

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	Phenocoumon
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 phenocoumon groups. Gastrointestinal complaints were greater in the aspirin and placebo cohorts relative to the phenocoumon

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 sulfinpyrazone 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. phenocoumaron 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
Combined Studies				
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
LIPID Study Demographics				
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%
CARE Study Demographics				
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 ± SD	209 ± 17	209 ± 16	209 ± 17	209 ± 16
Mean HDL chol ± SD	39 ± 9	40 ± 9	39 ± 9	39 ± 10
Mean LDL chol ± SD	139 ± 15	139 ± 14	139 ± 15	138 ± 14
Mean TG ± SD	157 ± 61	152 ± 63	155 ± 60	155 ± 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 PLAC I, PLAC II and Regress studies				
Number of patients	416	315	400	313
Age Mean ± SD	57 ± 8	57 ± 8	56 ± 9	57 ± 8
% male / % Female	91% / 9%	94% / 6%	92% / 8%	92% / 9%
Smoker %	86%	87%	83%	83%
Lipid levels (mg/dL)				
Mean total chol ± SD	233 ± 30	233 ± 29	230 ± 30	236 ± 29
Mean HDL Chol ± SD	38 ± 10	38 ± 9	37 ± 10	38 ± 10
Mean LDL Chol ± SD	166 ± 27	166 ± 26	163 ± 27	167 ± 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
LIPID Study				
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%)
CARE study				
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%)
PLAC I				
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%)
PLAC II				
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%)
REGRESS				
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

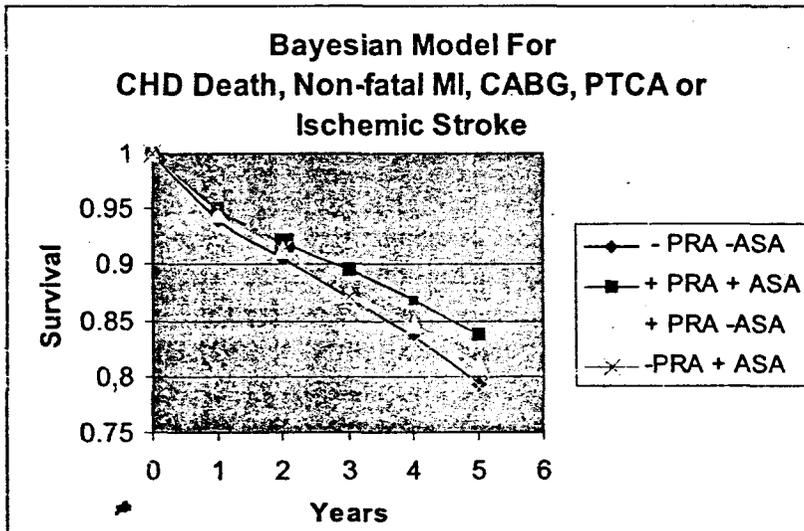


Table 26 Probability that X better than Y for the composite endpoint of CHD death, Non-fatal MI, CABG, PTCA or ischemic stroke

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

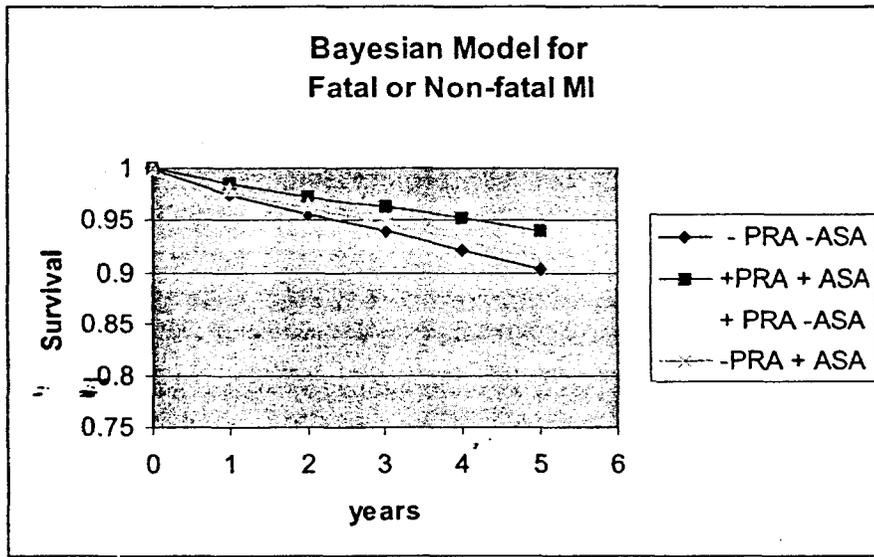
Year	+PRA + ASA	+ PRA -ASA	-PRA + ASA	-PRA-ASA
0 to 1	0.0508 + 0.0045	0.0564 + 0.0068	0.0510 + 0.0046	0.0615 + 0.0072
1 to 2	0.0309 + 0.0031	0.0355 + 0.0052	0.0415 + 0.0039	0.0378 + 0.0054
2 to 3	0.0286 + 0.0029	0.0429 + 0.0064	0.0445 + 0.0042	0.0338 + 0.0055
3 to 4	0.0305 + 0.0032	0.0321 + 0.0058	0.0485 + 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

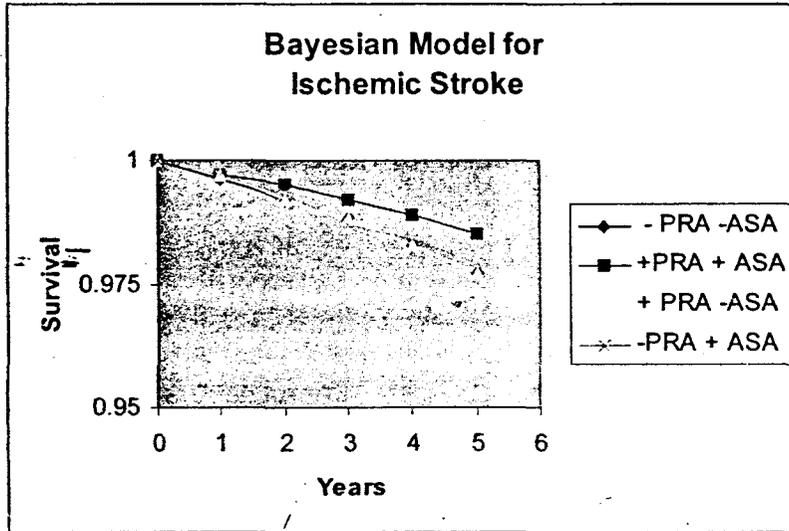
There appears to be time-dependent changes in the Hazard rates. For each year, however, the combination product was superior to placebo. Only during the first year was the combination product better than pravastatin monotherapy. The other years there was a trend toward superiority but no overwhelming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

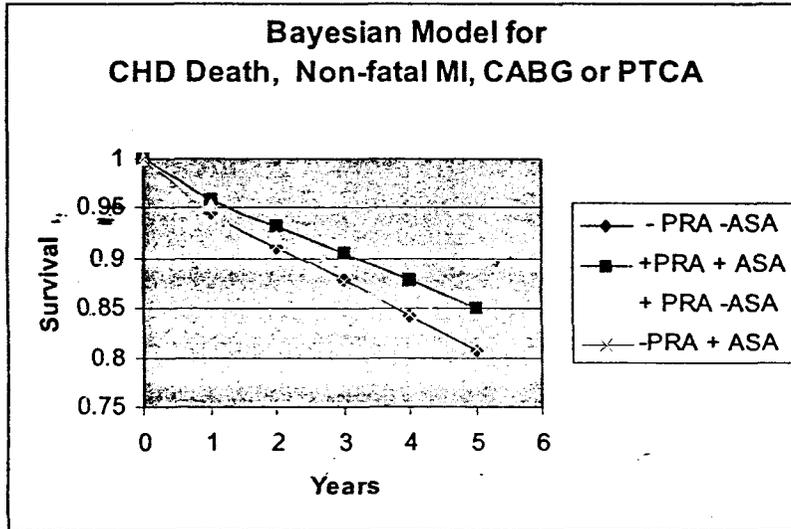


Table 32- Probability that X better than Y for CHD death, non-fatal MI, CABG or PTCA

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.

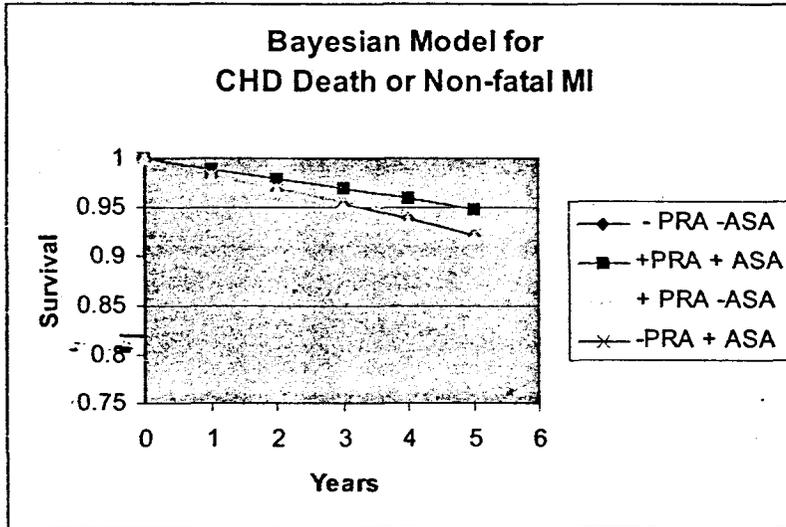
Year	+PRA + ASA	+ PRA -ASA	-PRA + ASA	-PRA-ASA
0 to 1	0.0477 + 0.0045	0.0529 + 0.0067	0.0487 + 0.0046	0.0581 + 0.0072
1 to 2	0.0285 + 0.0030	0.0324 + 0.0050	0.0370 + 0.0037	0.0330 + 0.0050
2 to 3	0.0251 + 0.0028	0.0353 + 0.0057	0.0414 + 0.0041	0.0321 + 0.0055
3 to 4	0.0281 + 0.0031	0.0290 + 0.0054	0.0436 + 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 95% Confidence Intervals (%, %)	26% (16, 35)	32% (10, 48)	14% (-1, 27)	23% (-11, 46)	3% (-9, 14)	7% (-21, 29)	-----	-----
Risk reduction vs. -PRA + ASA 95% Confidence Intervals (%, %)	34% (18, 29)	27% (11,40)						
Risk Reduction vs. + PRA -ASA 95% Confidence Intervals (%, %)	14% (2,25)	12% (-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 95% Confidence Intervals (%, %)	19% (7, 31)	36% (24, 47)	18% (+0, 33)	12% (-9, 29)	-1% (-17, 13)	8% (-9, 22)	-----	-----
Risk reduction vs. -PRA + ASA 95% Confidence Intervals (%, %)	20% (12, 27)	31% (22, 39)						
Risk Reduction vs. + PRA -ASA 95% Confidence Intervals (%, %)	2% (-15, 17)	27% (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 to 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 drug 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%)
REGRESS study				
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				
PLAC I and PLAC II				
Number of subjects	171	110	180	98
Number of Deaths	3 (1.8%)	3 (2.7%)	6 (3.3%)	5 (5.1%)
MI			1	3
Sudden cardiac death	2	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 pain	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%)	17 (1%)	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 REGRESS 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 (250%)
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 highest	N=	5358	1308	5267	1333
	# Markedly abnormal (%)	71 (1.3%)	18 (1.4%)	79 (1.5%)	14 (1.1%)
AST mg/dL highest	N=	2556	725	2585	724
	# Markedly abnormal (%)	27 (1.1%)	9 (1.2%)	28 (1.1%)	6 (0.8%)
CK U/L highest	N=	5604	1323	5494	1337
	# Markedly abnormal (%)	211 (3.8%)	55 (4.2%)	207 (3.8%)	45 (3.3%)
Hgb g/dL lowest	N=	3889	993	3804	995
	# 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"> • Post-MI (< 12 weeks). • For PTCA • For unstable angina. • For stable coronary artery disease. LDL cholesterol (\geq 130 but < 190 mg/dL)	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"> • A documented acute MI • Coronary angiography > 50% of one of the coronary arteries LDL-Cholesterol between 60-90 th 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"> • A least one stenosis of > 50 % in a major coronary artery 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"> • Post MI between (3 months to 3 years) • Or Acute admission for unstable angina (3 months to 3 years) • Or admission for ischemic pain but not a definite MI • Elective admission for unstable angina with evidence of coronary artery disease on angiogram. • And • Total cholesterol between 4.0 to 7.0 mmol/L 	9,014 subjects 5,754 MI 3,260 unstable angina	Prespecified end-points highly significant <ul style="list-style-type: none"> • Coronary mortality; • Non-fatal MI and fatal CHD; • Total stroke • Hemorrhagic stroke; • Cardiovascular mortality • Incidence of revascularization procedures 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.

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/s/

Abraham Karkowsky
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MEDICAL OFFICER