CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-387

Medical Review(s)

Pravastatin Tablets/Aspirin Tablets Co-Packaged Product

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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

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, lets 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.

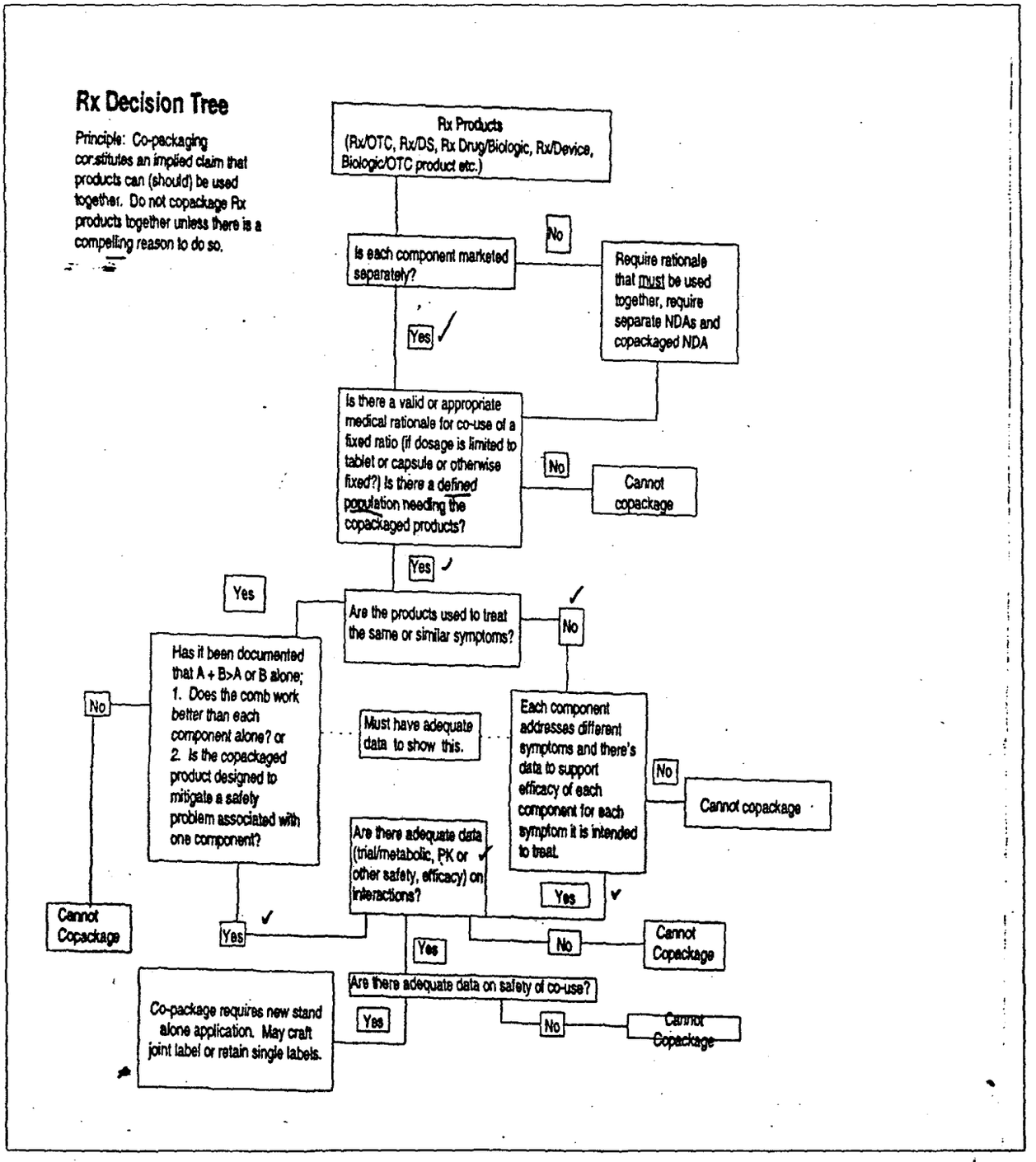
A second set of limitation should be considered, in that all credible dose combinations should be made available as the co-packaged products. The specific concern is that the apparent convenience of the co-packaged materials would predispose the physician to prescribe an inappropriate dose for the presumed 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 a 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

Figure 1- Approval of combination product:



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 • Ischemic stroke • TIA • Acute MI • Prevention of recurrent MI, • Unstable angina pectoris, and • Chronic stable angina.	Increased risk for atherosclerotic-related clinical events. • Primary prevention of coronary events • Secondary prevention of cardiovascular events • Hypercholesterolemia and mixed dyslipidemia
Mechanism of Action	Aspirin affects platelet aggregation	• HMG-CoA reductase inhibitor • Inhibits LDL-production by inhibiting hepatic synthesis of VLDL and LDL precursor.
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.	• Absolute bioavailability of 17% • Food effects on PK but not lipid lowering ability • Pravastatin when given at night was marginally better than when administered in the morning. • The lower systemic bioavailability suggests a greater extraction by the liver • Approximately 50% of active drug is protein bound • Is excreted both by hepatic and renal routes.
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.	• Place on cholesterol lowering diet prior to starting Pravachol • The recommended dose is 10, 20 or 40 mg daily, with or without food. • 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
Contraindications/Warnings	• Allergy to non-steroidals • Patients with asthma, rhinitis and nasal polyps • Increase in bleeding risk among those who consume alcohol • Increased risk among subjects with bleeding diatheses • GI side effects • Peptic ulcer disease	• Pregnancy or lactation • Acute liver disease • Liver enzymes (increases in transaminases) perform LFTs before starting and with each dose increase. • Myopathy, rhabdomyolysis,
Precautions	• Renal failure • Hepatic insufficiency • Sodium restricted diets	• Elevations in CPK • Subjects with renal failure should be monitored

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 sable 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

	All events			Excluding events occurring < 90 days from randomization [1]		
Cardiovascular event [2]	Prav n=206	PBO N=202	p-value[4]	Prav N=206	PBO N=202	p-value[4]
Non-fatal or fatal MI	8 (4%)[3]	17 (11%)[3]	0.050	5 (3%)[3]	17 (11%)[3]	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

[1] The 90 day waiting period was prespecified as one of the outcomes
[2] Events classified by independent review of documentation by clinical events adjudicator
[3] Kaplan-Meier estimate of 3-year event rate.
[4] 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 60-90th 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 sable 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 > 60-75th percentile and > 75-< 90th 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[1] (p-values are nominal)

Cardiovascular events[2]	Prav (n=75)	PBO (n=76) p-value	p-Value [3]
Coronary deaths	Not tabulated		
CVA	1 (1%)	3 (4%)	0.33
Coronary deaths and CVA	Not tabulated		
Non-fatal MI or all deaths [4]	5 (7%)	13 (17.1%)	0.049
Non-fatal or fatal MI[4]	2 (3%)	10 (13%)	0.02
Non-fatal MI, All deaths, stroke or PTCA/CABG[4]	12 (16%)	18 (24%)	0.2

[1] Kaplan-Meier estimate of 3-year event rate
[2] Event classification based on independent review of documentation by clinical event adjudicator
[3] Log rank Between-group p-Value
[4] 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.

Pravastatin→ / Aspirin↓	+	-
+	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 then 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 wit 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 –powering agents, cyclosporine or other investigational drugs.
- Hypersensitivity to HMG-CoA reductase inhibitors.
- Significant GI disease.
- Women of childbearing potential.
- Fasting triglyceride of ≥ 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	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 x 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 > 5x 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^2).
- 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 of 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 I 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%0	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
Ringing 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 log-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