

APPENDIX

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TABLE OF CONTENTS

TABLE OF CONTENTS	2
LIST OF TABLES.....	5
LIST OF FIGURES	8
1 INTRODUCTION.....	9
2 HUMAN PHARMACOKINETICS AND BIOAVAILABILITY	14
2.1 Overview of Pharmacokinetics and Bioavailability of Pravastatin.....	14
2.2 Clinical Pharmacology Studies	16
2.2.1 A Randomized, Open-Label, Single Dose, Drug Interaction Study of Pravastatin and Aspirin (Protocol CV123-234)	18
2.2.2 Demographic Characteristics of Pharmacokinetic Study Population	18
3 OVERVIEW OF CLINICAL SAFETY AND EFFICACY STUDIES.....	21
3.1 Relevant Published Studies.....	41
4 CLINICAL EFFICACY ANALYSIS	56
4.1 Statistical Methods.....	56
4.2 Demographic and Baseline Characteristics of the Subject Population	61
4.3 Disposition.....	69
4.4 EFFICACY RESULTS.....	71
4.4.1 Traditional Frequentist Meta-analysis (Model 1).....	71
4.4.2 Bayesian Meta-analysis (Models 2 and 3)	75
4.4.3 Demographic Subgroup Analysis	84

5	SUMMARY OF SAFETY	86
5.1	Introduction	86
5.2	Overview of Secondary Prevention Clinical Studies	86
5.3	Safety Assessment.....	87
5.3.1	Adverse Event Data Collection.....	88
5.4	Clinical Laboratory Analysis	89
5.4.1	Laboratory Data Collection	89
5.4.2	Laboratory Data Analysis	89
5.5	Extent of Exposure.....	90
5.5.1	Extent of Exposure Conclusion.....	93
5.6	Summary of Demographic and Baseline Characteristics of Study Population and Disposition of Subjects.....	93
5.7	Clinical Adverse Events	94
5.7.1	Clinical Adverse Events Conclusions.....	102
5.8	Deaths	102
5.8.1	Death Conclusions	103
5.9	Serious Adverse Events	103
5.10	Discontinuations Due to Adverse Events.....	107
5.10.1	Discontinuation Conclusion	108
5.11	Clinical Laboratory Analysis	108
5.11.1	Clinical Laboratory Analysis Conclusions	112
5.12	Demographic Subgroup Analyses	113
5.12.1	Demographic Subgroup Analysis Conclusions.....	113
5.13	Special Interest AEs	114
5.14	Conclusions.....	114

6	BENEFITS AND RISKS OF PRAVASTATIN/ASPIRIN TREATMENT	115
6.1	Efficacy and Safety of Pravastatin	115
6.2	Efficacy and Safety of Aspirin	116
6.3	Efficacy and Safety of Pravastatin/Aspirin	117
6.3.1	Efficacy	117
6.3.2	Safety	118
6.3.3	Selection of Dose.....	119
6.4	Conclusions	120
7	REFERENCES	121

LIST OF TABLES

Table 2.2:	Pravastatin/Aspirin Summary of Clinical Pharmacology Studies	17
Table 2.2.2A:	Demographic Characteristics of All Subjects Randomized in the Clinical Pharmacology Study-Healthy Volunteers	19
Table 2.2.2B:	Pharmacokinetic Parameters for Pravastatin (90 Percent Confidence Intervals) in Study CV123-234 (n = 30).....	20
Table 2.2.2C:	Pharmacokinetic Parameters for Salicylate (90 Percent Confidence Intervals) in Study CV123-234 (n = 30).....	20
Table 3A:	Summary of Clinical Trials	42
Table 3B:	Summary of Relevant Published Studies	47
Table 4.2A:	Demographic and Baseline Characteristics: LIPID, CARE, PLAC I, PLAC II and REGRESS	62
Table 4.2B:	Demography and Baseline Characteristics - LIPID	64
Table 4.2C:	Demography and Baseline Characteristics - CARE.....	66
Table 4.2D:	Demography and Baseline Characteristics – REGRESSION.....	68
Table 4.3A:	Subject Disposition - LIPID	69
Table 4.3B:	Subject Disposition - CARE	70
Table 4.3C:	Subject Disposition – PLAC I.....	70
Table 4.3D:	Subject Disposition – PLAC II.....	71
Table 4.3E:	Subject Disposition - REGRESS	71
Table 4.4.2A:	Composite Endpoint – CHD Death, Non-fatal MI, CABG, PTCA, or Ischemic Stroke	76
Table 4.4.2B:	Composite Endpoint – Fatal and Non-fatal MI.....	79
Table 4.4.2C:	Composite Endpoint – Ischemic Stroke.....	82
Table 4.4.2D:	Composite Endpoint – CHD Death, Non-fatal MI, CABG, or PTCA	83
Table 4.4.2E:	Composite Endpoint – CHD Death and Non-fatal MI.....	84
Table 5.2:	Overview of Subjects Treated with Pravastatin or Placebo, Stratified by Baseline Aspirin Use in the Secondary Prevention Clinical Studies	87

Table 5.3:	Study Group of Secondary Prevention Clinical Trials for Safety Analyses and Presentation	88
Table 5.5A:	Extent of Exposure to Pravastatin or Placebo Stratified by Baseline Aspirin Use in the LIPID Study	90
Table 5.5B:	Extent of Exposure to Pravastatin or Placebo Stratified by Baseline Aspirin Use in the CARE Study.....	91
Table 5.5C:	Extent of Exposure to Pravastatin or Placebo Stratified by Baseline Aspirin Use in the REGRESS Study	92
Table 5.5D:	Extent of Exposure to Pravastatin or Placebo Stratified by Baseline Aspirin Use in the PLAC I and PLAC II Studies.....	93
Table 5.7A:	Overview of Clinical ADEs, Deaths, SAEs, and Discontinuations in LIPID by Treatment Regimen Stratified by Baseline Aspirin Use.....	94
Table 5.7B:	Number (Percent) of Subjects with Treatment-Emergent Clinical ADEs in LIPID, by Body System and Treatment Regimen Stratified by Baseline Aspirin Use.....	95
Table 5.7C:	Overview of Treatment Emergent Clinical Adverse Events on Study Therapy in CARE by Treatment Regimen Stratified by Baseline Aspirin Use.....	96
Table 5.7D:	Number (Percent) of Subjects with Treatment-Emergent Clinical AEs in CARE by Body System and Treatment Regimen Stratified by Baseline Aspirin Use.....	97
Table 5.7E:	Overview of Clinical Adverse Events ADEs, Deaths, SAEs and Discontinuations in the REGRESS Study, by Treatment Regimen Stratified by Baseline Aspirin Use	98
Table 5.7F:	Number (Percent) of Subjects with Treatment-Emergent Clinical AEs in the REGRESS Study, by Body System and Treatment Regimen Stratified by Baseline Aspirin Use	99
Table 5.7G:	Overview of Clinical Adverse Events ADEs, Deaths, SAEs and Discontinuations in the Integrated PLAC I and PLAC II Studies, by Treatment Regimen Stratified by Baseline Aspirin Use.....	100
Table 5.7H:	Number (Percent) of Subjects with Treatment-Emergent Clinical AEs in PLAC I and PLAC II, by Body System and Treatment Regimen Stratified by Baseline Aspirin Use	101

Table 5.9A:	Number (Percent) of Subjects with SAEs in LIPID, by Body System and Treatment Regimen Stratified by Baseline Aspirin Use.....	104
Table 5.9B:	Number (Percent) of Subjects with SAEs in CARE, by Body System and Treatment Regimen Stratified by Baseline Aspirin Use.....	105
Table 5.9C:	Number (Percent) of Subjects with SAEs in the REGRESS Study, by Body System and Treatment Regimen Stratified by Baseline Aspirin Use.....	106
Table 5.9D:	Number (Percent) of Subjects with SAEs in PLAC I and PLAC II, by Body System and Treatment Regimen Stratified by Baseline Aspirin Use.....	107
Table 5.11A:	Number (Percent) of Subjects with Marked Abnormalities for Selected Analytes in LIPID, by Treatment Regimen Stratified by Baseline Aspirin Use.....	109
Table 5.11B:	Number (Percent) of Subjects with Marked Abnormalities for Selected Analytes in CARE, by Treatment Regimen Stratified by Baseline Aspirin Use.....	110
Table 5.11C:	Number (Percent) of Subjects with Marked Abnormalities for Selected Analytes in the REGRESS Study, by Treatment Regimen Stratified by Baseline Aspirin Use.....	111
Table 5.11D:	Number (Percent) of Subjects with Marked Abnormalities for Selected Analytes in the Integrated PLAC Studies, by Treatment Regimen Stratified by Baseline Aspirin Use.....	112

LIST OF FIGURES

Figure 4.4.1A:	Relative Risk for the Composite of CHD Death, Non-fatal MI, CABG, PTCA, or Ischemic Stroke, with 95 Percent CI	72
Figure 4.4.1B:	Relative Risk for the Composite of Fatal or Non-fatal MI with 95 Percent CI.....	73
Figure 4.4.1C:	Relative Risk for Stroke with 95 Percent CI.....	74
Figure 4.4.2A:	Cumulative Proportion of Events (CHD Death, Non-fatal MI, CABG, PTCA, or Ischemic Stroke).....	76
Figure 4.4.2B:	Hazard of Events (CHD Death, Non-fatal MI, CABG, PTCA, or Ischemic Stroke).....	77
Figure 4.4.2C:	Cumulative Hazard of Events (CHD Death, Non-fatal MI, CABG, PTCA, or Ischemic Stroke).....	78
Figure 4.4.2D:	Cumulative Proportion of Events (Fatal and Non-fatal MI)	79
Figure 4.4.2E:	Hazard of Fatal and Non-fatal MI	80
Figure 4.4.2F:	Cumulative Hazard of Fatal and Non-fatal MI	81
Figure 4.4.2G:	Cumulative Proportion of Events (Ischemic Stroke only)	82

1 INTRODUCTION

Total cardiovascular disease is the major cause of death in the United States.¹ It claimed 949,619 lives in 1998 or 40.6% of all deaths. Coronary artery disease (CAD) or coronary heart disease (CHD) is the major contributor to this total, with ischemic stroke also being important. Both of these conditions are outcomes of atherosclerotic disease. There has, however, been progress and the declines in death rates from cardiovascular diseases are largely responsible for the recent improvements in life expectancy.¹ The AHA Consensus Panel provided guidelines in 1995 for the reduction of risk in patients with coronary artery disease.² These guidelines included life style changes. They also recommended the use of aspirin 80-325 mg and a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (a statin) along with other risk reducing medications, e.g. antihypertensives, where appropriate. Similar therapeutic recommendations were made by the AHA/ACC Task Force in their recent guidelines for the management of patients with chronic stable angina.³ For the reduction of the risk of a cardiac event in chronic stable angina in those patients with a low-density lipoprotein cholesterol (LDL-C) > 130 mg/dL, the recommendation is aspirin and lipid-lowering therapy, such as a statin. Patients without CHD but with one or more risk factors associated with CHD are also candidates for statin therapy.⁴

Statins, which are competitive inhibitors of HMG-CoA reductase, have become the lipid-lowering therapy of choice. HMG-CoA reductase is the enzyme which catalyzes the early rate-limiting step in cholesterol biosynthesis, the conversion of HMG-CoA to mevalonate.^{5,6} Pravastatin, as has been shown in several large clinical trials, reduces cardiovascular clinical events in primary prevention and in secondary prevention populations.

In the landmark West of Scotland Coronary Prevention Study, pravastatin reduced the risk of myocardial infarction (MI), coronary and cardiovascular mortality and total mortality in men with moderate hypercholesterolemia and no history of MI.⁷ The Cholesterol and Recurrent Events (CARE) study demonstrated a reduction in risk of MI and stroke and the need for revascularization procedures in post-MI patients with normal (below the 75th percentile of the general population) cholesterol levels.⁸ These findings

were confirmed in the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) study of patients with average cholesterol and a history of unstable angina pectoris (UAP) or previous MI.⁹

Other studies have shown that pravastatin can slow the progression of atherosclerosis in the coronary arteries^{10,11} and in the common carotid artery.¹²

The ability of pravastatin, given as an oral 40 mg dose once a day, to reduce these total cardiovascular risks is appropriately described in the approved labeling by various worldwide regulatory authorities, including the US Food and Drug Administration.¹³

The other therapeutic agent that has been shown to reduce cardiovascular events in an at-risk population, aspirin,^{14,15} has a completely different mechanism of action to that of the statins. Aspirin, acetylsalicylic acid, is a potent inhibitor of cyclo-oxygenase, which is the enzyme for a key step in the conversion of arachidonic acid, and other essential fatty acids, into prostaglandins. Aspirin is an irreversible inhibitor of cyclo-oxygenase and as the platelet is not a nucleated cell, exposure of platelets to aspirin permanently impairs the ability of the platelet to synthesize thromboxane A₂ from arachidonic acid. Therefore while the pharmacokinetic half-life of aspirin in plasma is short, i.e. less than 30 minutes, its pharmacodynamic half-life is a function of platelet turnover, so that dosing more frequently than once a day is not required.¹⁴ Thromboxane A₂ (TXA₂) plays an important role in the aggregation of platelets in the presence of the appropriate stimulus. Inhibition of TXA₂ synthesis therefore decreases the thrombotic response to such a stimulus. Aspirin thus has a role in the management of thrombosis in cardiovascular events such as stable angina, stroke or acute myocardial infarction. In a meta-analysis by the Antiplatelet Trialists Collaboration, of some 145 randomized trials of aspirin versus control involving some 70,000 high risk patients and 30,000 low risk patients from the general population, it was shown that an aspirin dose of 75-325 mg/day was protective in four main categories; acute MI, post-MI, post-stroke or history of TIAs, and a fourth category that was a mix of vascular disorders, including stable and unstable angina.¹⁵ These findings by the Antiplatelet Trialist Collaboration, on the effectiveness of aspirin in reducing vascular events in an at-risk population, have been confirmed and extended by this group in a meta-analysis of 266 trials involving 200,000 high risk patients (personal

communication from Dr Colin Baigent). These findings also continue to receive support from other investigators.¹⁶

Aspirin treatment has also been shown in the Swedish Angina Pectoris Aspirin Trial (SAPAT) to be effective in reducing fatal and non-fatal MI or sudden death in patients with chronic stable angina.¹⁷

An assessment of the subjects in the Physicians Health Study¹⁸ who had stable chronic angina was made by Ridker et al.¹⁹ The results were consistent with the findings of the SAPAT study.¹⁷

The use of aspirin as a therapeutic agent in the management of patients with cardiovascular and cerebrovascular disease has been widely supported by the professional medical societies in their scientific statements, e.g., AHA^{2,20} on the management of cardiovascular risks and the consensus statement by ACC/AHA/ACP-ASIM on the management of chronic stable angina.³

These and other studies²¹ led the US FDA to provide a professional label for aspirin, which includes in its claims treatment of ischemic stroke and TIA (50-325 mg qd); suspected acute MI (160-162.5 mg qd); and prevention of recurrent MI, treatment of chronic stable angina, and unstable angina (75-325 mg qd).²²

As these two therapies for cardiovascular risk reduction, aspirin and pravastatin, work by such different mechanisms, i.e., impairing thrombus formation and reducing LDL-C respectively, it was considered probable that they would show an independence of effect in man. Although the combined administration of these two agents seems logical, to date, there are no published data demonstrating the independence of effect of these two agents which would justify the clinical use of the combination.

A recent abstract does suggest, though, that statin therapy given concomitantly with the antiplatelet agents clopidogrel or aspirin has additive benefits.²³ The authors concluded that the benefit of anti-platelet therapy appears to be independent and complementary to the benefits provided by lipid lowering. This NDA, however, provides the first analyses

of a robust body of clinical event data, which demonstrates the independence of effect of pravastatin and aspirin in a secondary prevention population.

Compliance issues exist in the management of the secondary prevention population even if the appropriate therapy is instituted. These issues exist both with pravastatin^{24,25,26} and to a considerable extent with aspirin,²⁷ as aspirin is often not perceived by the patient to be an important part of the therapeutic regimen. It has been suggested that providing a prescription for aspirin might help to correct this perception and increase compliance. Improvements in compliance have also been documented by reducing the number of medications.²⁸ This can be accomplished by the use of combination products or, for example, in the case of the management of H.pylori infection, by the co-packaging of the three drugs, which are required.²⁹ This co-package, Prevpac[®], contains the complete daily regimen in a single package.

This application describes two pravastatin/buffered aspirin co-packaged presentations both contain a pravastatin 40 mg tablet, as this is the dose used in the clinical event trials, and buffered aspirin either an 81 mg or a 325 mg tablet, so that both commonly used doses of aspirin are available.^{15,22}

The demonstration of the independence of effect of pravastatin and aspirin in man, and the need to devise new strategies to increase patient compliance, form the basis and the central objective of this application: to assess the efficacy of the combination of pravastatin 40 mg and aspirin compared with the individual components alone. In this application, existing databases from all five (5) pravastatin secondary prevention studies were retrospectively analyzed to assess the efficacy of these two agents when taken concomitantly. The five pravastatin studies were LIPID, Long Term Intervention with Pravastatin in Ischemic Disease, CARE, Cholesterol and Recurrent Events, PLAC I, Pravastatin Limitation of Atherosclerosis in the Carotids, PLAC II and REGRESS, Regression Growth Evaluation Statin Study.

Since both pravastatin and aspirin have proven benefits among subjects with CAD in extending the overall survival, decreasing the need for interventions such as percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass grafting (CABG), and reducing the incidence of subsequent MI and ischemic stroke, the following endpoints were considered for the meta-analysis:

- 1) Composite endpoint of CHD death, non-fatal MI, myocardial revascularization procedures (CABG/PTCA), or ischemic stroke;
- 2) Composite endpoint of CHD death, non-fatal MI, or myocardial revascularization procedures (CABG/PTCA);
- 3) Composite endpoint of CHD death or non-fatal MI;
- 4) Composite endpoint of fatal or non-fatal MI; and
- 5) Ischemic stroke.

Summary

This Briefing Document

- briefly reviews the very different mechanisms by which pravastatin and aspirin reduce clinical events.
- provides data to show the absence of any pharmacokinetic interaction between pravastatin and aspirin and *vice versa*.
- briefly reviews the absence of any age related effect on the pharmacokinetics of pravastatin.
- provides data to show the independence of the risk reductions in clinical events with pravastatin and aspirin in patients with cardiovascular and/or cerebrovascular disease.
- provides data to show the absence of any additivity in the side-effect profile of the combination and of any consistent pattern of increased laboratory abnormalities or adverse events in the ≥ 65 year old groups, when compared with the < 65 year old group.
- describes the two co-packaged products, 40 mg pravastatin with 325 mg of aspirin and 40 mg pravastatin with 81 mg of aspirin. The choice of the pravastatin dose being determined by its being the dose used in the studies for the meta-analyses. The choice of aspirin doses were the highest and lowest doses recommended for reduction of cardiovascular events in the label.
- briefly reviews the studies by which it may be expected this product will improve compliance.

2 HUMAN PHARMACOKINETICS AND BIOAVAILABILITY

2.1 Overview of Pharmacokinetics and Bioavailability of Pravastatin

Pravastatin is active when administered orally. In clinical pharmacology studies in man, pravastatin is rapidly but incompletely absorbed, with peak plasma levels of the parent compound attained 1 to 1.5 hours following oral ingestion. Based on urinary recovery of radiolabeled drug, the average oral absorption of pravastatin is 34% and absolute bioavailability is 17%. Pravastatin undergoes extensive first-pass extraction in the liver (extraction ratio 0.66), which is its primary site of action, and the primary site of cholesterol synthesis and of LDL-C clearance. *In vitro* studies demonstrated that pravastatin is transported into hepatocytes but there is substantially less uptake into cells of other tissues. In view of pravastatin's apparently extensive first-pass hepatic metabolism, plasma levels may not necessarily correlate perfectly with lipid-lowering efficacy. Pravastatin plasma concentrations [including: area under the concentration-time curve (AUC), peak (C_{max}), and steady-state minimum (C_{min})] are directly proportional to administered dose, over the approved dosage range.¹³

Pravastatin, like other HMG-CoA reductase inhibitors, has variable bioavailability. The coefficient of variance, based on between-subject variability, was 50% to 60% for AUC. Biotransformation pathways elucidated for pravastatin include: (a) isomerization to 6-epi pravastatin and the 3 α -hydroxyisomer of pravastatin (SQ 31,906), (b) enzymatic ring hydroxylation to SQ 31,945, (c) ω -1 oxidation of the ester side chain, (d) β -oxidation of the carboxy side chain, (e) ring oxidation followed by aromatization, (f) oxidation of a hydroxyl group to a keto group, and (g) conjugation. The major degradation product is the 3 α -hydroxy isomeric metabolite, (SQ 31,906) which has one-tenth to one-fortieth the HMG-CoA reductase inhibitory activity of the parent compound.¹³

Systemic bioavailability of pravastatin administered following a bedtime dose was decreased 60% compared to that following an AM dose. Despite this decrease in systemic bioavailability, the efficacy of pravastatin administered once daily in the evening was marginally more effective on LDL-C lowering, than that after a morning dose, although this difference was not statistically significant. This finding of lower systemic

bioavailability suggests greater hepatic extraction of the drug following the evening dose. Steady-state AUCs, C_{max} and C_{min} plasma concentrations showed no evidence of pravastatin accumulation following once or twice daily administration of pravastatin sodium tablets. Approximately 50% of the circulating drug is bound to plasma proteins.

As indicated above, the principal metabolite of pravastatin following oral ingestion is SQ 31,906. It is formed by an acid catalyzed process in the stomach. Given intravenously to man, 64% of dose of pravastatin is recovered as unchanged pravastatin.¹³ This absence of significant oxidative metabolism distinguishes pravastatin from other HMG-CoA reductase inhibitors, such as lovastatin, simvastatin and atorvastatin, which are subject to extensive oxidative metabolism, particularly by the cytochrome CYP3A4.³⁰

Two studies have been conducted to explore the potential for a drug interaction with aspirin. The first of these (27,201-6) compared the pharmacokinetics of pravastatin (20 mg) in twenty-four (24) healthy male subjects in an open, balanced, randomized, incomplete-block study. Each subject received 3 of 4 treatments, which were a 20 mg dose given either (1) alone, (2) concomitantly with 1 g of nicotinic acid, (3) 30 minutes after a single 324-mg dose of aspirin, or (4) concomitantly with 1 g of nicotinic acid 30 minutes after a single 324-mg dose of aspirin. Comparison of the pharmacokinetic data of pravastatin alone and with aspirin given 30 minutes prior to dosing showed that administration of aspirin did not affect the pharmacokinetics of pravastatin.³¹

The second study (CV123-234), was an open-label, single dose, randomized, 3-period, 3-treatment crossover study in 30 subjects comparing the pharmacokinetics of pravastatin (40 mg) and buffered aspirin (325 mg) when they were given separately, to when given concomitantly.

This study showed that addition of pravastatin to aspirin did not affect the clinical pharmacokinetics of salicylate nor did addition of aspirin to pravastatin affect the clinical pharmacokinetics of pravastatin. The full study report is filed with this application.

The pharmacokinetic drug interactions reported with aspirin have generally involved displacement of salicylic acid from plasma albumin, particularly with other NSAIDs.^{14,32} As pravastatin is only about 50% bound to plasma proteins, the absence of an effect on salicylate pharmacokinetics is therefore not unexpected. Pravastatin was not expected to

affect the rate and extent of absorption of aspirin, as had been seen with concomitant administration of charcoal, antacids, cholestyramine or metoclopramide.³²

2.2 Clinical Pharmacology Studies

One Clinical Pharmacology Study CV123-234 was submitted in support of the pravastatin (40 mg) and aspirin co-package application. This study involved 30 subjects, all of whom received in a randomized manner a single dose of pravastatin (40 mg) on two separate occasions, either with or without aspirin and on a third occasion a dose of aspirin (325 mg) alone. This study is summarized in Table 2.2.

Table 2.2: Pravastatin/Aspirin Summary of Clinical Pharmacology Studies

Protocol Number	Design Treatment(s): Dosage, Regimen and Number of Subjects Route of Administration	Age Range (Mean)	Diagnosis and Criteria for Inclusion	Duration of Treatment	Criteria for Evaluation	Results	Adverse Reactions (Number of Subjects)		
							Total AEs	SAEs/ Deaths	DCs Due to AEs
CV123-234 Start Date 27 January 2001 Completed 11 February 2001 1 Investigator 1 Center	Open label, single-dose, randomized, 3-period, 3- treatment crossover study Pravastatin (40 mg) Aspirin (325 mg) Pravastatin plus Aspirin N = 30 Route of Administration Oral	20–56 y (36.5) 83/17% 100% W	18–60 years normal healthy subjects BMI 18-30kg/m ²	Single dose 2 nights 2 days In the Clinic on 3 occasions separated by at least 4 days	PK: Cmax Tmax AUC0→inf T-half For aspirin salicylate SQ31906 Pravastatin Physical Exam ECG Adverse Events Clinical Lab Data	The ratios of least squares means (90% confidence intervals) are for pravastatin AUC inf 94.5% (84.7-105.3) and Cmax 92.0% (82.1-103.1) for salicylate AUCinf 101.8% (98.9-104.8) and Cmax 101.5% (95.1-108.4) There is no pharmacokinetic interaction between pravastatin and aspirin	11(7)	0/0	0/0

2.2.1 A Randomized, Open-Label, Single Dose, Drug Interaction Study of Pravastatin and Aspirin (Protocol CV123-234)

This study was an open-label, single dose, randomized, three period, three-treatment crossover study which was balanced for first order residual effects. It was conducted in 30 healthy subjects with the requirement that 24 complete all three treatments. As there were no subjects who discontinued, all 30 subjects were analyzed.

The three treatments which were separated by 7 days consisted of:

- Pravastatin, a single oral dose of 40 mg
- Bufferin[®], as a single tablet containing 325 mg of aspirin
- Concomitant administration of Pravastatin and Bufferin[®]

The analytes measured were pravastatin and its metabolite, SQ 31906, aspirin (acetylsalicylic acid) and its metabolite, salicylic acid.

2.2.2 Demographic Characteristics of Pharmacokinetic Study Population

The demographic characteristics of all normal subjects randomized in the Clinical Pharmacology study, are presented in Table 2.2.2A.

Table 2.2.2A: Demographic Characteristics of All Subjects Randomized in the Clinical Pharmacology Study-Healthy Volunteers

Demographics	Number (%) of Subjects
	Clinical Pharmacology Studies with Normal Healthy Volunteers (N = 30)
Age, years n (%)	
≤ 20	1 (3)
20-30	7 (23)
31-40	12 (40)
41-50	8 (27)
51-64	2 (7)
Mean (sd)	36.5 (8.3)
Range	20-56
Gender, n (%)	
Male	25 (83)
Female	5 (17)
Race, n (%)	
White	30 (100)
Body Weight, kg	
Mean (sd)	73.8 (7.8)
Range	55.7-83.8

As defined in the protocol, the analytes chosen for evaluation of a potential interaction were pravastatin and salicylic acid. This decision was taken based on historical data that suggested that unchanged aspirin would only be a small amount of the total salicylate measured.¹⁴ In this study, it was approximately 3%.

The pharmacokinetic parameters for pravastatin are shown in Table 2.2.2.B and for salicylate in Table 2.2.2.C.

The ratios of the geometric means and the 90% confidence intervals for the ln-transformed parameters AUC_{inf} and C_{max} for serum pravastatin and plasma salicylate were within the confidence interval of 67-150% outlined in the protocol to conclude absence of effect.

These ratios were also within the 80-125% equivalence intervals recommended by FDA in their Guidance for Industry document on drug interaction studies.³³

Based on these results, it is concluded that buffered aspirin has no effect on the pharmacokinetics of pravastatin when administered concurrently and pravastatin has no effect on the pharmacokinetics of buffered aspirin (as measured by salicylate) when administered concurrently.

Table 2.2.2B: Pharmacokinetic Parameters for Pravastatin (90 Percent Confidence Intervals) in Study CV123-234 (n = 30)

Analyte	C _{max} (ng/mL)	AUC _{inf} (ng•h/mL)
Pravastatin	55.15	122.16
Pravastatin with Aspirin	50.76	115.39
Ratio of Geometric Means (90%-confidence intervals)	92.0 (82.1-103.1)	94.5 (84.7-105.3)

Table 2.2.2C: Pharmacokinetic Parameters for Salicylate (90 Percent Confidence Intervals) in Study CV123-234 (n = 30)

Analyte	C _{max} (mcg/mL)	AUC _{inf} (mcg•h/mL)
Salicylate	23.57	101.24
Salicylate with Pravastatin	23.93	103.09
Ratio of Geometric Means (90%-confidence intervals)	101.5 (95.1-108.4)	101.8 (98.9-104.8)

3 OVERVIEW OF CLINICAL SAFETY AND EFFICACY STUDIES

All five (5) pravastatin randomized double-blind placebo controlled studies, CARE,⁸ LIPID,⁹ REGRESS,¹⁰ PLAC I¹¹ and PLAC II,¹² in a secondary prevention population were subjected to a traditional frequentist meta-analysis. The data were pooled together. Cox proportional hazard models adjusting baseline prognostic factors were fit. Four treatments, pravastatin with aspirin, pravastatin, aspirin with placebo and placebo were chosen. Estimates of relative risk between each pair of treatment groups and the 95% confidence intervals were calculated.

Two Bayesian analyses, one making the standard Cox proportional hazards assumption, the other allowing for changing hazards, were also conducted on the pooled data.

Overviews of the five studies used in the meta-analyses are provided.

CARE

Objectives: The primary objective of this study was to determine whether therapy with pravastatin administered over a five-year period to men and women with normal cholesterol levels and who had experienced a myocardial infarction 3 to 20 months before the beginning of the trial decreased the combined risk of fatal coronary heart disease (CHD) and nonfatal myocardial infarction (MI). The secondary objective of this study was to determine if pravastatin therapy reduced the incidence of fatal coronary heart disease. The tertiary objective of this study was to determine if pravastatin therapy reduced total mortality. Additional objectives were to determine whether pravastatin decreased the following measures of cardiovascular disease: cerebrovascular disease, fatal and nonfatal MI, total CHD, coronary revascularization procedures, and hospitalizations for cardiovascular disease.

Duration of Treatment: Subjects were followed for a median of 4.9 years.

Study Design and Methodology: This was a double-blind, randomized, placebo-controlled trial in men and women aged 21 to 75 with plasma total cholesterol level < 240 mg/dL (6.2 mmol/L) and low-density lipoprotein cholesterol (LDL-C) level

of 115-174 mg/dL (3.0-4.5 mmol/L) following a Step I diet and who had a documented myocardial infarction (MI) 3 to 20 months prior to randomization. Subjects who qualified (see Diagnosis and Main Criteria for Inclusion) were randomized in a double-blind manner to either pravastatin 40 mg once daily or matching placebo for the duration of the study. The dose was to remain constant throughout the course of the study, but study medication could be decreased, interrupted or permanently discontinued for safety reasons at any time.

Number of Subjects: 4159 men and women were randomized.

Diagnosis and Main Criteria for Inclusion: Men and women (post-menopausal or surgically sterile) aged 21 through 75 years of age were eligible to enroll in the study if they met the following criteria: 1) acute MI between 3 and 20 months prior to randomization, and 2) average of two consecutive lipid levels: plasma total cholesterol < 240 mg/dL (6.2 mmol/L), LDL-C (calculated) between 115 and 174 mg/dL (3.0 and 4.5 mmol/L), and triglycerides less than 350 mg/dL (4.0 mmol/L).

Efficacy

The primary endpoint of the trial was time to occurrence of definite nonfatal MI or death from CHD. The secondary endpoint was time to occurrence of fatal CHD and the tertiary endpoint was time to occurrence of death.

Safety

The clinical investigators were instructed to document the occurrence of clinical adverse events (AEs; illnesses, signs and symptoms, or clinically significant laboratory test abnormalities that had appeared or worsened during the course of the study), both those volunteered by subjects and those elicited by general questioning, at all scheduled visits. Clinical laboratory tests were performed for safety monitoring at all scheduled visits. Other safety assessments included a complete medical history at baseline, annual physical examinations, eye examinations: initial and follow-up (discontinued November 1991), and 12-lead ECGs: initial and follow-up (discontinued November 1993.)

Statistical Methods: The efficacy analysis included all available study endpoints up to and including the final study visit date from all randomized subjects regardless of their

compliance with study medication. Baseline characteristics were compared between treatment groups by a two-sample *t*-test or χ^2 -test, as appropriate, with a two-sided significance level of 0.05. The treatment group difference between the cumulative events curves was tested by the Mantel-Haenszel logrank test. The risk reduction and 95% confidence interval were obtained using the Cox proportional hazards model with a single binary covariate of treatment group. In addition, the Kaplan-Meier biannual event rates and standard errors were estimated as well as Kaplan-Meier cumulative event curves. An analysis adjusting for pre-specified risk factors was performed using the Cox regression model. The percent change in lipid levels from baseline to annual time points was analyzed by a rank-based analysis of covariance (ANCOVA). Significance of median percent change within treatment group was assessed by a signed rank test and significance of between-treatment difference was assessed by *F*-test based on ranks with a two-sided significance level of 0.05. Statistical analyses of safety data included all subjects who consumed at least one dose of study medication and events occurring up to and including 30 days after discontinuation of study therapy. Between-group comparisons of the AE and marked abnormality (MA) frequency rates were assessed by Fisher's Exact test.

Results:

Efficacy

Pravastatin was associated with a risk reduction of 24% ($P = 0.003$) for the primary endpoint of definite nonfatal MI or death from CHD. The results of the secondary (fatal CHD) and tertiary (total mortality) endpoints showed risk reductions of 20% ($P = 0.104$) and 9% ($P = 0.366$), respectively. In addition, for the other predefined endpoints, pravastatin significantly reduced the incidence of fatal and nonfatal cerebrovascular events (stroke or transient ischemic attack [TIA]) by 24% ($P = 0.039$); decreased the need for Coronary Artery Bypass Grafting (CABG) or nonsurgical coronary revascularization by 27% ($P < 0.001$); reduced the risk of fatal and nonfatal MIs by 25% ($P = 0.001$), total coronary heart disease events by 17% ($P = 0.001$) and total cardiovascular disease events by 13% ($P = 0.003$).

In the intent-to-treat population, statistically significant differences ($P < 0.001$) between the pravastatin and placebo treatment groups were observed for Total-C, LDL-C, HDL-C,

and TG at all annual time points. At Year 5, the median decrease from baseline in Total-C was 17.6% for the pravastatin group compared to an increase of 0.9% for the placebo group. Reductions in LDL-C were 30.1% for the pravastatin group, compared with 2.8% in the placebo group. For the pravastatin group, HDL-C increased 11.1%, compared with 5.9% for the placebo group. There was a reduction in TG levels of 4.8% for the pravastatin group, while TG levels increased 6.7% for the placebo group.

Safety

Pravastatin therapy was well tolerated by subjects in this study. No previously unreported adverse events (AEs), laboratory marked abnormalities (MAs), or serious adverse events (SAEs) were attributed to pravastatin therapy. Ninety-two (4.4%) pravastatin-treated and 121 (5.8%) placebo-treated subjects discontinued therapy due to AEs ($P = 0.017$). The most commonly reported AEs occurred with similar frequency in both treatment groups, with the exception of influenza (pravastatin 23.3%, placebo 20.5%), weight gain (pravastatin 17.2%, placebo 14.9%), weight loss (pravastatin 14.8%, placebo 12.3%), and sleep disturbance (pravastatin 11.4%, placebo 8.9%). There were no between-treatment group differences in the incidence of events of special interest (cancer, suicide/violent death, depression, and severe myopathy) with the exception of breast cancer which was reported in 12 pravastatin-treated women and 1 placebo-treated woman. This imbalance appears to be an anomalous finding in a small number of cases following multiple analyses of many subgroups representing different tumor types, with no imbalance seen in the overall incidence of cancer. The design of the trial, by not stratifying by sex, as well as the multiple comparisons done for safety analyses, favored the identification of such an isolated finding due to a chance effect. The incidence of breast cancer in the pravastatin-treatment group is consistent with the number that would be expected based on epidemiologic data from the US and Canada but lower than expected in the placebo group. There were also no between-treatment group differences in the incidence of MAs of alanine aminotransferase (ALT/ALAT), aspartate aminotransferase (AST/ASAT), or creatinine kinase (CK). One hundred twenty-eight (6.2%) pravastatin-treated subjects and 135 (6.5%) placebo-treated subjects died during blinded therapy, which includes the period up to 30 days following discontinuation of study medication.

Conclusions: The long-term administration of pravastatin to post-MI subjects with normal cholesterol levels:

- Reduces the risk of MI
- Reduces the risk of undergoing myocardial revascularization procedures
- Reduces the incidence of stroke and TIAs

LIPID

Objectives: The primary objective of this study was to determine whether therapy with pravastatin reduced mortality due to coronary heart disease (CHD) when administered over a five-year period to men and women with a history of myocardial infarction (MI) or unstable angina pectoris (UAP) who also had cholesterol levels typical for patients with CHD. Additional objectives were to determine the effect of pravastatin therapy on total mortality; on the combined incidence of fatal CHD and non-fatal MI; on the incidence of all-cause stroke and non-hemorrhagic stroke; on cardiovascular mortality; on the incidence of revascularization procedures (coronary artery bypass grafting [CABG] and percutaneous transluminal coronary angioplasty [PTCA]); on plasma levels of total cholesterol (Total-C), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglycerides (TG), Apolipoprotein A1 and Apolipoprotein B, and on the relationship between these lipid fractions and changes in these lipid fractions and CHD mortality and other endpoints; and on the total days of hospitalization.

Duration of Treatment: Subjects randomized to pravastatin were exposed to study medication for a mean duration of 5.1 years while subjects randomized to placebo were exposed to study medication for a mean duration of 4.9 years. Subjects were followed for a median of 5.9 years (mean of 5.6 years).

Study Design and Methodology: This study was a double-blind, parallel group, randomized, placebo-controlled trial in men and women aged 31 to 75 years with plasma Total-C between 4.0 and 7.0 mmol/L (155-271 mg/dL) after dietary intervention. In order to qualify for the study, each subject must have experienced an acute MI or UAP requiring hospital admission three months to three years prior to screening. Subjects who qualified were randomized in a double-blind manner to either pravastatin 40 mg or

matching placebo once-daily for the duration of the study. The dose was to remain constant throughout the course of the study, but study medication could be decreased, interrupted or permanently discontinued for safety reasons at any time.

Number of Subjects: Nine thousand fourteen (9,014) men and women were randomized.

Diagnosis and Main Criteria for Inclusion: Men and women (non-lactating and post-menopausal or surgically sterile) aged 31 to 75 years were eligible to enroll in the study if they met the following criteria: 1) acute MI or UAP requiring hospital admission three months to three years prior to screening, and 2) fasting plasma Total-C between 4.0 and 7.0 mmol/L (155-271 mg/dL). It should be noted that subjects with a wide range of baseline levels of triglycerides (up to 443 mg/dL [5.0 mmol/L]) were eligible for LIPID and there was no restriction on the baseline levels of HDL-C.

Efficacy

The primary efficacy measure was the time to occurrence of CHD mortality. Secondary efficacy measures included the time to the occurrence of: 1) mortality from all causes; 2) the combined incidence of CHD mortality and non-fatal MI; 3) all-cause total stroke; 4) non-hemorrhagic stroke; 5) cardiovascular mortality; 6) myocardial revascularization procedures (CABG and PTCA); 7) levels of Total-C, LDL-C, HDL-C, TG, Apolipoprotein A1 and Apolipoprotein B; 8) the relationship of the above lipid fractions and changes in them to CHD events (CHD mortality or non-fatal MI); 9) the total days of hospitalization. Tertiary efficacy measures included the time to occurrence of: 1) atherosclerotic events (CHD mortality, non-fatal MI, myocardial revascularization procedures, or all-cause stroke); 2) fatal or non-fatal MI.

Statistical Methods: All randomized subjects were assessed in the efficacy analyses regardless of compliance with the protocol, in accordance with the intent-to-treat principle. All outcomes occurring from randomization up to and including the last scheduled visit date were included in the efficacy assessments. Subjects who prematurely discontinued study medication were followed actively for all outcomes until the last scheduled visit date.

The treatment groups were compared using the Mantel-Haenszel logrank test statistic stratified by qualifying event (MI or UAP) as designated by the investigator. Estimates

of treatment effect were defined in terms of the risk reduction in the pravastatin randomized group compared with the placebo randomized group and the associated 95% confidence intervals around the risk reduction. The risk reduction and 95% confidence interval were obtained using the stratified Cox proportional hazards model with a single binary covariate for treatment group. In addition, the Kaplan-Meier biannual event rates and standard errors were estimated and the Kaplan-Meier cumulative event curves were plotted. A Cox proportional hazards model stratified by qualifying event (MI or UAP), adjusted for predefined baseline prognostic factors, was also used to compare the treatment groups. The percent change in lipid levels from baseline to post-randomization time points were summarized for each treatment group. Safety data were summarized for each treatment group.

For all-cause hospitalization, the treatment groups were compared using two methods. The mean days of hospitalization per 100 person-years of follow up were compared between the two treatment groups using a two-tailed *t-test*. Due to the fact that a *t-test* does not take into account the frequency of hospitalizations per subject, a multiplicative intensity model was also used to compare the frequency and duration of hospitalization between the two treatment groups.

Results:

Efficacy

Pravastatin significantly reduced the relative risk for the primary endpoint of CHD mortality with a risk reduction of 24% ($P = 0.0004$). The results of the secondary endpoints of total mortality, CHD events (CHD mortality or non-fatal MI), all-cause stroke, non-hemorrhagic stroke, cardiovascular mortality, and revascularization procedures showed significant risk reductions of 23% ($P < 0.0001$), 24% ($P < 0.0001$), 19% ($P = 0.0477$), 23% ($P = 0.0154$), 25% ($P < 0.0001$), and 20% ($P < 0.0001$), respectively. In addition, for other predefined endpoints of atherosclerotic events (CHD mortality, non-fatal MI, myocardial revascularization procedures, or stroke) and fatal or non-fatal MI, pravastatin significantly reduced the relative risk by 21% ($P < 0.0001$) and 29% ($P < 0.0001$), respectively.

The covariate-adjusted analyses using baseline prognostic factors confirmed the benefit of pravastatin. The following prespecified subgroups were analyzed for CHD mortality,

total mortality, and CHD events (CHD mortality or non-fatal MI): age (≥ 65 years, < 65 years), gender (male, female), history of hypertension (yes, no), history of diabetes mellitus (yes, no), and cigarette smoker (yes, no). The results of these analyses showed consistent treatment effects with pravastatin in all subgroups.

In the intent-to-treat population, there was a greater reduction from baseline LDL-C in the pravastatin group than in the placebo group at all time points. Similar reductions were also observed in Total-C, TG and Apolipoprotein B in the pravastatin group compared with the placebo group at all time points. For HDL-C and Apolipoprotein A1, pravastatin produced greater increases from baseline at all time points than placebo. At 1 year, 3 years, and 5 years after randomization, in the pravastatin group the mean decrease in LDL-C ranged from 24% to 28%; the mean decrease in Total-C ranged from 17% to 20%; the mean decrease in TG ranged from 5% to 6%; the mean increase in HDL-C ranged from 4% to 9%, the mean increase in Apolipoprotein A1 ranged from 7% to 13%; and the mean decrease in Apolipoprotein B ranged from 18% to 21%.

Safety

A total of 1,131 deaths were reported during the course of this study up to and including the date of the last scheduled visit for each subject. Of these 1,131 subjects who died, 498 (11.0%) received pravastatin and 633 (14.1%) received placebo. The most common cause of death, as adjudicated by the Outcome Assessment Committee (OAC), was coronary death reported for 287 (6.4%) subjects randomized to pravastatin and 373 (8.3%) subjects randomized to placebo. Non-cardiovascular mortality occurred with similar frequency in both treatment groups.

During this study 483 (10.7%) pravastatin-treated subjects and 574 (12.7%) placebo-treated subjects permanently discontinued study medication because of SAEs or ADRs. Acute unstable angina pectoris was the most commonly reported SAE leading to permanent discontinuation of study medication occurring in 31 (0.7%) pravastatin-treated subjects and 63 (1.4%) placebo-treated subjects.

Overall, SAEs were reported in 3,216 (71.3%) subjects in the pravastatin group and 3,272 (72.7%) subjects in the placebo group. Except for the cardiac body system, which had a higher rate of SAEs reported in the placebo group, SAEs occurred with similar

frequency when comparing the two treatment groups for body system or category. Serious ADRs were rare, occurring in only 0.4% of subjects in both treatment groups.

Serious ADRs attributed to pravastatin treatment occurred in 7 subjects and included three reports of myalgia and myositis, two reports of hepatitis, one report of an allergic reaction and one report of hematemesis. Hematemesis was the only event that was unexpected during treatment with HMG-CoA reductase inhibitors; this event occurred in conjunction with a seizure, reported as secondary to a cerebrovascular event (CVA) experienced by this subject one year prior to these events. Hematemesis was also thought to be possibly related to extended treatment with aspirin in this subject.

The overall incidence of ADRs (both serious and non-serious) was low, occurring in 5.0% of pravastatin-treated and 4.1% of placebo-treated subjects. Of the most commonly reported ADRs, rash (0.7% in the pravastatin group and 0.3% in the placebo group), elevations of ALT (0.4% in the pravastatin group and 0.2% in the placebo group), and elevations of GGT (0.3% in the pravastatin group and 0.2% in the placebo group) occurred more frequently in the pravastatin group. These events have previously been reported to occur with HMG-CoA reductase inhibitor therapy.

The incidence of all reported cancers was similar when comparing the two treatment groups for both overall rate and by individual primary term. No imbalance in the cases of breast cancer was observed between pravastatin-treated and placebo-treated women during this study.

Occurrences of marked abnormalities (MAs) for hemoglobin determinations, platelet count, ALT, AST, and CK were similar when comparing the two treatment groups. The majority of MAs were transient and were not noted by investigators on the CRF as being clinically significant.

Safety results analyzed by subgroups of gender and age (< 65 years and \geq 65 years) were similar to those for the entire LIPID population.

Conclusions: The long-term administration of pravastatin to subjects with a prior acute MI or a prior hospitalization for UAP was well tolerated and reduced:

- CHD mortality by 24%;
- total mortality by 23%;
- stroke by 19%;
- myocardial revascularization (CABG/PTCA) by 20%;
- MI by 29%;
- hospitalization by 15%.

REGRESS

Objectives: The objectives of the study were to determine whether treatment with pravastatin could retard the progression of coronary atherosclerosis and reduce clinical cardiovascular events in subjects with plasma total cholesterol (Total-C) levels of 4-8 mmol/L (160-310 mg/dL) and at least one lesion $\geq 50\%$ diameter stenosis in a major coronary artery. Secondary objectives were the efficacy of pravastatin in reducing plasma Total-C, low-density lipoprotein cholesterol (LDL-C), and triglycerides (TGs), and increasing high-density lipoprotein cholesterol (HDL-C).

Duration of Treatment: Subjects were treated for 24 months.

Study Design and Methods: This was a randomized, double-blind, multicenter, placebo-controlled study of subjects with plasma Total-C levels of 4-8 mmol/L (160-310 mg/dL) and at least one lesion $\geq 50\%$ diameter stenosis in a major coronary artery. Following a dietary lead-in period (European/the Netherlands Heart Association diet), subjects who qualified were stratified into one of three management category groups based on a medical evaluation of the subject's clinical status and in accordance with accepted medical practice: (1) medical management (MM), (2) percutaneous transluminal coronary angioplasty (PTCA), or (3) coronary artery bypass graft (CABG). Subjects in each management category were randomized 1:1 to pravastatin 40 mg or matching placebo daily (qd) at bedtime (hs). Subjects whose plasma Total-C was elevated above 8.0 mmol/L (310 mg/dL) for two consecutive visits received enhanced dietary instruction. If dietary reinforcement did not reduce plasma Total-C below 8.0 mmol/L (310 mg/dL), cholestyramine was added and then titrated to the maximum tolerated dose.

Subject Disposition and Demographic Characteristics: One thousand sixty-eight subjects were enrolled, 183 subjects were excluded before randomization, and 885 subjects were randomized to treatment (pravastatin, 450; placebo, 435). Of the 885 subjects randomized, 373 were in the medical management stratum, 282 were in the CABG stratum, and 230 were in the PTCA stratum. All subjects were men 31 to 70 years old with a mean age of 56 years (SD = 8). Seven hundred seventy-nine (88%) subjects were either former or present smokers.

Diagnosis and Inclusion Criteria: Men < 70 years old were eligible for enrollment into the study if they met the following criteria: plasma Total-C of 4.0-8.0 mmol/L (160-310 mg/dL) and TG < 4.0 mmol/L (350 mg/dL); symptomatic coronary artery disease (CAD) with subsequent diagnostic evaluation for myocardial ischemia before cardiac catheterization; and at least one coronary stenosis $\geq 50\%$ in a major coronary artery. Subjects with evidence of any of the following were excluded: life-threatening illnesses other than CAD where life expectancy was less than study duration; malignancy; cardiac valve disease requiring valve replacement; cardiomyopathy; previous CABG; previous PTCA within 1 year before randomization; cardiac pacemaker implant; clinical congestive heart failure requiring diuretics; left ventricular ejection fraction < 0.3; complete A-V block; complete left bundle branch block; Wolff-Parkinson-White syndrome; use of lipid-lowering drugs ≤ 6 weeks before qualifying lipid measurement (≤ 12 weeks for fibrates or HMG CoA reductase inhibitor); history of poor response to other HMG CoA reductase inhibitors; immune disorder or use of immunosuppressive therapy or corticosteroids; significant metabolic disease; renal disease or dysfunction; hepatobiliary disease with aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 1.5 times the upper limit of normal (ULN); chronic or recurrent pancreatitis; severe obesity; muscle disorder; diabetes mellitus; uncorrected hypo- or hyperthyroidism; treatment with chronic corticosteroids or androgens; porphyria; significant gastrointestinal disease or surgery that could interfere with drug absorption; and excessive ethanol consumption.

Criteria for Evaluation:Efficacy

The primary efficacy variables were the two quantitative coronary angiographic assessments: the change in mean segment diameter and the change in minimum obstruction diameter. The following composite endpoints of clinical cardiovascular events were analyzed as secondary efficacy outcomes: (1) nonfatal myocardial infarction (MI), all-cause mortality, stroke/transient ischemic attack (TIA), or unscheduled PTCA/CABG; (2) nonfatal or fatal MI; (3) nonfatal MI or all-cause mortality; and (4) nonfatal MI or coronary heart disease (CHD) death. Changes in plasma Total-C, LDL-C, TG, and HDL-C were also assessed.

Safety

Investigators were instructed to document the occurrence of clinical adverse events (AEs: illnesses, signs, or symptoms that had appeared or worsened during the course of the study), both those volunteered by the subjects and those elicited by general questioning, at all scheduled visits. Safety laboratory values were also evaluated periodically during the trial. Other safety tests included a complete medical history and periodic physical examinations, a chest X ray, and a 12-lead electrocardiogram.

Statistical Methods: The change in mean segment diameter, averaged over all available noninfluenced (by PTCA or CABG) segments, was analyzed by an analysis of covariance (ANCOVA) with terms of treatment and management category, and baseline mean segment diameter (MSD) as the covariate. The change in minimum obstruction diameter (MOD) averaged over all available stenoses was analyzed by a Wilcoxon test. Two endpoints were used so that both the global change (ie, the effects on the entire segment [MSD]) and the focal change (effects on the stenosed area [MOD]) could be assessed. All coronary segments judged to be influenced by PTCA or CABG were excluded from the analyses. Clinical events were analyzed by a time-to-event method. The mean percent change in lipid levels and selected clinical laboratory analytes were analyzed by ANCOVA. Between-group comparisons of adverse events and marked laboratory abnormalities were assessed by Fisher's Exact test.

Results:Efficacy

Narrowing of the lumen (mean segment diameter) of the coronary vessels was significantly ($P = .037$ between treatment groups) less in the pravastatin treatment group (-.087 mm) than in the placebo group (-.117 mm). Decrease in the minimum obstruction diameter was significantly ($P = 0.001$) smaller in the pravastatin treatment group (-.032 mm) compared to the placebo treatment group (-.091 mm). This effect of pravastatin was consistent across the three stratified subgroups.

The analyses of clinical events demonstrated a favorable trend for pravastatin on the event endpoints, particularly the composite endpoint of nonfatal MI, all-cause mortality, stroke/TIA, or PTCA/CABG (risk reduction = 41%; $P = 0.002$).

Pravastatin treatment produced statistically significant ($P < 0.001$ compared with placebo) mean decreases in plasma LDL-C and Total-C at all time points (-26.8% in LDL-C and -19.5% in Total-C at Month 24). For HDL-C, a statistically significant ($P < 0.001$ compared with placebo) mean increase in the pravastatin treatment group was observed at all time points during the study (7.9% at Month 24). Pravastatin produced a statistically significant ($P < 0.01$ compared with placebo) decrease in TG throughout the course of the study (-20.2% at Month 24).

Safety

Pravastatin was well tolerated during this study. No serious AEs were attributed to pravastatin therapy. Four subjects in the pravastatin group and seven subjects in the placebo group died during treatment or ≤ 30 days after discontinuation of study therapy. None of the deaths were attributed to study therapy.

Conclusions: Administration of pravastatin for 24 months to men with elevated plasma Total-C levels and at least one lesion $\geq 50\%$ diameter stenosis in a major coronary artery: (1) retards the progression of coronary atherosclerosis; (2) reduces adverse clinical cardiovascular events; and (3) lowers plasma LDL-C, Total-C, and TG and raises HDL-C.

PLAC I

Objectives: To determine whether treatment with pravastatin could reverse or retard the progression of coronary atherosclerosis and reduce adverse cardiovascular sequelae in moderately hypercholesterolemic subjects with coronary artery disease (CAD).

Duration of Treatment: Subjects were treated for 36 months.

Study Design and Methods: This was a randomized, double-blind, placebo-controlled, multicenter trial. Subjects undergoing baseline coronary angiography (CAG) were screened for inclusion. Following dietary assessment and counseling, subjects who qualified were randomized (1:1) to either pravastatin 40 mg qd or to matching placebo. The dose was to remain constant for the duration of the study; coronary angiography was repeated at the end of treatment. For ethical reasons, an escape provision was established for subjects with a sustained increase in serum low-density lipoprotein cholesterol (LDL-C) \geq 190 mg/dL. For those subjects, intensified diet and ancillary lipid-lowering therapy could have been added; a matching subject in the opposite treatment group was similarly treated.

Subject Disposition and Demographic Characteristics: Four-hundred eight subjects were randomized (pravastatin, 206; placebo, 202) and 264 subjects completed 36 months of study therapy including follow-up angiography. The mean age of the randomized subjects (77% men, 23% women) was 56.8 years in the pravastatin and 57.3 years in the placebo group.

Diagnosis and Inclusion Criteria: Men and postmenopausal or surgically sterile women < 75 years old were eligible for enrollment into the study if they met the following criteria: undergoing coronary angiography after recent myocardial infarction (MI) or for percutaneous transluminal coronary angioplasty (PTCA), provided that the angiography did not reveal only normal coronary arteries; or undergoing diagnostic coronary angiography for chronic or unstable angina that revealed at least one angiographically documented stenosis \geq 50% in a major coronary artery; serum LDL-C \geq 130 and < 190 mg/dL and triglycerides (TG) \leq 350 mg/dL. Subjects with any of the following conditions were excluded: uncontrolled hypertension; endocrine disease; Type III hyperlipoproteinemia; congestive heart failure; debilitating noncardiac chronic disease;

significant renal or hepatic disease; chronic pancreatitis; dysproteinemia; porphyria; lupus erythematosus; poorly controlled or insulin-dependent diabetes mellitus; likelihood of coronary artery bypass graft (CABG) surgery or PTCA to the qualifying coronary artery within 6 months; history of cerebrovascular disease; significant gastrointestinal disease; excessive ethanol consumption; hypersensitivity to 3-hydroxy-3-methylglutaryl Coenzyme A (HMG CoA) reductase inhibitors; treatment (which cannot be withdrawn) with corticosteroids, estrogen > 1.24 mg daily, androgens, fish oil, barbiturates, antacids, or other lipid-lowering drugs; or treatment with an investigational drug within 30 days of enrollment.

Criteria for Evaluation:

Efficacy

The quantitative angiographic efficacy variables included the rate of progression during the interval between baseline and follow-up angiograms in the mean, minimum, and maximum coronary artery lumen diameters, and percent lumen diameter stenosis (%DS) averaged over all available pre-defined coronary artery segments ($N \leq 10$ per subject). Any follow-up angiogram obtained > 90 days after randomization was eligible for inclusion in the analysis. Bypassed segments and vessels subjected to PTCA (within 9 months of baseline angiography or subsequent to randomization) were excluded from analysis. The effects of study drug on cardiovascular events and lipid measurements (total cholesterol [Total-C], LDL-C, HDL-C, and TG) were also evaluated. Cardiovascular events were analyzed in two ways: 1) > 90 days after randomization to allow for a maximum effect of pravastatin on serum lipids; and 2) from the time of randomization.

Safety

Investigators were instructed to document the occurrence of clinical adverse events (AEs; illnesses, signs, or symptoms that had appeared or worsened during the course of the study), both those volunteered by the subjects and those elicited by general questioning, at all scheduled visits. Safety laboratory values were also evaluated periodically during the trial. Other safety tests included a complete medical history and periodic physical examinations, a chest X-ray, and a 12-lead electrocardiogram.

Statistical Methods: The quantitative angiographic outcome variables, calculated as the rate of progression for mean, minimum, and maximum lumen diameters, and %DS averaged over all available native (unbypassed, non-PTCA) coronary artery segments, were analyzed by an analysis of covariance (ANCOVA) with terms for treatment, site, treatment-by-site interaction, and baseline lumen diameter as the covariate, weighting each site inversely proportional to its variance of the treatment difference. Consistency of results across sites was assessed by testing treatment-by-site interaction terms at a 10% significance level. Clinical cardiovascular events were analyzed by a time-to-event analysis. The mean percent change in lipid levels and selected clinical laboratory analytes were analyzed by ANCOVA. Between-group comparisons of adverse events and marked laboratory abnormalities were assessed by Fisher's Exact test.

Results:

Efficacy

Compared with placebo (N = 157), pravastatin (N = 163) reduced by 40%-50% the rate of progression in mean (pravastatin = -0.02 mm/yr; placebo = -0.04 mm/yr; $P = 0.16$) and minimum (pravastatin = -0.03 mm/yr; placebo = -0.05 mm/yr; $P = 0.04$) coronary artery lumen diameters and %DS (pravastatin = 0.69 %/yr; placebo = 1.12 %/yr; $P = 0.13$). A corresponding reduction was observed in maximum lumen diameter (pravastatin = -0.02 mm/yr; placebo = -0.04 mm/yr; $P = 0.20$).

The analysis of clinical cardiovascular events showed a benefit of pravastatin treatment on events that occurred > 90 days after randomization; pravastatin reduced the rates of nonfatal or fatal MI (pravastatin, 2.7%; placebo, 10.5%; $P = .006$), nonfatal MI or all deaths (pravastatin, 4.4%; placebo, 11.6%; $P = .020$), and nonfatal MI or coronary heart disease (CHD) death (pravastatin, 3.9%; placebo, 11.0%; $P = .016$). For events from the time of randomization, comparable effects were observed on the rates of nonfatal or fatal MI (pravastatin, 4.2%; placebo, 10.5%; $P = .0498$), nonfatal MI or all deaths (pravastatin, 5.9%; placebo, 12.0%; $P = .0720$), and nonfatal MI or CHD death (pravastatin, 5.3%; placebo, 11.4%; $P = .0652$).

For the composite endpoint of nonfatal MI, all deaths, stroke, or PTCA/CABG, pravastatin exerted a blunted effect compared to the other clinical event endpoints (> 90 days after randomization: pravastatin = 18.6%, placebo = 23.9%, $P = .249$; from

time of randomization: pravastatin = 23.3%; placebo = 26.8%, $P = .4843$). In this event category, for events more than 90 days after randomization, 3.9% of subjects in the pravastatin group experienced more than one event compared to 9.9% of subjects in the placebo group. Similarly, for events after randomization, 5.3% of subjects in the pravastatin group experienced more than one event compared to 10.9% of subjects in the placebo group.

Safety

Pravastatin was well tolerated during this study. No serious AEs were attributed to pravastatin therapy. Six subjects died during treatment or less than one month after discontinuation of study therapy, two in the pravastatin group and four in the placebo group. None of the deaths were attributed to study therapy.

Conclusions: The results demonstrate that pravastatin administration for 36 months to subjects with proven CAD and moderate hypercholesterolemia slowed the progression of coronary artery atherosclerosis and reduced adverse cardiovascular sequelae. The findings in this trial are consistent with previous studies showing a reduction of atherosclerotic progression and cardiovascular events following cholesterol-lowering therapy (*N Engl J Med.* 1990;323:1289-1298, *Lancet.* 1992;339:563-569, *N Engl J Med.* 1990;323:946-955).

PLAC II

Objectives: The primary objective was to determine if treatment with pravastatin retards the progression of atherosclerosis in the carotid arteries in subjects with coronary artery disease and moderately elevated low-density lipoprotein cholesterol (LDL-C). Secondary objectives were to: (1) determine the incidence of cardiovascular events in the study groups; (2) evaluate the long-term efficacy and safety of pravastatin treatment; and (3) conduct natural history studies of carotid atherosclerosis progression in subjects assigned to placebo.

Duration of Treatment: Subjects were to be treated for 36 months.

Study Design and Methods: This was a randomized, double-blind, placebo-controlled trial. The target of treatment was LDL-C ≤ 110 mg/dL but ≥ 90 mg/dL. Following

dietary assessment and counseling, subjects who qualified were randomized (1:1) to either pravastatin 20 mg qd or to matching placebo. During the first 6 months of treatment the dose was titrated (to a maximum of 40 mg qd) to lower LDL-C to ≤ 110 mg/dL but ≥ 90 mg/dL. Thereafter, dosages remained constant for the duration of the study.

Subject Disposition and Demographic Characteristics: One hundred fifty-one subjects were randomized (pravastatin, 75; placebo, 76), all of whom were included in the efficacy analysis (85% men, 15% women). The mean age of subjects was 61.8 years in the pravastatin group and 61.6 years in the placebo group.

Diagnosis and Inclusion Criteria: Men and postmenopausal or surgically sterile women who were 50-74 years old were eligible for enrollment into the study if they met the following criteria: coronary artery disease evidenced by a documented history of myocardial infarction (MI) or coronary angiography demonstrating at least 50% narrowing of one of the major coronary arteries; mean plasma LDL-C concentration ≥ 60 th and ≤ 90 th percentile for the U.S. population by age and sex despite dietary intervention; mean triglycerides (TG) concentration < 350 mg/dL; and atherosclerotic plaque demonstrated by B-mode ultrasound (absolute combined intimal-medial thickness (IMT) of at least 1.3 mm in one of six extracranial carotid artery segments bilaterally) and with no history or evidence of completed stroke. Subjects with evidence of any of the following conditions were excluded: endocrine disease; secondary hyperlipidemia; homozygous familial hypercholesterolemia; Type I, III, IV, or V hyperlipoproteinemia; congestive heart failure; debilitating noncardiac chronic disease; significant renal disease; significant hepatic disease; chronic pancreatitis; dysproteinemia; porphyria; lupus erythematosus; diabetes mellitus; MI within the past 6 months; severe or unstable angina pectoris; uncontrolled congestive heart failure or gross cardiac enlargement; hypertension (systolic blood pressure > 160 mmHg or diastolic blood pressure > 100 mmHg despite treatment); significant gastrointestinal disease or surgery; excessive ethanol consumption; expected life span of less than 5 years; treatment with an investigational drug within 30 days; or treatment with certain drugs including corticosteroids, androgens, other lipid-lowering agents, or antacids containing aluminum salts. Subjects treated with thiazide diuretics alone or in combination with β -adrenergic blockers were included if on a stable dose.

Criteria for Evaluation:Efficacy

The primary efficacy variable was the rate of atherosclerosis progression in the extracranial carotid arteries, as determined by the rate of change in mean-maximum intimal medial thickness (IMT) averaged over 12 carotid artery segments: near and far walls of the distal common carotid, the bifurcation region, and the internal carotid, bilaterally. Secondary ultrasound efficacy variables included rate of progression in mean-maximum IMT in the following individual segments: (1) distal common carotid; (2) bifurcation; (3) internal carotid; and (4) single maximum thickness of any segment identified at baseline. Secondary clinical and laboratory variables analyzed included cardiovascular events and lipid measurements.

Statistical Methods: A mixed-effects model (*Biometrics*. 1982;38:963-974) was used for these repeatedly measured ultrasonography data to estimate the average rates of progression (ie, slopes) in the treatment groups and the differences between the slopes. The model included treatment as a fixed effect and regarded each subject's slope and intercept as random quantities, with a common intercept for the two treatment groups. The treatment effect on the rate of progression was tested with the *F*-test by contrasting the estimated average slopes from the two groups. Clinical cardiovascular events were analyzed by time-to-event analysis. The mean percent change in lipid levels and selected clinical laboratory analytes were analyzed by the analysis of covariance. Between-group comparisons of adverse events and marked laboratory abnormalities were assessed by Fisher's Exact test.

Results:Efficacy

The atherosclerosis progression rates of the overall mean-maximum IMT, bifurcation segments, and single maximum thickness identified at baseline tended to be slower in the pravastatin group than in the placebo group (pravastatin = .07 mm/yr vs placebo = .08 mm/yr in the overall mean-maximum IMT; pravastatin = .10 mm/yr vs placebo = .12 mm/yr in the bifurcation segments; and pravastatin = .23 mm/yr vs placebo = .24 mm/yr in the single maximum thickness identified at baseline), but the differences

were not statistically significant. In the common carotid artery segments, significantly less progression was observed in the pravastatin group compared with the placebo group (pravastatin = .02 mm/yr vs. placebo = .03 mm/yr; $P = 0.02$). The internal carotid segments showed similar progression in both groups (pravastatin = .09 mm/yr vs placebo = .07 mm/yr).

The analysis of clinical cardiovascular events showed a benefit of treatment with pravastatin. All of the evaluated clinical outcomes showed a reduction in event rates in the pravastatin group compared with the placebo group. In particular, the incidence of the composite endpoint of nonfatal MIs or all deaths was 62% lower in the pravastatin group (pravastatin = 5 vs placebo = 13; $P = 0.049$). The composite endpoint of nonfatal or fatal MIs were 80% fewer in the pravastatin group compared with the placebo group (pravastatin = 2 vs placebo = 10; $P = 0.018$); and the composite endpoint of nonfatal MIs or CHD deaths were 60% fewer in the pravastatin group (pravastatin = 4 vs placebo = 10; $P = 0.096$).

Safety

Pravastatin therapy was well tolerated by subjects in this study. No AEs and no serious adverse events (SAEs) were attributed to pravastatin therapy during this study. Seven (9%) pravastatin-treated and 14 (18%) placebo-treated subjects discontinued study therapy due to AEs; no subjects discontinued due to laboratory abnormalities. No occurrences of myopathy (muscle pain in conjunction with elevations of creatine kinase [CK] > 10 times the upper limit of normal), and no clinically significant between-treatment group differences in aspartate aminotransferase (AST), alanine aminotransferase (ALT) or CK concentrations were noted. One pravastatin subject and one placebo subject died while on study therapy and six subjects (pravastatin, 2; placebo, 4) died more than 1 month posttreatment; none of the deaths were attributed to study treatments.

Conclusion: The results show that administration of pravastatin for 36 months to subjects with proven cardiovascular atherosclerosis retards the progression of atherosclerosis when assessed in the common carotid artery. Concomitantly, pravastatin therapy was associated with a significant reduction in cardiovascular events compared with the placebo group. The findings in this study are consistent with those of other studies

showing regression of atherosclerosis in the common carotid artery and coronary arteries (*JAMA*. 1987;257:3233-3240, *Circulation*. 1993;88:20-28) and the observed reduction in clinical cardiovascular sequelae (*N Engl J Med*. 1990;323:946-955, *N Engl J Med*. 1990;323:1289-1298, *Br Med J*. 1984;289:220-223) following lipid-lowering therapy.

3.1 Relevant Published Studies

Table 3A summarizes these five studies CARE, LIPID, PLAC I, PLAC II and REGRESS, which were used for the meta-analyses. Table 3B summarizes relevant published studies which were derived from a literature search.

Table 3A Summary of Clinical Trials CARE

Protocol Number	Design		Age Range (Mean)	Diagnosis and Criteria for Inclusion	Duration of Study	Criteria for Evaluation	Results (Efficacy)	
Completion Status (Start Date)	Test Product (No. of Subjects)	Sex (%M / F)						
Investigators	Centers	Publication	Dosage Regimen and Route of Administration	Race (%W / O)				
27,201-67 (CARE)	Completed (25 JUN 89)	<i>Am J Cardiol.</i> 1991;68:1436-1446.	Randomized, double-blind, placebo-controlled study.	21-75 (58.6)	Men and women (post-menopausal or surgically sterile) aged 21 through 75 years of age were eligible to enroll in the study if they met the criteria: 1) acute MI between 3 and 20 months prior to randomization, and 2) average of two consecutive lipid levels: plasma total cholesterol < 240 mg/dL (6.2 mmol/L), plasma LDL-C (calculated) between 115 and 174 mg/dL (3.0 and 4.5 mmol/L), and triglycerides less than 350 mg/dL (4.0 mmol/L).	Subjects were followed for a median of 4.9 years.	The primary (1 ^o) efficacy endpoint of the trial was time to occurrence of death from coronary heart disease (CHD) or definite nonfatal MI. The secondary (2 ^o) endpoint was time to occurrence of fatal CHD and the tertiary (3 ^o) endpoint was time to occurrence of death.	Pravastatin therapy was associated with a risk reduction of 24% ($P = 0.003$) for the 1 ^o endpoint of CHD death or definite nonfatal MI. Pravastatin was associated with risk reductions for the 2 ^o and 3 ^o endpoints as follows: 20% (NS) for fatal CHD, 9% (NS) for total mortality. In addition, for the other predefined endpoints, PRAV significantly reduced the incidence of CERBRO disease, including stroke and transient ischemic attack (TIA) by 24% ($P = 0.039$); decreased the need for CABG or nonsurgical coronary revascularization procedures by 27% ($P < 0.001$); reduced the risk of fatal and nonfatal MIs by 25% ($P = 0.001$), total coronary heart disease events by 17% ($P = 0.001$) and total cardiovascular disease events by 13% ($P = 0.003$). The covariate-adjusted analysis for risk factors confirmed the benefit of pravastatin. The following prespecified subgroup analyses were performed: Post menopausal estrogen replacement (yes/no within women), as requested by the U.S. FDA on November 14, 1989; age (≥ 65 , < 65); sex (M/F); race (White/non-White); baseline LDL-C (above/below 130mg/dL); baseline HDL (above/below 35mg/dL); baseline LDL/HDL (above/below 4.0); baseline TG (above/below 125mg/dL); left ventricular ejection fraction (above/below 40%); previous MIs (prior to CARE MI, yes/no); days from CARE MI to randomization (< 6 months, 6 to < 12 months, ≥ 12 months); history of coronary artery surgery or angioplasty (yes/no); hypertension (yes/no); diabetes (yes/no); smoking (yes/no). The analyses showed consistent treatment effects with pravastatin in all subgroups.
1 Principal investigator	80 investigational sites throughout the USA and Canada	<i>N Engl J Med.</i> 1996;335:1001-1009.	Pbo (2078) Matching placebo tablet po qd hs.	(86% / 14%) (93% / 7%)				

Table 3A Summary of Clinical Trials (LIPID)

Protocol Number	Completion Status (Start Date)	Design	Age Range (Mean)	Gender (%M/F)	Diagnosis and Criteria for Inclusion	Duration of Treatment	Criteria for Evaluation	Results (Efficacy)
27,201-95	Completed (15 Dec 1989)	Randomized, double-blind, placebo-controlled study	31-75 (60.8)	(83%/17%)	Men and women aged 31 to 75 years with fasting total plasma cholesterol between 4.0 and 7.0 mmol/L (155-271 mg/dL) and total plasma triglycerides <5.0 mmol/L (443 mg/dL) who had experienced a myocardial infarction or had been hospitalized for unstable angina pectoris between 3 months and 3 years prior to screening were randomized.	Median follow-up was 5.9 years	Primary Efficacy Measure: 1) CHD mortality Secondary Efficacy Measures: 1) Total mortality 2) CHD events (CHD mortality or non-fatal MI) 3) All-cause stroke 4) Non-hemorrhage stroke 5) Cardiovascular mortality 6) CABG or PTCA 7) Change in plasma lipids 8) Relationship of plasma lipids to CHD events 9) Total days of hospitalization (for any cause) Tertiary Efficacy Measures: 1) Atherosclerotic events (CHD events or CABG or PTCA or all-cause stroke) 2) Fatal or non-fatal MI	Compared with placebo, pravastatin provided a 24% reduction in the relative risk for CHD mortality (95% CI 12%, 35%, p = 0.0004). Pravastatin reduced the relative risk for total mortality by 23% (95% CI 13%, 31%, p<0.0001) and reduced the relative risk for CHD events (CHD mortality or non-fatal MI) by 24% (95% CI 15%, 32%, p<0.0001). Pravastatin reduced the relative risk for all-cause stroke by 19% (95% CI 0%, 34%, p = 0.0477) and reduced the relative risk for non-hemorrhage stroke (ischemic or other strokes) by 23% (95% CI 5%, 38%, p = 0.0154). Treatment with pravastatin reduced the relative risk for CV mortality by 25% (95% CI 13%, 35%, p>0.0001). Pravastatin reduced the number of days of hospitalization per 100 person-years of follow up by 15% (p<0.001). Pravastatin also reduced the relative risk for atherosclerotic events by 21% (95% CI 14%, 27%, p<0.0001) and reduced the relative risk for fatal or non-fatal MI by 29% (95% CI 18%, 38%, p<0.0001). There was no clear relationship between CHD event rate and achieved level of LDL-C in the pravastatin group. Of particular note was the absence of any trend towards greater reduction in CHD event rate in association with greater reduction in LDL-C.
1 Principal Investigator	87 investigational sites throughout Australia and New Zealand	Publication: <i>Med J Aust</i> 1995;162:455-456 <i>Am J Cardiol</i> 1995;76:474-479 <i>Am J Cardiol</i> 1995;76:107C-112C <i>N Engl J Med</i> 1998;339:1349-1357 Route: PO	Treatment(s): Number of Subjects: Prav 20 mg tablets, 2 PO QD HS (n=4,512) Pbo matching placebo tablets, 2 PO QD HS (n = 4,502)	Investigators Centers	Publication			

Table 3A Summary of Clinical Trials (PLAC I and PLAC II)

Protocol Number	Design	Age Range (Mean)					
Completion Status (Start Date)	Test Product (No. of Patients)	Sex (%M/F)					
Investigators	Dosage Regimen and Route of Administration	Race (%W/O)	Diagnosis and Criteria for Inclusion	Duration of Study	Criteria for Evaluation	Results (Efficacy)	
27,201-26 (PLAC II)	<i>Am J Cardiol</i> 1995;76:54C-59C	50 - 73 (61.7)	CAD with history of MI, or $\geq 50\%$ narrowing of one of the coronary arteries. LDL-C ≥ 60 th and ≤ 90 th percentile for the US population by age and sex. TG < 350 mg/dL. Atherosclerotic plaque demonstrated by B-mode ultrasound (focal combined IMT of at least 1.3 mm in one of six extracranial carotid artery segments bilaterally).	36 months	Progression of atherosclerosis in extracranial carotid arteries as determined by the rate of change (mm/yr) in IMTs. CV events and lipid measurements.	Pravastatin significantly slowed the progression rate (prav/pbo in mm/yr) in the common carotid artery segments compared with placebo (0.02/0.03; $P = .02$). Progression rates (prav/pbo in mm/yr) in other segments were similar between groups (1) bifurcation segments (0.10/0.12; NS); (2) internal carotid segments (0.09/0.07 NS); and (3) the average of the 12 carotid artery segments (0.07/0.08; NS). CV event incidence rates were lower in the pravastatin group as follows: nonfatal MIs or all deaths, 62% lower (5 vs 13; $P = .049$); nonfatal or fatal MIs, 80% lower (2 vs 10; $P = .018$); and nonfatal MIs or CHD deaths, 60% lower (4 vs 10; $P = .096$).	
Completed (27 MAR 87)	Prav (75) 20 mg po qd.	(85%/15%)					
4 Investigators	<i>Controlled Clinical Trials</i> , 1992; 13: 495-506. (35.11, 304)	(99%/1%)					
1 Center in the US	If LDL-C ≥ 110 mg/dL after 6 months: Increase dose of pravastatin or matching placebo to 40 mg po qd. Escape provision if LDL-C ≥ 190 mg/dL. Intensified diet and ancillary lipid-lowering therapy.						

Table 3A Summary of Clinical Trials (PLAC I and PLAC II)

Protocol Number	Design	Age Range (Mean)	Sex (%M/F)		Duration of Study	Criteria for Evaluation	Results (Efficacy)
Completion Status (Start Date)	Test Product (No. of Patients)		Race (%W/O)	Diagnosis and Criteria for Inclusion			
Investigators	Dosage Regimen and Route of Administration						
Centers	Publication						
27,201-50 (PLAC I)	<i>Am J. Cardiol.</i> 1993; 72:31-35.	Double-blind, randomized, placebo-controlled study.	33 - 75 (56)	Undergoing clinically indicated coronary angiography, with \geq 50% stenosis of at least one major coronary artery. LDL-C \geq 130 mg/dL and $<$ 190 mg/dL. TG \leq 350 mg/dL.	36 months	Progression of atherosclerosis in coronary arteries as determined by the change (mm/yr) in lumen diameters and %DS. CV events (those after 90 days and all events) and lipid measurements.	Pravastatin slowed progression in coronary arteriosclerosis by 40% - 50%. Pravastatin caused a significant reduction in progression of minimum lumen diameter compared with placebo (pravastatin = -0.03 mm/yr; placebo = -0.05 mm/yr; $P = .04$). Pravastatin treatment resulted in similar reductions in mean (prav = -0.02 mm/yr; pbo = -0.04 mm/yr) and maximum (prav = -0.03 mm/yr; pbo = -0.05 mm/yr) lumen diameters and %DS (prav = 0.69 mm/yr; pbo = 1.12 mm/yr [$P \leq .2$ for all three]). CV event rates for first event after 90 days on therapy were lower in the pravastatin group as follows: nonfatal or fatal MIs, 74% lower (5 vs 17; $P = .006$); nonfatal MIs or all deaths, 62% lower (8 vs 19; $P = .020$); and nonfatal MIs or CHD deaths, 65% lower (7 vs 18; $P = .016$). CV event rates for first event after randomization were lower in the pravastatin group as follows: nonfatal or fatal MIs, 60% lower, (8 vs 17; $P = .0498$); nonfatal MI or all deaths, 51% lower (11 vs 20; $P = .0720$); and nonfatal MI or CHD death, 54% lower (10 vs 19; $P = .0652$).
Completed (29 DEC 87)	(35.7, 328)	Prav (206) 40 mg po hs.	(77%/23%)				
47 Investigators		Pbo (202) Matching placebo tablet po hs.	(88%/12%)				
13 Centers in the US		Escape provision if LDL-C \geq 190 mg/dL. Intensified diet and ancillary lipid-lowering therapy.					

Table 3A Summary of Clinical Trials (REGRESS)

Protocol Number	Design	Age Range (Mean)	Sex (%M/F)	Diagnosis and Criteria for Inclusion	Duration of Study	Criteria for Evaluation	Results (Efficacy)
Completion Status (Start Date)	Test Product (No. of Patients)						
Investigators	Dosage Regimen and Route of Administration	Race (%W/O)					
Centers	Publication						
27,201-82	Can. J. Cardiol. 1992;8:925-932.	31 - 70 (56.2)		CAD with at least one \geq 50% stenosis in a major coronary artery. Total-C 160-310 mg/dL. TG < 350 mg/dL.	At least 24 months	Progression of atherosclerosis in coronary arteries as determined by the changes in mean and minimum lumen diameters of 13 coronary artery segments. CV events and lipid measurements.	Pravastatin caused a significant reduction in progression of atherosclerosis in the coronary arteries as measured by mean segment diameter (pravastatin = -.087 mm; placebo = -.117 mm; $P = .04$) and minimum obstruction diameter (pravastatin = -.032 mm; placebo = -.091 mm; $P = .001$) compared with placebo. CV event rate for the composite endpoint of nonfatal MIs, all deaths, stroke/TIA, and unscheduled PTCA/CABG was 41% lower in the pravastatin group (48 vs. 79; $P = .002$).
Completed (13 DEC 89)	(39.6, 343)	(100%/0%)					
26 Investigators	Randomized, double-blind, placebo-controlled study. Subjects stratified into three groups according to initial management plan: CABG, PTCA, or medical management.	(Information about race not collected)					
11 Centers in the Netherlands	Prav (450) 40 mg po qd. Pbo (435) Matching placebo tablet po qd.						

Table 3B: Summary of Relevant Published Studies

First Author	Publication (Vol., Page)	Design/Treatment/ Number of Subjects	Age Range (Mean) Gender (%M/F) Race (%W/B/H)	Diagnosis and Criteria for Inclusion	Duration of Treatment	Results
Betrand ME	J Am Coll Cardiol 1997;30:863-9	Randomized, double blind vs. placebo, multicenter study. 695 patients post- angioplasty all treated with aspirin 100 mg/day. 347 received pravastatin 40 mg/day 348 received placebo Randomization within 24 h of PTCA	Ages 25-75 mean not reported Gender and Race not reported	LVEF > 40% within 24 h post PTCA No recent H/O MI TG < 500 mg/dL Chol 200-310 mg/dL	6 months	Angiographic assessment at 6 months on 625 patients. 6 D/C d for AEs, 14 refused reangiography. Others lost to follow-up. There was no difference evident between placebo and pravastatin treated patients angiographically or in the safety profile of pravastatin plus aspirin or placebo plus aspirin.

Table 3B: Summary of Relevant Published Studies

First Author	Publication (Vol., Page)	Design/Treatment/ Number of Subjects	Age Range (Mean) Gender (%M/F) Race (%W/B/H)	Diagnosis and Criteria for Inclusion	Duration of Treatment	Results
Savonitto S	Cardiovas Drugs Ther 1998;12:197-210	Review of studies of stable coronary artery disease SAPAT BIP 4S study CARE ASIST APSIS TIBET	NA	Chronic stable angina	Years	Chronic stable angina should be managed with a optimally titrated anti-ischemic agent, aspirin and a statin

Table 3B: Summary of Relevant Published Studies

First Author	Publication (Vol., Page)	Design/Treatment/ Number of Subjects	Age Range (Mean) Gender (%M/F) Race (%W/B/H)	Diagnosis and Criteria for Inclusion	Duration of Treatment	Results
Wood D	Europ Heart J 1998;19:1434- 1503	Prevention of coronary heart disease in clinical practice. Recommendations of the Second Joint Task Force of European and other Societies on Coronary Prevention	NA	Patients with coronary heart disease		Aspirin, at least 75 mg, in virtually all patients with CAD or other atherosclerotic disease. Statins are first line drugs for lipid level control.

Table 3B: Summary of Relevant Published Studies

First Author	Publication (Vol., Page)	Design/Treatment/ Number of Subjects	Age Range (Mean) Gender (%M/F) Race (%W/B/H)	Diagnosis and Criteria for Inclusion	Duration of Treatment	Results
Ryan TJ	J Am Coll Cardiol 1996;28:1328-1428 (see 1999 Web update http://www.acc.org/ clinical/guidelines)	ACC/AHA Guidelines for the Management of Patients with Acute Myocardial Infarction	NA	Acute myocardial infarction	Indefinite	Long-Term Management post MI; for an indefinite period following an acute MI the patient should continue to receive aspirin at 75 mg/day. The patient with LDL > 130 mg/dL after diet should be given drug therapy to reduce LDL to < 100 mg/dL Statins suggested

Table 3B: Summary of Relevant Published Studies

First Author	Publication (Vol., Page)	Design/Treatment/ Number of Subjects	Age Range (Mean) Gender (%M/F) Race (%W/B/H)	Diagnosis and Criteria for Inclusion	Duration of Treatment	Results
Szczeklik A	J Am Coll Cardiol 1999;33:1286 -93	38 hypercholesterolemic men. Treated for 2 weeks with ASA (20-40 mg/day) then with simvastatin (20-40 mg) for 12 weeks. ASA was then added back for Weeks 15 and 16	34-61 (47.4) y % Male, Race: not reported	Chol > 250 mg/dL TG < 400 mg/dL Exclude DM, unstable angina, severe chronic illness or SBP > 180 and DBP > 100 mm Hg.	16 weeks	The 2 week lead-in with aspirin depressed total amount of thrombin formed but not the reaction rate. Simvastatin markedly depressed thrombin generation. However when LDL is lowered adding aspirin back did not enhance the dampening of thrombin formation (see comments by Kearney J Am Coll Cardiol 1999;33:1305-1307)

Table 3B: Summary of Relevant Published Studies

First Author	Publication (Vol., Page)	Design/Treatment/ Number of Subjects	Age Range (Mean) Gender (%M/F) Race (%W/B/H)	Diagnosis and Criteria for Inclusion	Duration of Treatment	Results Therapy (Class/Level of Evidence)
Braunwald E	J Am Coll Cardiol 2000;36:970- 1062	ACC/AHA Guidelines for the Management of Patients with Unstable Angina and non ST-segment elevation MI	NA	Unstable Angina Post-Hospital Care	Indefinite	Aspirin 75-325 mg/day in the absence of contraindications (I/A) Diet and lipid lowering therapy if LDL > 130 mg/dL Statins (I/A)

Table 3B: Summary of Relevant Published Studies

First Author	Publication (Vol., Page)	Design/Treatment/ Number of Subjects	Age Range (Mean) Gender (%M/F) Race (%W/B/H)	Diagnosis and Criteria for Inclusion	Duration of Treatment	Results Therapy Class/Level of Evidence
Yusuf S	Secondary Prevention of Ischemic Cardiac Events In: Barton S, Editor. Clinical Evidence 4 th Issue London BMJ; 2000, p. 83-84	Review	NA	Established Coronary artery disease	Years	Aspirin reduces the risk of serious vascular events. 75 mg daily is as effective as higher doses. Lowering cholesterol with statins substantially reduces the risk of CV morbidity and mortality, without evidence of an increase in non-CV mortality

Table 3B: Summary of Relevant Published Studies

First Author	Publication (Vol., Page)	Design/Treatment/ Number of Subjects	Age Range (Mean) Gender (%M/F) Race (%W/B/H)	Diagnosis and Criteria for Inclusion	Duration of Treatment	Results Therapy Class/Level of Evidence
Bhatt D	J Am Coll Cardiol 2000; 35 (Suppl 1): 326A (Abstract)	A subgroup analysis of CAPRIE. 1460 hypercholesterolemic patients treated with statins out of 19,143 who completed the study. Randomized DB study of clopidogrel 75 mg or aspirin 325 mg once daily	NA	H/O vascular disease (PVD, MI or stroke)	1-3 years to an event	Benefit of anti-platelet therapy with clopidogrel appears to be independent and complementary to benefits provided by lipid lowering

An extensive literature survey of the major databases of worldwide medical and scientific publications was conducted by an experienced librarian.

The search terms employed were:

Aspirin, acetyl salicylic acid, salicylate and HMGCoA-reductase inhibitor, statin and all US marketed statins by generic name.

Date Searched:

- March 7, 2001

Databases searched:

- ADIS LMS Drug Alerts 1983-2001/Feb W2
- MEDLINE[®] 1966-2000/Dec W4 © format only 2000 Dialog Corp. Derwent Drug File 1983-2001/Mar W2[©] Derwent Info Ltd.
- EMBASE 1974-2001/Feb W4[©] Elsevier Science B.V.
- EMBASE Alert 2001/Feb W4[©] Elsevier Science B.V.
- Biosis Previews[®] 1993-2001/Feb W4[©] Biosis

Published reports of clinical trials describing concomitant administration of statins, particularly pravastatin, and aspirin were reviewed. The relevant studies are summarized in Table 3B. Literature reports of the various guidelines for the management of patients with cardiovascular disease are included. These guidelines provide compelling evidence of the widespread view that concomitant use of a statin with aspirin is the present standard of care for reduction of cardiovascular events in a secondary prevention population.

4 CLINICAL EFFICACY ANALYSIS

The individual effectiveness of treatment with pravastatin and aspirin in the prevention of subsequent cardiovascular endpoints has been well established independently. The objective of this report was to assess the combined effectiveness of pravastatin and aspirin. The following criteria were used to select the studies that were included in the meta-analysis for this report:

- a) all pravastatin studies with or without concomitant use of aspirin; or all aspirin studies that the sponsor had access to the data, with or without concomitant use of pravastatin; and
- b) among subjects with documented CAD, and with mortality and morbidity endpoints as either primary or secondary endpoints of the study.

After an intensive literature survey of all published trials to identify possible trials that satisfy the criteria mentioned above, the following five placebo-controlled studies were selected to be included in the meta-analysis: (1) LIPID; (2) CARE; (3) PLAC I; (4) PLAC II; and (5) REGRESS.

4.1 Statistical Methods

Overview of Clinical Studies

The LIPID study was a multi-center, double-blind, parallel group, randomized, placebo-controlled trial in men and women aged 31 to 75 years, with plasma Total-C levels between 4.0 and 7.0 mmol/L (155-271 mg/dL) after dietary intervention, and with documented occurrence of MI or UAP requiring hospitalization within 3 months to 3 years prior to randomization. Subjects were randomized in a 1:1 ratio to receive either pravastatin 40 mg QD or matching placebo. The primary objective of this study was to determine whether therapy with pravastatin reduced mortality due to CHD when administered over a five year period to subjects with a history of MI or UAP who also had cholesterol levels typical for patients with CHD.

The CARE study was a multi-center, randomized, double-blind, placebo-controlled, secondary prevention study in men and women aged 21 through 75 years with a

documented MI occurring 3 to 20 months prior to randomization with Total-C levels < 240 mg/dL and LDL-C levels between 115-174 mg/dL after dietary intervention. Subjects were randomized in a 1:1 ratio to receive either pravastatin 40 mg QD or matching placebo. The primary objective of this study was to investigate the effects of pravastatin in preventing recurrent coronary events in subjects who have suffered a MI and have normal cholesterol levels.

The PLAC I study was a randomized, double-blind, multi-center, placebo-controlled trial in men and women 51 to 74 years old. Subjects were randomized in a 1:1 ratio to receive either pravastatin 40 mg QD or matching placebo. The mean of two consecutive LDL-C values obtained at least two (but not more than four) weeks apart had to be ≥ 130 mg/dL and < 190 mg/dL after at least 1 month of the American Heart Association Phase I diet. The primary objectives of this study were to determine whether therapy with pravastatin could reverse or retard the progression of coronary atherosclerosis and reduce adverse cardiovascular sequelae in moderately hypercholesterolemic subjects with coronary artery disease. Secondary objectives included the reduction in incidences of cardiovascular events.

The PLAC II study was a randomized, double-blind, placebo-controlled trial in men and women < 75 years old. Subjects were randomized in a 1:1 ratio to receive either pravastatin 20 mg QD or matching placebo, which was then titrated to 40 mg QD if LDL-C > 110mg/dL. The primary objective of this study was to determine whether therapy with pravastatin, over a three year period, would retard the progression of atherosclerosis in the carotid arteries as assessed by B-mode ultrasonography. Secondary objectives included the reduction in incidences of cardiovascular events.

The REGRESS study was a randomized, double-blind, multi-center, placebo-controlled trial of men with plasma Total-C levels of 4-8 mmol/L (160-310 mg/dL) and at least one lesion $\geq 50\%$ diameter stenosis in a major coronary artery. Subjects were randomized in a 1:1 ratio to receive either pravastatin 40 mg QD or matching placebo. This study was designed to investigate the effects of lipid-lowering therapy with pravastatin on the progression of CAD and morbidity. Secondary objectives included the reduction in incidences of cardiovascular events.

For the above selected studies, aspirin use at baseline was obtained for all subjects. However, for all studies, information regarding dose level or the end date of dosing of concomitant use of aspirin was not collected with much rigor. For this analysis, therefore, it is assumed that if concomitant use of aspirin occurred at baseline then it also occurred throughout the duration of the study. This assumption is reasonable because all the patients in these trials had CAD and the benefits of aspirin in this population had been well established at the time of their entry into these studies. It is therefore safe to assume that concomitant therapy of aspirin at baseline is more likely due to vascular indications than to symptomatic pain relief. An examination of the frequency distribution of aspirin use at baseline and at any time post randomization indicated fewer differences, thereby confirming the assumption that the subjects were on aspirin for prevention of vascular events.

Data Analysis

The statistical analysis for the studies of CARE, LIPID, PLAC I, PLAC II and REGRESS assesses the efficacy profile by treatment group and baseline aspirin use (yes or no).

The data sets used for the analyses of safety include data from all subjects who received at least one dose of study medication (placebo or pravastatin). Concomitant use of aspirin throughout each study is defined as those subjects receiving aspirin concomitantly at baseline.

Choice of Endpoints

The following endpoints were chosen for the meta-analysis:

- 1) Composite endpoint of CHD death, non-fatal MI, myocardial revascularization procedures (CABG/PTCA), or ischemic stroke;
- 2) Composite endpoint of CHD death, non-fatal MI, or myocardial revascularization procedures (CABG/PTCA);
- 3) Composite endpoint of CHD death or non-fatal MI;
- 4) Composite endpoint of fatal or non-fatal MI; and
- 5) Ischemic stroke.

The composite endpoint of CHD death, nonfatal MI, myocardial revascularization procedures (CABG/PTCA) or ischemic stroke was chosen as this endpoint would have the most events and should provide the most robust analysis. It was also an endpoint commonly employed in previous analyses of pravastatin data. The composite endpoint of fatal and non-fatal MI and the endpoint of ischemic stroke were also chosen because these endpoints were derivable from the intersection of the pravastatin and aspirin labels.

Conventions for Censoring

The conventions used for the analysis was similar to the conventions used for the individual trials chosen in this meta-analysis. Subjects who remained event-free were censored at the earlier date of last visit or at the date of death (for those subjects whose death was unrelated to CHD for the composite endpoint that included CHD death). For those subjects who were lost-to-follow-up, but for whom the vital status was known, the scheduled date of the last visit was used for all the studies.

Baseline Comparability

Demographic and baseline characteristics were summarized by treatment group and baseline aspirin use. Key demographic variables and baseline characteristics included age, gender, body mass index, systolic blood pressure (SBP), diastolic blood pressure (DBP), LDL-C, Total-C, HDL-C, and TG.

Statistical Analyses

Three approaches were used to assess the combined effectiveness of pravastatin and aspirin. First, a traditional frequentist meta-analysis was performed. The second approach is based on the Bayesian meta-analysis which does not assume that all patients with the same covariates are exchangeable from the different studies. The third approach is also based on the Bayesian meta-analysis which also permits the hazards to vary over time. All the Bayesian meta-analysis models were performed by Prof. Donald A. Berry and Dr. Scott M. Berry, Berry Consultants, LLC, 1515 Holcombe Boulevard, Houston, Texas, 77030.

Traditional Frequentist Meta-analysis (Model 1)

Five secondary prevention studies of pravastatin (LIPID, CARE, PLAC I, PLAC II, and REGRESS) were pooled together. Cox proportional hazard models adjusting baseline prognostic factors were fit. The baseline prognostic factors included commonly known risk factors, namely, age, gender (male vs. female), smoking status (no vs. yes), ANYCAD (any previous cardiac event; no vs. yes), and baseline LDL-C, HDL-C, TG, DBP and SBP. Treatment and study are included in the model as well. The four treatments are: placebo alone, placebo with baseline aspirin use, pravastatin alone, and pravastatin with baseline aspirin use. The estimates of the relative risk between each pair of treatment groups and the 95% confidence intervals were also calculated. In addition, Cox models without adjusting baseline prognostic factors were also fit.

Bayesian Meta-analyses (Models 2 and 3)

There are two types of assumptions in the frequentist analysis described above that may not be appropriate. One is the assumption that all patients with the same covariates are exchangeable even though they took part in different studies. It is possible that patients in different studies would respond differently to treatment even if their covariates (including treatment) are the same. The other assumption is the possibility that hazards vary over time. For example, an ordinary Cox proportional hazards model may evince additive or independent effects of aspirin and pravastatin even though aspirin has all its benefit in one time interval of follow-up while pravastatin has all its benefit in another time interval.

A Bayesian meta-analysis would relax both of these types of assumptions. In both Bayesian Models 2 and 3, we incorporate the possibility of study effects in a hierarchical model. In Model 2 the standard Cox proportional hazards assumption that the hazard reduction over time is constant is made. In Model 3 we assume for changing hazards-and changing reduction in hazards due to treatment-over time. Namely, each of the follow-up years 1 through 5 were modeled separately. An additional advantage of Model 3 is that it gives rise to what is essentially five separate studies (one for each of the five years of follow-up) to address the durability of treatment effect and the possibility of treatment interaction.

Assessment of Proportionality Assumptions

The proportionality assumption was assessed only for the composite endpoint of mortality due to CHD, non-fatal MI, myocardial revascularization procedures (CABG/PTCA), or stroke.

Demographic Subgroup Analysis

The demographic subgroups studied for their effect on efficacy measures were: age category (< 65, ≥ 65) and gender (male, female). The analysis of efficacy within these subgroups was performed on the pooled data from the five placebo-controlled studies only for the composite endpoint of mortality due to CHD death, non-fatal MI, myocardial revascularization procedures (CABG/PTCA), or stroke. Due to overall relatively fewer events in the endpoints 2, 3, 4 and 5 the results of the subgroup analyses based on these endpoints may not be meaningful. No statistical tests were performed.

4.2 Demographic and Baseline Characteristics of the Subject Population

This section presents the baseline demography and general subject characteristics of the randomized subjects in the 5 studies included in this meta-analysis: LIPID, CARE, PLAC I, PLAC II, and REGRESS.

Of the 14,617 subjects randomized in the combined five studies, there were 5,888 (40.3%) subjects in the pravastatin group and 5,833 (39.9%) subjects in the placebo group who received aspirin at baseline and 1436 (9.8%) subjects in the pravastatin group and 1460 (10.0%) subjects in the placebo group who did not receive aspirin at baseline. There were no differences in the baseline characteristics between the treatment groups with or without aspirin use at baseline that were deemed clinically significant. Table 4.2A presents the demography and baseline characteristics that were common to all 5 studies.

Table 4.2A: Demographic and Baseline Characteristics: LIPID, CARE, PLAC I, PLAC II and REGRESS

	Pravastatin With ASA	Placebo With ASA	Pravastatin Without ASA	Placebo Without ASA
Mean age, years (SD)	59.5 (8.8)	59.8 (8.8)	60.3 (8.8)	60.4 (8.8)
N for Mean age	5888	5833	1436	1460
Gender				
Male [n (%)]	5028 (85.4)	4997 (8.57)	1198 (83.4)	1188 (81.4)
Female [n (%)]	860 (14.6)	836 (14.3)	238 (16.6)	272 (18.6)
Lipid levels (mg/dL)				
Mean Total-C (SD)	216.6 (29.0)	216.1 (28.1)	220.1 (30.0)	221.3 (29.9)
N for Total-C	5888	5833	1436	1460
Mean HDL-C (SD)	37.4 (8.9)	37.5 (9.1)	38.0 (9.4)	38.4 (10.1)
N for HDL-C	5884	5832	1436	1457
Mean LDL-C (SD)	147.6 (25.9)	147.5 (25.9)	150.6 (28.0)	151.9 (27.4)
N for LDL-C	5884	5832	1436	1456
Mean TG (SD)	160.1 (82.6)	157.3 (73.4)	162.0 (76.8)	157.4 (74.4)
N for TG	5888	5833	1436	1459
Mean blood pressure (mmHg)				
Systolic/Diastolic	132.0/79.7	132.2/79.7	133.2/80.3	134.2/80.6
N for Systolic/N for Diastolic	5887/5886	5830/5830	1436/1436	1459/1459
Diabetes				
Yes, N (%)	544 (9.2)	535 (9.2)	137 (9.5)	156 (10.7)
No, N (%)	5344 (90.8)	5298 (90.8)	1299 (90.5)	1304 (89.3)
Unknown, N (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypertension				
Yes, N (%)	2375 (40.3)	2395 (41.1)	595 (41.4)	639 (43.8)
No, N (%)	3513 (59.7)	3438 (58.9)	841 (58.6)	821 (56.2)
Unknown, (%)	1 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)
Any Cardiac Event				
Yes, N (%)	4699 (79.8)	4649 (79.7)	1008 (70.2)	1023 (70.1)
No, N (%)	1189 (20.2)	1183 (20.3)	428 (29.8)	435 (29.8)
Unknown, N (%)	0 (0.0)	1 (0.0)	0 (0.0)	2 (0.1)
Smoking Status				
Yes, N (%)	1415 (24.0)	1501 (25.7)	298 (20.8)	323 (22.1)
No, N (%)	4467 (75.9)	4327 (74.2)	1131 (78.8)	1130 (77.4)
Unknown, N (%)	6 (0.1)	5 (0.1)	7 (0.5)	7 (0.5)

Baseline Demographic and General Subject Characteristics - LIPID

Of the 9,014 subjects randomized in the LIPID study, there were 3,730 (41.4%) subjects in the pravastatin group and 3,698 (41.0%) subjects in the placebo group who received aspirin at baseline and 782 (8.7%) subjects in the pravastatin group and 804 (8.9%) subjects in the placebo group who did not receive aspirin at baseline. Antihypertensive medications were defined to include beta blockers, ACE inhibitors, calcium channel blockers, diuretics, and other medications that lower blood pressure. There were no differences in the baseline characteristics between the treatment groups with or without aspirin use at baseline that were deemed clinically significant. Table 4.2B presents the demography and baseline characteristics for the LIPID study.

Table 4.2B: Demography and Baseline Characteristics - LIPID

	Pravastatin With ASA N = 3,730	Placebo With ASA N = 3,698	Pravastatin Without ASA N = 782	Placebo Without ASA N = 804
Mean age (yrs) [SD]	60.5 (8.5)	60.7 (8.4)	61.5 (8.7)	62.1 (8.3)
Non-elderly (age < 65 yrs) [n (%)]	2,343 (62.8)	2,282 (61.7)	428 (54.7)	446 (55.5)
Elderly (age ≥ 65 yrs) [n (%)]	1,387 (37.2)	1,415 (38.3)	354 (45.3)	358 (44.5)
Gender				
Male [n (%)]	3,137 (84.1)	3,122 (84.4)	619 (79.2)	620 (77.1)
Female [n (%)]	593 (15.9)	576 (15.6)	163 (20.8)	184 (22.9)
Qualifying event				
UAP [n (%)]	1,275 (34.2)	1,271 (34.4)	358 (45.8)	356 (44.4)
MI [n (%)]	2,455 (65.8)	2,427 (65.6)	424 (54.2)	448 (55.7)
Years since qualifying event^a	0.9 (0.5, 1.8)	1.0 (0.5, 1.8)	1.3 (0.6, 2.2)	1.3 (0.6, 2.2)
Risk factors				
Smoker ^b				
Yes [n (%)]	760 (20.4)	735 (19.9)	154 (19.7)	176 (21.9)
No [n (%)]	2,970 (79.6)	2,963 (80.1)	628 (80.3)	628 (78.1)
History of systemic hypertension n (%) ^c	1,529 (41.0)	1,538 (41.6)	338 (43.2)	353 (43.9)
Diabetes mellitus [n (%)]	319 (8.6)	298 (8.1)	77 (9.8)	88 (10.9)
Obesity (body mass index > 30 kg/m ²) [n (%)]	652 (17.5)	623 (16.8)	171 (21.9)	165 (20.5)
Lipid levels (mg/dL)				
Mean Total-C (SD)	218.6 (32.0)	218.0 (30.9)	219.7 (32.8)	221.3 (32.0)
Mean HDL-C (SD)	36.7 (8.8)	36.8 (9.0)	37.4 (9.7)	38.2 (10.2)
Mean LDL-C (SD)	149.8 (28.3)	149.9 (28.5)	149.3 (30.5)	151.9 (29.1)
Mean TG (SD)	161.7 (92.2)	157.6 (79.0)	167.0 (86.1)	156.3 (79.0)
Mean Apolipoprotein A1 (SD)	131.6 (21.2)	131.8 (21.9)	133.2 (23.1)	134.8 (24.6)
Mean Apolipoprotein B (SD)	133.6 (26.1)	132.7 (24.4)	134.1 (25.2)	133.5 (25.4)
Mean seated blood pressure (mmHg)				
Systolic/Diastolic	133.5/80.3	133.9/80.3	135.5/81.3	136.0/81.1
Other cardiovascular disease				
Claudication [n (%)] ^c	341 (9.1)	360 (9.7)	97 (12.4)	107 (13.3)
Stroke [n (%)] ^c	121 (3.2)	156 (4.2)	50 (6.4)	42 (5.2)
Transient ischemic attack [n (%)] ^c	112 (3.0)	137 (3.7)	44 (5.6)	39 (4.9)
Angina grade (CCVS)				
No angina [n (%)]	2,408 (64.6)	2,379 (64.3)	450 (57.5)	449 (55.8)
No limitation (I) [n (%)]	1,042 (27.9)	1,016 (27.5)	271 (34.7)	251 (31.2)
Slight limitation (II) [n (%)]	259 (6.9)	269 (7.3)	55 (7.0)	90 (11.2)
Marked limitation (III) [n (%)]	14 (0.4)	25 (.07)	5 (0.6)	10 (1.2)
Extreme limitation/angina at rest (IV) [n (%)]	7 (0.2)	9 (0.2)	1 (0.1)	4 (0.5)

Table 4.2B: Demography and Baseline Characteristics - LIPID

	Pravastatin With ASA N = 3,730	Placebo With ASA N = 3,698	Pravastatin Without ASA N = 782	Placebo Without ASA N = 804
Dyspnea grade (NYHA)				
No dyspnea/no limitation (I) [n (%)]	1,941 (52.0)	1,951 (52.8)	359 (45.9)	338 (42.0)
Dyspnea on normal exertion (II) [n (%)]	1,453 (39.0)	1,448 (39.2)	316 (40.4)	350 (43.5)
Dyspnea on mild exertion (III) [n (%)]	335 (9.0)	295 (8.0)	106 (13.6)	116 (14.4)
Dyspnea at rest (IV) [n (%)]	1 (0.0)	4 (0.1)	1 (0.1)	0 (0.0)
Other treatment				
Beta blocker [n (%)]	1,801 (48.3)	1,841 (49.8)	282 (36.1)	309 (38.4)
Calcium antagonist [n (%)]	1,247 (33.4)	1,267 (34.3)	296 (37.9)	309 (38.4)
ACE inhibitor [n (%)]	546 (14.6)	557 (15.1)	174 (22.3)	156 (19.4)
Nitrates [n (%)]	1,086 (29.1)	1,050 (28.4)	260 (33.2)	281 (35.0)
Antihypertensive medication [n (%)]	2,787 (74.7)	2,845 (76.9)	589 (75.3)	601 (74.8)
Myocardial revascularization procedures				
PTCA only [n (%)]	455 (12.2)	420 (11.4)	47 (6.0)	66 (8.2)
CABG only [n (%)]	1,031 (27.6)	1,064 (28.8)	186 (23.8)	155 (19.3)
Both PTCA and CABG [n (%)]	127 (3.4)	129 (3.5)	8 (1.0)	4 (0.5)

Abbreviations: ACE: angiotensin converting enzyme; CABG: coronary artery bypass grafting; CCVS: Canadian Cardiovascular Society; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; NYHA: New York Heart Association; MI: myocardial infarction; PTCA: percutaneous transluminal coronary angioplasty; TG: triglycerides; Total-C: total cholesterol; UAP: unstable angina pectoris.

^a Median (25th, 75th percentile).

^b Smoking (Yes [includes ex-smoker if time since stopped is ≤ 1 yr or missing]/No [Non-smokers, and ex-smokers if time since stopped is > 1 yr]).

^c Baseline data are missing for some subjects.

Baseline Demographic and General Subject Characteristics – CARE

Of the 4,159 subjects randomized in CARE study, there were 1,742 (41.9%) subjects in the pravastatin group and 1,735 (41.7%) subjects in the placebo group who received aspirin at baseline and 339 (8.2%) subjects in the pravastatin group and 343 (8.2%) subjects in the placebo group who did not receive aspirin at baseline. Antihypertensive medications were defined to include beta blockers, ACE inhibitors, calcium channel blockers, diuretics, and other medications that lower blood pressure. There were no differences in the baseline characteristics between the treatment groups with or without

aspirin use at baseline that were deemed clinically significant. The baseline demographic and general subject characteristics for the CARE study are shown in Table 4.2C.

Table 4.2C: Demography and Baseline Characteristics - CARE

	Pravastatin With ASA N = 1,742	Placebo With ASA N=1,735	Pravastatin Without ASA N = 339	Placebo Without ASA N = 343
Mean age (yrs) [SD]	58.3 (9.4)	58.6 (9.3)	60.1 (8.9)	59.4 (9.2)
Gender				
Male [n (%)]	1,511 (86.7)	1,506 (86.8)	284 (83.8)	282 (82.2)
Female [n (%)]	231 (13.3)	229 (13.2)	55 (16.2)	61 (17.8)
Race				
White [n (%)]	1,631 (93.6)	1,616 (93.1)	303 (89.4)	301 (87.8)
Other [n (%)]	111 (6.4)	119 (6.9)	36 (10.6)	42 (12.2)
Risk factors				
Smoker ^a				
Yes [n (%)]	1,361 (78.1)	1,354 (78.1)	260 (76.7)	252 (73.5)
No [n (%)]	381 (21.9)	381 (22.0)	79 (23.3)	91 (26.5)
History of systemic hypertension [n (%)]	716 (41.1)	734 (42.3)	159 (46.9)	164 (47.8)
Diabetes mellitus [n (%)]	222 (12.7)	236 (13.6)	60 (17.7)	68 (19.8)
Obesity (Mean BMI kg/m ²)[SD] ^b	27.7 (4.3)	27.4 (4.4)	27.6 (5.6)	27.7 (4.2)
Lipid levels (mg/dL)				
Mean Total-C (SD)	208.5 (17.1)	208.5 (17.3)	209.0 (16.3)	208.1 (16.4)
Mean HDL-C (SD)	38.6 (8.9)	38.9 (9.0)	39.7 (9.0)	39.2 (10.1)
Mean LDL-C (SD)	138.7 (14.7)	138.6 (14.7)	139.0 (13.7)	137.9 (14.0)
Mean TG (SD)	156.5 (60.9)	155.3 (59.8)	152.1 (62.6)	154.9 (65.4)
Mean seated blood pressure (mmHg)				
Systolic/Diastolic	128.8/78.5	129.1/78.6	128.2/78.4	128.8/78.8
Mean Heart Rate [SD]	66.3 (10.9)	67.5 (11.2)	68.7 (10.2)	69.4 (11.7)
Mean Ejection Fraction [SD]	53.4 (11.6)	53.5 (12.1)	49.9 (12.4)	51.4 (12.9)

Table 4.2C: Demography and Baseline Characteristics - CARE

	Pravastatin With ASA N = 1,742	Placebo With ASA N=1,735	Pravastatin Without ASA N = 339	Placebo Without ASA N = 343
Other treatment				
Anticoagulant/Platelet [n (%)]	1,742 (100)	1,735 (100)	84 (24.8)	87 (25.4)
Beta blocker [n (%)]	736 (42.3)	688 (39.7)	122 (36.0)	123 (35.9)
Calcium antagonist [n (%)]	712 (40.9)	669 (38.6)	130 (38.3)	137 (39.9)
ACE inhibitor [n (%)]	242 (13.9)	229 (13.2)	68 (20.1)	62 (18.1)
Nitrates [n (%)]	545 (31.3)	563 (32.4)	129 (38.1)	127 (37.0)
Diuretics [n (%)]	180 (10.3)	174 (10.0)	66 (19.5)	61 (17.8)
Myocardial revascularization procedures				
Both PTCA and CABG [n (%)]	983 (56.4)	979 (56.4)	156 (46.0)	156 (45.5)

Abbreviations: ACE: angiotensin converting enzyme; CABG: coronary artery bypass grafting; CCVS: Canadian Cardiovascular Society; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; NYHA: New York Heart Association; BMI: Body Mass Index; PTCA: percutaneous transluminal coronary angioplasty; TG: triglycerides; Total-C: total cholesterol.

^a Smoking (Yes [includes ex-smokers]; No [Never smokers]).

^b Baseline data are missing for some subjects.

Baseline Demographic and General Subject Characteristics – REGRESSION Studies

Of the 1,444 subjects randomized in the REGRESSION studies (PLAC I, PLAC II, and REGRESS), there were 416 (28.8%) subjects in the pravastatin group and 400 (27.7%) subjects in the placebo group who received aspirin at baseline and 315 (21.8%) subjects in the pravastatin group and 313 (21.7%) subjects in the placebo group who did not receive aspirin at baseline. There were no differences in the baseline characteristics between the treatment groups with or without aspirin use at baseline that were deemed clinically significant. Table 4.2D presents the demography and baseline characteristics for the REGRESSION studies.

Table 4.2D: Demography and Baseline Characteristics – REGRESSION

	Pravastatin With ASA N = 416	Placebo With ASA N= 400	Pravastatin Without ASA N = 315	Placebo Without ASA N = 313
Mean age (yrs) [SD]	56.5 (8.2)	56.3 (8.6)	57.2 (8.2)	56.9 (8.3)
Gender				
Male [n (%)]	380 (91.3)	369 (92.3)	295 (93.7)	2860 (91.4)
Female [n (%)]	36 (8.7)	31 (7.8)	20 (6.3)	27 (8.6)
Prior MI [n (%)]	197 (47.4)	143 (45.7)	165 (52.4)	143 (45.7)
Risk factors				
Smoker				
Yes [n (%)]	356 (85.5)	333 (83.3)	273 (86.7)	260 (83.1)
No [n (%)]	54 (13.0)	62 (15.5)	35 (11.1)	46 (14.7)
History of systemic hypertension [n (%)]	130 (31.3)	122 (39.0)	98 (31.1)	122 (39.0)
Diabetes mellitus [n (%)]	3 (0.7)	1 (0.3)	0 (0.0)	1 (0.3)
Lipid levels (mg/dL)				
Mean Total-C (SD)	232.8 (30.4)	230.4 (29.5)	232.9 (29.2)	235.7 (29.2)
Mean HDL-C (SD)	38.3 (9.6)	37.4 (9.5)	37.6 (8.9)	38.1 (9.8)
Mean LDL-C (SD)	165.5 (26.6)	163.3 (26.7)	166.0 (26.0)	167.2 (25.9)
Mean seated blood pressure (mmHg)				
Diastolic	79.3	78.5	79.9	81.4
Myocardial revascularization procedures				
PTCA [n (%)]	95 (22.8)	99 (24.8)	51 (16.2)	47 (15.0)
CABG [n (%)]	20 (4.8)	31 (7.8)	28 (8.9)	30 (9.6)

4.3 Disposition

Temporary interruptions in study therapy were disregarded and treated as if subjects continued on study medication. LIPID was the only study that allowed subjects to drop-in, i.e., subjects would start open-label concomitant therapy with any lipid-lowering drug, prior to death or the last scheduled visit date. Tables 4.3A, 4.3B, 4.3C, 4.3D, and 4.3E present the subject disposition data for the LIPID, CARE, PLAC I, PLAC II, and REGRESS studies, respectively.

Table 4.3A: Subject Disposition - LIPID

	Pravastatin With ASA N = 3,730^a	Placebo With ASA N = 3,698^a	Pravastatin Without ASA N = 782^a	Placebo Without ASA N = 804^a
Discontinuation of study medication	851 (22.9%)	1,097 (29.7%)	233 (29.8%)	285 (35.3%)
Drop-in prior to final date ^b	211 (5.7%)	839 (22.7%)	26 (3.3%)	147 (18.3%)
Drop-in prior to discontinuation of study medication	88 (2.4%)	582 (15.7%)	10 (1.3%)	102 (12.7%)

Note: Drop-ins are those subjects who started open-label concomitant therapy with any lipid-lowering drug.

^a Number of subjects randomized.

^b Final Date is defined as the earliest of the date of death or date of the last scheduled visit.

Table 4.3B: Subject Disposition - CARE

Reason for Discontinuation	Pravastatin With ASA N = 1,742^a	Placebo With ASA N = 1,735^a	Pravastatin Without ASA N = 339^a	Placebo Without ASA N = 343^a
Adverse Event	74	97	18	24
Protocol Violation ^b	7	29	1	3
Subject's Request	65	134	17	46
Death	85	108	43	25
Other	8	33	3	7
Unknown ^c	51	64	18	15
Total	290	465	100	120

^a Number of subjects randomized.

^b Subjects who were prescribed concomitant medication not permitted by the protocol.

^c Subjects who did not formally withdraw study medication and who were off study medication more than 30 days prior to the final close-out visit were categorized as unknown.

Table 4.3C: Subject Disposition – PLAC I

Reason for Discontinuation	Pravastatin With ASA N = 139	Placebo With ASA N = 143	Pravastatin Without ASA N = 67	Placebo Without ASA N = 59
CABG	13	15	4	6
Adverse Event	9	13	3	1
Subject's Request	6	7	4	2
Lost to Follow-Up	6	6	3	3
Protocol Violation	6	4	5	0
Physician's Request	0	8	0	2
Death	1	3	1	1
Prohibited Medication	1	2	0	2
Poor Compliance	1	1	1	1
Total	43	59	21	18

Table 4.3D: Subject Disposition – PLAC II

Reason for Discontinuation	Pravastatin With ASA N = 32	Placebo With ASA N = 37	Pravastatin Without ASA N = 43	Placebo Without ASA N = 39
Adverse Event	2	6	5	8
Subject's Request	1	0	0	2
Death	0	1	1	0
Prohibited Medication	0	2	0	1
Total	3	9	6	11

Table 4.3E: Subject Disposition - REGRESS

Reason for Discontinuation	Pravastatin With ASA N = 245	Placebo With ASA N = 220	Pravastatin Without ASA N = 205	Placebo Without ASA N = 215
Adverse Event	9	3	6	6
Laboratory Abnormality	0	2	1	0
Compliance Problem	22	15	15	15
Lost to Follow-Up	2	0	0	1
Death	1	3	3	4
Subject's Request	1	0	0	1
Total	35	23	25	27

4.4 EFFICACY RESULTS

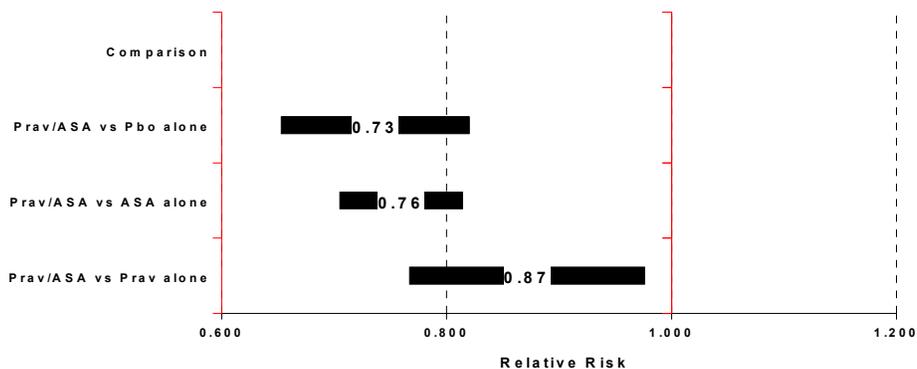
4.4.1 Traditional Frequentist Meta-analysis (Model 1)

Composite Outcome Measure - CHD Death, Non-fatal MI, CABG, PTCA, or Ischemic Stroke

As shown in Figure 4.4.1A, pravastatin with aspirin use significantly lowered the relative risk of the composite endpoint of CHD related death, non-fatal MI, CABG, PTCA, or stroke compared with the placebo group (with or without aspirin use) and compared with

the pravastatin group (without aspirin use). There were 3714 subjects who had either CHD related death, nonfatal MI, CABG, PTCA, or stroke as their first event subsequent to randomization: 22.3% of subjects in the pravastatin with aspirin group, 27.3% of subjects in the placebo without aspirin group, and 28.5% of subjects in the placebo with aspirin group, and 23.8% of subjects in the pravastatin without aspirin group. This represents a significant relative risk reductions of 26.8% in the pravastatin with aspirin group compared with placebo without aspirin treatment group; a significant relative risk reduction of 24.2% in the pravastatin with aspirin group compared with placebo with aspirin group; and a significant relative risk reduction of 13.5% in the pravastatin with aspirin group compared with pravastatin without aspirin group.

Figure 4.4.1A: Relative Risk for the Composite of CHD Death, Non-fatal MI, CABG, PTCA, or Ischemic Stroke, with 95 Percent CI



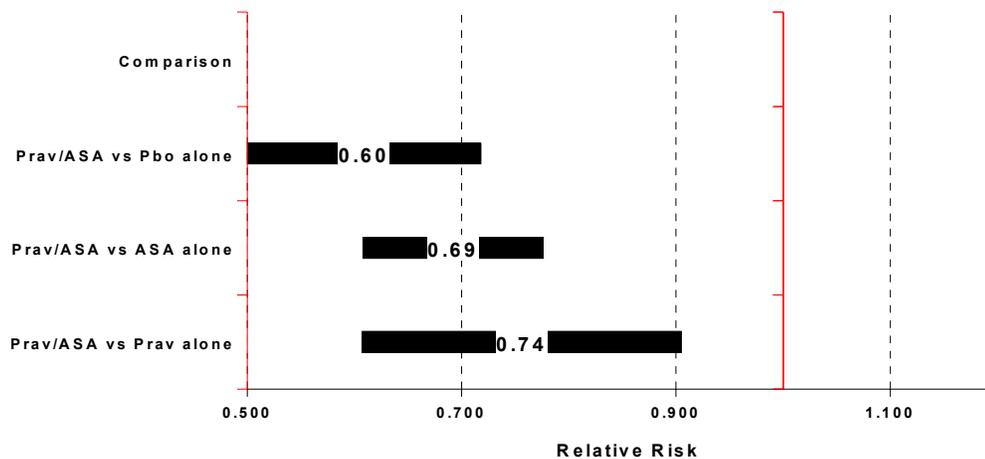
The results of the analyses including all-cause strokes were similar.

Composite Outcome Measure – Fatal or Non-fatal MI

As shown in Figure 4.4.1B, pravastatin with aspirin use significantly lowered the relative risk for fatal or non-fatal MI compared with the placebo group (with or without aspirin use) and the pravastatin group (without aspirin use). There were 1354 subjects who had either a fatal or a nonfatal MI as the first event subsequent to randomization; 7.6% of subjects in the pravastatin with aspirin group compared with 10.8% of subjects in the placebo without aspirin group, 10.7% of subjects in the placebo with aspirin group, and 8.7% of subjects in the pravastatin without aspirin group. This represents a significant

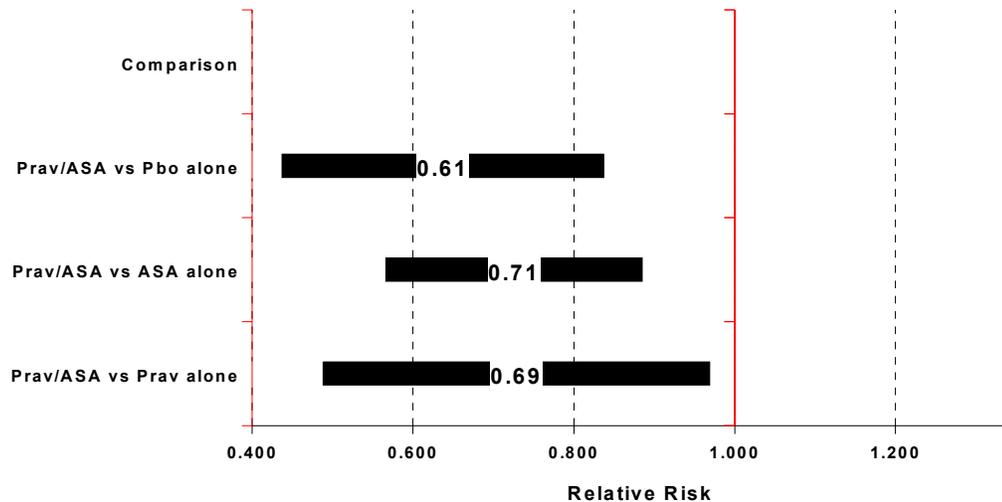
relative risk reduction of 40.2% in the pravastatin with aspirin group compared with placebo without aspirin group; a significant relative risk reduction of 31.3% in the pravastatin with aspirin group compared with placebo with aspirin group; and a significant relative risk reduction of 25.9% in the pravastatin with aspirin group compared with pravastatin without aspirin group.

Figure 4.4.1B: Relative Risk for the Composite of Fatal or Non-fatal MI with 95 Percent CI



Outcome Measure – Ischemic Stroke

As shown in Figure 4.4.1C, pravastatin with aspirin use significantly lowered the relative risk for stroke compared with the placebo group with or without aspirin use and with the pravastatin without aspirin group. There were 412 subjects who had a stroke; 2.3% of subjects in the pravastatin with aspirin group compared with 3.5% of subjects in the placebo without aspirin group, 3.1% of subjects in the placebo with aspirin group, and 3.1% of subjects in the pravastatin without aspirin group. This represents a significant relative risk reduction of 39.5% in the pravastatin with aspirin group compared with placebo without aspirin group; a significant relative risk reduction of 29.2% in the pravastatin with aspirin group compared with placebo with aspirin group; and a significant relative risk reduction of 31.2% in the pravastatin with aspirin group compared with pravastatin without aspirin group.

Figure 4.4.1C: Relative Risk for Stroke with 95 Percent CI

The results of the analyses including all-cause strokes were similar.

Composite Outcome Measure – CHD Death, Non-fatal MI, CABG, or PTCA

Pravastatin with aspirin use significantly lowered the relative risk for CHD death, non-fatal MI, CABG, or PTCA compared with the placebo with aspirin group (risk reduction = 24.4%) and with the placebo without aspirin group (risk reduction = 26.8%).

Composite Outcome Measure – CHD Death or Non-fatal MI

Pravastatin with aspirin use significantly lowered the relative risk for CHD death or non-fatal MI compared with the placebo with aspirin group (risk reduction = 30.7%), the placebo without aspirin group (risk reduction = 36.7%), and the pravastatin without aspirin group (risk reduction = 36.5%).

4.4.2 Bayesian Meta-analysis (Models 2 and 3)

Composite Outcome Measure – CHD Death, Non-fatal MI, CABG, PTCA, or Ischemic Stroke

Model 2

This section presents the results of the Bayesian hierarchical Cox proportional hazards model for all events (CHD, non-fatal MI, CABG, PTCA, or ischemic stroke).

From Table 4.4.2A, the probability that pravastatin and aspirin use was better than placebo alone is approximately 1 in reducing the incidence of the composite endpoint of mortality due to CHD, non-fatal MI, CABG, PTCA, or ischemic stroke. As shown in Figure 4.4.2A, pravastatin with aspirin use lowered the relative risk for CHD death, non-fatal MI, CABG, PTCA, or ischemic stroke compared with the placebo group with or without aspirin use and pravastatin only without aspirin use. The lack of statistically significant risk reductions in the pravastatin alone (pravastatin without aspirin) or the aspirin alone (placebo with aspirin) groups must be interpreted with caution because of the following reasons – (a) relatively fewer subjects in each group and (b) since aspirin was not a randomized drug in any of the studies included in the meta-analysis of this report unlike the meta-analysis by the Antiplatelet Trialists Collaboration.

As shown in Figure 4.4.2A, the pravastatin with aspirin group had consistently lower cumulative hazards of CHD death, non-fatal MI, CABG, PTCA or ischemic stroke events than each of the other three groups of pravastatin without aspirin use, placebo with aspirin use and placebo without aspirin use. Pravastatin without aspirin use had consistently lower cumulative hazards of CHD death, non-fatal MI, CABG, PTCA or ischemic stroke events than placebo with and placebo without aspirin use. While placebo with and placebo without aspirin use had similar cumulative hazards of CHD death, non-fatal MI, CABG, PTCA or ischemic stroke events.

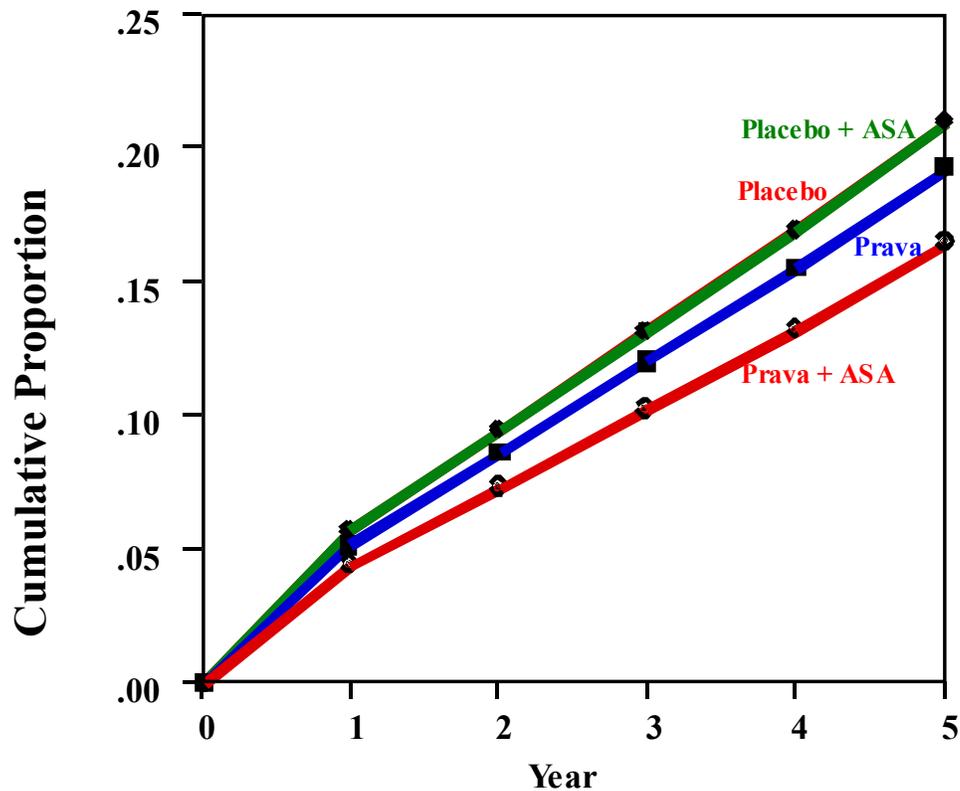
Table 4.4.2A: Composite Endpoint – CHD Death, Non-fatal MI, CABG, PTCA, or Ischemic Stroke

Posterior Probability that Row Variable is Better than Column Variable

Treatment Group Comparisons	Placebo Without Aspirin	Pravastatin Without Aspirin	Placebo With Aspirin	Pravastatin With Aspirin
Pravastatin With Aspirin	1	.999	1	--

It can therefore be concluded with certainty (> 0.99) that pravastatin/aspirin is better than either pravastatin or aspirin alone.

Figure 4.4.2A: Cumulative Proportion of Events (CHD Death, Non-fatal MI, CABG, PTCA, or Ischemic Stroke)



Model 3

This section presents the results of the Bayesian Extended Cox model with treatment-dependent time-varying hazards for all cardiovascular events (composite endpoint of CHD deaths, non-fatal MI, CABG, PTCA or ischemic stroke). In this model, hazards for a particular year are calculated by eliminating all events that occurred earlier in time and therefore, considers only those patients still at risk.

As shown in Figures 4.4.2B and 4.4.2C, pravastatin with aspirin use lowered the relative risk of the composite endpoint of CHD death, non-fatal MI, CABG, PTCA, or ischemic stroke compared to the placebo group with or without aspirin use and pravastatin only without aspirin use. Figure 4.4.2B clearly shows the durability of the combined effect of pravastatin with aspirin group over the entire time period being significantly better than pravastatin alone (pravastatin without aspirin) or aspirin alone (placebo with aspirin). The lack of significant risk reductions in the aspirin alone (placebo with aspirin) groups must be interpreted with caution.

Figure 4.4.2B: Hazard of Events (CHD Death, Non-fatal MI, CABG, PTCA, or Ischemic Stroke)

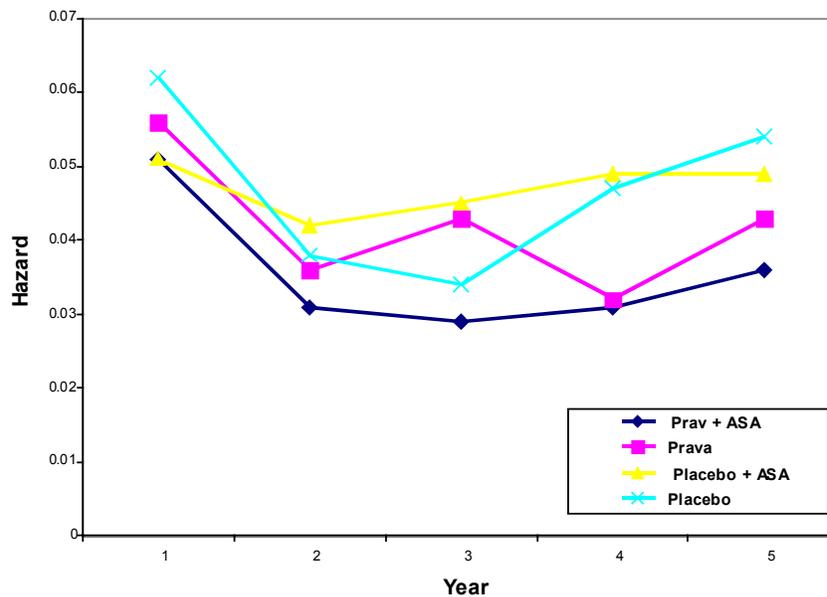
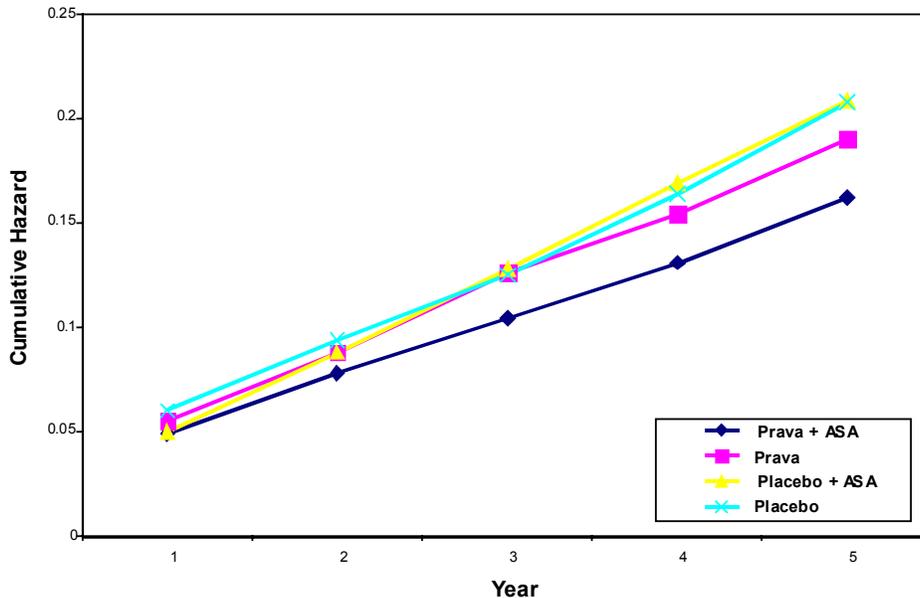


Figure 4.4.2C: Cumulative Hazard of Events (CHD Death, Non-fatal MI, CABG, PTCA, or Ischemic Stroke)



The results of the analyses including all-cause strokes were similar.

Composite Outcome Measure – Fatal or Non-fatal MI

Model 2

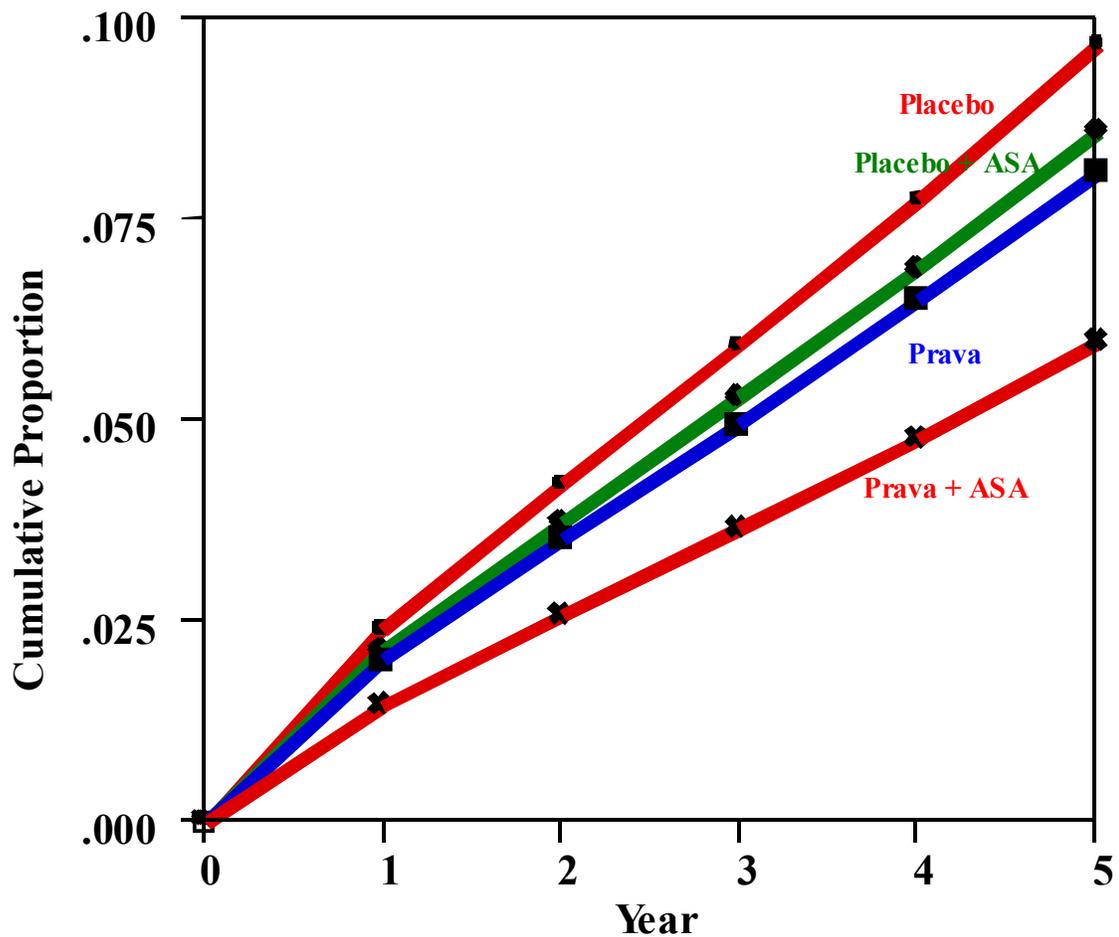
From Table 4.4.2B, the probability that pravastatin and aspirin use was better than placebo alone is approximately 1 in reducing the incidence of the composite endpoint of mortality due to fatal or non-fatal MI. As shown in Figure 4.4.2D, pravastatin with aspirin use lowered the relative risk of fatal or non-fatal MI compared with the placebo group with or without aspirin use and pravastatin only without aspirin use. The lack of significant risk reductions in the pravastatin alone (pravastatin without aspirin) or the aspirin alone (placebo with aspirin) groups must be interpreted with caution. As shown in Figure 4.4.2D the pravastatin with aspirin group had consistently lower cumulative hazards of fatal and nonfatal MI events than each of the other three groups of pravastatin without aspirin use, placebo with aspirin use and placebo without aspirin use. Pravastatin without aspirin use and placebo with aspirin use had similar cumulative hazards. Also, pravastatin without aspirin use and placebo with aspirin use had lower hazards fatal and nonfatal MI events than placebo without aspirin use.

Table 4.4.2B: Composite Endpoint – Fatal and Non-fatal MI
Posterior Probability that Row Variable is Better than Column Variable

Treatment Group Comparisons	Placebo Without Aspirin	Pravastatin Without Aspirin	Placebo With Aspirin	Pravastatin With Aspirin
Pravastatin With Aspirin	1	.998	1	--

It therefore can be concluded with certainty (> 0.99) that pravastatin/aspirin is better than either pravastatin or aspirin alone.

Figure 4.4.2D: Cumulative Proportion of Events (Fatal and Non-fatal MI)



Model 3

This section presents the results of the Bayesian Extended Cox model with treatment-dependent time-varying hazards for all cardiovascular events (composite endpoint of fatal or non-fatal MI). In this model, hazards for a particular year are calculated by eliminating all events that occurred earlier in time and therefore, considers only those patients still at risk.

As shown in Figures 4.4.2E and 4.4.2F, pravastatin with aspirin use lowered the relative risk for fatal or non fatal MI compared to the placebo group with or without aspirin use and pravastatin only without aspirin use. Figure 4.4.2E clearly shows the durability of the combined effect of pravastatin with aspirin group over the entire time period being better than pravastatin alone (pravastatin without aspirin) or aspirin alone (placebo with aspirin).

Figure 4.4.2E: Hazard of Fatal and Non-fatal MI

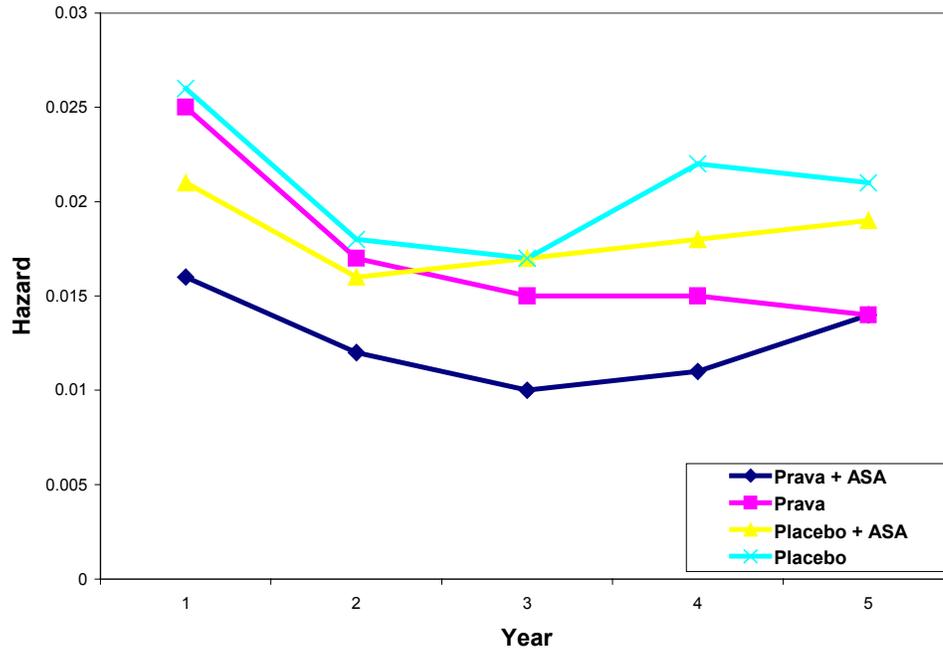
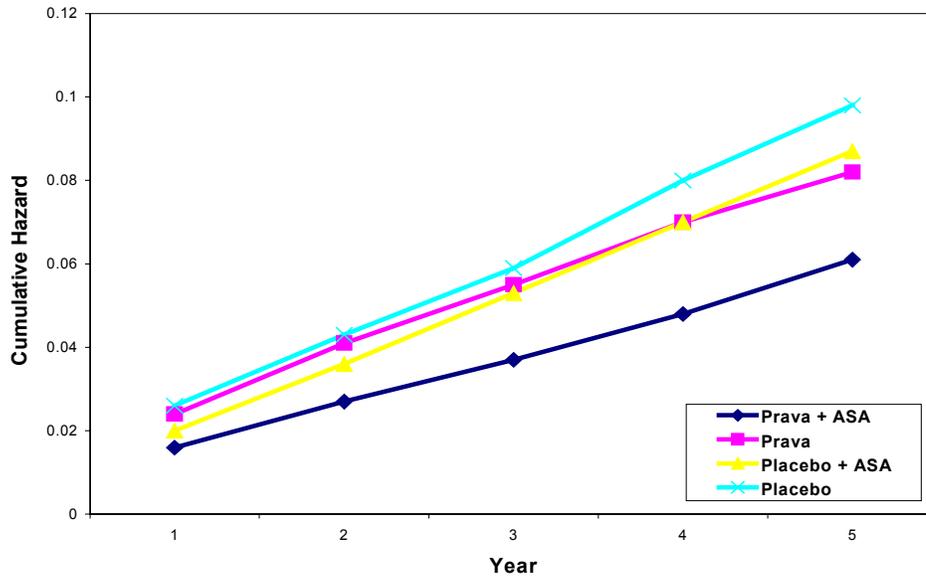


Figure 4.4.2F: Cumulative Hazard of Fatal and Non-fatal MI

Outcome Measure – Ischemic Stroke

Model 2:

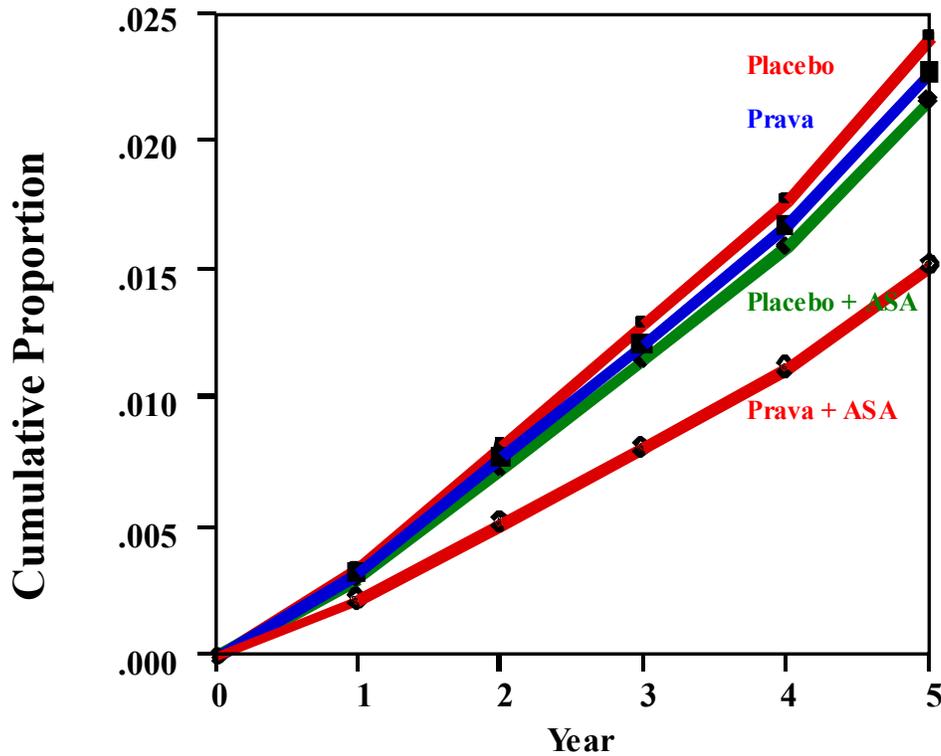
From Table 4.4.2C, the probability that pravastatin and aspirin use was better than placebo alone is approximately 1 in reducing the incidence of the composite endpoint of stroke. As shown in Figure 4.4.2G, pravastatin with aspirin use lowered the relative risk of stroke compared with the placebo group with or without aspirin use and pravastatin without aspirin use. The lack of significant risk reductions in the pravastatin alone (pravastatin without aspirin) or the aspirin alone (placebo with aspirin) groups must be interpreted with caution. As shown in Figure 4.4.2G, the pravastatin with aspirin group had consistently lower cumulative hazards of stroke events than each of the other three groups of pravastatin without aspirin use, placebo with aspirin use and placebo without aspirin use. The remaining three groups of pravastatin without aspirin use, placebo with aspirin use and placebo without aspirin use had similar cumulative hazards of stroke events.

Table 4.4.2C: Composite Endpoint – Ischemic Stroke
Posterior Probability that Row Variable is Better than Column Variable

Treatment Group Comparisons	Placebo Without Aspirin	Pravastatin Without Aspirin	Placebo With Aspirin	Pravastatin With Aspirin
Pravastatin With Aspirin	.999	.993	.999	--

It can therefore be concluded with certainty (> 0.99) that pravastatin/aspirin is better than either pravastatin or aspirin alone.

Figure 4.4.2G: Cumulative Proportion of Events (Ischemic Stroke only)



Model 3:

This section presents the results of the Bayesian Extended Cox model with treatment-dependent time-varying hazards stroke events. In this model (Model 3),

hazards for a particular year are calculated by eliminating all events that occurred earlier in time and therefore, considers only those patients still at risk.

Pravastatin with aspirin use lowered the relative risk for stroke compared to the placebo group with or without aspirin use and pravastatin only without aspirin use. Due to the fact that there are few events, this effect is less clear in a year to year analysis.

Composite Outcome Measure – CHD Death, Non-fatal MI, CABG, or PTCA

Model 2:

From Table 4.4.2D, the probability that pravastatin and aspirin use was better than placebo alone is approximately 1 in reducing the incidence of the composite endpoint of mortality due to CHD, non-fatal MI, CABG or PTCA. As shown in Table 4.4.2D, pravastatin with aspirin use lowered the relative risk for CHD, non-fatal MI, CABG or PTCA, compared with placebo with or without aspirin use as well as pravastatin without aspirin use.

Table 4.4.2D: Composite Endpoint – CHD Death, Non-fatal MI, CABG, or PTCA

Posterior Probability that Row Variable is Better than Column Variable

Treatment Group Comparisons	Placebo Without Aspirin	Pravastatin Without Aspirin	Placebo With Aspirin	Pravastatin With Aspirin
Pravastatin With Aspirin	1	.990	1	--

It therefore can be concluded with certainty (> 0.99) that pravastatin/aspirin is better than either pravastatin or aspirin alone.

Composite Outcome Measure – CHD Death and Non-fatal MI

As shown in Table 4.4.2E, pravastatin with aspirin use lowered the relative risk for CHD death and non-fatal MI compared with the placebo group (with or without aspirin use) and with the pravastatin without aspirin group.

**Table 4.4.2E: Composite Endpoint – CHD Death and Non-fatal MI
Posterior Probability that Row Variable is Better than Column Variable**

Treatment Group Comparisons	Placebo Without Aspirin	Pravastatin Without Aspirin	Placebo With Aspirin	Pravastatin With Aspirin
Pravastatin With Aspirin	1	1	1	--

It therefore can be concluded with certainty (> 0.99) that pravastatin/aspirin is better than either pravastatin or aspirin alone.

4.4.3 Demographic Subgroup Analysis

Gender

Risk reductions are summarized by treatment group and gender. Pravastatin with aspirin use consistently lowered the relative risk for CHD death, non-fatal MI, CABG, PTCA, or stroke compared with the placebo without aspirin group for both males and females, with risk reductions of 26.2% and 31.9%, respectively. Pravastatin with aspirin use also consistently lowered the relative risk compared with the placebo with aspirin group and the pravastatin without aspirin group for both males and females with risk reductions of 23.7% and 26.7%, respectively. Overall, there was no significant difference between males and females. Similar results were observed from Bayesian meta-analysis.

Age

Risk reductions are summarized by treatment group and age category. Pravastatin with aspirin use consistently lowered the relative risk for CHD death, non-fatal MI, CABG, PTCA, or ischemic stroke compared with the placebo without aspirin group for both the non-elderly (< 65 years) and elderly ($65 +$ years) with risk reductions of 19.6% and 36.4%, respectively. Pravastatin with aspirin use consistently lowered the relative risk compared with the placebo with aspirin group for both the non-elderly and elderly with risk reductions of 20.1% and 30.7%, respectively. However, for non-elderly subjects, pravastatin with aspirin use lowered the relative risk compared with the pravastatin without aspirin group with a 2.1% risk reduction; the risk reduction is 27.4% for the elderly subjects. Small risk reduction in the non-elderly subjects may be due to the small

number of events and to the fact that there had been no prospective randomization to either age or aspirin usage. Similar results were observed from Bayesian meta-analysis.

5 SUMMARY OF SAFETY

5.1 Introduction

The objective of this integrated summary of safety, is to assess the safety of pravastatin and aspirin when given concomitantly, using existing databases from 5 pravastatin secondary prevention studies (LIPID, CARE, PLAC I, PLAC II, and REGRESS). Safety analyses include the following:

- Extent of exposure
- Demographic and baseline characteristics of the study population
- Clinical adverse events (AEs), including most common AEs, and discontinuations due to AEs
- Deaths and other Serious Adverse Events (SAEs)
- Clinical Laboratory Analyses
- Safety in selected subgroup populations (age and gender)

5.2 Overview of Secondary Prevention Clinical Studies

A total of 14,617 subjects were treated in 5 pravastatin secondary prevention studies. Concomitant aspirin use status was assigned retrospectively based on the subject's aspirin use at baseline. It was assumed that if aspirin use was documented at baseline, it continued throughout the duration of the study. An overview of the subjects treated with pravastatin or placebo with and without aspirin is presented in Table 5.2.

Table 5.2: Overview of Subjects Treated with Pravastatin or Placebo, Stratified by Baseline Aspirin Use in the Secondary Prevention Clinical Studies

Study Protocol No.	Number of Subjects				Total Subjects N = 14,617
	Pravastatin N = 7,324		Placebo N = 7,293		
	Aspirin N = 5,888	No Aspirin N = 1,436	Aspirin N = 5,833	No Aspirin N = 1,460	
LIPID	3,730	782	3,698	804	9,014
CARE	1,742	339	1,735	343	4,159
REGRESS	245	205	220	215	885
PLAC I	139	67	143	59	408
PLAC II	32	43	37	39	151

5.3 Safety Assessment

This section describes safety data collection and analyses for the 5 pravastatin secondary prevention studies.

The analysis of safety includes data from all subjects who received at least one dose of pravastatin or placebo during the secondary prevention studies. Subjects were categorized, retrospectively, into one of 4 treatment regimens: pravastatin with aspirin, pravastatin without aspirin, placebo with aspirin and placebo without aspirin. Concomitant aspirin use status was determined based on a subject's use of aspirin at baseline. In the 5 secondary prevention studies, data documenting concomitant aspirin use were collected at baseline, but not appropriately collected throughout the course of these studies (i.e., no information was recorded regarding dose level or duration of aspirin use). Due to this fact, it is assumed that if concomitant use of aspirin occurred at baseline it continued throughout the duration of the study. Likewise, if there was no use of aspirin at baseline it was presumed that there was no chronic use of aspirin throughout the study. No other modifications to the safety data were made.

For the purposes of safety assessment and presentation, safety data from the 5 secondary prevention studies are presented in 4 separate groups as shown below.

Table 5.3: Study Group of Secondary Prevention Clinical Trials for Safety Analyses and Presentation

Study	Data Presentation
LIPID	Not integrated
CARE	Not integrated
REGRESS	Not integrated
PLAC I	Integrated
PLAC II	Integrated

Because of differences in AE collection and analysis, the LIPID, CARE, and REGRESS studies are presented separately; data from the two regression studies, PLAC I and PLAC II, are integrated.

No statistical tests were performed on any safety variable among or within treatment groups.

5.3.1 Adverse Event Data Collection

Clinical adverse events (AEs) were collected as specified in the individual protocols of the 5 secondary prevention studies. For details regarding AE collection and reporting, see the individual final study reports for the secondary prevention studies.

Generally, subjects were monitored for the appearance of AEs and laboratory test abnormalities during the secondary prevention studies. In these studies, an AE was any illness, sign, symptom, or clinically significant laboratory test abnormality that appeared or worsened during the course of the study, regardless of the investigator's attribution of the event to study treatment. Investigators were instructed to document, as appropriate, the occurrence of AEs, both those volunteered by the subjects and those elicited by general questioning and examination of the subjects. Investigators were also asked to record their opinion regarding the relationship of the AE to study treatment. For AEs deemed by the investigator to be unrelated to the study drug, the investigator was asked to report the underlying cause of the AE.

Adverse events were classified as either nonserious or serious. A serious AE (SAE) was defined as an AE that met any of the following criteria: fatal, life-threatening, permanently disabling, resulted in inpatient hospitalization or prolonged hospitalization, congenital anomaly, cancer, or overdose. Investigators were required to promptly report all SAEs to the Sponsor.

In the LIPID study, the case report form (CRF) was not designed to thoroughly collect AEs that were not serious or that were judged unrelated to the study drug. Hence, only SAEs and AEs suspected of being related to the study drug (ADEs) are presented for LIPID in the ISS.

5.4 Clinical Laboratory Analysis

This section describes laboratory data collection and analyses for the 5 secondary prevention studies.

5.4.1 Laboratory Data Collection

Laboratory safety assessments (hematology, blood chemistry, and urinalysis) were performed at various time intervals as specified within the individual study protocols. The specific analytes collected for laboratory safety assessments are identified in the individual final study reports.

5.4.2 Laboratory Data Analysis

In this summary of safety, laboratory data analysis is limited to marked abnormalities (MA). Marked abnormalities were values that met pre-specified (Sponsor-defined) criteria for identifying potentially clinically important changes that may have occurred during study treatment. Subjects were included in the MA analysis if they received at least one dose of study medication, had a baseline measurement and at least one laboratory value during the study. Because not all subjects had laboratory determinations for all analytes at all visits, the sample size may vary from analyte to analyte.

5.5 Extent of Exposure

Extent of exposure is defined as the number of days from the first dose to the last dose of study medication, regardless of interruptions.

Overall a total of 9,014 subjects were exposed to pravastatin or placebo in the LIPID study. Table 5.5A presents the overall extent of exposure by baseline aspirin use in the LIPID study.

Table 5.5A: Extent of Exposure to Pravastatin or Placebo Stratified by Baseline Aspirin Use in the LIPID Study

Duration of Treatment	Treatment Regimens			
	Pravastatin		Placebo	
	Aspirin N (%)	No Aspirin N (%)	Aspirin N (%)	No Aspirin N (%)
< 1 Year	236 (6.3)	88 (11.3)	283 (7.7)	98 (12.1)
1 - 2 years	150 (4.0)	37 (4.7)	175 (4.7)	62 (7.7)
> 2 - 3 years	104 (2.8)	25 (3.2)	171 (4.6)	37 (4.6)
> 3 - 4 years	142 (3.8)	33 (4.2)	168 (4.5)	34 (4.2)
> 4 - 5 years	409 (11.0)	90 (11.5)	459 (12.4)	80 (10.0)
> 5 - 6 years	1,551 (41.6)	259 (33.1)	1,459 (39.5)	270 (33.6)
> 6 - 7 years	1,128 (30.2)	245 (31.3)	973 (26.3)	220 (27.4)
> 7 years	10 (0.3)	5 (0.6)	10 (0.3)	3 (0.4)
Mean Years of Exposure	5.2	4.9	5.0	4.6
Total Subjects	3,730	782	3,698	804

In LIPID the prava/ASA group had the highest mean extent of exposure to study drug while the placebo-alone group had the lowest exposure.

In the CARE study, a total of 4,159 subjects were exposed to pravastatin or placebo. Table 5.5B presents the extent of exposure to study medication stratified by baseline aspirin use.

Table 5.5B: Extent of Exposure to Pravastatin or Placebo Stratified by Baseline Aspirin Use in the CARE Study

Duration of Treatment	Treatment Regimens			
	Pravastatin		Placebo	
	Aspirin N (%)	No Aspirin N (%)	Aspirin N (%)	No Aspirin N (%)
< 1 Year	63 (3.6)	22 (6.5)	91 (5.2)	30 (8.7)
1 - 2 years	48 (2.8)	22 (6.5)	84 (4.8)	24 (7.0)
> 2 - 3 years	43 (2.3)	16 (4.7)	91 (5.2)	20 (5.8)
> 3 - 4 years	57 (3.3)	20 (5.9)	95 (5.5)	26 (7.6)
> 4 - 5 years	797 (45.8)	120 (35.4)	738 (42.5)	111 (32.4)
> 5 - 6 years	711 (40.8)	131 (38.6)	613 (35.3)	128 (37.3)
> 6	23 (1.3)	8 (2.4)	23 (1.3)	4 (1.2)
Mean Years of Exposure	4.6	4.3	4.3	4.2
Total Subjects	1,742	339	1,735	343

In CARE, and in LIPID, the prava/ASA group had the highest mean extent of exposure and the placebo-alone group the lowest.

In the REGRESS study, a total of 885 subjects were treated with pravastatin or placebo. Table 5.5C presents the extent of exposure stratified by baseline aspirin use.

Table 5.5C: Extent of Exposure to Pravastatin or Placebo Stratified by Baseline Aspirin Use in the REGRESS Study

Duration of Treatment	Treatment Regimens			
	Pravastatin		Placebo	
	Aspirin N (%)	No Aspirin N (%)	Aspirin N (%)	No Aspirin N (%)
0-25 weeks	11 (4.5)	10 (4.9)	8 (3.6)	11 (5.1)
26-50 weeks	10 (4.1)	6 (2.9)	3 (1.4)	6 (2.8)
51-75 weeks	4 (1.6)	3 (1.5)	4 (1.8)	2 (0.9)
76-100 weeks	11 (4.5)	7 (3.4)	10 (4.5)	16 (7.4)
101-125 weeks	209 (85.3)	178 (86.8)	195 (88.6)	179 (83.3)
> 125 weeks	0	1 (0.5)	0	1 (0.5)
Mean Days of Exposure	683	691	698	687
Total Subjects	245	205	220	215

In REGRESS, in contrast to LIPID and CARE, it was the placebo/ASA group who had the highest mean extent of exposure and the prava/ASA the lowest.

A total of 559 subjects were randomized to pravastatin or placebo in the PLAC studies. Table 5.5D presents the extent of exposure, stratified by aspirin use.

Table 5.5D: Extent of Exposure to Pravastatin or Placebo Stratified by Baseline Aspirin Use in the PLAC I and PLAC II Studies

Duration of Treatment	Treatment Regimens			
	Pravastatin		Placebo	
	Aspirin N (%)	No Aspirin N (%)	Aspirin N (%)	No Aspirin N (%)
0-30 weeks	16 (9.4)	8 (7.3)	21 (11.7)	10 (10.2)
31-60 weeks	11 (6.4)	6 (5.5)	13 (7.2)	10 (10.2)
61-90 weeks	5 (2.9)	2 (1.8)	12 (6.7)	1 (1.0)
91-120 weeks	6 (3.5)	2 (1.8)	8 (4.4)	3 (3.1)
121-150 weeks	42 (24.6)	22 (20.0)	47 (26.1)	24 (24.5)
> 150 weeks	91 (53.3)	70 (63.6)	79 (43.9)	50 (51.0)
Mean Days of Exposure	906	957	850	889
Total Subjects	171	110	180	98

Note: Table includes PLAC I and PLAC II

In the integrated PLAC studies it was the prava-alone group that had the highest extent of exposure and the placebo/ASA group the lowest.

5.5.1 Extent of Exposure Conclusion

In the LIPID and CARE studies there was a trend towards a higher extent of exposure in the prava/ASA group although this was less clear in the smaller studies. The increased extent of exposure is consistent with a mortality benefit and an increased tolerability and safety of prava/ASA.

5.6 Summary of Demographic and Baseline Characteristics of Study Population and Disposition of Subjects

The baseline characteristics of the subjects in the 4 treatment groups across all the studies were well balanced. However, the non-aspirin users were on average slightly older than the aspirin users in all the studies, and were more likely to be hypertensive.

5.7 Clinical Adverse Events

All subjects who received at least one dose of study medication are included in the analyses of clinical AEs.

An overview of the clinical AE profile in the LIPID study is presented in Table 5.7A.

Table 5.7A: Overview of Clinical ADEs, Deaths, SAEs, and Discontinuations in LIPID by Treatment Regimen Stratified by Baseline Aspirin Use

	Number (%) of Subjects			
	Pravastatin		Placebo	
	With Aspirin N = 3730	No Aspirin N = 782	With Aspirin N = 3698	No Aspirin N = 804
ADEs ^a	178 (4.8)	49 (6.3)	156 (4.2)	30 (3.7)
Deaths	375 (10.1)	123 (15.7)	491 (13.3)	142 (17.7)
SAEs ^a	2629 (70.5)	587 (75.1)	2674 (72.3)	598 (74.4)
Discontinuations Due to ADEs or SAEs	378 (10.1)	105 (13.4)	448 (12.1)	126 (15.7)

^a In LIPID only ADEs and SAEs were collected

Table 5.7B shows the breakdown of the ADEs in LIPID by body system.

Table 5.7B: Number (Percent) of Subjects with Treatment-Emergent Clinical ADEs in LIPID, by Body System and Treatment Regimen Stratified by Baseline Aspirin Use

Body System	Number (%) of Subjects			
	Pravastatin		Placebo	
	With Aspirin N = 3730	No Aspirin N = 782	With Aspirin N = 3698	No Aspirin N = 804
Cardiac	0	0	6 (0.2)	1 (0.1)
Complications of medical care	2 (0.1)	0	3 (0.1)	0
Dermatologic	34 (0.9)	14 (1.8)	35 (0.9)	7 (0.9)
Endocrine/Metabolic	8 (0.2)	1 (0.1)	3 (0.1)	0
Gastrointestinal	31 (0.8)	10 (1.3)	26 (0.7)	8 (1.0)
Hematologic	3 (0.1)	1 (0.1)	2 (0.1)	0
Hepatic/biliary	33 (0.9)	7 (0.9)	20 (0.5)	4 (0.5)
Infections	1 (0.0)	1 (0.1)	1 (0.0)	1 (0.1)
Malignancy	0	0	1 (0.0)	0
Musculoskeletal	53 (1.4)	7 (0.9)	48 (1.3)	8 (1.0)
Nervous System	31 (0.8)	10 (1.3)	31 (0.8)	4 (0.5)
Renal/genitourinary	4 (0.1)	0	8 (0.2)	0
Respiratory	2 (0.1)	1 (0.1)	5 (0.1)	1 (0.1)
Special Senses	5 (0.1)	3 (0.4)	4 (0.1)	1 (0.1)
Vascular (non-cardiac)	2 (0.1)	0	2 (0.1)	1 (0.1)
<i>Overall Total ADEs</i>	261	68	233	47
<i>Overall Total Subjects</i>	178 (4.8)	49 (6.3)	156 (4.2)	30 (3.7)

In LIPID the highest percentage of subjects was in the prava-alone group and the lowest in the placebo-alone group.

An overview of the clinical AE profile in the CARE study is presented in Table 5.7C.

Table 5.7C: Overview of Treatment Emergent Clinical Adverse Events on Study Therapy in CARE by Treatment Regimen Stratified by Baseline Aspirin Use

	Number (%) of Subjects			
	Pravastatin		Placebo	
	With Aspirin N = 1742	No Aspirin N = 339	With Aspirin N = 1735	No Aspirin N = 343
AEs	1719 (98.7)	332 (97.9)	1697 (97.8)	333 (97.1)
ADEs ^a	1122 (64.4)	225 (66.4)	1094 (63.1)	205 (59.8)
Deaths ^{a,b}	85 (4.9)	43 (12.7)	108 (6.2)	25 (7.3)
SAEs ^a	1015 (58.3)	218 (64.3)	1051 (60.6)	222 (64.7)
Discontinuations Due to AEs	74 (4.2)	18 (5.3)	97 (5.6)	24 (7.0)

^a Subset of all AEs

^b Represents death on study therapy. There were an additional 2 deaths \leq 30 days post-discontinuation. There were an additional 113 deaths in the study period which were $>$ 30 days post-discontinuation.

Table 5.7C shows that the smallest percentage of subjects who died was in the pravastatin/aspirin group.

Table 5.7D shows the breakdown of AEs in CARE by body system.

Table 5.7D: Number (Percent) of Subjects with Treatment-Emergent Clinical AEs in CARE by Body System and Treatment Regimen Stratified by Baseline Aspirin Use

Body System	Number (%) of Subjects			
	Pravastatin		Placebo	
	With Aspirin N = 1742	No Aspirin N = 339	With Aspirin N = 1735	No Aspirin N = 343
Cardiovascular	1264 (72.6)	250 (73.3)	1272 (73.3)	256 (74.6)
Dermatologic	603 (34.6)	124 (36.6)	571 (32.9)	106 (30.9)
Drug interaction	10 (0.6)	6 (1.8)	20 (1.2)	3 (0.9)
Endocrine/metabolic/electrolyte imbalance	315 (18.1)	60 (17.7)	255 (14.7)	52 (15.2)
Gastrointestinal	1098 (63.0)	202 (59.6)	1088 (62.7)	207 (60.3)
General	1298 (74.5)	248 (73.2)	1255 (72.3)	228 (66.5)
Hematopoietic	61 (3.5)	12 (3.5)	87 (5.0)	12 (3.5)
Hepatic/biliary	85 (4.9)	25 (7.4)	86 (5.0)	23 (6.7)
Immunology/sensitivity disorder	74 (4.2)	13 (3.8)	73 (4.2)	14 (4.1)
Musculoskeletal/connective tissue	1354 (77.7)	250 (73.7)	1318 (76.0)	238 (69.4)
Nervous system	1056 (60.6)	207 (61.1)	1003 (57.8)	203 (59.2)
Other SAE (unknown)	96 (5.5)	25 (7.4)	86 (5.0)	21 (6.1)
Renal/genitourinary	496 (28.5)	95 (28.0)	474 (27.3)	82 (23.9)
Respiratory	1354 (77.7)	252 (74.3)	1291 (74.4)	234 (68.2)
Special Senses	553 (31.7)	110 (32.4)	551 (31.8)	102 (29.7)
<i>Overall Total AEs</i>	21597	4252	20753	4145
<i>Overall Total Subjects</i>	1719 (98.7)	332 (97.9)	1697 (97.8)	333 (97.1)

An overview of the clinical event profile in REGRESS is presented in Table 5.7E.

Table 5.7E: Overview of Clinical Adverse Events AEs, Deaths, SAEs and Discontinuations in the REGRESS Study, by Treatment Regimen Stratified by Baseline Aspirin Use

	Number (%) of Subjects			
	Pravastatin		Placebo	
	With Aspirin N = 245	No Aspirin N = 205	With Aspirin N = 220	No Aspirin N = 215
AEs	199 (81.2)	170 (82.9)	194 (88.2)	186 (86.5)
ADEs ^a	142 (58.0)	115 (56.1)	135 (61.4)	137 (63.7)
Deaths ^{a,b}	1 (0.4)	3 (1.5)	3 (1.4)	4 (1.9)
SAEs ^a	73 (30.0)	56 (27.3)	75 (34.1)	71 (33.0)
Discontinuations Due to AEs	11 (4.5)	6 (2.9)	4 (1.8)	5 (2.3)

^a Subset of all AEs

^b Includes deaths that occurred during study therapy and ≤ 30 day following discontinuation or completion of study therapy

The overall incidence of AEs by body system in the REGRESS study is presented in Table 5.7F

Table 5.7F: Number (Percent) of Subjects with Treatment-Emergent Clinical AEs in the REGRESS Study, by Body System and Treatment Regimen Stratified by Baseline Aspirin Use

Body System	Number (%) of Subjects			
	Pravastatin		Placebo	
	With Aspirin N = 245	No Aspirin N = 205	With Aspirin N = 220	No Aspirin N = 215
Cardiovascular	150 (61.2)	121 (59.0)	140 (63.6)	139 (64.7)
Dermatologic	26 (10.6)	20 (9.8)	18 (8.2)	23 (10.7)
Endocrine/metabolic/electrolyte imbalance	10 (4.1)	6 (2.9)	11 (5.0)	10 (4.7)
Gastrointestinal	36 (14.7)	37 (18.0)	37 (16.8)	43 (20.0)
General	67 (27.3)	53 (25.9)	52 (23.6)	51 (23.7)
Hematopoietic	8 (3.3)	2 (1.0)	7 (3.2)	2 (0.9)
Hepatic/biliary	1 (0.4)	0	1 (0.5)	1 (0.5)
Immunology/sensitivity disorder	5 (2.0)	1 (0.5)	2 (0.9)	2 (0.9)
Musculoskeletal/connective tissue	47 (19.2)	57 (27.8)	41 (18.6)	47 (21.9)
Nervous system	61 (24.9)	38 (18.5)	41 (18.6)	45 (20.9)
Renal/genitourinary	13 (5.3)	13 (6.3)	21 (9.5)	10 (4.7)
Respiratory	48 (19.6)	39 (19.0)	25 (11.4)	36 (16.7)
Special Senses	21 (8.6)	16 (7.8)	16 (7.3)	27 (12.6)
<i>Overall Total AEs</i>	657	546	568	604
<i>Overall Total Subjects</i>	199 (81.2)	170 (82.9)	194 (88.2)	186 (86.5)

An overview of the clinical event profile in the Integrated PLAC studies is presented in Table 5.7G.

Table 5.7G: Overview of Clinical Adverse Events AEs, Deaths, SAEs and Discontinuations in the Integrated PLAC I and PLAC II Studies, by Treatment Regimen Stratified by Baseline Aspirin Use

	Number (%) of Subjects			
	Pravastatin		Placebo	
	With Aspirin N = 171	No Aspirin N = 110	With Aspirin N = 180	No Aspirin N = 98
AEs	167 (97.7)	107 (97.3)	172 (95.6)	92 (96.9)
ADEs ^a	128 (74.9)	71 (64.5)	132 (73.3)	69 (70.4)
Deaths ^{a,b}	1 (0.6)	2 (1.8)	4 (2.2)	1 (1.0)
SAEs ^a	62 (36.3)	48 (43.6)	91 (47.9)	53 (54.1)
Discontinuations Due to AEs	11 (6.4)	8 (7.3)	19 (10.6)	9 (9.2)

Note: The integrated regression studies include, PLAC I and PLAC II

^a Subset of all AEs

^b Includes deaths that occurred during study therapy and ≤ 30 days following discontinuation or completion of study therapy.

The overall incidence of AEs by body system in the PLAC studies is presented in Table 5.7H.

Table 5.7H: Number (Percent) of Subjects with Treatment-Emergent Clinical AEs in PLAC I and PLAC II, by Body System and Treatment Regimen Stratified by Baseline Aspirin Use

Body System	Number (%) of Subjects			
	Pravastatin		Placebo	
	With Aspirin N = 171	No Aspirin N = 110	With Aspirin N = 180	No Aspirin N = 98
Cardiovascular	125 (73.1)	76 (69.1)	124 (68.9)	71 (72.4)
Dermatologic	45 (26.3)	25 (22.7)	50 (27.8)	32 (32.7)
Drug interaction	0	1 (0.9)	1 (0.6)	0
Endocrine/metabolic/electrolyte imbalance	16 (9.4)	18 (16.4)	20 (11.1)	15 (15.3)
Gastrointestinal	86 (50.3)	66 (60.0)	76 (42.2)	61 (62.2)
General	88 (51.5)	67 (60.9)	92 (51.1)	54 (55.1)
Hematopoietic	3 (1.8)	1 (0.9)	4 (2.2)	1 (1.0)
Hepatic/biliary	1 (0.6)	1 (0.9)	2 (1.1)	0
Immunology/sensitivity disorder	7 (4.1)	6 (5.5)	6 (3.3)	2 (2.0)
Musculoskeletal/connective tissue	99 (57.9)	69 (62.7)	104 (57.8)	55 (56.1)
Nervous system	73 (42.7)	56 (50.9)	77 (42.8)	46 (46.9)
Renal/genitourinary	34 (19.9)	35 (31.8)	40 (22.2)	24 (24.5)
Respiratory	86 (50.3)	69 (62.7)	92 (51.1)	65 (66.3)
Special Senses	46 (26.9)	40 (36.4)	45 (25.0)	38 (38.8)
<i>Overall Total AEs</i>	1145	918	1200	755
<i>Overall Total Subjects</i>	167 (97.7)	107 (97.3)	172 (95.6)	95 (96.9)

Note: The integrated studies include PLAC I and PLAC II

5.7.1 Clinical Adverse Events Conclusions

The adverse event rates in the four treatment groups are largely comparable in each of the studies with no one treatment group showing consistently the highest or lowest adverse event rates.

5.8 Deaths

A total of 1,131 deaths were reported during the course of the LIPID study and up to and including 30 days after discontinuation of study drug. Cause of death was categorized into one of 7 groups: coronary, cardiac (non-coronary), other vascular (non-cardiac), or non-cardiovascular (cancer, trauma, suicide or other causes). The prava/ASA group had the lowest proportion of total deaths (10.1%) and the placebo-alone group had the highest (17.6%). The prava/ASA group also had the lowest proportion of coronary deaths, vascular (non-cardiac) deaths, cancer deaths, suicides, and 'other' deaths.

A total of 376 deaths were reported during CARE and its long-term follow-up. Of these, 263 subjects died during double-blind therapy or within 30 days following discontinuation of study medication. One hundred and thirteen (113) subjects died more than 30 days following discontinuation of study drug. Cause of death was categorized into 4 groups: atherosclerotic CHD, atherosclerotic vascular, non-atherosclerotic vascular and non-cardiovascular. The prava/ASA group had the lowest proportion of total deaths (7.0%) and the prava-alone group had the highest (17.1%).

In the REGRESS study a total of 11 (1.2%) subjects, (4 subjects treated with pravastatin and 7 subjects receiving placebo) died while receiving study therapy or within one month after discontinuation or completion of study therapy. Of these, 1 pravastatin-treated subject and 3 placebo treated-subjects were also treated with aspirin concomitantly. An additional 4 subjects, 2 subjects receiving prava/ASA and 2 subjects receiving placebo alone, died ≥ 30 days following discontinuation of study therapy.

A total of 17 deaths were reported during the PLAC I and PLAC II studies. Of these, 8 deaths occurred during study therapy or ≤ 30 days following discontinuation or completion of study therapy 9 other deaths occurred > 30 days post discontinuation of study therapy. The overall incidence of death was lowest in the prava/ASA treatment

group (3/171; 1.8%). In this treatment group, one subject died while on study therapy and 2 subjects died > 30 days following discontinuation of study therapy.

5.8.1 Death Conclusions

In the LIPID, CARE, REGRESS and Integrated PLAC studies described above, the total death rate in the prava/ASA groups was consistently the lowest. This was particularly the case when just coronary or atherosclerotic CHD deaths were considered. The rates of death from the causes other than CHD were comparable across the treatment groups.

5.9 Serious Adverse Events

Overall, 6,488 subjects experienced SAEs during the LIPID study. Table 5.9A presents the number of subjects experiencing SAEs by body system and treatment regimen stratified by baseline aspirin use.

Table 5.9A: Number (Percent) of Subjects with SAEs in LIPID, by Body System and Treatment Regimen Stratified by Baseline Aspirin Use

Body System	Number (%) of Subjects			
	Pravastatin		Placebo	
	With Aspirin N = 3730	No Aspirin N = 782	With Aspirin N = 3698	No Aspirin N = 804
Cardiac	1411 (37.8)	354 (45.3)	1566 (42.3)	377 (46.9)
Complications of medical care	111 (3.0)	37 (4.7)	151 (4.1)	29 (3.6)
Dermatologic	352 (9.4)	81 (10.4)	342 (9.2)	71 (8.8)
Endocrine/metabolic	111 (3.0)	33 (4.2)	108 (2.9)	35 (4.4)
Gastrointestinal	784 (21.0)	227 (29.0)	795 (21.5)	206 (25.6)
Hematologic	87 (2.3)	24 (3.1)	96 (2.6)	28 (3.5)
Hepatic/biliary	124 (3.3)	34 (4.3)	156 (4.2)	39 (4.9)
Infections	87 (2.3)	23 (2.9)	84 (2.3)	30 (3.7)
Malignancy	461 (12.4)	104 (13.3)	447 (12.1)	94 (11.7)
Musculoskeletal	457 (12.3)	121 (15.5)	462 (12.5)	109 (13.6)
Nervous system	247 (6.6)	69 (8.8)	261 (7.1)	79 (9.8)
Other reasons for hospital admissions	110 (2.9)	39 (5.0)	110 (3.0)	25 (3.1)
Renal/genitourinary	604 (16.2)	150 (19.2)	543 (14.7)	145 (18.0)
Respiratory	590 (15.8)	164 (21.0)	541 (14.6)	155 (19.3)
Special Senses	234 (6.3)	63 (8.1)	224 (6.1)	64 (8.0)
Trauma	176 (4.7)	37 (4.7)	164 (4.4)	47 (5.8)
Vascular (non-cardiac)	495 (13.3)	136 (17.4)	587 (15.9)	135 (16.8)
No category assigned	0	0	1 (0.0)	0
<i>Overall Total SAEs</i>	12927	3467	13775	3457
<i>Overall Total Subjects</i>	2629 (70.5)	587 (75.1)	2674 (72.3)	598 (74.4)

In CARE, a total of 2,506 subjects experienced SAEs. The incidence of SAEs by Body System is presented in Table 5.9B.

Table 5.9B: Number (Percent) of Subjects with SAEs in CARE, by Body System and Treatment Regimen Stratified by Baseline Aspirin Use

Body System	Number (%) of Subjects			
	Pravastatin		Placebo	
	With Aspirin N = 1742	No Aspirin N = 339	With Aspirin N = 1735	No Aspirin N = 343
Cardiovascular	669 (38.4)	150 (44.2)	733 (42.2)	155 (45.2)
Dermatologic	86 (4.9)	17 (5.0)	70 (4.0)	15 (4.4)
Drug interaction	5 (0.3)	2 (0.6)	8 (0.5)	0
Endocrine/metabolic/electrolyte imbalance	50 (2.9)	9 (2.7)	39 (2.2)	10 (2.9)
Gastrointestinal	171 (9.8)	56 (16.5)	201 (11.6)	51 (14.9)
General	147 (8.4)	47 (13.9)	166 (9.6)	35 (10.2)
Hematopoietic	31 (1.8)	7 (2.1)	44 (2.5)	5 (1.5)
Hepatic/biliary	64 (3.7)	22 (6.5)	71 (4.1)	16 (4.7)
Immunology/sensitivity disorder	3 (0.2)	3 (0.9)	3 (0.2)	1 (0.3)
Musculoskeletal/connective tissue	140 (8.0)	35 (10.3)	130 (7.5)	31 (9.0)
Nervous system	121 (6.9)	51 (15.0)	142 (8.2)	41 (12.0)
Renal/genitourinary	162 (9.3)	32 (9.4)	154 (8.9)	26 (7.6)
Respiratory	153 (8.8)	43 (12.7)	167 (9.6)	38 (11.1)
Special Senses	19 (1.1)	9 (2.7)	30 (1.7)	10 (2.9)
<i>Overall Total SAEs</i>	2969	771	3209	738
<i>Overall Total Subjects</i>	1015 (58.3)	218 (64.3)	1051 (60.6)	222 (64.7)

In REGRESS, a total of 129 subjects receiving pravastatin and 146 subjects receiving placebo experienced SAEs. Table 5.9C presents the incidence of SAEs by treatment regimen stratified by baseline aspirin use.

Table 5.9C: Number (Percent) of Subjects with SAEs in the REGRESS Study, by Body System and Treatment Regimen Stratified by Baseline Aspirin Use

Body System	Number (%) of Subjects			
	Pravastatin		Placebo	
	With Aspirin N = 245	No Aspirin N = 205	With Aspirin N = 220	No Aspirin N = 215
Cardiovascular	56 (22.9)	51 (24.9)	61 (27.7)	47 (21.9)
Dermatologic	1 (0.4)	0	0	1 (0.5)
Endocrine/metabolic/electrolyte imbalance	1 (0.4)	0	0	1 (0.5)
Gastrointestinal	4 (1.6)	3 (1.5)	3 (1.4)	5 (2.3)
General	4 (1.6)	6 (2.9)	4 (1.8)	6 (2.8)
Hematopoietic	1 (0.4)	0	2 (0.4)	1 (0.5)
Immunology/sensitivity disorder	1 (0.4)	0	0	0
Musculoskeletal/connective tissue	2 (0.8)	2 (1.0)	5 (2.3)	6 (2.8)
Nervous system	2 (0.8)	1 (0.5)	4 (1.8)	2 (0.9)
Renal/genitourinary	3 (1.2)	3 (1.5)	4 (1.8)	3 (1.4)
Respiratory	11 (4.5)	6 (2.9)	0	8 (3.7)
Special Senses	0	1 (0.5)	0	1 (0.5)
<i>Overall Total SAEs</i>	116	73	123	105
<i>Overall Total Subjects</i>	73 (30.0)	56 (27.3)	75 (34.1)	71 (33.0)

The highest SAE rate in REGRESS is seen in the placebo/ASA group and the lowest in the prava-alone group.

In the integrated PLAC studies a total of 110 subjects receiving pravastatin and 144 subjects receiving placebo experienced SAEs. Table 5.9D presents the incidence of SAEs by study and treatment regimen stratified by baseline aspirin use.

Table 5.9D: Number (Percent) of Subjects with SAEs in PLAC I and PLAC II, by Body System and Treatment Regimen Stratified by Baseline Aspirin Use

Body System	Number (%) of Subjects			
	Pravastatin		Placebo	
	With Aspirin N = 171	No Aspirin N = 110	With Aspirin N = 180	No Aspirin N = 98
Cardiovascular	47 (27.5)	32 (29.1)	71 (39.4)	40 (40.8)
Dermatologic	7 (4.1)	6 (5.5)	5 (2.8)	5 (5.1)
Drug Interaction	0	1 (0.9)	0	0
Endocrine/Metabolic	1 (0.6)	0	0	1 (1.0)
Gastrointestinal	8 (4.7)	6 (5.5)	7 (3.9)	3 (3.1)
General	0	2 (1.8)	6 (3.3)	2 (2.0)
Hepatic/Biliary	0	1 (0.9)	1 (0.6)	0
Immunology/Sensitivity	0	0	2 (1.1)	0
Musculoskeletal	6 (3.5)	7 (6.4)	11 (6.1)	2 (2.0)
Nervous System	4 (2.3)	3 (2.7)	3 (1.7)	7 (7.1)
Renal/Genitourinary	3 (1.8)	8 (7.3)	6 (3.3)	2 (2.0)
Respiratory	2 (1.2)	6 (5.5)	3 (1.7)	7 (7.1)
Special Senses	1(0.6)	0	1 (0.6)	0
<i>Number of Subjects with SAEs</i>	62 (36.3)	48 (43.6)	91 (50.6)	53 (54.1)

Note: The integrated regression studies include: PLAC I and PLAC II

The greatest percentage of subjects with SAEs in the Integrated PLAC studies was seen in the placebo-alone and the lowest rate in the prava/ASA group.

5.10 Discontinuations Due to Adverse Events

In the LIPID study 1057 subjects permanently discontinued study medication because of ADEs or SAEs. The lowest discontinuation rate for such events was in the prava/ASA

group (10.1%) and the highest rate was in the placebo-alone group (15.7%). The most frequently occurring ADEs or SAEs that led to discontinuations were acute unstable angina, CABG and heart failure, all of which were seen less frequently in the prava/ASA group.

In the CARE study 213 subjects permanently discontinued study medication because of AEs. The lowest discontinuation rate for such events was in the prava/ASA group (4.2%) and the highest rate was in the placebo-alone group (7.0%), as in LIPID. The most frequently occurring SAEs or ADEs that led to discontinuation in CARE were fatigue and rash.

In the REGRESS study, 30 subjects discontinued study medication because of AEs. The discontinuation rate was highest in the prava/ASA group (3.7%) and lowest in the placebo/ASA group (2.7%).

In the Integrated PLAC studies 47 subjects discontinued study medication because of AEs. The highest discontinuation rate was in the placebo/ASA group (10.6%) and the lowest rate was in the prava/ASA group.

5.10.1 Discontinuation Conclusion

The discontinuation rates in the prava/ASA treatment group were lower than those seen in the other treatment groups in both LIPID and CARE. The numbers of discontinuations in REGRESS, PLAC I and PLAC II are too low for meaningful comparison between treatment groups but they do not appear to contradict the findings in these large studies.

5.11 Clinical Laboratory Analysis

Marked abnormalities (MAs) were values that met pre-specified criteria for identifying potentially clinically important changes that may have occurred during study treatment. Because not all subjects had laboratory determinations for all analytes at all visits, the sample size varies from analyte to analyte.

The presentation of MAs focuses on alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine kinase (CK), and hemoglobin (with the exception of CARE where MA criteria were not applied to hemoglobin).

The incidence of MAs of ALT, AST, CK and hemoglobin, the lab values of particular interest in LIPID, is presented in Table 5.11A. Generally, the incidence of MAs for ALT, AST, CK and Hgb in LIPID were comparable across the 4 treatment regimens.

Table 5.11A: Number (Percent) of Subjects with Marked Abnormalities for Selected Analytes in LIPID, by Treatment Regimen Stratified by Baseline Aspirin Use

Analyte	MA criteria	Number (%) of Subjects							
		Pravastatin				Placebo			
		With ASA		No ASA		With ASA		No ASA	
		N	n(%)	N	n (%)	N	n (%)	N	n (%)
ALT mg/dL (high)	> 3x ULN or if PreTx > ULN then 4x PreTx	3217	53 (1.6)	666	11 (1.7)	3157	49 (1.6)	693	7 (1.0)
AST mg/dL (high)	> 3x ULN or if PreTx > ULN then 4x PreTx	414	4 (1.0)	83	1 (1.2)	475	3 (0.6)	84	0
CK U/L (high)	4x PreTx	3513	93 (2.6)	697	17 (2.4)	3430	87 (2.5)	710	16 (2.3)
Hgb g/dL (low)	> 3 g/dL decrease from PreTx	3501	60 (1.7)	694	26 (3.7)	3419	67 (2.0)	705	16 (2.3)

Abbreviations: MA: marked abnormality; N: number of subjects included in the analysis; n: number of subjects with MA

In CARE, MA criteria were not applied to Hgb so the only lab values of particular interest were ALT, AST and CK. The incidence of MAs of ALT, AST, and CK is presented in Table 5.11B.

Table 5.11B: Number (Percent) of Subjects with Marked Abnormalities for Selected Analytes in CARE, by Treatment Regimen Stratified by Baseline Aspirin Use

Analyte ^a	MA criteria	Number (%) of Subjects							
		Pravastatin				Placebo			
		With ASA		No ASA		With ASA		No ASA	
		N	n(%)	N	n (%)	N	n (%)	N	n (%)
ALT mg/dL (high)	> 3x ULN or if PreTx > ULN then 4x PreTx	1734	18 (1.0)	337	6 (1.8)	1718	27 (1.6)	336	7 (2.1)
AST mg/dL (high)	> 3x ULN or if PreTx > ULN then 4x PreTx	1735	21 (1.2)	337	6 (1.8)	1718	22 (1.3)	336	6 (1.8)
CK U/L (high)	4x PreTx	1684	94 (5.6)	321	22 (6.9)	1672	98 (5.9)	323	16 (5.0)

^a MA criteria were not applied to Hgb

Overall no clinically significant differences were observed in the occurrence of MAs across the 4 treatment regimens.

The incidence of MAs of ALT, AST, CK and Hgb for the REGRESS Study is presented in Table 5.11C.

Table 5.11C: Number (Percent) of Subjects with Marked Abnormalities for Selected Analytes in the REGRESS Study, by Treatment Regimen Stratified by Baseline Aspirin Use

Analyte	MA criteria	Number (%) of Subjects							
		Pravastatin				Placebo			
		With ASA		No ASA		With ASA		No ASA	
		N	n(%)	N	n (%)	N	n (%)	N	n (%)
ALT mg/dL (high)	> 3x ULN or if PreTx > ULN then 4x PreTx	240	0	198	0	215	0	208	0
AST mg/dL (high)	> 3x ULN or if PreTx > ULN then 4x PreTx	240	1 (0.4)	198	1 (0.5)	215	2 (0.9)	208	0
CK U/L (high)	4x PreTx	240	10 (4.2)	198	1 (0.5)	215	10 (4.7)	208	5 (2.4)
Hgb g/dL (low)	> 3 g/dL decrease from PreTx	221	2 (0.9)	192	1 (0.5)	208	4 (1.9)	194	1 (0.5)

The highest MA rate for AST, CK, and Hgb was in the placebo/ASA group. No MAs were reported for ALT in any of the treatment regimens.

The incidence of MAs of ALT, AST, CK and Hgb for the integrated PLAC studies is presented in Table 5.11D.

Table 5.11D: Number (Percent) of Subjects with Marked Abnormalities for Selected Analytes in the Integrated PLAC Studies, by Treatment Regimen Stratified by Baseline Aspirin Use

Analyte	MA criteria	Number (%) of Subjects							
		Pravastatin				Placebo			
		With ASA		No ASA		With ASA		No ASA	
		N	n (%)	N	n (%)	N	n (%)	N	n (%)
ALT mg/dL (high)	> 3x ULN or if PreTx > ULN then 4x PreTx	167	0	107	1 (0.9)	177	2 (1.1)	96	0
AST mg/dL (high)	> 3x ULN or if PreTx > ULN then 4x PreTx	167	1 (0.6)	107	1 (0.9)	177	1 (0.6)	96	0
CK U/L (high)	4x PreTx	167	14 (8.4)	107	15 (14.0)	177	12 (6.8)	96	8 (8.3)
Hgb g/dL (low)	> 3 g/dL decrease from PreTx	167	3 (1.8)	107	5 (4.7)	177	2 (1.1)	96	0

Note: Integrated regression studies include PLAC I and PLAC II

In the Integrated PLAC studies the incidence of MAs was highest in the prava-alone group for all four of the analytes investigated, except for ALT where placebo/aspirin was the highest. However, the numbers of subjects with MAs were small.

5.11.1 Clinical Laboratory Analysis Conclusions

There was no consistent pattern in the rates of marked abnormalities across treatment groups in the 5 studies.

5.12 Demographic Subgroup Analyses

The effects of concomitant administration of aspirin and pravastatin or placebo were examined in selected demographic subgroups in the secondary prevention studies. These included:

- age: non-elderly, < 65 years; and elderly, \geq 65 years
- gender: males and females

Safety assessment includes extent of exposure, incidence of clinical adverse events, and laboratory marked abnormalities. The presentation of MAs focused on ALT, AST, CK and hemoglobin.

5.12.1 Demographic Subgroup Analysis Conclusions

No consistent pattern of higher or lower extent of exposures, AEs or marked abnormalities were seen between treatment groups within or across studies. There may be a weak association between age and extent of exposure in the large studies (with the non-elderly having a greater exposure) but this is not supported by smaller studies. Likewise there may be a weak association between gender and extent of exposure in the larger studies (with males having a greater exposure) but again this is not supported by the smaller studies. Regarding clinical adverse events, the incidence of AEs in CARE was higher in the elderly patients regardless of treatment group. However in the LIPID and REGRESS the elderly pravastatin-treated patients had lower ADE and AE rates respectively than their non-elderly equivalents whereas for placebo-treated patients this association was reversed with elderly placebo-treated patients having the higher rates.

There appeared to be a weak association between gender and AE rate, with female subjects having higher rates, but no one treatment group of either gender had consistently high incidences of AEs.

Age did not appear to be associated with laboratory MA frequency and neither did gender and no one treatment group consistently showed the highest incidence of MAs.

5.13 Special Interest AEs

It appears that the only special interest area where the concomitant use of aspirin with pravastatin may be increasing the adverse event rates is in hematological body system. Even here aspirin's effect may be restricted to minor hematological events (AEs) because SAEs are not increased by the concomitant use of aspirin. In the 3 other body systems of special interest (gastrointestinal, musculoskeletal and hepato-biliary) the concomitant use of pravastatin and aspirin appears to actually decrease the frequency of the more serious events (SAEs and discontinuations). One possible explanation for this is that the patients receiving aspirin tended to be slightly younger, presumably as a result of clinicians reluctance to give aspirin to the elderly, because of the perceived poorer risk/benefit ratio in these patients. Thus the reduced rates of GI, M/S and H/B events in aspirin-treated patients could simply be an artifact of the lack of aspirin randomization. Whatever the reason, these comparisons of adverse events in special interest body systems do not suggest an additivity of side-effect of pravastatin and aspirin. If anything, the expected event rate when pravastatin and aspirin are given concomitantly appears to be lower than the event rate observed for either treatment given alone.

5.14 Conclusions

In summary, it appears that the concomitant administration of pravastatin 40 mg with aspirin is well tolerated, possibly leading to an increased exposure to study drug in the larger trials, although the results of the clinical pharmacology study do not support this. It is not associated with any increases in discontinuations, serious adverse events or adverse events. Neither are there significant differences in adverse event rates or lab abnormalities between treatment groups when the study populations are analyzed by gender or age. None of the analyses reported here suggest an additivity of side-effect of pravastatin and aspirin and the expected event rates may even be lower than those observed for either treatment given alone.

6 BENEFITS AND RISKS OF PRAVASTATIN/ASPIRIN TREATMENT

A total of 14,617 subjects, from the CARE,⁸ LIPID,⁹ REGRESS,¹⁰ PLAC I¹¹ and PLAC II¹² studies, were treated with pravastatin 40 mg or placebo of whom 11,721 also received concomitant aspirin with either pravastatin, 5,888 subjects or with placebo 5,833 subjects.

This application summarizes the evidence which supports the independence of effect of pravastatin and aspirin in these secondary prevention populations. Pravastatin and aspirin have different mechanisms of action by which they reduce cardiovascular events. There is no pharmacokinetic interaction between them. This independence of effect therefore provides increased risk reduction with the concomitant use of pravastatin and aspirin with an adverse event profile not different from that of them taken individually.

6.1 Efficacy and Safety of Pravastatin

In the CARE trial, which was conducted in post-MI patients with normal cholesterol, the primary end-point was a fatal coronary event or a non-fatal myocardial infarction.⁸ There was a 24% reduction in risk (95% CI, 9-36%). Comparable risk reductions were observed in the secondary end-points of stroke and the need for CABG or PTCA. There were no significant differences in overall mortality or mortality from noncardiovascular causes.

In the LIPID trial, which was conducted in patients with a history of MI or unstable angina and with a wide range of cholesterol values, the primary end-point was death from coronary heart disease.⁹ There was a 22% reduction in risk (95% CI, 12-35%) for this primary end-point. The incidence of all cardiovascular outcomes was considerably lower among patients assigned to receive pravastatin. There were no clinically significant adverse events associated with pravastatin treatment. Overall mortality was lower in the pravastatin group.

The safety and efficacy of pravastatin at a 40 mg daily dose are described in the current Pravachol[®] labeling: “Pravachol[®] is effective in reducing the risk of acute coronary events in hypercholesterolemic patients with and without previous myocardial

infarction.”¹³ The “Indications and Usage” section also indicates that Pravachol[®] will reduce the risk of myocardial infarction, of undergoing myocardial revascularization procedures and the risk of cardiovascular mortality, with no increase in death from non-cardiovascular causes. Pravastatin is generally well tolerated. Adverse events are usually mild and transient. During clinical trials the overall incidence of adverse events in the elderly has not been different from the incidence observed in younger patients at the 40 mg dose.³⁴

6.2 Efficacy and Safety of Aspirin

The Antiplatelet Trialist’s meta-analysis of 49 randomized trials involving more than 3000 secondary prevention subjects at doses of aspirin of 500-1500 mg, 160-325 mg and 75-150 mg showed significant reductions in MI, stroke or vascular death.¹⁵ (% odds reduction (SD); 21 (4), 28 (3), 26 (11), respectively). It was concluded that there was an absence of a dose-response relationship and that the only situation favoring the 160-325 mg dose regimen, was that a 75 mg single aspirin dose did not completely inhibit platelet cyclo oxygenase.³⁵ Therefore in an acute setting the 325 mg dose is more appropriate. Subsequent aspirin studies have supported this view.²¹ The dosage range given in the professional label of aspirin, for vascular indications (ischemic stroke, TIA, acute MI, prevention of recurrent MI, unstable angina and chronic stable angina) is 50 to 325 mg/day.²²

The adverse event profile of aspirin has been known for a long time and particularly that some adverse events are idiosyncratic, such as rhinitis, asthma and angioedema.^{36,37} Gastrointestinal bleeding is, however, mechanism based. It was consistently present in the aspirin-treated population, even after exclusion of subjects with a history of previous GI bleeding, peptic ulcer disease or any contraindication to aspirin. A recent meta-analysis by Loke of 24 randomized controlled trials (almost 66,000 subjects)³⁸ showed that GI bleeding occurred in 2.47% of patients on aspirin compared with 1.42% of patients taking placebo (odds ratio 1.68; 95% CI 1.51 to 1.88) based on 28 months of treatment. There was no dose-response effect over the dosage range studied (50-1500 mg). In a subset analysis of the low dose aspirin trials (50–162.5 mg), GI

bleeding occurred in 2.30% of those taking aspirin versus 1.45% of those taking placebo (odds ratio 1.59; 95% CI 1.40 to 1.81).

Intracerebral bleeding is also mechanism based, however while much less frequently encountered than GI bleeding, the clinical sequelae are much more serious.

A meta-analysis of 16 randomized, controlled trials with 55,462 subjects was conducted.³⁹ A total of 108 hemorrhagic stroke cases from 13 of the 16 trials were analyzed of which 75 were in the aspirin and 33 in the placebo group. The mean duration of treatment was 37 months and mean dose of aspirin was 273 mg/day. The calculated absolute risk for hemorrhagic stroke was 12/10,000 subjects (95% CI 5 to 20). However, the population studied was predominantly patients with ischemic heart disease or stroke. Aspirin treatment therefore caused a risk reduction in ischemic stroke of 39/10,000 subjects (95% CI -17 to -61) and in total myocardial infarctions of 137/10,000 (95% CI -107 to -167), so there was a favorable risk/benefit for the use of aspirin in a secondary prevention population. The risk/benefit for use of aspirin in primary prevention of cardiovascular events is of less certain benefit, although attempts have been made to define it. A recent analysis by Ramsey⁴⁰ suggested that the benefit from daily aspirin administration was uncertain to outweigh the risk in a primary prevention population, unless the population had a coronary event risk exceeding 1.5%/year. However, this meta-analysis reaffirmed the value of aspirin in reducing overall cardiovascular events in a secondary prevention population.

6.3 Efficacy and Safety of Pravastatin/Aspirin

6.3.1 Efficacy

In the combined CARE,⁸ LIPID,⁹ REGRESS,¹⁰ PLAC I¹¹ and PLAC II¹² meta-analysis involving 14,617 patients, there were 3714 patients who experienced either CHD death, non-fatal MI, CABG, PTCA or stroke, following their randomization to pravastatin 40 mg or placebo. Thirteen hundred and fourteen (1314; 22.3%) of these events occurred in the pravastatin with aspirin group whereas 398 (27.3%) occurred in the pravastatin only group. This represents a significant relative risk reduction of 26.8%. The pravastatin only group had a significantly lower risk compared with the placebo without aspirin group (risk reduction 15.4%). Pravastatin with aspirin showed significant risk reduction

in all other composite endpoints of the traditional frequentist meta-analysis, (Model 1), i.e., CHD death, non-fatal MI, CABG or PTCA; CHD death or non-fatal MI or stroke.

A Bayesian meta-analysis of the data, using two models (Models 2 and 3), demonstrated that the pravastatin plus aspirin is better than aspirin plus placebo and pravastatin plus placebo, for all composite endpoints. These analyses provide clear evidence of the independence of effect of the two drugs. The second of these models (Model 3) provided four (4) hazard estimates over time, which do not vary greatly, and thereby support the consistency of the event reduction over the five year study period. In some of the composite end-points there was a lack of significant risk reduction in the aspirin group (aspirin with placebo), when compared with placebo alone. However the group sizes were small and aspirin was not a randomized drug in any of the studies in these meta-analyses unlike those of the Antiplatelet Trialist Collaboration¹⁵ or Ramsey,⁴⁰ which demonstrated a robust effect of aspirin risk reduction of cardiovascular events.

Pravastatin with aspirin use consistently lowered the relative risk for CHD death, non-fatal MI, CABG, PTCA or stroke compared to the placebo without aspirin group for both males and females. Overall there was no significant difference between males and females. Similar results were observed from the Bayesian meta-analysis. There does not appear to be a gender effect in the response to pravastatin/aspirin.

Pravastatin with aspirin use consistently lowered the relative risk for CHD death, non-fatal MI, CABG, PTCA or stroke compared with the placebo without aspirin group for both the non-elderly (< 65 years) and elderly (\geq 65 years) for the composite endpoint. The risk reductions were 18.7% and 35.9% respectively. Similar results were observed from the Bayesian meta-analysis. A recent subanalysis of LIPID reported the absolute benefit of pravastatin is significantly greater in older patients.⁴¹

6.3.2 Safety

The independence of the mechanistic effects of pravastatin and aspirin can be expected to pertain to clinical safety. However, the safety profiles of pravastatin and aspirin are quite different. There is therefore no evidence of an additivity, which would present as a clinical safety issue. An analysis of body systems where pravastatin and aspirin adverse effects and SAEs would be anticipated, e.g., gastrointestinal, musculoskeletal,

hematological and hepatobiliary showed no increase for pravastatin with aspirin relative to pravastatin as aspirin given alone. In a review of the discontinuations for adverse events, there was also no suggestion of additivity in either the laboratory abnormalities or the clinical adverse event that had led to the patient being discontinued from the study.

The benefit, the increased reduction in cardiovascular events by use of the pravastatin with aspirin co-packaged product, is therefore not offset by an increase in specific adverse events or clinical laboratory abnormalities.

The suggestion of increased efficacy of pravastatin with aspirin in reducing cardiovascular events in the elderly is similarly not offset by increased adverse events.

The greater reduction in clinical events in the over 65 years population is then more probably attributable to the increased effectiveness of the therapy in a higher risk population, than it is to increased drug exposure. The metabolism of pravastatin involves several pathways and both hepatic and renal routes of elimination. This is a metabolic profile unlikely to be affected significantly by age. The published pharmacokinetic data support this view.³⁰ PROSPER, a study in several thousand elderly (70-82 years of age) men and women randomized to placebo or pravastatin 40 mg qd, will be completed in 2002. A recent review by the safety monitoring board, which has considerable clinical trials experience with pravastatin, has not identified any unusual safety issues in this population.⁴² Aspirin usage is permitted in PROSPER.

For patients for whom the combination product is inappropriate, i.e., the renally or hepatically impaired, or those taking cyclosporine or those with a history of aspirin sensitivity or bleeding, monotherapy should be considered or administration of the individual drugs. Monotherapy should also be considered for the patients who discontinue from the pravastatin with aspirin combination product.

6.3.3 Selection of Dose

As all five (5) clinical event trials in the meta-analyses employed a 40 mg qd dose of pravastatin, this was the dose selected for the combination product. The doses of aspirin chosen were the upper lower doses (325 and 81 mg) of the recommended range for reduction of cardiovascular events in a secondary prevention population.²²

The safety data in the Application do not indicate there is a particular population with higher AEs, for which a reduction in dosage should be recommended. The elderly tolerate a 40 mg dose of pravastatin well, with an AE profile comparable with that seen in the non-elderly. A large on-going trial with 40 mg of pravastatin in the elderly has not encountered safety problems.⁴² A dose reduction to 20 mg in the elderly would provide a reduction in LDL-C less than that seen with 40 mg of pravastatin in the non-elderly. There is therefore no basis not to provide all patients with a dose of pravastatin, which has been proven to reduce cardiovascular events.

6.4 Conclusions

This application provides meta-analyses which fully support the independence of effect of pravastatin and aspirin in the reduction of cardiovascular events in a population at risk for such events. This conclusion is additionally supported by the quite different mechanisms of action of pravastatin and aspirin and also that there is no pharmacokinetic interaction between them.

The 40 mg pravastatin/325 mg buffered aspirin and 40 mg pravastatin/81 mg buffered aspirin co-packages are therefore indicated as long term management to reduce the risk of the following cardiovascular events in patients with clinically evident coronary heart disease: death, non-fatal MI, myocardial revascularization procedures and ischemic stroke.

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