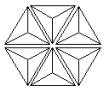

BRISTOL-MYERS SQUIBB
PHARMACEUTICAL RESEARCH INSTITUTE

Meeting of the Cardiovascular and Renal Drugs
FDA Advisory Committee
January 18, 2002

ADVISORY COMMITTEE BRIEFING BOOK FOR THE NDA OF PRAVACHOL® (PRAVASTATIN SODIUM) 40 MG TABLETS CO-PACKAGED WITH BUFFERIN® (BUFFERED ACETYLSALICYLIC ACID) 81 OR 325 MG

NDA 21-387

Bristol-Myers Squibb Pharmaceutical Research Institute
Bristol-Myers Squibb Company
P.O. Box 400
Princeton, NJ USA, 08543-4000

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

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Executive Summary

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1 INTRODUCTION

This briefing book outlines the data to be presented at the meeting of the Cardiovascular and Renal Drugs Advisory Committee on January 18, 2002. The Committee will be asked for its advice on the approval of the New Drug Application (NDA) for the co-packages of Pravachol® (pravastatin sodium) 40 mg and Bufferin® (buffered acetylsalicylic acid) 81 or 325 mg.

Fixed dose combination tablets of pravastatin and aspirin have been prepared. It is intended that a SNDA will be filed for these combination products, when the requisite stability testing is completed.

Both pravastatin and aspirin are approved for the reduction of cardiac events in a secondary prevention population. As they work by different mechanisms, i.e., slowing of the atherosclerotic process and reducing platelet agreeability, respectively, a combination of pravastatin and aspirin would therefore be expected to provide greater risk reduction than either drug taken alone. This risk reduction in the long-term care of patients with coronary artery disease would be in:

- Cardiovascular death
- Non-fatal myocardial infarction
- Myocardial revascularization procedures
- Ischemic stroke

This briefing book summarizes the clinical evidence for this independence of effects. It also describes a study that shows that there is no pharmacokinetic interaction between pravastatin and aspirin and provides information on the clinical safety of pravastatin and aspirin in combination in long-term usage. A more detailed presentation of the information contained in this Executive Summary is attached in the Appendix.

2 BACKGROUND

2.1 Demographic Considerations

The incidence of acute myocardial infarction has remained relatively constant over the past couple of decades at around 180-200 hospitalizations per 100,000 population.[1] However, because of new methods of management using thrombolytics and angioplasty, there has been a significant decline in hospital fatality rates from acute myocardial infarction (AMI) and coronary heart disease (CHD). These death rates have declined from 30% to 15%, in the over 65 population, of those who made it into the hospital. Such improvements in the in-patient management of myocardial infarction increase the size of the secondary prevention population. Demographic trends, as the baby boomers age, also will increase the population at risk of cardiac events. It is therefore likely that ischemic heart disease will remain the single leading cause of death in the United States into the foreseeable future.

2.2 Evidence for the Individual Effectiveness of Pravastatin and Aspirin

Guidelines for the management of chronic stable angina, which is the most common manifestation of ischemic heart disease, were published in 1999 by a joint committee of ACC/AHA/ACP-ASIM.[2] These guidelines recommend, for the prevention of MI and death, treatment with aspirin, in the absence of contraindications, and lipid-lowering agents. These treatments were assigned the highest weight of evidence level, A, because the clinical evidence, on which the treatment recommendations were derived, came from multiple randomized clinical trials involving large numbers of patients.

In the case of aspirin there were eight trials considered by the FDA Advisory Committee in 1997. Six of these were in recurrent myocardial infarction Cardiff I, Cardiff II, AMIS, CDP-A, GAMIS and Micristin. Two were in angina, the VA Cooperative Study in unstable angina and the SAPAT study in stable angina. The FDA review of these studies has been published,[3] along with the aspirin label.

In the reports by the Antithrombotic Trialists Collaboration,[4,5] in which the majority of the studies compared aspirin and placebo, the use of aspirin (75-325 mg daily) for all patients at significant risk of occlusive events, myocardial infarction or stroke was reinforced.

Aspirin is indicated[3] to reduce;

- the combined risk of death and non-fatal stroke
- the risk of death in patients with acute MI and unstable angina
- the combined risk of death and non-fatal MI in survivors of a previous MI
- the combined risk of MI and sudden death in patients with chronic stable angina.

It was concluded at the FDA Advisory Committee in 1997 that aspirin therapy in survivors of an MI was associated with a significant reduction (about 20%) in the risk of the combined end-points of subsequent death and/or non-fatal reinfarction.

For pravastatin such trials are, WOSCOPS,[6] CARE[7] and LIPID[8] in which a total of 19,768 patients were enrolled and randomized to pravastatin (40 mg) or placebo.

Pravastatin is indicated, in patients with clinically evident coronary heart disease, to:

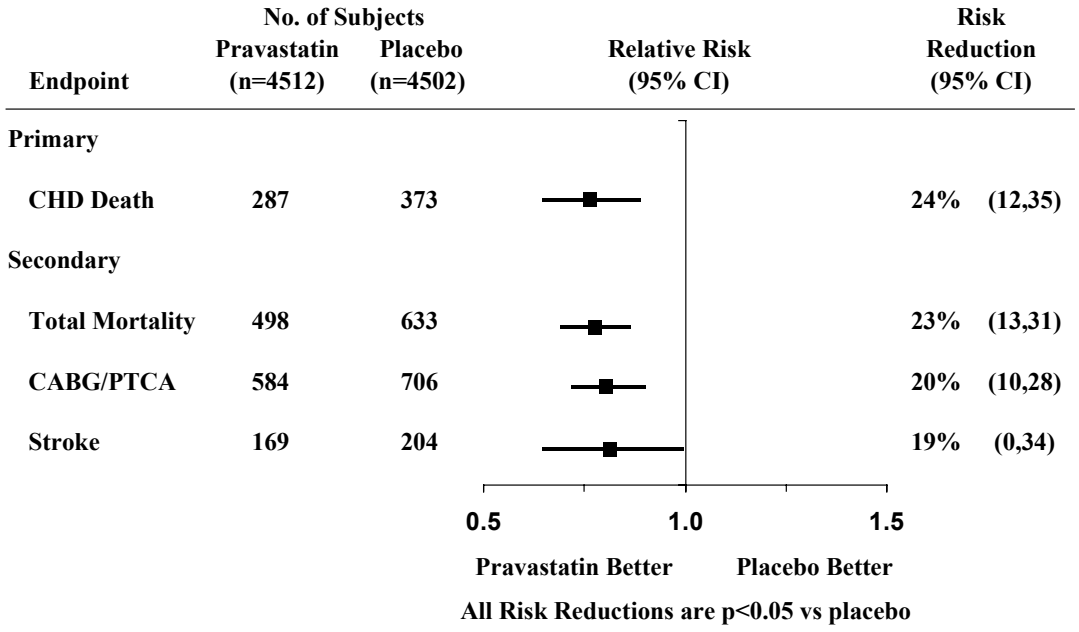
- reduce the risk of total mortality by reducing coronary death
- reduce the risk of myocardial infarction
- reduce the risk of undergoing myocardial revascularization procedures
- reduce the risk of stroke and stroke/TIA
- slow the progression of coronary atherosclerosis

These indications were based on an analysis of the clinical results from the LIPID[8] and CARE[7] trials, along with three trials which investigated pravastatin for its effects on plaque regression, i.e., REGRESS,[9] PLAC I[10] and PLAC II.[11]

The LIPID[8] trial was a double-blind randomized trial in which the effects of pravastatin (40 mg qd) were compared with placebo in 9014 patients aged 31 to 75 years, who had a history of MI or hospitalization for unstable angina. The patients had initial plasma total

cholesterol levels of 155-271 mg/dL. The study ran for a mean period of 6.1 years. The results are shown in Figure 1.

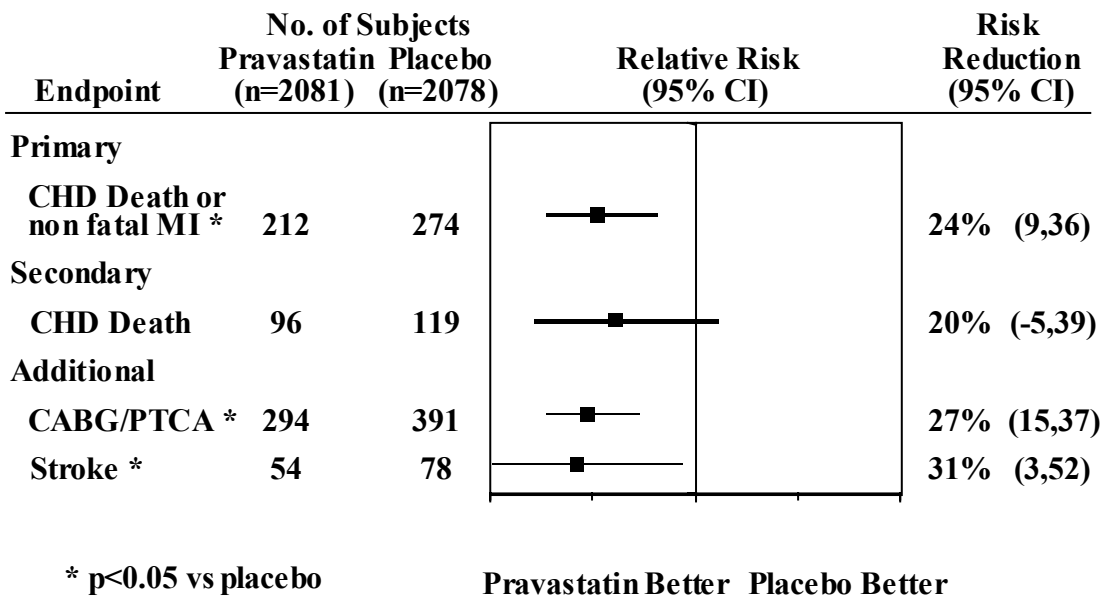
Figure 1: LIPID Trial Results: Patients with MI or Unstable Angina



Source: LIPID Study Group (NEJM 1998)

The CARE Study,[7] was a randomized placebo controlled double-blind study of pravastatin (40 mg qd) in 4159 patients who were 3-20 months post-MI prior to randomization. They had total plasma cholesterol levels of less than 240 mg/dL. The primary end-point was a fatal or non-fatal MI. The study lasted for 5 years. The results are shown in Figure 2.

Figure 2: CARE Trial Results: Post MI Patients



Source: Sacks et al (NEJM 1996)

For the purposes of the meta-analysis, it was appropriate to consider all randomized placebo-controlled trials with pravastatin in a secondary prevention population. The three regression studies were therefore included.

REGRESS,[9] was a 2 year study in 885 symptomatic men with coronary artery disease. They were randomized to pravastatin (40 mg daily) or placebo. Using quantitative coronary arteriography changes in average mean segment diameter/patient and change in average minimum obstruction diameter/patient were measured. Clinical events were also analyzed as a secondary end-point. In the pravastatin treated group, there was less progression of coronary atherosclerosis and fewer new cardiovascular events.

PLAC I was a three-year study in 408 men and women with coronary artery disease who were randomized to pravastatin (40 mg qd) or placebo. The effects of treatment on the progression of coronary atherosclerosis were assessed by quantitative coronary arteriography. Reduction in the progression of coronary arthrosclerosis was observed in the pravastatin group relative to placebo. There was also a reduction in fatal and non-fatal myocardial infarctions, which was a secondary end-point.

PLAC II[11] was a small study (151 men and women with established coronary artery disease). It was a three year double-blind, placebo controlled study of the effects of pravastatin (40 mg qd; 21 patients received a lower dose based on the responsiveness of their LDL values to treatment) on the intimal-medial thickness of the extra cranial arteries using B-mode ultrasonography. A 12% non-significant reduction in the progression of the mean-maximum carotid intimal-medial thickness was observed. A significant (35%) reduction was seen in one segment, the common carotid. However, significant reductions in cardiovascular events were also seen in the treated group.

A pooled analysis of the data from these three pravastatin regression trials (REGRESS, PLAC I, PLAC II) has been published by Byington.[12]

Table 1: Regression Trials Results

End-point	No. of Subjects		Risk Reduction (95% CI)
	Pravastatin (n = 955)	Placebo (n = 936)	
Fatal or non-fatal MI	21	46	62 (37-80)
All cause mortality	15	23	46 (-9-75)
Non-fatal MI, stroke PTCA, CABG, all cause mortality	115	160	30 (12-45)

Source: Byington Circulation 1995

These data provided additional support for the role of pravastatin in cardiac event reduction.

Based on these data, the use of aspirin and pravastatin in a patient population with established coronary artery disease represents good evidence-based medicine. However, in the 2001 update to the AHA/ACC guidelines,[13] it was stated that from multiple studies of the actual use of these recommended therapies in appropriate patients there was a discouraging conclusion. It was that a large proportion of patients in whom the therapies are indicated are not receiving them in actual clinical practice. The availability of the pravastatin/Bufferin® combination will provide the convenience of having both drugs immediately to hand and at no additional cost to the patient. It will also provide for the

physician the reassurance that he has prescribed for his coronary artery disease patient both recommended therapies at the appropriate doses.

3 CONCOMITANT USE OF PRAVASTATIN AND ASPIRIN

3.1 Prospective Approaches

As indicated in the Background section, the totality of evidence demonstrates that pravastatin and aspirin given separately to a patient with coronary artery disease are effective in the risk reduction of coronary events. As the mechanisms of action of these two drugs differ significantly, in the case of pravastatin by affecting lipoprotein metabolism and thus lipid deposition in atheromatous plaques and in the case of aspirin by affecting platelet agreeability. One might presume that they would act independently. However, for the approval of a combination product, it is necessary to demonstrate that the combination is more effective than either therapy given alone. The hypothesis of additive benefit would ideally be tested by a prospective, randomized, double-blind, placebo controlled study with a 2x2 factorial design, in patients with established coronary artery disease and conducted for an adequate period of time for a sufficient number of cardiac events to occur. Such a trial would then permit randomized comparisons of pravastatin plus aspirin vs. aspirin alone, vs. pravastatin alone and vs. placebo (additionally pravastatin alone and aspirin alone could be compared with placebo). However, elegant such a study might seem, it is ethically impossible to enroll a placebo group for such a study and ethically questionable for the separate components.

3.2 Aspirin Use in LIPID

LIPID enrolled 9014 post-MI or unstable angina patients with a primary end-point of death from coronary heart disease. They were randomized to either pravastatin (40 mg, qd) or to placebo. There was a mean follow-up of 6.1 years. In this study 83% of the patients took aspirin.

If one makes the randomized comparison of the group that took pravastatin and aspirin versus the group that took placebo and aspirin for the primary end-point of CHD death and then for fatal/nonfatal MI, ischemic stroke and a composite end-point (CHD deaths, non-fatal MI, CABG, PTCA and ischemic stroke), it is clear that adding pravastatin to aspirin provides additional relative risk reduction (Tables 2 and 3).

Table 2: LIPID Trial Primary Endpoint: CHD Death

	Prava	Placebo	RRR*
All Patients	**6.4%**	**8.3%**	**24.0%**
Aspirin Users	**5.8%**	**8.1%**	**28.3%**

*** Relative risk reduction based on Cox Proportional Hazards model**

Table 3: LIPID Trial Label Overlap Endpoints

		Prava	Placebo	RRR*
Aspirin Users	**Fatal and Non-fatal MI**	**7.1%**	**10.4%**	**34.7%**
	Ischemic Stroke	**2.6%**	**3.6%**	**29.7%**
	CHD Death, NF-MI, CABG, PTCA, Ischemic Stroke	**23.5%**	**29.7%**	**23.9%**

*** Relative risk reduction based on Cox Proportional Hazards model**

The issue of whether adding aspirin to pravastatin provides additional risk reduction over pravastatin alone can also be addressed from the LIPID data.

This comparison, though, is observational. Based on the primary end-point of CHD death, if one compares the event rate of the pravastatin without aspirin group (8.8%) to that of the pravastatin with aspirin group (5.8%), it appears that adding aspirin to pravastatin does provide additional benefit.

3.3 Aspirin Use in CARE

CARE enrolled 4159 post-MI patients, who were randomized to pravastatin (40 mg, qd) or placebo. The primary end-points were a fatal coronary event or non-fatal MI. There was a mean follow-up of 5 years. In this study there was 84% use of aspirin.

A similar comparison of the pravastatin and aspirin group versus the group that took placebo and aspirin for the primary end-point and then for fatal and non-fatal MI, ischemic stroke and the composite end-point previously defined, again shows the additional relative risk reduction obtained by adding pravastatin to aspirin (Tables 4 and 5).

Table 4: CARE Trial Primary Endpoint: CHD Death or Non-Fatal MI

	Prava	Placebo	RRR*
All Patients	**10.2%**	**13.2%**	**24.0%**
Aspirin Users	**9.3%**	**12.6%**	**28.2%**

*** Relative risk reduction based on Cox Proportional Hazards model**

Table 5: CARE Trial Label Overlap Endpoints

		Prava	Placebo	RRR*
Aspirin Users	Fatal and Non-fatal MI	10.1%	12.5%	20.6%
	Ischemic Stroke	2.0%	2.7%	28.9%
	CHD Death, NF-MI, CABG, PTCA, Ischemic Stroke	21.6%	27.4%	23.6%

*** Relative risk reduction based on Cox Proportional Hazards model**

The CARE data can also be used to address the issue of whether adding aspirin to pravastatin provides additional risk reduction. This comparison, though, is observational. However, using the primary end-point of the CARE study, i.e., CHD death and non-fatal MI, the event rate in the pravastatin without aspirin group was 14.8%. In the pravastatin with aspirin group the event rate was 9.3%. This finding again suggests that there is additional risk reduction from adding aspirin to pravastatin.

3.4 Meta-Analyses

Meta-analyses of the entire dataset of the trials of pravastatin in the reduction of cardiovascular risk in a secondary prevention population were undertaken. The baseline covariates were corrected to minimize bias. Age, gender, smoking status, any previous cardiac event, baseline LDL-C, HDL-C, TG and baseline DBP and SBP were chosen. These analyses were undertaken in order to provide additional support for the conclusions derived from the observational comparisons made in LIPID and CARE that addition of aspirin to pravastatin provides additional risk reduction.

3.4.1 Model 1

This model used a Cox proportional hazards model with adjustments for baseline risk factors. It assumed that all patients with the same covariates are exchangeable even though they were in different studies.

The meta-analysis involved 14,617 patients. (Table 6)

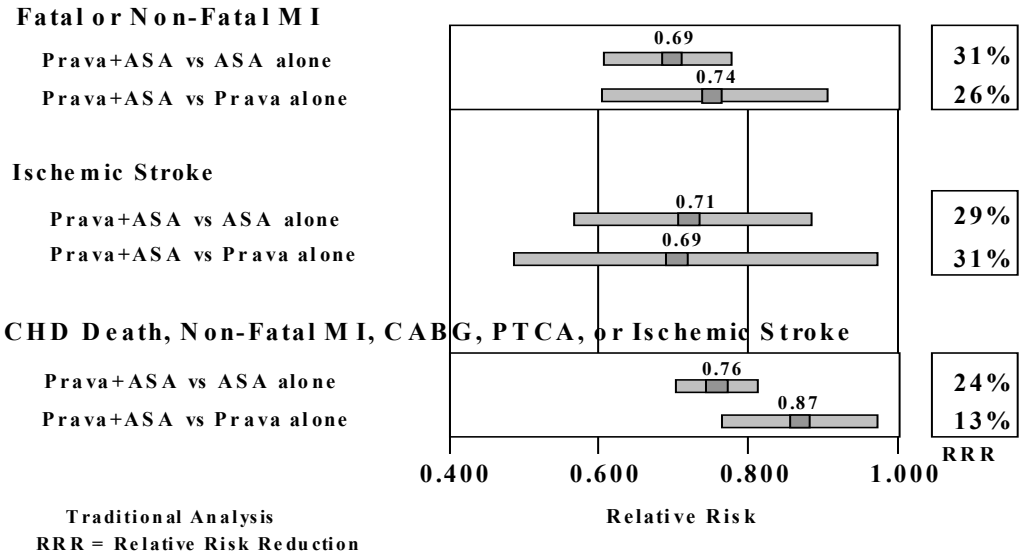
Table 6: Aspirin Usage in All Pravastatin Secondary Prevention Trials

Trial	Number of Subjects*	% on Aspirin	Primary Endpoint
LIPID	**9014**	**82.7**	**CHD mortality**
CARE	**4159**	**83.7**	**CHD death & non-fatal MI**
REGRESS	**885**	**54.4**	**Atherosclerotic progression (& events)**
PLAC I	**408**	**67.5**	**Atherosclerotic progression (& events)**
PLAC II	**151**	**42.7**	**Atherosclerotic progression (& events)**
Totals	***14,617***	***80.4***	

***99.7 % of pravastatin-treated subjects received 40mg dose**

The three end-points chosen were derived from the commonality of the aspirin and pravastatin labels. These were fatal and non-fatal MI, ischemic stroke and a composite of CHD death, non-fatal MI, CABG, PTCA and ischemic stroke. The comparisons made were as for LIPID and CARE, namely pravastatin with aspirin compared to aspirin and pravastatin with aspirin compared to pravastatin. The relative risk reductions were compared (Figure 3).

Figure 3: Cox Proportional Hazards All Studies Combined (Model 1)

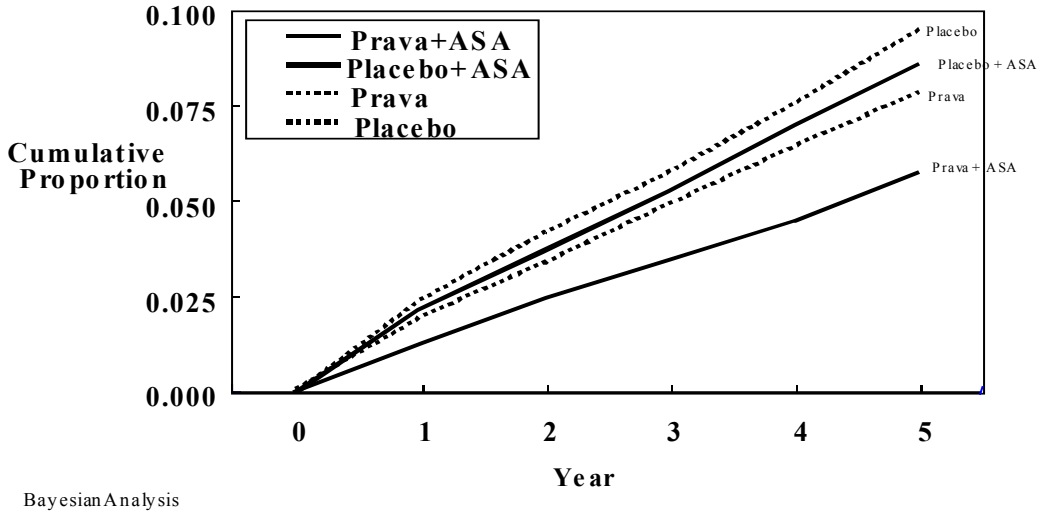


3.4.2 Model 2

This model is a standard Bayesian hierarchical Cox proportional hazards model. It is a model that does not assume that all patients with the same covariates are exchangeable from the different studies. It also permits the hazards to vary over time. This is helpful in addressing the issue that for the combination product it is important to know whether the effects of aspirin and pravastatin had a consistent effect during the five years they were studied in this population.

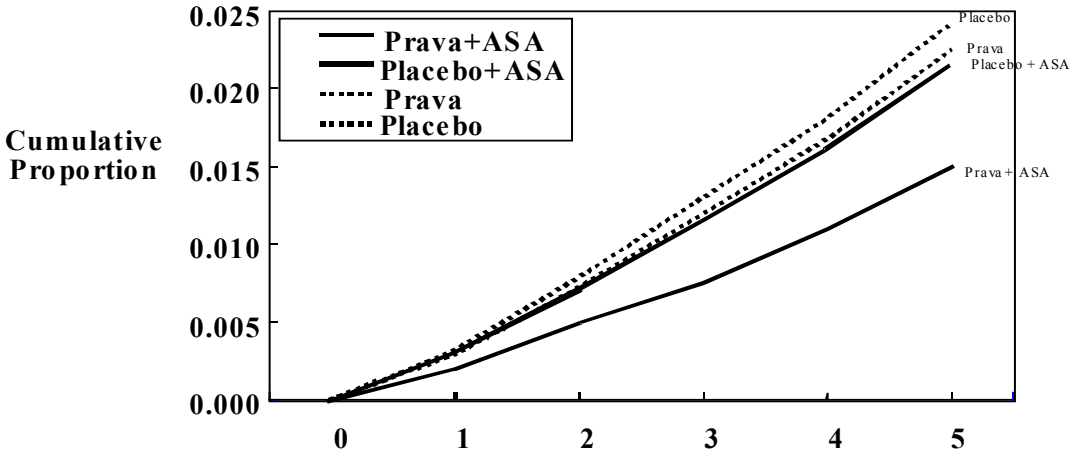
The end-points chosen were the same as for Model 1, fatal and non-fatal MI, ischemic stroke and the composite end-point. The data are shown graphically (Figures 4, 5 and 6).

Figure 4: Cumulative Proportion of Events (Model 2): Fatal and Non-Fatal MI



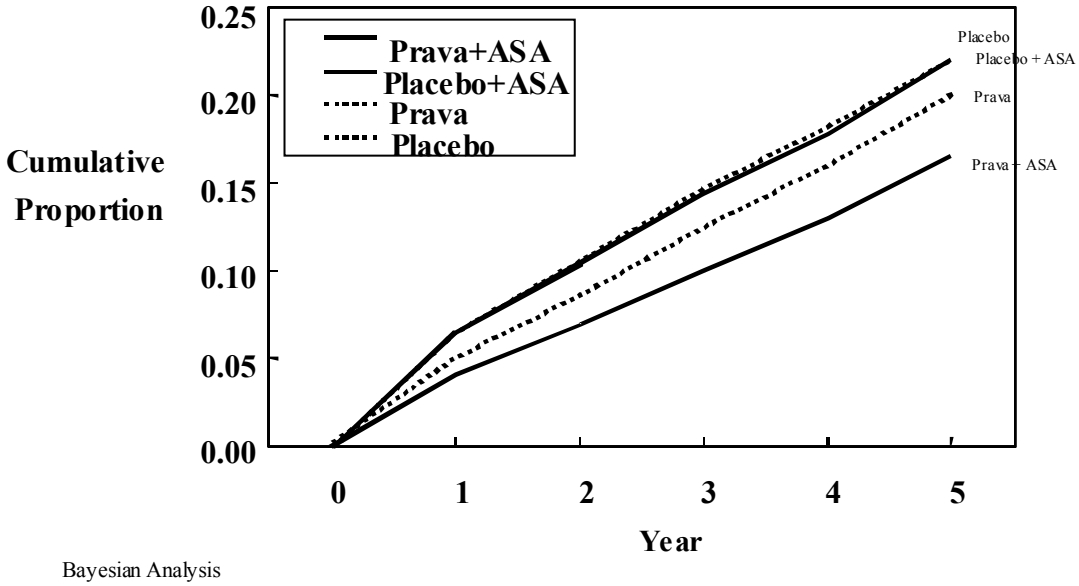
Bayesian Analysis

Figure 5: Cumulative Proportion of Events (Model 2): Ischemic Stroke Only



Bayesian Analysis

Figure 6: Cumulative Proportion of Events (Model 2): CHD Death, Non-Fatal MI, CABG, PTCA, or Ischemic Stroke



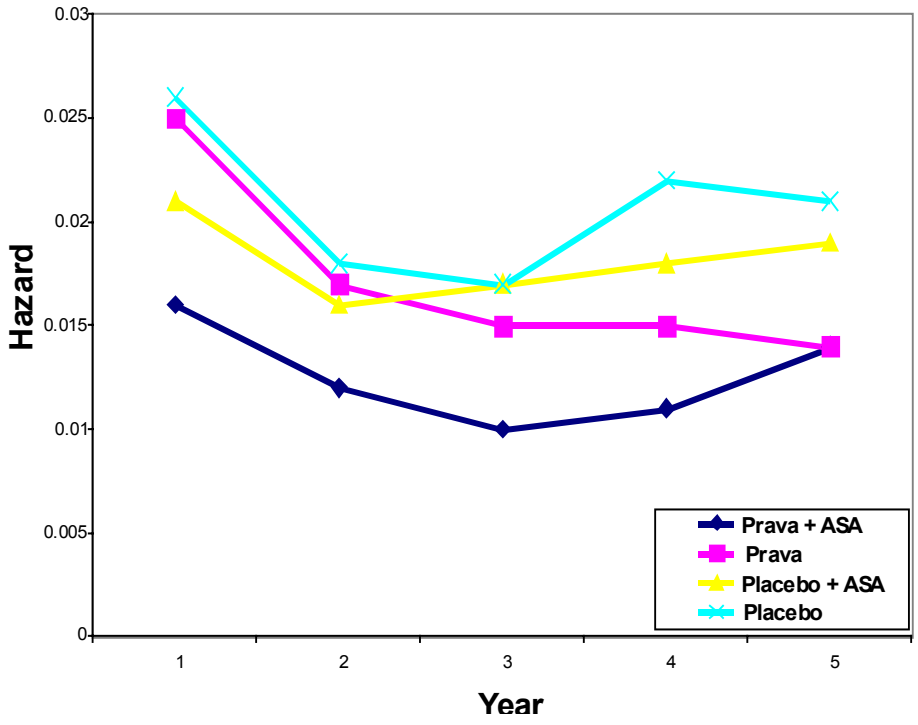
Bayesian Analysis

The randomized comparison of pravastatin plus aspirin vs. placebo plus aspirin confirms the conclusion from Model 1. The observational comparisons of pravastatin plus aspirin to pravastatin alone or to placebo alone also support the independence of effect of pravastatin and aspirin and that pravastatin plus aspirin is superior to either component alone. This effect is consistent, when one considers all the principal end-points, of myocardial infarctions (fatal and non-fatal), ischemic stroke and the composite end-point (Figures 4, 5 and 6).

3.4.3 Model 3

Model 2 considers that if any treatment is better at one time it is presumed to be better at other times. In Model 3 this restrictive assumption is relaxed. It, therefore, permits individual analyses for each of the 5 study years. A plot on the hazards by year for fatal and non-fatal MI shows that the effect of pravastatin and aspirin on hazard reduction is consistent on a year to year basis (Figure 7).

Figure 7: Fatal and Non-Fatal MI (Model 3)



3.5 Conclusions

It was therefore concluded from all three meta-analyses models that the pravastatin-aspirin combination provides a consistent benefit in risk reduction of vascular events in a coronary artery disease population, greater than that seen with pravastatin or aspirin given alone. This additional benefit was seen for all the principal endpoints chosen and for the duration of the treatments.

4 OTHER CONSIDERATIONS IN THE CONCOMITANT USE OF PRAVASTATIN AND ASPIRIN

4.1 Choice of Doses

Aspirin

For the reduction of vascular events in a coronary artery disease population, the aspirin label recommends 75 to 325 mg once daily and indefinite continuation of therapy.[3] Eighty-one (81) mg is the most widely used dose for use in risk reduction in a secondary prevention population and 325 mg is the highest dose approved for this indication. The pravastatin combinations will provide both doses of aspirin.

Pravastatin

All the secondary prevention trials were conducted with a 40-mg dose. There are no clinical event data in a population with established coronary artery disease, which would support the use of the product at lower doses. The 40-milligram dose of pravastatin was well tolerated in all the studies and there was no requirement for down titration in any subject because of tolerability or clinical safety concerns. The present labeling for pravastatin does not require dose adjustment in the elderly. An on-going study of pravastatin in the elderly (PROSPER) is presently nearing completion in Scotland, Ireland and the Netherlands.[14] This study has enrolled 5804 elderly (> 70 years of age) men (2806) and women (2998), who have been randomized to pravastatin (40 mg) and placebo. They will have been studied for three and a half years. While the study remains blinded, the Safety Board has regularly reviewed the safety and efficacy data. The Safety Board has approved continuation of the study, suggesting that a pravastatin dose of 40 mg is well tolerated in the elderly.

A lower starting dose of pravastatin is only appropriate in special populations such as the renal or hepatically impaired patients and patients who have undergone transplantation. The combination products are not suitable in these settings, in which the patients require specialized medical management. It was therefore concluded that the co-packages should consist of pravastatin 40 mg plus Bufferin® 81 mg and pravastatin 40 mg plus Bufferin® 325 mg.

Administration

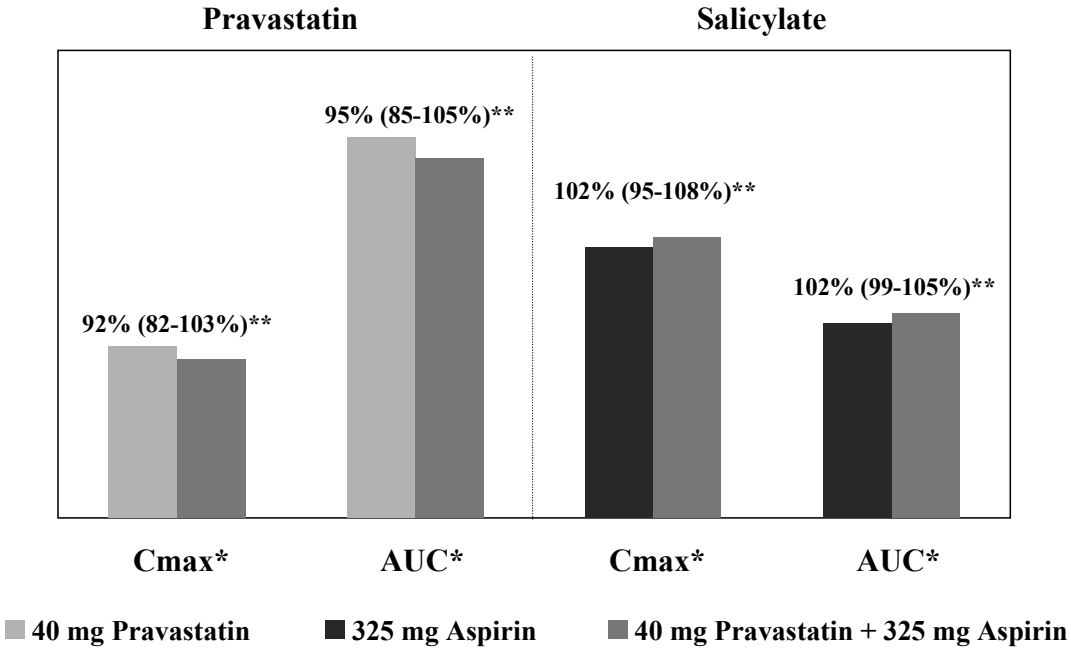
Neither the pravastatin nor the aspirin label requires that they be taken at a specific time of the day. Nor are there restrictions with regard to meals, although the aspirin label suggests that it be taken with water. This is presumably to reduce localized gastric irritation. The pravastatin-Bufferin® combination can than be given without regard to the time of day.

4.2 Drug-Drug Interaction

As significant drug-drug interactions have been observed with other statins, it was considered important to ensure the concomitant administration of pravastatin and aspirin did not affect the pharmacokinetics of either drug.

An open-label, single dose, randomized, three-period, three treatment crossover study was conducted in 30 healthy male and female volunteers. In this study each subject received on three separate occasions, separated by a week, a single dose of pravastatin (40 mg), a single dose of Bufferin® (325 mg) and concomitant administration of both drugs. The pharmacokinetic parameters are not different for either drug, whether given separately or concomitantly, within the guidelines for demonstration of bioequivalence (Figure 8).

Figure 8: Absence of Pharmacokinetic Interaction in Single Dose Study



* Cmax (µg/mL); AUCinf (µg•h/mL);
**Ratio of Geometric Least Square Means (90%CI)

4.3 Clinical Safety Profile

While the clinical event data was readily pooled across the five trials because of the similarity of the data which was captured, the safety data from the US study (CARE) and Australian study (LIPID) used different methodologies for coding adverse event data. They therefore cannot be pooled. Only PLAC I and PLAC II could be pooled, as REGRESS also differed in this regard.

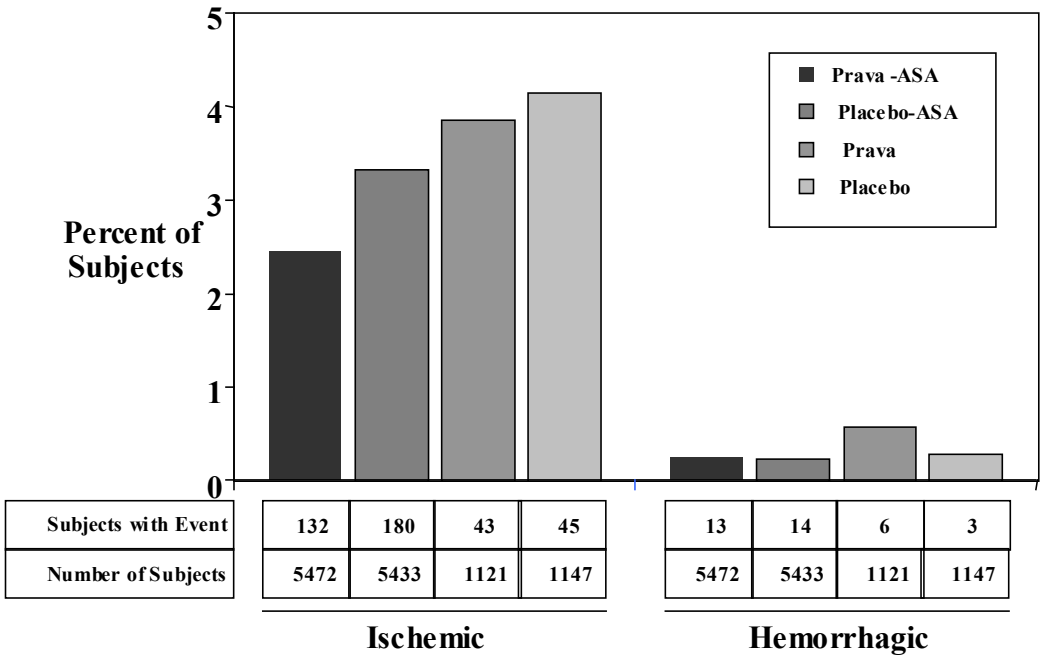
A review of all the patients in the five trials, comparing the clinical safety data by body system of the pravastatin plus aspirin group vs. the placebo plus aspirin group suggests no differences between the treatment groups.

Of particular interest is the incidence of hemorrhagic stroke seen with aspirin. In the recent report, by the Antithrombotic Trialists (ATT) Collaboration,[15] which analyzed the effect of antiplatelet therapy vs. no such therapy in a high risk-population (i.e., a 3% risk

of a vascular event per year), there was an incidence of probable or definite, fatal plus non-fatal hemorrhagic strokes of 0.65% by study, in the antiplatelet groups. This compared with 0.54% in the adjusted controls. While other antiplatelet drugs were included in this analysis, the vast majority of cases represented treatment with aspirin.

If one considers the incidence of ischemic and hemorrhagic stroke in the LIPID[8] and CARE[7] studies, (Figure 13) the net benefit is evident. The incidence of hemorrhagic strokes appears comparable with the ATT data[15] and most importantly, although the numbers are very small, the addition of pravastatin to aspirin does not appear to increase the incidence of hemorrhagic strokes.

Figure 9: Ischemic and Hemorrhagic Stroke Rates LIPID and CARE Combined



4.4 Other Considerations

There are no prospective rigorously designed studies that demonstrate that convenience for the patient translates into improved compliance with the therapy. There are, however,

several surveys that suggest, for all but the willfully non-compliant patient, convenience does significantly help compliance.[16,17]

For the pravastatin/aspirin combination product, there is an additional advantage. Its availability would permit the physician to be assured that the patient is being provided with the correct NSAID for reduction of cardiovascular events, i.e. aspirin, at a dose the physician considers to be appropriate. The combination also delivers the second component of the recommended regimen for the management of a secondary prevention patient, i.e. pravastatin, and at a dose which has been shown to be effective in the reduction of cardiac events.

5 CONCLUSIONS

- From meta analyses that have been conducted of the CARE,[7] LIPID,[8] REGRESS,[9] PLAC I[10] and PLAC II[11] databases, it can be concluded that the combination of pravastatin and aspirin is more effective in risk reduction in a secondary prevention population than either pravastatin or aspirin given alone.
- In the secondary prevention population with established coronary artery disease, the risk reduction is particularly seen in the end-points of
  - CHD death, nonfatal MI, CABG, PTCA or ischemic stroke
  - Fatal and non-fatal myocardial infarction
  - Ischemic stroke

The combination of pravastatin and aspirin was consistently better than either pravastatin or aspirin alone and the benefit of the treatment was evident throughout the duration of the studies.

An analysis of the clinical laboratory and clinical safety data did not yield any signal suggestive of potentiation of a particular adverse event.

There was no pharmacokinetic interaction between pravastatin and aspirin.

Use of the pravastatin-aspirin combination product will:

- Reduce cardiovascular morbidity and mortality in a coronary artery disease population over that achieved with the individual components.

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