

**Pravastatin Tablets/Aspirin Tablets Co-Packaged Product**

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## Table of Contents

Title page	1
Table of contents	2
Materials utilized in this review	3
Chemistry, manufacturing and controls	3
Scientific Investigations	3
Animal Pharmacology	3
Biopharmaceutic	3
Executive summary	5
Introduction	7
Pivotal Studies with Pravastatin	10
PLAC I	12
PLAC 2	15
CARE	17
LIPID	20
REGRESS	22
Aspirin Studies	24
AMIS study	24
Coronary Drug Project Research Group	26
Randomized Controlled Trial of Acetyl Salicylic Acid in the Secondary Prevention of Mortality from Myocardial infarction	28
PARIS study	29
Aspirin and Secondary Mortality after Myocardial Infarction	31
The German Aspirin Trial: A Comparison of Acetylsalicylic Acid , Placebo and Phencoumon in Secondary Prevention of Myocardial Infarction	31
Collaborative Overview of Aspirin Trials	33
Is the effect of combining aspirin and Pravastatin Beneficial? That is, is $A = B > A$ and $A + B > B$ with $A =$ the effects of aspirin and $B =$ the effect of pravastatin?	35
Overview of Efficacy from the Pravastatin Studies	36
Demographics	36
Dispositions	39
Statistical Treatment	39
Method 1	39
Bayesian Models (2 and 3)	40
Endpoints:	40
Endpoint 1- Composite outcome measurement of CHD death, non-fatal MI, CABG, PTCA or ischemic stroke	40
Method 1	40
Endpoint 2- Fatal and non-fatal MI	41
Endpoint 3- Ischemic strokes	42
Endpoint 4- Composite outcome measure of CHD death, non-fatal MI, CABG or PTCA	42
Endpoint 5- Composite endpoint of CHD death or non-fatal MI	43
Bayesian Meta analysis	43
Endpoint 1- Composite outcome measurement of CHD death, non-fatal MI,	43

CABG, PTCA or ischemic stroke: Bayesian Model 1	
Model 2	44
Endpoint 2- Fatal and non-fatal MI: Model 1	44
Model 2	45
Endpoint 3- Ischemic strokes: Bayesian Model 1	46
Model 2	46
Endpoint 4- Composite outcome measure of CHD death, non-fatal MI, CABG or PTCA : Bayesian Model 1	47
Model 2	47
Endpoint 5- Composite endpoint of CHD death or non-fatal MI: Bayesian Model 1	48
Model 2	48
Subgroup analysis	49
Gender	49
Age	49
Race	49
Dose	49
Reviewer's conclusions on efficacy	50
Safety	50
Collection of data	50
Extent of exposure	51
Demographics	51
Deaths	51
Serious adverse events	52
Discontinuations	55
Adverse events	57
Subgroups	58
Gender and age< 65 and > 65	58
Laboratory	59
Urine	59
ECG	59
Vital signs	60
Dose relationship of adverse events to aspirin or pravastatin	60
Overall safety conclusion	60
Labeling	60

Materials utilized in this review:

The information utilized in this review consisted of the NDA submission (NDA21-387) volumes 1.1-1.5; and 1.12 –1.23, submitted June 25, 2001 as well as the communications dated November 30, 2001 and December 4, 2001.

The review drew on the pravastatin reviews from HFD-510 and associated statistical reviews dated November 30, 1994; December 30, 1994; January 31, 1996; March 10, 1998 and February 1, 2000

This reviewer also utilized publications that are cited in the review.

This reviewer also referred to the briefing document and transcripts from the joint Cardio-Renal-OTC advisory committee meeting of January 23, 1997.

Chemistry, Manufacturing and Controls:

There are some as yet unresolved manufacturing issues with respect to the proposed product. Please refer to the Chemistry review for additional details.

Scientific Investigations:

No new clinical studies were performed and no audits were requested.

Animal Pharmacology:

No data were submitted

Biopharmaceutic :

A single study was submitted that demonstrated no interaction between buffered aspirin or regular aspirin and pravastatin, Please see the biopharmaceutic review for more details.

Executive summary:

This submission seeks approval of the co-packaged products of pravastatin-40 mg with 81- mg of buffered aspirin as well as the co-packaged product of pravastatin-40 mg plus 325-mg of buffered aspirin. The only new study that was submitted for this application was pharmacokinetic interaction study, which found no interaction between the aspirin and pravastatin.

There is at present no Agency standard for the approval of such co-packaged products. One potential rationale for approval is the approval co-packaging of any drugs for which a population could be defined that would benefit by both of the components. A more limiting algorithm for approval would limit such co-packaged products to drugs that treat the same symptoms in a defined population. The most limiting algorithm would be to impose on such co-packaged products the same algorithm as imposed in combination products. In essence the co-packaged product would have to demonstrate superiority of the combination over the individual components ( $A + B > A$  and  $A + B > B$ ).

Recommendation of a co-packaged product as primary therapy would require even more rigorous data.

Additional considerations before approving a co-packaged product would be the demonstration that the two components are chemically compatible, there are no pharmacokinetic interactions of concern, all usable formulations are available as co-packaged products and dosing instructions for the components are not inconsistent with each other.

With respect to the co-packaged aspirin and pravastatin formulation, there is a population, which could be identified, that would potentially benefit by this product. This population would include patients who are post MI, with unstable angina or with symptomatic coronary artery disease.

In order to address the combination product question, the sponsor analyzed five secondary prevention protocols for pravastatin (PLAC I, PLAC II, REGRESS, LIPID and CARE) for the cohort who received combination treatment with pravastatin and aspirin relative to the cohorts who were treated with pravastatin alone and those who were treated with aspirin alone. Five inter-related outcomes were analyzed.

- Composite of CHD death, non-fatal MI, myocardial revascularization procedures or ischemic stroke
- Composite of CHD death, non-fatal MI or myocardial revascularization procedures
- Composite of CHD death or non-fatal MI
- Composite of fatal or non-fatal MI
- Ischemic stroke.

For each of these outcome measurements, the cohort who received pravastatin plus aspirin were numerically superior (with nominal statistical significance in most cases) to the individual components.

There is, however, no dose-response, or time of dosing information for either pravastatin. The particular formulation of aspirin is not defined.

Safety of the cohort who received the combination product was not distinguishable from the safety of the cohorts who received the individual components. Even events known to be more frequent in aspirin i.e. gastric upset and bleeding diathesis were not seen even in the aspirin alone group when compared to placebo (i.e. no pravastatin, no aspirin)

It is unclear if this database is adequate to arrive at any conclusion. The cohorts were that were analyzed were neither randomized cohorts or stratified cohorts within a randomized study. The reason these subjects did not receive aspirin is a matter of conjecture. In addition, there were clear differences in demographic characteristics in comparing the "no aspirin" to the "yes aspirin" cohort. In addition, the cohorts were predicated on aspirin use or non-use at baseline. Although the CRFs inquired about the addition, cessation or change of doses, only one study specifically inquired about aspirin. Lastly, among those who were not treated with aspirin it is unclear how many were treated with other platelet active medications.

It is most difficult to quantify the benefit of any co-packaged product. The presumption is that compliance would be increased among those who received the co-packaged product relative to those who receive individual prescriptions. There is no specific data to either convince the reader that this benefit would occur. If such a benefit occurs, the magnitude of such benefit is unknown.

### Introduction:

This review considers the approval of the co-packaged product of aspirin and pravastatin. Two dose combinations are sought for approval. The first is 81-mg buffered aspirin with 40-mg pravastatin. The second product is 325-mg buffered aspirin with 40-mg pravastatin. Both pravastatin and aspirin are approved medications. Pravastatin is approved as a prescription therapy and aspirin is approved as an OTC product but with professional labeling for the treatment of certain medical conditions.

There are few co-packaged products presently approved for marketing and the logic behind their approval is not entirely clear. This review will, therefore, attempt to outline the extremes in algorithms for approaching the approval for co-packaged products with the application of these principles to the proposed pravastatin/aspirin combination.

The first algorithm would allow the marketing any already approved drugs or devices (this review will only consider drug co-packaged with drugs), if a population can be identified that would benefit by both therapeutic modalities. The only additional data that would be required is that the co-packaging does not alter the stability of either therapeutic modality and that the biopharmaceutic properties of the co-packaged products are also not altered. Under this algorithm, no further toxicology or clinical efficacy or safety studies would be necessary for a co-packaged product.

All sorts of combinations would therefore be approval. For example, birth control pills could be co-packaged with antihypertensives for those fertile hypertensive women. Anti-anginal drugs could be co-packaged with anti-depressants for those subjects with angina who are concurrently depressed. The scope of co-packaged products would essential be unlimited.

A modification of this algorithm would allow marketing of a co-packaged product if each of the products were meant to treat the same symptoms or disease processes in a defined population.

The other extreme road map for approval for approval would limit such products from being marketed. An algorithm for the approval of co-packaging is shown in the flow diagram (Figure 1, obtained from Dr. Wylie Chambers). A key feature of this pathway towards approval is that the co-packaged material should be treated in the same way as combination products are treated. That is, that the co-packaged moieties must be superior in activity to each of the components. A second implied requirement of this flow diagram is that the therapeutic modalities are geared towards the same symptoms. As with the first method, proof of chemical stability as well as biopharmaceutic compatibility would be required in advance of approval.

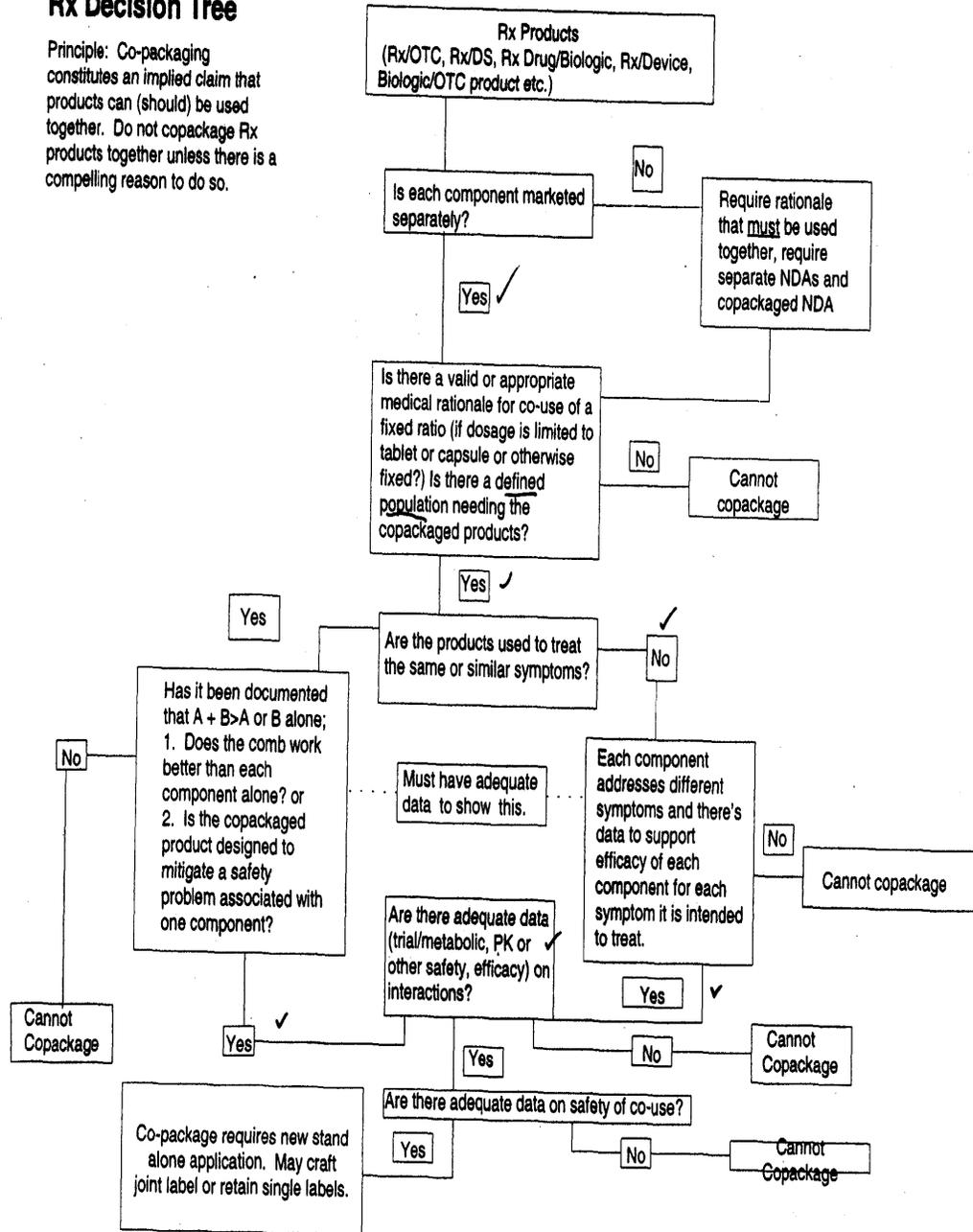
Recommendation of a co-packaged product as primary therapy would require even more rigorous data.

This reviewer would add two additional limitations to approval for co-packaged products, independent of which of the above algorithms for approval is chosen. The first is that the optimum instructions for use for each of the components should be entirely compatible. It makes no sense to co-package drugs of which one is administered at night and one at breakfast. It also

Figure 1- Approval of combination product:

### Rx Decision Tree

Principle: Co-packaging constitutes an implied claim that products can (should) be used together. Do not copackage Rx products together unless there is a compelling reason to do so.



makes no sense to co-package a drug, meant for administration on an empty stomach, with one that requires a fatty diet. If a product is taken once a day, it also makes little sense to co-package the product with one taken multiple times a day.

What one should do when the specific recommendation for one product is unstated and the other product stipulates a certain dosing behavior? For example, let's assume that the co-packaged product consists of an ACE-I (angiotensin converting enzyme inhibitor) that demonstrated a mortality effect but subjects were not specifically told to take the drug at a certain time, and a statin that is instructed for nighttime use. The obvious set of instructions would be to recommend both products be taken at night. Yet there is no support to specifically indicate the ACE-I be used at night. In essence, the co-packaging of the two products, with package instructions for nighttime doses advocates for a dosing regimen not specifically known to be beneficial.

However, if the mechanism of action of the benefit is well known perhaps the efficacy of a nighttime dosing recommendation could reasonably be inferred and the co-packaged product can be recommended for nighttime use. Safety also must be considered in the dosing instructions. For example, if the ACE-I is a gastric irritant and perhaps taking the drug on an empty stomach is frequently not tolerated. Under these circumstances, the likely use of the co-packaged product would be with food during the daytime, contrary to the optimum recommendation for the use of the statin. This co-packaged product would be more problematic.

A second set of limitation should be considered, in that all credible dose combinations should be made available as the co-packaged products. The specific concern is that the apparent convenience of the co-packaged materials would predispose the physician to prescribe an inappropriate dose for the presumed convenience engendered in the availability of the co-packaged product. For dosing instructions which accommodate a small fraction of the population, however, particularly if they are under the care of an expert, such as patients with renal or hepatic dysfunction, this limitation may not be of concern for the expert would not opt for the product of convenience.

If the therapeutic index is so large and no dose-ranging adverse events are known, then the concern of overdosing a small fraction of the population by opting for the combination product would be minimized.

With respect to any potential benefits of co-packaging, the presumption is that the co-packaging would add to the patient's compliance with both formulations. However, there is no information cited that supports a conclusion that co-packaging is in any way beneficial. In fact the sponsor submits one paper which implies that compliance is not dependent on the number of medications that are taken but rather on the number of times during the day at which medications is required. In essence any benefit on patient compliance is presumed but not demonstrated. Even if the benefit is logical, the magnitude of benefit is unknown. No risk benefit assessment can therefore be assigned to the co-packaged product.

This review will not attempt to critically examine the data that led to the approval of aspirin for its various cardiovascular treatments. Nor will this review critically address the rationale for specifying the dosing range for cardiovascular indications to 75-325 mg/day of

aspirin. Furthermore, this review will not reproduce the rationale, which expanded the use of aspirin for these cardiovascular indications to many aspirin containing product, either immediate release or buffered product.

Table 1 contains a summary of some specifics of the currently approved labeling for both aspirin and pravastatin. The overlap population is underlined.

Table 1- Side by side comparison of aspirin with pravastatin

	Aspirin	Pravastatin
Indications for Use	Vascular indications <ul style="list-style-type: none"> <li>• Ischemic stroke</li> <li>• TIA</li> <li>• Acute MI</li> <li>• <u>Prevention of recurrent MI,</u></li> <li>• <u>Unstable angina pectoris, and</u></li> <li>• <u>Chronic stable angina.</u></li> </ul>	Increased risk for atherosclerotic-related clinical events. <ul style="list-style-type: none"> <li>• Primary prevention of coronary events</li> <li>• <u>Secondary prevention of cardiovascular events</u></li> <li>• Hypercholesterolemia and mixed dyslipidemia</li> </ul>
Mechanism of Action	Aspirin affects platelet aggregation	<ul style="list-style-type: none"> <li>• HMG-CoA reductase inhibitor</li> <li>• Inhibits LDL-production by inhibiting hepatic synthesis of VLDL and LDL precursor.</li> </ul>
Metabolism/Excretion	Deacetylated to salicylic acid, which is further conjugated in the liver to salicyluric acid. Renal excretion of unchanged salicylic acid is pH-dependent. Following therapeutic doses of aspirin, 10% of the dose is excreted as salicylic acid, 75 percent as salicyluric acid and 15 percent as glucuronide conjugates.	<ul style="list-style-type: none"> <li>• Absolute bioavailability of 17%</li> <li>• Food effects on PK but not lipid lowering ability</li> <li>• Pravastatin when given at night was marginally better than when administered in the morning.</li> <li>• The lower systemic bioavailability suggests a greater extraction by the liver</li> <li>• Approximately 50% of active drug is protein bound</li> <li>• Is excreted both by hepatic and renal routes.</li> </ul>
Dosing Instructions	Aspirin should be taken with a full glass of water. For prevention of recurrent MIs a dose of 75-325 mg daily is recommended.	<ul style="list-style-type: none"> <li>• Place on cholesterol lowering diet prior to starting Pravachol</li> <li>• The recommended dose is 10, 20 or 40 mg daily, with or without food.</li> <li>• Patients with a history of renal or hepatic insufficiency, a dose of 10 mg is recommended. Patients taking immunosuppressive drugs such as cyclosporine should begin therapy with 10 mg once a day at bedtime</li> </ul>
Contraindications/Warnings	<ul style="list-style-type: none"> <li>• Allergy to non-steroidals</li> <li>• Patients with asthma, rhinitis and nasal polyps</li> <li>• Increase in bleeding risk among those who consume alcohol</li> <li>• Increased risk among subjects with bleeding diatheses</li> <li>• GI side effects</li> <li>• Peptic ulcer disease</li> </ul>	<ul style="list-style-type: none"> <li>• Pregnancy or lactation</li> <li>• Acute liver disease</li> <li>• Liver enzymes (increases in transaminases) perform LFTs before starting and with each dose increase.</li> <li>• Myopathy, rhabdomyolysis,</li> </ul>
Precautions	<ul style="list-style-type: none"> <li>• Renal failure</li> <li>• Hepatic insufficiency</li> <li>• Sodium restricted diets</li> </ul>	<ul style="list-style-type: none"> <li>• Elevations in CPK</li> <li>• Subjects with renal failure should be monitored</li> </ul>

There are several observations that can be drawn by the side by side comparison on the two components of these co-packaged materials. The first is that the overlap population between

the two components reflect those subjects with elevated lipid levels (cholesterol or LDL-cholesterol) and a history of myocardial infarction, unstable or stable angina, who are to be treated to prevent recurrent events. Of note is that aspirin does not presently have a claim for primary prevention of cardiovascular events.

From a mechanistic vantage point there appears to be no cross-interaction between the two co-packaged components. The WARNING and PRECAUTION sections do not suggest any untoward interaction.

#### Pivotal studies with Pravastatin:

In order to address whether Pravastatin plus aspirin is superior to the individual components, the sponsor performed a meta-analysis of the following five studies (PLAC I, PLAC II, REGRESS, CARE and LIPID). All these studies were performed among patients with coronary artery disease. There are additional outcome studies (e.g. West of Scotland study and KAPS) with pravastatin that demonstrated a benefit in subjects who were hypercholesterolemic but these studies did not require that the subjects have underlying cardiovascular disease.

The intent of the meta-analysis is to support the contention that the combination of aspirin and pravastatin is superior to each of the monotherapy components.

Some cautionary notes are appropriate before exploring the analysis.

First, the analysis assumes that the population included within the “no aspirin” group is representative of the entire population enrolled. However, since those who received “no aspirin” are not a randomized group, nor a stratified group within the randomized sample, this assumption is unproven. The reason these patients did not receive aspirin is not specified. There is therefore, no guarantee that the proposed comparison is meaningful.

Second, the analysis defines aspirin use or lack of use solely by the baseline use of the drug. There is only minimal information, which was supplied (see later p. 36) that the baseline use or lack of use of aspirin was maintained during the 3-5 years of follow-up, during which events were collected. The conclusion therefore is predicated on the assumption that those who were on aspirin at baseline were maintained on baseline and those not on aspirin at no time started this medication.

Third, the end-point for cardiac benefit for each study was not identical. Each individual study had a unique composite end point that defined the cardiovascular benefit. The particular composite most appropriate to answer the question of benefit was not prespecified before the database was unblinded.

Fourth, The definition of an event differed from study to study. There was no uniformity in the classification of an event. In particular, adjudication was used in some studies and not used in other study.

Fifth, the studies enrolled a varied population. There was no analysis that looked within each study at the subgroup of benefit of the combination of aspirin + pravastatin versus the individual components. It is possible that all benefit is derived from a single study.

Last, this analysis suffers from all the limitations of all meta-analyses.

A summary review of the five pivotal, secondary prevention studies for pravastatin are described below. The key information stressed in these summaries by these summaries is the patient population, the dosing instructions and the primary and secondary metrics of efficacy.

### 1. PLAC I-

Title of study: Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC I)

#### Inclusion Criteria:

The study proposed to enroll a total of 400 subjects. Those subjects, eligible for enrollment, are those undergoing coronary angiography for the following reasons

- Post-MI (< 12 weeks).
- For PTCA
- For unstable angina.
- For stable coronary artery disease.

In addition the mean of two consecutive LDL cholesterol obtained (at >2 but < 4) weeks apart of > 130 mg/dL and < 190 mg/dL and after at least one-month of an AHA Phase I diet. Those with a recent MI were to have the cholesterol measured at least 8 weeks post event

#### Exclusion criteria:

- Inability or unwillingness to comply with protocol including the requirement for a repeat angiogram.
- Other life-threatening conditions which would likely limit life-span to < 3 years
- Age > 75 years.
- Likely revascularization within 6 months.
- Type III hyperlipoproteinemia.
- Mean fasting triglycerides > 350 mg/dL.
- Endocrine disorders e.g. hyper or hypo-, thyroidism unless on stable thyroid hormone.
- Renal disease (Cr > 2.5 mg/dL, urinary protein > 2+, serum albumin < 3.0 g/dL).
- Hepatic or biliary disease
- Chronic pancreatitis.
- Dysproteinemia.
- Porphyria.
- SLE.
- Diabetes mellitus fasting blood sugar > 140 mg/dL or who are treated with insulin or hypoglycemic agents.
- Congestive heart failure (LVEF  $\leq$  30%).
- Hypertension (Sitting SBP (> 160 mm Hg) or DBP > 100 mm Hg despite treatment)

- History of recent (< 3 months) CVA.
- GI disease or surgery that might interfere with drug absorption.
- Excessive alcohol consumption.
- Treatment with medications that could interfere with lipid metabolism e.g. corticosteroids, conjugated estrogens (subjects with low stable doses are allowed), androgens, fish oil preparations, barbiturates, antacids, other lipid lowering drugs, thiazides, diuretics, beta adrenergic blockers, amiodarone (unless stable doses).
- Hypersensitivity to HMG-CoA reductase inhibitors.
- Potentially fertile women.
- Unreliability.

End points:

The primary end point of this study is the mean coronary artery diameter averaged over the number of segments analyzed.

Secondary endpoints:

Angiographic end-points:

- The directional changes in minimum and maximum diameters and percent stenosis averaged over the number of segments analyzed.
- Lesion development in coronary arteries, normal at baseline.
- The average numbers of stenosis and average numbers of new stenosis per patient.
- The change in average lesion severity per patient.
- The change in severity of lesions measured as 0-16%, 17-50%, 51-75% and 76-100% at baseline.
- The incidence of progression, regression and mixed or no response of stenosis.

Clinical event end points:

Events will be tabulated in two ways. The first analysis includes any event that occurred after the start of treatment. The second method includes any event for any time during the study but which occurred > 90 days after the start of treatment.

- Fatal and non-fatal myocardial infarctions as defined as:
  - An event reported by the investigator as an adverse event and confirmed by an external adjudication committee.
  - Or an event meeting two of the following three 1) chest pain, 2) with Q-wave changes in two consecutive leads, 3) elevations of CK or CK-MB
- All deaths and non-fatal myocardial infarctions combined
- All deaths non-fatal MIs, strokes and cardiovascular procedures (PTCA, CABG) combined.

Lipid measurements:

- The lowering of total cholesterol, LDL cholesterol and triglycerides and raising HDL cholesterol.

Tertiary end points:

- Lowering lipoprotein A and raising lipoprotein B

- Preventing coronary artery disease progression and clinical events based on categories of baseline LDL-cholesterol levels.
- Prevention in coronary artery events in subjects with LDL-C of between 150-169 and 170-189 and HDL-C below 35 mg/dL.
- Prevention of coronary artery disease related to degree of LDL-cholesterol.
- Determine effectiveness in coronary artery disease progression at sites of PTCA at > 6 months post randomization.
- To determine the effectiveness of pravastatin in decreasing the rate of coronary artery disease progression at the sites of PTCA performed during the trial > 6 months after randomization.
- To determine the effects on bypass graft patency, lesion development in bypass grafts and atherosclerosis affecting the native coronary artery circulation of patients with CABG.
- To determine the effect on stenosis roughness.

Dosing:

Patients will receive 2 x 20-mg tablets or matching placebo at bedtime. The dosage could be decreased for safety (not further stated) consideration.

Randomization considerations:

Patients are to be stratified by clinical baseline conditions (MI, PTA, or unstable angina including stable CAD; low density cholesterol (130-169) versus > 170.

Results:

There were a total of 408 subjects enrolled. Of these subjects 176/408 (43%) were post MI, 225/408 (55%) were post PTCA and 19/408 (5 %) were post CABG.

According to the sponsor all subjects were treated with 40-mg pravastatin.

There was no statistical difference in the primary end point i.e. the mean coronary artery diameter averaged over the number of segments analyzed.

There were many secondary end points. Those endpoints associated with cardiovascular endpoints are shown below:

Cardiovascular end points and nominal p-values are shown below.

Table 2- Secondary endpoints for PLAC I

Cardiovascular event <sup>2</sup>	All events			Excluding events occurring < 90 days from randomization <sup>1</sup>		
	Prav n=206	PBO N=202	p-value <sup>4</sup>	Prav N=206	PBO N=202	p-value <sup>4</sup>
Non-fatal or fatal MI	8 (4%) <sup>3</sup>	17 (11%) <sup>3</sup>	0.050	5 (3%) <sup>3</sup>	17 (11%) <sup>3</sup>	0.006
Non-fatal MI or CHD deaths	11 (6%)	20 (12%)	0.07	8 (4%)	19 (12%)	0.02
Non-fatal MI, all deaths, stroke or PTCA CABG	44 (23%)	49 (27%)	0.5	34 (19%)	42 (24%)	0.3

<sup>1</sup> The 90 day waiting period was prespecified as one of the outcomes  
<sup>2</sup> Events classified by independent review of documentation by clinical events adjudicator  
<sup>3</sup> Kaplan-Meier estimate of 3-year event rate.  
<sup>4</sup> Logrank between group p-value.

The specific population that benefited i.e. post MI, post-CABG or post PTCA was not submitted.

2. PLAC II:

Title of study: Efficacy and Safety of Pravastatin in Coronary Patients with Asymptomatic Carotid Artery Atherosclerosis: An Ultrasound Study of Plaque Progression Pravastatin Limitation of Atherosclerosis in the Carotid Arteries (PLAC II).

Inclusion criteria:

The study was to enroll at least 150 patients aged 50-74 males or post-menopausal females with established coronary artery disease, carotid atherosclerosis and LDL-C levels between 60-90<sup>th</sup> percentiles, inclusive.

- Coronary artery disease was defined as an acute MI (ECG and enzyme changes).
- Or coronary angiography demonstrating at least 50% narrowing of one of the coronary arteries.

Exclusion criteria:

- Inability or unwillingness to comply with protocol including repeat angiogram.
- CHD or other diseases which would likely limit life-span to < 5 years.
- Dysproteinemia.
- Likely revascularization within 6 months.
- Types I, III, IV or V hyperlipoproteinemia.
- Mean fasting triglycerides > 350 mg/dL.
- Endocrine disorders e.g. hyper- or hypo- thyroidism unless on stable thyroid hormone.
- Renal disease (Cr > 2.5 mg/dL, urinary protein > 2+, serum albumin < 3.0 g/dL).
- Hepatic or biliary disease.
- Chronic pancreatitis.
- Dysproteinemia.
- Porphyria.
- SLE.
- Diabetes mellitus fasting blood sugar > 140 mg/dL or who are treated with insulin or hypoglycemic agents.

- Congestive heart failure.
- Hypertension (Sitting SBP > 160 mm Hg or DBP > 100 mm Hg despite treatment).
- History of recent (< 3 months) CVA.
- GI disease or surgery, which might interfere with drug absorption.
- Excessive alcohol consumption.
- Treatment with medications that could interfere with lipid metabolism e.g. corticosteroids, conjugated estrogens (subjects with low stable doses re allowed), androgens, fish oil preparations, barbiturates, antacids, other lipid lowering drugs, thiazides, diuretics, beta adrenergic blockers, amiodarone (unless stable doses).
- Hypersensitivity to HMG CoA reductase inhibitors.
- Potentially fertile women.
- Unreliability.

#### Endpoints:

The primary objective to the study is to determine if pravastatin over a three-year period will retard the progression of atherosclerosis in the carotid arteries (ultrasound measurements).

Patients will prospectively be stratified into two groups > 60-75<sup>th</sup> percentile and > 75-< 90<sup>th</sup> percentile for LDL-Cholesterol.

#### Secondary objectives:

- To determine the safety of long-term treatment with pravastatin.
- To quantify the long-term effects of pravastatin on the lipid profile.
- To determine the incidence of coronary (MI and sudden) deaths as well as CVA (stroke and TIA) in the study groups.
- Natural history among patients assigned to placebo group.

#### Dosing Instructions:

Each subject will be started on a dose of 1 (20-mg tablet) or placebo to be taken 3-4 hours after the evening meals. The dose is to be maintained for the first three months. After three months the dose could be doubled predicated on a LDL > 110 or the dose halved if the LDL-C was < 90 mg/dL.

#### Results:

There were 151 subjects enrolled.

Of those enrolled three subjects were maintained on 10-mg, 18 on 20-mg and 54- on 40-mg of pravastatin

There was no benefit to the primary end-point, which was progression of the rate of the mean-maximum intimal-medial thickness, averaged over 12 carotid artery segment walls.

The FDA reviewer (Dr. Aurecchia) does not tabulate the cardiovascular end points as described in the protocol but tabulated other outcomes as listed in the table below.

Table 3. Comparison of cardiovascular event rates by treatment group<sup>1</sup> (p-values are nominal)

Cardiovascular events <sup>2</sup>	Prav (n=75)	PBO (n=76) p-value	p-Value <sup>3</sup>
Coronary deaths	Not tabulated		
CVA	1 (1%)	3 (4%)	0.33
Coronary deaths and CVA	Not tabulated		
Non-fatal MI or all deaths <sup>4</sup>	5 (7%)	13 (17.1%)	0.049
Non-fatal or fatal MI <sup>4</sup>	2 (3%)	10 (13%)	0.02
Non-fatal MI, All deaths, stroke or PTCA/CABG <sup>4</sup>	12 (16%)	18 (24%)	0.2
<sup>1</sup> Kaplan-Meier estimate of 3-year event rate			
<sup>2</sup> Event classification based on independent review of documentation by clinical event adjudicator			
<sup>3</sup> Log rank Between-group p-Value			
<sup>4</sup> The statistician's review of the study shows these event as end points but notes that they were stipulated after completion of the study			

Safety:

With respect to safety, 26.1% of those in the pravastatin and 42.1% of those in the placebo cohort experienced adverse events. Nine percent of the pravastatin and eighteen percent of the placebo subjects discontinued due to adverse events, There were no discontinuations due to due to laboratory abnormalities but one subject treated with pravastatin had elevations of AST and ALT. These resolved without discontinuation of treatment.

3. CARE study:

Title of study: Cholesterol and Recurrent Events (CARE): A Secondary Prevention Trial of Lowering Blood Cholesterol After Myocardial Infarction.

Inclusion Criteria:

Subjects eligible for enrollment are subjects:

- 3-20 Months post-MI.
- Between the ages of 21-75 of either gender (if female needs to be post-menopausal or surgically sterile).
- With total cholesterol < 240 mg/dL and plasma LDL-cholesterol between 115-174 mg/dL.

Exclusion Criteria:

Subjects were excluded for:

- Initial plasma cholesterol > 270 mg/dl.
- Mean fasting plasma total cholesterol > 240 mg/dL or plasma LDL-C < 115 mg/dL or > 174 mg/dl by measurements of the core laboratory.
- Serum triglycerides > 750 mg/dL by local laboratory or > 350 mg/dL by core laboratory.
- Ejection fraction < 25 % obtained within 20 months before randomization and the absence of an intercurrent MI between the measurement and randomization.
- CHF (Class III-IV).
- Sensitivity or non-response to HMG-CoA reductase inhibitors.
- No coronary atherosclerosis on arteriogram.
- Renal disease.
- Excessive ethanol intake.
- Hepatobiliary disease.

- Malignancy or other medical condition likely to limit survival, require radiation or chemotherapy or interfere with participation in the study.
- History of immune disorder.
- Untreated endocrine disorders.
- Significant GI disease.
- Treatment with lipid lowering drugs.
- Severe valvular heart disease, requiring surgery.
- Psychosocial condition or geographical distance that would make the subject unsuitable for enrollment.
- Recent other experimental treatments.

Deferrals:

Six months must elapse after angioplasty for the subject to enroll. Three-months must elapse after bypass surgery for the subject to enroll or one-month must elapse after major surgery.

Dosing:

Subjects will take a dose of 40-mg pravastatin at bedtime. If the LDL-C on two consecutive measurements was < 50 mg/dL the dose of pravastatin is to be halved.

End Points:

The primary end-point is to determine if pravastatin will decrease recurrent coronary heart disease events (i.e. combination of fatal coronary heart disease and definite nonfatal MI).

Secondary end point:

To determine the benefit on fatal coronary heart disease

Tertiary end point:

To determine the benefit on total mortality

Additional outcome variables:

- MI, non-fatal (definite and probable).
- MI fatal and nonfatal (definite and probable).
- Development of overt CHF.
- Need for coronary artery bypass surgery or non-surgical interventions.
- Hospitalization for cardiovascular disease.
- Cerebrovascular disease, fatal and non-fatal stroke or TIA.
- Hospitalization for peripheral arterial disease.
- Hospitalization for unstable angina.
- Total coronary heart disease events.
- Cardiovascular mortality.
- Total cardiovascular disease.
- Atherosclerotic cardiovascular disease fatal.
- Atherosclerotic cardiovascular disease fatal (fatal and non-fatal).

**Results:**

A total of 4,159 subjects were randomized into this study. Of these, 2,081 were randomized to pravastatin and 2,078 to placebo. The sponsor claims that all subjects were treated with 40-mg pravastatin at baseline.

The various outcomes are summarized below:

Table 4. Outcomes of CARE study.

	Pravastatin N=2081	Aspirin N=2078	Relative Risk	p-value
Fatal CHD plus Non-fatal MI	212 (10%)	284 (13%)	0.76	0.003
Fatal CHD	96 (5%)	119 (6%)	0.80	0.1
Total mortality	180 (9%)	196 (9%)	0.91	0.37
Need for CABG or non-surgical intervention	294 (14%)	391 (19%)	0.73	0.0001
Myocardial infarction nonfatal	182 (9%)	231 (11%)	0.77	0.01
Myocardial infarction, nonfatal and fatal	216 (10%)	283 (14%)	0.75	0.002
Development of overt CHF	146 (7%)	160 (8%)	0.9	0.38
Cerebrovascular disease, fatal and non-fatal	99 (5%)	129 (6%)	0.76	0.04
Hospitalization for CV disease	852 (41%)	949 (46%)	0.87	0.004
Hospitalization for peripheral artery disease	54 (3%)	61 (3%)	0.88	0.49
Hospitalization of unstable angina	317 (15%)	359 (17%)	0.87	0.07
First coronary heart disease	624 (30%)	729 (53%)	0.83	0.0008
First cardiovascular disease	890 (43%)	991 (48%)	0.87	0.003
Cardiovascular mortality	112(5%)	130 (6%)	0.85	0.22
Atherosclerotic cardiovascular disease, fatal	111 (5%)	129 (6%)	0.85	0.22
Atherosclerotic cardiovascular heart disease, fatal and nonfatal	710 (34%)	816 (39%)	0.85	0.002

The primary end-point of this study fatal CHD plus non-fatal MI was highly statistically significant relative to placebo.

The results in the two sub-groups of interest for this review, i.e. with and without aspirin, for CHF and non-fatal MI are shown below. Reading off the curves at 2000 days, this reviewer’s estimates of at 2,000 days is shown below.

Table 5. Estimates of event-free survival at 2,000 days.

Aspirin	Pravastatin	+	-
+		0.91	0.86
-		0.86	0.84

The effect of aspirin on the benefit of among those treated with pravastatin is approximately 44% decrease in event rate. Among those not treated with aspirin the effect is approximately a 12% decrease in event rate.

**Safety:**

There were more subjects who discontinued from the placebo group than the pravastatin group (121 versus 92). The vast majority of these adverse event difference were the incidence of increased triglycerides or lipids (16 versus 1) comparing placebo to pravastatin.

#### IV. LIPID (Long term Intervention with Pravastatin in Ischemic Disease).

Title of Study: Randomized Study of the Effects of Prolonged treatment with Pravastatin on Mortality and Morbidity In Patients with Coronary Heart Disease.  
A Multicentre Australian and New Zealand Study

##### Inclusion Criteria:

Two types of patients were eligible for enrollment, those with a history of an acute MI (three months to three years prior to randomization) and those with a history of unstable angina (three months to three years before enrollment).

Patients were considered eligible if the MI was the discharge hospital diagnosis for the subject or if two of the following three were observed 1) typical ischemic pain 2) CK elevations 3) ECG changes consisting of new Q waves or ST-T wave changes lasting > 1 day.

Patients were also considered as eligible if they were discharged from the hospital with a diagnosis of unstable angina pectoris. The diagnosis may arise from an acute admission or could be for a subsequent elective admission with evidence of stenosis on coronary angiogram. Unstable angina is defined as a definite ischemic pain of increasing frequency and duration or anginal pain at rest. Subjects could also be enrolled after a non-MI admission but with definite ischemic pain.

A serum cholesterol measurement of between 4.0 and 7.0 mmol/L as measured by a core laboratory prior to randomization was required.

##### Exclusion Criteria:

- Patients who are unlikely to be available for the duration of follow-up due to unreliability or expectation of survival of < 6 years.
- Recent cardiac surgery, angioplasty or major illnesses within 3 months.
- Any acute MI admission or admission for unstable angina within 3 months.
- Severely compromised cardiac function (NYHA class III-IV; ejection fraction < 25%)
- History of cerebrovascular disease (stroke or TIA).
- Renal or hepatic disease.
- Uncontrolled endocrine disease.
- Chronic pancreatitis, dysproteinemia, porphyria, SLE.
- Treatment with lipid-lowering agents, cyclosporine or other investigational drugs.
- Hypersensitivity to HMG-CoA reductase inhibitors.
- Significant GI disease.
- Women of childbearing potential.
- Fasting triglyceride of  $\geq 5$  mmol/L.

Dosing:

The initial dose is 2 x 20-mg pravastatin or placebo, at bedtime. If the cholesterol falls below 3.0 mmol/L on two successive samples, the dose could be decreased to 20 mg/day. If the cholesterol falls below 3.0 mmol/dL on two successive occasions while on 20 mg the dose should be decreased.

Randomization will be stratified by inclusion diagnosis (MI or unstable angina).

Primary objective

The primary objective of the study is to determine if cholesterol reduction with pravastatin reduces mortality due to coronary heart disease among patients with a history of myocardial infarction or unstable angina.

Secondary end-point:

The secondary end-points are:

- Effect on total mortality.
- Effect on incidence of non-fatal MI and fatal coronary heart disease.
- Total stroke
- Non-hemorrhagic stroke.
- Incidence of cardiovascular mortality.
- Incidence of revascularization procedures.
- Effect on total cholesterol, LDL-C, HDL-C, triglycerides, apolipoprotein A1 and apolipoprotein B.
- Relationship between change in lipid fraction and coronary heart disease mortality and other end points.
- Effect on days of hospitalization.

Results:

There were 9,014 subjects who were randomized into this study, 4,512 subjects to pravastatin and 4,502 subjects to placebo. Approximately 82% of those enrolled received aspirin at baseline. Approximately 1/3 of those enrolled was enrolled because of unstable angina and the other 2/3 of those enrolled because of a previous MI.

The sponsor notes that all subjects were treated with the 40-mg pravastatin dose.

With respect to end points the following table shows the metrics evaluated.

Table 6- Outcomes of LIPID study

	Pravastatin N=4512	Placebo N= 4502	p-value
Coronary mortality	287 (6.3%)	373 (8.3%)	0.0004
Total mortality	498 (11.0%)	633 (14.1%)	0.0001
Non-fatal MI + fatal coronary artery disease	557 (12.3%)	715 (15.9%)	0.0001
Cerebrovascular accident	169 (3.8%)	204 (4.5%)	0.05
Non-hemorrhagic stroke	154 (3.4%)	196 (4.4%)	0.02
Cardiovascular mortality	331 (7.3%)	433 (9.6%)	0.0001
Revascularization procedures	584 (12.9%)	706 (15.7%)	0.0001
Additional end-points from previous studies			
Coronary death + CVA	Data not available. These are composite endpoints with all components included above.		
Non-fatal MI + all deaths			
Non-fatal MI, all deaths, stroke or PTCA/CABG			

The study prospectively indicated endpoints all appear as statistically superior to placebo in this population.

#### Safety:

Four hundred and eighty three (10.7%) patients randomized to pravastatin versus (12.7% treated with placebo discontinued study drug permanently due to an serious adverse event or an adverse drug reaction. Abnormalities in liver function studies (defined as  $> 3 \times$  ULN) were more common in the pravastatin group than placebo group (27 versus 11 events). For the pravastatin and placebo groups respectively, 14 and 2 of these episodes were  $> 5 \times$  ULN. No cases of rhabdomyolysis were reported among those treated with pravastatin.

#### Study # 5:Regression Growth Evaluation Statin Study (REGRESS)

##### Inclusion criteria:

The study proposed to enroll 720 subjects. These subjects were to be

- Male patients younger than 70 years old undergoing cine-angiography to assess anginal complaints.
- A qualifying lipid measurement of the patient, as measured by the core laboratory, with a total cholesterol of between 4.0 –8.0 mmol/L after 4 or more weeks of dietary advice. If, the subject is post-myocardial infarction, eight weeks must elapse prior to the index measurement. Subjects undergoing intervention should have the cholesterol measured prior to the procedure.
- At least one coronary stenosis  $\geq 50\%$ .

##### Exclusion Criteria:

Subjects ere excluded for the following reason or conditions:

- $>70$  years old
- Inability or unwillingness to comply.
- Fasting cholesterol  $< 4.0$  mmol/L or  $> 8.0$  mmol/L or triglycerides  $> 4.0$  mmol/L (by the Core laboratory).
- Life threatening illnesses other than coronary artery diseases where life expectancy is less than the study duration; e.g. Malignancy
- Cardiac valvular disease.

- Cardiomyopathy.
- Previous CABG.
- Previous PTCA (within 1 year of randomization).
- Clinical CHF, requiring diuretics; ejection fraction < 0.3.
- Complete A-V block.
- Complete LBBB.
- WWPW syndrome.
- Recent use of lipid lowering drugs or poor response to HMG-CoA reductase inhibitors.
- Immune disorder (e.g. SLE, dysproteinemia, major allergic or hypersensitivity disorders).
- Significant metabolic disease.
- Renal disease.
- Hepatobiliary disease.
- Severe overweight (> 30 kg/M<sup>2</sup>).
- Muscle disorders.
- Diabetes mellitus.
- Treatment with chronic corticosteroids or androgens.
- Porphyria.
- Significant gastrointestinal disease or disorder.
- Excess ethanol use.

End points:

Primary end point: The primary purpose of the study is to define the anatomic changes to the coronary artery by repeated quantitative analysis, in relationship to coronary flow reserve and functional cardiac parameters and treatment stratum.

• Secondary objectives

To determine the effectiveness of pravastatin on decreasing the incidence of the following clinical and ischemic events:

- Unstable angina pectoris.
- Myocardial infarction
- Total deaths, cardiac deaths and unexpected sudden deaths.
- To assess the relationship of coronary flow reserve and cardiac parameter modification with anatomical changes and therapeutic approach modes.
- To assess progression/regression of atherosclerosis by measuring wall thickness, lumen diameter and peak flow velocity in both carotid and left femoral arteries by ultrasound
- The effects of pravastatin in lowering lipids.
- Visual assessment of coronary angiograms
- Cost-benefit.
- Compliance with dietary/nutritional advice.

Doses: The initial dose of pravastatin/ placebo was to be 40 mg /day at bedtime. If the serum cholesterol decreased to < 2.0 mmol/L the dose was to be decreased to 20 mg pravastatin/placebo.

Study design: Subjects will be randomized and stratified by baseline management i.e., 1) PTCA; 2) CABG or 3) CAD with medical management. Subjects are to be followed for two years.

Results: (These results were summarized from Dr. Aurecchia’s review of January 1996.)

There were a total of 885 subjects who were randomized into this study. Among these subjects the percent of those who were treated with PTCA (31%), CABG (20%) or maintained on medical management (49%). The fraction of those patients enrolled who were concurrently treated with aspirin is not stated in the review. The duration of follow-up was for 24 months.

The primary metric was decreasing progressive shortening of the mean segmental diameter, which was significant for pravastatin –treated patients. A composite secondary endpoint of non-fatal MI, all cause mortality, stroke/TIA or unscheduled PTCA/CABG favored pravastatin. The other three composite endpoints although favoring pravastatin were not nominally significant (data not included in the MO review).

Table 7. Clinical outcome for the REGRESS study.

Event	Pravastatin (n=450)	Placebo (n=435)	P-value
Non-fatal MI, All cause mortality, stroke/TIA or unscheduled PTCA/CABG	48 (11%)	79 (18%)	0.002

Aspirin:

Aspirin is presently approved for over the counter use for several indications but also contains professional labeling for additional indications. The rationale for the approval of aspirin for its use in subjects with cardiovascular disease was reviewed in the Federal Register (1988; 53: 46204-46259 and 1996 61: 30002-30009). Use of aspirin for the treatment of cardiovascular disease was also the subject of a joint Cardio-renal-OTC advisory committee meeting held on 23 January 1997. Approval of this NDA would be the first non-OTC approval for any aspirin-containing drug.

All studies were reviewed from the specific publication results

1. The AMIS study (The Aspirin Myocardial Infarction Study). (Circulation 1980, 62, V79-84)

Inclusion criteria:

Subjects were enrolled in 30 clinical centers within the US if they were at least 8 weeks but within 5 years of a myocardial infarction. The total number of subjects enrolled was 4,524 subjects.

Exclusion criteria:

Subjects were excluded if they were aspirin intolerant, had severe ulcer disease, had prior cardiovascular surgery, had uncontrolled hypertension or needed other platelet-active drugs.

Primary end points:

The primary objective of this trial was to test the hypothesis that total mortality over a three-year period would be decreased among those treated with aspirin.

Secondary objectives:

Included

- The incidence of coronary heart disease mortality (definite MI or sudden death believed to be caused by a MI).
- Coronary incidence (a combination of coronary heart disease mortality or definite MI
- Fatal or non-fatal stroke.

For events other than death the exact date was not included (so the measurement was not a time to first event but rather total number of events during the three-year observation period).

Dose: Aspirin 0.5 gram twice daily or placebo

Results:

Those who enrolled were largely > 6 months post MI.

The results are shown below (Table 3 of the paper).

Table 8- Results of the AMIS study

	% Patients		Z-value	Cox Adjusted Z
	Aspirin	Placebo		
Total mortality	10.8	9.7	1.27	0.02
Coronary death	8.7	8.0	0.82	-0.35
Non-atherosclerotic CV disease	0.6	0.7	-0.38	-0.58
Non CV disease	1.4	0.9	1.78	1.5
Sudden death (excluding suicide, homicide or accident)				
< 1 hour from onset of symptoms	2.7	2.0	1.44	0.92
< 24 hours within onset of symptoms	3.5	3.0	0.90	0.32
Recurrent MI				
Definite	6.3	8.1	-2.34	
Definite or probable	7.7	9.5	-2.11	
Definite, probable or suspect	9.5	11.6	-2.28	
Stroke				
Definite	1.2	2.0	-2.26	
Definite probable or suspect	1.4	2.2	2.15	
Intermittent cerebral attack				
New event	3.2	3.5	-0.61	
Peripheral arterial occlusion				
Definite	0.4	0.5	-0.67	
Definite, probable or suspect	0.7	0.8	-0.19	
Pulmonary embolism				
Definite	0.3	0.3	-0.28	
Definite, probable or suspect	1.1	1.5	-1.22	
Angina Pectoris				
New events	27.6	28.0	-0.18	
Recurrent angina or chest pain	79.8	81.9	-1.24	
Intermittent claudication (new event)	6.0	5.8	0.26	
Heart failure (new event)	9.9	9.9	-0.04	
Coronary arteriography (w/o surgery)	3.6	4.0	-0.65	
ECG-documented arrhythmias	14.2	13.1	1.07	
Cardiovascular surgery	6.6	7.9	-1.65	

There was no benefit in overall mortality. Secondary end points included coronary incidence, mildly trended towards aspirin 14.1% versus 14.8% ( $Z=-0.61$ ). None of the non-fatal cardiovascular events were statistically significant, though they favored aspirin treatment.

Safety:

The percent of subjects with side effects are shown below. The safety profile favored placebo.

Table 9- Safety from AMIS study

Event	Aspirin (%)	Placebo (%)	Z-Value
Symptom of ulcer or gastritis	23.7	14.9	7.52
Bloody stools	4.9	2.9	3.38
Stomach pains	14.5	4.4	11.56
Heartburn	11.9	4.8	8.54
Nausea	6.3	1.9	7.41
Vomiting	1.3	0.2	4.12
Constipation	3.6	0.9	6.12

2. The Coronary Drug Project Research Group ( J Chron Dis ; 1976; 29: 625-642)

Inclusion Criteria: Those enrolled were male NYHA functional Class I-III with at least one ECG documented MI prior to entry. Patients were recruited from previous Coronary Artery Drug Project studies, which tested the following treatments: dextrothyroxine; estrogen 5.0 mg/day; or estrogen 2.5 mg/day. A total of 1,529 subjects were enrolled into the study.

Exclusion criteria: Subjects were excluded if they had other diseases such as cancer, chronic renal disease, chronic hepatic disease and pulmonary insufficiency. They were excluded for use of aspirin or an aspirin containing drugs on a regular basis and inability to be removed from these regimens. They were excluded for use of anticoagulant therapy or for hypersensitivity to aspirin.

Dose: The subject received 324 mg TID of aspirin or placebo control.

End points:

- The primary parameter of interest was all cause mortality.

End points of secondary interest were:

- Cause specific mortality
- Nonfatal events (MI, PE, thrombophlebitis, stroke, intermittent cerebral ischemic attacks) as well as the combination of fatal and nonfatal events.

Results:

There were a total of 1,529 subjects enrolled. Subjects were followed between 10-28 months. The average follow-up was 22 months. The amount of time from the index MI to entry was > 5 years for approximately 75% of those enrolled. Approximately 505 of those enrolled were NYHA class II-III.

**Outcomes:**

Table 10- Outcomes of the Coronary Drug Project Research Group

Event	Aspirin, number (%) N=758	Placebo, number (%) N=771	Z-Value
Death			
All Causes	44 (5.8%)	64 (8.3%)	-1.9
All cardiovascular	41 (5.4%)	60 (7.8%)	-1.87
All non-cardiovascular	2 (0.3%)	4 (0.5%)	-0.80
Cause unknown	1 (0.1%)	0	1.01
Coronary heart disease	35 (4.6%)	49 (6.4%)	-1.49
Sudden cardiovascular	20 (2.6%)	25 (3.2%)	-0.70
All cancer	1 (0.1%)	3 (0.4%)	-0.98
Other non-cardiovascular	1 (0.1%)	1 (0.1%)	0.01
Definite non-fatal MI	28 (3.7%)	32 (4.2%)	-0.46
Coronary death of definite nonfatal MI	61 (8.0%)	79 (10.2%)	-1.49
Definite (fatal and nonfatal) pulmonary embolism	2 (0.3%)	3 (0.4%)	-0.43
Definite or suspected fatal or nonfatal pulmonary embolism or thrombophlebitis	9 (1.2%)	9 (1.2%)	0.04
Definite or suspected fatal or nonfatal stroke or intermittent cerebral ischemic attack	37 (4.9%)	41 (5.3%)	-0.39
Any definite or suspected fatal or nonfatal cardiovascular event	364 (48%)	377 (49%)	-0.34

None of the events were by themselves statistically significant. All cause mortality and cardiovascular mortality approached significance. There were no differences in hospitalization; 26.3% of those treated with aspirin versus 26.7% of those treated with placebo had at least one hospitalization.

**Safety:**

The tabular listing of new clinical findings is shown below.

Table 11 Outcomes of the Coronary Drug Project Research Group for safety

Event	Aspirin , number at risk (%) with event)	Placebo m number at risk (%) with event)	Z-value
Gastrointestinal			
Peptic ulcer	727 (2.8%)	744 (2.2%)	0.75
Gastritis	727 (5.4%)	744 (3.9%)	1.34
Hematemesis	727 (0.4%)	744 (0.3%)	0.47
Bloody stools	727 (3.0%)	744 (2.8%)	0.23
Black tarry stools	727 (2.8%)	744 (1.5%)	1.70
Blood in urine (macroscopic)	722 (1.2%)	741 (0.3%)	2.16
Metabolism			
Acute gouty arthritis	540 (2.6%)	544 (0.9%)	2.1
Podagra	542 (1.4%)	550 (0.2%)	2.15
Tophi	546 (0%)	553 (0.2%)	-0.99
Uric acid stones	545 (0.6%)	551 (0.9%)	-0.69

Only macroscopic blood in the urine and evidence of gout were increased among patients during the follow-up period. Abdominal pains and diarrhea were also more common among those treated with aspirin.

The percentage of patients reporting problems at one or more visits is shown below.

Table 12- Percent of patients reporting one or more problems

Problem reported	Aspirin (% patients), n= 727	Placebo (%patients), n=744	Z-value
Nausea without vomiting	5.1%	3.2%	1.79
Vomiting	0.8%	0.7%	0.34
Heartburn	5.6%	3.9%	1.57
Stomach pains	12.5%	6.3%	4.08
Diarrhea	1.2%	0.3%	2.16
Itching of the skin	1.1%	0.5%	1.20
Uticaria	0.6%	0.1%	1.37
Other types of rash	1.2%	0.9%	0.55
Ringling of ears	0.1%	0.3%	-0.56

3. A Randomized Controlled Trial of Acetyl Salicylic Acid in the Secondary Prevention of Mortality from Myocardial Infarction (Elwood PC, Cochrane, AL, Burr, ML, Sweetnam PM, Williams G, Welsby E, Hughes SJ, Renton R ; Br Med J 1974; 19: 436-440)

Inclusion criteria:

The study enrolled males under 65 years old, recently discharged with a diagnosis of myocardial infarction (as specified by the diagnosing hospital). At some point the admission criteria was changed to allow enrollment those who were discharged with a diagnosis of myocardial infarction within 6 months.

Exclusion Criteria:

Subjects were excluded if they were receiving anticoagulant therapy or had peptic ulcer disease.

Dose:

The dose was 300-mg aspirin or placebo to be taken with water prior to breakfast.

End points:

The primary end-point was the prevention of death.

Results.

A total of 1,239 male patients were enrolled. The mean time since the index myocardial infarction was approximately 10 weeks. Approximately 50% of these patients were < 6 weeks post myocardial infarction. The mean age was approximately 55 years. The observation period was for 24 months.

The mortality rates at 24 months were 61 (10.9%) among those treated with placebo versus 47 (8.3 %) among those treated with aspirin. The differences were not statistically different.

Safety:

The safety aspects of the study were not described.

4. The Persantine and Aspirin in Coronary Heart Disease (the PARIS study) (Circulation, 1980, 62: 3: 449-461)

Inclusion Criteria:

Patients between 8 weeks and 60 months after a documented myocardial infarction were eligible for enrollment. These subjects must avoid aspirin-containing or platelet active drugs.

Exclusion criteria:

Patients with life threatening disease or problems that might affect long-term follow-up were excluded.

Dose:

Subjects were treated with one of three regimens. 1) Persantine 75 mg + Aspirin 324 mg three times a day (PER/ASA group) 2) Aspirin 324 mg three times a day plus placebo persantine (ASA group) or 3) placebo persantine plus placebo aspirin (PBO group). The primary comparison was between persantine + aspirin and aspirin. Patients were therefore randomized in a 2:2:1 ratio to PER/ASA: ASA: PBO.

Primary metric of concern:

The primary metric was total mortality, coronary artery mortality, and coronary incidence (coronary death or definite non-fatal MI).

Secondary metrics of concern:

Secondary metrics of concern included nonfatal cardiovascular events such as recurrent MI, angina pectoris, congestive heart failure, stroke, pulmonary embolism and cardiovascular surgery.

A Mortality and Morbidity committee verified the data.

Results:

A total of 2,026 patients were enrolled (1,759 men and 267 women) aged 30-74 years. The number of subjects in the PER/ASA: ASA: PBO groups was 810: 810: 406. The duration of observation was a mean of 41 months. Vital status was available for all but 6 subjects 2 in the PER/ASA and 4 in the ASA group

Table 13- Events during the PARIS study

Events	Percent subjects			Differences in percent (Z-Value)		
	PER/ASA	ASA	PBO	PER/ASA vs. ASA	PER/ASA vs. PBO	ASA Vs. PBO
Death						
All cause	10.7	10.5	12.8	0.25 (0.07)	-2.07 (-1.00)	-2.31 (-1.05)
All cardiovascular	9.0	9.1	11.1	-0.12 (-0.18)	-2.07 (-1.02)	-1.95 (-0.86)
All non-cardiovascular	1.7	1.2	1.7	0.49 (0.70)	0 (-0.18)	-0.49 (-0.77)
Cause unknown	0	0	0			
Coronary heart disease	7.7	8.0	10.1	-0.37 (-0.25)	-2.44 (-1.32)	-2.07 (-1.01)
Sudden coronary	3.7	5.6	4.4	-1.85 (-1.55)	-0.73 (-0.35)	1.12 (0.94)
Non-sudden coronary	4.0	2.5	5.7	1.48 (1.29)	-1.71 (-1.61)	-3.20 (-2.65)
All Cancer	1.1	0.9	0.2	0.25 (0.45)	0.85 (1.33)	0.62 (1.10)
Other non-cardiovascular	0.6	0.4	1.5	0.25 (0.58)	-0.86 (-1.57)	-1.11 (-1.99)
Definite nonfatal MI	7.9	6.9	9.9	0.99 (0.70)	-1.95 (-1.54)	-2.94 (-2.11)

Definite acute coronary insufficiency	3.5	4.1	3.0	-0.62 (-0.51)	0.50 (0.45)	1.12 (0.84)
Definite angina pectoris with hospitalization	5.9	6.2	7.4	-0.25 (-0.23)	-1.46 (-1.14)	-1.22 (-0.95)
Definite stroke	1.2	1.1	2.0	0.12 (0.28)	-0.74 (-1.06)	-0.86 (-1.29)
Coronary incidence (primary endpoint)	13.8	14.0	18.5	-0.12 (-0.13)	-4.65 (-2.30)	-4.52 (-2.18)
All death or definite nonfatal MI	16.8	16.0	20.9	0.74 (0.28)	-4.15 (-1.97)	-4.89 (-2.19)

(Comment: By usual criteria, the primary metric of consideration i.e. all deaths comparing the PER/ASA vs. ASA group was not significant. There were nominal differences, uncorrected for multiple comparisons, when comparing PER/ASA vs. PBO or ASA vs. PBO)

Table 14-Other events during the PARIS study

Event	Percent Patients			Z-values		
	PER/ASA	ASA	PBO	PER/ASA vs. ASA	P/ASA vs. PBO	ASA vs. PBO
Definite CHF	4.0	4.2	7.2	-0.22	-2.46	-2.28
De novo arrhythmias	9.4	10.4	11.3	-0.57	-0.85	-0.39
Recurrent arrhythmias	18.4	19.5	25.2	-0.32	-1.62	-1.35
Definite intermittent cerebral ischemic attacks	0.9	0.6	0.2	0.63	1.28	0.76
Definite peripheral arterial occlusion	0.4	0.1	0.7	0.85	-1.02	-1.72
Definite intermittent claudication (new)	5.3	3.4	4.9	1.73	0.27	-1.15
Definite angina pectoris (new)	28.9	25.2	23.4	1.22	1.46	0.47
Definite angina pectoris (recurrent)	68.7	69.0	64.9	-0.08	0.91	0.98
Cardiovascular surgery	5.1	5.5	5.7	-0.31	-0.42	-0.17
Hospitalization longer than 2-weeks Any	13.0	12.5	16.4	0.83	-1.61	-1.88
MI	3.4	3.1	6.5	0.28	-2.60	-2.83
Open heart and circulatory disease	5.0	5.2	6.9	-0.20	-1.40	-1.23
GI disorder	1.1	1.5	1.2	-0.65	-0.17	0.37

(Comment: There were no apparent differences between the primary groups of interest PER/ASA vs. ASA. There were nominal differences favoring PER/ASA or ASA vs. PBO for definite CHF or hospitalization of greater than 2 weeks for MI.).

**Safety:**

The safety of the treatments is shown below:

Table 15- Safety for those enrolled in the PARIS study

Event	Percent Patients			Z-values		
	P/ASA	ASA	PBO	P/ASA vs. ASA	P/ASA vs. PBO	ASA vs. PBO
Patient Complaints						
Stomach pain	15.8	17.2	7.7	-0.82	3.74	4.41
Heartburn	9.6	9.4	5.2	0.19	2.58	2.43
Vomiting	2.5	3.2	1.0	-0.95	1.59	2.37
Hematemesis, bloody stools or black tarry stools	4.0	4.1	2.0	-0.12	1.77	1.87
Constipation	4.0	4.7	2.0	-0.76	1.71	2.34
Dizziness	8.5	6.5	5.2	1.58	2.12	0.82
Headache	9.6	4.1	3.7	4.56	4.01	0.27
Symptoms reported by physicians as problems						
Hematemesis, bloody stools or black tarry stools	5.9	6.4	2.5	-0.42	2.47	2.81
Symptoms suggestive of peptic ulcer disease, gastritis, or erosion of gastric mucosa	20.7	18.1	13.2	1.35	3.19	2.09
Reason for permanent or temporary discontinuation from medications						
Stomach pains	10.0	10.2	4.5	-0.16	3.16	3.29
Heartburn	3.4	4.2	1.2	-0.97	1.96	2.79
Nausea without vomiting	3.9	4.7	2.2	-0.89	1.39	2.12
Vomiting	1.2	2.4	0.7	-1.79	0.66	2.12
Hematemesis, bloody stools and/or black tarry stools	3.6	3.4	1.7	0.30	1.77	1.53
Headache	3.4	1.7	1.0	2.20	2.63	0.83

(Comment: Aside from patient complaint and reason for discontinuation for headache that was greater in the PER/ASA group than in the ASA group, there were no differences between the two groups. In comparing either the PER/ASA group or the ASA group to the placebo group there were increases in gastric symptoms as reported by the patient, by the physician or as reason for temporary or permanent discontinuation).

5. Aspirin and Secondary Mortality After Myocardial Infarction (Elwood PC, Sweetam, PM The Lancet ii; 1979. 1313-1315.)

Inclusion Criteria:

Patients with confirmed myocardial infarction were enrolled into the study

Exclusion Criteria:

Patients treated with anticoagulants or patients with peptic ulcer disease were not included.

Prespecified end points: not stated.

Dose: 300 mg three times a day or corresponding placebo for one year.

Results:

A total of 1,682 subjects were enrolled (1,434 males and 248 females). Twenty five percent were enrolled within 3 days of the infarction with a total of 50% within 7 days of the index infarction. Of these subjects, 832 were treated with aspirin and 850 were treated with placebo. An additional 43 patients (15 in the aspirin and 28 in the placebo group were excluded as not having a baseline infarction). Subjects were followed for a total of 1 year.

There were 102 (12.3%) deaths among those treated with aspirin and 126 (14.8%) among those treated with placebo. The difference was not significant. The authors note that the data on re-infarction was were "limited and uncertain". Based on their available data, there were 133 (16.0%) of those on aspirin and 189 (22.2%) of those taking placebos who died or who survived but were admitted to hospital with a non-fatal myocardial infarction.

Safety:

There was no specific listing of adverse events. There were 98 subjects taking aspirin (12%) and 89 (10%) among those taking placebo who discontinued due to adverse events. The text notes that there were 8 subjects on aspirin and 4 on placebo who were discontinued due to gastrointestinal bleeding.

6. The German Aspirin Trial: A Comparison of Acetylsalicylic Acid, Placebo and Phenocoumon in Secondary Prevention of Myocardial Infarction. Breddin K, Loew D, Lechner K, Oberla K, Walter E, Circulation, 1980; 62: V-63- V72

**Inclusion Criteria:**

Male patients aged 45-70 years who were 30-42 days post-myocardial infarction were eligible for enrollment.

**Exclusion Criteria:**

Patients with hypertension (DBP > 110 mm Hg), recent ulceration of the gastrointestinal tract, cerebral ischemia severe hepatic or renal insufficiency, as well as patients who were unwilling or unable to cooperate were excluded.

**Dose:** Aspirin 1.5 g/day (divided into three doses); phenprocoumon (the dose was based either on thrombotest or prothrombin time prolongation of 1-12% and 15-25%, respectively), or placebo.

**Primary End point:** Coronary deaths (fatal myocardial infarction and sudden death) and coronary events (coronary death and nonfatal myocardial infarctions).

**Results:** There were a total of 946 subjects enrolled, 317 to the aspirin group, 309 to the placebo group and 320 to the phenprocoumon group. The patients were to be followed for two years. The primary analyses were comparing ASA to phenocoumon and ASA versus placebo. Subjects were apparently censored when any one of the following events occurred: death, fatal or nonfatal MI, other medical reasons, loss to follow up, treatment changed by physician or completion of 2 years of study.

With respect to total mortality there were 27/317 (8.5%) aspirin, 32/309 (10.4%) placebo and 32/320 (12.9%) in the phenocoumon patients who died during the observation period. With respect to coronary deaths there were 13/ 317 (4.1%), 22 /309 (7.1%) and 26/ 320 (8.1%) in the aspirin, placebo and phenocoumon groups, respectively.

Other causes of death that were not included under coronary deaths were as follows:

Table 16: Other causes of death in the German Aspirin trial

	Aspirin	placebo	Phenocoumon
Other causes of death	14	10	13
Cardiac failure	4	2	5
Ruptured aneurism	1	0	0
Stroke	0	2	1
Carcinoma	2	1	1
Postoperative death	2	1	0
Septicemia	0	0	1
Liver cirrhosis	1	0	0
Unknown	4	4	5

(Comment: by the usual conventions of this Division many of those deaths not counted, as coronary would certainly be considered as cardiovascular deaths. In addition, the category of unknown is of concern and may hide relevant data.)

The number of coronary events (i.e. the number of coronary deaths, which excluded the deaths in table 16 as well as myocardial infarctions) were 24/317 (7.6%), 37/309 (12.0%) and 32/320 (10%) in the aspirin, placebo and phenocoumon, respectively.

Safety:

The safety information was limited to those who discontinued for medical reasons. These are listed below.

Table 17- Safety outcome for those in the German aspirin trial.

	Aspirin	Placebo	Phencoumon
Total	34	19	18
Specific events			
Hemorrhage	9	0	12
Gastrointestinal complaints	16	11	0
Gastric Ulcer	4	1	0
Thrombosis/embolism	1	5	1
Other intercurrent disease	4	2	5

Many more bleeding events were observed in both the aspirin and phencoumon groups. Gastrointestinal complaints were greater in the aspirin and placebo cohorts relative to the phencoumon

Collaborative Overview of Randomized Trials of antiplatelet therapy -I

Prevention of death, myocardial infarction and stroke by prolonged anti-platelet therapy in various categories of patients (Br Med J. 1994; 304: 81-106).

This publication is a meta-analysis of the outcomes of the long term use of anti-platelet treatment derived from the results of 145 studies that included patients with “high risk” and “low risk” conditions. Two other companion meta-analyses were simultaneously published that included an analysis of the outcome of use of anti-platelet therapy to maintain vessel patency after vascular procedures and to prevent thromboembolism after general or hip replacement surgery

Among the studies that enrolled “high risk “ patients were 11 studies, which enrolled patients with previous myocardial infarctions (not an acute infarction). The antiplatelet treatment in these studies was usually aspirin (at several various doses and dose regimens) and/or sulfipyrazone or dipyridamole.

The antiplatelet trialists analyzed various outcome measurements, which are shown below.

Table 18: Meta analysis from the Anti-platelet trialists’ meta-analysis.

End point	Adjusted event rates		% Odds reduction (SD)	O-E	Variance
	Anti-platelet (%)	Controls (%)			
Non-fatal MI, Stroke or Vascular Death	1331/9877 (13.5%)	1693/9914 (17.1%)	25% (4)	-158.5	561.6
Non-fatal MI	560/9877 (4.7%)	645/9914 (6.5%)	31% (6)	-81.9	224.8
Non-fatal stroke	82/8375 (1.0%)	129/8372 (1.5%)	39% (11)	-24.1	48.3
Vascular death	797/9877 (8.1%)	933/9914 (9.4%)	15% (5)	-56.0	347.4
Death for any cause	91/9877 (9.2%)	1029/9914 (10.4%)	12% (5)	-46.9	383.5

The tabular results of the meta-analysis suggest strong anti-platelet benefit for MI, stroke and vascular death as well as non-fatal MI and non-fatal stroke. There was apparent significance for vascular deaths and death from any cause, but this outcome was marginal.

The results and conclusions of the meta-analysis should be tempered by the following considerations.

- There were decisions made as to which studies to include within the meta-analysis.
- The outcomes that were measured were surveyed prior to the inception of the analysis and the choices of which outcomes to include in the meta-analysis is clearly a retrospective decision.
- The choice of which treatments and which disease processes to include within a meta-analysis are also retrospective to knowledge of the vast majority of the results i.e. the inclusion of some drugs e.g. dipyridamole and excluding other drugs e.g. phencomoron was retrospective to the results.
- For some end-points data was not clearly available and decisions were made as to how to treat this missing data. In general, missing data was censored.
- It should be noted that since the trials which constituted the data base were performed more than 20 years ago, the relevancy of the outcomes have to be assumed as unchanged.
- Endpoints such as revascularization procedures, which would frequently be included in outcome measurements in current studies, were not often collected. Other concurrent therapies that are now readily available are assumed only to minimally effect the conclusions.
- The meta-analysis appears to be a total event rate. Time to event is not specifically analyzed.
- For many of the metrics outlined above, there was informative censoring. For example a subject who died a non-cardiovascular death (this could be pneumonia or trauma or a neoplasm) was censored at the time of event. Other events would often preclude further follow up. For example, if a subject suffered a non-lethal myocardial infarction and died at some distant time (but during the study duration) from a stroke, the stroke and death may not have been captured.
- Pooled studies were tested for heterogeneity and the homogeneity of events was assumed if heterogeneity could not be ascertained.

Notwithstanding all these concerns (the trialists made efforts to mitigate many of these concerns), the effects of aspirin on the composite outcome of cardiovascular death, non-fatal MI and stroke, as well as the effect on the individual outcomes of non-fatal MI, and vascular death were so strongly favored aspirin, that it is difficult to deny the existence of a benefit of aspirin treatment.

Is the effect of combining aspirin and pravastatin beneficial? That is, is  $A+B > A$  and  $A + B > B$ : with A = to the effect of aspirin and B= to the effect of pravastatin?

There is no specific randomized database that defines the individual benefit of the components i.e. pravastatin and aspirin. The sponsor, however, analyzed the sum of data from five studies (PLAC I, PLAC II, REGRESS, CARE and LIPID). The specific analytic plan is shown below. The essence of the analysis was to examine the relative effects among those who were taking pravastatin + aspirin, those taking pravastatin with no aspirin, those taking aspirin with no pravastatin and those taking neither pravastatin or aspirin. The sponsor analyzed the five following end-points.

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 nonfatal MI
5. Ischemic stroke

Before describing the results of this analysis, there are several limitations to this analysis

1. Any analysis that is performed is post-hoc. The results for the individual studies were already known before the analyses were performed. The choice of covariates that were employed in any analysis was also a retrospective decision.
2. There were no prespecified endpoints. That is, the sponsor could choose among a large number of outcomes to decide which of these would show benefit.
3. Was there a heterogeneity analysis of adequate power to detect relevant differences and thereby validate pooling of all studies?
4. It is unclear how missing data were handled. Were these subjects presumed to be alive and well? Some endpoints are not assessable since censoring occurred at the time of the first index events. For example, apparently death was only monitored for 30 days post index event, even if the event was revascularization. Thus total mortality or cardiovascular mortality may not be accurately ascertained.
5. The groups studied do not represent randomized or even stratified groups embedded within the randomized study. The equivalence of the four compared groups is an unproven assumption. By the time the study was completed, the use of aspirin in a high-risk population was already an accepted therapy. The reason that aspirin was not used in approximately 18% of those enrolled is a matter of conjecture. It is unclear if the differences that precluded the use of aspirin at baseline were related to some prognostic characteristic, and these prognostic characteristics might be reflected in outcomes. There are clear differences in the demographics among those not treated with aspirin (see below). Not only are the numbers different, but the intensity of each baseline concern is unknown.

6. The analysis is predicated on aspirin-use at baseline. The analysis presumes that those who used aspirin at baseline used aspirin for the duration of the study. Conversely, those who did not use aspirin at baseline did not use aspirin throughout the study. The sponsor claims that when tested at some stage during the study there was no crossover among those treated with and without aspirin

With respect to the use of aspirin, only the CRFs from the CARE study specifically inquire about aspirin use. The CRFs for the other studies utilize a check-off box if “any” medications were added or the dose was changed. There was, therefore, no specific information on the use of aspirin in these studies. As an OTC medication, whether aspirin would be specifically acknowledged as a medication is unclear.

It should be appreciated that aspirin use was not a particularly important metric in any of these studies. Consequently, the compliance of a subject with aspirin has to be assumed to be less than the index drug of concern.

In addition, all these studies were carried out in the late 1980s and early 1990s. The degree by which subjects were aggressively treated with aspirin and the degree by which compliance was implemented are not clear. Consequently, the time effect on inception of aspirin or other anti-platelet drugs must be considered to be non-trivial.

7. The analysis presented by the sponsor does not take into account the potential use of other anti-platelet drugs. That is, did those in the non-aspirin group receive other antiplatelet therapies, e.g. ticlopidine? Of note, among those treated in the CARE study, approximately 25% of those enrolled were on antiplatelet/anticoagulant treatment at baseline (See demographics below).
1. The results for each individual study for the cohorts are not supplied.

#### Overview of data from the Pravastatin studies:

The five studies that are included within this meta-analysis are described above. The studies include the PLACI, PLAC II, REGRESS, CARE and LIPID studies.

#### Demographics:

The five studies enrolled a total of 14,617 subjects. The post-hoc distribution of patients was based on the randomization to pravastatin (+PRA) or placebo pravastatin (-PRA) as well as the happenstance use of aspirin (+ASA) or non-use of aspirin (-ASA). The demographic characteristics are shown below. Of those included in the database, 9,014 subjects of the 14,617 subjects (62%) were derived from the LIPID Study.

Table 19- Demographics for the pravastatin trial database.

Characteristic	+PRA + ASA	+PRA -ASA	-PRA + ASA	-PRA -ASA
<b>Combined Studies</b>				
Number of patients	5,888	1,436	5,833	1,460
Age years (mean ± SD)	59.5 ± 8.8	60.3 ± 8.8	59.8 ± 8.8	60.4 ± 8.8
Bender M/F (%/%)	85.4/14.6	83.4/16.6	85.7/14.3	81.4/18.6
Lipid levels mg/dl				
Mean Total Chol ± SD	217 ± 29	220 ± 30	216 ± 28	221 ± 30
Mean HDL Chol ± SD	37 ± 9	38 ± 9	38 ± 9	38 ± 10
Mean LDL Chol ± SD	148 ± 26	151 ± 28	148 ± 26	152 ± 27
Mean TG ± SD	160 ± 83	162 ± 77	157 ± 73	157 74
Blood Pressure SBP/DBP	132/80	133/80	132/80	134/81
Hypertension % yes/% no	40.3/59.7	41.4/58.6	41.1/58.9	43.8/56.2
Any cardiac event % yes/% no	80/20	70/30	80/20	70/30
Smoking status % yes/% no	24/76	21/79	26/74	22/77
<b>LIPID Study Demographics</b>				
Number of patients	3,730	782	3,698	804
Age years (mean ± SD)	60.5 ± 8	62 ± 9	61 ± 8	62 ± 8
% > 65 years	37%	45%	38%	15%
Gender % male / % Female	84/16	79/21	84/16	77/23
Baseline Event				
Unstable angina	34%	46%	34%	44%
MI	66%	54%	66%	56%
Smoking % yes/% no	20/80	20/80	20/80	20/80
History of hypertension	41%	43%	42%	44%
Diabetes (%)	9	10	8	11
% with Body Mass Index > 30 kg/M2	18	22	17	21
Lipid levels mg/dl				
Mean Total Chol ± SD	219 ± 32	220 ± 30	216 ± 28	221 ± 30
Mean HDL Chol ± SD	37 ± 9	38 ± 9	38 ± 9	38 ± 10
Mean LDL Chol ± SD	150 ± 28	151 ± 28	148 ± 26	152 ± 27
Mean TG ± SD	160 ± 83	162 ± 77	157 ± 73	157 74
Mean ± SD apolipoprotein A1	132 ± 21	133 ± 23	132 ± 22	135 ± 25
Mean ± SD apolipoprotein B	134 ± 26	134 ± 25	133 ± 24	134 ± 25
Blood pressure SBP/DBP	134/80	136/81	134/80	136/81
Other cardiovascular diseases				
Claudication %	9.1%	12.4%	9.7%	13%
Stroke %	3.2%	6.4%	4.2%	5%
TIAs %	3.0%	5.6%	3.7%	5%
Angina % (any)	35%	42%	36%	44%
Any dyspnea %	48%	54%	47%	58%
Previous revascularizations				
PTCA only (%)	12%	6%	11%	8%
CABG only (%)	28%	24%	29%	20%
Both PTCA and CABG	3%	1%	4%	1%
Baseline other treatments				
Beta blockers %	48%	36%	50%	38%
Calcium antagonists %	33%	38%	24%	38%
ACE-I %	15%	22%	15%	20%
Nitrates %	29%	33%	28%	35%
Antihypertensive medications %	75%	75%	77%	75%
<b>CARE Study Demographics</b>				
Number of patients	1,742	339	1,735	343
Age, years mean ± SD	58 ± 9	60 ± 9	59 ± 9	59 ± 9
Race % white % non-white	94%/6%	89%/11%	93%/7%	88%/12%
Smokers current or past (% yes)	78%	76%	78%	74%
History HBP	41%	47%	42%	48%
History diabetes mellitus	13%	18%	14%	20%
Mean body mass index ± SD	28 ± 4	28 ± 6	28 ± 4	28 ± 4

Lipid levels mg/dl				
Mean total chol $\pm$ SD	209 $\pm$ 17	209 $\pm$ 16	209 $\pm$ 17	209 $\pm$ 16
Mean HDL chol $\pm$ SD	39 $\pm$ 9	40 $\pm$ 9	39 $\pm$ 9	39 $\pm$ 10
Mean LDL chol $\pm$ SD	139 $\pm$ 15	139 $\pm$ 14	139 $\pm$ 15	138 $\pm$ 14
Mean TG $\pm$ SD	157 $\pm$ 61	152 $\pm$ 63	155 $\pm$ 60	155 $\pm$ 74
Seated BP (SBP/DBP)	129/79	128/78	129/79	129/79
Other Treatments:				
Anticoagulant/platelet (%)	100%	25%	100%	25%
Beta blockers (%)	42%	36%	40%	36%
Calcium antagonists (%)	41%	38%	39%	40%
ACE-inhibitors (%)	14%	20%	13%	18%
Nitrates (%)	31%	38%	32%	37%
Diuretics (%)	10%	20%	10%	18%
Myocardial Revascularization procedures Both PTCA and CABG %	56%	46%	56%	46%
Demographics Combined PLACI, PLAC II and Regress studies				
Number of patients	416	315	400	313
Age Mean $\pm$ SD	57 $\pm$ 8	57 $\pm$ 8	56 $\pm$ 9	57 $\pm$ 8
% male/ % female	91% / 9%	94% / 6%	92% / 8%	92% / 9%
Smoker %	86%	87%	83%	83%
Lipid levels (mg/dL)				
Mean total chol $\pm$ SD	233 $\pm$ 30	233 $\pm$ 29	230 $\pm$ 30	236 $\pm$ 29
Mean HDL Chol $\pm$ SD	38 $\pm$ 10	38 $\pm$ 9	37 $\pm$ 10	38 $\pm$ 10
Mean LDL Chol $\pm$ SD	166 $\pm$ 27	166 $\pm$ 26	163 $\pm$ 27	167 $\pm$ 26
Previous MI (%)	47%)	52%	46%	46%
Previous revascularization procedures				
PTCA	23%	16%	25%	15%
CABG	5%	9%	8%	10%

The percentage of subjects in each of the studies who were taking not taking aspirin clearly differed. In the CARE and LIPID studies, only approximately 19% of the subjects were not taking aspirin. In the PLAC I, PLAC II and REGRESS studies, 44% of those enrolled were not taking aspirin. The PLAC I and II studies were started in 1987, The other studies were initiated June-December 1989. PLAC I, PLAC II and REGRESS were completed in 1993. CARE was completed in 1996 and LIPID in 1997. It is unclear to this reviewer if the use of aspirin was increasing for the various disease processes during this interval.

What is most striking to this reviewer is that within each study the two + ASA groups were virtually identical and the two non-aspirin groups (-ASA) were essentially identical, yet there were clear differences within studies comparing the + ASA group to the -ASA group. For example, in the LIPID study concomitant cardiovascular diseases as well as concomitant treatments looked different in the + ASA and -ASA groups. For the CARE study the concomitant medications looked different for the two + ASA and two -ASA groups.

There is some evidence that other anti-platelet/anticoagulant medications were used. In the CARE study the approximately 25% of those enrolled and classified as not taking aspirin were concomitantly treated with anti-platelet/anticoagulation medications. The data for the other studies is unclear. In particular were those not taking aspirin on ticlopidine?

**Dispositions**

Table 20- Dispositions among the clinical studies.

	Pravastatin + ASA	Pravastatin -ASA	-Pravastatin + ASA	-Pravastatin - ASA
<b>LIPID Study</b>				
The CRFs for this study did not assign a reason for discontinuation				
Number enrolled	3730	782	3698	804
Discontinued study medication	851 (23%)	233 (30%)	1097 (30%)	285 (35%)
Started open-label anti-lipid medication before final date	211 (6%)	26 (3%)	839 (23%)	147 (18%)
Started open-label medication	88 (2%)	10 (1%)	582 (16%)	102 (13%)
<b>CARE study</b>				
Number randomized	1742	339	1735	343
Total discontinued	290 (17%)	100 (29%)	465 (27%)	120 (35%)
Adverse event	74 (4%)	18 (5%)	97 (6%)	24 (7%)
Protocol violation (prescribed Concomitant prohibited medications)	7 (< 1%)	1 (< 1%)	29 (2%)	3 (1%)
Subject's request	65 (4%)	17 (5%)	134 (8%)	46 (13%)
Death	85 (5%)	43 (13%)	108 (6%)	25 (7%)
Other	8 (<1%)	3 (1%)	33 (2%)	7 (2%)
Unknown (off study medication for > 30 days prior to final close out)	51 (3%)	18 (5%)	64 (4%)	15 (4%)
<b>PLAC 1</b>				
Number randomized	139	67	143	59
Total discontinued	43 (31%)	21 (31%)	15 (10%)	6 (10%)
CABG	13 (9%)	4 (6%)	15 (10%)	6 (10%)
Adverse event	9 (6%)	3 (5%)	13 (9%)	1 (2%)
Subject's request	6 (4%)	4 (6%)	7 (5%)	2 (3%)
Lost to follow-up	6 (4%)	3 (4%)	6 (4%)	3 (5%)
Protocol violation	6 (4%)	5 (8%)	4 (3%)	0
Physician's request	0	0	8 (6%)	2 (3%)
Death	1 (1%)	1 (1%)	3 (2%)	1 (2%)
Prohibited medication	1 (1%)	0	2 (1%)	2 (3%)
Poor compliance	1 (1%)	1 (1%)	1 (1%)	1 (2%)
<b>PLAC II</b>				
Total enrolled	32	43	37	39
Total withdrawn	3 (9%)	6 (14%)	9 (24%)	11 (28%)
Adverse event	2 (1%)	5 (12%)	6 (17%)	8 (20%)
Subject's request	1 (3%)	0	0	2 (5%)
Death	0	1 (2%)	1 (3%)	0
Prohibited medication	0	0	2 (5%)	1 (2%)
<b>REGRESS</b>				
Total Enrolled	245	205	220	215
Total Discontinued	35 (14%)	25 (12%)	23 (10%)	27 (13%)
Adverse event	9 (4%)	6 (3%)	3 (1%)	6 (3%)
Laboratory abnormality	0	1 (< 1%)	2 (1%)	0
Compliance problem	22 (9%)	15 (7%)	15 (7%)	15 (7%)
Lost to follow up	2 (1%)	0	0	1 (< 1%)
Death	1 (< 1%)	3 (1%)	3 (1%)	4 (2%)
Subject's request	1 (< 1%)	0	0	1 (< 1%)

**Statistical Treatment:** The sponsor performed the pooled data by three different methods.

**Method 1:** This method is a traditional method for meta-analysis. A Cox proportional hazard model was employed, adjusting for baseline conditions such as age, gender, smoking status, previous cardiac event and LDL-C, HDL-C, TG and DBP and SBP.

Treatment and study were also included as in the model. It should be appreciated that the terms included within the model were not pre-specified before the data was collected and already explored. Other terms could have been included within the model or excluded from the model.

### Models 2 and 3.

Two types of Bayesian analyses were performed. The intent of both analyses is to deal with the heterogeneity of studies by treating patient as one level of analysis while treating study outcome as a second level of analysis. The distribution of outcomes within each study (with the covariates estimated uniquely for each study) was then embedded within the distribution of outcomes for all the studies.

The second Bayesian model addresses the underlying assumption that the effects that are measured are independent of the duration of treatment. In this analysis each of the individual years are analyzed separately.

Model 2: This model is similar to the Cox model with and without adjustments for baseline prognostic factors. Treatment and study were considered separately from the covariates. The baseline Hazard function was assumed to apply to all years.

Model 3: This model was similar to the above Bayesian model but allowed flexibility for time-dependant changes in Hazard ratios.

### Endpoints:

(Please note: Only two studies the CARE and LIPID followed outcomes for 5 years. The other studies PLAC I, PLAC II and REGRESS only followed the cohorts for 3 years. These last three studies are listed under the REGRESSION label enrolled approximately the same number of + ASA and –ASA patients were not followed for longer than 3 years. The fraction of the cohort that were followed who were not treated with aspirin dropped from 20% at baseline to 17% when the REGRESSION studies were terminated. The differences in baseline characteristics are also modified by the end of the three-year period.)

(There were other potential endpoints that were not included into any of these analyses. These include total mortality, total strokes [also including hemorrhagic strokes], TIA/RINDS or peripheral vascular events.

Endpoint 1: Composite outcome measurement of CHD death, non-fatal MI, CABG, PTCA or ischemic stroke

### Method 1:

There were 3,714 subjects of the 14, 617 who had CHD related death, non-fatal MI, CABG, PTCA or stroke as their first event after randomization. The results are tabulated below.

Table 21- Composite outcome measurement of CHD death, non-fatal MI, CABG, PTCA or ischemic stroke by the Cox method

	+ PRA + ASA	+ PRA -ASA	-PRA + ASA	-PRA -ASA
Number enrolled	5,888	1,436	5,833	1,460
Number of events (% in cohort) –crude rate	1314 (22.3%)	341 (23.8%)	1661 (28.5%)	398 (27.3%)
Risk reduction versus –PRA –ASA Confidence intervals	26.8% (18.0, 34.7)	15.4% (2.2, 26.8)	3.4% (-7.9 ,13.6)	-----
Risk reduction versus –PRA + ASA Confidence intervals	24.2% (18.6, 29.5)		-----	
Risk reduction versus + PRA –ASA Confidence intervals	13.5% (2.4 , 23.3)	-----		

The results of this analysis show a difference between the cohorts of pravastatin plus aspirin versus the individual components i.e. pravastatin alone or aspirin alone (i.e. + PRA + ASA versus + PRA –ASA and + PRA + ASA versus –PRA + ASA).

The effects of aspirin on this endpoint, however, seem less than that usually attributed to this treatment. The crude event rate for the aspirin group (-PRA + ASA) alone is actually worse than the placebo (-PRA –ASA) group (28.5% versus 27.3%, respectively). Correcting for baseline imbalances of covariates indicates a very small and non-significant benefit for aspirin (3.4%). It is unclear what value should be expected for this endpoint. The anti-platelet trialist's meta- analysis did not include revascularization procedures in their estimate of aspirin effects. One would have to assume a trivial or negative effect of aspirin on PTCA/CABG to arrive at the small difference observed in this analysis.

In considering the benefit of aspirin superimposed on pravastatin (+ PRA +ASA versus + PRA –ASA), the benefit is modest (13.5%) but the confidence intervals span the generally observed effects of aspirin.

Endpoint 2: Fatal and Nonfatal MI s

The analysis for the combined end-point of fatal and non-fatal MIs is shown below.

Table 22- Composite end-point for fatal and non-fatal MIs by the Cox method.

	+ PRA + ASA	+ PRA -ASA	-PRA + ASA	-PRA –ASA
Number at risk	5,888	1,436	5,833	1,460
Number of subjects (%) –crude rate	445 (7.6%)	125 (8.7%)	626 (10.7%)	158 (10.8%)
Risk reduction versus –PRA –ASA (Confidence intervals)	40.2 % (28.2, 50.2)	19.4 (-2.0, 36.3)	13.0 (-3.8, 27.1)	-----
Risk reduction versus –PRA + ASA (confidence interval)	31.3% (22.4, 39.2)		-----	
Risk reduction versus + PRA –ASA (confidence interval)	25.9% (9.5, 39.3)			

It is unclear how the sponsor treated those who achieved an alternate endpoint i.e. CABG/PTCA. It seems that those, whose death was other than CHD in origin, were not included and censored at that time of the event.

The corrected rate of fatal and non-fatal MI per sponsor's analysis show a benefit of + PRA + ASA to either individual component.

The crude fatal and non-fatal event rate, however, in the -PRA + ASA (aspirin) versus -PRA -ASA (placebo group) only minimally favors treatment (the trialist’s analysis does not look at this endpoint). The aspirin effect among those treated with pravastatin (+ PRA + ASA versus + PRA -ASA) was approximately 31.2%.

Endpoint 3: Ischemic strokes.

The sponsor’s analysis for ischemic strokes is shown below.

Table 23- Ischemic strokes by the Cox method

	+PRA +ASA	+ PRA -ASA	-PRA + ASA	-PRA -ASA
Number of subjects	5,888	1,436	5,833	1,460
Number events (%)	134 (2.3%)	44 (3.1%)	183 (3.1%)	51 (3.5%)
Risk reduction versus -PRA -ASA Confidence intervals	39.5% (16.3,56.3)	12.0% (-31.7, 41.2)	14.5% (-16.9, 37.5)	-----
Risk reduction versus -PRA + ASA Confidence intervals	29.2% (11.5-43.4)		-----	
Risk reduction versus + PRA -ASA Confidence intervals	31.2% (3.1, 51.2)			

Based on the sponsor’s analysis this analysis implies that the effect in the + PRA + ASA is superior to each of the individual components. Again, the crude effect comparing the -PRA + ASA to -PRA -ASA cohorts (the basic comparison in the aspirin meta-analysis) shows minimal effect.

Endpoint 4: Composite Outcome Measure: CHD death, Non-fatal MI, CABG or PTCA.

This outcome is very similar to the first metric with the exclusion of the small number of subjects with ischemic stroke (Again no revascularization events were included in the trialist’s analysis).

Table 24- Outcome for CHD death, non-fatal MI, CABG or PTCA by the Cox method

	+PRA +ASA	+PRA -ASA	-PRA + ASA	-PRA -ASA
Number of subjects	5,888	1,436	5,833	1,460
Number of events (%)	1218 (20.7%)	308 (21.5%)	1543 (26.5%)	1,460 (25.2%)
Risk reduction versus -PRA -ASA Confidence intervals	26.8% (17.6, 35.9)	17.4% (3.9, 29)	3.2% (-8.7, 13.7)	
Risk reduction versus -PRA + ASA Confidence interval	24.4% (18.4, 29.8)			
Risk reduction versus + PRA -ASA Confidence interval	11.3% (-0.6, 21.9)			

Based on the sponsor’s analysis the combination of + PRA + ASA was superior to ASA alone but not relative to PRA alone (the confidence intervals overlap 0).

Again, relative to the usual comparisons -PRA +ASA versus -PRA -ASA, the results here are less than anticipated. The crude rate actually favors -PRA -ASA. The adjusted values were slightly in favor of the ASA group but much less than usually observed for other endpoints.

**Endpoint 5: Composite CHD death or non-fatal MI:**

Table 25 outcome for CHD death or non-fatal MI

	+PRA +ASA	+PRA -ASA	-PRA + ASA	-PRA -ASA
Number of subjects	5,888	1,436	5,833	1,460
Number of events (%)	597 (10.1%)	196 (13.7%)	830 (14.2%)	203 (13.9%)
Risk reduction versus -PRA -ASA Confidence intervals	36.7% (25.7, 46.1)	0.5% (-21.2, 18.2)	8.8% (-6.5, 21.9)	-----
Risk reduction versus -PRA + ASA Confidence interval	30.7% (23.0, 37.6)			
Risk reduction versus + PRA -ASA Confidence interval	36.5% (25.3, 46.0)			

The sponsor’s analysis suggests that the cohort treated with +PRA + ASA is superior to the cohort who was treated with PRA alone or ASA alone. Again, the observed effect comparing the -PRA + ASA to -PRA -ASA have a crude event rate favoring placebo, but a corrected rate that minimally favors aspirin.

**Bayesian Meta-analysis:**

Two separate analyses based on Bayesian assumption were performed. The first model assumes that the Hazard ration is not time dependent and all years were considered within the same model. A second Bayesian analysis analyzes five separate time periods (i.e. each of the individual years of treatment).

**Endpoint 1: CHD death, Non-fatal MI, CABG, PTCA or Ischemic Stroke: Bayesian model 1:**

The sponsor’s analysis for the individual treatments are better is shown in Figure 2 below.

Figure 2- Survival without event for CHD death, non-fatal MI. CABG, PTCA or ischemic stroke

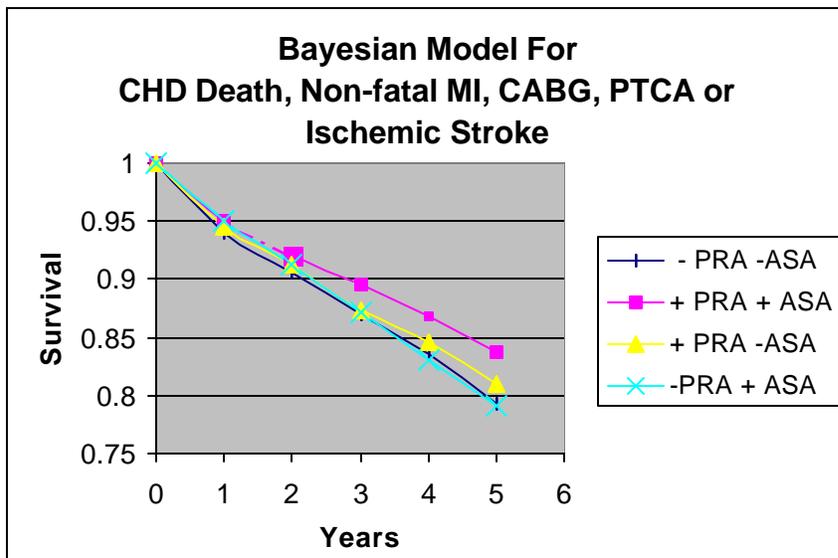


Table 26 Probability that X better than Y for the composite endpoint of CHD death, Non-fatal MI, CABG, PTCA or ischemic stroke

X	Y	PROBAILITY
+ PRA + ASA (combined)	+ PRA –ASA (pravastatin monotherapy)	0.99
+ PRA + ASA (combined)	-PRA + ASA (aspirin monotherapy)	1.0
+PRA +ASA (combined)	-PRA –ASA (placebo)	1.0
-PRA + ASA (aspirin monotherapy)	-PRA –ASA (placebo)	0.48

This analysis suggests that there is > 99% probability that the combination of + PRA + ASA is superior to the individual components. It also suggests less than a 50% probability that aspirin (-PRA + ASA) is better than placebo (-PRA –ASA).

Bayesian Model 2 Endpoint 1: Time dependent factors.

There is apparently a change in the placebo (-PRA –ASA) over time. The Hazard is greatest during the first year and remains lower during the second and third year. At the end of the fourth year and during the fifth year the Hazard ratios increase again.

Table 27 Yearly hazard functions (mean + SD) for CHD death, Non-fatal MI, CABG, PTCA or ischemic stroke

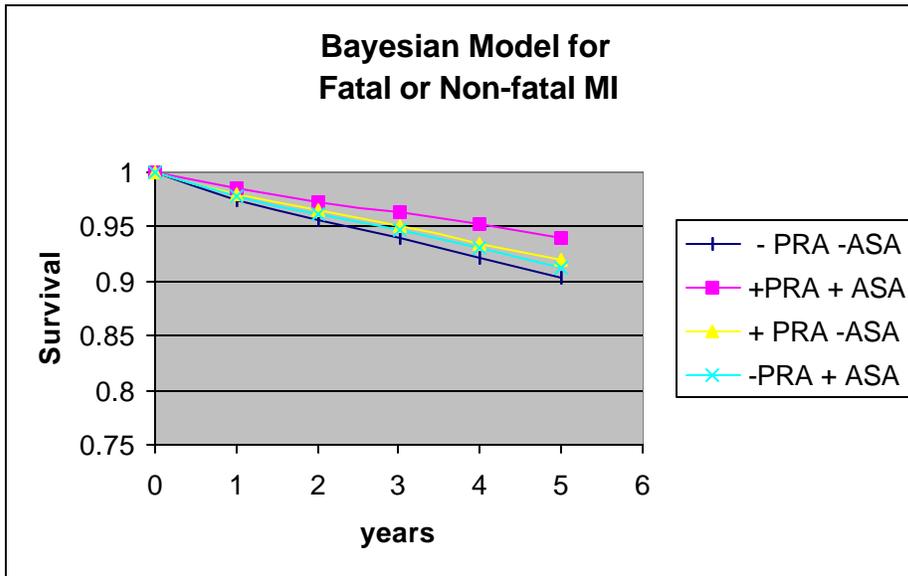
Year	+PRA + ASA	+ PRA -ASA	-PRA + ASA	-PRA-ASA
0 to 1	0.0508 ± 0.0045	0.0564 ± 0.0068	0.0510 ± 0.0046	0.0615 ± 0.0072
1 to 2	0.0309 ± 0.0031	0.0355 ± 0.0052	0.0415 ± 0.0039	0.0378 ± 0.0054
2 to 3	0.0286 ± 0.0029	0.0429 ± 0.0064	0.0445 ± 0.0042	0.0338 ± 0.0055
3 to 4	0.0305 ± 0.0032	0.0321 ± 0.0058	0.0485 ± 0.0046	0.0465 ± 0.0071
4 to 5	0.0364 ± 0.0034	0.0434 ± 0.0058	0.0492 ± 0.0044	0.0538 ± 0.0067

Relative to the monotherapy components, + PRA + ASA versus the individual components (+ PRA –ASA and -PRA + ASA), the hazard function is numerically less for the combined product than the individual components during each year. During each yearly interval the combination product was superior to the aspirin subgroup. With the exception of year 4, the combination was superior to pravastatin monotherapy.

ENDPOINT 2: Fatal and non-fatal MI, Bayesian Model 1.

The Bayesian model for fatal and non-fatal MIs is shown below. Mortal events that were not adjudicated as CHD events are not included. The event-free survival is greatest for the combined (+ PRA + ASA) compared to the individual monotherapy components (+ PRA –ASA and –PRA + ASA). There was no difference between the event rate in the aspirin monotherapy group to the placebo group (-PRA + ASA to -PRA –ASA).

Figure 3. Survival for fatal or non-fatal MI



The probability of that the individual cohorts are shown below.

Table 28 Probability that X is better than Y for fatal and non-fatal MI.

X	Y	PROBAILITY
+ PRA + ASA (combined)	+ PRA -ASA (pravastatin monotherapy)	0.99
+ PRA + ASA (combined)	-PRA + ASA (aspirin monotherapy)	1.0
+PRA +ASA (combined)	-PRA -ASA (placebo)	1.0
-PRA + ASA (aspirin monotherapy)	-PRA -ASA (placebo)	0.92

This analysis suggests that the combined therapy was better than Aspirin monotherapy or Pravastatin monotherapy

End point 2- Bayesian Model 2: Time dependent factors

Table 29- Hazard functions (mean + SD) for fatal and non-fatal MI

Year	+PRA + ASA	+ PRA -ASA	-PRA + ASA	-PRA-ASA
0 to 1	0.0157 ± 0.0025	0.0245 ± 0.0050	0.0205 ± 0.0031	0.0262 ± 0.0051
1 to 2	0.0120 ± 0.0020	0.0173 ± 0.0040	0.0161 ± 0.0025	0.0179 ± 0.0041
2 to 3	0.0104 ± 0.0018	0.0153 ± 0.0039	0.0174 ± 0.0027	0.0167 ± 0.0041
3 to 4	0.0107 ± 0.0019	0.0151 ± 0.0041	0.0183 ± 0.0029	0.0222 ± 0.0051
4 to 5	0.0137 ± 0.0021	0.0140 ± 0.0033	0.0190 ± 0.0028	0.0205 ± 0.0042

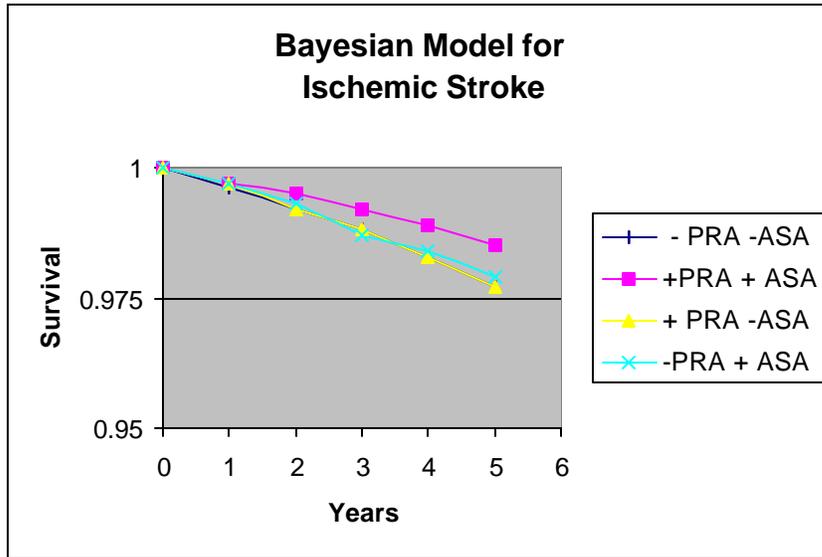
There appears to be time-dependent changes in the Hazard rates. For each year, however, the combination product was superior to placebo. Only during the first year was the combination product better than pravastatin monotherapy. The other years there was a trend toward superiority but no overwhelming signal.

In none of the years was Aspirin monotherapy superior to placebo.

**ENDPOINT Number 3: Stroke Bayesian method 1**

The event free survival for stroke (excludes subjects with any death) is shown below.

Figure 4: Survival without ischemic stroke



Those patients with other end points were apparently censored.

Table 30: Probability that X better than Y for stroke Bayesian method 1.

X	Y	PROBAILITY
+ PRA + ASA (combined)	+ PRA -ASA (pravastatin monotherapy)	0.99
+ PRA + ASA (combined)	-PRA + ASA (aspirin monotherapy)	0.99
+PRA +ASA (combined)	-PRA -ASA (placebo)	0.99
-PRA + ASA (aspirin monotherapy)	-PRA -ASA (placebo)	0.074

**Bayesian Model 2:**

There is greater than 99% probability that the combined product is superior to the individual components. There is little likelihood that Aspirin (-PRA + ASA) is superior to placebo (-PRA -ASA)

Table 31 Yearly hazard functions (Mean ± SD) for stroke.

Year	+PRA + ASA	+ PRA -ASA	-PRA + ASA	-PRA-ASA
0 to 1	0.0030 ± 0.0009	0.0034 ± 0.0015	0.0022 ± 0.0007	0.0048 ± 0.0018
1 to 2	0.0031 ± 0.0009	0.0037 ± 0.0016	0.0047 ± 0.0012	0.0057 ± 0.0021
2 to 3	0.0035 ± 0.0008	0.0068 ± 0.0025	0.0042 ± 0.0012	0.0024 ± 0.0013
3 to 4	0.0026 ± 0.0008	0.0029 ± 0.0015	0.0058 ± 0.0015	0.0055 ± 0.0023
4 to 5	0.0039 ± 0.0010	0.0071 ± 0.0023	0.0062 ± 0.0015	0.0069 ± 0.0023

The combination product was superior to aspirin during years 2, 4, and 5. The combination product was superior to pravastatin monotherapy during years 3 and 5. Placebo (-PRA -ASA) was superior to aspirin during year 1 only. There was no benefit of aspirin relative to placebo during any year.

ENDPOINT 4- CHD death, Non-fatal MI, CABG or PTCA: Bayesian method 1.

This endpoint is similar to end-point 1 with the exception that ischemic stroke is excluded.

Endpoint 4- Bayesian Model 1:

Figure 5: Survival without event for CHD death, non-fatal MI, CABG or PTCA

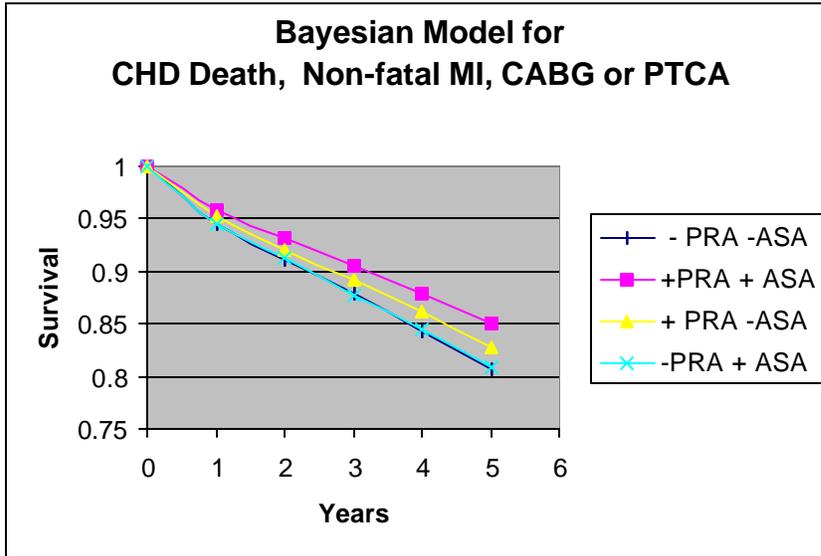


Table 32- Probability that X better than Y for CHD death, non-fatal MI, CABG or PTCA

X	Y	PROBAILITY
+ PRA + ASA (combined)	+ PRA -ASA (pravastatin monotherapy)	0.99
+ PRA + ASA (combined)	-PRA + ASA (aspirin monotherapy)	1.0
+PRA +ASA (combined)	-PRA -ASA (placebo)	1.0
-PRA + ASA (aspirin monotherapy)	-PRA -ASA (placebo)	0.54

There is greater than 99% probability that the combined cohort was superior to the individual components. There was no difference between aspirin and placebo for this endpoint.

Endpoint 4: Bayesian Method 2.

Table 33- Hazard functions (Mean + SD) for CHD death, non-fatal MI, CABG or PTCA.

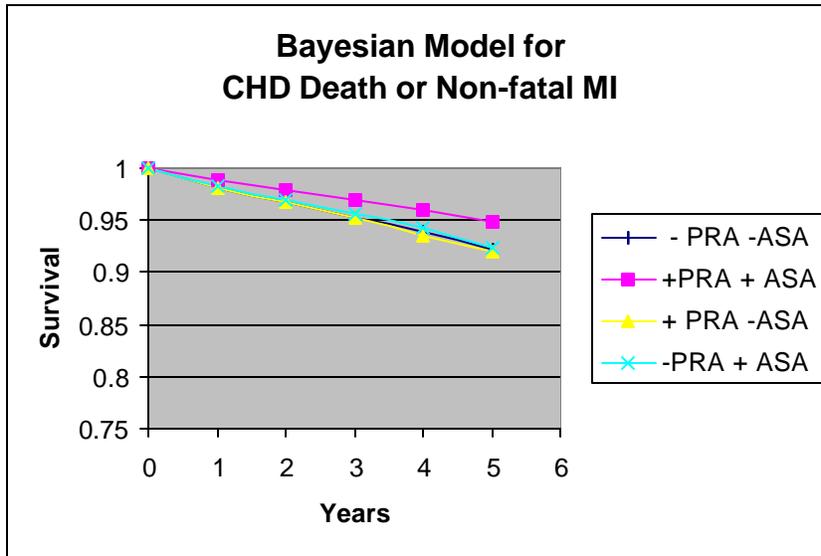
Year	+PRA + ASA	+ PRA -ASA	-PRA + ASA	-PRA-ASA
0 to 1	0.0477 ± 0.0045	0.0529 ± 0.0067	0.0487 ± 0.0046	0.0581 ± 0.0072
1 to 2	0.0285 ± 0.0030	0.0324 ± 0.0050	0.0370 ± 0.0037	0.0330 ± 0.0050
2 to 3	0.0251 ± 0.0028	0.0353 ± 0.0057	0.0414 ± 0.0041	0.0321 ± 0.0055
3 to 4	0.0281 ± 0.0031	0.0290 ± 0.0054	0.0436 ± 0.0044	0.0437 ± 0.0069
4 to 5	0.0327 ± 0.0033	0.0374 ± 0.0053	0.044 ± 0.0043	0.0485 ± 0.0063

The results show combination therapy is superior to aspirin monotherapy at all years except the first year. The combination product is superior to pravastatin only during year 3. Aspirin monotherapy was not superior to placebo during any of the years.

Endpoint # 5 CHD death and Non-fatal MI

The survival curves for CHD death or non-fatal MI is shown below.

Figure 6- Survival for CHD death or non-fatal MI



The analysis shows that pravastatin + Aspirin is superior to the individual components. There is no evidence that aspirin is superior to placebo,

Table 34: Probability that X better than Y for CHD death or non-fatal MI

X	Y	PROBAILITY
+ PRA + ASA (combined)	+ PRA -ASA (pravastatin monotherapy)	1.0
+ PRA + ASA (combined)	-PRA + ASA (aspirin monotherapy)	1.0
+PRA +ASA (combined)	-PRA -ASA (placebo)	1.0
-PRA + ASA (aspirin monotherapy)	-PRA -ASA (placebo)	0.79

Endpoint # 5- CHD death and Non-fatal MI: Bayesian Model 2-

Table 35: Hazard functions (Mean ± SD) for CHD death or non-fatal MI.

Year	+PRA + ASA	+ PRA -ASA	-PRA + ASA	-PRA-ASA
0 to 1	0.0122 ± 0.0017	0.0242 ± 0.0039	0.0159 ± 0.0021	0.0201 ± 0.0036
1 to 2	0.0103 ± 0.0015	0.0182 ± 0.0034	0.0135 ± 0.0018	0.0145 ± 0.0029
2 to 3	0.0086 ± 0.0013	0.0136 ± 0.0030	0.0151 ± 0.0020	0.0132 ± 0.0029
3 to 4	0.0099 ± 0.0015	0.0131 ± 0.0030	0.0158 ± 0.0021	0.0179 ± 0.0036
4 to 5	0.0128 ± 0.0017	0.0165 ± 0.0030	0.0175 ± 0.0022	0.0173 ± 0.0030

For this end point the combination cohort is superior to aspirin during each year, and superior to pravastatin during years 1-3. There were no differences between aspirin and placebo during any of the years.

Subgroups

Gender:

The event rate and risk reduction comparing the cohort taking combined therapy versus the individual components for males and females is shown below. This analysis is limited to endpoint 1 (CHD death, non-fatal MI, CABG, PTCA or ischemic stroke).

Table 36: The effect of gender on risk reduction for the outcomes of CHD death, non-fatal MI, CABG, PTCA or ischemic stroke

	+ PRA + ASA		+ PRA –ASA		-PRA + ASA		-PRA-ASA	
	Male	Female	Male	Female	Male	Female	Male	Female
Number	5,028	860	1,198	238	4997	836	1188	272
Crude number with event (%) -of subjects	1140 (23%)	174 (20%)	291 (24%)	50 (21%)	1436 (29%)	225 (27%)	325 (27%)	73 (27%)
Risk Reduction vs. –PRA –ASA	26%	32%	14%	23%	3%	7%	-----	-----
95% Confidence Intervals (%, %)	(16, 35)	(10, 48)	(-1, 27)	(-11, 46)	(-9, 14)	(-21, 29)		
Risk reduction vs. –PRA + ASA	34%	27%						
95% Confidence Intervals (%, %)	(18, 29)	(11,40)						
Risk Reduction vs. + PRA –ASA	14%	12%						
95% Confidence Intervals (%, %)	(2,25)	(-21, 36)						

There did not appear to be major differences between the genders.

Age:

The event rate and risk reduction comparing the cohort who received combined therapy versus the cohorts who received the individual components for the outcomes (CHD death, Non-fatal MI, CABG, PTCA or ischemic stroke) is shown below.

Table 37- The effect of age (< 65 and ≥ 65 years) on risk reduction for the outcomes of CHD death, non-fatal MI, CABG, PTCA or stroke

	+ PRA + ASA		+ PRA –ASA		-PRA + ASA		-PRA-ASA	
	<65	≥ 65	<65	≥ 65	<65	≥ 65	<65	≥ 65
Number	3906	1982	902	534	3816	2017	926	534
Crude number with event (%) -of subjects	849 (22%)	465 (24%)	185 (21%)	156 (29%)	1011 (27%)	650 (32%)	221 (24%)	177 (33%)
Risk Reduction vs. –PRA –ASA	19%	36%	18%	12%	-1%	8%	-----	-----
95% Confidence Intervals (%, %)	(7, 31)	(24, 47)	(+0, 33)	(-9, 29)	(-17, 13)	(-9, 22)		
Risk reduction vs. –PRA + ASA	20%	31%						
95% Confidence Intervals (%, %)	(12, 27)	(22, 39)						
Risk Reduction vs. + PRA –ASA	2%	27%						
95% Confidence Intervals (%, %)	(-15, 17)	(13, 40)						

There did not appear to be major differences between the age comparing those < 65 years and the > 65 years for the cohort treated with the composite treatments relative to those treated with pravastatin. The effect of the cohort treated with combined therapy relative to pravastatin alone (+PRA –ASA) was non-existent for those < 65 years but substantial for those > 65 years.

Race: No subgroup analysis for race was supplied.

Dose: There is no data that allows differentiation of either the dose of pravastatin or aspirin, nor the formulation of aspirin (immediate release, buffered, etc.)

### Reviewer's Conclusions on efficacy:

The key question in interpreting the sponsor's analyses is the adequacy of the cohorts to reflect a randomized group and thereby arrive at any conclusion with respect the superiority of the combination product to the individual components. The baseline demographics comparing the two cohorts receiving aspirin (+ ASA) differ from the two cohort with no aspirin (-ASA). In particular, in the CARE and LIPID studies the baseline medical conditions and the baseline co-treatments appear similar within the two groups but differs in comparing the two groups. Since the reason for the non-use of aspirin is obscure, the validity of the analyses performed by the sponsor is also unclear.

In addition, the cohorts are defined by the use of aspirin at baseline. The presumption is that those treated with aspirin at baseline were maintained throughout the study with aspirin. Those who were not receiving aspirin at baseline were treated as though they continuously received aspirin. The assessment of continued use or non-use of aspirin is not overwhelmingly convincing.

Other potential anti-platelet or anticoagulants were apparently used during this time were not considered in defining the cohorts for benefit.

There is no information as to the time for the onset of effects in the different cohorts. The greater the duration before curves separate, the greater the uncertainty that the baseline aspirin use is responsible for the benefit.

Lastly, any assertion of efficacy of combination products versus individual components must accept the assumptions engendered in meta-analysis. All meta-analyses are by definition retrospective to unblinding in the choice of studies, endpoints and analyses.

In summary, the analysis which demonstrates the superiority of the composite treatment (+PRA + ASA) to that of the individual components (+ PRA-ASA and -PRA + ASA) must be taken with some skepticism. Of note, the effect of aspirin alone (-PRA + ASA) versus placebo (-PRA -ASA) has much less of an effect than would be expected from the trialists analysis of several endpoints.

### Safety:

#### Collection of Data:

In most studies an AE was defined as any illness, sign, symptom or laboratory abnormality that appeared or worsened during the study. Such events were defined as non-serious or serious adverse events (SAE). Treatment emergent events were adverse events were those that began or worsened after randomization.

Serious adverse events were, as usually defined as events that included fatal, life-threatening, permanently disabling, resulting in new or prolonged hospitalization, congenital anomaly, and cancer or was due to an overdose. In the LIPID study, the CRFs were only not

designed to collect all AEs, but were only collected those that were serious and related to dug treatment.

Laboratory values were measured at different times during the different protocols.

Extent of exposure:

The mean extent of exposure, for each of the cohorts for each of the studies is shown below.

Table 38: Exposure during each of the studies.

		+PRA + ASA	+ PRA -ASA	-PRA + ASA	-PRA -ASA
LIPID	N=	3730	782	3698	804
	Duration (years)	5.2	4.9	5.0	4.6
CARE	N=	1742	339	1735	343
	Duration (years)	4.6	4.3	4.3	4.2
REGRESS	N=	245	205	220	215
	Duration (years)	1.9	1.9	1.9	1.9
PLAC I + PLAC II	N=	171	110	180	98
	Duration (years)	2.5	2.6	2.3	2.4

The duration of exposure was substantially greater for the LIPID and CARE studies than for the REGRESS, the PLAC I or PLAC II studies. The fraction of –ASA patients (either with or without PRA) are disproportionately drawn from the REGRESS, PLAC I and PLAC II studies. Consequently, the mean duration of exposure for the –ASA groups is not quite the same as that of the + ASA groups.

Demographics: The demographics have been previously described.

Deaths:

Overall deaths for the individual studies are shown below. In some studies patients were censored at the time of a non-lethal event (e.g., revascularization) were censored. If anything this would allow for greater censoring among those with higher event rates and if anything the composite treatment would be superior.

Table 39- Overall Death rate from each study.

LIPID study				
	+PRA + ASA	+PRA -ASA	-PRA + ASA	-PRA –ASA
Number enrolled	3730	782	3698	804
Total Deaths (%)	375 (10.1%)	123 (16%)	491 (13%)	142 (18%)
Coronary	218 (6%)	69 (9%)	298 (8%)	75 (9%)
Cardiac (non-coronary)	2 (<1%)	0	1 (< 1%)	3 (< 1%)
Vascular (non-cardiac)	26 (1%)	16 (2%)	106 (3%)	12 (2%)
Cancer	104 (3%)	24 (3%)	2 (< 1%)	35 (4%)
Trauma	5 (<1%)	0	5 (< 1%)	3 (< 1%)
Suicide	0	1 (< 1%)	35 (1%)	1 (< 1%)
Other	20 (1%)	13 (2%)	491 (13%)	13 (2%)
CARE Study				
Number Enrolled	1742	339	1735	343
Total number of deaths	122 (7%)	58 (17%)	158 (9%)	37 (11%)
Atherosclerotic CHD				
Fatal MI	18 (1%)	6 (2%)	28 (2%)	10 (3%)
Sudden death	39 (2%)	19 (6%)	50 (3%)	11 (3%)

Other CHD	11 (1%)	3 (1%)	15 (1%)	5 (2%)
Atherosclerotic vascular				
Cerebrovascular	4 (< 1%)	6 (2%)	3 (1%)	3 (1%)
Other atherosclerotic vascular	5 (< 1%)	0	3 (< 1%)	1 (< 1%)
Non-atherosclerotic vascular	0	1 (< 1%)	1 (< 1%)	0
Non-cardiovascular				
Cancer	34 (2%)	15 (4%)	40 (92%)	5 (2%)
Accidents/suicide	3 (< 1%)	5 (2%)	3 (< 1%)	1 (< 1%)
Other/unknown	8 (< 1%)	3 (1%)	16 (91%)	1 (< 1%)
<b>REGRESS study</b>				
Number enrolled	245	205	220	215
Number of deaths*	1 (< 1%)	3 (1%)	3 (1%)	4 (2%)
MI	1			2
Sudden cardiac death		2	1	1
Cerebral hemorrhage			1	
Congestive heart failure			1	
Pulmonary embolism				1
Other		1		
* deaths limited to those on study or within 30 days of study completion				
<b>PLAC I and PLAC II</b>				
Number of subjects	171	110	180	98
Number of Deaths	3 (1.8%)	3 (2.7%)	6 (3.3%)	5 (5.1%)
MI			1	1
Sudden cardiac death	2	1	1	1
Cerebral hemorrhage				1
Congestive heart failure				
Pulmonary embolism				
Other	1	1	4	2

Serious adverse events:

As noted above, serious adverse events were the only events collected for the LIPID study. The Body system and the number of adverse events (%) attributed to each system are shown below.

LIPID study

Table 40: Serious adverse events in the LIPID study by body system

	+PRA + ASA	+PRA -ASA	-PRA + ASA	-PRA -ASA
Number of subjects	3730	782	3698	804
Total number of patients with SAEs	2629 (71%)	587 (75%)	2674 (72%)	598 (74%)
Total SAEs	12927 (347%)	3467 (443%)	13775 (372%)	3457 (420%)
Cardiac	1411 (38%)	354 (45%)	1566 (42%)	377 (47%)
Complications of medical care	111 (3%)	37 (5%)	151 (4%)	29 (4%)
Dermatological	352 (9%)	81 (19%)	342 (9%)	71 (9%)
Endocrine/metabolic	111 (3%)	33 (4%)	108 (3%)	35 (4%)
Gastrointestinal	782 (21%)	227 (29%)	795 (22%)	206 (26%)
Hematologic	87 (2%)	24 (3%)	96 (3%)	28 (4%)
Hepatic biliary	124 (3%)	34 (4%)	156 (4%)	39 (5%)
Infections	87 (2%)	23 (3%)	84 (2%)	30 (4%)
Malignancy	461 (12%)	104 (13%)	447 (12%)	94 (12%)
Musculoskeletal	457 (12%)	121 (16%)	462 (13%)	109 (14%)
Nervous system	247 (6%)	69 (9%)	261 (7%)	79 (10%)
Other reasons for hospital admission	110 (3%)	39 (5%)	110 (3%)	25 (3%)
Renal/genitourinary	604 (16%)	150 (19%)	543 (15%)	145 (18%)
Respiratory	590 (16%)	164 (21%)	541 (15%)	155 (19%)
Special senses	234 (6%)	63 (8%)	224 (6%)	64 (8%)
Trauma	176 (5%)	37 (5%)	164 (4%)	47 (6%)
Vascular (non-cardiac)	495 (13%)	136 (17%)	587 (16%)	135 (17%)

No category assigned	0 (0%)	0 (0%)	1 (< 1%)	0 (0%)
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The numbers of serious adverse events were greater in the non-aspirin-treated group than in the aspirin treated group. Even gastrointestinal events were increased among those not taking aspirin. There were no signs of excessive bleeding in this database.

Cardiovascular and Gastrointestinal serious adverse events that were among the most frequently reported 30 events in the LIPID study are shown below:

Table 41: Cardiac and gastrointestinal serious adverse events from the LIPID study.

	+PSA + ASA	+PSA -ASA	-PRA + ASA	-PRA -ASA
Number of subjects	3730	782	3698	804
Unstable angina pectoris acute	689 (19%)	177 (23%)	737 (20%)	193 (24%)
Coronary arteriography	543 (15%)	96 (13%)	610 (17%)	121 (15%)
CABG	220 (6%)	39 (5%)	270 (7%)	50 (6%)
Chest pin	211 (6%)	45 (6%)	190 (5%)	47 (6%)
Angina pectoris	178 (5%)	50 (6%)	207 (6%)	50 (6%)
Colonoscopy	181 (5%)	43 (6%)	162 (4%)	49 (6%)
Atrial fibrillation	161 (4%)	51 (7%)	168 (5%)	40 (5%)
Gastroscopy	168 (5%)	41 (5%)	158 (4%)	46 (6%)
Unstable angina for investigation	170 (5%)	33 (4%)	206 (6%)	36 (5%)
Left heart failure	133 (4%)	42 (5%)	148 (4%)	42 (5%)
Subendocardial infarct	117 (3%)	35 (4%)	185 (5%)	33 (4%)
Coronary angiography (single vessel)	130 (4%)	21 (3%)	164 (4%)	27 (3%)
Instantaneous death	112 (3%)	37 (5%)	142 (4%)	31 (4%)
Esophogogastroduodenoscopy	107 (3%)	41 (5%)	106 (3%)	31 (4%)
Congestive heart failure	86 (2%)	43 (6%)	89 (2%)	28 (4%)
Heart failure	80 (2%)	27 (4%)	92 (3%)	33 (4%)
Left heart cardiac catheterization	80 (2%)	22 (3%)	105 (3%)	9 (1%)
Pneumonia	69 (2%)	22 (3%)	70 (2%)	16 (2%)
Syncope and collapse	67 (2%)	21 (3%)	83 (2%)	16 (2%)

Given the fact that this is a flawed database there is no signal of harm. In fact, most of the serious adverse events were lower in the combination treatment cohort than in the other cohorts.

**CARE study:**

The body systems for which serious adverse events reported from the CARE study are shown below.

Table 42: Serious adverse events during the CARE study

	+PRA + ASA	+PRA -ASA	-PRA + ASA	-PRA -ASA
Number of Subjects	1742	339	1735	343
Total number of patients with SAEs	1015 (58%)	218 (64%)	1051 (61%)	222 (65%)
Total SAEs	2969 (170%)	771 (227%)	3209 (185%)	738 (215%)
Cardiac	669 (38%)	150 (44%)	733 (42%)	155 (45%)
Dermatological	86 (5%)	17 (5%)	70 (4%)	15 (4%)
Endocrine/Metabolic/electrolyte	50 (.3%)	9 (3%)	39 (2%)	10 (3%)
Gastrointestinal	171 (10%)	56 (17%)	201 (12%)	51 (15%)
General	147 (8%)	47 (14%)	166 (10%)	35 (10%)
Hematolo-poietic	31 (2%)	7 (2%)	44 (3%)	5 (2%)
Hepatic Biliary	164 (4%)	22 (7%)	177 (10%)	16 (5%)
Immunology/sensitivity disorder	3 (<1%)	3 (1%)	3 (<1%)	1 (<1%)
Musculoskeletal/Connective tissue	140 (8%)	35 (10%)	130 (8%)	31 (9%)
Nervous system	121 (7%)	51 (15%)	142 (8%)	41 (12%)
Renal/Genitourinary	162 (9%)	32 (9%)	154 (9%)	26 (8%)
Respiratory	153 (9%)	43 (13%)	167 (10%)	38 (11%)

Special Senses	19 (1%)	9 (3%)	30 (2%)	10 (3%)
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Even gastrointestinal adverse events are greater for those in the non-aspirin group.

The incidences of the most common serious adverse events (of >3%) in the CARE study are shown below. There were no events that were increased in the combined group than the individual component groups.

Table 43: Most common serious adverse events in the CARE study

	+PSA + ASA	+PSA -ASA	-PRA + ASA	-PRA -ASA
Number of Subjects	1742	339	1735	343
Angina pectoris acute	363 (21%)	63 (19%)	373 (22%)	85 (25%)
CABG	220 (6%)	39 (5%)	270 (7%)	50 (6%)
Myocardial infarction	167 (10%)	38 (11%)	195 (11%)	56 (16%)
Heart failure	94 (5%)	31 (9%)	99 (6%)	27 (8%)
Chest pain	73 (4%)	19 (6%)	84 (5%)	17 (5%)
Atrial rhythm disturbance	62 (4%)	22 (7%)	77 (4%)	13 (4%)
Invasive peripheral vascular procedures	61 (4%)	13 (4%)	65 (4%)	14 (4%)
Pulmonary infection	59 (3%)	13 (4%)	42 (4%)	15 (4%)
Malignant dermal neoplasm	54 (3%)	12 (4%)	48 (3%)	10 (3%)

## REGRESS

Serious adverse events related to body system are displayed in Table 44.

Table 44: Serious adverse events by body system from the REGRESS study.

	+PRA + ASA	+PRA -ASA	-PRA + ASA	-PRA -ASA
Number of Subjects	245	205	220	215
Total number of patients with SAEs	73 (30%)	56 (27%)	75 (34%)	71 (33%)
Total SAEs	116 (47%)	73 (36%)	123 (56%)	105 (215%)
Cardiovascular	56 (23%)	51 (25%)	61 (28%)	47 (22%)
Dermatological	1 (<1%)	0 (0%)	0 (0%)	1 (<1%)
Endocrine/Metabolic/electrolyte	1 (<1%)	0 (0%)	0 (0%)	1 (<1%)
Gastrointestinal	4 (2%)	3 (1%)	3 (1%)	5 (2%)
General	4 (2%)	6 (3%)	4 (2%)	6 (3%)
Hematopoietic	1 (<1%)	0 (0%)	0 (0%)	0 (0%)
Immunology/sensitivity disorder	1 (<1%)	3 (1%)	3 (<1%)	1 (<1%)
Musculoskeletal/connective tissue	2 (1%)	2 (1%)	5 (2%)	6 (3%)
Nervous system	0 (1%)	1 (<1%)	5 (2%)	6 (3%)
Renal/Genitourinary	3 (1%)	3 (1%)	4 (2%)	3 (1%)
Respiratory	11 (4%)	6 (3%)	0 (0%)	8 (4%)
Special Senses	0 (0%)	1 (<1%)	0 (0%)	1 (<1%)

The incidence of serious adverse events were less in the REGESS study than in the CARE or LIPID studies partially because of the shorter duration of observation.

## PLAC I and PLAC II combined:

Serious events associated with a particular body system from the combined PLAC I and II studies are shown below.

Table 45- Serious adverse events by body system for PLAC I and II.

	+PRA + ASA	+PRA -ASA	-PRA + ASA	-PRA -ASA
Number of Subjects	171	110	180	98
Total number of patients with SAEs	62 (36%)	48 (44%)	91 (51%)	53 (54%)
Cardiovascular	47 (28%)	32 (29%)	71 (39%)	40 (41%)
Dermatological	7 (4%)	6 (6%)	5 (3%)	5 (5%)
Drug Interaction	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Endocrine/Metabolic	1 (.1%)	0 (0%)	0 (0%)	1 (1%)
Gastrointestinal	8 (5%)	6 (6%)	7 (4%)	3 (3%)
General	0 (0%)	2 (2%)	6 (3%)	2 (2%)
Hepatic Biliary	0 (0%)	1 (1%)	2 (1%)	0 (0%)
Immunology/sensitivity	0 (0%)	0 (0%)	2 (1%)	0 (0%)
Musculoskeletal/Connective tissue	6 (4%)	7 (6%)	11 (6%)	2 (2%)
Nervous system	4 (2%)	3 (3%)	3 (2%)	7 (7%)
Renal/Genitourinary	3 (2%)	8 (7%)	6 (3%)	2 (2%)
Respiratory	2 (1%)	6 (6%)	3 (2%)	7 (7%)
Special Senses	1 (1%)	0 (0%)	1 (1%)	0 (0%)

The event rates in the PLAC I and II databases are less than those in the CARE and LIPID study due to the shorter duration of follow-up.

Overall, considering all studies in this imperfect database, there appears to be no signal that there is an increase in adverse events among those treated with aspirin.

### Discontinuations

The system associated with discontinuations for the LIPID study (Table 46), The CARE study (Table 47), The REGRESS study (Table 48) and the PLAC I and II study (Table 49) indicate no increase in event rate in the combination therapy cohort versus monotherapy cohorts.

Table 46- Body systems associated with discontinuation for the LIPID study.

	+PRA + ASA	+PRA -ASA	-PRA + ASA	-PRA -ASA
Number of Subjects	3730	782	3698	804
Total number of patients with SAEs	378 (10%)	105 (13%)	448 (12%)	129 (16%)
Total SAEs	791 (21%)	230 (29%)	448 (12%)	126 (16%)
Cardiac	129 (4%)	39 (5%)	196 (5%)	57 (7%)
Complications of medical care	5 (<1%)	3 (<1%)	7 (<1%)	2 (<1%)
Dermatological	18 (<1%)	6 (1%)	16 (<1%)	3 (<1%)
Endocrine/metabolic	20 (<1%)	0 (0%)	14 (<1%)	3 (<1%)
Gastrointestinal	55 (1%)	17 (2%)	71 (2%)	23 (3%)
Hematologic	11 (<1%)	3 (<1%)	13 (<1%)	3 (<1%)
Hepatic biliary	24 (1%)	3 (<1%)	25 (1%)	6 (1%)
Infections	7 (<1%)	6 (1%)	16 (<1%)	1 (<1%)
Malignancy	81 (2%)	19 (2%)	86 (2%)	30 (4%)
Musculoskeletal	457 (12%)	121 (16%)	462 (13%)	109 (4%)
Nervous system	46 (1%)	7 (1%)	38 (1%)	10 (1%)
Other reasons for hospital admission	0 (0%)	0 (0%)	4 (<1%)	1 (<1%)
Renal/genitourinary	36 (1%)	7 (1%)	30 (1%)	11 (1%)
Respiratory	44 (1%)	22 (3%)	59 (2%)	19 (2%)
Special senses	4 (<1%)	3 (<1%)	6 (<1%)	1 (<1%)
Trauma	7 (<1%)	0 (0%)	7 (<1%)	6 (1%)
Vascular (non-cardiac)	53 (1%)	24 (3%)	67 (2%)	12 (1%)

Table 47- Body systems associated with discontinuation from the CARE study.

	+PRA + ASA	+PRA -ASA	-PRA + ASA	-PRA -ASA
Number of subjects	1742	339	1735	343
Overall total subjects who discontinued	74 (4%)	18 (5%)	97 (6%)	24 (7%)
Cardiovascular	12 (1%)	1 (<1%)	19 (1%)	3 (1%)
Dermatological	0 (<1%)	2 (<1%)	7 (<1%)	1 (<1%)
Drug Interaction	0 (0%)	0 (0%)	0 (0%)	1 (<1%)
Endocrine/metabolic/electrolyte	4 (<1%)	1 (<1%)	10 (1%)	1 (<1%)
Gastrointestinal	12 (1%)	3 (1%)	6 (<1%)	0 (0%)
General	8 (<1%)	3 (1%)	6 (<1%)	0 (0%)
Hematopoietic	3 (<1%)	0 (0%)	6 (<1%)	0 (0%)
Hepatic biliary	6 (<1%)	2 (1%)	6 (<1%)	1 (<1%)
Immunology/sensitivity disorder	0 (0%)	0 (0%)	1 (<1%)	0 (0%)
Musculoskeletal/Connective tissue	5 (<1%)	0 (0%)	6 (<1%)	1 (<1%)
Nervous system	7 (<1%)	3 (1%)	6 (<1%)	6 (2%)
Renal/genitourinary	6 (<1%)	1 (<1%)	3 (<1%)	0 (0%)
Respiratory	2 (<1%)	43 (13%)	167 (10%)	38 (11%)
Special senses	0 (0%)	1 (<1%)	1 (<1%)	0 (0%)

Even gastrointestinal adverse events are greater for those in the non-aspirin group.

Table 48 Number of discontinuations during the REGRESS study.

	+PRA + ASA	+PRA -ASA	-PRA + ASA	-PRA -ASA
Number of Subjects	245	205	220	215
Total number of patients with SAEs	11 (4%)	7 (3%)	6 (3%)	5 (2%)
Total SAEs	116 (47%)	73 (36%)	123 (56%)	105 (215%)

The specifics of the discontinuations from this study are shown below.

For the +PRA +ASA cohort: The adverse events were: Conjunctivitis; Lung cancer; Thyroid carcinoma; Insomnia; Aneurysm spurium; Intravertebral disc herniation; Diplopia; Lung carcinoma; GI/ icterus/ unstable walking; and Gastric pain/heartburn.

For the + PRA -ASA cohort: The events leading to discontinuation were: Liver function disturbance; Abdominal pain; Rash; Heart failure; and Carotid artery stenosis.

For the -PRA + ASA cohort: The reasons for discontinuation were: Left muscle pain; primary hypothyroidism; bilateral carotid artery stenosis; prostate carcinoma; elevated LFTs; and acute leukemia.

For the -PRA -ASA cohort: The reasons for discontinuation were: Respiratory distress; Lung carcinoma; Lung cancer; Back pain; and Addison’s disease

PLAC I and II

Adverse events leading to discontinuation in the PLAC I and II studies are shown below.

Table 49- Body systems associated with discontinuation for the PLAC I and PLAC II combined

	+PRA + ASA	+PRA -ASA	-PRA + ASA	-PRA -ASA
Number of Subjects	171	110	180	98
Total number of discontinued patients with SAEs	11 (6%)	8 (7%)	19 (11%)	9 (9%)
Cardiovascular	3 (2%)	3 (3%)	6 (3%)	3 (3%)
Dermatological	0 (0%)	1 (1%)	1 (1%)	0 (0%)
Gastrointestinal	0 (0%)	0 (0%)	3 (2%)	1 (1%)
General	0 (0%)	0 (0%)	1 (1%)	0 (0%)
Hepatic Biliary	0 (0%)	0 (0%)	1 (1%)	1 (1%)
Musculoskeletal/Connective tissue	1 (1%)	1 (1%)	1 (1%)	1 (1%)
Nervous system	1 (1%)	0 (0%)	3 (2%)	2 (2%)
Renal/Genitourinary	1 (1%)	0 (0%)	0 (0%)	0 (0%)
Respiratory	1 (1%)	2 (2%)	0 (0%)	2 (2%)
Special Senses	4 (2%)	1 (1%)	3 (2%)	0 (0%)

Adverse events:

LIPID study

None of the reported adverse events were noted in greater than 0.7 % of the + PRA + ASA cohort.

The most common adverse events are shown below. Please note, only serious adverse events were captured in this study.

Table 50: Adverse events of > 0.7% in the + PRA + ASA cohort

	+PRA + ASA	+PRA -ASA	-PRA + ASA	-PRA -ASA
Number of Subjects enrolled	3730	782	3698	804
Myalgia and myositis	26 (1%)	6 (1%)	27 (1%)	1 (16%)
Rash or non-specific skin eruption	23 (1%)	7 (1%)	14 (<1%)	1 (<1%)

CARE study:

The most common adverse events during the CARE study are shown below.

Table 51: CARE –Selected adverse events

	+PRA + ASA	+PRA -ASA	-PRA + ASA	-PRA -ASA
Number of subjects	1742	339	1735	343
Musculoskeletal pain	1153 (66%)	215 (63%)	1112 (64%)	203 (59%)
Angina pectoris	867 (50%)	172 (51%)	886 (51%)	186 (54%)
Chest pain	649 (37%)	128 (38%)	658 (38%)	112 (33%)
Fatigue	569 (33%)	111 (33%)	553 (32%)	91 (26%)
Dyspnea	545 (31%)	122 (36%)	551 (32%)	102 (30%)
Dizziness	453 (26%)	83 (25%)	412 (24%)	86 (25%)
Musculoskeletal trauma	434 (25%)	79 (23%)	407 (24%)	78 (23%)
Invasive cardiac procedure	430 (25%)	76 (22%)	457 (26%)	88 (26%)
Dyspepsia /heartburn	40 (23%)	65 (19%)	417 (24%)	58 (17%)
Abdominal pain	375 (22%)	76 (22%)	374 (22%)	87 (25%)
Headache	351 (20%)	72 (21%)	333 (19%)	61 (18%)
Muscle cramp	343 (20%)	72 (21%)	305 (18%)	62 (18%)
Nausea vomiting	342 (20%)	65 (19%)	346 (20%)	79 (23%)
Heart rhythm disturbances	200 (12%)	39 (12%)	205 (2%)	35 (10%)

There is no overwhelming signal. Muscle cramps and musculoskeletal pain was slightly greater among pravastatin patients. Gastrointestinal symptoms were not more frequent among those treated with aspirin.

### REGRESS:

The most common adverse events among those treated in the REGRESS. The 10 most common adverse events are shown below:

Table 52: Some common adverse events during the REGRESS study

	+PRA + ASA	+ PRA -ASA	-PRA +ASA	-PRA -ASA
Total Number enrolled	245	205	220	215
Invasive cardiovascular procedures	95 (39%)	78 (38%)	106 (48%)	89 (41%)
Angina pectoris	53 (22%)	41 (20%)	58 (26%)	56 (26%)
Musculoskeletal pain	35 (14%)	46 (22%)	31 (14%)	39 (18%)
Fatigue	23 (9%)	18 (9%)	14 (6%)	18 (8%)
Chest pain	22 (9%)	16 (9%)	14 (6%)	18 (8%)
Subjective rhythm disturbances	20 (7%)	13 (6%)	10 (4%)	16 (7%)
Dizziness	20 (8%)	17 (8%)	4 (2%)	12 (6%)
Dyspnea	16 (6%)	14 (7%)	8 (4%)	10 (5%)
Headache	15 (6%)	6 (3%)	4 (2%)	8 (4%)
Influenza	14 (6%)	9 (4%)	7 (3%)	14 (7%)

### PLAC I and PLAC II

The 10 most common adverse events during these two studies are shown below:

Table 53- The most common adverse events during PLAC I and II

	+PRA + ASA	+ PRA -ASA	-PRA + ASA	-PRA -ASA
Total number enrolled	171	110	180	98
Angina pectoris	82 (48%)	44 (40%)	80 (44%)	44 (45%)
Musculoskeletal pain	63 (37%)	55 (50%)	71 (39%)	40 (41%)
URI	55 (32%)	30 (27%)	41 (23%)	31 (32%)
Chest pain	41 (24%)	30 (27%)	41 (23%)	31 (32%)
Invasive cardiac procedure	38 (22%)	24 (22%)	29 (16%)	11 (11%)
Dizziness	31 (18%)	24 (22%)	47 (26%)	24 (25%)
Dyspepsia/heartburn	28 (16%)	19 (17%)	16 (9%)	13 (13%)
Influenza	27 (16%)	22 (20%)	36 (20%)	20 (20%)
Abdominal pain	23 (14%)	19 (17%)	18 (10%)	16 (16%)
Fatigue	22 (13%)	16 (15%)	23 (13%)	8 (8%)

### Subgroups:

#### Gender and Age < 65 and > 65

The duration of exposure for the various subgroups and various studies is shown below.

Table 54 Duration of exposure for all studies based on gender and on age < 65 and ≥ 65 years

Study	Parameter	+PRA + ASA	+PRA -ASA	-PRA + ASA	-PRA -ASA
LIPID	Male	5.2 (N=3137)	4.9 (N=619)	5.0 (N=3122)	4.6(N=620)
	Female	5.1 (N=593)	4.7(N=163)	4.8(N=576)	4.7 (n=184)
CARE	Male	4.6 (N=1511)	4.3 (N=284)	4.4 (N=1506)	4.1 (N=282)
	Female	4.5 (N=231)	4.3 (N=55)	4.1 (N=229)	4.3 (N=61)
REGRESS	Male	1.9 (N=245)	1.9 (N=205)	1.9 (N=220)	1.9 (N=215)
	Female	---	-----	-----	-----
PLAC I and II	Male	2.5 (N=135)	2.6 (N=90)	2.3 (N=149)	2.4 (N=71)
	Female	2.6 (N=36)	2.8 (N=20)	2.5 (N=31)	2.5 (N=27)
LIPID	< 65 years	5.3 (N=2343)	5.0 (N=428)	5.1 (N=2283)	4.7 (N=446)
	≥ 65 years	5.0 (N=1387)	4.7 (N=354)	4.8 (N=1415)	4.5 (N=358)
CARE	< 65 years	4.7 (N=1221)	4.4 (N=220)	4.4 (N=1209)	4.3 (N=226)
	≥ 65 years	4.5 (N=521)	4.2 (N=119)	4.3 (N=526)	3.9 (N=117)
REGRESS	< 65 years	1.9 (N=208)	1.9 (N=170)	1.9 (N=192)	1.9 (N=183)
	≥ 65 years	1.9 (N=37)	1.9 (N=35)	1.8 (N=28)	1.9 (N=32)
PLAC I and II	< 65 years	2.4 (N=134)	2.6 (N=84)	2.3 (N=132)	2.4 (N=71)
	≥ 65 years	2.7 (N=37)	2.4 (N=27)	2.6 (N=48)	2.3 (N=27)

Within each study each of the subgroups were observed for approximately the same duration of time. The proportion of each demographic subgroup across studies however differs. The sponsor within their submission tabulates the adverse event profile for the gender and age. There was no consistent pattern that defined one subgroup has a greater frequency of events.

Laboratory:

The sponsor limits their discussion of laboratory to ALT, AST, CK and Hgb. The timing and the frequency of laboratory assessments were not clear and the number with measurements of a particular parameter was far from complete. The sum of objects across all studies with MARKED abnormality of these parameters is shown below.

Table 55- Selected laboratory abnormalities :

Parameter		+PRA + ASA	+PRA -ASA	-PRA + ASA	-PRA-ASA
ALT mg/dL	N=	5358	1308	5267	1333
highest	# Markedly abnormal (%)	71 (1.3%)	18 (1.4%)	79 (1.5%)	14 (1.1%)
AST mg/dL	N=	2556	725	2585	724
highest	# Markedly abnormal (%)	27 (1.1%)	9 (1.2%)	28 (1.1%)	6 (0.8%)
CK U/L	N=	5604	1323	5494	1337
highest	# Markedly abnormal (%)	211 (3.8%)	55 (4.2%)	207 (3.8%)	45 (3.3%)
Hgb g/dL	N=	3889	993	3804	995
lowest	# Markedly abnormal (%)	65 (1.7%)	32 (3.2%)	73 (1.9%)	17 (1.7%)
ALT/AST Marked is defined as > 3 x ULN if normal at enrollment or 4 x Pre therapy if baseline > ULN					
CK Marked defined as 4 x pre-therapy value					
Hgb Marked is defined as > 3 g/dL decrease from pre-therapy. Hgb not measured in the CARE study					

There is no strong signal from this data that any of these laboratory values are modified by the four cohorts of treatment. Perhaps there is a small excess of CK elevations among those treated with pravastatin. There did not appear to be a

Urine: Not reported

ECG: not reported

Vital Signs: Not reported

Dose relationship of adverse events to aspirin or pravastatin: There is no information of adverse event profile of either pravastatin or aspirin as a function of dose or formulation of aspirin from this database. There is no information as to when subjects took their dose of aspirin or which formulation of aspirin subjects received.

Overall safety conclusions: Within this flawed database there is no signal of an increase in adverse events with the cohort treated with combination drugs than each of the individual components.

Labeling:

Should the advisory committee approve of this formulation several additional issues deserve consideration.

The indicated population: The indicated population should be the overlap of the population to be treated with aspirin and the population to be treated with pravastatin.

This reviewer considered the data base as sufficient to indicate that pravastatin is useful in the treatment of patients, with evidence of increased lipid levels (either total cholesterol or LDL-Cholesterol), who are either post-myocardial infarction, post unstable angina and patients with symptomatic coronary artery disease subjects. Pravastatin, however, based on the totality of the smaller studies (PLAC I and II) may warrant a greater treatment population that might include patients at risk for coronary or vascular events. This population might include subjects with coronary artery disease, other evidence of cardiovascular disease (post-PTCA post-stroke, TIA, peripheral vascular disease etc) but the data is not as overwhelming for these populations.

With respect to the indications for aspirin, this drug is recommended for long term use ( $\geq$  1 year) under the following cardiovascular indications post-MI, chronic stable angina, unstable angina, ischemic stroke and TIA, CABG, PTCA, carotid endarterectomy.

Since aspirin does not have a “primary prevention claim”, no such claim should therefore be made for the combination product. The sum of the studies is shown below.

Table 56: Summary of enrolled patients and outcome

Study	Population	N=	Outcome
PLAC I	Patients undergoing angiography for <ul style="list-style-type: none"> <li>• Post-MI (&lt; 12 weeks).</li> <li>• For PTCA</li> <li>• For unstable angina.</li> <li>• For stable coronary artery disease.</li> </ul> LDL cholesterol ( $\geq$ 130 but < 190 mg/dL0)	408  Hx of: PTCA=225 CABG=19 MI=176	Two end-points Fatal + non-fatal MI or Non-fatal MI + CHD deaths marginally significant (P = 0.05 < p < 0.1). Including only events post-90 days shows significance for both sets of events.
PLAC II	Diagnosis of coronary artery disease <ul style="list-style-type: none"> <li>• A documented acute MI</li> <li>• Coronary angiography &gt; 50% of one of the coronary arteries</li> </ul> LDL-Cholesterol between 60-90 <sup>th</sup> percentile (inclusive)	N=151 Hx of CABG=90 PTCA=15 MI=93	Prespecified end-point Coronary deaths + CVA not tabulated.
REGRESS	Patients undergoing coronary cine-angiography for symptomatic coronary artery disease <ul style="list-style-type: none"> <li>• A least one stenosis of &gt; 50 % in a major coronary artery</li> </ul> Total cholesterol between 4.0 –8.0 mmol/L	885 subjects	Non-fatal MI, all cause mortality, stroke/TIA or unscheduled PTCA/CABG favored pravastatin p<0.002
CARE	Post MI population Plasma cholesterol > 240 mg/dL or LDL-Cholesterol > 174 mg/dL	7,180 subjects	Highly significant for pre-specified endpoint fatal CHD + Non-fatal MI
LIPID	<ul style="list-style-type: none"> <li>• Post MI between (3 months to 3 years)</li> <li>• Or Acute admission for unstable angina (3 months to 3 years)</li> <li>• Or admission for ischemic pain but not a definite MI</li> <li>• Elective admission for unstable angina with evidence of coronary artery disease on angiogram.</li> <li>• And</li> <li>• Total cholesterol between 4.0 to 7.0 mmol/L</li> </ul>	9,014 subjects  5,754 MI 3,260 unstable angina	Prespecified end-points highly significant <ul style="list-style-type: none"> <li>• Coronary mortality;</li> <li>• Non-fatal MI and fatal CHD;</li> <li>• Total stroke</li> <li>• Hemorrhagic stroke;</li> <li>• Cardiovascular mortality</li> <li>• Incidence of revascularization procedures</li> </ul> Benefit among MI and unstable angina patients

- 1) Wording of the Indication: It is unclear how the co-packaged product should be labeled since no specific studies were performed with this combination.
- 2) Dosing instruction: The current labeling for pravastatin indicates use with or without food and at any time. The current labeling for aspirin also indicates no time of day or limitation other than the dose is taken with generous amounts of water. There is no additional data from this database that further defines the appropriate dose of aspirin for use with pravastatin. The presumption is that standard doses of aspirin were used throughout these studies is reasonable but unproven.
- 3) Clinical pharmacology: The sum of data that is included under clinical pharmacology should be limited to those the intersection of the granted indication.
- 4) Safety. The description of safety should again be the intersection of aspirin and pravastatin. The adequacy of the sponsor’s analysis should be considered in accepting any modifications of the description of safety.