary measurement of cholesterol made on

<sup>\*</sup>Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but in general a difference of at least 3 standard deviations in an interim analysis of a major end-point would be needed to justify halting, or modifying, such a study prematurely. This criterion has the practical advantage that the exact number of interim analyses is of little importance, and so no fixed schedule is proposed<sup>(27)</sup>.

one small portion of it using an Accutrend autoanalyser (which was found to produce values in close agreement with those obtained by the central laboratory). All screened patients were given dietary information similar to that contained in the American Heart Association stage I diet guidelines, and other personalised information about modification of risk factors for vascular disease.

Those patients who appeared eligible for the trial were provided with a written description of the study and invited to participate (after, if they wished, discussing it with their family and general practitioner). All who agreed to participate were asked for their written consent in a form acceptable to the local ethics committee. Of 31 458 patients who attended screening but did not enter the pre-randomization run-in phase, 56% indicated that they would have difficulty attending regular clinics or refused for other reasons, 21% had some life-threatening disease other than vascular disease or diabetes, 5% had had a myocardial infarction, stroke or hospitalization for angina within the previous 6 months, 12% were already on a statin (or, in a few cases, some other contraindicated drug) and 10% were not eligible for some other reason.

### *Run-in period prior to randomization*

32 145 patients agreed to enter the pre-randomization run-in phase of the study and were given a run-in treatment pack. All of these packs contained a 10-week calendar-blister supply of the same study treatment combination: an initial 4 weeks of placebo-simvastatin and active-vitamins (to give time for the central laboratory to check whether liver enzymes, creatinine or creatine kinase were abnormal: see Fig. 1), followed by 6 weeks of both active treatments (to allow an assessment of responsiveness to the study treatments: see below). The screening blood samples from these patients were sent to the coordinating centre laboratory for immediate assay (lipid profile, liver enzymes, creatinine, creatine kinase and, in those with diabetes, HbA<sub>1c</sub>) and for long-term storage of plasma and buffy coat aliquots in liquid nitrogen for analyses in future years. Beckman autoanalysers used standard spectrophotometric enzymatic methods to measure total cholesterol and lipid fractions (including LDL directly) and immunoturbidometric methods to measure apolipoproteins A<sub>1</sub> and B. Quality control is maintained by making repeat measurements in Center for Disease Control certified reference lipid material and in a human plasma pool, and by participation in various external quality assurance schemes, with coefficients of variation for all lipid measurements typically less than 5%. Alanine transaminase and creatine kinase were measured on Beckman autoanalysers using an enzymatic rate method, and creatinine by a modified rate Jaffe method.

Patients with significantly abnormal blood results were advised by the coordinating centre during the initial placebo-simvastatin run-in phase to stop study

Table 1 Impact of screening blood lipid levels on changes in lipid levels produced by 40 mg daily simvastatin during the pre-randomization run-in phase

Blood lipid, and subdivision of screening value* (mmol.l <sup>-1</sup> )	Unbiased mean** at screening (mmol.l <sup>-1</sup> )	Reduction during run-in	
		Absolute (mmol.l <sup>-1</sup> ± SE)	Proportional (% ± SE)
Total cholesterol			
<6.0	5.21	1.52 ± 0.03	29% ± 0.6
≥6.0	6.46	1.90 ± 0.04	29% ± 0.7
LDL cholesterol			
<3.5	2.86	1.13 ± 0.03	39% ± 0.9
≥3.5	3.85	1.42 ± 0.04	37% ± 1.0
HDL cholesterol			
<1.0	0.84	0.02 ± 0.005	2% ± 0.6
≥1.0	1.25	0.02 ± 0.008	1% ± 0.7
Triglycerides			
<2.0	1.41	0.22 ± 0.02	15% ± 1.6
≥2.0	2.89	0.41 ± 0.07	14% ± 2.3

\*Patients were subdivided into groups by their initial screening blood values; \*\*and unbiased estimates of the mean values in these groups, with correction for regression to the mean, are obtained by using follow-up (i.e. post-randomization) values for a random sample of placebo-allocated patients (n=about 1200) in each screening-defined group. As indicated, the levels of all lipids (including HDL cholesterol) fell during run-in.

treatment. The general practitioner of each patient started on run-in treatment was informed of their patient's screening lipid profile and other relevant blood results by the coordinating centre (and, for any patient on oral anticoagulants, was advised to check anticoagulant control), and asked to advise the coordinating centre if they were likely to prescribe a statin or high-dose vitamin supplements for that particular patient (or, conversely, considered such treatment or inclusion in the study to be clearly contraindicated), in which case the patient was not to be randomized.

One aim of the run-in period was to help increase the likelihood that those randomized would continue taking their allocated study treatment for an extended period. Any patients who, during run-in, had any apparent side-effects to treatment, appeared to be non-compliant, wished to drop out for any reason or whose general practitioner wished to treat them with a non-study statin (or high-dose vitamins) were not to be randomized. By this process, many potential drop-outs should have been excluded before becoming part of the randomized comparison, with a consequent improvement in statistical sensitivity for assessing the effects of prolonged treatment<sup>(46)</sup>. In addition, the use of active study treatments during the pre-randomization run-in period should allow unbiased randomized comparisons of the effects of the study treatments on clinical outcomes within subgroups of patients defined by their responsiveness to the active treatments. For, a blood sample was collected from each patient at the screening visit before active treatment starts and at the randomization visit after 4-6 weeks on the active treatments. If some combination of measurements in these blood samples can identify subgroups in which the effects of the study treatments on blood biochemistry differ substantially (for example, see

Table 1), this would allow separate unbiased randomized comparisons within each such subgroup of coronary heart disease incidence by allocated treatment (by contrast with the non-randomized, and hence potentially biased, comparisons reported previously<sup>(47-50)</sup>).

#### Randomization clinic visit (0 months)

Compliant patients who had not had a major vascular event or other problem during the run-in period were asked at their randomization clinic visit if they were willing to continue taking study treatment for at least the next 5 years. Of 11 609 patients who entered the run-in period but were not randomized, 65% chose not to continue, 17% did not seem likely to be compliant long-term, 13% were considered by their own doctor to have a clear indication for (or contraindication to) statin therapy after review of the screening lipid results provided, 10% had abnormal screening blood results, 9% reported problems associated with the run-in treatment, 1% had had myocardial infarction, stroke, hospitalization for angina or cancer diagnosed during run-in, and 1% had other reasons for not continuing.

For those who agreed to enter the randomized phase of the study, a non-fasting blood sample was taken for immediate central laboratory assay (lipid profile, liver enzymes) and for storage in liquid nitrogen for subsequent analyses. A central randomization service was then telephoned which allowed the coordinating centre to conduct a final check of eligibility prior to randomization, and to balance the randomization with respect to important patient characteristics (in particular, eligibility criteria and other major prognostic factors) using a minimization algorithm<sup>(70)</sup>. A treatment pack was then

Table 2(a) Randomized men subdivided by prior diagnosis, age and total cholesterol level (and % of all randomized)

Age (years):	≤65			>65			Total: any age or cholesterol
	<5.5	>5.5 ≤7.0	>7.0	<5.5	>5.5 ≤7.0	>7.0	
<b>Previous myocardial infarction*</b>							
Alone	517	705	128	509	599	102	2560
With cerebrovascular disease	104	141	35	170	215	45	710
With peripheral vascular disease	323	449	110	379	498	91	1850
With diabetes mellitus	217	181	37	239	204	37	915
With treated hypertension	550	689	113	604	699	133	2788
Subtotal: any with prior myocardial infarction*	1346 (7%)	1735 (8%)	336 (2%)	1443 (7%)	1706 (8%)	316 (2%)	6882 (34%)
<b>Other coronary heart disease*</b>							
Alone	231	386	65	185	235	43	1145
With cerebrovascular disease	61	87	19	92	107	20	386
With peripheral vascular disease	241	302	58	216	242	60	1119
With diabetes mellitus	138	158	10	138	111	19	574
With treated hypertension	284	376	58	288	300	58	1364
Subtotal: any with other coronary heart disease*	704 (3%)	993 (5%)	168 (1%)	674 (3%)	737 (3%)	149 (1%)	3425 (17%)
<b>No history of coronary heart disease</b>							
Cerebrovascular disease	265	354	71	262	317	80	1249
Peripheral vascular disease	394	536	134	400	463	118	2045
Diabetes mellitus	919	753	126	503	317	40	2658
Treated hypertension	403	476	99	475	480	102	2035
Subtotal: any with no coronary heart disease*	1326 (6%)	1376 (7%)	278 (1%)	1011 (5%)	950 (5%)	206 (1%)	5147 (25%)
<b>Total: any diagnosis</b>	<b>3376 (16%)</b>	<b>4104 (20%)</b>	<b>782 (4%)</b>	<b>3128 (15%)</b>	<b>3393 (17%)</b>	<b>671 (3%)</b>	<b>15454 (75%)</b>

\*'Previous myocardial infarction' group includes any patients with a history of prior myocardial infarction irrespective of whether other evidence of coronary heart disease was recorded; 'Other coronary heart disease' group includes patients without a history of prior myocardial infarction but with some other history of coronary heart disease (i.e. angina, prior CABG or PTCA).

specified for the patient which contained calendar-blisters of simvastatin tablets (40 mg every evening) or matching placebo, and of vitamin capsules (two every evening, each containing 300 mg vitamin E, 125 mg vitamin C, and 10 mg beta-carotene) or matching placebo.

A total of 15 454 men and 5082 women entered the randomized phase of the study between July 1994 and May 1997 (Tables 2(a) and (b)). Of these, 8510 (41%) reported that they had had a previous myocardial infarction (most of whom were either female, or elderly or with low blood cholesterol), 4869 (24%) had some other history of coronary heart disease and 7157 (35%) had no history of coronary heart disease. 3288 (16%) of those randomized had had cerebrovascular disease diagnosed, 6748 (33%) had some other evidence of peripheral vascular disease, 5963 (29%) had diabetes mellitus and 8455 (41%) were being treated for hypertension. There was overlap between these various diagnostic categories, but still 1822 of those with cerebrovascular disease, 3985 with diabetes, and 2860 with treated hypertension did not report any history of coronary heart disease. Table 3 shows the non-study treatments being used at the time of randomization in different diagnostic categories. Aspirin or some other antiplatelet agent was being used by 77% of patients with a history of myocardial infarction, other coronary heart disease or stroke, and by 47% of those

with peripheral vascular disease. However, in the absence of diagnosed occlusive vascular disease, antiplatelet therapy was being taken by only 7% of those with diabetes and 19% of those with treated hypertension. Of the women randomized, only 582 (11%) reported that they were taking hormone replacement therapy.

9515 (46%) of the participants were aged over 65 at entry to the study. Screening non-fasting levels of blood total cholesterol were less than 5.5 mmol.l<sup>-1</sup> in 7882 (38%), between 5.5 and 7.0 mmol.l<sup>-1</sup> in 10 067 (49%), and above 7 mmol.l<sup>-1</sup> in only 2587 (13%); with a greater preponderance in this latter group of women, of older individuals and of those without diagnosed coronary heart disease). LDL cholesterol levels were less than 3.0 mmol.l<sup>-1</sup> in 6888 (34%) participants, between 3.0 and 3.4 mmol.l<sup>-1</sup> in 4119 (20%) and above 3.4 mmol.l<sup>-1</sup> in 9529 (46%). The mean screening levels of total cholesterol were higher in the randomized women (6.2 ± 1.1 mmol.l<sup>-1</sup>) than in the men (5.7 ± 1.0 mmol.l<sup>-1</sup>), reflecting higher levels of both LDL (3.3 ± 0.9 vs 3.3 ± 0.8 mmol.l<sup>-1</sup>) and HDL (1.2 ± 0.4 vs 1.0 ± 0.29 mmol.l<sup>-1</sup>) in the women. Non-fasting triglyceride levels were similar in the women (2.0 ± 1.3 mmol.l<sup>-1</sup>) and the men (2.1 ± 1.4 mmol.l<sup>-1</sup>).

Table 2(b) Randomized women subdivided by prior diagnosis, age and total cholesterol level (and % of all randomized)

Age (years): Cholesterol (mmol.l <sup>-1</sup> )	≤65			>65			Total: any age or cholesterol
	≤5.5	>5.5 ≤7.0	>7.0	≤5.5	>5.5 ≤7.0	>7.0	
<b>Previous myocardial infarction*</b>							
Alone	74	143	45	44	138	62	506
With cerebrovascular disease	18	33	30	19	48	38	186
With peripheral vascular disease	59	108	52	54	135	114	522
With diabetes mellitus	19	51	19	38	50	33	210
With treated hypertension	87	169	73	83	225	141	778
Subtotal: with prior myocardial infarction*	197 (1%)	380 (2%)	152 (1%)	169 (1%)	453 (2%)	277 (1%)	1628 (8%)
<b>Other coronary heart disease*</b>							
Alone	76	97	32	29	89	45	368
With cerebrovascular disease	18	39	17	19	56	27	176
With peripheral vascular disease	82	176	74	33	122	64	551
With diabetes mellitus	43	90	30	20	68	28	279
With treated hypertension	87	193	74	49	183	79	665
Subtotal: any with other coronary heart disease*	223 (1%)	411 (2%)	159 (1%)	113 (1%)	364 (2%)	174 (1%)	1444 (7%)
<b>No history of coronary heart disease</b>							
Cerebrovascular disease	77	110	38	60	124	64	473
Peripheral vascular disease	107	201	63	79	131	80	661
Diabetes mellitus	373	411	122	132	212	77	1327
Treated hypertension	154	209	75	96	190	101	825
Subtotal: any with no coronary heart disease*	474 (2%)	579 (3%)	184 (1%)	202 (1%)	383 (2%)	188 (1%)	2010 (10%)
<b>Total: any diagnosis</b>	<b>894 (4%)</b>	<b>1370 (7%)</b>	<b>495 (2%)</b>	<b>484 (2%)</b>	<b>1200 (6%)</b>	<b>639 (3%)</b>	<b>5082 (25%)</b>

\*'Previous myocardial infarction' group includes any patients with a history of prior myocardial infarction irrespective of whether other evidence of coronary heart disease was recorded; 'Other coronary heart disease' group includes patients without a history of prior myocardial infarction but with some other history of coronary heart disease (i.e. angina, prior CABG or PTCA).

Table 3 Percentages of patients using non-study treatments at randomization

Treatment	Post myocardial infarction or other coronary heart disease* (n=13379)	Without coronary heart disease*				Any diagnosis (n=20536)
		Cerebrovascular disease (n=1822)	Peripheral vascular disease (n=2185)	Diabetes (n=2913)	Treated hypertension (n=237)	
Aspirin or other antiplatelet	77%	77%	67%	7%	19%	63%
Oral anticoagulant	5%	9%	5%	1%	9%	5%
Nitrate	47%	2%	1%	1%	1%	31%
Beta-blocker	34% (23%)	17% (4%)	7% (2%)	7% (1%)	38%	26% (16%)
Calcium antagonist	36% (26%)	24% (5%)	20% (4%)	12% (<1%)	37%	30% (18%)
ACE inhibitor	19% (10%)	20% (3%)	17% (3%)	20% (3%)	32%	20% (8%)

\*Patients are counted only once; if they fall into more than one disease category, they are counted in the category nearest to the left. Percentages in brackets are for use of beta-blocker, calcium antagonist or ACE inhibitor therapy, respectively, in patients not being treated for hypertension.

### Post-randomization follow-up

After randomization, patients are to be seen in the clinic for routine follow-up checks at 4, 8 and 12 months post-randomization, and then at 6-monthly intervals. By the end of August 1998, there was a mean of 25 months of follow-up after randomization (range 13 to 47 months). Details are recorded at follow-up of the main

reasons for all hospital admissions (including day cases) and of any suspected myocardial infarctions, strokes, coronary angioplasty, coronary artery or other vascular surgery, or other serious adverse experiences (see below). Any new unexplained muscle pain or weakness is also recorded: at each of the scheduled follow-up times about 5% of patients have reported such muscle symptoms, but at no stage has there been any significant difference in

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Table 4 Percentage of randomized patients reporting compliance with study treatment

Scheduled follow-up (months)	No. of patients	Taken $\geq$ 80% of tablets		Taken $\geq$ 80% of capsules	
		Simvastatin	Placebo	Vitamins	Placebo
4	20 314	94%	94%	94%	94%
8	20 077	91%	90%	92%	92%
12	19 922	89%	87%	90%	90%
18	18 279	87%	83%	89%	89%
24	13 561	86%	80%	88%	88%
30	7797	85%	77%	86%	87%

Table 5 Reasons for randomized patients stopping study treatments (% of all randomized)

Reason(s) given*	Tablets		Capsules	
	Simvastatin (10 269)	Placebo (10 267)	Vitamins (10 269)	Placebo (10 267)
Patient unable or unwilling to attend clinics	2.3%	2.8%	1.7%	1.5%
Patient wishes to stop (other than to start statin)	6.1%	6.8%	5.9%	5.3%
Non-study statin started	1.7%	5.6%	1.3%	1.2%
Other contraindicated drug started	0.03%	0.11%	0.07%	0.09%
Abnormal liver or muscle enzymes	0.07%	0.06%	0.01%	0.01%
Muscle pain or weakness	0.15%	0.17%	0.03%	0.11%
Other symptoms	1.0%	1.1%	0.8%	0.7%
Other reasons	1.4%	2.0%	1.3%	1.2%
Any of above*	11.6%	16.3%	9.6%	8.8%

\*Patients may give more than one reason for stopping study tablets and/or capsules.

the frequency of such reports between patients allocated simvastatin tablets and those allocated placebo tablets (or between those allocated vitamin or matching placebo capsules).

Compliance with taking the study treatments is checked (and defined as taking at least 80% of scheduled treatment) and, for patients who stop this treatment, the reasons for doing so recorded. For the vitamin or placebo capsules, compliance fell to about 90% during the first year and has then remained approximately steady, with no apparent difference between the treatment groups (Table 4). By contrast, for the simvastatin or placebo tablets, the initial fall in compliance to about 90% during the first 8 to 12 months (which was similar in both treatment groups) was followed by a further fall of similar size among those allocated placebo tablets, but by a smaller fall among those allocated simvastatin tablets. There is no evidence that any side-effects with the study simvastatin or vitamins are leading to the study treatments being stopped: indeed, despite the large numbers being studied, there are no apparent differences between the treatment groups in any reported side-effects or in any biochemical abnormalities (see below).

As can be seen from Table 5, by far the most common reason for stopping the tablets or capsules is that the patient was unable or unwilling to continue attending clinic follow-up (in which case the simvastatin or

placebo tablets were to be stopped, since routine blood monitoring could not continue, but the vitamin or placebo capsules could be continued) or wished to stop for some other reason, but there was no excess among those on the active treatments. The only clearly significant difference between the treatment groups in the numbers stopping the study treatments was, as might be expected, in patients allocated placebo tablets being somewhat more likely to be prescribed a non-study statin than those allocated the study simvastatin tablets. Until spring 1998, patients prescribed non-study statins were routinely advised to stop their simvastatin or placebo tablets, but subsequently that policy was changed so that non-study statin regimens of up to the equivalent, in lipid-lowering potency, of about 40 mg daily simvastatin could be added to the study simvastatin or placebo tablets (unless considered contraindicated). About one-third of the patients taking non-study statins are continuing with their study tablets, and most of the rest are continuing with their capsules.

At each follow-up visit, a non-fasting blood sample is taken for immediate central laboratory assay of alanine transaminase and, in any patient with significant new unexplained muscle pain or weakness, of creatine kinase. Biochemical abnormalities requiring action are reported back to the clinic staff promptly, and appropriate follow-up arrangements made by the coordinating

**Table 6** Numbers of patients with elevated liver or muscle enzymes

Liver or muscle enzymes*	Simvastatin (10 269)	Placebo (10 267)
Alanine transaminase >2 ≤3 × ULN	52	52
>3 × ULN	39	32
Creatine kinase >5 ≤10 × ULN	4	2
>10 × ULN	3	2

ULN=Upper limit of normal: for alanine transaminase is 45 IU . l<sup>-1</sup> and for creatine kinase is 250 IU . l<sup>-1</sup>. \*Alanine transaminase is measured routinely at each follow-up visit. Creatine kinase is measured routinely only when patients complain of muscle pain and as part of the annual random sample, but it may also be measured, and abnormalities reported, on hospitalization for whatever reason.

centre for further clinic monitoring of the patient, and for any study treatment modifications, according to pre-specified guidelines. Table 6 shows that only slightly, and non-significantly, more patients allocated simvastatin tablets have been found to have elevated levels of alanine transaminase or of creatine kinase. One man allocated active simvastatin developed an asymptomatic elevation of alanine transaminase >3 times the upper limit of normal at about 18 months after randomization and stopped the study tablets; his alanine transaminase did not return to normal and, about 1 year later, he developed acute hepatitis from which he subsequently recovered (although his liver function tests remain abnormal). Of the five patients found to have creatine kinase >10 times the upper limit of normal, two had been detected in hospital with muscle symptoms (one allocated simvastatin and one allocated placebo tablets), two had creatine kinase measured because of muscle symptoms reported at the study clinic (one allocated simvastatin and one allocated placebo who was also found to be hypothyroid) and one asymptomatic patient was picked up by measurements in the annual random sample (see below).

In addition to events recorded at the scheduled follow-up visits, any serious adverse experiences that a doctor believes with a reasonable probability to be due to study treatment are, for regulatory purposes, to be reported immediately to the coordinating centre via a 24-hour telephone service. So far, during a mean of 25 months of follow-up, only 12 such events have been reported and there is no significant difference between the treatment groups (seven on simvastatin vs five on placebo tablets; seven on vitamins vs five on placebo capsules).

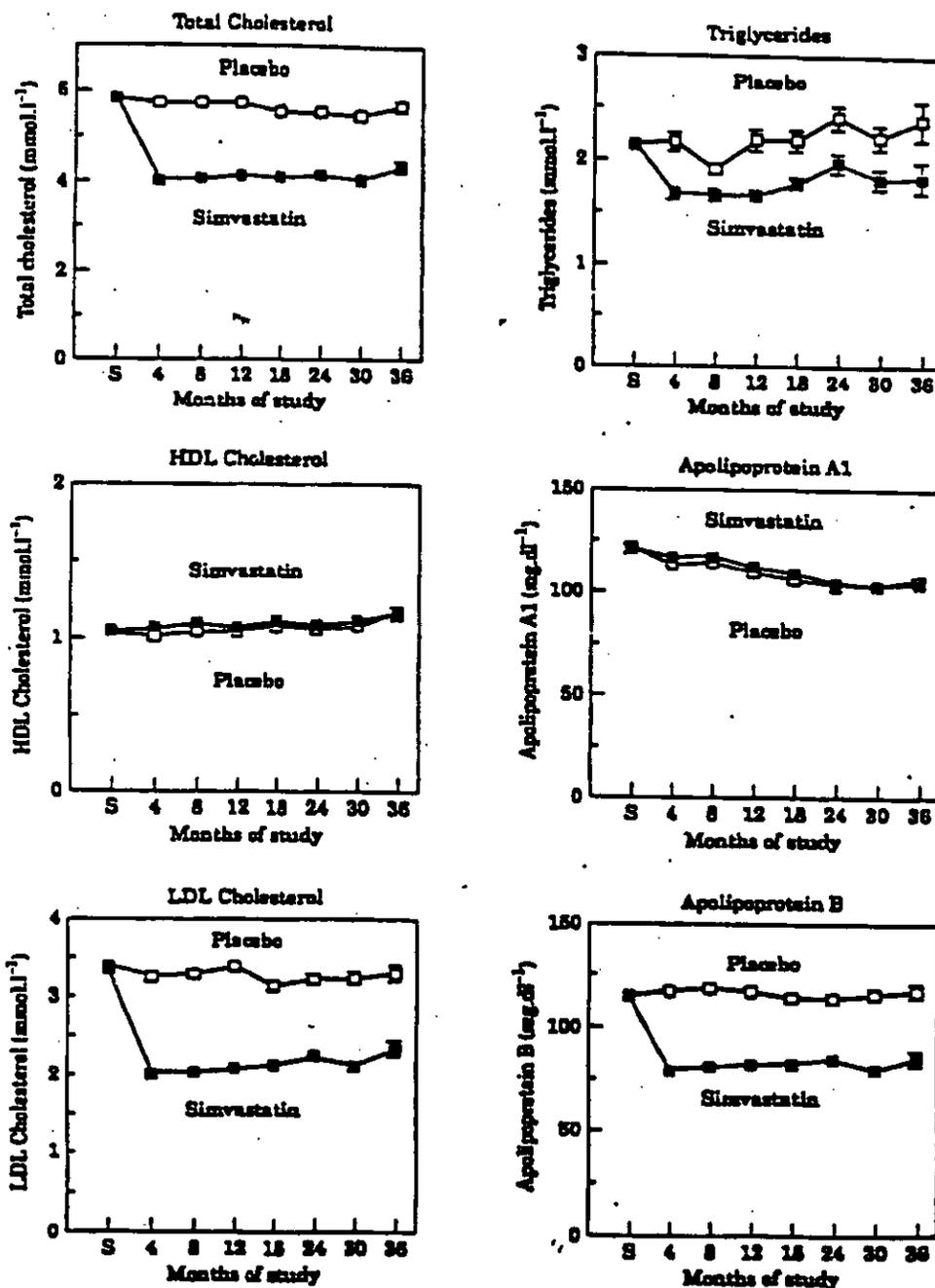
### *Effects of study treatments on blood lipids and vitamins*

To assess reliably the overall effects of the study treatments on the detailed lipid profile and vitamin levels in

the different treatment groups in this placebo-controlled trial, it is not necessary to assay blood samples from every patient. Instead it suffices, and is more cost-effective, to perform assays only in a random sample of the patients during the study. Each year, therefore, about 1300 of the randomized patients are selected (irrespective of whether or not they are continuing to take the study treatments or to attend the follow-up clinics) for extensive analysis of their non-fasting blood samples, with storage of aliquots of plasma in liquid nitrogen for any subsequent analyses required. Compared with those allocated placebo tablets, allocation to 40 mg daily simvastatin is producing reductions of about 1.5–1.6 mmol . l<sup>-1</sup> in blood total cholesterol, 1.1–1.2 mmol . l<sup>-1</sup> in LDL cholesterol, and 0.4–0.5 mmol . l<sup>-1</sup> in triglycerides, but an increase of only about 0.04 mmol . l<sup>-1</sup> in HDL (Fig. 2). Comparable changes in the levels of apolipoproteins B and A<sub>1</sub> are also seen, and these differences are maintained during, at least, the first 2 years of follow-up. Compared with plasma vitamin E levels of about 23 mg . l<sup>-1</sup> among those allocated placebo capsules, allocation to the active vitamin capsules is producing an increase of about 18 mg . l<sup>-1</sup>.

### *Rates of non-fatal and fatal events*

The coordinating centre seeks additional information from the patient's general practitioner (plus, if necessary, any relevant hospital discharge records) about each possible myocardial infarction, stroke, coronary angioplasty, vascular surgery, cancer, and other relevant hospitalization or serious adverse experience reported at each follow-up visit. It also seeks the certified causes of any deaths and details of any registered non-fatal cancers from the Office for National Statistics. It was anticipated at the start that, among the types of patient to be included in the study, the annual rate of total (i.e. fatal and non-fatal) coronary heart disease events would be about 3.5%. Based on events reported (i.e. with or without confirmation) during a mean of 25 months of follow-up, Table 7 suggests that the observed annual total coronary heart disease event rate is about 2.4%, but this should rise slightly after classification of those deaths that are, as yet, from unknown causes. The annual rates estimated from all those deaths reported during the 25 months of follow-up are also somewhat lower than the rates of 1.8% for fatal coronary heart disease and of 3.0% for total mortality predicted prior to the start. To some extent these lower than anticipated rates reflect the particular mix of patients included in the study, with more lower-risk patients (such as those with diabetes without any evidence of coronary heart disease at baseline), but it may also reflect a 'healthy volunteer' effect (due to exclusion at study entry of some sick individuals) that will diminish as follow-up becomes more prolonged. As would be expected, the event rates tend to be higher among participants who are older, have higher baseline cholesterol levels and present with a



**Figure 2** Non-fasting lipid levels by allocated simvastatin or matching placebo treatment. Analyses were to include all randomized patients scheduled for follow-up during a selected period each year: blood was obtained from 1251 (97%) of 1293 selected in spring 1996, from 1224 (96%) of 1276 in spring 1997 and from 1156 (94%) of 1230 in spring 1998, with the assumption made of no change from the screening value for any patient with a missing follow-up value. Mean values and their standard errors are estimated from 3583 individuals at screening (denoted 'S'), 723 at 4 months, 687 at 8 months, 854 at 12 months, 551 at 18 months, 555 at 24 months, 268 at 30 months and 144 at 36 months.

Table 7 Estimated annual rates of coronary heart disease and of death (based on all reported events, irrespective of confirmation of the diagnosis and of allocated treatment group)

Baseline characteristics	Total coronary heart disease	Fatal coronary heart disease	Total mortality
Gender			
Male	2.6%	1.2%	2.4%
Female	1.6%	0.6%	1.6%
Age (years)			
≤65	1.8%	0.7%	1.4%
>65	2.9%	1.4%	3.1%
Cholesterol (mmol.l <sup>-1</sup> )			
≤5.5	2.2%	1.0%	2.2%
>5.5≤7.0	2.3%	1.0%	2.1%
>7.0	2.9%	1.4%	2.8%
Diagnosis			
Prior myocardial infarction	3.4%	1.6%	2.8%
Other coronary heart disease	2.0%	0.8%	1.8%
Other*	1.3%	0.6%	1.8%
Any	2.4%	1.0%	2.2%

\*Cerebrovascular disease, peripheral vascular disease, diabetes mellitus or treated hypertension (but no history of myocardial infarction or other coronary heart disease).

previous history of myocardial infarction. So far, the estimated annual rate of reported strokes (excluding transient ischaemic attacks) is 1.3% and of cancers of all sites (except non-melanomatous skin cancer) is 1.4%.

## Discussion

Previous randomized trials have shown that there are reductions in non-fatal myocardial infarction and in fatal coronary heart disease within just a few years of lowering blood cholesterol levels<sup>(9-16,18-19)</sup>, and various guidelines for the use of such treatments have been proposed (particularly for middle-aged men with coronary heart disease and above-average cholesterol levels)<sup>(71-74)</sup>. However, there is still substantial uncertainty—both in the medical profession and in the general population—about the overall survival benefits of cholesterol-lowering drug therapy for particular types of patient, and the extent of their use is limited<sup>(73,76)</sup>. Uncertainty as to the possible benefits, or risks, of antioxidant vitamin supplementation is even greater.

The Heart Protection Study has now recruited large numbers of individuals at increased risk of coronary heart disease death in each of a wide range of different disease categories (including those with occlusive disease of non-coronary arteries, diabetes mellitus or hypertension) and of several other major subgroups (including women, the elderly or those with low blood cholesterol levels) for whom uncertainty still remains as to how worthwhile, and safe, are cholesterol-lowering drug treatment and antioxidant vitamin supplementation. Despite the large numbers of patients in the study, neither the statin regimen (40 mg simvastatin daily) nor the vitamin supplement (600 mg vitamin E, 250 mg

vitamin C, 20 mg beta-carotens daily) being investigated appears to be associated with significant excesses of any reported side-effects (including muscle pain or weakness, which had previously been reported with statin therapy<sup>(12,13)</sup>) or of any blood biochemical abnormalities (in particular, liver or muscle enzymes) during a mean follow-up of 25 months. These findings, which are consistent with the limited information reported on such outcomes from other large-scale trials<sup>(15-19)</sup>, demonstrate that prolonged simvastatin therapy (and antioxidant vitamin supplementation) is well tolerated and remarkably free of side-effects.

Compliance with the study treatments in the Heart Protection Study is good and, as a consequence, allocation to the simvastatin regimen is producing large and sustained reductions in blood total and LDL cholesterol levels (along with a small increase in HDL-cholesterol, which is consistent with previous statin trials<sup>(13-19)</sup>), and the vitamin supplement is producing a large increase in vitamin E levels. So, even though the coronary heart disease event and death rates during the initial follow-up period among the particular mix of patients being studied (many of whom had no previous history of coronary disease) are somewhat lower than anticipated, the study should be able to provide reliable evidence about the effects of cholesterol-lowering drug therapy and of antioxidant vitamin supplements on all-cause and cause-specific mortality and on major morbidity (including strokes and cancers) in a range of different individuals. Moreover, the special feature in this study of a pre-randomization run-in period on the active study treatments should provide the first unbiased randomized comparisons of the effects on coronary heart disease incidence among subgroups in which the effects of the treatments on blood levels of lipids and vitamins differ substantially.

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## Appendix

MRC Steering Committee: T. Meade (chairman), P. Sleight (vice-chairman), R. Collins, J. Armitage (study coordinators and writing committee), S. Parish, R. Peto (statisticians), L. Youngman (laboratory director), M. Buxton, D. de Bono, J. Fuller, A. Keech, A. Mansfield, B. Pentecost, D. Simpson, C. Warlow, L. O'Toole (MRC observer).

Independent Data Monitoring Committee: R. Doll (chairman), L. Wilhelmsen (vice-chairman), K. Fox, C. Hill, P. Sandercock.

Coordinating centre: J. Barton, C. Bray, K. Jayne (administrative coordinators); R. Collins, J. Armitage (clinical coordinators); A. Lawson (nursing liaison); L. Youngman (laboratory director); P. Harding, M. Lay, S. Parish, K. Wallendszus (computing coordinators).

740 MRC/BHF Heart Protection Study Collaborative Group

Collaborators (doctors, nurses, receptionists): *Aberdeen Royal*: N. Benjamin, J. Webster, J. Jamieson; L. Donald. *Bassettlaw Hospital*: R. Blandford; L. Carrington, H. McMahon; D. Cheetham. *Royal United, Bath*: J. Reckless; L. Brice, R. Carpenter, J. Christmas; C. Flower. *Bedford*: I. Cooper, S. Frampton, E. Pickerell; J. Wells. *Belfast City*: M. Scott; V. Crowe, A. Shaw; L. Shannon. *Birmingham City*: S. Jones; G. Faulkner, A. Lavery, H. O'Leary, R. Watson; C. Capewell, S. Hughes. *Birmingham Heartlands*: S. Bain, A. Jones; G. Holmes, C. Jewkes; T. Bellamy, P. Harrison. *Queen Elizabeth, Birmingham*: N. Buller; H. Nield, E. Smith, P. Vint; P. Crook, J. Williams. *Bishop Auckland General*: M. Bateson; P. Cawley, P. Gill; K. Simpson. *Royal Bournemouth*: M. Armitage; C. Cope, J. Tricksey, M. Wilson; S. Cottrell. *Princess of Wales, Bridgend*: C. Jones; M. Llewellyn, P. Smith; T. Woodsford. *Royal Sussex County, Brighton*: R. Vincent; E. Joyce, N. Skipper; P. 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P. Thomas; R. Thomas; C. Alexander, R. Chohan, K. Wood. *Princess Royal, Telford*; N. Capps; C. Stiles, L. Tonks; S. Crank. *Manor, Walsall*; A. Cunnington, P. Giles; N. Groves, E. Walton; W. Dance. *Watford General*; M. Clements; C. Faben, A. Hunter, E. Walker, L. Atkins, R. Williats. *Sandwell District General, West Bromwich*; E. Hughes; J. Sidaway, S. Sumara; G. Banks, R. Glover, K. Hall. *Worcester Royal Infirmary*; A. Munro, C. Pycock, D. Tibbutt; J. Cadwell, M. Greenwood; M. Betts. *Worthing*; M. Signy; E. Joyce, C. Wrapson; G. McCourt, R. Moore. *Wycombe General*; S. Price, R. Regan; M. Aldersley; P. Pendry.

**Funding:** The study is being funded by the UK Medical Research Council, the British Heart Foundation, Merck Sharp & Dohme (manufacturers of simvastatin; E. John, A. Tate, J. Tobert, R. Tomiak), and Hoffmann-La Roche (manufacturers of the vitamins; R. Salkeld). It was, however, designed independently of the pharmaceutical companies, who have no representation in its organisation and who, like the Steering Committee and investigators, remain blind to the main results as they accumulate. This arrangement is intended to ensure that no suggestions of lack of objectivity of the findings can be justified.

Charles L. Hyman, M.D.  
Director  
Regulatory Affairs

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June 30, 1998

Central Document Room  
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Center for Drug Evaluation and Research  
12229 Wilkins Avenue  
Rockville, MD 20850



**NDA 19-766: ZOCOR™ (simvastatin) Tablets**

**SUPPLEMENTAL NEW DRUG APPLICATION  
Simvastatin-40-mg Alternative Starting Dose**

Pursuant to Section 505(b) of the Food Drug and Cosmetic Act and in accordance with 21 CFR 314.70(b), Merck Research Laboratories (MRL), a division of Merck & Co., Inc., submits, for your approval, a supplement to NDA 19-766, ZOCOR™ (simvastatin) Tablets. This supplemental application is formatted as required in Title 21, paragraph 314.50 of the Code of Federal Regulations.

As indicated on the attached Form FDA 356h, this supplemental New Drug Application (sNDA) contains data to support revisions to the DOSAGE AND ADMINISTRATION section of the label to provide the option of a starting dose of 40 mg ZOCOR™ for patients who require a large reduction in LDL-C (more than 45%). Patients requiring such a reduction in LDL-C in order to reach treatment goals usually have CHD or multiple risk factors and are at high risk of coronary events. The usual recommended starting dose of 20 mg ZOCOR™ produces reductions in LDL-C of 45% or greater in only a minority of patients (<25%), thus rendering this dose less than optimal for patients requiring this magnitude of LDL-C lowering. Furthermore, because data indicate that physicians frequently do not titrate drugs past the recommended starting dose, providing 40 mg ZOCOR™ as an option for a starting doses should increase the numbers of patients who require large reductions in LDL-C to reach their treatment target levels without the need for titration. The safety and tolerability of 40 mg ZOCOR™ has been amply documented over the 14 years since it was first studied, both in clinical studies and postmarketing experience. The other proposed changes to the DOSAGE AND ADMINISTRATION section as indicated in the annotated label are intended to improve conciseness and clarity of prescribing information and to remove outdated information.

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NDA 19-766: ZOCOR™ (simvastatin) Tablets  
Supplemental New Drug Application  
Page 2

As required by the Food and Drug Administration Modernization Act of 1997 (FDAMA),  
a check in the amount of [REDACTED] User Fee ID No:  
was sent to the [REDACTED]

Submitted with this letter, in accordance with the *Guidance for Industry - Providing Regulatory Submissions in Electronic Format - NDAs: January 1999*, Merck Research Laboratories (MRL), a division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the sNDA for NDA 19-766: ZOCOR™ (simvastatin) Tablets (see Attachment 1). All documents requiring signatures for certification are included as paper for archival purposes.

A list of Reviewers from the Division of Metabolic and Endocrine Drug Products who should be provided access to this electronic submission from their desktops may be obtained from Ms. Margaret Simoneau, Project Manager. MRL will follow-up with Ms. Simoneau to ensure that the appropriate Reviewers have been given access to the electronic dossier.

Merck & Co., Inc. is requesting a categorical exclusion from the requirements to prepare an Environmental Assessment under 21 CFR §25.33(a). This supplement meets the requirements of a categorical exclusion under 21 CFR §25.33(a) because it will not increase the use of the drug. To the best of the firm's knowledge no extraordinary circumstances exist in regards to this action.

All information is in an electronic format as indicated in the attached Table of Contents for the supplemental application NDA 19-643. Review copies of selected sections are also being submitted in hard copy as described in Attachment 1.

All of the information is contained on one CD and has an approximate size of 20 MB.

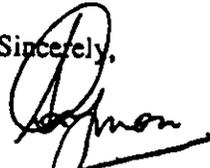
We have taken precautions to insure that any software on the CD is free of computer viruses (Norton AntiVirus © 4.0, Symantec Corp., 1991-1997) and we authorize the use of anti-virus software, as appropriate.

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NDA 19-766: ZOCOR™ (simvastatin) Tablets  
Supplemental New Drug Application  
Page 3

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

If you have any questions or need additional information regarding the contents of this submission, please contact Charles L. Hyman, MD (610-397-2850) or, in my absence, to Robert E. Silverman, MD, PhD (610-397-2944).

Sincerely,



Charles L. Hyman, MD  
Director  
Regulatory Affairs

Enclosures:  
Federal Express #1

cc (Cover Letter Only):

Ms. Margaret Simoneau, Project Manager  
Division of Metabolic & Endocrine Drug Products  
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Ms. Mary Ann Holovac,  
Food and Drug Administration, HFD-090  
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24 Page(s) Redacted

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Michael C. Elia, Ph.D.  
Director  
Regulatory Affairs

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April 6, 2000



**MERCK**

Research Laboratories



Ms. Margaret Simoneau  
Regulatory Project Manager  
Division of Metabolic and Endocrine  
Drug Products, HFD-510, Room 14B-04  
Office of Drug Evaluation II (CDER)  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

Dear Ms. Simoneau:

**NDA 19-766: ZOCOR™ Tablets  
40 mg sNDA**

**RESPONSE TO FDA REQUEST**

Please refer to our telephone conversation on April 3, 2000 requesting a copy of the administrative documentation for the ZOCOR™ 40 mg sNDA submitted to the Agency on June 30, 1999.

Enclosed per your request is the requested volume.

Please direct questions or need for additional information to Michael C. Elia, Ph.D. (610-397-3180) or, in my absence, Bonnie J. Goldmann, M.D. (610-397-2383).

Sincerely,

Michael C. Elia, Ph.D.  
Director  
Regulatory Affairs

Enclosure

Federal Express

Robert E. Silverman, M.D., Ph.D.  
Senior Director  
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DESK COPY

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December 2, 1999



Solomon Sobel, MD, Director  
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Rockville, MD 20850

Dear Dr. Sobel:

NDA 19-766/S-040: ZOCOR™  
(Simvastatin)

**General Correspondence**

Reference is made to Financial Disclosure Information (Item 19) in the above Supplemental New Drug Application (SNDA) originally submitted on June 30, 1999; a conversation between Dr. Silverman, Merck Research Laboratories (MRL), a Division of Merck & Co., Inc. and Ms. Galliers, (FDA) on March 31, 1999, concerning requirements for financial disclosure information; and the Agency's recent Draft Guidance for Industry: "Financial Disclosure by Clinical Investigators" released on October 25, 1999.

The above noted SNDA contains data (published manuscript) from an ongoing study, the MRC/BHF Heart Protection Study (discussed in several submissions to IND [redacted] dated December 3, 1993 [Serial No. 557], February 2, 1994 [Serial No. 564] and March 31, 1994 [Serial No. 570]). Based on the March 31, 1999 conversation between Dr. Silverman and Ms. Galliers, and as documented in the SNDA (Item 19), MRL has been pursuing collection of financial disclosure information from investigators in this study.

The October 25, 1999, draft guidance from FDA (Section IV.12) states that the Agency will consider a waiver to exempt applicants from collecting financial disclosure information for large, multi-center studies initiated before February, 1999. As previously documented, the Heart Protection Study was: begun in 1994; involves more than 200 investigators; is funded through four independent organizations (UK Medical Research Council, British Heart Foundation, Merck & Co., Inc and Hoffman-LaRoche) under the primary sponsorship of [redacted] was designed independently from either

Solomon Sobel, MD, Director  
NDA 19-766/S-040: ZOCOR™  
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pharmaceutical company; does not have representation from either company in the study's organization; and the Steering Committee members, investigators and all funding organizations involved with this study remain blinded to study endpoints.

Therefore, in light of these study characteristics and in conformance with the recent draft guidance, MRL, herein, requests a waiver from the reporting of financial disclosure information for clinical investigators participating in the Heart Protection Study.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

If you have any questions or need additional information please contact Robert Silverman, M.D., Ph.D. (610) 397-2944 or, in my absence, Bonnie J. Goldmann, M.D. (610) 397-2383.

Sincerely,



Robert E. Silverman, MD, PhD  
Senior Director, Regulatory Affairs

Federal Express #1

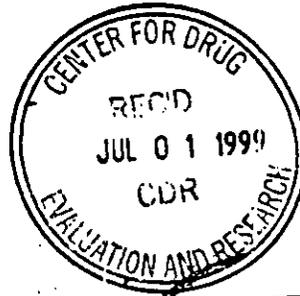
Desk Copy: Ms. Margaret Simoneau, HFD-510, Rm. 14B-04

APPEARS THIS WAY  
ON ORIGINAL

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NDA NO. 19-766 REF NO. 040  
NDA SUPPLEMENT 562  
June 30, 1999



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**NDA 19-766: ZOCOR™ (simvastatin) Tablets**

**SUPPLEMENTAL NEW DRUG APPLICATION  
Simvastatin-40-mg Alternative Starting Dose**



Pursuant to Section 505(b) of the Food Drug and Cosmetic Act and in accordance with 21 CFR 314.70(b), Merck Research Laboratories (MRL), a division of Merck & Co., Inc., submits, for your approval, a supplement to NDA 19-766, ZOCOR™ (simvastatin) Tablets. This supplemental application is formatted as required in Title 21, paragraph 314.50 of the Code of Federal Regulations.

As indicated on the attached Form FDA 356h, this supplemental New Drug Application (sNDA) contains data to support revisions to the DOSAGE AND ADMINISTRATION section of the label to provide the option of a starting dose of 40 mg ZOCOR™ for patients who require a large reduction in LDL-C (more than 45%). Patients requiring such a reduction in LDL-C in order to reach treatment goals usually have CHD or multiple risk factors and are at high risk of coronary events. The usual recommended starting dose of 20 mg ZOCOR™ produces reductions in LDL-C of 45% or greater in only a minority of patients (<25%), thus rendering this dose less than optimal for patients requiring this magnitude of LDL-C lowering. Furthermore, because data indicate that physicians frequently do not titrate drugs past the recommended starting dose, providing 40 mg ZOCOR™ as an option for a starting doses should increase the numbers of patients who require large reductions in LDL-C to reach their treatment target levels without the need for titration. The safety and tolerability of 40 mg ZOCOR™ has been amply documented over the 14 years since it was first studied, both in clinical studies and postmarketing experience. The other proposed changes to the DOSAGE AND ADMINISTRATION section as indicated in the annotated label are intended to improve conciseness and clarity of prescribing information and to remove outdated information.

REVIEWS COMPLETED	
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As required by the Food and Drug Administration Modernization Act of 1997 (FDAMA), a check in the amount of [redacted] User Fee ID No. [redacted] was sent to the [redacted] on June 22, 1999.

Submitted with this letter, in accordance with the *Guidance for Industry - Providing Regulatory Submissions in Electronic Format - NDAs: January 1999*, Merck Research Laboratories (MRL), a division of Merck & Co., Inc., is providing one Compact Disk (CD) which contains the sNDA for NDA 19-766: ZOCOR™ (simvastatin) Tablets (see Attachment 1). All documents requiring signatures for certification are included as paper for archival purposes.

A list of Reviewers from the Division of Metabolic and Endocrine Drug Products who should be provided access to this electronic submission from their desktops may be obtained from Ms. Margaret Simoneau, Project Manager. MRL will follow-up with Ms. Simoneau to ensure that the appropriate Reviewers have been given access to the electronic dossier.

Merck & Co., Inc. is requesting a categorical exclusion from the requirements to prepare an Environmental Assessment under 21 CFR §25.33(a). This supplement meets the requirements of a categorical exclusion under 21 CFR §25.33(a) because it will not increase the use of the drug. To the best of the firm's knowledge no extraordinary circumstances exist in regards to this action.

All information is in an electronic format as indicated in the attached Table of Contents for the supplemental application NDA 19-643. Review copies of selected sections are also being submitted in hard copy as described in Attachment 1.

All of the information is contained on one CD and has an approximate size of 20 MB.

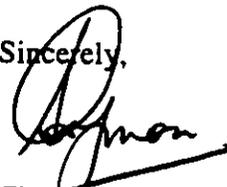
We have taken precautions to insure that any software on the CD is free of computer viruses (Norton AntiVirus © 4.0, Symantec Corp., 1991-1997) and we authorize the use of anti-virus software, as appropriate.

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We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

If you have any questions or need additional information regarding the contents of this submission, please contact Charles L. Hyman, MD (610-397-2850) or, in my absence, to Robert E. Silverman, MD, PhD (610-397-2944).

Sincerely,



Charles L. Hyman, MD  
Director  
Regulatory Affairs

Enclosures:  
Federal Express #1

cc (Cover Letter Only):

Ms. Margaret Simoneau, Project Manager  
Division of Metabolic & Endocrine Drug Products  
HFD-510, Room 14B04  
Federal Express #2

Dr. David Orloff, HFD-510, Rm. 14B-04  
Division of Metabolic & Endocrine Drug Products  
HFD-510, Room 14B04  
Federal Express #3

Mr. Kenneth Edmunds, Computer Specialist  
Division of Technology Support Services Staff  
HFD-073, Room 8B45  
Federal Express #4

Desk Copy (Cover Letter and Patent Information Only):

Ms. Mary Ann Holovac,  
Food and Drug Administration, HFD-090  
5516 Nicholson Lane, Room 235  
Rockville, MD 20895  
Federal Express #5

## Electronic Mail Message

**Date:** 4/26/00 11:15:09 AM  
**From:** Linda Carter ( CARTERL )  
**To:** Margaret Simoneau ( SIMONEAUM )  
**To:** Enid Galliers ( GALLIERS )  
**Subject:** NDA 19-766/S-040

I had a telephone conversation on April 25 with Dr. Michael Elia of Merck concerning the requirement for financial disclosure information for NDA 19-766/S-040. Dr. Elia explained to me that Merck's supplement contained published studies completed years ago in support of a labeling change. Because the studies are in support of a labeling change and were completed a number of years ago, we will waive the requirement to report any financial disclosure information on these studies.

With regard to the study that is ongoing and conducted by [redacted] [redacted] I understand that this study was referenced in the supplement as supportive. In a December 2, 1999 letter to Dr. Sobel, Dr. Silverman of Merck requested a waiver of reporting financial disclosure information for this study. I understood from this letter that this was the only study supporting the labeling change, and I had several conversations with both Dr. Silverman and Dr. Elia about what information was required to be reported. When I spoke with Dr. Elia on April 25, he informed me that this study was still ongoing, and that it is only referenced in the supplement as providing some support for the labeling change. Therefore, I told Dr. Elia that there would be no need to report financial disclosure information on this study because it does not meet the definition of covered clinical study. For this supplement, no financial information is required.

The issue of whether studies supporting certain labeling changes has come up previously, and our Financial Disclosure Working Group will be discussing this at a future meeting. But my understanding of this supplement and the studies supporting the change in labeling, leads me to the conclusion that no financial information is required to be reported.

**APPEARS THIS WAY  
ON ORIGINAL**

**DSI**

**NOT NEEDED**