CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 019898/S018

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

NDA 19898/S-018

Food and Drug Administration
Rockville MD 20857

Bristol-Myers Squibb Company
Attention: Warren C. Randolph
P.O. Box 4000
Princeton, NJ 08543-4000

MAR 27 1998

APPEARS THIS WAY
ON ORIGINAL

Dear Mr. Randolph:

Please refer to your supplemental new drug application dated March 31, 1997, received March 31, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pravachol (pravastatin sodium) tablets.

We acknowledge receipt of your submissions dated February 18, May 28, 29 (2), and 30, July 15, and November 26, 1997, and March 11, 25 (2 faxes) and 26, 1998. The User Fee goal date for this application is March 31, 1998.

The supplemental application provides for a new indication for use in patients with previous MI and normal cholesterol levels, to reduce risk of recurrent MI, myocardial revascularization, and cerebrovascular disease events.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling submitted March 26, 1998. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling submitted on March 26, 1998, and must incorporate the changes in your most recently approved supplement, S-020.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING for approved supplemental NDA 19898/S-018." Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Should a letter communicating important information about this drug product (i.e., a "Dear Doctor" letter) be issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20852-9787

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Margaret Simoneau, R.Ph., Regulatory Management Officer, at (301) 827-6418.

Sincerely yours,

/S/

Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 19898/
HFD-510/Div. files
HFD-510/CSO/M. Simoneau
HFD-510/D.Orloff/E.Barbehenn/R.Steigerwalt/W.Berlin/S.Moore/J.Mele/E. Galliers
HFD-002/ORM (with labeling)
HFD-102/Office Director
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-735/DPE (with labeling) - for all NDAs and supplements for adverse reaction changes.
HFI-20/Press Office (with labeling)

Drafted by: Mas/March 20, 1998/19898s18
Initialed by: D.Orloff3.26.98/E.Barbehenn & for
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final: Mas3.27.98

APPROVAL (AP)

FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA.

DRAFT LABELING IS NO LONGER BEING SUPPLIED SO AS TO ENSURE ONLY CORRECT AND CURRENT INFORMATION IS DISSEMINATED TO THE PUBLIC.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 019898/S018

JOINT MEDICAL/STATISTICAL REVIEW(S)

MAR 10 1998

Joint Clinical and Statistical Review

NDA #: 19-898/S-018 (efficacy supplement)

Drug: PRAVACHOL (pravastatin sodium) tablets

Sponsor: Bristol-Myers Squibb Company

Proposed indication: In patients with previous MI and normal cholesterol levels, to reduce risk of MI, revascularization, and cerebrovascular disease events.

Date of Submission: March 31, 1997

Documents Reviewed: Volumes 46.1 to 46.22

Medical Reviewer: David G. Orloff, M.D. (HFD-510)

Statistical Reviewer: Joy Mele, M.S. (HFD-715)

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I. Introduction

A. Clinical and Historical Perspective

At the time of the design and initiation of the Cholesterol and Recurrent Events (CARE) study in the late 1980's, the relationship of plasma cholesterol to coronary heart disease risk was well established. Dating back to the 1930's, the link between elevated cholesterol and atherosclerotic coronary heart disease was established initially on the basis of experiments of nature in the form of familial disorders of lipoprotein metabolism and on animal models (CHD) and later on a large body of epidemiological evidence. Within populations as well as across countries and geographical areas, the incidence of CHD was known to be directly correlated with plasma cholesterol levels. This relationship appeared to be continuous and graded down to total cholesterol levels of ., perhaps best exemplified in the follow up data from the ~350,000 MRFIT screenees. Further bolstering the cholesterol hypothesis, in the 1970's and 1980's, interventional trials using diet and lipid-altering drugs had demonstrated that lowering cholesterol was associated with delays in the onset of coronary disease in asymptomatic patients and in the incidence of recurrent myocardial infarction in patients with existing symptomatic CHD. Finally, the combined epidemiological, clinical trial, and basic scientific evidence lent support to the role of LDL-C as the culprit in atherosclerosis, with HDL-C levels negatively correlated with CHD risk.

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Statin trials (WOSCOPS and 4S)

Two major placebo-controlled morbidity and mortality trials using statins were completed prior to CARE. These were WOSCOPS, a 5-year study in high-risk hypercholesterolemic men, without a previous MI, using pravastatin, and 4S, a 5-year study in hypercholesterolemic men and women, with a previous MI and/or angina (80% with MI) using simvastatin. Both trials achieved the landmark outcome of demonstrating reductions in non-fatal MI and fatal cardiovascular disease, without a countervailing excess of non-cardiovascular deaths in the active treatment groups. Indeed, 4S confirmed its primary hypothesis by demonstrating a highly statistically significant reduction in total mortality in the simvastatin group as compared to placebo. These consistent findings with regard to morbid and mortal cardiovascular events within both studies would have been expected based on the natural history of atherosclerotic disease (MI followed by recurrent MI with or without cardiac debility followed by death, sudden or otherwise). Thus, a reduction in the rate of non-fatal events, should, logically, eventually translate into a reduction in the rate of cardiovascular fatalities. These trials were, in retrospect, adequately powered to demonstrate an impact of cholesterol lowering on this pathogenic cascade. CARE was a trial designed and sized similarly to WOSCOPS and 4S, though this time asking whether cholesterol lowering would reduce the rate of combined non-fatal and fatal coronary events in men and women with a previous MI but with "normal" cholesterol levels.

Unresolved questions regarding cholesterol lowering:

What causes atherosclerosis in CHD patients with "normal" cholesterol levels?

Despite all this evidence for the role of cholesterol in heart disease, the CARE study was designed in a climate when several nagging questions in the field of cholesterol lowering remained unanswered. The first among these was spurred by the knowledge that the distribution of serum total and LDL cholesterol levels was similar among patients with and without CHD and that, indeed, many (if not most) patients with CHD had plasma cholesterols of less than 240 mg/dL (thus "average" or "normal"). Furthermore, an oft-cited finding of the primary prevention component of the Helsinki Heart Study using gemfibrozil, a drug which effects minimal lowering of LDL-C, was that the treatment benefit was actually limited to the subgroup with high triglycerides, low HDL-C, and only moderately elevated LDL-C. Taken together, these and other facts left open the question of whether cholesterol-rich lipoproteins were causative in atherosclerosis in patients with apparently "normal" levels of total and LDL-cholesterol.

Does cholesterol lowering benefit women and the elderly?

The second unanswered question was whether the benefits of cholesterol lowering applied to elderly patients and women, two groups grossly underrepresented in the earlier cholesterol lowering trials. Elderly patients had been excluded apparently out of a desire to enroll generally healthy CHD patients so as not to confound outcomes. Women had been underrepresented because of the low rate of CHD in middle-age women as compared to men. Furthermore, epidemiological data do not show a relationship between cholesterol levels and CHD risk in the elderly, though clearly the incidence of CHD does increase with age. This paradox has been resolved in recent years with the elucidation of the principle of time integrated cholesterol exposure, so-called cholesterol-years. Thus, the risk of CHD is directly related to the integral of cholesterol level and time. Since the initiation of the CARE study, the results of 4S have been published, suggesting consistent effects of cholesterol lowering with simvastatin with regard to atherosclerotic morbidity and mortality across men and women and across age groups, including those over age 65.

The total mortality question

The third nagging question, also addressed in the design of the 4S and WOSCOPS trials, both completed prior to CARE, was the result of a failure to demonstrate consistent improvements in total and cardiovascular mortality in cholesterol lowering trials, despite clear reductions in the rates of non-fatal coronary events. Prior to the completion of the large statin trials, the only two examples of significant reductions in overall mortality were the 5-year Stockholm Ischemic Heart Disease Trial using clofibrate and niacin in patients beginning 4 months after MI, and the fifteen year follow up (this being 8 years out from the closure of the trial) of the niacin arm of another secondary prevention study, the Coronary Drug Project. This inconsistency between the effects on morbid events and mortality outcomes was rationalized by the poor average reductions in total cholesterol in early trials, between 5 and 15%,

contributed to by poor drug tolerability and poor compliance, although the specter of subtle toxicity of the drugs (or of cholesterol lowering generally) as a countervailing negative influence on survival was raised. Indeed, several trials as well as meta-analyses have shown an excess of cancer deaths and traumatic deaths associated with active treatment to lower cholesterol. This concept of risk outweighing benefit in situations where the benefit is small is particularly relevant to the CARE population (see below). If the cardiovascular benefits associated with cholesterol reduction were attenuated in the population with lower baseline cholesterols, then any adverse effects of the intervention might have a proportionately greater effect to offset that benefit.

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B. Uniqueness of the CARE design

The first two of the above questions were addressed in the design of CARE by the entry criteria that rendered a study cohort of both men and women up to age 75, and with average LDL-C representative of the average patient with MI. In addition, the use of pravastatin at a dose predicted to effect a lowering of LDL-C in this population was theorized to lower (potentially) recurrent cardiovascular event rates by 30-40% such that cardiovascular benefit would be expected to exceed that seen in earlier trials in the pre-statin era. The trial was not designed to test whether pravastatin therapy would have an effect to reduce overall mortality. The large sample size, in conjunction with the design feature that there would be no fixed duration of follow up, but rather that the trial would continue until a predetermined number of primary endpoint events occurred, was intended to insure a statistically valid result by preserving the power of the study to address the prospectively defined hypotheses.

C. NCEP Guidelines and the significance of CARE results

The Adult Treatment Panel of the National Cholesterol Education Program published its revised guidelines for the treatment of hypercholesterolemia in 1993. These guidelines target patients like those enrolled in the CARE study for aggressive lipid lowering. Specifically, the goal LDL-C level in patients with established coronary artery disease is less than 100 mg/dL, with nominal drug treatment initiation LDL-C level > 130 mg/dL on a low-cholesterol, low-saturated-fat diet, but optionally anywhere above 100 mg/dL, depending upon physician discretion. These guidelines were apparently written with the knowledge that the CARE study was underway, with the intent that they not be obsolete should the results of that trial confirm a place for cholesterol lowering in CHD patients with otherwise normal (in the absence of heart disease or multiple risk factors) cholesterol levels. Clearly, though, the panel felt, based on existing evidence, that this population should be treated. The overall CARE results highlight their prescience.

In effect, then, the CARE results discussed in this review confirm the validity of currently accepted guidelines for treatment, and demonstrate that for many patients with coronary heart disease, whatever the cholesterol level, it is too high. In such patients, in whom, after the fact, we can deduce that LDL-C was a culprit in atherogenesis, benefit may be reaped from cholesterol reduction, albeit from a relatively low baseline. For these patients, the cholesterol level is obviously not

"normal." Perhaps it would be better to state that these are patients with average cholesterol levels, implying that by cholesterol level alone, they are indistinguishable from the population without coronary disease. An alternative description is that these are patients, who, in the absence of CHD or multiple risk factors, would be considered to have normal cholesterol levels, not mandating treatment with drugs.

D. Pravachol labeling

Current labeling

Pravachol is currently indicated for the primary prevention of coronary events in hypercholesterolemic patients to reduce the risk of MI, to reduce the risk of undergoing a revascularization procedure, and to reduce the risk of cardiovascular mortality. In addition, in hypercholesterolemic patients with CHD, pravastatin is indicated to slow the progression of coronary atherosclerosis and to reduce the risk of acute coronary events. Finally, pravastatin is indicated to reduce total and LDL-C and triglycerides in patients with Fredrickson Types IIa and IIb hyperlipoproteinemia.

Major proposed changes in labeling based on CARE

In Clinical Pharmacology, proposed is a paragraph summarizing the design of the CARE study, with description of results for the primary endpoint for the total study population and among women. In addition, the data on coronary revascularization are summarized. Finally, the data regarding the effect of pravastatin on the risk for "stroke and transient ischemic attack (TIA)" are conveyed.

In Indications and Usage, proposed is the addition of a section under the heading "Myocardial Infarction" stating "in patients with previous MI, and normal cholesterol levels, PRAVACHOL is indicated to: reduce the risk of recurrent MI, reduce the risk of undergoing myocardial revascularization procedures, reduce the risk of stroke and TIA."

In Adverse Reactions, proposed is a revision to include CARE in a statement already applied to the WOSCOPS results that "the adverse events profile in the PRAVACHOL group was comparable to that of placebo for the duration of the studies."

II. Review of CARE (Cholesterol and Recurrent Events study)

A. Objectives of the CARE Study

The stated objectives of the CARE study were to determine whether intensive therapy with pravastatin to lower plasma cholesterol in patients with myocardial infarction would decrease recurrent coronary heart disease events, i.e. combination of fatal coronary heart disease and definite nonfatal myocardial infarction (primary endpoint); further objectives were to test the effect of pravastatin therapy on fatal coronary heart disease (secondary endpoint) as well as on total mortality (tertiary endpoint) in this population.

B. Trial Design

Table 1 summarizes the main features of the design of the CARE trial.

Table 1. Summary of the CARE Trial

# of sites	Design	Treatment Groups (N)	Duration of Treatment (yrs)	Primary Endpoint	Entry Criteria
Total of 80 Canada:12 USA:68 Geographically dispersed	Randomized, double-blind, parallel	Pravastatin 40 mg (2081) Placebo (2078) 86% men 14% women	Approximately 5 years	Time to death due to CHD or definite non-fatal MI	MI w/ prior to rand. TC<240 mg/dl

1. Pre-randomization procedures included the following:

- medication washout including discontinuation of lipid-altering therapy, including probucol or fibric acid derivatives (12 weeks before qualifying blood draw), statins (8 weeks prior), and resins, nicotinic acid, or other prohibited drugs (4 weeks)
- dietary instruction instituted at the time of drug withdrawal (the dietary program was taught using guideline and materials provided by the AHA and NCEP)
- for eligible patients, during a placebo run-in period (2 weeks to 2 months prior to randomization), compliance was assessed based on pill counts. Patients with compliance < 70% compliance were excluded from the trial

2. Determination of eligibility with regard to plasma lipids:

- lipids measured after no less than 4 weeks of diet and no earlier than 8 weeks after hospital discharge after MI (first qualifying visit)
- average of the lipid levels for two qualifying visits determines eligibility (second qualifying visit 7 days to 1 month after the first and no less than 12 weeks after hospital discharge)
- if mean lipid levels borderline
  a third determination is averaged with the previous two to determine eligibility

3. Entry Criteria

Inclusion Criteria

1. Acute MI to randomization

(The ECG core facility could either confirm the diagnosis of MI, request additional documentation, or refuse to validate the ECG as confirmatory of an MI. A non-confirmatory ECG could be overridden by history of typical symptoms and record of enzyme elevations by criteria set out in the Manual of Operations for the study.)

2. Age
3. Men and women (post-menopausal or surgically sterile)
4. Plasma total cholesterol < 240 mg/dl (< 6.2 mmol/L)

5. Plasma LDL-cholesterol (approximately equivalent to total cholesterol

Exclusion Criteria

1. Initial screening plasma cholesterol >270 mg/dl (>7.0 mmol/L) by local laboratories (guideline only).
2. Mean qualifying fasting plasma total cholesterol >240 mg/dl (>6.2 mmol/L), or plasma LDL cholesterol <115 mg/dl (<3.0 mmol/L) or >174 mg/dl (>4.5 mmol/L) on samples measured by the
3. Screening triglyceride values >750 mg/dl (>8.5 mmol/L) measured by any local laboratory, or $ 350 mg/dl (>4.0 mmol/L) measured by the
4. Ejection fraction <25% obtained no more than 20 months before randomization and no intervening infarct between the EF measurement and study entry.
5. Overt congestive heart failure (symptomatic despite drug therapy), defined as rales not caused by a primary pulmonary condition, or Class III-IV symptoms.
6. Prior sensitivity to HMG-CoA reductase inhibitors. History of non-responsiveness to HMG-CoA reductase inhibitors (<10% decrease in total cholesterol).
7. No coronary atherosclerosis on arteriogram, if performed.
8. Nephrotic syndrome or other renal disease (creatinine >1.5 x ULN for the laboratory, serum albumin <3.0 g/dl, urinary protein ≥2+) by
9. Excessive ethanol intake, defined as > 3 drinks/day.
10. Hepatobiliary disease, chronic hepatitis, biliary cirrhosis, alcoholic cirrhosis, other causes of chronic jaundice or significant other hepatic disease (SGOT, SGPT, total bilirubin, or alkaline phosphatase >1.5 x ULN for the laboratory. Any exception must be approved by the medical monitor).
11. Malignancy or other medical condition thought to limit survival, require radiation or chemotherapy, or interfere with participation.
12. History of immune disorders (dysproteinemia, porphyria, lupus erythematosis) or treatment with immunosuppressive agents. Cyclosporin is specifically contraindicated. If there is a history of prolonged treatment with corticosteroids (asthma, serious allergy), patient should not be enrolled.
13. Untreated endocrine disorders or other uncontrolled endocrine disease. A patient euthyroid on a stable replacement dose of thyroid hormone is acceptable. Any T4 value outside normal range (see Appendix A1) may be further evaluated by obtaining TSH levels. TSH must be within normal range before a patient may be enrolled. Poorly-controlled diabetes mellitus (Blood sugar >220 + Hgb A1C >11.0) will exclude the patient from further participation. Treatment with estrogens (except replacement therapy) or androgens is prohibited.
14. Significant gastrointestinal disease or surgery which may interfere with drug absorption.
15. Treatment with other lipid-lowering drugs, unless they are withdrawn: i) 8 weeks prior to obtaining the first qualifying lipid specimen for HMG-CoA reductase inhibitors; ii) 12 weeks prior for fibric acid derivatives or probucol; and iii) 4 weeks prior for nicotinic acid or resins.
16. Severe valvular heart disease requiring surgery.

17. Psychosocial condition that would make a person unsuitable for a clinical trial.
18. Geographic location, i.e. distance to clinic making attendance difficult or itinerant lifestyle.
19. Participation in another drug trial that could affect the endpoint of this study, or use of any investigational drug within 30 days of enrollment.
20. Women unless post-menopausal or surgically sterile (post-menopausal estrogen use is allowed).
21. Unwilling to consent.

C. Deferments

1. Coronary angioplasty: 6 months must elapse after coronary angioplasty before randomization.
2. Coronary artery bypass surgery: 3 months must elapse after bypass surgery before randomization.
3. Major surgery: 1 month must elapse after major surgery before randomization

4. Drug Treatments

- randomization 1:1 blocking on center to either pravastatin 40 mg per day or placebo administered at bedtime
- enhanced dietary counseling for patients with LDL-C above 174 mg/dl (4.5 mmol/L) on two follow up visits
- cholestyramine resin, 2-4 packets daily for patients with LDL-C still > 174 mg/dl (4.5 mmol/L) on two consecutive visits
- decrease in dose of cholestyramine resin first (if on resin) or pravastatin dose by 50% for patients with LDL-C decreased to below 50 mg/dl (1.3 mmol/L) on two consecutive follow-up visits
- matching patients in other treatment group would have parallel changes made in their treatment regimens.
- medication was discontinued at subject's request, if investigator deemed that continuation was not in the best interest of the patient, if LDL-C >174 mg/dL after dietary counseling and resin therapy and/or if there was a serious intercurrent illness.

5. Follow-up

a. Lipid Measurements

Direct measurement of fasting lipids (TC, HDL-C, TG; LDL-C) calculated using the Friedewald formula were performed at 1.5, 3, and 6 months after randomization and thereafter every 6 months throughout the trial

b. Procedures

- full history and physical exam annually
- interim histories and physical as indicated
- adverse events documented at each full visit by the clinic nurse.
- LFTs at weeks 6 and 12, then every 3 months for the first year, then every 6 months for the duration of the study

- dietary reinforcement at each 3-month follow up visit.
- full chemistry and hematology at baseline and yearly, CK only in symptomatic patients
- ECG at baseline and optionally as part of clinical follow up
- ejection fraction (if not done during routine clinical management) at baseline.
- Limited safety assessments at six week intervals during the first 3 months, then at 3 month intervals during year 1, then at 6 month intervals through end of study

c. Adverse events

- Clinical adverse events (AEs) are defined in the protocol as illnesses, signs, or symptoms that have appeared or worsened during the course of the study.
- Laboratory adverse events are defined as laboratory values outside of the normal range.
- Serious adverse events were those AEs that were fatal, immediately life-threatening, permanently disabling, cancer, congenital anomaly, overdose, or that required at least overnight hospitalization.
- An AE was classified as an adverse drug experience (ADE) or a concomitant event (CE) by a causality assessment done by the investigator.
- Treatment-emergent events were AEs that began or worsened after randomization. AE's beginning prior to randomization and recurring after it were not treatment-emergent unless the AE worsened or it was classified as an ADE.

d. Liver function tests

For serum transaminases, levels between 2 and 3 times the upper limit of normal were to be repeated for monitoring purposes every 2 weeks until returned to normal. Levels >3 times ULN were to be repeated within one week, and if further elevated, were cause for discontinuation of drug. Dose adjustments were called for if the elevation was persistent but stable relative to normal. If not fallen to <3X ULN after 4 weeks, drug was to be discontinued. A recurrence to a level >3X ULN also mandated discontinuation of study drug. Once transaminases had returned to normal, consideration could be given to rechallenging the patient with the study drug, albeit at the lowest dose (10 mg/day).

e. Creatine kinase

Creatine kinase (CK) elevations up to 4 times the upper limit of normal in a symptomatic patient did not mandate discontinuation of medication. Follow up until symptom resolution would suffice. Levels greater than 4 times ULN were to be repeated and if confirmed, mandated discontinuation. Rechallenge starting at the lowest dose could be considered in a patient once CK had returned to normal and symptoms had resolved.

6. Safety and Data Monitoring Committee

Its function was to review data on adverse effects and endpoints. It was empowered to recommend termination of the trial for adverse effects or improved survival early in the

trial. As reviewed above, the trial could be terminated early for favorable outcome only with regard to fatal events. The sponsor was not to be a member of this committee.

7. Changes to the protocol

There were no changes to the protocol with regard to the choice of endpoints. The revisions of 10-31-95 clarified the study endpoints and the outcome variables and their definitions.

8. Outcome Variables

- 1. Fatal coronary heart disease and definite nonfatal MI combined (primary outcome variable)
- 2. Fatal coronary heart disease (secondary outcome variable)
- 3. Total mortality (tertiary outcome variable)
- 4. Additional outcome variables:

a. Myocardial infarction, nonfatal (definite and probable)
b. Myocardial infarction, fatal and nonfatal (definite and probable)
c. Development of overt CHF
d. Need for coronary artery bypass surgery or nonsurgical coronary revascularization
e. Hospitalization for cardiovascular disease
f. Cerebrovascular disease, fatal and nonfatal (stroke, or transient ischemic attack)
g. Hospitalization for peripheral arterial disease (intermittent claudication, arterial thrombosis or embolism, abdominal aortic aneurysm)
h. Hospitalization for unstable angina
i. Total coronary heart disease events (2,4b,4c,4d,4h)
j. Cardiovascular mortality (including nonatherosclerotic)
k. Total cardiovascular disease events (4b-4h, 4j)
l. Atherosclerotic cardiovascular disease, fatal
m. Atherosclerotic cardiovascular disease, fatal and nonfatal (4b,4c,4d,4f,4g,4h,4l)

a. Definitions of "definite" and "probable"

"Definite" refers to a report of a clinical MI by a clinical center that meets the criteria of MI described in the manual of operations, as determined by the MI Confirmation Laboratory (MICL) and could be based on combined symptoms, EKG changes, and enzymes or on symptoms and enzymes alone. A "probable" non-fatal MI was based solely on the report by a clinical center (no confirmation by the MICL).

Fatal MIs were adjudicated by the endpoints committee. The committee used the same criteria as the MICL for adjudication of a fatality attributed to a definite MI. Death within 7 days of an MI or prior to hospital discharge was judged due to fatal MI, in the absence of evidence of another unrelated cause as determined by review by the MI confirmation center. A definite fatal MI was declared when there was evidence of recent necrosis or intracoronary thrombus at autopsy. Where timed collection of serum cardiac enzymes or serial EKGs were not available, the committee classified such an

MI as "probable" if the subject's death was associated with at least two of the following:

- prolonged chest pain
- CK rise above normal
- new EKG changes
- evidence of new or presumed new infarction by EKG, radionuclide study, or thallium imaging

b. Cerebrovascular disease events

The endpoint of cerebrovascular disease, fatal and nonfatal (stroke or TIA) included events of cerebral thrombosis, hemorrhage, infarction cerebrum, brain infarction, cerebrovascular accident or stroke, and amaurosis fugax or TIA.

Transient ischemic attack (TIA) was defined as "acute disturbance of focal neurological or monocular function with signs and/or symptoms of presumed vascular etiology which normalize in less than 24 hours.

Stroke was defined as acute disturbance of focal neurological or monocular function resulting in death or signs and/or symptoms of presumed vascular etiology which persist for greater or equal to 24 hours.

It is important to note that these diagnoses do not require confirmation by CT or MRI, and for stroke, there is no distinction between events of embolic and hemorrhagic origin.

During the study, the Data Coordinating Committee reviewed all the CRFs, source documents, and supporting information (clinical and lab reports, scans, pathology reports) for the events reported as TIA or stroke. Post-study, a Stroke and TIA Classification Committee was convened to refine the interpretation of the trial results particularly regarding etiology of cerebrovascular events. Final classification was by consensus agreement either between two independent reviewers, or if that failed, by the entire committee in conference.

C. Results of CARE

1. Patient disposition

11,207 subjects were screened to enroll 7180 subjects. About 42% of the enrolled subjects (3021) were not randomized primarily due lipids out of range (1881 subjects; 62%). Other reasons for exclusion were concomitant disease, use of lipid altering drugs, CHF/low EF/valvular heart disease, no CAD on angiogram, deferred or died, psychosocial or geographic factors, subject or physician disapproval, poor compliance, and other.

Subjects were randomized to pravastatin (2081) or placebo (2078) at 80 sites in Canada and the USA (Table 2). The four largest sites were located in Canada, however the majority of the subjects were enrolled at USA sites (60%). All randomized patients, save one, regardless of treatment compliance, were followed for the duration of the trial.

Table 2. Disposition of Randomized Patients

	Pravastatin	Placebo
Randomized	2081	2078
Discontinued Treatment	390 (19%)	585 (28%)
Reasons for discontinuation		
ADE	92 (4%)	121 (6%)
Protocol violation	8 (<1%)	32 (2%)
Subject request	82 (4%)	180 (9%)
Death	128 (6%)	133 (6%)
Other	11 (1%)	40 (2%)
Unknown	69 (3%)	79 (4%)
Completers by year on study		
Year 1	1996 (96%)	1956 (94%)
Year 2	1926 (94%)	1849 (89%)
Year 3	1867 (90%)	1738 (84%)
Year 4	1790 (86%)	1617 (78%)
Year 5	869 (42%)	766 (37%)

Over the course of the trial, 28% of placebo patients and 19% of pravastatin patients discontinued medication permanently ($p<0.05$ for the difference). The annual discontinuation rates were constant within the two groups (about 4% for the pravastatin group and about 6% for the placebo group). The difference in the discontinuation rates appears to be primarily due to the difference in the number of patients discontinuing due to "subjects request" (180 (9%) placebo patients versus 82 (4%) pravastatin patients). The discontinuations due to subject request in the placebo group speak to the difficulties of conducting a placebo-controlled trial in an era where use of cholesterol lowering agents was steadily increasing, as one assumes that many of the placebo patients who discontinued did so in order to attempt to further lower their cholesterols under a doctor's care. One would expect that the influence of this "crossover" to active treatment, if anything, would be to diminish the apparent treatment effect of pravastatin therapy

compared to placebo. At the same time, however, depending on the drug to which placebo patients were switched (e.g., to another statin), there might be a tendency toward diminished imbalance in true drug-related adverse events between the two groups.

2. Patient Demographics and Baseline Characteristics

The randomization was successful in generating treatment groups well-matched for baseline demographics and patient characteristics (Table 3) and for baseline concomitant medication use (Table 4).

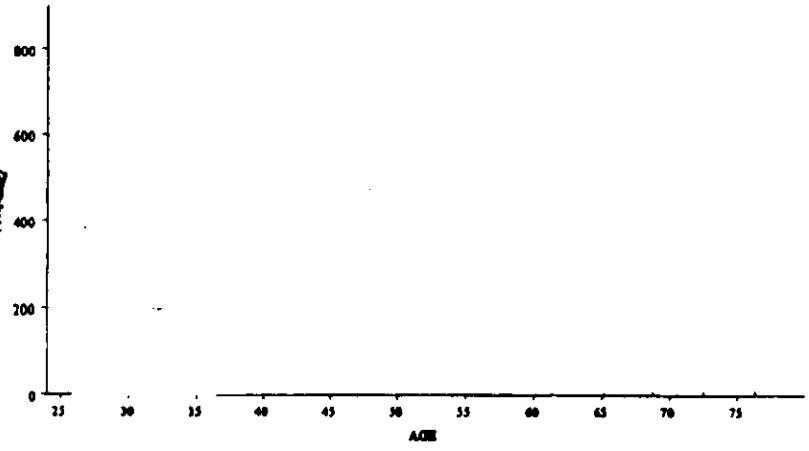
Table 3. Baseline demographics and patient characteristics for CARE study cohort

	Pravastatin	Placebo
Age (mean yrs)	58.6	58.7
sex: male	86%	86%
female	14%	14%
race: white	93%	93%
other	7%	7%
BMI	27.7	27.5
systolic BP	128.7	129.1
diastolic BP	78.5	78.6
heart rate	66.7	67.8
history of hypertension	42%	43%
history of diabetes	14%	15%
prior CABG/PTCA	55%	55%
MI prior to CARE MI	15%	16%
smoking history: never	22%	23%
former	62%	61%
present	16%	16%
baseline EF (mean)	53%	53%
baseline Total-C	208.6	208.5
LDL-C	138.8	138.5
HDL-C	38.7	39.0
TG	155.9	155.2

The majority of the patients were male (84%) and white (93%). About half of the patients had had a revascularization procedure before entering CARE and only about 15% had an MI before their CARE MI.

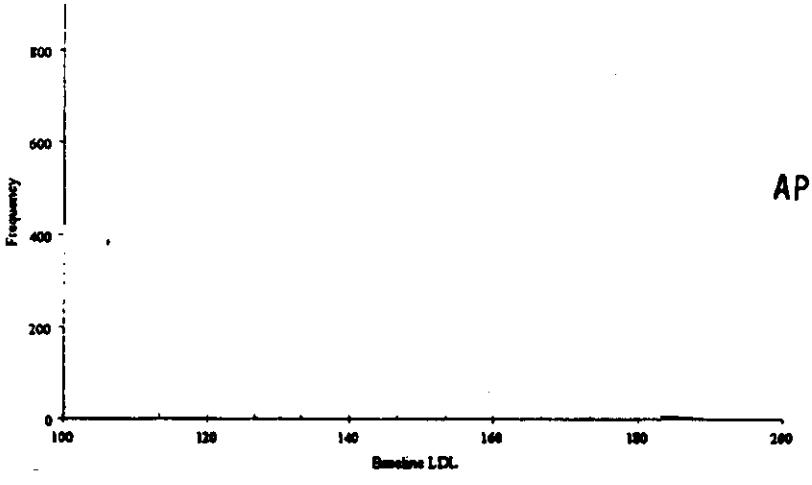
The average age of the patients in the total cohort was 59 years (median:60 (Figure 1); 31% of the patients were 65 or older.

Figure 1 CARE Age Distribution (total cohort)



The groups were comparable at baseline regarding baseline lipoproteins (Table 3). Baseline cholesterol was 209 (mean and median) and LDL-C was 139 (mean, median=138) at baseline and . About ⅓ of the patients had an LDL at baseline of less than 130. The distribution of LDL-C for the whole cohort is shown in Figure 2 (the graphs for the 2 treatment groups were indistinguishable).

Figure 2 CARE Baseline LDL Distribution (total cohort)



Concomitant medication use at baseline is listed in Table 4. A large percentage of patients were taking aspirin (84%) and/or antihypertensives (82%) at baseline About half the

patients were taking antiarrhymics, beta-blockers or calcium channel blockers. It should be noted that the aspirin and antiplatelet agent groups overlapped save for a small percentage of the patients.

Table 4. Concomitant Medication Use at Baseline

	Pravastatin	Placebo
aspirin	84%	83%
antiplatelet agents	85%	85%
anticoagulants	4%	3%
beta blockers	41%	39%
nitrates	32%	33%
calcium channel blockers	41%	38%
ACE inhibitors	15%	14%
diuretics	12%	11%
antihypertensives	82%	81%
antiarrhythmics	50%	48%
digitalis	8%	8%
quinidine	1%	1%
insulin	3%	3%
oral hypoglycemics	6%	7%
thyroid	3%	3%

3. Statistical Methods

All randomized patients were included in the analyses regardless of treatment compliance and all of the sponsor's analyses were planned prior to completion of the trial.

The main analyses were time-to-event analyses where the treatment groups were compared using the log rank test. All p-values presented in the tables in this review are the results of log rank tests performed by FDA. A Cox proportional hazards model with just treatment in the model was used by the sponsor and FDA to estimate the relative risk after checking the proportionality assumption of the model.

In addition, the sponsor performed the following analyses of the efficacy variables (the first 2 were only performed for the primary efficacy variable): a time-to-event analysis stratifying by LDL quartiles, a time-to-event analysis excluding patients with LDL>160 mg/dl, subgroup analyses to show consistency of effect and covariate-adjusted analyses.

The protocol listed the following potential subgroups: gender, age, nation of origin, plasma LDL and HDL, LDL/HDL, LDL minus HDL, ejection fraction, number of previous myocardial infarctions, months from MI to enrollment, hx of CABG or PTCA, concurrent CV medications, post-menopausal estrogen replacement, use of insulin, and glucose control. Results for subgroups defined by age, gender, baseline LDL, and smoking status were produced by FDA and are presented for the primary, secondary and tertiary endpoints and for one additional endpoint (time to CABG or non-surgical coronary

revascularization). Also included are the results for non-fatal MI (definite); a component of the combined primary endpoint. The latter was not specified in the protocol as an endpoint for the study but should be fully examined to aid in interpretation of the results for the primary endpoint.

Covariate-adjusted analyses performed by the sponsor used the following covariates: baseline LDL/HDL, ejection fraction, hypertension (yes/no), diabetes (yes/no), days from MI to enrollment, age, sex and smoking (yes/no with former smokers=no). These results were reviewed but are not presented here.

A total of five interim analyses, in addition to the final analysis, were performed as planned. Two interim analysis methods were described in the protocol; stochastic curtailment and the Lan and DeMets method. The Lan and DeMets method was used to specify the stopping rules and the level of significance at the final look. The latter was set at .04 (using an O'Brien-Fleming spending function) for the primary endpoint only. No adjustments to p-values for secondary endpoints were made.

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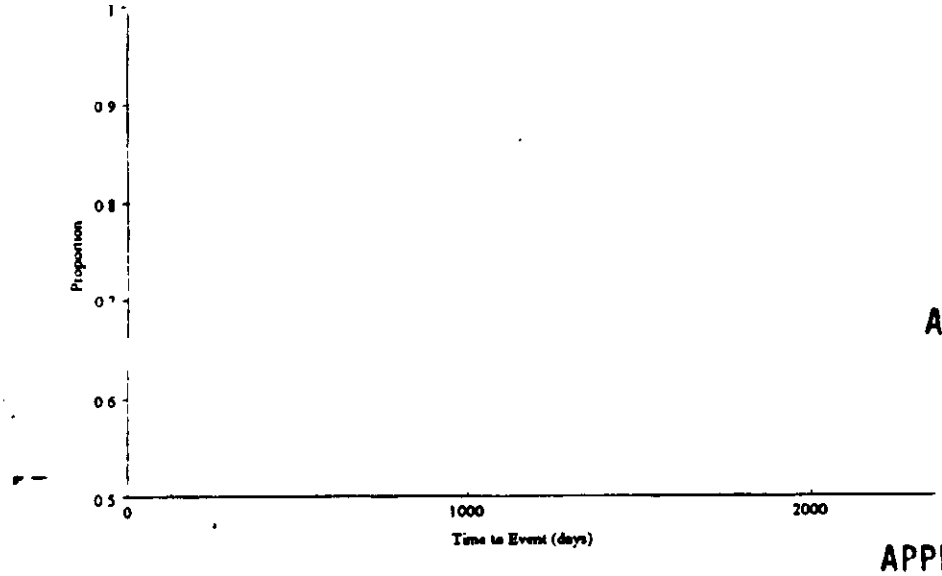
4. Efficacy Results

Primary Endpoint: Fatal CHD and Non-fatal Myocardial Infarction
The primary endpoint was death from CHD or definite non-fatal MI. CHD death was defined as

- fatal MI, definite or probable
- sudden death
- death during a coronary intervention procedure
- other coronary death

The results for the primary efficacy variable, time to non-fatal MI (definite) or fatal CHD (whichever occurred first), showed a statistically significant treatment difference between pravastatin and placebo with a decrease in event rates of about 3% and a relative risk (RR) of 0.76. The survival curves (Figure 3) begin to separate after about 2½ years of exposure and treatment differences continue to be evident until the end of the treatment period (p=.003).

Figure 3 Survival Curves for Fatal CHD and NFMI



Event	Pravastatin (n=2081)	Placebo (n=2078)
NFMI (definite)	135 (6%)	173 (8%)
Fatal CHD	77 (4%)	101 (5%)
Censored	1869 (90%)	1804 (87%)

Table 5. CARE Primary Endpoint Results
Non-fatal MI (definite) or Fatal CHD

	Pravastatin	Placebo	Relative Risk	95% Confidence Interval	P-value
All patients	212/2081 (10%)	274/2078 (13%)	0.76	0.64, 0.91	.003
Gender					
Male	189/1795 (11%)	235/1788 (13%)	0.79	0.65, 0.96	.02
Female	23/286 (8%)	39/290 (13%)	0.58	0.34, 0.96	.04
Age					
<65	143/1441 (10%)	163/1435 (11%)	0.87	0.69, 1.1	.21
≥65	69/640 (11%)	111/643 (17%)	0.61	0.45, 0.82	.001
Baseline LDL Quartiles					
≤126.5	49/517 (9%)	55/529 (10%)	0.91	0.62, 1.3	.62
>126.5-137.5	50/525 (10%)	69/519 (13%)	0.71	0.50, 1.0	.07
>137.5-149	59/525 (11%)	72/528 (14%)	0.80	0.57, 1.1	.21
>149	54/514 (11%)	78/502 (16%)	0.67	0.47, 0.94	.02
Baseline LDL					
<130	61/657 (9%)	80/673 (12%)	0.78	0.56, 1.1	.13
≥130	151/1424 (11%)	194/1405 (14%)	0.76	0.61, 0.94	.01
Smoker					
Yes	43/337 (13%)	63/334 (19%)	0.62	0.42, 0.91	.01
No	169/1744 (10%)	209/1744 (12%)	0.80	0.66, 0.98	03

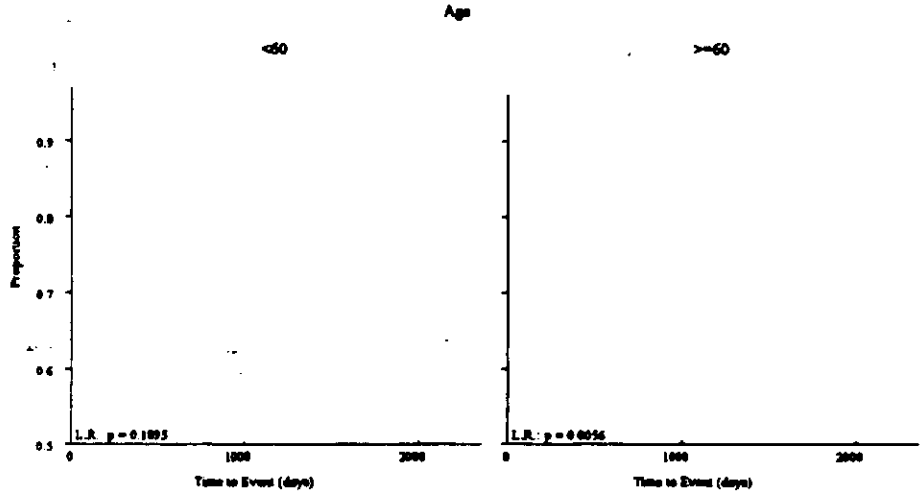
The event rate for pravastatin is quite consistent (generally 10% or 11% with a range of across subgroups shown in Table 5. The placebo rates, on the other hand, appear to be higher in high-risk subgroups (note a rate of 19% for smokers and the increasing rates with increasing baseline LDL).

The apparent benefit of pravastatin therapy held for both the men and the women, though only 14% of the trial subjects were female.

When the primary endpoint outcome was examined as a function of age at baseline, there was no statistically significant benefit of pravastatin compared to placebo in the group under age 65. It is interesting that the event rate in the placebo group for those under 65 was much lower than that in the patients aged >65 years (11% vs. 17%). This is perhaps expected based on the assumption that, on average, the extent and severity of atherosclerosis is greater in older patients. That is, a simple history of MI does not convey the full story of an individual's atherosclerosis. What is quite striking is that while 70% of the study cohort were <65 years old at trial entry, and while most of the total primary endpoint events (63%) occurred in this subgroup, there was no statistically significant benefit of pravastatin in this majority subgroup of the trial population. The trend, however, favored pravastatin, though less dramatically than in the group over age 65. Further analyses using cutpoints of 50, 55 and 60 (the median), also showed that patients in the older subgroup reaped a greater benefit from the use of

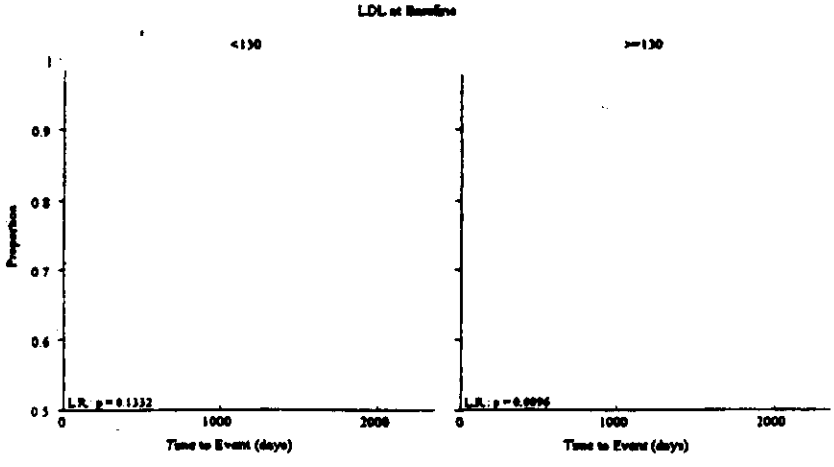
pravastatin compared to placebo than younger patients. The results for subgroups based on the median age of 60 are shown in Figure 4, below.

Figure 4 Survival Curves for Fatal CHD or Non-fatal MI by Median Age



When the primary endpoint outcomes were examined as a function of LDL-C level at entry into the trial, subgrouping by quartile did reveal a trend in relative risk suggesting decreasing benefit with decreasing baseline risk (Table 5). This trend was also observed in 4S and WOSCOPS. As expected from the epidemiology and as seen in earlier trials, in CARE, the analysis by LDL-C quartiles does show that placebo event rates decrease slightly with decreasing LDL-C at baseline. Insofar as pravastatin rates do not decrease to a similar degree, the difference between treatment groups is attenuated with decreasing baseline LDL-C. Relevant to current guidelines for treatment of hypercholesterolemic CHD patients, subdividing the study cohort by baseline LDL-C greater than or less than 130 mg/dL reveals similar trends (pravastatin vs. placebo) in the two subgroups, though the results for the group with LDL-C < 130 do not reach statistical significance (see Table 5 above and Figure 5 below).

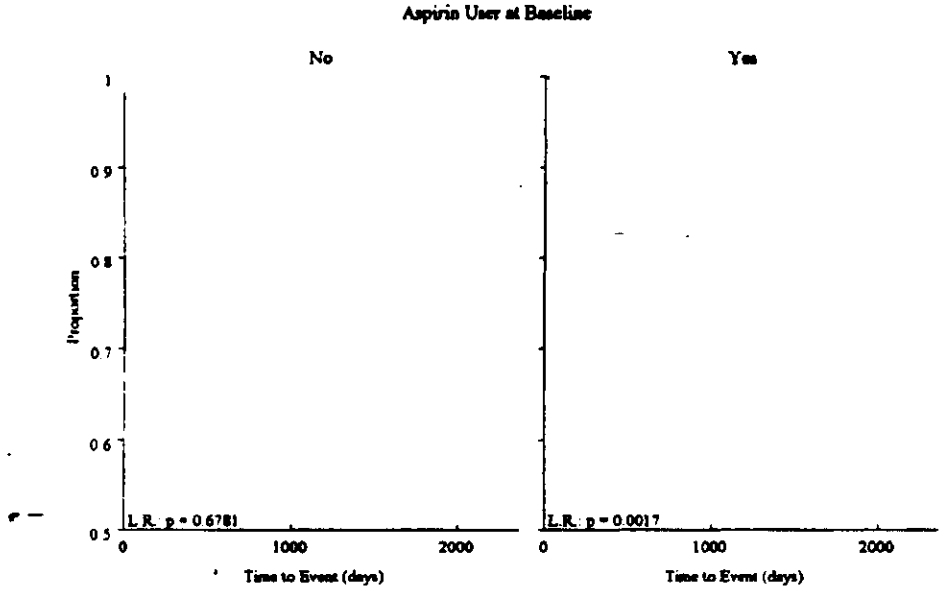
Figure 5 Survival Curves for Fatal CHD of Non-fatal MI by Baseline LDL



Finally, it is interesting to point out the low rate of smoking in this trial (16%), the high event rate among the placebo-treated smokers, and the apparent benefit of pravastatin in both smokers and non-smokers.

Tests for homogeneity of response for the above listed subgroups as well as for subgroups defined by baseline concomitant medication use and by variables related to medical history (such as hypertension, diabetes, prior MI, etc.) generally showed a consistent effect for pravastatin over placebo with a few notable exceptions (e.g., age, aspirin (ASA) use). The apparent lack of effect of pravastatin in non-ASA users (see Figure 6, below) is confounded by the fact that fully 84% of the study cohort was on aspirin at the start of the trial, that there were thus few events in the no-aspirin subgroup, and finally, that patients were not randomized to aspirin or no-aspirin treatment arms. No conclusions can be drawn from this finding. Prospective trials would be necessary to assess the impact on ASA on the overall outcome in a CARE-like population.

Figure 6 Survival Curves for Fatal CHD or Non-fatal MI by Aspirin Use at Baseline



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Secondary endpoint: fatal CHD

Fatal CHD (a component of the primary outcome variable) was prespecified in the protocol as a secondary endpoint. The survival curves for this endpoint (Figure 7) are similar to the curves observed for the primary outcome variable, however, the curves are not statistically significant (p=.10). The difference between the event rates is only 1% (pravastatin:5%, placebo:6%) with a relative risk of 0.80 (Table 6).

Figure 7 Survival Curves for Fatal CHD

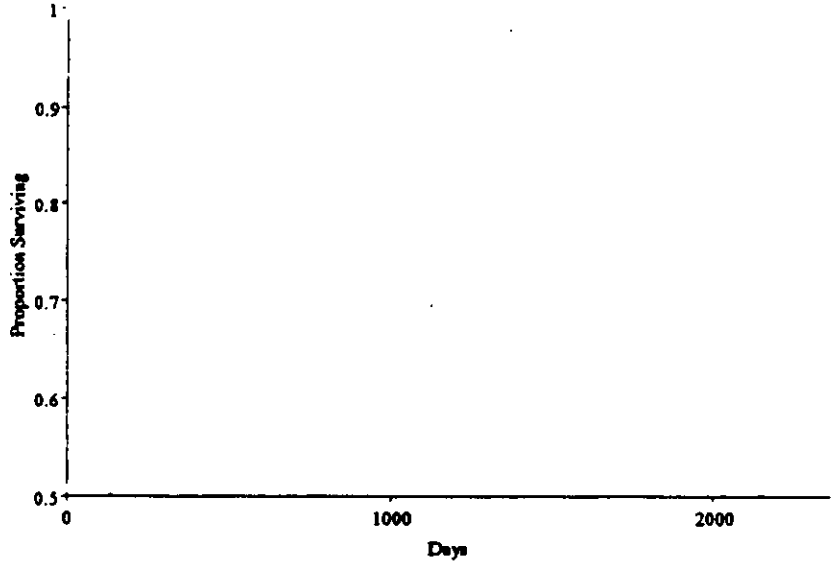

Table 6. CARE Secondary Endpoint Results

Fatal CHD

	Pravastatin	Placebo	Relative Risk	95% Confidence Interval	P-value
All patients	96/2081 (5%)	119/2078 (6%)	0.80	0.61, 1.1	.10
Gender					
Male	85/1795 (5%)	105/1788 (6%)	0.80	0.60, 1.1	.13
Female	11/286 (4%)	14/290 (5%)	0.79	0.36, 1.7	.56
Age					
<65	59/1441 (4%)	53/1435 (4%)	1.1	0.77, 1.6	.59
≥65	37/640 (6%)	66/643 (10%)	0.55	0.37, 0.83	.004
Baseline LDL Quartiles					
≤126.5	25/517 (5%)	20/529 (4%)	1.3	0.72, 2.3	.39
>126.5-137.5	27/525 (5%)	38/519 (7%)	0.70	0.43, 1.1	.16
>137.5-149	22/525 (4%)	29/528 (6%)	0.75	0.43, 1.3	.30
>149	22/514 (4%)	32/502 (6%)	0.62	0.39, 1.2	.14
Baseline LDL					
<130	32/657 (5%)	32/673 (5%)	1.0	0.64, 1.7	.89
≥130	64/1424 (5%)	87/1405 (6%)	0.72	0.52, 0.99	.04
Smoker					
Yes	14/337 (4%)	26/334 (8%)	0.52	0.27, 0.99	.05
No	82/1744 (5%)	93/1744 (5%)	0.88	0.65, 1.2	.40

It is interesting to note that while, overall, the magnitude of the trends favoring pravastatin are similar for the fatal events and for the overall combined primary endpoint events, again the effect is attenuated in the group aged < 65 years at entry and in the subgroups with lower baseline LDL-C. The death rate from CHD was quite low in the younger patients (4%) and pravastatin showed no benefit relative to placebo. Likewise, there was no demonstrated benefit in the low LDL-C subgroups (< 126.5, < 130 mg/dL). Again, there was a striking effect of pravastatin among the smokers, reducing rate of death from CHD by 50%, albeit based on small numbers of events.

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Non-prespecified endpoint: Non-fatal Myocardial Infarction (Definite)

Non-fatal MI (a component of the primary outcome variable) was not prespecified in the protocol as a secondary endpoint, however, it is important to look at the results of this endpoint to aid in the interpretation of the primary endpoint. As seen in earlier trials in which the effect of therapy on rate of non-fatal MI and CHD death is examined, the primary endpoint findings in CARE are driven by the non-fatal CHD events which occurred at an overall rate approximately 1.5 times that of fatal events.

The survival curves are statistically significantly different (Figure 8, p=.02). There were 135 events (6%) in the pravastatin group versus 173 events (8%) in the placebo group; relative risk of 0.77.

Figure 8 Survival Curves for Non-fatal MI (definite)

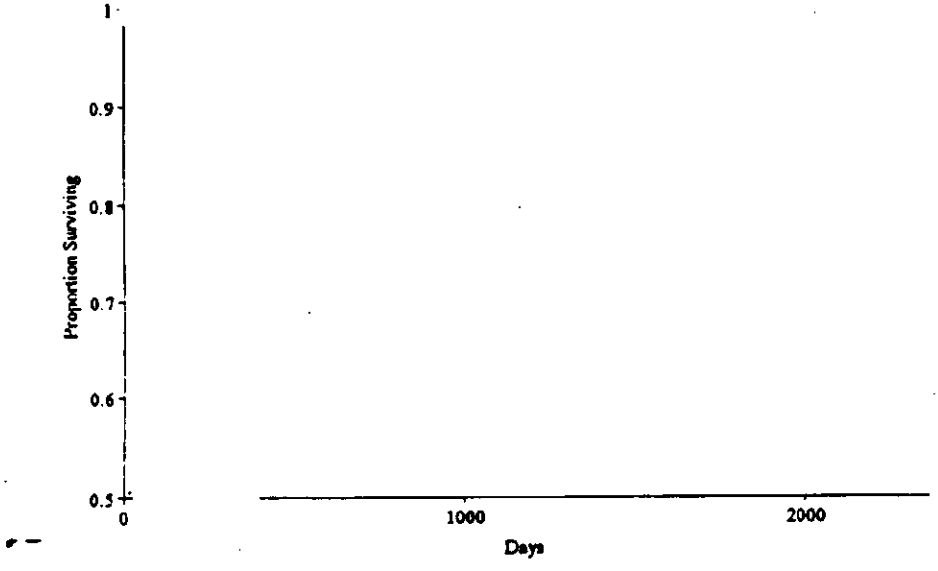

Table 7. CARE Non-prespecified Endpoint Results

Non-fatal MI

	Pravastatin	Placebo	Relative Risk	95% Confidence Interval	P-value
All patients	135/2081 (6%)	173/2078 (8%)	0.77	0.61, 0.96	.02
Gender					
Male	121/1795 (7%)	145/1788 (8%)	0.82	0.65, 1.0	.11
Female	14/286 (5%)	28/290 (10%)	0.49	0.26, 0.92	.02
Age					
<65	84/1441 (7%)	116/1435 (8%)	0.80	0.61, 1.0	.11
≥65	41/640 (6%)	57/643 (8%)	0.70	0.47, 1.1	.09
Baseline LDL Quartiles					
≤126.5	26/517 (5%)	39/529 (7%)	0.68	0.41, 1.1	.12
>126.5-137.5	31/525 (6%)	37/519 (7%)	0.82	0.51, 1.3	.42
>137.5-149	44/525 (8%)	48/528 (9%)	0.90	0.60, 1.4	.62
>149	34/514 (7%)	49/502 (10%)	0.66	0.43, 1.0	.07
Baseline LDL					
<130	34/657 (5%)	52/673 (8%)	0.67	0.43, 1.0	.06
≥130	100/1744 (6%)	121/1405 (9%)	0.81	0.62, 1.1	.12
Smoker					
Yes	35/337 (10%)	44/334 (13%)	0.74	0.48, 1.2	.19
No	100/1744 (6%)	129/1744 (12%)	0.77	0.59, 1.0	.05

For the overall cohort and across subgroups, the trends (pravastatin vs. placebo) were consistent with the primary endpoint results.

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Tertiary endpoint: Total Morality

Figure 9 Survival Curves for Total Mortality

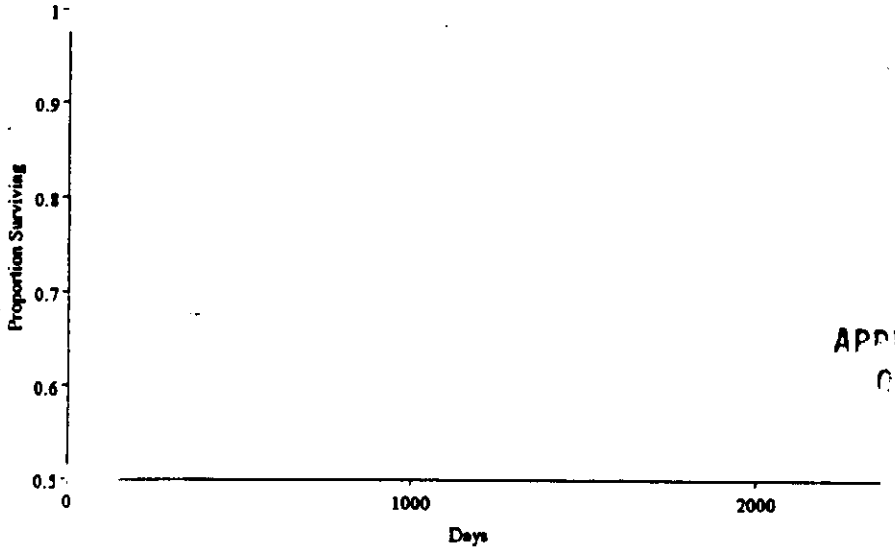


Table 8. CARE Tertiary Endpoint Results
Total Mortality

	Pravastatin	Placebo	Relative Risk	95% Confidence Interval	P-value
All patients	180/2081 (9%)	196/2078 (9%)	0.91	0.74, 1.1	.37
Gender					
Male	159/1795 (9%)	173/1788 (10%)	0.91	0.73, 1.1	.39
Female	21/286 (7%)	23/290 (8%)	0.92	0.51, 1.7	.78
Age					
<65	103/1441 (7%)	88/1435 (6%)	1.2	0.88, 1.6	.29
≥65	77/640 (12%)	108/643 (17%)	0.70	0.52, 0.94	.02
Baseline LDL Quartiles					
≤126.5	53517 (10%)	40/529 (8%)	1.4	0.91, 2.1	.13
>126.5-137.5	46/525 (9%)	58/519 (11%)	0.78	0.53, 1.2	.22
>137.5-149	44/525 (8%)	54/528 (10%)	0.80	0.54, 1.2	.27
>149	37/514 (7%)	44/502 (9%)	0.81	0.53, 1.3	.35
Baseline LDL					
<130	67/657 (10%)	58/673 (9%)	1.2	0.84, 1.7	.31
≥130	113/1424 (8%)	138/1405 (10%)	0.80	0.62, 1.0	.07
Smoker					
Yes	36/337 (11%)	39/334 (12%)	0.88	0.56, 1.4	.59
No	144/1744 (8%)	157/1744 (9%)	0.92	0.73, 1.1	.45

The trend in rate of death due to all causes (pravastatin vs. placebo) did not reach statistical significance. When cause-specific mortality rates were examined (Table 9), there appears to be no imbalance in the rate of death due to non-cardiovascular causes between treatment groups, and no remarkable differences in rates of specific causes of death within the non-cardiovascular category. Thus, pravastatin therapy was associated with a decrease in the rate of cardiovascular death with no countervailing increase in the rate of death due to non-cardiovascular causes.

Table 9. Cause-specific Mortality Rates

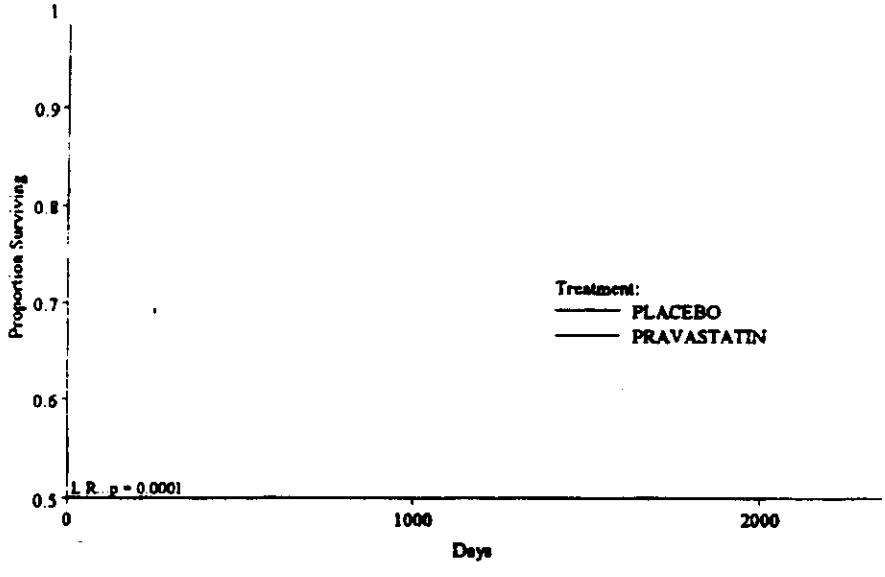
Cause of death	pravastatin N=2081	placebo N=2078
atherosclerotic CHD	96	119
fatal MI	24	38
sudden death	58	61
other CHD	14	20
atherosclerotic vascular	15	10
cerebrovascular	10	6
other ath vascular	5	4
total atherosclerotic	111	129
non-atherosclerotic CV	1	1
total CV	**112**	**130**
cancer	49	45
accident/suicide	8	4
other/unknown	11	17
total non-CV	**68**	**66**
total, all cause	**180**	**196**

Pre-specified endpoint: Need for coronary artery bypass surgery or nonsurgical coronary revascularization

In the U.S. and Canada, myocardial revascularization is readily available and frequently used. It is not, *per se*, part of the natural history of CHD, though it is a reality of clinical trials in this disease that revascularization will often preempt clinical events. That is, based on studies of the safety and efficacy of these procedures, overall rates of fatal and non-fatal MI in such a trial are thus likely to be reduced by these interventions. In addition, the need for revascularization is not absolutely standardized, and rates of CABG and PTCA do differ across nations, centers, and individual practitioners treating, on average, patients with equally severe CHD. In a blinded, randomized trial (where it is hoped, too, that the interventional cardiologists and surgeons are blinded to treatment), perhaps the only obvious bias is introduced if these physicians are not blinded to cholesterol levels. Again, though, in this study in particular, because none of the patients had markedly elevated cholesterol even at baseline, even such knowledge might not be expected to bias the surgeon or cardiologist in his or her decision whether or not to intervene. In sum, the revascularization data from such a trial are an important measure of treatment effect.

The trial outcome with regard to the rate of myocardial revascularization was highly statistically significant in favor of pravastatin (Figure 10) with a difference in event rates of 5% and a relative risk of 0.73 (Table 10).

Figure 10 Survival Curves for CABG or Non-surgical Coronary Revascularization



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Significant treatment differences were evident in most subgroups with the exception of the subgroups defined by the lowest LDL quartile or by LDL < 130 (Table 10).

Table 10. CARE Endpoint Results

Need for coronary artery bypass surgery or nonsurgical coronary revascularization

	Pravastatin	Placebo	Relative Risk	95% Confidence Interval	P-value
All patients	294/2081 (14%)	391/2078 (19%)	0.73	0.63, 0.85	.0001
Gender					
Male	266/1795 (15%)	334/1788 (19%)	0.78	0.66, 0.92	.002
Female	28/286 (10%)	57/290 (20%)	0.47	0.30, 0.74	.001
Age					
<65	221/1441 (15%)	287/1435 (20%)	0.75	0.63, 0.89	.001
≥65	73/640 (11%)	104/643 (16%)	0.69	0.51, 0.92	.01
Baseline LDL Quartiles					
≤126.5	72/517 (14%)	88/529 (17%)	0.83	0.61, 1.1	.25
>126.5-137.5	75/525 (14%)	106/519 (20%)	0.68	0.51, 0.91	.01
>137.5-149	74/525 (14%)	91/528 (17%)	0.79	0.58, 1.1	.14
>149	73/514 (14%)	106/502 (21%)	0.65	0.48, 0.88	.004
Baseline LDL					
<130	95/657 (15%)	113/673 (17%)	0.86	0.66, 1.1	.28
≥130	199/1424 (14%)	278/1405 (20%)	0.68	0.57, 0.82	.0001
Smoker					
Yes	57/337 (17%)	72/334 (22%)	0.73	0.52, 1.0	.08
No	237/1744 (14%)	319/1744 (18%)	0.73	0.62, 0.86	.0002

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Other Cardiovascular Events Measured in CARE

Table 11 summarizes the outcomes for pre-specified outcome variables in CARE. These are direct and indirect measures of atherosclerotic vascular disease. It is significant that pravastatin use was associated with reduced rates of events across all the categories examined and serves to provide internal validation of the primary efficacy outcome.

Table 11. Results for protocol-defined cardiovascular endpoints measured in CARE

On-Study Event	Pravastatin (n=2081)	Placebo (n=2078)	Relative Risk	95% Confidence Interval	P-value
Myocardial infarction, nonfatal (definite and probable)	182 (9%)	231 (11%)	0.77	0.64, 0.94	.01
Myocardial infarction, nonfatal and fatal (definite and probable)	216 (10%)	283 (14%)	0.75	0.63, 0.90	.002
Development of overt CHF	146 (7%)	160 (8%)	0.90	0.72, 1.1	.38
Cerebrovascular disease , fatal and nonfatal	99 (5%)	129 (6%)	0.76	0.59, 0.99	.04
Hospitalization for CV disease	852 (41%)	949 (46%)	0.87	0.80, 0.96	.004
Hospitalization for peripheral arterial disease	54 (3%)	61 (3%)	0.88	0.61, 1.3	.49
Hospitalization for unstable angina	317 (15%)	359 (17%)	0.87	0.75, 1.0	.07
First coronary heart disease event	624 (30%)	729 (35%)	0.83	0.75, 0.93	.0008
First cardiovascular disease event	890 (43%)	991 (48%)	0.87	0.80, 0.95	.003
Cardiovascular Mortality	112 (5%)	130 (6%)	0.85	0.66, 1.1	.22
Atherosclerotic cardiovascular disease, fatal	111 (5%)	129 (6%)	0.85	0.66, 1.1	.22
Atherosclerotic cardiovascular disease, fatal and nonfatal	710 (34%)	816 (39%)	0.85	0.77, 0.94	.002

CARE cerebrovascular disease results

After review by the Stroke and TIA Classification Committee, post study, four analyses were performed, two for the endpoint of stroke or TIA (including and excluding hemorrhagic events) and two for the endpoint of stroke alone (including and excluding hemorrhagic events).

The treatment groups were comparable with regard to history of stroke or TIA:

- pravastatin 62 (3%) of 2081
- placebo 60 (3%) of 2078.

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The Stroke and Classification Committee reviewed 279 events in the data base. All but 18 of these plus one additional event, determined by the Endpoints Committee to be a death due to cerebral hemorrhage, were included in the sponsor's analyses. The eighteen events (10 pravastatin, 8 placebo) were "unclassifiable" and therefore not included in the analyses. Of 261 cerebrovascular disease events, 217 were first on-trial occurrences and included in the time-to-event analyses. These analyses are consistent with analyses of the CVD events in the original study data base, classified based on ICD-codes. The table below is reproduced from the submission.

Table 12. Classified CVD events in CARE

Event	Prava (N=2081)	Placebo (N=2078)	Risk reduction (95% CI)	logrank P-value
fatal and nonfatal stroke or TIA, including hemorrhagic events	93 (4,7)	124 (6,3)	26 (3, 43)	0.029
fatal and nonfatal stroke, including hemorrhagic events	53 (2,8)	76 (4, 0)	31 (2, 51)	0.037
fatal and nonfatal stroke or TIA	91 (4,6)	118 (6,0)	24 (0, 42)	0.052
fatal or nonfatal stroke	51 (2, 7)	70 (3, 6)	28 (-4, 50)	0.075

A number of other analyses of interest are included in the submission. For these, the data analyzed are those from the study data base, as reported by the Data Coordinating Committee.

When the distributions of first on-study fatal and non-fatal stroke events (excluding hemorrhagic events) and stroke alone were examined by history of cerebrovascular disease, pravastatin therapy was associated with reductions in events rates in patients with and without a prior history of stroke or TIA. Sixteen of 60 (26%) placebo patients with a history of CVD had an event on study while 11 of 62 (17%) pravastatin patients with a history of CVD had an event on study. Thus, pravastatin appeared effective in both the primary prevention as well as the secondary prevention of CVD in this trial.

In light of this, it is interesting to note that the distribution of subjects with one or more on-study CVD events by treatment group shows a large difference for patients with a

first event (108 placebo, 76 pravastatin) but no difference for second events (27 vs. 26) and beyond. This may be a function of the relative paucity of secondary events.

Conclusions regarding the CVD outcome in CARE

Based on analyses of the CVD event data both from the original study data base as well as after refinement by the Stroke and TIA Classification Committee, it appears that pravastatin therapy was associated with a reduction in risk for combined stroke and TIA. This holds true both including and excluding hemorrhagic events. This, of course, is consistent with the effect on cardiovascular events, and expected based on existing data from other studies, including those using statins, and based on the presumed shared pathogenesis (related to atherosclerosis) between ischemic coronary disease and ischemic cerebrovascular disease (excluding at least some cases of hemorrhagic stroke).

With regard to labeling, the language used to describe the above outcomes should speak to the reduction of cerebrovascular events (stroke or TIA), as the result for TIA alone was not statistically significant (likely as a result of low event rates). In addition, the analysis cited should be that based on the findings of the Stroke Classification Committee.

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Changes in plasma lipids

With the exception of TG, the mean changes in plasma lipids were relatively constant for the duration of treatment. At the five-year follow up visit, the mean changes in total-C, LDL-C, HDL-C, and TG from baseline in the pravastatin group were -16.1%, -27.6%, +12.5%, and +4.8%, respectively. The corresponding results for the placebo group were +1.3%, -3%, +8%, and +17.9%, respectively. It is interesting to note the small apparent effect of pravastatin to raise HDL-C levels relative to placebo, and the effect to stabilize TG, even as TG increased over the course of the trial in the placebo group.

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5. Safety data

The AE data set for safety analyses as well as the clinical laboratory data set included all randomized subjects who took at least one dose of medication and events up to and including 30 days after discontinuation of therapy. Cancer AEs were included regardless of the relationship between time of diagnosis and date of discontinuation of study medication. Clinical AEs were coded using an ICD-9 based dictionary.

Recurrent or continuing treatment-emergent events were counted only once. For the purposes of safety reporting and analysis, interruptions in treatment were disregarded. Thus the discontinuations counted were permanent discontinuations. AE frequency rates were calculated using the denominator of all subjects taking at least one dose of drug (by treatment group). For those events that tend to occur as a result of cumulative exposure to drug, inclusion of patients treated for periods of time shorter than is

necessary for the induction of the AE will result in underestimation of the rate of the adverse event. As a primary safety analysis, however, this is an acceptable approach.

A long-term, placebo-controlled, randomized trial like CARE provides an opportunity to examine the safety and tolerability of a drug to an extent not permitted by the shorter controlled exposures in the NDA database. With regard to pravastatin, the previously reported WOSCOPS trial, examining the effects of pravastatin in the primary prevention of CHD in high risk patients, enrolled only middle-aged men in a geographical region where treatments for dyslipidemia and interventions, including drugs, for other cardiovascular disease symptoms, signs, and risk factors were underutilized. By contrast, CARE enrolled men and women from many of whom were receiving concomitant medications for their CHD or risk-conferring condition, and the safety experience thus may better approximate that to be expected in extended actual use.

Exposure in CARE

As discussed above, the dropout rate was somewhat higher in the placebo group than among pravastatin-treated patients, and consistent year by year during the trial. Overall, ~28% of placebo patients and ~19% of pravastatin patients withdrew prematurely from the trial. Nevertheless, the groups are fairly comparable in term of exposure, with means of 1670 days for the pravastatin group and 1576 days for the placebo group.

Deaths

The total mortality in this trial, including those deaths occurring during the study period and both on treatment and up to 30 days after discontinuation of drug as well as more than 30 days after discontinuation, and finally including 6 deaths occurring after closure of the trial (up to 63 days after study closure), was 184 (8.8%) in the pravastatin group and 198 (9.5%) in the placebo group. Note that these data do not agree with those analyzed for the study endpoint of total mortality, above, though the difference is not significant. Fully 30% of the deaths in each treatment group occurred more than 30 days after discontinuation of drug.

The most common cause of death was cardiovascular disease, with 115 deaths due to cardiovascular disease in the pravastatin group and 133 in the placebo group. This overall trend in favor of pravastatin was generally echoed in trends among the specific cardiovascular causes of death.

The most common cause of non-cardiovascular death in CARE was malignancy, with 51 total deaths in the pravastatin group and 45 among the placebo patients. This difference is not statistically significant.

Discontinuations due to adverse events

121 placebo patients and 92 pravastatin patients discontinued study medication due to adverse events. Cardiovascular and gastrointestinal causes predominated, both more common among placebo patients, accounting for approximately one third of the discontinuations. Among the specific causes, several points bear noting:

- breast cancer: prava 3, plac 0
- abnormal TG or increased lipids: prava 1, plac 16
- fatigue: prava 6, plac 1
- LFTs increased: prava 3, plac 3
- abnormal liver function: prava 3, plac 0
- increased CK: prava 0, plac 2

The breast cancer data will be discussed below. Withdrawals for abnormal lipids simply speak to the ineffectiveness of placebo and the problems of conducting a placebo-controlled study in lipid altering.. Finally, hepatic and muscular abnormalities are rare causes of discontinuation in both treatment groups. As in other trials with pravastatin, it appears well tolerated in this regard.

Clinical adverse events

Overall adverse events, adverse drug experiences, and adverse events by body system were reported with similar frequency in the two treatment groups. For the 30 most common adverse events, there were no marked differences in the percentage of patients experiencing the event across treatment groups.

Breast cancer

There were several adverse events that were reported with greater frequency among pravastatin-treated than among placebo-treated patients and for which the difference was statistically significant. Notable among these was an excess of breast cancer cases among the women treated with pravastatin. Twelve (4.2%) pravastatin-treated women were found to have a malignant neoplasm of the breast compared to 1 (0.3%) placebo-treated woman. Three documents addressing this issue were appended to the submission and will be briefly reviewed, summarizing the nature of the information offered in support of the conclusion that the imbalance between treatment groups in the incidence of breast cancer in this trial was an anomalous finding.

Document 1: "An interim report and update on the occurrence of breast cancer in women who participated in the CARE study."

The preclinical carcinogenicity, reproductive toxicity, and genotoxicity studies of pravastatin suggest no potential for this drug as an inducer or promotor of breast cancer. The effects of pravastatin on female endocrine function were studied in a placebo-controlled trial in premenopausal women. Preliminary analyses show that neither pravastatin nor lovastatin affect the mid-luteal estradiol or progesterone levels in these subjects.

The sponsor also surveyed data bases from other studies using pravastatin, most notably from the LIPID study, an Australian secondary prevention study now recently concluded. At the time of the analyses presented in the CARE submission, the follow up in LIPID was >4 years. The sponsor also presented data on breast cancer cases from two other pravastatin clinical trial databases. Finally, the Worldwide Safety and Surveillance data base, covering an estimated 8 million person years of exposure, contained 9 reports of breast cancer. In the clinical trial data base, only in the CARE study was there a trend toward increased breast cancer in the pravastatin group. The incidence figures for LIPID, which enrolled ~2.5 times the number of women than did CARE, with similar mean age, were 5/755 and 7/755 in the pravastatin and placebo groups, respectively.

The sponsor also examined the findings of the CARE study in light of the incidence rates for breast cancer in the general U.S. and Canadian populations. Utilizing these data, the distribution of women enrolled across U.S. and Canadian sites, and adjusting for age and race, excluding those patients with a known prior history of breast cancer at study entry (6 pravastatin, 8 placebo), the expected number of new invasive cancers was derived for the CARE cohort of women, by treatment group. The expected number of new cases was 5 (95% CI 0.6-9.3) and 5 (95% CI 0.5-9.1) for the pravastatin and placebo group, respectively. Thus, the incidence of invasive cancers in the pravastatin group (seven) is within the range of expectation, while the absence of even a single case in the placebo group is unexpected.

When the demographics and baseline characteristics were compared for the pravastatin-treated women who developed breast cancer in CARE, the non-affected pravastatin-treated women, and the placebo-treated women, excluding women with a previous history of breast cancer, there were no major differences. The sponsor noted that the breast cancer patients were 1-2 years older, on average, and had a higher average body mass index than the non-affected patients (28.6 vs. 27.7). Thus, demographic and baseline differences in a number of characteristics do distinguish the breast cancer patients from those without breast cancer, regardless of treatment group.

- Document 2. An update on the occurrence of breast cancer in women who participated in the CARE study.

The CARE Women's Health Survey was an evaluation of 9 risk factors for breast cancer among the women in CARE. These were age, mother or sister with breast cancer, any family member with breast cancer, history of benign breast disease, nulliparity or age at first full-term pregnancy, age at menarche, age at menopause, history of estrogen use, and BMI. For all of the risk factors analyzed, the percentage of pravastatin-treated women with each risk factor was higher than that for the placebo-treated women. In addition, all 9 of the pravastatin-treated women with new invasive breast cancer had 3 or more of the 9 breast cancer risk factors examined. This post-hoc finding may distinguish the two treatment groups with respect to overall risk of breast cancer, but is certainly not definitive.

Document 3.

This is simply a letter from chair of the LIPID Safety and Data Monitoring Committee stating that as of June 1996, there were no concerns over the incidence, overall or across treatment groups, of breast cancer in that study.

Conclusions regarding the breast cancer outcome in CARE

Based on the above information and analyses, in particular the absence of a similar finding in a larger study, enrolling more women, using pravastatin, and the absence of any such outcomes in the other large statin trial enrolling women completed to date, 4S, the CARE result appears potentially to be an anomalous finding. While follow up of the women in CARE continues, at present, the breast cancer data from the study have no place in labeling for pravastatin.

Cancer

Overall numbers of subjects with an adverse event of primary cancer in CARE were 216 in the pravastatin group and 196 in the placebo group. As discussed above, there were 12 cases of breast cancer in the pravastatin group (none in placebo). In addition, there were 56 cases listed as malignant neoplasm reproductive in the pravastatin group and 46 in the placebo group. The corresponding numbers for the males alone were 54 (2.6%) and 44 (2.1%). This is mentioned only to point out that there appeared to be no imbalance in female reproductive system cancers that might have paralleled the breast cancer finding.

Myopathy

There were no cases of severe myopathy (symptoms with CK>10 times ULN). Five patients in the pravastatin group and one in the placebo group had isolated instances of CK >10 times ULN without symptoms. No one was discontinued because of elevated CK or myopathy.

Serious AEs

There were no between-treatment-group differences in the incidence of serious AEs in CARE.

There were three serious adverse events in two patients taking pravastatin attributed to study therapy in CARE. One patient developed chest pain and bradycardia and was found to have CK 264, ALT 59, AST 36, GGT 56. Symptoms and lab abnormalities resolved without interruption of medication. The second patient developed pancreatitis which resolved on discontinuation of pravastatin.

Laboratory data

The incidence of marked abnormalities of ALT, AST, and CK was similar across treatment groups. For ALT and AST, overall rates were 1.2 to 1.8%, respectively. Only one pravastatin-treated patient and 2 placebo-treated patient had consecutive elevations of either ALT or AST >3 times ULN. Five placebo-treated patients and 3 pravastatin-treated patients were discontinued from the study due to elevated ALT or AST values.

Two placebo subjects and no pravastatin subjects were discontinued due to elevated CK levels. As above, all the instances of CK >10 times ULN were asymptomatic and resolved spontaneously without interruption of study medication.

Conclusion from the safety data
No new safety concerns were raised in this study. Save for the breast cancer incidence data, no unexpected findings arose from this trial. The sponsor's proposed changes to the Adverse Reactions section of the labeling are supported by the data from CARE.

III. Reviewers' Comments Pertaining to Labeling

Clinical Pharmacology, Clinical Studies
The description of the CARE study should include an enumeration (with percentages) of the distribution of men and women in the trial. In addition, the description of the study population should included the facts that 84% were taking ASA at baseline and 82% were taking antihypertensive medication at baseline.

The mean (or median) baseline LDL-C as well as the range of LDL-C levels at baseline should be stated.

The citation of the study results should include not only the numbers of patients with events but what percentage of the total treatment group this represented.

No statement of the magnitude of the treatment effect among the women should be included. Examination of the effect of treatment by gender was not a primary objective of the study. Indeed, the result in the female subgroup is hardly robust, being based on a small number of events. A statement that the treatment effect was consistent across the sexes enrolled is acceptable.

The inclusion of primary endpoint results, those for the rate of revascularization, and for the rate of cerebrovascular events is acceptable. The CVD event results cited should be based on the reclassified data from the Stroke Classification Committee. Finally, the results should be described as an effect on the risk of stroke or TIA, as the data for TIA did not reach statistical significance.

Indications and Usage, Secondary Prevention of Cardiovascular Events
The use of the term "normal" to describe the cholesterol levels at baseline of the CARE cohort is problematic. The range of LDL-C levels in the trial was from
70% of randomized subjects had LDL-C > 130 mg/dL. Based on current guidelines (NCEP) that are included in the labeling for this and all other cholesterol-lowering drugs, those CHD patients with LDL-C on diet of >130 mg/dL should all be treated to goal LDL-C <100 mg/dL. In addition, NCEP counsels that CHD patients with LDL-C may be treated with drugs at the physician's discretion. Thus, based on the current standard of care, the LDL-C levels at baseline in this trial are not considered

normal for CHD patients. Finally, it is precisely the group in CARE with baseline LDL-C <130 mg/dL in whom no statistically significant benefit of pravastatin therapy was demonstrated, likely because of low numbers of patients and low event rates relative to the subgroup with LDL-C > 130 mg/dL at baseline.

The CARE study thus tested the validity of the treatment approach advocated by the NCEP, and confirmed the current guidelines. What was shown was that in CHD patients with baseline LDL-C levels not, in the absence of CHD, mandating pharmacological intervention, pravastatin therapy reduced the rate of recurrent coronary events, CABG or PTCA, and stroke or TIA when compared to placebo. Again, the levels treated in this trial are not "normal" for CHD patients. In sum, the use of "normal" in Indications is potentially misleading.

The term "average" may be substituted in place of "normal." In all promotional pieces related to the CARE results and CARE-supported indications, the sponsor should be required to commit to the inclusion of information on the CARE cohort; specifically mean (or median) and range of LDL-C levels at entry should be included. Such information should be displayed with similar prominence to any references to the CARE results or to CARE-supported indications in promotional pieces.

Adverse reactions
The addition of a description of the CARE safety outcomes is acceptable as proposed.

IV. Recommendations
Contingent on the changes in the proposed labeling described above, this supplement should be approved.

David Orloff, M.D.
Medical Officer
/S/ 3-10-98

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Joy D. Mele, M.S.
Mathematical Statistician
/S/ 3/11/98

Concur:
Ed Nevius, Ph.D.
Director of DOB2
/S/ 3-11-98

APPEARS THIS WAY
ON ORIGINAL

Recommendation code: AE
cc:
Archival NDA# 19-898
HFD-510
HFD-510/DOrloff, SSobel, MSimoneau
HFD-715/Biometrics Division 2 File, Chron, JMele

Word-Carerev.doc/March

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 019898/S018

CHEMISTRY REVIEW(S)

CHEMISTS REVIEW	1. ORGANIZATION	2. NDA NUMBER OCT 2 3 1997
	DMEDP II, HFD-510	19-898
3. NAME AND ADDRESS OF APPLICANT		4. SUPPLEMENT NUMBER, DATE
Bristol-Myers Squibb Co. P.O. Box 4000 Princeton, NJ 08543-4000		SE1-018 3-31-97
5. NAME OF THE DRUG	6. PROPRIETARY NAME	7. AMENDMENTS, REPORT, DATE
Pravastatin Sodium	Pravachol	5-29-97

8. SUPPLEMENT PROVIDES FOR

Changes in labeling to reflect revised labeling based on the results from the Cholesterol and Recurrent Events (CARE) trial.

9. PHARMACOLOGICAL CATEGORY	10. HOW DISPENSED	11. RELATED IND, NDA, DMF
antihypercholestremia	RX	APPEARS THIS WAY ON ORIGINAL
12. DOSAGE FORM	13. POTENCY	
Tablets, oral	10,20,40 mg.	

14. CHEMICAL NAME AND STRUCTURE

15. COMMENTS

The sponsor has provided revised labeling based the results from the CARE study. The principal changes in the labeling effect the "Indications" for the drug. The revised labeling is acceptable based on chemistry issues. In addition, the amendment of 5-29-97 provided for a request for categorical exclusion from the requirement to prepare an EA in support of this application under 21 CFR 25.24(c). The sponsor noted that the EIC is under 1 ppb, and the subject of the proposed action will not have a significant effect on the environment. This request is acceptable.

16. CONCLUSION AND RECOMMENDATION

The sponsor has requested a categorical exclusion from the requirement to prepare an EA in support of this application as per 21 CFR 25.24(c). This request is acceptable and there is no need to prepare a FONSI. From a chemistry point of view, this supplement may be approved.

17. NAME	18. REVIEWERS SIGNATURE	19. DATE COMPLETED
WILLIAM K. BERLIN	/S/	10-23-97

DISTRIBUTION: ORIGINAL JACKET CSO REVIEWER DIVISION FILE

/S/

10/23/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 019898/S018

JOINT MEDICAL/STATISTICAL REVIEW(S)

MAR 10 1998

Joint Clinical and Statistical Review

NDA #: 19-898/S-018 (efficacy supplement)

Drug: PRAVACHOL (pravastatin sodium) tablets

Sponsor: Bristol-Myers Squibb Company

Proposed indication: In patients with previous MI and normal cholesterol levels, to reduce risk of MI, revascularization, and cerebrovascular disease events.

Date of Submission: March 31, 1997

Documents Reviewed: Volumes 46.1 to 46.22

Medical Reviewer: David G. Orloff, M.D. (HFD-510)

Statistical Reviewer: Joy Mele, M.S. (HFD-715)

Table of Contents

I. Introduction

A. Clinical and Historical Perspective

At the time of the design and initiation of the Cholesterol and Recurrent Events (CARE) study in the late 1980's, the relationship of plasma cholesterol to coronary heart disease risk was well established. Dating back to the 1930's, the link between elevated cholesterol and atherosclerotic coronary heart disease was established initially on the basis of experiments of nature in the form of familial disorders of lipoprotein metabolism and on animal models (CHD) and later on a large body of epidemiological evidence. Within populations as well as across countries and geographical areas, the incidence of CHD was known to be directly correlated with plasma cholesterol levels. This relationship appeared to be continuous and graded down to total cholesterol levels of ., perhaps best exemplified in the follow up data from the ~350,000 MRFIT screenees. Further bolstering the cholesterol hypothesis, in the 1970's and 1980's, interventional trials using diet and lipid-altering drugs had demonstrated that lowering cholesterol was associated with delays in the onset of coronary disease in asymptomatic patients and in the incidence of recurrent myocardial infarction in patients with existing symptomatic CHD. Finally, the combined epidemiological, clinical trial, and basic scientific evidence lent support to the role of LDL-C as the culprit in atherosclerosis, with HDL-C levels negatively correlated with CHD risk.

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Statin trials (WOSCOPS and 4S)

Two major placebo-controlled morbidity and mortality trials using statins were completed prior to CARE. These were WOSCOPS, a 5-year study in high-risk hypercholesterolemic men, without a previous MI, using pravastatin, and 4S, a 5-year study in hypercholesterolemic men and women, with a previous MI and/or angina (80% with MI) using simvastatin. Both trials achieved the landmark outcome of demonstrating reductions in non-fatal MI and fatal cardiovascular disease, without a countervailing excess of non-cardiovascular deaths in the active treatment groups. Indeed, 4S confirmed its primary hypothesis by demonstrating a highly statistically significant reduction in total mortality in the simvastatin group as compared to placebo. These consistent findings with regard to morbid and mortal cardiovascular events within both studies would have been expected based on the natural history of atherosclerotic disease (MI followed by recurrent MI with or without cardiac debility followed by death, sudden or otherwise). Thus, a reduction in the rate of non-fatal events, should, logically, eventually translate into a reduction in the rate of cardiovascular fatalities. These trials were, in retrospect, adequately powered to demonstrate an impact of cholesterol lowering on this pathogenic cascade. CARE was a trial designed and sized similarly to WOSCOPS and 4S, though this time asking whether cholesterol lowering would reduce the rate of combined non-fatal and fatal coronary events in men and women with a previous MI but with "normal" cholesterol levels.

Unresolved questions regarding cholesterol lowering:

What causes atherosclerosis in CHD patients with "normal" cholesterol levels?

Despite all this evidence for the role of cholesterol in heart disease, the CARE study was designed in a climate when several nagging questions in the field of cholesterol lowering remained unanswered. The first among these was spurred by the knowledge that the distribution of serum total and LDL cholesterol levels was similar among patients with and without CHD and that, indeed, many (if not most) patients with CHD had plasma cholesterols of less than 240 mg/dL (thus "average" or "normal"). Furthermore, an oft-cited finding of the primary prevention component of the Helsinki Heart Study using gemfibrozil, a drug which effects minimal lowering of LDL-C, was that the treatment benefit was actually limited to the subgroup with high triglycerides, low HDL-C, and only moderately elevated LDL-C. Taken together, these and other facts left open the question of whether cholesterol-rich lipoproteins were causative in atherosclerosis in patients with apparently "normal" levels of total and LDL-cholesterol.

Does cholesterol lowering benefit women and the elderly?

The second unanswered question was whether the benefits of cholesterol lowering applied to elderly patients and women, two groups grossly underrepresented in the earlier cholesterol lowering trials. Elderly patients had been excluded apparently out of a desire to enroll generally healthy CHD patients so as not to confound outcomes. Women had been underrepresented because of the low rate of CHD in middle-age women as compared to men. Furthermore, epidemiological data do not show a relationship between cholesterol levels and CHD risk in the elderly, though clearly the incidence of CHD does increase with age. This paradox has been resolved in recent years with the elucidation of the principle of time integrated cholesterol exposure, so-called cholesterol-years. Thus, the risk of CHD is directly related to the integral of cholesterol level and time. Since the initiation of the CARE study, the results of 4S have been published, suggesting consistent effects of cholesterol lowering with simvastatin with regard to atherosclerotic morbidity and mortality across men and women and across age groups, including those over age 65.

The total mortality question

The third nagging question, also addressed in the design of the 4S and WOSCOPS trials, both completed prior to CARE, was the result of a failure to demonstrate consistent improvements in total and cardiovascular mortality in cholesterol lowering trials, despite clear reductions in the rates of non-fatal coronary events. Prior to the completion of the large statin trials, the only two examples of significant reductions in overall mortality were the 5-year Stockholm Ischemic Heart Disease Trial using clofibrate and niacin in patients beginning 4 months after MI, and the fifteen year follow up (this being 8 years out from the closure of the trial) of the niacin arm of another secondary prevention study, the Coronary Drug Project. This inconsistency between the effects on morbid events and mortality outcomes was rationalized by the poor average reductions in total cholesterol in early trials, between 5 and 15%,

contributed to by poor drug tolerability and poor compliance, although the specter of subtle toxicity of the drugs (or of cholesterol lowering generally) as a countervailing negative influence on survival was raised. Indeed, several trials as well as meta-analyses have shown an excess of cancer deaths and traumatic deaths associated with active treatment to lower cholesterol. This concept of risk outweighing benefit in situations where the benefit is small is particularly relevant to the CARE population (see below). If the cardiovascular benefits associated with cholesterol reduction were attenuated in the population with lower baseline cholesterols, then any adverse effects of the intervention might have a proportionately greater effect to offset that benefit.

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B. Uniqueness of the CARE design

The first two of the above questions were addressed in the design of CARE by the entry criteria that rendered a study cohort of both men and women up to age 75, and with average LDL-C representative of the average patient with MI. In addition, the use of pravastatin at a dose predicted to effect a lowering of LDL-C in this population was theorized to lower (potentially) recurrent cardiovascular event rates by 30-40% such that cardiovascular benefit would be expected to exceed that seen in earlier trials in the pre-statin era. The trial was not designed to test whether pravastatin therapy would have an effect to reduce overall mortality. The large sample size, in conjunction with the design feature that there would be no fixed duration of follow up, but rather that the trial would continue until a predetermined number of primary endpoint events occurred, was intended to insure a statistically valid result by preserving the power of the study to address the prospectively defined hypotheses.

C. NCEP Guidelines and the significance of CARE results

The Adult Treatment Panel of the National Cholesterol Education Program published its revised guidelines for the treatment of hypercholesterolemia in 1993. These guidelines target patients like those enrolled in the CARE study for aggressive lipid lowering. Specifically, the goal LDL-C level in patients with established coronary artery disease is less than 100 mg/dL, with nominal drug treatment initiation LDL-C level > 130 mg/dL on a low-cholesterol, low-saturated-fat diet, but optionally anywhere above 100 mg/dL, depending upon physician discretion. These guidelines were apparently written with the knowledge that the CARE study was underway, with the intent that they not be obsolete should the results of that trial confirm a place for cholesterol lowering in CHD patients with otherwise normal (in the absence of heart disease or multiple risk factors) cholesterol levels. Clearly, though, the panel felt, based on existing evidence, that this population should be treated. The overall CARE results highlight their prescience.

In effect, then, the CARE results discussed in this review confirm the validity of currently accepted guidelines for treatment, and demonstrate that for many patients with coronary heart disease, whatever the cholesterol level, it is too high. In such patients, in whom, after the fact, we can deduce that LDL-C was a culprit in atherogenesis, benefit may be reaped from cholesterol reduction, albeit from a relatively low baseline. For these patients, the cholesterol level is obviously not

"normal." Perhaps it would be better to state that these are patients with average cholesterol levels, implying that by cholesterol level alone, they are indistinguishable from the population without coronary disease. An alternative description is that these are patients, who, in the absence of CHD or multiple risk factors, would be considered to have normal cholesterol levels, not mandating treatment with drugs.

D. Pravachol labeling

Current labeling

Pravachol is currently indicated for the primary prevention of coronary events in hypercholesterolemic patients to reduce the risk of MI, to reduce the risk of undergoing a revascularization procedure, and to reduce the risk of cardiovascular mortality. In addition, in hypercholesterolemic patients with CHD, pravastatin is indicated to slow the progression of coronary atherosclerosis and to reduce the risk of acute coronary events. Finally, pravastatin is indicated to reduce total and LDL-C and triglycerides in patients with Fredrickson Types IIa and IIb hyperlipoproteinemia.

Major proposed changes in labeling based on CARE

In Clinical Pharmacology, proposed is a paragraph summarizing the design of the CARE study, with description of results for the primary endpoint for the total study population and among women. In addition, the data on coronary revascularization are summarized. Finally, the data regarding the effect of pravastatin on the risk for "stroke and transient ischemic attack (TIA)" are conveyed.

In Indications and Usage, proposed is the addition of a section under the heading "Myocardial Infarction" stating "in patients with previous MI, and normal cholesterol levels, PRAVACHOL is indicated to: reduce the risk of recurrent MI, reduce the risk of undergoing myocardial revascularization procedures, reduce the risk of stroke and TIA."

In Adverse Reactions, proposed is a revision to include CARE in a statement already applied to the WOSCOPS results that "the adverse events profile in the PRAVACHOL group was comparable to that of placebo for the duration of the studies."

II. Review of CARE (Cholesterol and Recurrent Events study)

A. Objectives of the CARE Study

The stated objectives of the CARE study were to determine whether intensive therapy with pravastatin to lower plasma cholesterol in patients with myocardial infarction would decrease recurrent coronary heart disease events, i.e. combination of fatal coronary heart disease and definite nonfatal myocardial infarction (primary endpoint); further objectives were to test the effect of pravastatin therapy on fatal coronary heart disease (secondary endpoint) as well as on total mortality (tertiary endpoint) in this population.

B. Trial Design

Table 1 summarizes the main features of the design of the CARE trial.

Table 1. Summary of the CARE Trial

# of sites	Design	Treatment Groups (N)	Duration of Treatment (yrs)	Primary Endpoint	Entry Criteria
Total of 80 Canada:12 USA:68 Geographically dispersed	Randomized, double-blind, parallel	Pravastatin 40 mg (2081) Placebo (2078) 86% men 14% women	Approximately 5 years	Time to death due to CHD or definite non-fatal MI	MI w/ prior to rand. TC<240 mg/dl

1. Pre-randomization procedures included the following:

- medication washout including discontinuation of lipid-altering therapy, including probucol or fibric acid derivatives (12 weeks before qualifying blood draw), statins (8 weeks prior), and resins, nicotinic acid, or other prohibited drugs (4 weeks)
- dietary instruction instituted at the time of drug withdrawal (the dietary program was taught using guideline and materials provided by the AHA and NCEP)
- for eligible patients, during a placebo run-in period (2 weeks to 2 months prior to randomization), compliance was assessed based on pill counts. Patients with compliance < 70% compliance were excluded from the trial

2. Determination of eligibility with regard to plasma lipids:

- lipids measured after no less than 4 weeks of diet and no earlier than 8 weeks after hospital discharge after MI (first qualifying visit)
- average of the lipid levels for two qualifying visits determines eligibility (second qualifying visit 7 days to 1 month after the first and no less than 12 weeks after hospital discharge)
- if mean lipid levels borderline
  a third determination is averaged with the previous two to determine eligibility

3. Entry Criteria

Inclusion Criteria

1. Acute MI to randomization

(The ECG core facility could either confirm the diagnosis of MI, request additional documentation, or refuse to validate the ECG as confirmatory of an MI. A non-confirmatory ECG could be overridden by history of typical symptoms and record of enzyme elevations by criteria set out in the Manual of Operations for the study.)

2. Age
3. Men and women (post-menopausal or surgically sterile)
4. Plasma total cholesterol < 240 mg/dl (< 6.2 mmol/L)

5. Plasma LDL-cholesterol (approximately equivalent to total cholesterol

Exclusion Criteria

1. Initial screening plasma cholesterol >270 mg/dl (>7.0 mmol/L) by local laboratories (guideline only).
2. Mean qualifying fasting plasma total cholesterol >240 mg/dl (>6.2 mmol/L), or plasma LDL cholesterol <115 mg/dl (<3.0 mmol/L) or >174 mg/dl (>4.5 mmol/L) on samples measured by the
3. Screening triglyceride values >750 mg/dl (>8.5 mmol/L) measured by any local laboratory, or $ 350 mg/dl (>4.0 mmol/L) measured by the
4. Ejection fraction <25% obtained no more than 20 months before randomization and no intervening infarct between the EF measurement and study entry.
5. Overt congestive heart failure (symptomatic despite drug therapy), defined as rales not caused by a primary pulmonary condition, or Class III-IV symptoms.
6. Prior sensitivity to HMG-CoA reductase inhibitors. History of non-responsiveness to HMG-CoA reductase inhibitors (<10% decrease in total cholesterol).
7. No coronary atherosclerosis on arteriogram, if performed.
8. Nephrotic syndrome or other renal disease (creatinine >1.5 x ULN for the laboratory, serum albumin <3.0 g/dl, urinary protein ≥2+) by
9. Excessive ethanol intake, defined as > 3 drinks/day.
10. Hepatobiliary disease, chronic hepatitis, biliary cirrhosis, alcoholic cirrhosis, other causes of chronic jaundice or significant other hepatic disease (SGOT, SGPT, total bilirubin, or alkaline phosphatase >1.5 x ULN for the laboratory. Any exception must be approved by the medical monitor).
11. Malignancy or other medical condition thought to limit survival, require radiation or chemotherapy, or interfere with participation.
12. History of immune disorders (dysproteinemia, porphyria, lupus erythematosis) or treatment with immunosuppressive agents. Cyclosporin is specifically contraindicated. If there is a history of prolonged treatment with corticosteroids (asthma, serious allergy), patient should not be enrolled.
13. Untreated endocrine disorders or other uncontrolled endocrine disease. A patient euthyroid on a stable replacement dose of thyroid hormone is acceptable. Any T4 value outside normal range (see Appendix A1) may be further evaluated by obtaining TSH levels. TSH must be within normal range before a patient may be enrolled. Poorly-controlled diabetes mellitus (Blood sugar >220 + Hgb A1C >11.0) will exclude the patient from further participation. Treatment with estrogens (except replacement therapy) or androgens is prohibited.
14. Significant gastrointestinal disease or surgery which may interfere with drug absorption.
15. Treatment with other lipid-lowering drugs, unless they are withdrawn: i) 8 weeks prior to obtaining the first qualifying lipid specimen for HMG-CoA reductase inhibitors; ii) 12 weeks prior for fibric acid derivatives or probucol; and iii) 4 weeks prior for nicotinic acid or resins.
16. Severe valvular heart disease requiring surgery.

17. Psychosocial condition that would make a person unsuitable for a clinical trial.
18. Geographic location, i.e. distance to clinic making attendance difficult or itinerant lifestyle.
19. Participation in another drug trial that could affect the endpoint of this study, or use of any investigational drug within 30 days of enrollment.
20. Women unless post-menopausal or surgically sterile (post-menopausal estrogen use is allowed).
21. Unwilling to consent.

C. Deferments

1. Coronary angioplasty: 6 months must elapse after coronary angioplasty before randomization.
2. Coronary artery bypass surgery: 3 months must elapse after bypass surgery before randomization.
3. Major surgery: 1 month must elapse after major surgery before randomization

4. Drug Treatments

- randomization 1:1 blocking on center to either pravastatin 40 mg per day or placebo administered at bedtime
- enhanced dietary counseling for patients with LDL-C above 174 mg/dl (4.5 mmol/L) on two follow up visits
- cholestyramine resin, 2-4 packets daily for patients with LDL-C still > 174 mg/dl (4.5 mmol/L) on two consecutive visits
- decrease in dose of cholestyramine resin first (if on resin) or pravastatin dose by 50% for patients with LDL-C decreased to below 50 mg/dl (1.3 mmol/L) on two consecutive follow-up visits
- matching patients in other treatment group would have parallel changes made in their treatment regimens.
- medication was discontinued at subject's request, if investigator deemed that continuation was not in the best interest of the patient, if LDL-C >174 mg/dL after dietary counseling and resin therapy and/or if there was a serious intercurrent illness.

5. Follow-up

a. Lipid Measurements

Direct measurement of fasting lipids (TC, HDL-C, TG; LDL-C) calculated using the Friedewald formula were performed at 1.5, 3, and 6 months after randomization and thereafter every 6 months throughout the trial

b. Procedures

- full history and physical exam annually
- interim histories and physical as indicated
- adverse events documented at each full visit by the clinic nurse.
- LFTs at weeks 6 and 12, then every 3 months for the first year, then every 6 months for the duration of the study

- dietary reinforcement at each 3-month follow up visit.
- full chemistry and hematology at baseline and yearly, CK only in symptomatic patients
- ECG at baseline and optionally as part of clinical follow up
- ejection fraction (if not done during routine clinical management) at baseline.
- Limited safety assessments at six week intervals during the first 3 months, then at 3 month intervals during year 1, then at 6 month intervals through end of study

c. Adverse events

- Clinical adverse events (AEs) are defined in the protocol as illnesses, signs, or symptoms that have appeared or worsened during the course of the study.
- Laboratory adverse events are defined as laboratory values outside of the normal range.
- Serious adverse events were those AEs that were fatal, immediately life-threatening, permanently disabling, cancer, congenital anomaly, overdose, or that required at least overnight hospitalization.
- An AE was classified as an adverse drug experience (ADE) or a concomitant event (CE) by a causality assessment done by the investigator.
- Treatment-emergent events were AEs that began or worsened after randomization. AE's beginning prior to randomization and recurring after it were not treatment-emergent unless the AE worsened or it was classified as an ADE.

d. Liver function tests

For serum transaminases, levels between 2 and 3 times the upper limit of normal were to be repeated for monitoring purposes every 2 weeks until returned to normal. Levels >3 times ULN were to be repeated within one week, and if further elevated, were cause for discontinuation of drug. Dose adjustments were called for if the elevation was persistent but stable relative to normal. If not fallen to <3X ULN after 4 weeks, drug was to be discontinued. A recurrence to a level >3X ULN also mandated discontinuation of study drug. Once transaminases had returned to normal, consideration could be given to rechallenging the patient with the study drug, albeit at the lowest dose (10 mg/day).

e. Creatine kinase

Creatine kinase (CK) elevations up to 4 times the upper limit of normal in a symptomatic patient did not mandate discontinuation of medication. Follow up until symptom resolution would suffice. Levels greater than 4 times ULN were to be repeated and if confirmed, mandated discontinuation. Rechallenge starting at the lowest dose could be considered in a patient once CK had returned to normal and symptoms had resolved.

6. Safety and Data Monitoring Committee

Its function was to review data on adverse effects and endpoints. It was empowered to recommend termination of the trial for adverse effects or improved survival early in the

trial. As reviewed above, the trial could be terminated early for favorable outcome only with regard to fatal events. The sponsor was not to be a member of this committee.

7. Changes to the protocol

There were no changes to the protocol with regard to the choice of endpoints. The revisions of 10-31-95 clarified the study endpoints and the outcome variables and their definitions.

8. Outcome Variables

- 1. Fatal coronary heart disease and definite nonfatal MI combined (primary outcome variable)
- 2. Fatal coronary heart disease (secondary outcome variable)
- 3. Total mortality (tertiary outcome variable)
- 4. Additional outcome variables:

a. Myocardial infarction, nonfatal (definite and probable)
b. Myocardial infarction, fatal and nonfatal (definite and probable)
c. Development of overt CHF
d. Need for coronary artery bypass surgery or nonsurgical coronary revascularization
e. Hospitalization for cardiovascular disease
f. Cerebrovascular disease, fatal and nonfatal (stroke, or transient ischemic attack)
g. Hospitalization for peripheral arterial disease (intermittent claudication, arterial thrombosis or embolism, abdominal aortic aneurysm)
h. Hospitalization for unstable angina
i. Total coronary heart disease events (2,4b,4c,4d,4h)
j. Cardiovascular mortality (including nonatherosclerotic)
k. Total cardiovascular disease events (4b-4h, 4j)
l. Atherosclerotic cardiovascular disease, fatal
m. Atherosclerotic cardiovascular disease, fatal and nonfatal (4b,4c,4d,4f,4g,4h,4l)

a. Definitions of "definite" and "probable"

"Definite" refers to a report of a clinical MI by a clinical center that meets the criteria of MI described in the manual of operations, as determined by the MI Confirmation Laboratory (MICL) and could be based on combined symptoms, EKG changes, and enzymes or on symptoms and enzymes alone. A "probable" non-fatal MI was based solely on the report by a clinical center (no confirmation by the MICL).

Fatal MIs were adjudicated by the endpoints committee. The committee used the same criteria as the MICL for adjudication of a fatality attributed to a definite MI. Death within 7 days of an MI or prior to hospital discharge was judged due to fatal MI, in the absence of evidence of another unrelated cause as determined by review by the MI confirmation center. A definite fatal MI was declared when there was evidence of recent necrosis or intracoronary thrombus at autopsy. Where timed collection of serum cardiac enzymes or serial EKGs were not available, the committee classified such an

MI as "probable" if the subject's death was associated with at least two of the following:

- prolonged chest pain
- CK rise above normal
- new EKG changes
- evidence of new or presumed new infarction by EKG, radionuclide study, or thallium imaging

b. Cerebrovascular disease events

The endpoint of cerebrovascular disease, fatal and nonfatal (stroke or TIA) included events of cerebral thrombosis, hemorrhage, infarction cerebrum, brain infarction, cerebrovascular accident or stroke, and amaurosis fugax or TIA.

Transient ischemic attack (TIA) was defined as "acute disturbance of focal neurological or monocular function with signs and/or symptoms of presumed vascular etiology which normalize in less than 24 hours.

Stroke was defined as acute disturbance of focal neurological or monocular function resulting in death or signs and/or symptoms of presumed vascular etiology which persist for greater or equal to 24 hours.

It is important to note that these diagnoses do not require confirmation by CT or MRI, and for stroke, there is no distinction between events of embolic and hemorrhagic origin.

During the study, the Data Coordinating Committee reviewed all the CRFs, source documents, and supporting information (clinical and lab reports, scans, pathology reports) for the events reported as TIA or stroke. Post-study, a Stroke and TIA Classification Committee was convened to refine the interpretation of the trial results particularly regarding etiology of cerebrovascular events. Final classification was by consensus agreement either between two independent reviewers, or if that failed, by the entire committee in conference.

C. Results of CARE

1. Patient disposition

11,207 subjects were screened to enroll 7180 subjects. About 42% of the enrolled subjects (3021) were not randomized primarily due lipids out of range (1881 subjects; 62%). Other reasons for exclusion were concomitant disease, use of lipid altering drugs, CHF/low EF/valvular heart disease, no CAD on angiogram, deferred or died, psychosocial or geographic factors, subject or physician disapproval, poor compliance, and other.

Subjects were randomized to pravastatin (2081) or placebo (2078) at 80 sites in Canada and the USA (Table 2). The four largest sites were located in Canada, however the majority of the subjects were enrolled at USA sites (60%). All randomized patients, save one, regardless of treatment compliance, were followed for the duration of the trial.

Table 2. Disposition of Randomized Patients

	Pravastatin	Placebo
Randomized	2081	2078
Discontinued Treatment	390 (19%)	585 (28%)
Reasons for discontinuation		
ADE	92 (4%)	121 (6%)
Protocol violation	8 (<1%)	32 (2%)
Subject request	82 (4%)	180 (9%)
Death	128 (6%)	133 (6%)
Other	11 (1%)	40 (2%)
Unknown	69 (3%)	79 (4%)
Completers by year on study		
Year 1	1996 (96%)	1956 (94%)
Year 2	1926 (94%)	1849 (89%)
Year 3	1867 (90%)	1738 (84%)
Year 4	1790 (86%)	1617 (78%)
Year 5	869 (42%)	766 (37%)

Over the course of the trial, 28% of placebo patients and 19% of pravastatin patients discontinued medication permanently ($p<0.05$ for the difference). The annual discontinuation rates were constant within the two groups (about 4% for the pravastatin group and about 6% for the placebo group). The difference in the discontinuation rates appears to be primarily due to the difference in the number of patients discontinuing due to "subjects request" (180 (9%) placebo patients versus 82 (4%) pravastatin patients). The discontinuations due to subject request in the placebo group speak to the difficulties of conducting a placebo-controlled trial in an era where use of cholesterol lowering agents was steadily increasing, as one assumes that many of the placebo patients who discontinued did so in order to attempt to further lower their cholesterols under a doctor's care. One would expect that the influence of this "crossover" to active treatment, if anything, would be to diminish the apparent treatment effect of pravastatin therapy

compared to placebo. At the same time, however, depending on the drug to which placebo patients were switched (e.g., to another statin), there might be a tendency toward diminished imbalance in true drug-related adverse events between the two groups.

2. Patient Demographics and Baseline Characteristics

The randomization was successful in generating treatment groups well-matched for baseline demographics and patient characteristics (Table 3) and for baseline concomitant medication use (Table 4).

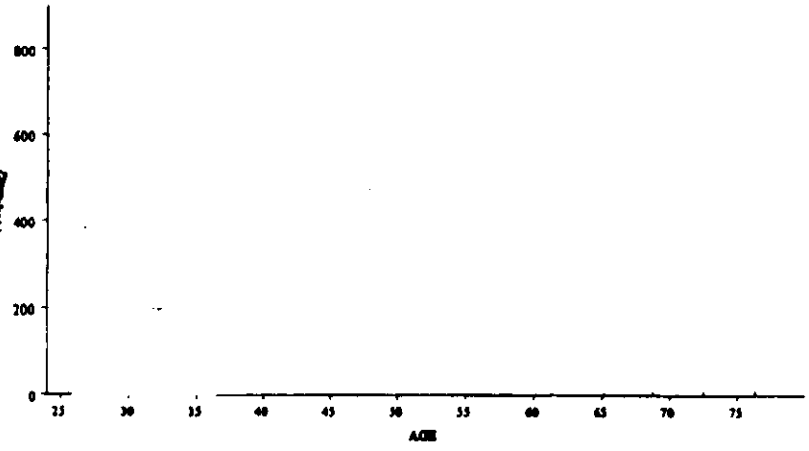
Table 3. Baseline demographics and patient characteristics for CARE study cohort

	Pravastatin	Placebo
Age (mean yrs)	58.6	58.7
sex: male	86%	86%
female	14%	14%
race: white	93%	93%
other	7%	7%
BMI	27.7	27.5
systolic BP	128.7	129.1
diastolic BP	78.5	78.6
heart rate	66.7	67.8
history of hypertension	42%	43%
history of diabetes	14%	15%
prior CABG/PTCA	55%	55%
MI prior to CARE MI	15%	16%
smoking history: never	22%	23%
former	62%	61%
present	16%	16%
baseline EF (mean)	53%	53%
baseline Total-C	208.6	208.5
LDL-C	138.8	138.5
HDL-C	38.7	39.0
TG	155.9	155.2

The majority of the patients were male (84%) and white (93%). About half of the patients had had a revascularization procedure before entering CARE and only about 15% had an MI before their CARE MI.

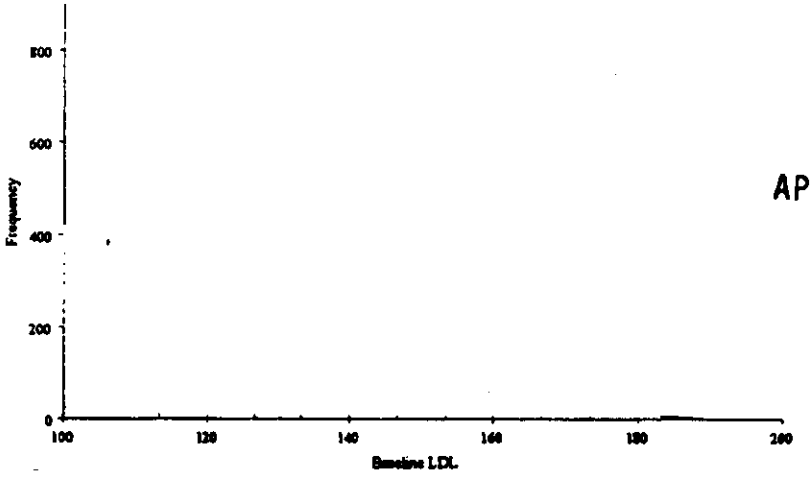
The average age of the patients in the total cohort was 59 years (median:60 (Figure 1); 31% of the patients were 65 or older.

Figure 1 CARE Age Distribution (total cohort)



The groups were comparable at baseline regarding baseline lipoproteins (Table 3). Baseline cholesterol was 209 (mean and median) and LDL-C was 139 (mean, median=138) at baseline and . About ⅓ of the patients had an LDL at baseline of less than 130. The distribution of LDL-C for the whole cohort is shown in Figure 2 (the graphs for the 2 treatment groups were indistinguishable).

Figure 2 CARE Baseline LDL Distribution (total cohort)



Concomitant medication use at baseline is listed in Table 4. A large percentage of patients were taking aspirin (84%) and/or antihypertensives (82%) at baseline About half the

patients were taking antiarrhymics, beta-blockers or calcium channel blockers. It should be noted that the aspirin and antiplatelet agent groups overlapped save for a small percentage of the patients.

Table 4. Concomitant Medication Use at Baseline

	Pravastatin	Placebo
aspirin	84%	83%
antiplatelet agents	85%	85%
anticoagulants	4%	3%
beta blockers	41%	39%
nitrates	32%	33%
calcium channel blockers	41%	38%
ACE inhibitors	15%	14%
diuretics	12%	11%
antihypertensives	82%	81%
antiarrhythmics	50%	48%
digitalis	8%	8%
quinidine	1%	1%
insulin	3%	3%
oral hypoglycemics	6%	7%
thyroid	3%	3%

3. Statistical Methods

All randomized patients were included in the analyses regardless of treatment compliance and all of the sponsor's analyses were planned prior to completion of the trial.

The main analyses were time-to-event analyses where the treatment groups were compared using the log rank test. All p-values presented in the tables in this review are the results of log rank tests performed by FDA. A Cox proportional hazards model with just treatment in the model was used by the sponsor and FDA to estimate the relative risk after checking the proportionality assumption of the model.

In addition, the sponsor performed the following analyses of the efficacy variables (the first 2 were only performed for the primary efficacy variable): a time-to-event analysis stratifying by LDL quartiles, a time-to-event analysis excluding patients with LDL>160 mg/dl, subgroup analyses to show consistency of effect and covariate-adjusted analyses.

The protocol listed the following potential subgroups: gender, age, nation of origin, plasma LDL and HDL, LDL/HDL, LDL minus HDL, ejection fraction, number of previous myocardial infarctions, months from MI to enrollment, hx of CABG or PTCA, concurrent CV medications, post-menopausal estrogen replacement, use of insulin, and glucose control. Results for subgroups defined by age, gender, baseline LDL, and smoking status were produced by FDA and are presented for the primary, secondary and tertiary endpoints and for one additional endpoint (time to CABG or non-surgical coronary

revascularization). Also included are the results for non-fatal MI (definite); a component of the combined primary endpoint. The latter was not specified in the protocol as an endpoint for the study but should be fully examined to aid in interpretation of the results for the primary endpoint.

Covariate-adjusted analyses performed by the sponsor used the following covariates: baseline LDL/HDL, ejection fraction, hypertension (yes/no), diabetes (yes/no), days from MI to enrollment, age, sex and smoking (yes/no with former smokers=no). These results were reviewed but are not presented here.

A total of five interim analyses, in addition to the final analysis, were performed as planned. Two interim analysis methods were described in the protocol; stochastic curtailment and the Lan and DeMets method. The Lan and DeMets method was used to specify the stopping rules and the level of significance at the final look. The latter was set at .04 (using an O'Brien-Fleming spending function) for the primary endpoint only. No adjustments to p-values for secondary endpoints were made.

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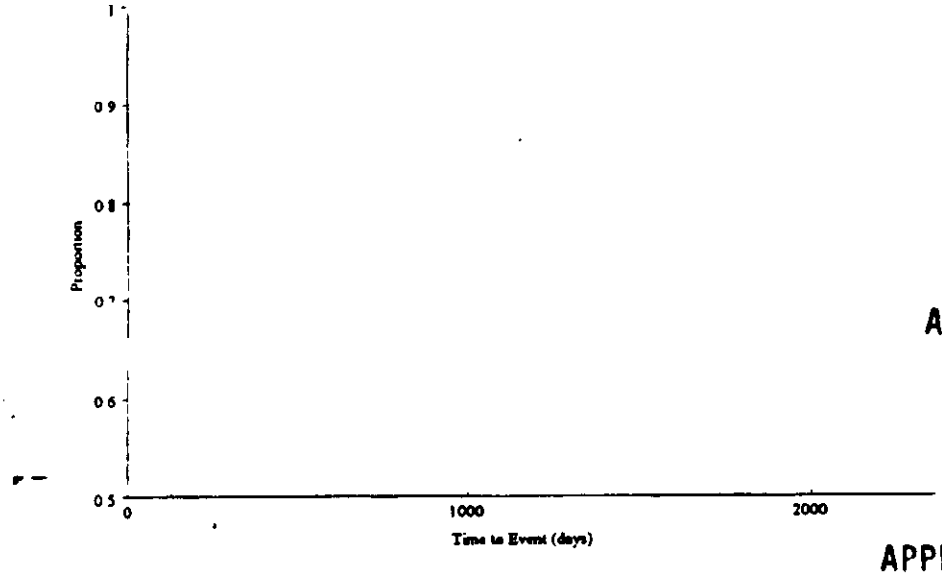
4. Efficacy Results

Primary Endpoint: Fatal CHD and Non-fatal Myocardial Infarction
The primary endpoint was death from CHD or definite non-fatal MI. CHD death was defined as

- fatal MI, definite or probable
- sudden death
- death during a coronary intervention procedure
- other coronary death

The results for the primary efficacy variable, time to non-fatal MI (definite) or fatal CHD (whichever occurred first), showed a statistically significant treatment difference between pravastatin and placebo with a decrease in event rates of about 3% and a relative risk (RR) of 0.76. The survival curves (Figure 3) begin to separate after about 2½ years of exposure and treatment differences continue to be evident until the end of the treatment period (p=.003).

Figure 3 Survival Curves for Fatal CHD and NFMI



Event	Pravastatin (n=2081)	Placebo (n=2078)
NFMI (definite)	135 (6%)	173 (8%)
Fatal CHD	77 (4%)	101 (5%)
Censored	1869 (90%)	1804 (87%)

Table 5. CARE Primary Endpoint Results
Non-fatal MI (definite) or Fatal CHD

	Pravastatin	Placebo	Relative Risk	95% Confidence Interval	P-value
All patients	212/2081 (10%)	274/2078 (13%)	0.76	0.64, 0.91	.003
Gender					
Male	189/1795 (11%)	235/1788 (13%)	0.79	0.65, 0.96	.02
Female	23/286 (8%)	39/290 (13%)	0.58	0.34, 0.96	.04
Age					
<65	143/1441 (10%)	163/1435 (11%)	0.87	0.69, 1.1	.21
≥65	69/640 (11%)	111/643 (17%)	0.61	0.45, 0.82	.001
Baseline LDL Quartiles					
≤126.5	49/517 (9%)	55/529 (10%)	0.91	0.62, 1.3	.62
>126.5-137.5	50/525 (10%)	69/519 (13%)	0.71	0.50, 1.0	.07
>137.5-149	59/525 (11%)	72/528 (14%)	0.80	0.57, 1.1	.21
>149	54/514 (11%)	78/502 (16%)	0.67	0.47, 0.94	.02
Baseline LDL					
<130	61/657 (9%)	80/673 (12%)	0.78	0.56, 1.1	.13
≥130	151/1424 (11%)	194/1405 (14%)	0.76	0.61, 0.94	.01
Smoker					
Yes	43/337 (13%)	63/334 (19%)	0.62	0.42, 0.91	.01
No	169/1744 (10%)	209/1744 (12%)	0.80	0.66, 0.98	03

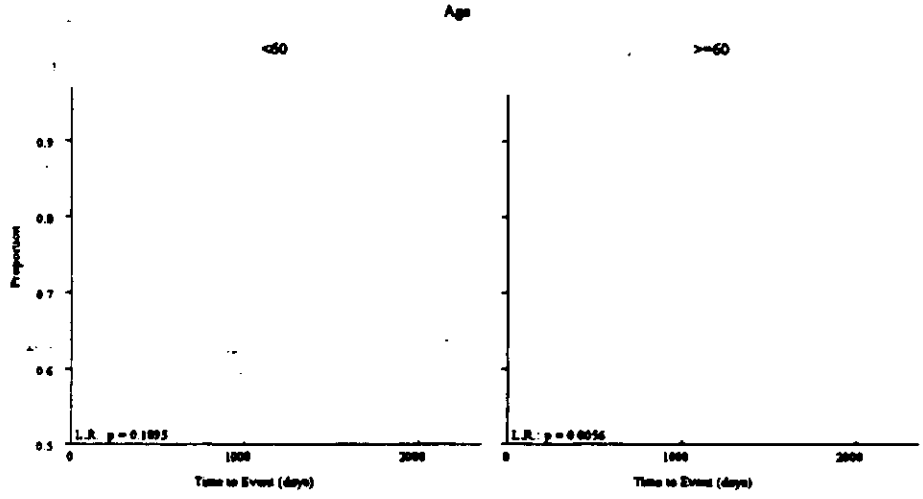
The event rate for pravastatin is quite consistent (generally 10% or 11% with a range of across subgroups shown in Table 5. The placebo rates, on the other hand, appear to be higher in high-risk subgroups (note a rate of 19% for smokers and the increasing rates with increasing baseline LDL).

The apparent benefit of pravastatin therapy held for both the men and the women, though only 14% of the trial subjects were female.

When the primary endpoint outcome was examined as a function of age at baseline, there was no statistically significant benefit of pravastatin compared to placebo in the group under age 65. It is interesting that the event rate in the placebo group for those under 65 was much lower than that in the patients aged >65 years (11% vs. 17%). This is perhaps expected based on the assumption that, on average, the extent and severity of atherosclerosis is greater in older patients. That is, a simple history of MI does not convey the full story of an individual's atherosclerosis. What is quite striking is that while 70% of the study cohort were <65 years old at trial entry, and while most of the total primary endpoint events (63%) occurred in this subgroup, there was no statistically significant benefit of pravastatin in this majority subgroup of the trial population. The trend, however, favored pravastatin, though less dramatically than in the group over age 65. Further analyses using cutpoints of 50, 55 and 60 (the median), also showed that patients in the older subgroup reaped a greater benefit from the use of

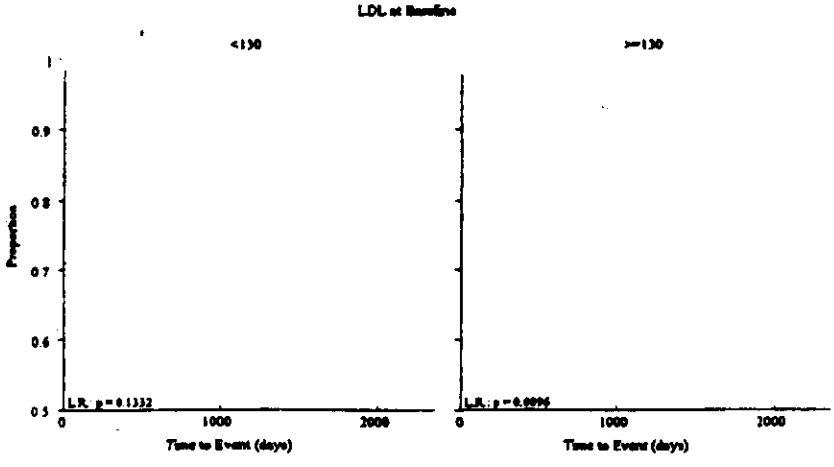
pravastatin compared to placebo than younger patients. The results for subgroups based on the median age of 60 are shown in Figure 4, below.

Figure 4 Survival Curves for Fatal CHD or Non-fatal MI by Median Age



When the primary endpoint outcomes were examined as a function of LDL-C level at entry into the trial, subgrouping by quartile did reveal a trend in relative risk suggesting decreasing benefit with decreasing baseline risk (Table 5). This trend was also observed in 4S and WOSCOPS. As expected from the epidemiology and as seen in earlier trials, in CARE, the analysis by LDL-C quartiles does show that placebo event rates decrease slightly with decreasing LDL-C at baseline. Insofar as pravastatin rates do not decrease to a similar degree, the difference between treatment groups is attenuated with decreasing baseline LDL-C. Relevant to current guidelines for treatment of hypercholesterolemic CHD patients, subdividing the study cohort by baseline LDL-C greater than or less than 130 mg/dL reveals similar trends (pravastatin vs. placebo) in the two subgroups, though the results for the group with LDL-C < 130 do not reach statistical significance (see Table 5 above and Figure 5 below).

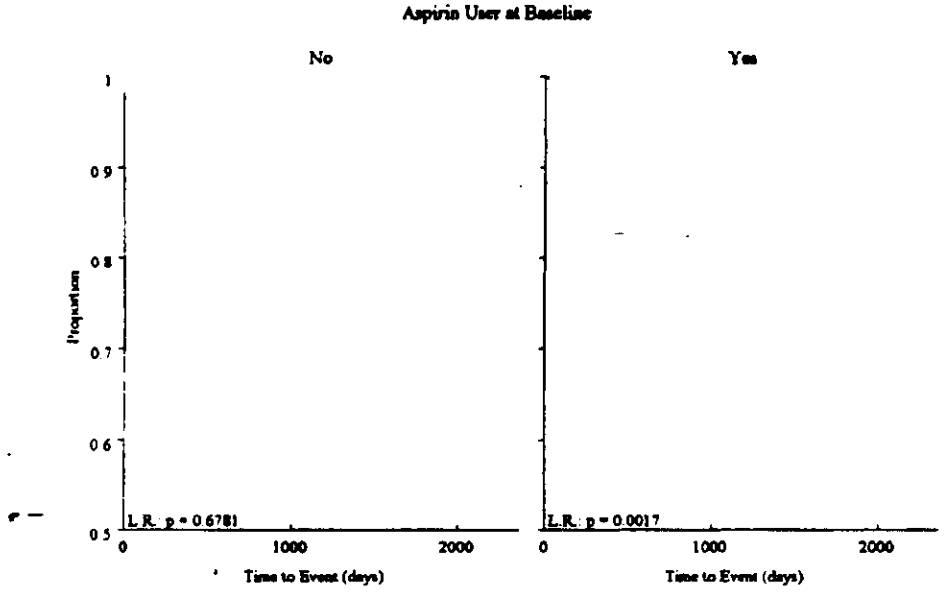
Figure 5 Survival Curves for Fatal CHD of Non-fatal MI by Baseline LDL



Finally, it is interesting to point out the low rate of smoking in this trial (16%), the high event rate among the placebo-treated smokers, and the apparent benefit of pravastatin in both smokers and non-smokers.

Tests for homogeneity of response for the above listed subgroups as well as for subgroups defined by baseline concomitant medication use and by variables related to medical history (such as hypertension, diabetes, prior MI, etc.) generally showed a consistent effect for pravastatin over placebo with a few notable exceptions (e.g., age, aspirin (ASA) use). The apparent lack of effect of pravastatin in non-ASA users (see Figure 6, below) is confounded by the fact that fully 84% of the study cohort was on aspirin at the start of the trial, that there were thus few events in the no-aspirin subgroup, and finally, that patients were not randomized to aspirin or no-aspirin treatment arms. No conclusions can be drawn from this finding. Prospective trials would be necessary to assess the impact on ASA on the overall outcome in a CARE-like population.

Figure 6 Survival Curves for Fatal CHD or Non-fatal MI by Aspirin Use at Baseline



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Secondary endpoint: fatal CHD

Fatal CHD (a component of the primary outcome variable) was prespecified in the protocol as a secondary endpoint. The survival curves for this endpoint (Figure 7) are similar to the curves observed for the primary outcome variable, however, the curves are not statistically significant (p=.10). The difference between the event rates is only 1% (pravastatin:5%, placebo:6%) with a relative risk of 0.80 (Table 6).

Figure 7 Survival Curves for Fatal CHD

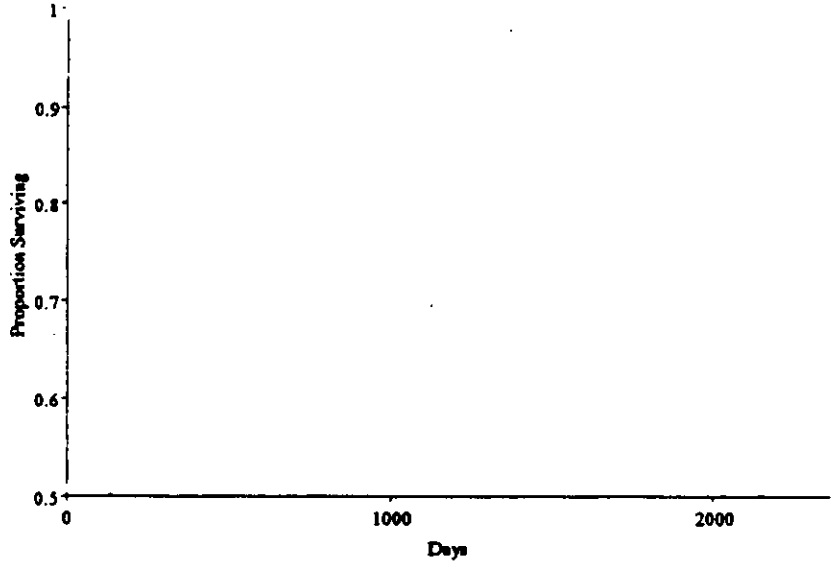

Table 6. CARE Secondary Endpoint Results

Fatal CHD

	Pravastatin	Placebo	Relative Risk	95% Confidence Interval	P-value
All patients	96/2081 (5%)	119/2078 (6%)	0.80	0.61, 1.1	.10
Gender					
Male	85/1795 (5%)	105/1788 (6%)	0.80	0.60, 1.1	.13
Female	11/286 (4%)	14/290 (5%)	0.79	0.36, 1.7	.56
Age					
<65	59/1441 (4%)	53/1435 (4%)	1.1	0.77, 1.6	.59
≥65	37/640 (6%)	66/643 (10%)	0.55	0.37, 0.83	.004
Baseline LDL Quartiles					
≤126.5	25/517 (5%)	20/529 (4%)	1.3	0.72, 2.3	.39
>126.5-137.5	27/525 (5%)	38/519 (7%)	0.70	0.43, 1.1	.16
>137.5-149	22/525 (4%)	29/528 (6%)	0.75	0.43, 1.3	.30
>149	22/514 (4%)	32/502 (6%)	0.62	0.39, 1.2	.14
Baseline LDL					
<130	32/657 (5%)	32/673 (5%)	1.0	0.64, 1.7	.89
≥130	64/1424 (5%)	87/1405 (6%)	0.72	0.52, 0.99	.04
Smoker					
Yes	14/337 (4%)	26/334 (8%)	0.52	0.27, 0.99	.05
No	82/1744 (5%)	93/1744 (5%)	0.88	0.65, 1.2	.40

It is interesting to note that while, overall, the magnitude of the trends favoring pravastatin are similar for the fatal events and for the overall combined primary endpoint events, again the effect is attenuated in the group aged < 65 years at entry and in the subgroups with lower baseline LDL-C. The death rate from CHD was quite low in the younger patients (4%) and pravastatin showed no benefit relative to placebo. Likewise, there was no demonstrated benefit in the low LDL-C subgroups (< 126.5, < 130 mg/dL). Again, there was a striking effect of pravastatin among the smokers, reducing rate of death from CHD by 50%, albeit based on small numbers of events.

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Non-prespecified endpoint: Non-fatal Myocardial Infarction (Definite)

Non-fatal MI (a component of the primary outcome variable) was not prespecified in the protocol as a secondary endpoint, however, it is important to look at the results of this endpoint to aid in the interpretation of the primary endpoint. As seen in earlier trials in which the effect of therapy on rate of non-fatal MI and CHD death is examined, the primary endpoint findings in CARE are driven by the non-fatal CHD events which occurred at an overall rate approximately 1.5 times that of fatal events.

The survival curves are statistically significantly different (Figure 8, p=.02). There were 135 events (6%) in the pravastatin group versus 173 events (8%) in the placebo group; relative risk of 0.77.

Figure 8 Survival Curves for Non-fatal MI (definite)

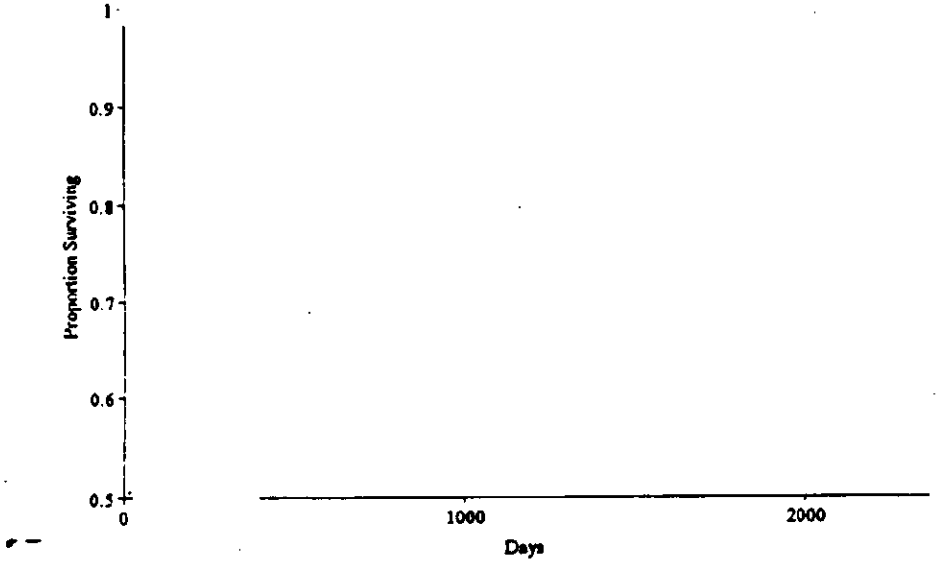

Table 7. CARE Non-prespecified Endpoint Results

Non-fatal MI

	Pravastatin	Placebo	Relative Risk	95% Confidence Interval	P-value
All patients	135/2081 (6%)	173/2078 (8%)	0.77	0.61, 0.96	.02
Gender					
Male	121/1795 (7%)	145/1788 (8%)	0.82	0.65, 1.0	.11
Female	14/286 (5%)	28/290 (10%)	0.49	0.26, 0.92	.02
Age					
<65	84/1441 (7%)	116/1435 (8%)	0.80	0.61, 1.0	.11
≥65	41/640 (6%)	57/643 (8%)	0.70	0.47, 1.1	.09
Baseline LDL Quartiles					
≤126.5	26/517 (5%)	39/529 (7%)	0.68	0.41, 1.1	.12
>126.5-137.5	31/525 (6%)	37/519 (7%)	0.82	0.51, 1.3	.42
>137.5-149	44/525 (8%)	48/528 (9%)	0.90	0.60, 1.4	.62
>149	34/514 (7%)	49/502 (10%)	0.66	0.43, 1.0	.07
Baseline LDL					
<130	34/657 (5%)	52/673 (8%)	0.67	0.43, 1.0	.06
≥130	100/1744 (6%)	121/1405 (9%)	0.81	0.62, 1.1	.12
Smoker					
Yes	35/337 (10%)	44/334 (13%)	0.74	0.48, 1.2	.19
No	100/1744 (6%)	129/1744 (12%)	0.77	0.59, 1.0	.05

For the overall cohort and across subgroups, the trends (pravastatin vs. placebo) were consistent with the primary endpoint results.

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Tertiary endpoint: Total Morality

Figure 9 Survival Curves for Total Mortality

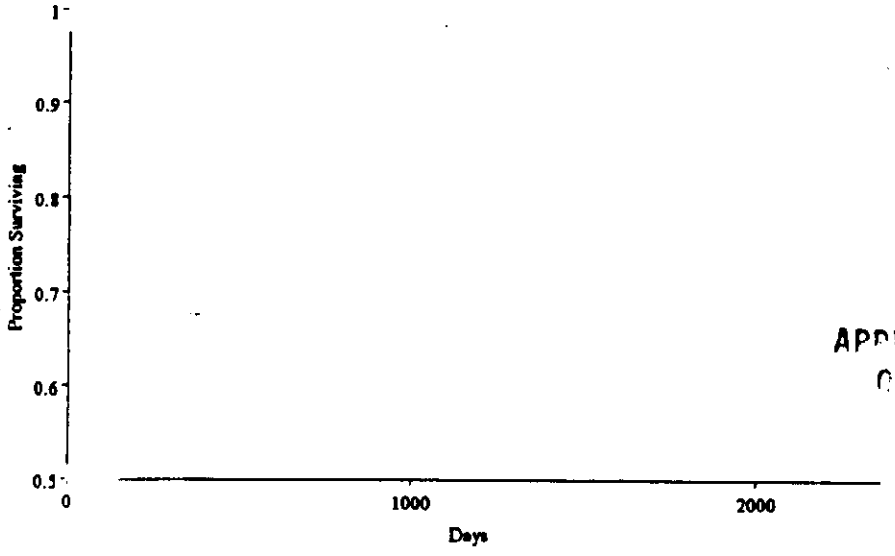


Table 8. CARE Tertiary Endpoint Results
Total Mortality

	Pravastatin	Placebo	Relative Risk	95% Confidence Interval	P-value
All patients	180/2081 (9%)	196/2078 (9%)	0.91	0.74, 1.1	.37
Gender					
Male	159/1795 (9%)	173/1788 (10%)	0.91	0.73, 1.1	.39
Female	21/286 (7%)	23/290 (8%)	0.92	0.51, 1.7	.78
Age					
<65	103/1441 (7%)	88/1435 (6%)	1.2	0.88, 1.6	.29
≥65	77/640 (12%)	108/643 (17%)	0.70	0.52, 0.94	.02
Baseline LDL Quartiles					
≤126.5	53517 (10%)	40/529 (8%)	1.4	0.91, 2.1	.13
>126.5-137.5	46/525 (9%)	58/519 (11%)	0.78	0.53, 1.2	.22
>137.5-149	44/525 (8%)	54/528 (10%)	0.80	0.54, 1.2	.27
>149	37/514 (7%)	44/502 (9%)	0.81	0.53, 1.3	.35
Baseline LDL					
<130	67/657 (10%)	58/673 (9%)	1.2	0.84, 1.7	.31
≥130	113/1424 (8%)	138/1405 (10%)	0.80	0.62, 1.0	.07
Smoker					
Yes	36/337 (11%)	39/334 (12%)	0.88	0.56, 1.4	.59
No	144/1744 (8%)	157/1744 (9%)	0.92	0.73, 1.1	.45

The trend in rate of death due to all causes (pravastatin vs. placebo) did not reach statistical significance. When cause-specific mortality rates were examined (Table 9), there appears to be no imbalance in the rate of death due to non-cardiovascular causes between treatment groups, and no remarkable differences in rates of specific causes of death within the non-cardiovascular category. Thus, pravastatin therapy was associated with a decrease in the rate of cardiovascular death with no countervailing increase in the rate of death due to non-cardiovascular causes.

Table 9. Cause-specific Mortality Rates

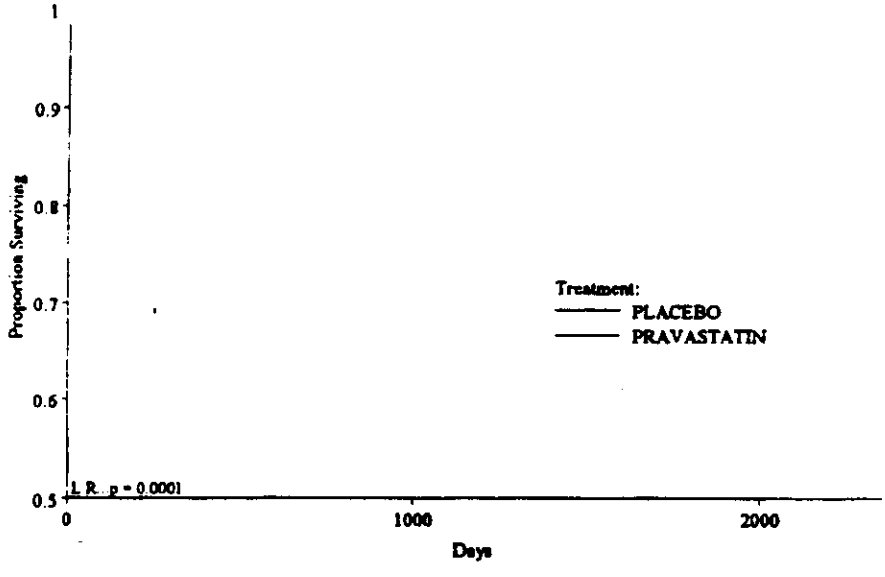
Cause of death	pravastatin N=2081	placebo N=2078
atherosclerotic CHD	96	119
fatal MI	24	38
sudden death	58	61
other CHD	14	20
atherosclerotic vascular	15	10
cerebrovascular	10	6
other ath vascular	5	4
total atherosclerotic	111	129
non-atherosclerotic CV	1	1
total CV	**112**	**130**
cancer	49	45
accident/suicide	8	4
other/unknown	11	17
total non-CV	**68**	**66**
total, all cause	**180**	**196**

Pre-specified endpoint: Need for coronary artery bypass surgery or nonsurgical coronary revascularization

In the U.S. and Canada, myocardial revascularization is readily available and frequently used. It is not, *per se*, part of the natural history of CHD, though it is a reality of clinical trials in this disease that revascularization will often preempt clinical events. That is, based on studies of the safety and efficacy of these procedures, overall rates of fatal and non-fatal MI in such a trial are thus likely to be reduced by these interventions. In addition, the need for revascularization is not absolutely standardized, and rates of CABG and PTCA do differ across nations, centers, and individual practitioners treating, on average, patients with equally severe CHD. In a blinded, randomized trial (where it is hoped, too, that the interventional cardiologists and surgeons are blinded to treatment), perhaps the only obvious bias is introduced if these physicians are not blinded to cholesterol levels. Again, though, in this study in particular, because none of the patients had markedly elevated cholesterol even at baseline, even such knowledge might not be expected to bias the surgeon or cardiologist in his or her decision whether or not to intervene. In sum, the revascularization data from such a trial are an important measure of treatment effect.

The trial outcome with regard to the rate of myocardial revascularization was highly statistically significant in favor of pravastatin (Figure 10) with a difference in event rates of 5% and a relative risk of 0.73 (Table 10).

Figure 10 Survival Curves for CABG or Non-surgical Coronary Revascularization



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Significant treatment differences were evident in most subgroups with the exception of the subgroups defined by the lowest LDL quartile or by LDL < 130 (Table 10).

Table 10. CARE Endpoint Results

Need for coronary artery bypass surgery or nonsurgical coronary revascularization

	Pravastatin	Placebo	Relative Risk	95% Confidence Interval	P-value
All patients	294/2081 (14%)	391/2078 (19%)	0.73	0.63, 0.85	.0001
Gender					
Male	266/1795 (15%)	334/1788 (19%)	0.78	0.66, 0.92	.002
Female	28/286 (10%)	57/290 (20%)	0.47	0.30, 0.74	.001
Age					
<65	221/1441 (15%)	287/1435 (20%)	0.75	0.63, 0.89	.001
≥65	73/640 (11%)	104/643 (16%)	0.69	0.51, 0.92	.01
Baseline LDL Quartiles					
≤126.5	72/517 (14%)	88/529 (17%)	0.83	0.61, 1.1	.25
>126.5-137.5	75/525 (14%)	106/519 (20%)	0.68	0.51, 0.91	.01
>137.5-149	74/525 (14%)	91/528 (17%)	0.79	0.58, 1.1	.14
>149	73/514 (14%)	106/502 (21%)	0.65	0.48, 0.88	.004
Baseline LDL					
<130	95/657 (15%)	113/673 (17%)	0.86	0.66, 1.1	.28
≥130	199/1424 (14%)	278/1405 (20%)	0.68	0.57, 0.82	.0001
Smoker					
Yes	57/337 (17%)	72/334 (22%)	0.73	0.52, 1.0	.08
No	237/1744 (14%)	319/1744 (18%)	0.73	0.62, 0.86	.0002

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Other Cardiovascular Events Measured in CARE

Table 11 summarizes the outcomes for pre-specified outcome variables in CARE. These are direct and indirect measures of atherosclerotic vascular disease. It is significant that pravastatin use was associated with reduced rates of events across all the categories examined and serves to provide internal validation of the primary efficacy outcome.

Table 11. Results for protocol-defined cardiovascular endpoints measured in CARE

On-Study Event	Pravastatin (n=2081)	Placebo (n=2078)	Relative Risk	95% Confidence Interval	P-value
Myocardial infarction, nonfatal (definite and probable)	182 (9%)	231 (11%)	0.77	0.64, 0.94	.01
Myocardial infarction, nonfatal and fatal (definite and probable)	216 (10%)	283 (14%)	0.75	0.63, 0.90	.002
Development of overt CHF	146 (7%)	160 (8%)	0.90	0.72, 1.1	.38
Cerebrovascular disease , fatal and nonfatal	99 (5%)	129 (6%)	0.76	0.59, 0.99	.04
Hospitalization for CV disease	852 (41%)	949 (46%)	0.87	0.80, 0.96	.004
Hospitalization for peripheral arterial disease	54 (3%)	61 (3%)	0.88	0.61, 1.3	.49
Hospitalization for unstable angina	317 (15%)	359 (17%)	0.87	0.75, 1.0	.07
First coronary heart disease event	624 (30%)	729 (35%)	0.83	0.75, 0.93	.0008
First cardiovascular disease event	890 (43%)	991 (48%)	0.87	0.80, 0.95	.003
Cardiovascular Mortality	112 (5%)	130 (6%)	0.85	0.66, 1.1	.22
Atherosclerotic cardiovascular disease, fatal	111 (5%)	129 (6%)	0.85	0.66, 1.1	.22
Atherosclerotic cardiovascular disease, fatal and nonfatal	710 (34%)	816 (39%)	0.85	0.77, 0.94	.002

CARE cerebrovascular disease results

After review by the Stroke and TIA Classification Committee, post study, four analyses were performed, two for the endpoint of stroke or TIA (including and excluding hemorrhagic events) and two for the endpoint of stroke alone (including and excluding hemorrhagic events).

The treatment groups were comparable with regard to history of stroke or TIA:

- pravastatin 62 (3%) of 2081
- placebo 60 (3%) of 2078.

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The Stroke and Classification Committee reviewed 279 events in the data base. All but 18 of these plus one additional event, determined by the Endpoints Committee to be a death due to cerebral hemorrhage, were included in the sponsor's analyses. The eighteen events (10 pravastatin, 8 placebo) were "unclassifiable" and therefore not included in the analyses. Of 261 cerebrovascular disease events, 217 were first on-trial occurrences and included in the time-to-event analyses. These analyses are consistent with analyses of the CVD events in the original study data base, classified based on ICD-codes. The table below is reproduced from the submission.

Table 12. Classified CVD events in CARE

Event	Prava (N=2081)	Placebo (N=2078)	Risk reduction (95% CI)	logrank P-value
fatal and nonfatal stroke or TIA, including hemorrhagic events	93 (4,7)	124 (6,3)	26 (3, 43)	0.029
fatal and nonfatal stroke, including hemorrhagic events	53 (2,8)	76 (4, 0)	31 (2, 51)	0.037
fatal and nonfatal stroke or TIA	91 (4,6)	118 (6,0)	24 (0, 42)	0.052
fatal or nonfatal stroke	51 (2, 7)	70 (3, 6)	28 (-4, 50)	0.075

A number of other analyses of interest are included in the submission. For these, the data analyzed are those from the study data base, as reported by the Data Coordinating Committee.

When the distributions of first on-study fatal and non-fatal stroke events (excluding hemorrhagic events) and stroke alone were examined by history of cerebrovascular disease, pravastatin therapy was associated with reductions in events rates in patients with and without a prior history of stroke or TIA. Sixteen of 60 (26%) placebo patients with a history of CVD had an event on study while 11 of 62 (17%) pravastatin patients with a history of CVD had an event on study. Thus, pravastatin appeared effective in both the primary prevention as well as the secondary prevention of CVD in this trial.

In light of this, it is interesting to note that the distribution of subjects with one or more on-study CVD events by treatment group shows a large difference for patients with a

first event (108 placebo, 76 pravastatin) but no difference for second events (27 vs. 26) and beyond. This may be a function of the relative paucity of secondary events.

Conclusions regarding the CVD outcome in CARE

Based on analyses of the CVD event data both from the original study data base as well as after refinement by the Stroke and TIA Classification Committee, it appears that pravastatin therapy was associated with a reduction in risk for combined stroke and TIA. This holds true both including and excluding hemorrhagic events. This, of course, is consistent with the effect on cardiovascular events, and expected based on existing data from other studies, including those using statins, and based on the presumed shared pathogenesis (related to atherosclerosis) between ischemic coronary disease and ischemic cerebrovascular disease (excluding at least some cases of hemorrhagic stroke).

With regard to labeling, the language used to describe the above outcomes should speak to the reduction of cerebrovascular events (stroke or TIA), as the result for TIA alone was not statistically significant (likely as a result of low event rates). In addition, the analysis cited should be that based on the findings of the Stroke Classification Committee.

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Changes in plasma lipids

With the exception of TG, the mean changes in plasma lipids were relatively constant for the duration of treatment. At the five-year follow up visit, the mean changes in total-C, LDL-C, HDL-C, and TG from baseline in the pravastatin group were -16.1%, -27.6%, +12.5%, and +4.8%, respectively. The corresponding results for the placebo group were +1.3%, -3%, +8%, and +17.9%, respectively. It is interesting to note the small apparent effect of pravastatin to raise HDL-C levels relative to placebo, and the effect to stabilize TG, even as TG increased over the course of the trial in the placebo group.

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5. Safety data

The AE data set for safety analyses as well as the clinical laboratory data set included all randomized subjects who took at least one dose of medication and events up to and including 30 days after discontinuation of therapy. Cancer AEs were included regardless of the relationship between time of diagnosis and date of discontinuation of study medication. Clinical AEs were coded using an ICD-9 based dictionary.

Recurrent or continuing treatment-emergent events were counted only once. For the purposes of safety reporting and analysis, interruptions in treatment were disregarded. Thus the discontinuations counted were permanent discontinuations. AE frequency rates were calculated using the denominator of all subjects taking at least one dose of drug (by treatment group). For those events that tend to occur as a result of cumulative exposure to drug, inclusion of patients treated for periods of time shorter than is

necessary for the induction of the AE will result in underestimation of the rate of the adverse event. As a primary safety analysis, however, this is an acceptable approach.

A long-term, placebo-controlled, randomized trial like CARE provides an opportunity to examine the safety and tolerability of a drug to an extent not permitted by the shorter controlled exposures in the NDA database. With regard to pravastatin, the previously reported WOSCOPS trial, examining the effects of pravastatin in the primary prevention of CHD in high risk patients, enrolled only middle-aged men in a geographical region where treatments for dyslipidemia and interventions, including drugs, for other cardiovascular disease symptoms, signs, and risk factors were underutilized. By contrast, CARE enrolled men and women from many of whom were receiving concomitant medications for their CHD or risk-conferring condition, and the safety experience thus may better approximate that to be expected in extended actual use.

Exposure in CARE

As discussed above, the dropout rate was somewhat higher in the placebo group than among pravastatin-treated patients, and consistent year by year during the trial. Overall, ~28% of placebo patients and ~19% of pravastatin patients withdrew prematurely from the trial. Nevertheless, the groups are fairly comparable in term of exposure, with means of 1670 days for the pravastatin group and 1576 days for the placebo group.

Deaths

The total mortality in this trial, including those deaths occurring during the study period and both on treatment and up to 30 days after discontinuation of drug as well as more than 30 days after discontinuation, and finally including 6 deaths occurring after closure of the trial (up to 63 days after study closure), was 184 (8.8%) in the pravastatin group and 198 (9.5%) in the placebo group. Note that these data do not agree with those analyzed for the study endpoint of total mortality, above, though the difference is not significant. Fully 30% of the deaths in each treatment group occurred more than 30 days after discontinuation of drug.

The most common cause of death was cardiovascular disease, with 115 deaths due to cardiovascular disease in the pravastatin group and 133 in the placebo group. This overall trend in favor of pravastatin was generally echoed in trends among the specific cardiovascular causes of death.

The most common cause of non-cardiovascular death in CARE was malignancy, with 51 total deaths in the pravastatin group and 45 among the placebo patients. This difference is not statistically significant.

Discontinuations due to adverse events

121 placebo patients and 92 pravastatin patients discontinued study medication due to adverse events. Cardiovascular and gastrointestinal causes predominated, both more common among placebo patients, accounting for approximately one third of the discontinuations. Among the specific causes, several points bear noting:

- breast cancer: prava 3, plac 0
- abnormal TG or increased lipids: prava 1, plac 16
- fatigue: prava 6, plac 1
- LFTs increased: prava 3, plac 3
- abnormal liver function: prava 3, plac 0
- increased CK: prava 0, plac 2

The breast cancer data will be discussed below. Withdrawals for abnormal lipids simply speak to the ineffectiveness of placebo and the problems of conducting a placebo-controlled study in lipid altering.. Finally, hepatic and muscular abnormalities are rare causes of discontinuation in both treatment groups. As in other trials with pravastatin, it appears well tolerated in this regard.

Clinical adverse events

Overall adverse events, adverse drug experiences, and adverse events by body system were reported with similar frequency in the two treatment groups. For the 30 most common adverse events, there were no marked differences in the percentage of patients experiencing the event across treatment groups.

Breast cancer

There were several adverse events that were reported with greater frequency among pravastatin-treated than among placebo-treated patients and for which the difference was statistically significant. Notable among these was an excess of breast cancer cases among the women treated with pravastatin. Twelve (4.2%) pravastatin-treated women were found to have a malignant neoplasm of the breast compared to 1 (0.3%) placebo-treated woman. Three documents addressing this issue were appended to the submission and will be briefly reviewed, summarizing the nature of the information offered in support of the conclusion that the imbalance between treatment groups in the incidence of breast cancer in this trial was an anomalous finding.

Document 1: "An interim report and update on the occurrence of breast cancer in women who participated in the CARE study."

The preclinical carcinogenicity, reproductive toxicity, and genotoxicity studies of pravastatin suggest no potential for this drug as an inducer or promotor of breast cancer. The effects of pravastatin on female endocrine function were studied in a placebo-controlled trial in premenopausal women. Preliminary analyses show that neither pravastatin nor lovastatin affect the mid-luteal estradiol or progesterone levels in these subjects.

The sponsor also surveyed data bases from other studies using pravastatin, most notably from the LIPID study, an Australian secondary prevention study now recently concluded. At the time of the analyses presented in the CARE submission, the follow up in LIPID was >4 years. The sponsor also presented data on breast cancer cases from two other pravastatin clinical trial databases. Finally, the Worldwide Safety and Surveillance data base, covering an estimated 8 million person years of exposure, contained 9 reports of breast cancer. In the clinical trial data base, only in the CARE study was there a trend toward increased breast cancer in the pravastatin group. The incidence figures for LIPID, which enrolled ~2.5 times the number of women than did CARE, with similar mean age, were 5/755 and 7/755 in the pravastatin and placebo groups, respectively.

The sponsor also examined the findings of the CARE study in light of the incidence rates for breast cancer in the general U.S. and Canadian populations. Utilizing these data, the distribution of women enrolled across U.S. and Canadian sites, and adjusting for age and race, excluding those patients with a known prior history of breast cancer at study entry (6 pravastatin, 8 placebo), the expected number of new invasive cancers was derived for the CARE cohort of women, by treatment group. The expected number of new cases was 5 (95% CI 0.6-9.3) and 5 (95% CI 0.5-9.1) for the pravastatin and placebo group, respectively. Thus, the incidence of invasive cancers in the pravastatin group (seven) is within the range of expectation, while the absence of even a single case in the placebo group is unexpected.

When the demographics and baseline characteristics were compared for the pravastatin-treated women who developed breast cancer in CARE, the non-affected pravastatin-treated women, and the placebo-treated women, excluding women with a previous history of breast cancer, there were no major differences. The sponsor noted that the breast cancer patients were 1-2 years older, on average, and had a higher average body mass index than the non-affected patients (28.6 vs. 27.7). Thus, demographic and baseline differences in a number of characteristics do distinguish the breast cancer patients from those without breast cancer, regardless of treatment group.

- Document 2. An update on the occurrence of breast cancer in women who participated in the CARE study.

The CARE Women's Health Survey was an evaluation of 9 risk factors for breast cancer among the women in CARE. These were age, mother or sister with breast cancer, any family member with breast cancer, history of benign breast disease, nulliparity or age at first full-term pregnancy, age at menarche, age at menopause, history of estrogen use, and BMI. For all of the risk factors analyzed, the percentage of pravastatin-treated women with each risk factor was higher than that for the placebo-treated women. In addition, all 9 of the pravastatin-treated women with new invasive breast cancer had 3 or more of the 9 breast cancer risk factors examined. This post-hoc finding may distinguish the two treatment groups with respect to overall risk of breast cancer, but is certainly not definitive.

Document 3.

This is simply a letter from chair of the LIPID Safety and Data Monitoring Committee stating that as of June 1996, there were no concerns over the incidence, overall or across treatment groups, of breast cancer in that study.

Conclusions regarding the breast cancer outcome in CARE

Based on the above information and analyses, in particular the absence of a similar finding in a larger study, enrolling more women, using pravastatin, and the absence of any such outcomes in the other large statin trial enrolling women completed to date, 4S, the CARE result appears potentially to be an anomalous finding. While follow up of the women in CARE continues, at present, the breast cancer data from the study have no place in labeling for pravastatin.

Cancer

Overall numbers of subjects with an adverse event of primary cancer in CARE were 216 in the pravastatin group and 196 in the placebo group. As discussed above, there were 12 cases of breast cancer in the pravastatin group (none in placebo). In addition, there were 56 cases listed as malignant neoplasm reproductive in the pravastatin group and 46 in the placebo group. The corresponding numbers for the males alone were 54 (2.6%) and 44 (2.1%). This is mentioned only to point out that there appeared to be no imbalance in female reproductive system cancers that might have paralleled the breast cancer finding.

Myopathy

There were no cases of severe myopathy (symptoms with CK>10 times ULN). Five patients in the pravastatin group and one in the placebo group had isolated instances of CK >10 times ULN without symptoms. No one was discontinued because of elevated CK or myopathy.

Serious AEs

There were no between-treatment-group differences in the incidence of serious AEs in CARE.

There were three serious adverse events in two patients taking pravastatin attributed to study therapy in CARE. One patient developed chest pain and bradycardia and was found to have CK 264, ALT 59, AST 36, GGT 56. Symptoms and lab abnormalities resolved without interruption of medication. The second patient developed pancreatitis which resolved on discontinuation of pravastatin.

Laboratory data

The incidence of marked abnormalities of ALT, AST, and CK was similar across treatment groups. For ALT and AST, overall rates were 1.2 to 1.8%, respectively. Only one pravastatin-treated patient and 2 placebo-treated patient had consecutive elevations of either ALT or AST >3 times ULN. Five placebo-treated patients and 3 pravastatin-treated patients were discontinued from the study due to elevated ALT or AST values.

Two placebo subjects and no pravastatin subjects were discontinued due to elevated CK levels. As above, all the instances of CK >10 times ULN were asymptomatic and resolved spontaneously without interruption of study medication.

Conclusion from the safety data
No new safety concerns were raised in this study. Save for the breast cancer incidence data, no unexpected findings arose from this trial. The sponsor's proposed changes to the Adverse Reactions section of the labeling are supported by the data from CARE.

III. Reviewers' Comments Pertaining to Labeling

Clinical Pharmacology, Clinical Studies
The description of the CARE study should include an enumeration (with percentages) of the distribution of men and women in the trial. In addition, the description of the study population should included the facts that 84% were taking ASA at baseline and 82% were taking antihypertensive medication at baseline.

The mean (or median) baseline LDL-C as well as the range of LDL-C levels at baseline should be stated.

The citation of the study results should include not only the numbers of patients with events but what percentage of the total treatment group this represented.

No statement of the magnitude of the treatment effect among the women should be included. Examination of the effect of treatment by gender was not a primary objective of the study. Indeed, the result in the female subgroup is hardly robust, being based on a small number of events. A statement that the treatment effect was consistent across the sexes enrolled is acceptable.

The inclusion of primary endpoint results, those for the rate of revascularization, and for the rate of cerebrovascular events is acceptable. The CVD event results cited should be based on the reclassified data from the Stroke Classification Committee. Finally, the results should be described as an effect on the risk of stroke or TIA, as the data for TIA did not reach statistical significance.

Indications and Usage, Secondary Prevention of Cardiovascular Events
The use of the term "normal" to describe the cholesterol levels at baseline of the CARE cohort is problematic. The range of LDL-C levels in the trial was from
70% of randomized subjects had LDL-C > 130 mg/dL. Based on current guidelines (NCEP) that are included in the labeling for this and all other cholesterol-lowering drugs, those CHD patients with LDL-C on diet of >130 mg/dL should all be treated to goal LDL-C <100 mg/dL. In addition, NCEP counsels that CHD patients with LDL-C may be treated with drugs at the physician's discretion. Thus, based on the current standard of care, the LDL-C levels at baseline in this trial are not considered

normal for CHD patients. Finally, it is precisely the group in CARE with baseline LDL-C <130 mg/dL in whom no statistically significant benefit of pravastatin therapy was demonstrated, likely because of low numbers of patients and low event rates relative to the subgroup with LDL-C > 130 mg/dL at baseline.

The CARE study thus tested the validity of the treatment approach advocated by the NCEP, and confirmed the current guidelines. What was shown was that in CHD patients with baseline LDL-C levels not, in the absence of CHD, mandating pharmacological intervention, pravastatin therapy reduced the rate of recurrent coronary events, CABG or PTCA, and stroke or TIA when compared to placebo. Again, the levels treated in this trial are not "normal" for CHD patients. In sum, the use of "normal" in Indications is potentially misleading.

The term "average" may be substituted in place of "normal." In all promotional pieces related to the CARE results and CARE-supported indications, the sponsor should be required to commit to the inclusion of information on the CARE cohort; specifically mean (or median) and range of LDL-C levels at entry should be included. Such information should be displayed with similar prominence to any references to the CARE results or to CARE-supported indications in promotional pieces.

Adverse reactions
The addition of a description of the CARE safety outcomes is acceptable as proposed.

IV. Recommendations
Contingent on the changes in the proposed labeling described above, this supplement should be approved.

David Orloff, M.D.
Medical Officer
/S/ 3-10-98

APPEARS THIS WAY
ON ORIGINAL

Joy D. Mele, M.S.
Mathematical Statistician
/S/ 3/11/98

Concur:
Ed Nevius, Ph.D.
Director of DOB2
/S/ 3-11-98

APPEARS THIS WAY
ON ORIGINAL

Recommendation code: AE
cc:
Archival NDA# 19-898
HFD-510
HFD-510/DOrloff, SSobel, MSimoneau
HFD-715/Biometrics Division 2 File, Chron, JMele

Word-Carerev.doc/March

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 019898/S018

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

PATENT INFORMATION

The products and uses thereof for which approval is sought are covered by the following patents:

U.S. Patent No. 4,346,227 (assigned to Sankyo Co. Ltd.) expires October 20, 2005, and its claims cover pravastatin sodium as a new chemical entity or composition;

U.S. Patent No. 5,030,447 (assigned to E.R. Squibb & Sons, Inc.) expires July 9, 2008, and its claims cover a formulation containing pravastatin sodium;

U.S. Patent No. 5,180,589 (assigned to E.R. Squibb & Sons, Inc.) expires July 9, 2008, and its claims cover a formulation containing pravastatin sodium.

U.S. Patent No. 5,622,985 (assigned to Bristol-Myers Squibb Company) expires April 22, 2014, and its claims cover the use of pravastatin sodium in the prevention of a second myocardial infarction in men and women who have normal cholesterol.

The Pravachol® composition patent is owned by Sankyo Co. Ltd. E.R. Squibb & Sons, Inc. a wholly owned subsidiary of Bristol-Myers Squibb Company, is a licensee under this patent, has a place of business at Province Line Road and Route 206, P.O. Box 4000, Princeton, NJ 08543 and is authorized to receive notice of patent certification under §505(b)(3) and (j)(2)(B) of the Act and §§314.52 and 314.95.

The two Pravachol® formulation patents are owned by E.R. Squibb & Sons, Inc., a wholly owned subsidiary of Bristol-Myers Squibb Company.

The Pravachol® use patent is owned by Bristol-Myers Squibb Company.

In accordance with 21 CFR §§314.53(c) and 314.53(d)(2), certification of the above-listed patents, which cover Pravachol® products and uses described in this supplemental application is made on the attached sheet.

APPEARS
ON ORIGINAL

CERTIFICATION OF PATENT INFORMATION

As the undersigned, I hereby make the following declaration under 21 CFR §§314.53(c) and 314.53(d)(2) concerning the following composition, formulation and use patents that cover the Pravachol® products as described in Bristol-Myers Squibb Company's pending Supplemental Application to NDA No. 19-898 for the secondary prevention of coronary events and the reduction in risk of stroke and transient ischemic attack (TIA) in men and women who have had a myocardial infarction, and have normal cholesterol levels.

The undersigned declares that

U.S. Patent No. 4,346,227 (assigned to Sankyo Co. Ltd.) expiring October 20, 2005, covers the Pravachol® composition and the use of Pravachol® in the secondary prevention of coronary events and reduction of the risk of stroke and transient ischemic attack in men and women who have had a myocardial infarction and have normal cholesterol. This product is the subject of this application for which approval is being sought:

> Secondary prevention of coronary events and reduction of the risk of stroke and transient ischemic attack in men and women who have had a myocardial infarction and have normal cholesterol levels.

U.S. Patent No. 5,030,447 (assigned to E.R. Squibb & Sons, Inc.) expiring July 9, 2008, covers the Pravachol® formulation and the use of the Pravachol® formulation in the secondary prevention of coronary events and reduction of the risk of stroke and transient ischemic attack in men and women who have had a myocardial infarction and have normal cholesterol levels. This product is the subject of this application for which approval is being sought:

> Secondary prevention of coronary events and reduction of the risk of stroke and transient ischemic attack in men and women who have had a myocardial infarction and have normal cholesterol levels.

U.S. Patent No. 5,180,589 (assigned to E.R. Squibb & Sons, Inc.) expiring July 9, 2008, covers the Pravachol® formulation and the use of the Pravachol® formulation in the secondary prevention of coronary events and reduction of the risk of stroke and transient ischemic attack in men and women who have had a myocardial infarction and have normal cholesterol levels. This product is the subject of this application for which approval is being sought:

Secondary prevention of coronary events and reduction of the risk of stroke and transient ischemic attack in men and women who have had a myocardial infarction and have normal cholesterol levels.

U.S. Patent No. 5,622,985 (assigned to Bristol-Myers Squibb Company) expiring April 22, 2014, covers use of Pravachol® and the Pravachol® formulation in the prevention of a secondary myocardial infarction in men and women who have had a myocardial infarction and have normal cholesterol levels. This use of the product is the subject of this application for which approval is sought:

Prevention of a second myocardial infarction in men and women who have had a myocardial infarction and who have normal cholesterol.

Burton Rodney
Senior Associate Patent Counsel
Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, NJ 08543-4000

Dated: May 21, 1997

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

PATENT INFORMATION

The products for which approval is sought are covered by the following patents:

U.S. Patent No. 4,346,227, (assigned to Sankyo Co. Ltd.) expires October 20, 2005, and its claims cover pravastatin sodium as a new chemical entity or composition;

U.S. Patent No. 5,030,447, (assigned to E.R. Squibb & Sons, Inc.) expires July 9, 2008, and its claims cover a formulation containing pravastatin sodium;

U.S. Patent No. 5,180,589, (assigned to E.R. Squibb & Sons, Inc.) expires July 9, 2008, and its claims cover a formulation containing pravastatin sodium.

The Pravachol® composition patent is owned by Sankyo Co. Ltd. E.R. Squibb & Sons, Inc., a wholly owned subsidiary of Bristol-Myers Squibb Company, is a licensee under this patent, has a place of business at Province Line Road and Route 206, P.O. Box 4000, Princeton, NJ 08543 and is authorized to receive notice of patent certification under §505(b)(3) and (j)(2)(B) of the Act and §§314.52 and 314.95.

The two Pravachol® formulation patents are owned by E.R. Squibb & Sons, Inc., a wholly-owned subsidiary of Bristol-Myers Squibb Company. In accordance with 21 CFR §§314.53(c) and 314.53(d)(2), certification of the above-listed patents, which cover Pravachol® products described in this supplemental application is made on the attached sheet.

APPEARS THIS WAY
ON ORIGINAL

CERTIFICATION OF PATENT INFORMATION

As the undersigned, I hereby make the following declaration under 21 CFR §§314.53(c) and 314.53(d)(2) concerning the following composition and formulation patents that cover the Pravachol® products as described in Bristol-Myers Squibb Company's pending Supplemental Application to NDA No. 19-898 for the secondary prevention of coronary events in men and women who have had a myocardial infarction.

The undersigned declares that

U.S. Patent No. 4,346,227 (assigned to Sankyo Co. Ltd.) expiring October 20, 2005, covers the Pravachol® composition and the use of Pravachol® in the secondary prevention of coronary events in men and women who have had a myocardial infarction. This product is the subject of this application for which approval is being sought:

> Secondary prevention of coronary events in men and women who have had a myocardial infarction.

U.S. Patent No. 5,030,447 (assigned to E.R. Squibb & Sons, Inc.) expiring July 9, 2008, covers the Pravachol® formulation and the use of the Pravachol® in the secondary prevention of coronary events in men and women who have had a myocardial infarction. This product is the subject of this application for which approval is being sought:

> Secondary prevention of coronary events in men and women who have had a myocardial infarction.

U.S. Patent No. 5,180,589 (assigned to E.R. Squibb & Sons, Inc.) expiring July 9, 2008, covers the Pravachol® formulation and the use of the Pravachol® formulation in the secondary prevention of coronary events in men and women who have had a myocardial infarction. This product is the subject of this application for which approval is being sought:

> Secondary prevention of coronary events in men and women who have had a myocardial infarction.

Burton Rodney
Senior Associate Patent Counsel
Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, NJ 08543-4000

Dated: 1/7/97

Simonea

EXCLUSIVITY SUMMARY for NDA # 4 898 SUPPL # 18

Trade Name Pravachol **Generic Name** Pravastatin
Applicant Name Bristol-Myers Squibb **HFD-** 510

Approval Date _____

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PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it an original NDA?
YES /__/ NO /✓/

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b) Is it an effectiveness supplement?

YES /✓/ NO /__/

If yes, what type? (SE1), SE2, etc.) SE1

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /__/ NO /__/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

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_____

_____

Form OGD-011347 Revised 8/7/95; edited 8/8/95
cc: Original NDA Division File HFD-86 Mary Ann Holovac HFD-510/M Summary

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d) Did the applicant request exclusivity?

YES / ✓ / NO / __ /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 under 21 CFR 314.108(b)(5)

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES / __ / NO / ✓ /

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES / __ / NO / ✓ /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /✓/ NO /__/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 19891 PRAVACHOL

NDA # _____ _____

NDA # _____ _____

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2. Combination product. N/A

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /__/ NO /__/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

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ON ORIGINAL

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

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PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_✓_/ NO /___/

APPEARS THIS WAY
ON ORIGINAL

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_✓_/ NO /___/

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ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /V/ NO /__/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /__/ NO /V/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /__/ NO /V/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # 27,201-067 (CARE)

Investigation #2, Study # _____

Investigation #3, Study # _____

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ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /✓/ NO /___/

Investigation #2

Investigation #3

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # 19898 Study # CARE Protocol 27, 201-067

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /✓/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

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ON ORIGINAL

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #_, Study # _____

Investigation #_, Study # _____

Investigation #_, Study # _____

APPEARS THIS WAY ON ORIGINAL

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # YES /✓/ NO /__/ Explain: ____

_____

Investigation #2

IND # ____ YES /__/ NO /__/ Explain: ____

_____

APPEARS THIS WAY ON ORIGINAL

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /__/ Explain _____ NO /__/ Explain _____

_____ _____

_____ _____

APPEARS THIS WAY ON ORIGINAL

APPEARS THIS WAY ON ORIGINAL

Investigation #2

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /✓/

If yes, explain: _____

_____

_____

_____

/S/ 3/23/98

Signature Date

Title:_____

APPEARS THIS WAY
ON ORIGINAL

/S/ 5/27/98

Signature of Division Director Date

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

cc: Original NDA Division File HFD-85 Mary Ann Holovac

HFD-510 M Ammerman

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

DA/BLA # [illegible] Supplement # 018 Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HF 1 Trade and generic names/dosage form: [illegible] Action: AP AE NA

Applicant [illegible] Therapeutic Class [illegible]

BEST POSSIBLE COPY

Indication(s) previously approved _____

Pediatric information in labeling of approved indication(s) is adequate ___ inadequate ___

Proposed indication in this application [illegible]

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ___Yes (Continue with questions) ✓ No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

__Neonates (Birth-1month) __Infants (1month-2yrs) __Children (2-12yrs) __Adolecents(12-16yrs)

APPEARS THIS WAY ON ORIGINAL

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___ c. The applicant has committed to doing such studies as will be required.

___ (1) Studies are ongoing.

___ (2) Protocols were submitted and approved.

___ (3) Protocols were submitted and are under review.

___ (4) If no protocol has been submitted, attach memo describing status of discussions.

APPEARS THIS WAY ON ORIGINAL

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. **If none of the above apply, attach an explanation, as necessary.**

APPEARS THIS WAY ON ORIGINAL

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? ___ Yes ___ No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from team leader (e.g., medical review, medical officer, team leader)

/S/ 3/26/98

Signature of Preparer and Title Team leader Date

Orig NDA/BLA #_____

HF_____/Div File

NDA/BLA Action Package

HFD-006/ KRoberts

(revised 10/20/97)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)

PRAVACHOL® (Pravastatin Sodium) Tablets

DEBARMENT CERTIFICATION
UNDER THE GENERIC DRUG ENFORCEMENT ACT OF 1992

Bristol-Myers Squibb Company certifies that it did not and will not use, in any capacity, the services of any person debarred under subsections (a) or (b) [Section 306(a) or (b)], in connection with this supplemental application.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL