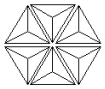

BRISTOL-MYERS SQUIBB
PHARMACEUTICAL RESEARCH INSTITUTE

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

ADVISORY COMMITTEE BRIEFING BOOK FOR THE NDA OF PRAVACHOL® (PRAVASTATIN SODIUM) 20, 40 AND 80 MG TABLETS CO-PACKAGED WITH BUFFERIN® (BUFFERED ACETYLSALICYLIC ACID) 81 OR 325 MG NDA 21-387

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1 INTRODUCTION

Bristol-Myers Squibb (BMS) has re-submitted an NDA for approval of a co-package of pravastatin and aspirin for use in reducing the risk of cardiovascular (CV) events in the secondary prevention population. This resubmission is intended to address concerns raised by both the Food and Drug Administration (FDA) during their review of the original application, and the Cardio-Renal Advisory Committee at their January 18, 2002 meeting. Two concerns have been cited:

1) The original application provided for only a 40 mg dose of pravastatin; greater dose flexibility is desirable for this combination product.
2) Because this product will contain aspirin, BMS was asked to provide additional information on how it will ensure patient safety regarding the use of aspirin, and to comment on the risk of aspirin use during surgery.

Revisions to the NDA to address these concerns include the following:

1) Data to allow for provision of 20 mg and 80 mg pravastatin doses, in addition to the 40 mg dose offered in the original application. Thus, the following co-packaged combinations will be available:

    a) pravastatin 20 mg/aspirin 81 mg
    b) pravastatin 20 mg/aspirin 325 mg
    c) pravastatin 40 mg/aspirin 81 mg
    d) pravastatin 40 mg/aspirin 325 mg
    e) pravastatin 80 mg/aspirin 81 mg
    f) pravastatin 80 mg/aspirin 325 mg.

These combinations will allow physicians greater flexibility to titrate to the desired dose of each component.

2) In addition, in this revised application, BMS is offering packaging which will be clearly marked to describe that this product contains aspirin, as well as a Patient Information Leaflet (PIL).

This Briefing Book contains a review and commentary on the use and safety of aspirin during surgery, a section on the range of pravastatin doses to be available in the

combination product and a section on the ability of pravastatin to achieve treatment goals. In addition, an independent review of the benefits and risks of a pravastatin-aspirin combination product, including a comprehensive literature review, performed by Jerry Avorn, M.D. and Yuka Kiyota, M.D., M.P.H. from the Division of Pharmacoepidemiology and Pharmacoeconomics from Harvard Medical School is included as Appendix F.

2 RATIONALE FOR A PRAVASTATIN/ASPIRIN COMBINATION PRODUCT

2.1 Public Health Benefit

The pravastatin-aspirin combination products offer an opportunity to provide an important benefit to the U.S. public health. Vascular disease is the major cause of death in the United States and coronary artery disease (CAD) patients represent the largest segment of this vascular disease population. Considerable progress has been made in their management with significant gains in life expectancy.[1] These gains have been achieved through lifestyle modifications (e.g., discontinuation of smoking, reduction of saturated fat and cholesterol in the diet, increased physical activity) and through the use of appropriate medications.

Even though several medications are used for secondary prevention of clinical events in this at risk population depending on the clinical status of individual patients, such as angiotensin-converting enzyme inhibitors and beta-adrenergic blocking agents, current guidelines recommend the use of both statins (HMG-CoA reductase inhibitors) and aspirin for risk reduction in essentially all patients with coronary artery disease.[2]

Despite these recommendations, data suggest that actual use of statins and aspirin by the at-risk population is less than optimal. Dr. George A. Beller, past president of the American College of Cardiology commented in his address to the College last year on the data obtained from a review of hospital discharge medications, which were provided to patients post myocardial infarction (MI).[3] Only 77% received aspirin and only 37% received a statin. The recent report from the Duke Databank for Cardiovascular Diseases also suggest that compliance with aspirin in a CAD population was about 81%.[4] In this report, Califf et. al. commented on the absence of effective systems to ensure that patients with chronic CAD get the basic secondary prevention therapy.

Some of the problems of compliance with the recommendations for aspirin may arise because of the OTC nature of aspirin. There have been reports not only of the under-utilization of aspirin but also of medication error in the use of aspirin. Some 11% of patients who had been instructed by their physicians to obtain aspirin from their local pharmacy for CV disease prevention or treatment actually obtained acetaminophen or an

over-the-counter (OTC) nonsteroidal anti-inflammatory drug (NSAID).[5] As a prescription product, the pravastatin-aspirin combination product will allow the prescribing physician more involvement and influence in ensuring that the patient is provided aspirin, at the dose desired by the prescriber, and that the product actually is aspirin rather than something else.

By combining these two important cardiovascular protection drugs in a single package (and ultimately as a fixed dose combination), the pravastatin/aspirin combination product potentially offers an important tool to maximize compliance with the guidelines regarding the use of these two drugs. Even a modest improvement in adherence to the guidelines could result in an important positive impact on the public health, as it has been estimated that 80,000 additional lives would be saved per year if there was a shift from the actual use of proven-effective therapy with anti-platelet agents, statins, beta-blockers and ACE inhibitors, to ideal compliance.[3]

In addition, some physicians are reluctant to overwhelm patients by starting them on multiple medications at once, concerned about the patient's acceptance. The pravastatin/aspirin combination product may help reduce this concern.

In summary, there is considerable potential public health benefit to this combination product. By possibly facilitating adherence to current guidelines for use of pravastatin and aspirin in the vast secondary prevention population, even small improvements could translate into marked reductions in morbidity and mortality. As a prescription product, the prescriber is better positioned to have influence on ensuring that the patient actually receives aspirin and at a dose chosen by the prescriber.

2.2 Regulatory Guidelines for Approval of Combination Products

In 1971 FDA regulations set out the current policy with regard to combination products, as FDA attempted to remove irrational and inappropriate combination products from the market. Regulations state that: "[two] or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined

in the labeling for the drug." [21 C.F.R. § 300.50 (a)]. While this policy refers specifically to fixed dose combination products, it is relevant for this co-packaging application as BMS has made it clear that once this application is approved, it will proceed with the necessary chemistry, manufacturing and control (CMC) data to provide for analogous fixed dose combinations of pravastatin/aspirin.

The regulatory process and interpretation of the guidelines have matured over the years. Then as now, they represent a sound basis for determining which drugs can be legitimately combined together as a single product. The key consideration is the stipulation that the two components should each contribute separately and independently to the effect of the combination. Therefore, the combination product should be able to demonstrate superiority over the individual components in the chosen endpoint. This endpoint may be either a clinical event, such as fatal or non-fatal MI, or a surrogate marker, such as a reduction in LDL-cholesterol. The individual components should also be physically stable together in a combination tablet and they should not interact together pharmacokinetically *in vivo*. It should be possible to label the combination product based on some commonality in the labels of the components. In addition, there should be a defined population for this combination; i.e., it should be well established that both compounds should be taken concomitantly for an appropriate medical condition. Compounds that are once a day drugs and that can be taken at any time of the day, without regard for meals, are well suited for such a combination.

It is intuitive that patients would prefer to take one pill rather than two, particularly in chronic, often asymptomatic conditions that require multiple medications. However, whether availability of a combination product translates to improved compliance compared to taking two separate medications has not been rigorously studied in prospective randomized trials, largely because these trials are confounded by fundamental design issues. Lack of blinding and observation effects (a.k.a. Hawthorne effects) have plagued attempts to prospectively study compliance behavior. Consequently, FDA have not required as a condition for approval, demonstration of improved compliance with the combination product over its components.

Pravastatin and aspirin meet all of the regulatory preconditions discussed above and represent a very appropriate choice for a single combination product. Pravastatin-aspirin is a combination of two *approved* drugs that share a *common indication*; each component

has been demonstrated to be safe and effective in reducing the risk of cardiovascular events in the secondary prevention population. In addition, current treatment guidelines recommend the use of each component in this CAD population, demonstrating medical need. BMS has presented substantial evidence in the form of meta-analyses of the placebo-controlled pravastatin secondary prevention trials to demonstrate that the combination results in a significant and clinically important reduction *in a common clinical endpoint* (cardiovascular events) over what can be achieved with the individual components. No new safety issues were identified in the use of the combination.

2.3 Registrational Program

Details of the original registrational program for pravastatin-aspirin can be found in Appendix A, which is the Executive Summary, from the briefing book, which was provided for the January 18th meeting.

3 THE CARDIO-RENAL ADVISORY COMMITTEE MEETING, JANUARY 18, 2002

The Cardio-Renal Advisory Committee considered the pravastatin-aspirin application at its January 18, 2002 Meeting. This section first summarizes the issues for which there was agreement that BMS had satisfactorily provided the Committee with adequate information. The second part details the issues for which the Committee felt that BMS had not provided adequate information and now provides additional data and analyses to address these concerns.

3.1 ISSUES RESOLVED

- Although BMS had not studied the pravastatin-aspirin combination product in a prospective, randomized, double-blind, placebo-controlled trial with a 2X2 factorial design in a secondary prevention population, it was agreed that approval of the NDA should still be considered.
- It was agreed that an appropriate population could be defined for treatment with pravastatin-aspirin, namely, a secondary prevention population with pre-existing cardiac disease.
- The Committee also agreed that the availability of studies that only show the absence of pharmacokinetic and pharmacodynamic interactions would not alone be a sufficient basis for approval. Nonetheless, for pravastatin and aspirin specifically, the Committee agreed that sufficient data had been presented to show the lack of a pharmacokinetic interaction.
- The Committee agreed that the meta-analyses of all the pravastatin secondary prevention trials (namely CARE, LIPID, REGRESS, PLAC I and PLAC II) provide evidence of the superiority of the combination of pravastatin and aspirin over pravastatin or aspirin given alone. The Committee also agreed that the level of evidence, in this particular case, was similar to that of an adequate and well controlled trial.
- The Committee agreed that the aspirin doses that were chosen for this combination product were reasonable.

3.2 ISSUES REMAINING

This section provides additional data and analyses with respect to the main unresolved issues from the January 18 meeting:

- The safe use of aspirin as it relates to this combination product, detailed in Sub-Section 3.2.1.
- The pravastatin doses that should be available for this combination product, detailed in Sub-Section 3.2.2.

Also, as was requested at the January 18 meeting, BMS has conducted analyses to provide the percentage of patients in the CARE and LIPID studies reaching National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III treatment goals. These analyses are detailed in Sub-Section 3.2.3. Finally, Sub-Section 3.2.4 contains a brief discussion on statin therapy.

3.2.1 The Safe Use of an Aspirin Containing Combination Product

One of the main issues raised by the Advisory Committee was the aspirin content of the combination product and the safety issues related to its use. In particular, the committee was concerned that patients and physicians may not be aware of the aspirin component of this combination product, and would therefore fail to discontinue its use prior to elective surgery. Theoretically, this inadvertent use of the product could lead to an increased incidence of surgical complications, perhaps outweighing the benefits of this product.

BMS Response

There are several components to BMS's response to this issue.

First, it clearly is most desirable that patients (and their physicians) are made aware that this product contains aspirin to allow for an educated decision as to whether the product should be interrupted for surgical procedures owing to its aspirin content. Thus, BMS will provide clear packaging and labeling to increase awareness of the aspirin content of the product as described in Sub-Section 3.2.1.1 below.

Second, we would maintain that the pravastatin-aspirin product, by nature of the fact that it will be a *prescription* product, presents less of a risk of being inadvertently continued

during surgery than do the scores of aspirin-containing products available OTC. In addition, as a prescription product, prescribers will be able to select the dose of aspirin to minimize the risk of bleeding. Further detail on this item is described in Sub-Section 3.2.1.2.

Third, although we anticipate that packaging, which clearly states that the product contains aspirin and a Patient Information Leaflet (PIL) will markedly increase the likelihood that patient and prescriber will know the product contains aspirin, we recognize that there will be occasions when even these measures are not successful. Thus, there will be cases when the product is continued peri-operatively. However, even in such instances, we would argue that the benefit-risk ratio of peri–operative aspirin use, particularly in the secondary prevention population with pre-existing cardiac disease, may even favor continuation of aspirin. There are emerging data that suggest that aspirin's protective effects outweigh the risk of significant peri-operative bleeding in many cases, particularly with newer operative management techniques in this CV risk population. To address this final point, in Section 3.2.1.3 we present a review of the current recommendations regarding the peri-operative use of aspirin in the secondary prevention population, and the risks of surgical bleeding. A literature review is attached (Appendix F).

3.2.1.1 Awareness of the Aspirin Content

The primary strategy to ensure patient safety regarding the use of aspirin and to reduce the risk for bleeding during surgery owing to inadvertent use is to provide packaging and educational material to allow patients and physicians the best opportunity to understand that this combination product contains aspirin. To meet this objective BMS will display the word "aspirin" prominently on the packaging of the product and on any promotional material. In addition, a Patient Information Leaflet (PIL) has been developed to further increase patient awareness of the product's contents. A picture of the proposed packaging and the PIL are available in Appendix C and D, respectively.

3.2.1.2 Safety Advantages of a Prescription Aspirin Product versus Over the Counter Aspirin Products

There are scores of OTC preparations that contain aspirin as shown in Table 3.2.1.2A. These products are readily available to the patient without any physician oversight and

may actually pose a greater risk to inadvertent exposure to aspirin than a clearly labeled prescription product that contains aspirin.

It is reasonable to believe that it is more likely that a patient will recollect or bring to the doctor's attention prescription products rather than OTC products and/or that physicians are more likely to know the active ingredients of prescription products than those of OTC products. One would not expect that many patients would be aware of the active ingredients of the many brands of aspirin-containing products that are available OTC. Furthermore, one would expect that a physician will know, or will have easy access to information about, the active ingredients of prescription products.

Table 3.2.1.2A: OTC Aspirin-Containing Mixtures

Brand	No. of Products	ASA Doses	Selected Other Ingredients
Goody's®	3	260, 500, 520	Acetaminophen, caffeine
Vanquish®	1	227	Acetaminophen, caffeine
Excedrin®	6	250	Acetaminophen, caffeine
Block®	3	650, 742	Caffeine, salicylamide
Anacin®	3	400, 500	Caffeine
Alka-Seltzer®	1	325	Sodium bicarbonate, Citric Acid
Cope®	1	421	Caffeine
Gelprin®	1	240	Acetaminophen, caffeine
Supac®	1	230	Acetaminophen, caffeine
Stanback®	1	650	Caffeine, salicylamide
Plus 41 generics containing aspirin			

In addition, the fact that pravastatin-aspirin will be a prescription product will allow the physician to exert more influence on the dose of aspirin received. Data from the recently completed CURE study (Table 3.2.1.2B) demonstrate that the risk of bleeding increases with increasing doses of aspirin. Prescribers particularly concerned about this risk in certain patients will be able to specify the smaller desired dose of aspirin (81 mg)

available in the pravastatin-aspirin combination products rather than leaving this choice to the patient as would occur with a patient-selected OTC aspirin product.

Table 3.2.1.2B: Major Bleeding by Aspirin Dose

Aspirin Dose	Placebo + Aspirin Incidence
< 100 mg	2.0%
100-200 mg	2.3%
> 200 mg	4.0%

Source: Plavix® Prescribing Information

3.2.1.3 Review of Aspirin as a Surgical Risk

The issue raised by the Advisory Committee regarding the safety of aspirin, due to the risk of bleeding during surgery, is important. In this section a discussion of some recent evidence of the potential benefit of aspirin in the peri-operative period is presented. A literature review of this area is also attached (Appendix F).

Several older studies have shown that the presence of aspirin in surgeries, particularly cardiothoracic surgeries, was associated with increased operative blood loss.[6,7,8] In addition, the presence of aspirin in general surgery has been shown to increase the need for a re-operation to control bleeding.[9] Collectively these studies led to a uniform recommendation to discontinue aspirin until "anti-platelet effects have worn off". There is therefore general agreement that in otherwise healthy patients requiring elective surgery, aspirin use should be stopped for 10-14 days prior to surgery.

However, since these reports were published, several developments have made some surgeons reconsider the decision to also withhold aspirin in patients with underlying coronary artery disease, who are scheduled for elective surgery.

Improvements in transfusion-sparing practices and autologous cell salvaging techniques are two newer practices that have changed the views with respect to the risk of continuing aspirin in patients with CAD. For example, in a small series of Coronary Artery Bypass Graft (CABGs) surgeries, for which aspirin use or no-aspirin use could be determined retrospectively, it was shown that while there was increased bleeding in the

aspirin–treated group, there was no difference between the groups in the requirements for platelets, fresh frozen plasma, cryoprecipitate or blood.[10] This was primarily because the blood from the mediastinal tube drainage was autotransfused. Similar findings have been reported elsewhere.[11]

In addition, an increasing appreciation by surgeons of the role that aspirin has in cardiovascular risk reduction in a secondary prevention population, even during the surgical period, is another factor leading to the consideration of continuing aspirin during surgical procedures. This view is held mainly because several recent studies suggest that there are benefits to continuing aspirin throughout the operation, in terms of reductions in mortality and significant morbidity, which greatly offset the short-term problems created by non-life-threatening bleeds.

One such study by Neilipovitz et.al.[12] was a decision analysis derived from literature data on peripheral vascular disease patients who were undergoing revascularization. The model in this study showed that while aspirin increased hemorrhagic complications by 2.46%, these events were not associated with mortality or long-term morbidity. In contrast, use of aspirin throughout the operation decreased perioperative mortality rates from 2.78% to 2.05%.

The Northern New England Cardiovascular Disease Study Group conducted the largest clinical study to address the preoperative use of aspirin.[13] This was a case-controlled study in 8,641 consecutive patients undergoing CABG in the five hospitals of Northern New England that carry out such procedures. They concluded that perioperative use of aspirin was associated with a significant decrease in risk of mortality during the CABG procedure, without a significant increase in hemorrhage, blood product requirements or related morbidities. In a follow-up letter to the editor of the *Annals of Thoracic Surgery*,[14] in response to a letter from a group in the UK with similar findings, Dacey, the lead author for the group, indicated that they have studied a further 13,350 CABG patients and have shown a 28% decrease in mortality in the aspirin group compared with those who did not receive aspirin (adjusted odds ratio 0.78; 95% confidence interval 0.61-0.99).

Despite, the studies mentioned above and the increased awareness that cardiovascular and cerebrovascular risk reduction, during the preoperative, the operative and postoperative

period is important, the primary focus has been on the use of beta-blockers. With these compounds two studies have shown the benefits of atenolol[15] and bisoprolol[16] in patients with CAD undergoing a surgical procedure. Unfortunately, no randomized double-blind studies of aspirin versus placebo during the peri-operative period in coronary artery patients where event reduction has been used as an end-point have been reported.

Several guidelines and reviews demonstrate that there is a lack of consensus with respect to the use of aspirin in the perioperative management of patients with CAD, perhaps because of the absence of prospective randomized placebo controlled data. The recent ACC/AHA Guideline Update for Perioperative Cardiovascular Evaluation for Non-cardiac Surgery mentions the perioperative use of atenolol[15] and bisoprolol[16] and is supportive of the use of beta-blockers. However, the guideline is silent on the specific continuation or discontinuation of aspirin during the operative procedure, although it recommends that aspirin be restarted as soon as possible after the surgical procedure.[17] The recent review in the Medical Clinics of North America on stopping and restarting medications in the perioperative period provides a brief commentary on the use of aspirin.[18] It also recommends prompt resumption of aspirin without specifically mentioning that it should be stopped, in patients with atherosclerotic disease. Moreover, it also mentions that aspirin is continued in many vascular surgeries but recognizes the absence of a consensus. A recent report from a peripheral vascular surgery group recommends that aspirin be present during the procedure, in the absence of contraindications.[19] They stated: "a compelling reason to administer aspirin to patients with peripheral arterial disease is to prevent death and disability from stroke and MI."

There is a consensus about discontinuing aspirin for neurological surgeries, where bleeding is likely to occur into a closed space. Such surgeries are unlikely to be undertaken electively without a thorough investigation of whether the patient is taking aspirin. Ophthalmologic surgery is another similar situation.

In patients who are taking aspirin for secondary prevention, additional bleeding during dental surgeries does not seem to be a concern; continued use of aspirin is recommended in these patients.[20]

It is therefore clear, that in patients with coronary artery disease who take aspirin for secondary prevention, the peri-surgical management with respect to aspirin use remains controversial.

Regarding actual hospital specific policies, some hospitals require cessation of all anti-platelet therapy for several days prior to elective surgery, regardless of the cardiovascular status of the patient. The Cleveland Clinic was identified as one such center, in a recent paper on the conduct of the CURE study.[21,22] In order to better understand current hospital policies around the continuation or discontinuation of aspirin before elective surgery in patients with CAD, BMS performed a limited survey of 24 teaching hospitals across the US. The results of this survey indicate that most hospitals do not have a policy. One hospital (UCLA Medical Center) that did have a policy to stop aspirin for all elective surgeries has recently changed to a "case by case" assessment. Other hospitals only withhold aspirin on the day of surgery. These findings are consistent with the absence of clear guidelines endorsed by professional societies on this issue. A description of the methods and the results of this hospital survey are included as Appendix E in this submission.

In summary, it is clear that patients who are inadvertently taking aspirin and continue it through the operative period will have an increased risk of bleeding. However, it is also clear that with the range of newer options available, e.g., the use of autologous transfusions,[10,23] and improvements in hemostasis these bleeding tendencies do not appear to result in major morbidity and mortality. Furthermore, some evidence even suggests that many patients with coronary artery disease may, in fact, be better served by perioperative use of aspirin, rather than by discontinuation.[13] The absence of hospital policies regarding strict discontinuation of aspirin prior to surgery and the silence of perioperative guidelines on its discontinuation in secondary prevention patients suggest that peri-operative bleeding sequelae due to aspirin may be a less serious issue now than it was in the past. Nonetheless clearly worded packaging and increased awareness by the physician that this prescription product contains aspirin are important barriers to inadvertent use.

3.2.2 Choice of Pravastatin Doses

The Advisory Committee was concerned about flexible dosing options for the pravastatin component.

BMS Response

This issue has been addressed in the re-filed NDA by providing for multiple doses of pravastatin, specifically 20, 40 and 80 mg, for this combination product. Thus, six combination packages will be made available: pravastatin 20 mg (with aspirin 81 mg or 325 mg), pravastatin 40 mg (with aspirin 81 mg or 325 mg) or pravastatin 80 mg (with aspirin 81 mg or 325 mg).

First, it is important to note that this combination product will not replace the presently marketed pravastatin 20, 40 and 80 mg tablets, it will only provide an additional choice for those physicians who find a combination product attractive.

While multiple pravastatin doses will be provided, it is important to note that the clinical event data supporting this application were amassed using the 40 mg pravastatin dose. Specifically, the meta-analyses comprising 5 long-term placebo-controlled morbidity and mortality trials on which the efficacy of the combination is based only used the 40 mg dose of pravastatin. The primary (CARE[24] and LIPID[25]) and secondary (PLAC-I, PLAC-II and REGRESS[26,27,28]) endpoints in these trials were clinical outcomes such as coronary mortality and nonfatal myocardial infarctions. Although the 20 mg dose of pravastatin is effective in lowering LDL-cholesterol, no studies evaluated its effectiveness in reducing cardiovascular event endpoints in a secondary prevention population. Accordingly, the labeling of pravastatin has recently been changed to specify that: "The recommended starting dose is 40 mg once daily."

The 40 mg dose is also an appropriate starting dose for the elderly. In the two secondary prevention trials, CARE[24] and LIPID,[25] including 6,593 subjects treated with pravastatin 40 mg for periods ranging up to 6 years, 36.1% (2381) of these subjects were aged 65 or older and 0.8% (56) were aged 75 or older. The recently completed PROSPER trial, a randomized, double-blind placebo-controlled study of pravastatin 40 mg, enrolled 5,804 elderly subjects (2,806 men and 2,998 women) aged 70 to 82 years.[29] The duration

of treatment was on average 3.5 years. Although this study has yet to be unblinded, there were no remarkable safety findings during the conduct of the study.

The 20 mg dose of pravastatin is now primarily reserved for hyperlipidemic patients with renal or hepatic impairment and patients on immunosuppressive drugs, such as cyclosporine. These patients, who would be under close medical management, are less likely to benefit from the convenience of a combination product and might be better served with the individual dosage forms of the components. The 20 mg tablet will remain available for the management of these patients. We therefore suggest that the starting dose for the pravastatin-aspirin combination product be the dose that has been shown to prevent cardiovascular events in patients with atherosclerotic disease, namely 40 mg.

Another recent change to the pravastatin label, since the original NDA filing of the pravastatin-aspirin combination in June of 2001, is the FDA approval of the 80 mg dose of pravastatin. While there are also no clinical event reduction data on this dose the additional cholesterol lowering potency will allow prescribers an additional option if they wish to treat toward National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III treatment goals (see below). As the 80 mg tablet is now an approved dose, the re-filed NDA for pravastatin-aspirin contains the chemistry manufacturing and control (CMC) data to support the 80 mg pravastatin dose as a dose for the combination product.

3.2.3 Pravastatin's Ability to Achieve NCEP ATP III Treatment Goals

The Advisory Committee at the January 18 meeting requested an analysis of the percentage of patients achieving NCEP ATP III treatment goals with pravastatin in the CARE and LIPID study.

BMS Response

As requested, BMS has performed a detailed analysis to determine how many patients in the CARE and LIPID trials actually achieved ATP III treatment goals. The results of these analyses are summarized below and presented in more detail in Appendix B. In addition, we calculated how many patients would achieve the ATP III goal if those who did not achieve their goal would have been titrated to the 80 mg dose. In this model we used the relative differences in cholesterol lowering which was observed between doses

in a dose ranging study (CV123-161) with pravastatin 40, 80 and 160 mg; in this study, a 7% difference in LDL-C lowering was observed between each dose. (See Appendix B for more detail.)

The CARE study randomized patients with LDL-C levels at baseline that ranged between 101 and 175 mg/dL. In the intent-to-treat population pravastatin, on average, lowered the LDL-C levels by 29.7 %; from an average baseline level of 139 mg/dL to 97 mg/dL. In this population about 75% of patients achieved their ATP III treatment goal for LDL-C of < 100 mg/dL. If those patients who did not achieve their ATP III goal had been titrated to 80 mg of pravastatin, this proportion would have increased to 90%. The LIPID study randomized patients with LDL-C levels at baseline that ranged between 46 and 274 mg/dL. In the intent-to-treat population pravastatin, on average, lowered the LDL-C levels by 27.5%; from an average baseline level of 150 mg/dL to 108 mg/dL. In this population about 50% achieved their ATP III treatment goal for LDL-C of < 100 mg/dL. If those patients who did not achieve their ATP III goal had been titrated to 80 mg of pravastatin, this proportion would have increased to 70%.

The CARE and LIPID studies randomized patients who are representative of the U.S. secondary prevention population. The CARE authors pointed out that the large majority of patients with coronary artery disease have cholesterol levels that are comparable with those of the general population, i.e., in the average rather than the elevated range.[30,31] In LIPID, a broader range of total cholesterol levels were studied in patients who were post MI or post admission for unstable angina. The baseline plasma total cholesterol values ranged from 155 to 271 mg/dL. However, it is important to appreciate that the CARE and LIPID studies were designed solely to study the effects of treatment with 40 mg pravastatin on clinical events relative to placebo, not on LDL-C lowering. The design of the CARE and LIPID studies did not include or allow a titration step according to achieved cholesterol levels. In addition, the initiation of these studies predates the ATP III guidelines and reductions in LDL-C, which, while measured, were not considered to be either primary or secondary outcomes.

FDA efficacy criteria for approval of a lipid-lowering drug do not stipulate that a certain proportion of patients need to achieve NCEP ATP III treatment goals. In general, when a lipid-lowering drug is able to lower LDL-C by more than 15% from baseline, which is

statistically significantly different from placebo, the efficacy hurdle has been met for approval.

In summary, the pravastatin-aspirin combination products with the 40 and 80 mg doses are appropriate both for secondary prevention of cardiovascular events and for achieving ATP III treatment goals with respect to LDL-C levels.

3.2.4 Risk of Discontinuing Statin Therapy

As indicated before, many physicians will advise discontinuation of aspirin use before an elective surgical procedure. The question therefore may arise whether discontinuation of this combination product in these cases would pose a risk to the patient, because of the discontinuation of pravastatin.

The continued availability of pravastatin and aspirin as individual components assures that a physician will always have the opportunity to discontinue the combination product and continue one of its components if so desired.

Currently there are no known adverse consequences to brief interruptions of long-term cholesterol-lowering therapy. One recent publication suggested that discontinuing statin treatment in a particular situation namely, at the time of hospitalization for an Acute Coronary Syndrome (ACS), was associated with a significantly worse outcome compared to continuation of statin therapy.[32] This should not be a concern for the pravastatin-aspirin combination product, because in this particular clinical situation, continuation of aspirin therapy would also be preferred.

4 CONCLUSIONS

The population that would benefit from this pravastatin-aspirin combination product is large. There are estimated to be about 12.4 million patients with established coronary artery disease, of whom 16% have contraindications to aspirin and 3% to statins. This leaves more than 10 million patients who could benefit from the combination.[33] To reiterate the compelling data cited in the Presidential Address at the American College of Cardiology last year regarding prescription use at hospital discharge following an MI, only 77% of such patients received aspirin and only 37% received a statin.[3] The availability of the combination product will add an important tool to improve the utilization of both drugs.

We hope that resubmission has adequately addressed the Advisory Committee's concerns regarding the flexible dosing for pravastatin, the safe use of aspirin, and the awareness of the patient.

5 SUMMARY

- **The Aspirin Safety Issues:** The fact that the product contains aspirin will be evident from the packaging and from the Patient Information Leaflet. Therefore, the inadvertent ingestion of aspirin prior to surgery seems less likely than with many OTC products currently available that include aspirin as part of their formulation. Furthermore, the discontinuation of aspirin prior to surgery in a secondary prevention population is no longer mandatory or deemed advisable in many centers.
- **The Pravastatin Doses:** The 20, 40 and 80 mg combination products with buffered aspirin 81 and 325 mg have been filed in the new application. Even so, attention should be paid to the fact that virtually all data on clinical events for pravastatin has been generated using the 40 mg dose.
- **The NCEP Guidelines:** We have presented an analysis to suggest that inclusion of the choice of an 80 mg dose of pravastatin for the combination product would have made it possible that 90% of the patients in CARE and 70% of the patients in LIPID would have achieved their "goal". This higher dose should allow more patients requiring additional lipid lowering therapy to achieve their LDL-C goals at a dose that logically should still achieve clinical event reductions.
- **Conclusion:** The pravastatin-aspirin combination product has been agreed to be safe and effective for cardiovascular risk reduction in a coronary artery disease population. The product and program meets the regulatory standards for approval of a combination product. The remaining issues raised by the Cardio-Renal Advisory Committee have been addressed. Approval of this product would also facilitate compliance by these patients, with the principal therapeutic recommendations of the treatment guidelines. Therefore, it would have a favorable public health effect in the reduction of secondary cardiovascular events.

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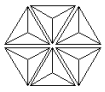
Appendix A:

Executive Summary of Previous Advisory Committee Briefing Book (January 18, 2002)

FDA Advisory Committee Briefing Book for Pravastatin/Aspirin

29 page(s) excluding cover page



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

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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:

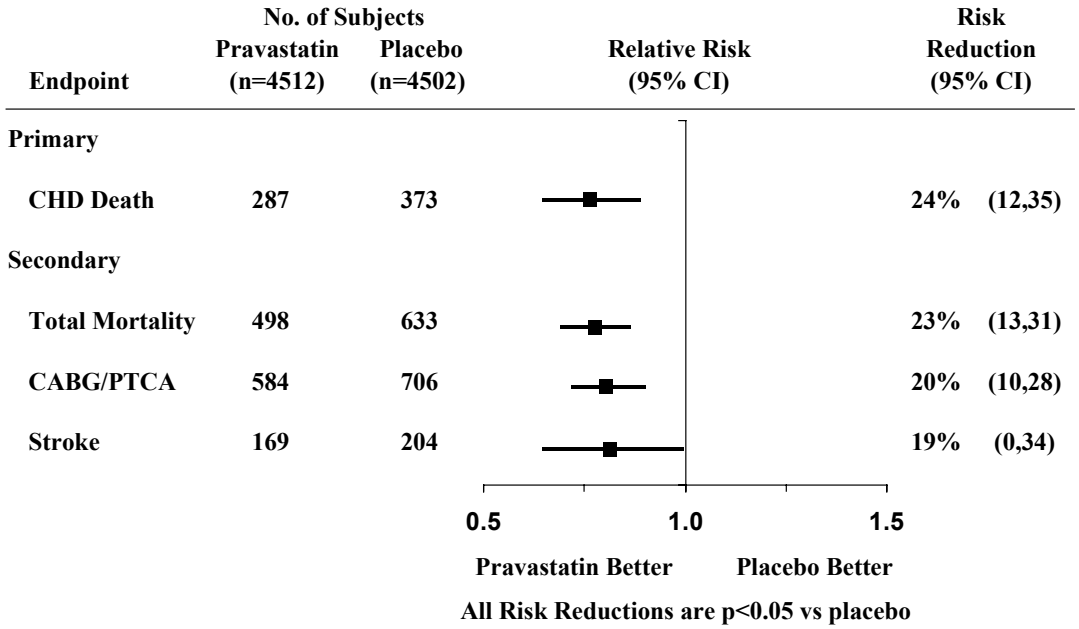
- reduce the risk of total mortality by reducing coronary death
- reduce the risk of myocardial infarction
- reduce the risk of undergoing myocardial revascularization procedures
- reduce the risk of stroke and stroke/TIA
- slow the progression of coronary atherosclerosis

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.

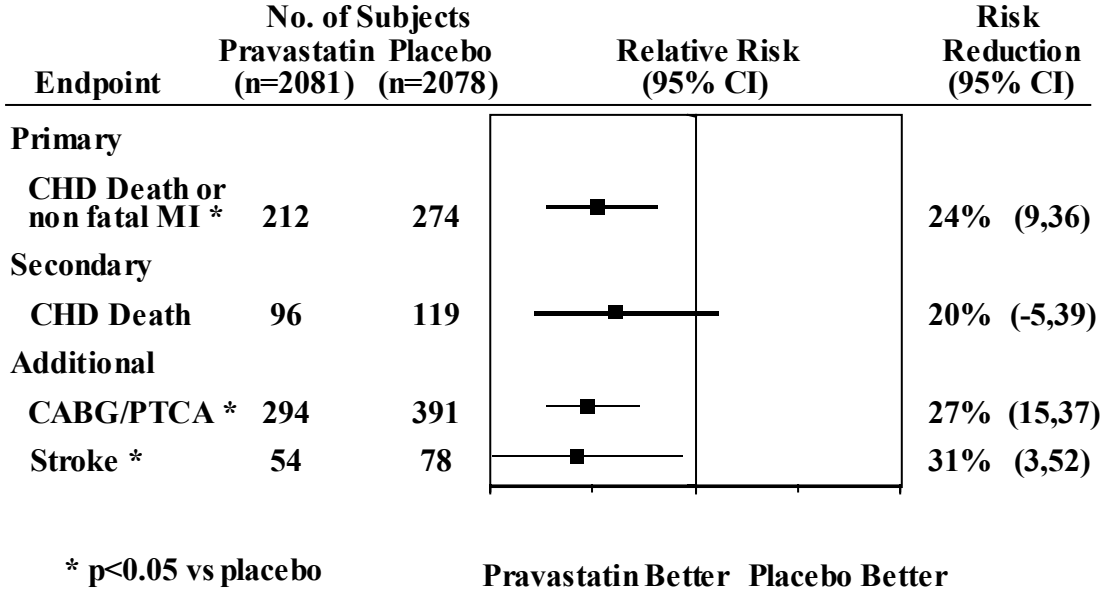
Figure 1: LIPID Trial Results: Patients with MI or Unstable Angina



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)

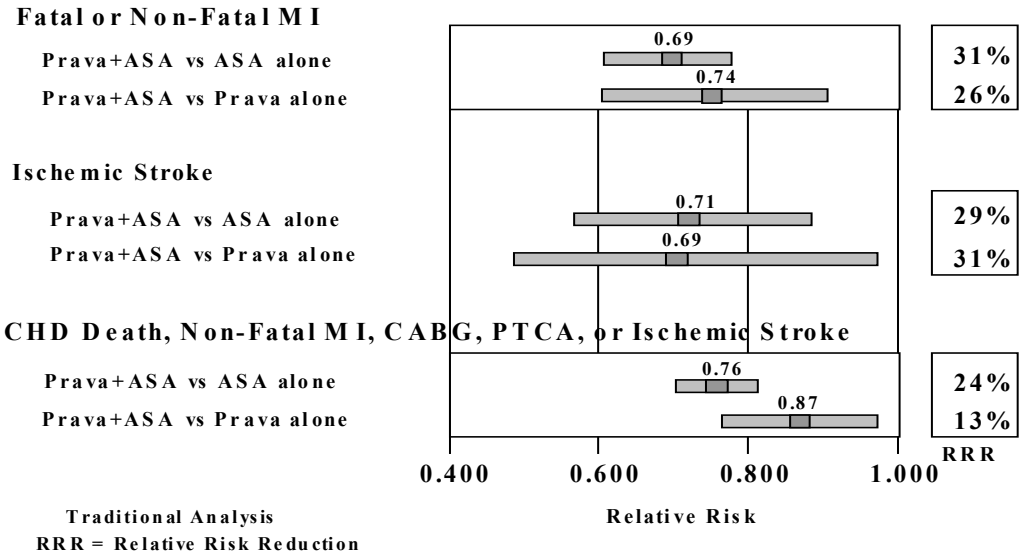
Table 6: Aspirin Usage in All Pravastatin Secondary Prevention Trials

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)

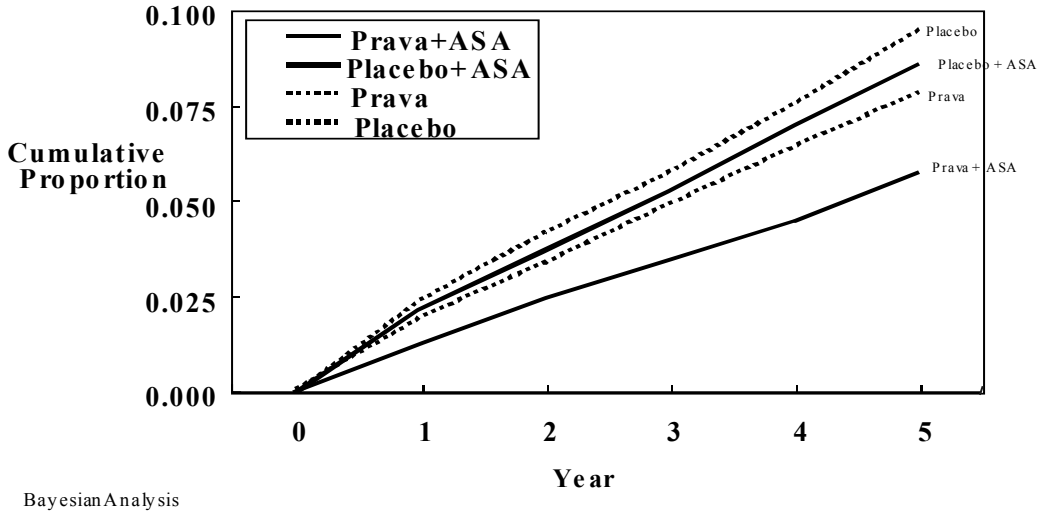


3.4.2 Model 2

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.

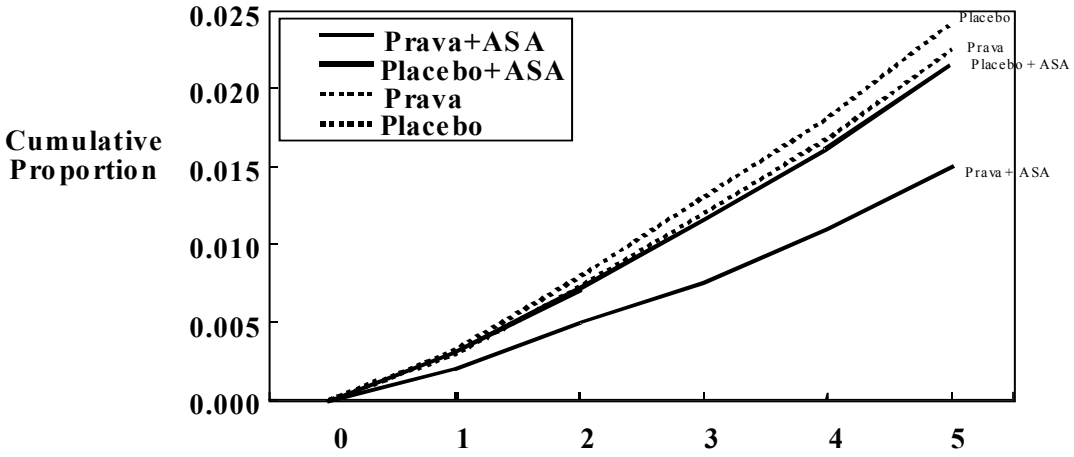
The end-points chosen were the same as for Model 1, fatal and non-fatal MI, ischemic stroke and the composite end-point. The data are shown graphically (Figures 4, 5 and 6).

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



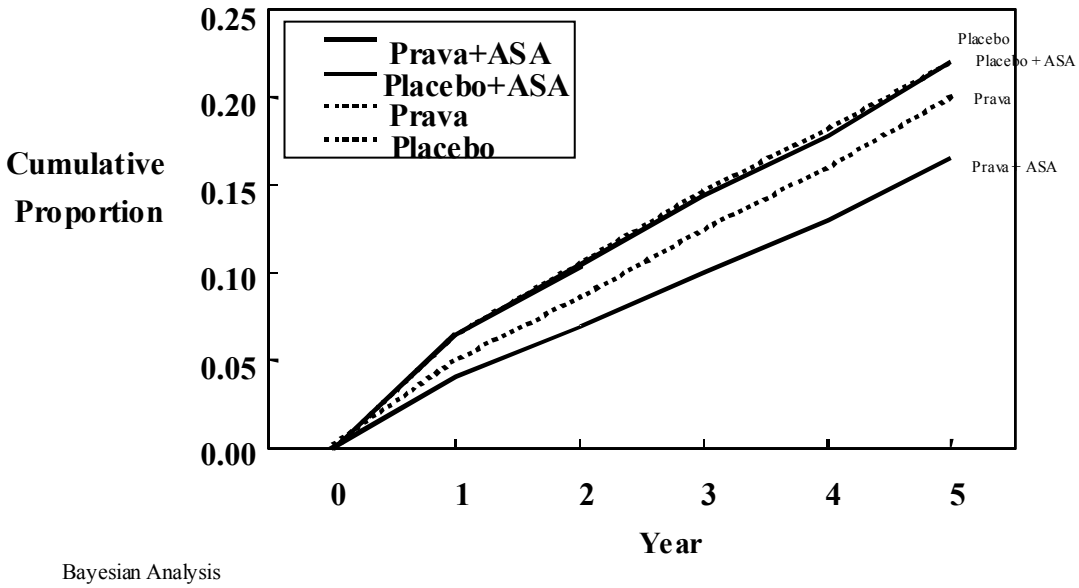
Bayesian Analysis

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



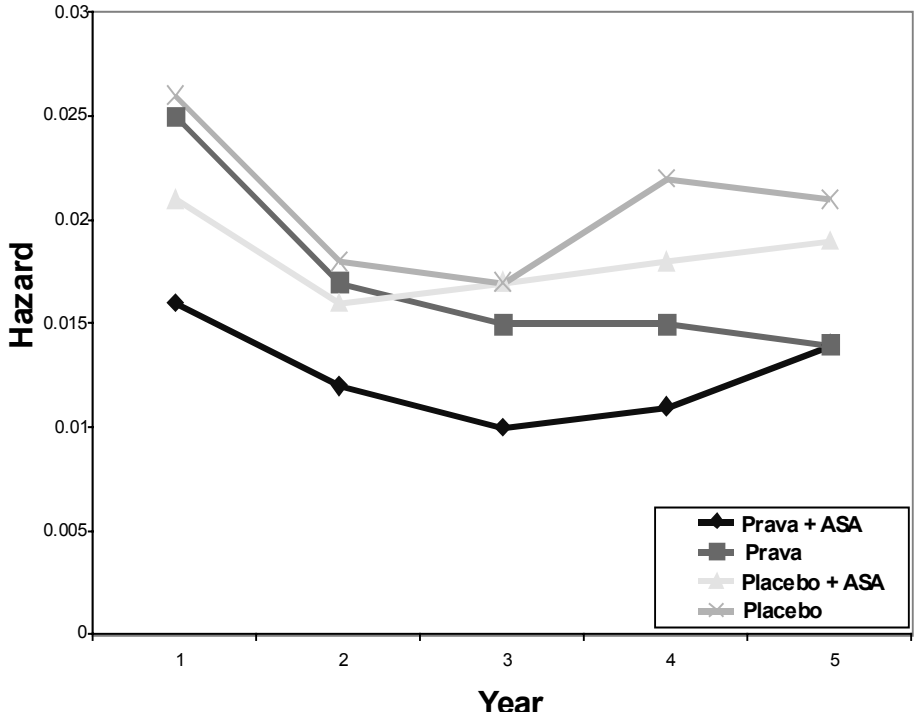
Bayesian Analysis

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

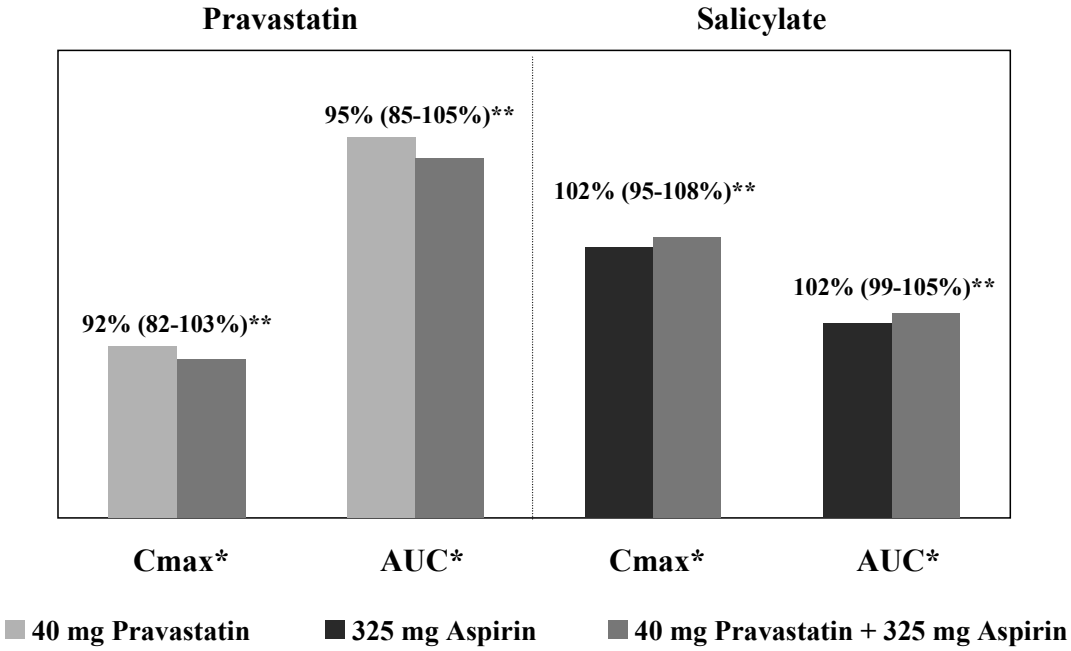
Neither the pravastatin nor the aspirin label requires that they be taken at a specific time of the day. Nor are there restrictions with regard to meals, although the aspirin label suggests that it be taken with water. This is presumably to reduce localized gastric irritation. The pravastatin-Bufferin® 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.

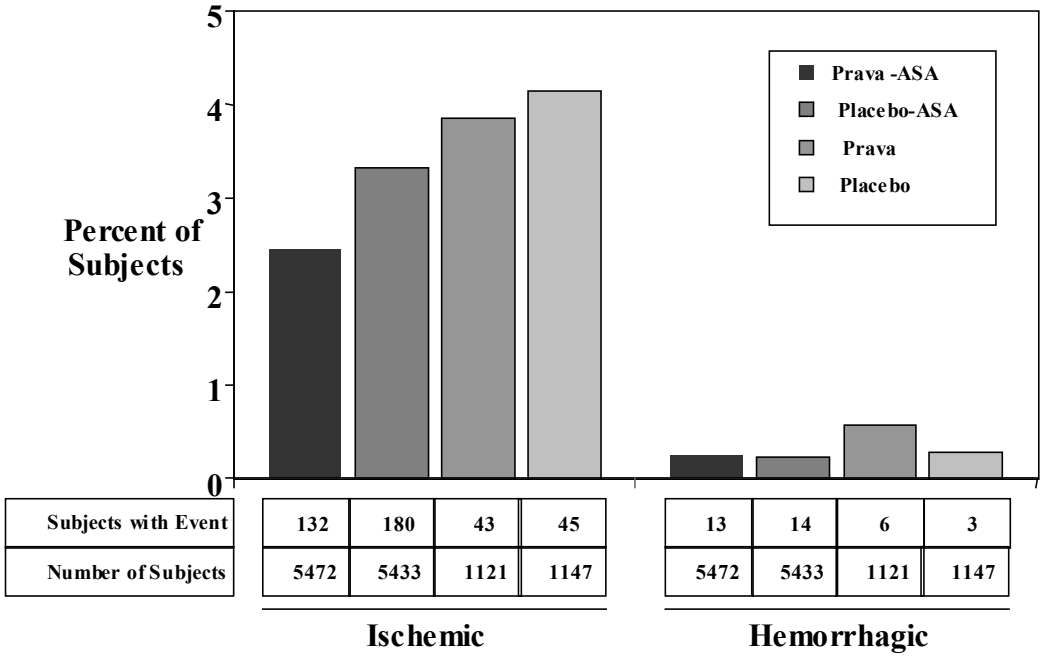
A review of all the patients in the five trials, comparing the clinical safety data by body system of the pravastatin plus aspirin group vs. the placebo plus aspirin group suggests no differences between the treatment groups.

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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Appendix B:

LDL-Cholesterol Lowering Relative to NCEP Guidelines

FDA Advisory Committee Briefing Book for Pravastatin/Aspirin

2 page(s) excluding cover page

Model		CARE	LIPID
I: No patients were excluded	1st or 2nd LDL < 100	75.2%	51.4%
	1st or 2nd LDL < 100 (imputed)[a]	89.1%	68.2%
II: Patients < 10% reduction (1st and 2nd measures) were excluded	1st or 2nd LDL < 100	77.3%	54.3%
	1st or 2nd LDL < 100 (imputed)[a]	91.4%	71.8%
III: Patients < 15% reduction (1st and 2nd measures) were excluded	1st or 2nd LDL < 100	78.7%	55.5%
	1st or 2nd LDL < 100 (imputed)[a]	92.6%	73.2%
IV: Patients < 80% compliance were excluded	1st or 2nd LDL < 100	76.2%	53.8%
	1st or 2nd LDL < 100 (imputed)[a]	89.8%	71.0%

[a] imputed data derived from data in Study CV123-161; see table below

For Model I, the intent-to-treat population, only patients without any post-baseline LDL-C measurements were excluded from the analysis.

For Model II: Patients on 40 mg of pravastatin with 1st and 2nd LDL-C measurements less than a 10% reduction or patients without any post-baseline LDL-C measurements were excluded from the analysis. For the rest of patients, the proportion of patients with either 1st or 2nd LDL-C measurements less than 100 mg/dL were calculated. For the 80 mg dose (imputed data), an additional 7% reduction was added to the LDL-C. The proportion of patients with either 1st or 2nd LDL-C measurements less than 100 mg/dL was then recalculated. Patients without any post-baseline LDL-C measurements or with 1st and 2nd LDL-C measurements less than 10% reduction were excluded from the imputed calculations.

For Model III: same as Model II, except using 15% reduction.

For Model IV: same as Model II, except patients with less than 80% compliance or patients without any post-baseline LDL-C measurements were excluded from the analysis.

LDL-C Data from Study CV123-161

Results:

Efficacy: Substantial and clinically significant reductions in LDL-C were seen for all three regimens of pravastatin compared with placebo at 6 weeks of treatment. Pravastatin administered in doses of 40, 80, and 160 mg, produced mean reductions in LDL-C of 29%, 37%, and 45%, whereas the mean reduction in the placebo group was minimal (< 3%). In addition, a substantial reduction in LDL-C was observed at Weeks 2 and 4 for the pravastatin groups. With one-daily dosing of pravastatin there was a significant dose-related response (p-value < 0.001).

Results of Efficacy Analysis of LDL-C at Week 6 for Randomized Subjects

Lipid	Visit	N	Placebo 44	Prav 40 mg 45	Prav 80 mg 48	Prav 160 mg 47
LDL-C[a] (mg/dL)	Baseline	Mean	187.1	192.8	195.6	196.7
	Week B6	Mean	184.1	139.0	124.7	108.4
		% Δ	-2.6	-28.6	-36.7	-45.2
		95% CI	-7.2, 2.4	-32.0, -25.0	-39.6, -33.7	-47.7, -42.5

CV123-161

Note: N = number of subjects with available efficacy data at Week B6

Reference: Supplemental Table S.6.1A

% Δ is the adjusted percent change from baseline obtained from the ANCOVA model with terms for treatment and baseline

[a] Calculated

Appendix C:

Product Packaging

FDA Advisory Committee Briefing Book for Pravastatin/Aspirin

6 page(s) excluding cover page

Contains 30 buffered aspirin tablets
Contains 30 PRAVACHOL® tablets

NDC XXXX-XXXX-XX

(buffered aspirin and pravastatin sodium)
325 mg aspirin tablets/20 mg PRAVACHOL® tablets

This product contains ASPIRIN

Pharmacist Place Label Here

Rx only

Bristol-Myers Squibb Company

(buffered aspirin and pravastatin sodium)
325 mg aspirin tablets/20 mg PRAVACHOL® tablets

Each buffered aspirin tablet contains 325 mg of aspirin in a formulation buffered with calcium carbonate, magnesium oxide and magnesium carbonate.
Each PRAVACHOL® tablet contains 20 mg of pravastatin sodium.
Store at 20° C - 25° C (68° F - 77° F); excursions permitted to 15° C - 30° C (59° F - 86° F). [See USP Controlled Room Temperature.]
Take with a full glass of water.
Keep out of reach of children.
Warning: Children and teenagers should not use aspirin for chicken pox or flu symptoms before a doctor is consulted about Reye's syndrome, a rare but serious illness reported to be associated with aspirin.
Alcohol Warning: If you consume 3 or more alcoholic drinks every day, ask your doctor whether you should take aspirin or other pain relievers/fever reducers. Aspirin may cause stomach bleeding.
Buffered aspirin and PRAVACHOL® should be taken at the same time. **See Package Insert for Full Prescribing Information.**

Rx only

US Patent No.: buffered aspirin 4,664,915
US Patent Nos.: PRAVACHOL® 4,346,227; 5,030,447; 5,180,589; 5,622,985

Bristol-Myers Squibb Company
Princeton, New Jersey 08543 USA

XXXXXXX 0000-00

(buffered aspirin and pravastatin sodium)
325 mg aspirin tablets/20 mg PRAVACHOL® tablets

Contains 30 buffered aspirin tablets
Contains 30 PRAVACHOL® tablets

NDC XXXX-XXXX-XX

(buffered aspirin and pravastatin sodium)
81 mg aspirin tablets/20 mg PRAVACHOL® tablets

This product contains ASPIRIN

Pharmacist Place Label Here

Rx only

Bristol-Myers Squibb Company

(buffered aspirin and pravastatin sodium)
81 mg aspirin tablets/20 mg PRAVACHOL® tablets

(buffered aspirin and pravastatin sodium)
81 mg aspirin tablets and 20 mg PRAVACHOL® tablets

Each buffered aspirin tablet contains 81 mg of aspirin in a formulation buffered with calcium carbonate, magnesium oxide and magnesium carbonate.
Each PRAVACHOL® tablet contains 20 mg of pravastatin sodium.
Store at 20° C - 25° C (68° F - 77° F); excursions permitted to 15° C - 30° C (59° F - 86° F). [See USP Controlled Room Temperature.]
Take with a full glass of water.
Keep out of reach of children.
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US Patent Nos.: PRAVACHOL® 4,346,227; 5,030,447; 5,180,589; 5,622,985

Bristol-Myers Squibb Company
Princeton, New Jersey 08543 USA

XXXXXXX 0000-00

(buffered aspirin and pravastatin sodium)
81 mg aspirin tablets/20 mg PRAVACHOL® tablets

Contains 30 buffered aspirin tablets
Contains 30 PRAVACHOL® tablets

NDC XXXX-XXXX-XX

(buffered aspirin and pravastatin sodium)
81 mg aspirin tablets/40 mg PRAVACHOL® tablets

This product contains ASPIRIN

Pharmacist Place Label Here

Rx only

Bristol-Myers Squibb Company

(buffered aspirin and pravastatin sodium)
81 mg aspirin tablets/40 mg PRAVACHOL® tablets

Each buffered aspirin tablet contains 81 mg of aspirin in a formulation buffered with calcium carbonate, magnesium oxide and magnesium carbonate.
Each PRAVACHOL® tablet contains 40 mg of pravastatin sodium.
Store at 20° C - 25° C (68° F - 77° F); excursions permitted to 15° C - 30° C (59° F - 86° F). [See USP Controlled Room Temperature.]
Take with a full glass of water.
Keep out of reach of children.
Warning: Children and teenagers should not use aspirin for chicken pox or flu symptoms before a doctor is consulted about Reye's syndrome, a rare but serious illness reported to be associated with aspirin.
Alcohol Warning: If you consume 3 or more alcoholic drinks every day, ask your doctor whether you should take aspirin or other pain relievers/fever reducers. Aspirin may cause stomach bleeding.
Buffered aspirin and PRAVACHOL® should be taken at the same time. **See Package Insert for Full Prescribing Information.**

Rx only

US Patent No.: buffered aspirin 4,664,915
US Patent Nos.: PRAVACHOL® 4,346,227; 5,030,447; 5,180,589; 5,622,985

Bristol-Myers Squibb Company
Princeton, New Jersey 08543 USA

XXXXXXX 0000-00

(buffered aspirin and pravastatin sodium)
81 mg aspirin tablets and 40 mg PRAVACHOL® tablets

(buffered aspirin and pravastatin sodium)
81 mg aspirin tablets/40 mg PRAVACHOL® tablets

(buffered aspirin and pravastatin sodium)
81 mg aspirin tablets/40 mg PRAVACHOL® tablets

Contains 30 buffered aspirin tablets
Contains 30 PRAVACHOL® tablets

NDC XXXX-XXXX-XX

(buffered aspirin and pravastatin sodium)
325 mg aspirin tablets/40 mg PRAVACHOL® tablets

This product contains ASPIRIN

Pharmacist Place Label Here

Rx only

Bristol-Myers Squibb Company

(buffered aspirin and pravastatin sodium)
325 mg aspirin tablets/40 mg PRAVACHOL® tablets

(buffered aspirin and pravastatin sodium)
325 mg aspirin tablets and 40 mg PRAVACHOL® tablets

Each buffered aspirin tablet contains 325 mg of aspirin in a formulation buffered with calcium carbonate, magnesium oxide and magnesium carbonate.
Each PRAVACHOL® tablet contains 40 mg of pravastatin sodium.
Store at 20° C - 25° C (68° F - 77° F); excursions permitted to 15° C - 30° C (59° F - 86° F). [See USP Controlled Room Temperature.]
Take with a full glass of water.
Keep out of reach of children.
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Alcohol Warning: If you consume 3 or more alcoholic drinks every day, ask your doctor whether you should take aspirin or other pain relievers/fever reducers. Aspirin may cause stomach bleeding.
Buffered aspirin and PRAVACHOL® should be taken at the same time. **See Package Insert for Full Prescribing Information.**

Rx only

US Patent No.: buffered aspirin 4,664,915
US Patent Nos.: PRAVACHOL® 4,346,227; 5,030,447; 5,180,589; 5,622,985

Bristol-Myers Squibb Company
Princeton, New Jersey 08543 USA

XXXXXXX 0000-00

(buffered aspirin and pravastatin sodium)
325 mg aspirin tablets/40 mg PRAVACHOL® tablets

Contains 30 buffered aspirin tablets
Contains 30 PRAVACHOL® tablets

NDC XXXX-XXXX-XX

(buffered aspirin and pravastatin sodium)

81 mg aspirin tablets/80 mg PRAVACHOL® tablets

This product contains ASPIRIN

Pharmacist Place Label Here

Rx only

Bristol-Myers Squibb Company

(buffered aspirin and pravastatin sodium)

81 mg aspirin tablets/80 mg PRAVACHOL® tablets

(buffered aspirin and pravastatin sodium)
81 mg aspirin tablets and 80 mg PRAVACHOL® tablets

128 FPO
1234567

Each buffered aspirin tablet contains 81 mg of aspirin in a formulation buffered with calcium carbonate, magnesium oxide and magnesium carbonate.
Each PRAVACHOL® tablet contains 80 mg of pravastatin sodium.
Store at 20° C - 25° C (68° F - 77° F); excursions permitted to 15° C - 30° C (59° F - 86° F). [See USP Controlled Room Temperature.]
Take with a full glass of water.
Keep out of reach of children.
Warning: Children and teenagers should not use aspirin for chicken pox or flu symptoms before a doctor is consulted about Reye's syndrome, a rare but serious illness reported to be associated with aspirin.
Alcohol Warning: If you consume 3 or more alcoholic drinks every day, ask your doctor whether you should take aspirin or other pain relievers/fever reducers. Aspirin may cause stomach bleeding.
Buffered aspirin and PRAVACHOL® should be taken at the same time. **See Package Insert for Full Prescribing Information.**

Rx only

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US Patent Nos.: PRAVACHOL® 4,346,227; 5,030,447; 5,180,589; 5,622,985

Bristol-Myers Squibb Company
Princeton, New Jersey 08543 USA

XXXXXXX 0000-00

(buffered aspirin and pravastatin sodium)
81 mg aspirin tablets/80 mg PRAVACHOL® tablets

Contains 30 buffered aspirin tablets
Contains 30 PRAVACHOL® tablets

NDC XXXX-XXXX-XX

(buffered aspirin and pravastatin sodium)
325 mg aspirin tablets/80 mg PRAVACHOL® tablets

This product contains ASPIRIN

Pharmacist Place Label Here

Rx only

Bristol-Myers Squibb Company

(buffered aspirin and pravastatin sodium)
325 mg aspirin tablets/80 mg PRAVACHOL® tablets

(buffered aspirin and pravastatin sodium)
325 mg aspirin tablets and 80 mg PRAVACHOL® tablets

Each buffered aspirin tablet contains 325 mg of aspirin in a formulation buffered with calcium carbonate, magnesium oxide and magnesium carbonate.
Each PRAVACHOL® tablet contains 80 mg of pravastatin sodium.
Store at 20° C - 25° C (68° F - 77° F); excursions permitted to 15° C - 30° C (59° F - 86° F). [See USP Controlled Room Temperature.]
Take with a full glass of water.
Keep out of reach of children.
Warning: Children and teenagers should not use aspirin for chicken pox or flu symptoms before a doctor is consulted about Reye's syndrome, a rare but serious illness reported to be associated with aspirin.
Alcohol Warning: If you consume 3 or more alcoholic drinks every day, ask your doctor whether you should take aspirin or other pain relievers/fever reducers. Aspirin may cause stomach bleeding.
Buffered aspirin and PRAVACHOL® should be taken at the same time. **See Package Insert for Full Prescribing Information.**

Rx only

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US Patent Nos.: PRAVACHOL® 4,346,227; 5,030,447; 5,180,589; 5,622,985

Bristol-Myers Squibb Company
Princeton, New Jersey 08543 USA

XXXXXXX 0000-00

(buffered aspirin and pravastatin sodium)
325 mg aspirin tablets/80 mg PRAVACHOL® tablets

Appendix D:

Patient Information Leaflet

FDA Advisory Committee Briefing Book for Pravastatin/Aspirin

4 page(s) excluding cover page

PATIENT INFORMATION

THIS PRODUCT CONTAINS ASPIRIN

TRADENAME

(buffered aspirin tablets and pravastatin sodium tablets)

Q.1 What is TRADENAME?

TRADENAME is made up of two well-studied drugs, buffered aspirin and pravastatin sodium (PRAVACHOL®), taken together as a pair of tablets. TRADENAME is clinically proven to help prevent heart attack and stroke, or to reduce the risk of death from a heart attack, in people with heart disease including those who have had previous heart attacks. While taking TRADENAME, continue to exercise and follow the diet advised by your doctor.

Q.2 Who should not take TRADENAME?

Do not take TRADENAME if you:

- have ever had a serious allergic reaction to any of the ingredients that make up TRADENAME (pravastatin and aspirin) or to aspirin-related products.
- are pregnant or may become pregnant, or if you are breastfeeding a child. Tell your doctor immediately if you become pregnant while taking the medicine and discontinue taking it immediately.
- have bleeding problems,
- have any problems with your liver,
- have gastric ulcers or stomach problems (such as heartburn, upset stomach or stomach pain) that last or come back unless directed by a doctor,
- consume 3 or more alcoholic drinks every day,

- are taking any other prescription drugs for anticoagulation (thinning the blood), diabetes, gout or arthritis unless directed by a doctor,

- are 18 years of age or younger - **[Reye's syndrome: Children and teenagers should not use aspirin for chicken pox or flu symptoms before a doctor is consulted about Reye's syndrome, a rare but serious illness reported to be associated with aspirin. Keep out of reach of children.]**

- have been diagnosed with a syndrome (combination of signs and symptoms) which includes asthma and nasal polyps.

Q.3 How should I take TRADENAME?

To get the most out of the drug, take your TRADENAME exactly as your doctor prescribes it. The usual dose of TRADENAME is 1 pair of tablets daily (1 buffered aspirin tablet with 1 pravastatin sodium tablet). They can be taken any time of day, with or without food. They should be taken with a full glass of water, unless you have been told by your doctor to restrict your intake of fluids.

Try not to miss a dose, but if you do take it as soon as possible that day. DO NOT take a double dose to make up for the one you missed.

In case of overdose, get medical help or contact a poison control center immediately. If overdose is suspected, call a doctor. If you experience ringing in the ears (a symptom of aspirin overdose), consult a doctor immediately.

While you are taking TRADENAME, tell your doctor if you:

- plan to have surgery, medical or dental procedures. You may need to stop taking TRADENAME for a short time to prevent bleeding,

- start to take other medicines or change how you take a medicine. Because serious side effects may result, tell your doctor about any other drugs you are taking, including those obtained without a prescription or herbal remedies.

- develop any conditions that may increase your risk of muscle breakdown, such as severe infection, very low blood pressure, major surgery, trauma, severe metabolic,

endocrine or electrolyte disorders, or seizures. Call your doctor immediately to see if you should discontinue taking TRADENAME.

Q4. Should I keep taking TRADENAME every day?

TRADENAME should be taken every day by people with heart disease, for long-term prevention of heart attack and stroke, or to reduce the risk of death from a heart attack. So keep taking TRADENAME as prescribed by your doctor, unless you develop any of the conditions listed above in Q2.

Q.5 What are the side effects of TRADENAME?

TRADENAME uses buffered aspirin and PRAVACHOL to help protect the heart when taken over a long period of time. Aspirin is also found in many over-the-counter products for pain or fever relief. Like all prescription drugs, TRADENAME may cause side effects, and some of them may be serious (listed below). Although rare, possible serious side effects of taking TRADENAME include:

Bleeding problems:

Aspirin can inhibit the ability of the blood to clot leading to an increase in bleeding time. Call your doctor if you notice any unusual or unexplained signs of bleeding.

Stomach problems:

Aspirin may cause stomach bleeding or ulcers. Call your doctor if you have stomach problems, such as heartburn, upset stomach, or pain, that last or come back.

Allergic reactions:

Aspirin may cause a severe allergic reaction, which may include hives, facial swelling, asthma (wheezing) or shock. Call a doctor immediately if you have any of these symptoms.

Muscle pain:

Tell your doctor immediately if you experience any unexplained muscle pain, tenderness, or weakness at any time during treatment with TRADENAME so your doctor can decide if TRADENAME should be stopped. It may be a sign of a rare but serious condition called rhabdomyolysis that results in muscle breakdown or kidney damage.

Liver function problems:

Your doctor may recommend that liver function tests be performed prior to initiation of therapy and prior to increasing dosage of TRADENAME.

Other Side Effects:

Side effects that do occur are usually mild and short-lived. The most common side effects that may occur during treatment include heartburn, abdominal pain, nausea, vomiting, indigestion, fatigue, dizziness, and rashes. This information is not intended to cover all possible side effects. If you experience any unpleasant or unusual effects while taking TRADENAME talk to your doctor.

General advice about prescription medicines

This medicine was prescribed for your particular condition. Do not use TRADENAME for another condition or give it to others. Keep TRADENAME and all other medicines out of the reach of children. Throw away TRADENAME when it is outdated.

This summary does not include everything there is to know about TRADENAME. Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. If you have questions or concerns, or want more information about TRADENAME, your physician and pharmacist have the complete prescribing information upon which this leaflet was based. You may want to read it and discuss it with your doctor or other healthcare professional. Remember, no written summary can replace careful discussion with your doctor.

Appendix E:

Hospital Survey on Aspirin Use in Surgery

FDA Advisory Committee Briefing Book for Pravastatin/Aspirin

10 page(s) excluding cover page

Responses to a telephone survey were obtained from 24 affiliated teaching hospitals, selected from the approximately 125 accredited U.S. medical schools. The states represented in this survey are: Alabama, Arizona, California (X2), Colorado, Connecticut, Delaware (X2), Georgia, Illinois, Louisiana, Massachusetts, Michigan, Minnesota, New Hampshire, New York (X3), North Carolina, Ohio (X2), Pennsylvania, Texas, and Utah. Efforts were made to include a geographically diverse sample, as well as to allow proportionate representation for the number of medical schools and resident population size of the various states. Most inquiries were directed to the hospital's in-patient pharmacy or drug information department. In four cases, a message received return calls from two individuals at the same hospital and both of these responses are reflected for that institution. Complete identification and contact information for each responding hospital and individual are included in the table that follows. Three individuals were willing to respond to the questionnaire, but were unwilling to provide their last names; and these are so indicated in the table.

The lead-off question asked whether that hospital has a **formal policy** regarding the continuation or discontinuation of aspirin (ASA) for patients prior to surgery. In every case (24/24) the answer was "No." A number of individuals asked for time to consult others within their institution to confirm that answer and all of them did confirm it. In the response for one hospital, the UCLA Medical Center, it was explained that such a policy had formerly existed, but had been dropped. The second question was whether the hospital pharmacy did see physicians'/surgeons' orders to **discontinue ASA** for patients prior to surgery. The responses obtained were: Yes: 18 ; Maybe/Usually: 6. In response to **"How long prior?"** These response frequencies were obtained:

Day of surgery:	2		
1-5 days prior:	2	*7-10 days prior*:	2
5-7 days prior:	8	14 *days prior*:	1
7 days prior:	5	*Unspecified*:	4

The respondent was then asked if the length of discontinuation **"Varies by procedure?"** and to **"Describe"** this variation. Given the open-ended nature of these latter questions, a vast array of responses and situational descriptions were obtained; and these are summarized in the table. The great majority (19/24), however, answered *"Yes"*, ASA discontinuation and its length of interruption

prior to surgery does vary with the procedure (and surgeon) within their hospital. The remaining 5/24 said it was *"unknown"* to them.

We then asked specifically about cardiac surgeries, or surgical procedures scheduled for patients with high-risk cardiovascular histories. Many respondents were unsure of details, saying only that such decisions were up to each surgeon to determine the best course for the individual patient. Nine (9/24) did respond that cardio-thoracic surgeons, especially newer/younger ones (mentioned by 2/24), were the most likely to hold ASA for their patients only the night before or the day of the procedure, and some observed patients who remained on their ASA therapy through the surgery. Three people noted that their cardiac catheterization laboratory does not discontinue patients' ASA at all. In calls where a discussion of this cardiovascular question occurred, it was consistently agreed that for high-risk patients with cardiovascular disease, the use of ASA around surgery clearly represents a risk/benefit situation. It was pointed out by several respondents that their hospital would never hesitate to perform any type of emergency surgery because the patient was known to be on ASA.

Hospital/Institution	City	State	Phone #	Name/Title/Role	Formal Policy	Observed Practice/Comments
University of California LA Medical Center	Los Angeles	CA	310-319-4872	Ms. Salpy, R.Ph. Staff Pharmacist Dispensed meds 7 years in this position	NO	ASA D/C'd? Yes How long prior? Varies Varies by procedure?* Yes *Describe:* Used to have a D/C policy but newer surgeons do not D/C & policy was droppped.
University of California SF Medical Center	San Francisco	CA	415-719-8204 (pager)	Herman Wong, Pharm.D. Cardiology Pharmacist	NO	ASA D/C'd? Yes *How long prior?* Usually 5-7 days Varies by procedure?* Yes *Describe:* Left to individual surgical groups
Hartford Hospital (University of Connecticut School of Medicine)	Hartford	CT	860-545-2221	Bob Quercia, Pharm.D. Drug Information Dept.	NO	ASA D/C'd? Yes How long prior? Usually 7 days Varies by procedure?* Yes, by surgeon *Describe:* Some do not D/C at all

Hospital/Institution	City	State	Phone #	Name/Title/Role	Formal Policy	Observed Practice/Comments
Albany Medical Center (Albany Medical College)	Albany	NY	518-262-3125	Denise _?_,R.Ph., In-patient pharmacy	NO	*ASA D/C'd?* Ususally held day of surgery *How long prior?* Some D/C 5-7 days Varies by procedure?* Varies by surgeon *Describe:* Pre-op policy may specify to stop ASA (protocol) prior to surgery or order to be held for day of surgery- not D/C
Mt. Sinai Hospital (Mt.Sinai School of Medicine)	New York	NY	212-241-6500	Adrienne _?_,R.Ph. Drug Information Dept.	NO	ASA D/C'd? Yes How long prior? 1-5 days Varies by procedure?* Yes *Describe:* Usually recommend 4-5 days but most physicians will continue ASA up to the day before
St. Joseph's Hospital & Medical Center (University of Arizona)	Phoenix	AZ	602-406-3240	Jay Jones, Pharm.D. In-patient pharmacist	NO	ASA D/C'd? Yes How long prior? Usually 1 week Varies by procedure?* Unknown, probably *Describe:* Each surgeon/service determines order for individual patient

Hospital/Institution	City	State	Phone #	Name/Title/Role	Formal Policy	Observed Practice/Comments
Grant-Riverside Methodist Hospital (Ohio State University)	Columbus	OH	614-566-9773	David Robinson, Pharm.D. Coumadin Clinic Williams, Pharm.D. In-patient pharmacist	NO	ASA D/C'd? Yes How long prior? Usually 5-7 days Varies by procedure?* Unknown Describe: Each surgeon/service determines order for individual patient
Hospital of the University of Pennsylvania	Philadelphia	PA	215-349-8822	Sarah Erush, Pharm.D. Director, Drug Information	NO	ASA D/C'd? Yes How long prior? Usually 2 weeks Varies by procedure?* Unknown Describe: Each surgeon/service determines order for individual patient
Carraway Methodist Medical Center (University of Alabama)	Birmingham	AL	205-487-7787	Tim Bradford, R.Ph. In-patient pharmacist	NO	ASA D/C'd? Yes How long prior? Usually 2 days Varies by procedure?* Most, including cardiologists hold for ~1-2 days Describe: Each surgeon/service determines order for individual patient

Hospital/Institution	City	State	Phone #	Name/Title/Role	Formal Policy	Observed Practice/Comments
Parkland Hospital, Dallas Co., Hospital (University of Texas Southwestern Medical School)	Dallas	TX	214-590-8210	Bill Casey, R.Ph. In-patient pharmacist Drug Information Department	NO	ASA D/C'd? Yes How long prior? 7-10 days (usually 7) Varies by procedure?* Unknown Describe: Up to each surgeon to decide
Christiana Care Health Service (Thomas Jefferson Medical College)	Wilmington	DE	302-428-2229	Anne-Marie -?-, R.Ph. 35 years at this hospital	NO	ASA D/C'd? Yes How long prior? Usually ~7 days Varies by procedure?* Unknown Describe: This hospital doesn't do cardiology procedures
Wilmington Hospital (Thomas Jefferson Medical College)	Wilmington	DE	302-733-6364	Terry Corbo, Pharm.D. Clinical Pharmacist	NO	ASA D/C'd? Usually How long prior? Up to 7 days Varies by procedure?* Yes Describe: Varies by surgeon, with younger cardiologists usually continuing the ASA
Grady Memorial Hospital (Emory University School of Medicine)	Atlanta	GA	404-616-7725	Erica Werts, Pharm.D. Drug Information Dept.	NO	ASA D/C'd? Yes, usually How long prior? 1 - 7 days Varies by procedure?* Yes Describe: Decision of each surgeon

Hospital/Institution	City	State	Phone #	Name/Title/Role	Formal Policy	Observed Practice/Comments
Northwestern Memorial Hospital (Northwestern University Medical School)	Chicago	IL	312-926-0751	Mike Fotis, Pharm.D. Drug Information Director	NO	ASA D/C'd? Yes How long prior? 5-7 days Varies by procedure?* Yes Describe: Could D/C up to 2 week as per MD; optional pt education pre-surgery brochure states "D/C ASA for 2 weeks prior." Specific surgery services(cardiothoracic & orthopedic) do not mention ASA D/C in their policies.
Alton Ochsner Clinic Foundation (Louisiana State and Tulane U. Medical Schools)	New Orleans	LA	504-842-6398	Debbie Simonson, Pharm.D. In-patient pharmacy	NO	ASA D/C'd? Maybe? How long prior? Depends on individual surgeon Varies by procedure?* Yes Describe: Cardiology likes to keep ASA on
Strong Memorial Hospital (University of Rochester School of Medicine)	Rochester	NY	585-275-2181 585-275-6860	Kelly Lawrence, Pharm.D. General Pharmacy Sabina Heitz, Pharm.D., Cardiovascular Pharmacy	NO	ASA D/C'd? Yes How long prior? >3 days, usually 7 days Varies by procedure?* Yes Describe: Cardiology & cardio-thoracic surgeons do not hold the ASA > day of procedure, if at all

Hospital/Institution	City	State	Phone #	Name/Title/Role	Formal Policy	Observed Practice/Comments
Brigham & Women's Hospital (Harvard Medical School)	Boston	MA	617-732-3696 617-732-7153	David Zacchini, R.Ph. Drug Information Allen Silverman, R.Ph. In-patient pharmacy	NO	ASA D/C'd? Does not see many orders to D/C How long prior? If D/C'd, usually 7 days Varies by procedure?* Yes Describe: Up to individual surgeon; could be up to 14 days prior; A. Silverman sees most pts on 81mg
University of Michigan Medical Center (University of Michigan Medical School)	Ann Arbor	MI	731-936-2279	Julie Golembiewsky, Pharm.D., Drug Information Wei Lau, M.D., cardio-thoracic anesthesiologist	NO	ASA D/C'd? Yes, , including the 81mg dose is D/C'd How long prior? Usually 7 days Varies by procedure?* Yes Describe: Cardiac cath lab does not D/C the ASA
Dartmouth/Hitchcock Medical Center (Dartmouth Medical School)	Hanover	NH	603-650-5593	Mark Busch, R.Ph In-patient pharmacist	NO	ASA D/C'd? Yes How long prior? Usually hold day of surgery Varies by procedure?* Yes Describe: Surgical orders are decision of each specialty. Cardiac cath lab does not D/C the ASA

Hospital/Institution	City	State	Phone #	Name/Title/Role	Formal Policy	Observed Practice/Comments
Cleveland Clinic Foundation (Case Western & Ohio State University Medical Schools)	Cleveland	OH	216-444-4194	Mike Militello, Pharm.D. Dug Information Dept.	NO	ASA D/C'd? Yes How long prior? Often day of for CV surgery Varies by procedure? Yes Describe: General surgeons may leave pts on or may D/C up to 7 days prior Cardiac cath lab does not D/C the ASA
University of Colorado Medical Center	Denver/Aurora	CO	303-315-8489	Megan Brewer, Pharm.D. Drug Information Dept.	NO	ASA D/C'd? Usually How long prior? Recommend 7-10 days Varies by procedure? Yes Describe: Don't always follow Chest guidelines; oral surgeons usually continue for high risk CV pts, one surgeon refused gastric stapling until pt had 7 days off
University of Utah Medical Center	Salt Lake City	UT	801-581-2073	Tony Dalapaiz, Pharm.D. Drug Information Dept.	NO	ASA D/C'd? Usually How long prior? Varies from 1 day to 2 weeks Varies by procedure? Yes Describe: Subject is under consideration & see changes in more doctors holding only day of surgery

Hospital/Institution	City	State	Phone #	Name/Title/Role	Formal Policy	Observed Practice/Comments
St. Mary's Hospital/Mayo Clinic (Mayo Medical School)	Rochester	MN	507-255-5062	Clement Akogyeram, Pharm.D., Drug Information	NO	ASA D/C'd? Yes How long prior? Usually 5-7 days Varies by procedure?* Yes Describe: Cardiac surgery holds only night before
Duke University Medical Center	Chapel Hill	NC	919-684-5125	Sarah Paradise, Pharm.D. Drug Information		ASA D/C'd? Yes How long prior? Unknown Varies by procedure?* Yes Describe: Each surgeon determines whether to stop

Appendix F:

Considerations Concerning an Aspirin-Statin Combination Product

FDA Advisory Committee Briefing Book for Pravastatin/Aspirin

26 page(s) excluding cover page

Considerations concerning an aspirin-statin combination product

A Report from the Division of Pharmacoepidemiology
and Pharmacoeconomics
Department of Medicine
Brigham and Women's Hospital
Harvard Medical School

Yuka Kiyota, M.D., M.P.H.
Project Director
Jerry Avorn, M.D.
Division Chief

June 6, 2002

Aspirin and pravastatin are among the most-studied drugs for the prevention of cardiovascular disease, with substantial data from randomized controlled trials demonstrating their efficacy and safety when prescribed appropriately. However, considerable evidence also indicates that these agents are underused in patients in whom they are indicated, and that even when they are prescribed by a physician, compliance is poor.

The regulatory decision concerning approval of a pravastatin-aspirin combination therefore does not hinge on the efficacy of either ingredient, since these have been well established. The decision rests instead on evaluation of (1) whether there would be any risk associated with inclusion of aspirin in a statin-ASA formulation, and if this is a concern, (2) whether there would be a countervailing benefit in terms of (a) greater awareness that the patient is on an aspirin-containing regimen on the part of the patient and/or physicians caring for the patient; and/or (b) an increase in aspirin use in patients in whom it is indicated who would otherwise not be taking it; and/or (c) other clinical benefit.

Levels of aspirin utilization in secondary prevention

Several studies have measured the prevalence of aspirin use for secondary prevention.[1] [2] [3] [4] [5] These have reported widely varying rates from 26%[1] to 90%[5] of appropriate patients, depending on the clinical context and time of study. One recent study reported that 77% of patients indicated for aspirin prophylaxis were receiving it.[6] Stated differently, nearly one in four such patients were not on aspirin therapy.

Another large analysis of data from 2000 and 2001 surveyed 26,000 participants in large health insurance plans and asked about daily aspirin use in patients with diabetes, hyperlipidemia, hypertension, coronary artery disease, or congestive heart failure. Among those with these risk factors, only 37.7% reported daily use of prophylactic aspirin. Utilization rates of daily aspirin were lower for women and for patients with diabetes. For patients with hyperlipidemia, fully 46.3% of men and 61.4% of women reported that they were **not** taking daily aspirin. For those with a history of myocardial infarction, the data were better, with 82.1% of men and 67.4% of women reporting that they **were** taking daily aspirin.[7]

Fonarow et al evaluated the impact of a program to initiate secondary prevention measures (aspirin, lipid-lowering drugs, beta-blocker, and ACE inhibitor with lifestyle modification counseling) at an academic medical center.[8]Among patients who were eligible for both ASA and statins (without excluding patients with contraindications), use of ASA at discharge improved from 68% to 92% ($p<0.01$), and statin use increased from 6% to 86% ($p<0.01$) between 1992-1993 (baseline period) and 1994-1995 following their special intervention program. [8] It should be noted that this is the proportion of patients so treated at the time of discharge, following an experimental intervention. It is likely that the ongoing rate of adherence in community practice is not as high.

Stafford used the data from National Ambulatory Medical Care Surveys to estimate the prevalence of aspirin use for secondary prevention in an outpatient setting.[1] There was an increase in use in the early 1990s, culminating in a rate of just

26% in 1996. Independent predictors of aspirin use included female gender (adjusted OR [AOR] 0.74, 95% CI 0.59-0.94), age ≤ 80 (AOR 0.65, 95% CI 0.45-0.95), and diagnosis of hyperlipidemia (AOR 2.55, 95% CI 1.77-3.54).

Data from the Third National Health and Nutrition Examination Survey (NHANES III), conducted 1988 – 1994,[9] were extracted by L'Italien[10] to identify subjects reporting a history of myocardial infarction or stroke. Of these, only 53.9% reported use of OTC aspirin, and 1.4% reported use of prescribed aspirin.

More recently, Hassan and Amonkar conducted a telephone survey in 1999 to estimate the prevalence of aspirin use.[3] Among the respondents, 72% were taking aspirin for secondary prevention purposes. Independent predictive factors were older age, particularly 55-64 (OR=2.36, 95%CI 2.34-2.38), black race (OR=0.81, 95% CI 0.80-0.81), male gender (OR=1.30, 95% CI 1.39-1.31), health care coverage (OR=1.29, 95% CI 1.28-1.31), and risk factors for CHD such as hypertension (OR=1.29, 95%CI 1.28-1,29) and smoking status (OR=1.42, 95%CI 1.41-1.43).

Califf et al investigated the use of aspirin in patients who had undergone coronary angiography.[2] Among 25,409 patients who were followed up annually with a questionnaire during the period 1995 to 1999, aspirin use increased from 59% to 80%. Independent predictive factors were male gender (OR=1.51, 95% CI 1.35-1.70), hypercholesterolemia (OR=1.36, 95% CI 1.22-1.51), history of MI (OR=1.17, 95% CI 1.05-1.31), prior cardiac catheterization (OR=1.76, 95% CI 1.54-2.00), and prior CABG (OR=1.55, 95% CI 1.37-1.74).

Caution is required in interpreting these treatment rates. The first two studies[13] did not differentiate sporadic aspirin users versus regular aspirin users, an important distinction pharmacologically. The last study[2] did use stricter criteria for aspirin use, yet still did not depict regular users only. ASA availability over the counter makes it difficult to capture utilization accurately in large populations. In a British study, Hopper et al reported that among patients with previous MI who were taking regular aspirin (80%), 22% were using it from OTC sources.[11] In their cohort, OTC use was significantly more common in those paying prescription charges.

Even if OTC use is incorporated in such analyses, there is an important potential problem of mis-medication, since other analgesics that can be mistaken as aspirin are also available OTC. Cook et al found among OTC aspirin users, 11% of those who reported aspirin use were mistakenly taking non-aspirin analgesics for secondary prevention purposes. [12] Women were more likely than men to take non-aspirin analgesics erroneously for this purpose.

Aspirin use is of particular concern among the elderly and among women. In patients over 65 who were admitted to the hospital with AMI, 24% were not prescribed aspirin at the time of discharge,[13] though some of these patients were started on aspirin in the course of follow-up. In the most recent study, Aronow et al found that only 59% of elderly (mean age, 81 +/- 9 years) patients were treated with aspirin for secondary prevention.[4] Despite this improvement during the period of follow-up, the prevalence of ASA use among older patients with documented prior

MI has been shown to be dramatically low (17%) at the time of admission to a nursing home.[14]

Guidelines for aspirin use perioperatively

For percutaneous coronary intervention, preoperative aspirin (81 or 325 mg) started at least 2 hours before the procedure is generally recommended by the American College of Cardiology and American Heart Association (ACC/AHA) in light of the evidence that aspirin reduces the frequency of ischemic complications after the procedure.[15]

For CABG, ACC/AHA notes that the value of aspirin in the treatment of acute coronary syndromes will often outweigh the increased risk of perioperative bleeding, though it is recommended to discontinue aspirin and other antiplatelet agents 7-10 days prior the surgery in patients with chronic stable angina and low-risk plaque morphology.[16] Current available studies have shown mixed outcomes for aspirin effect on graft patency, and ACC/AHA has judged that it is premature to make any suggestions based on them.

For patients undergoing peripheral vascular surgery, there is consensus as to aspirin's favorable effect on graft patency, but the best time to start therapy needs to be further studied.[17]

For patients undergoing carotid endarterectomy, guidelines published in *Circulation* recommend that aspirin therapy should be given before surgery unless contraindicated, though the optimal dose is not clear.[18]

Use of aspirin and surgery

One important question about an aspirin-statin combination product is what effect such a product would have on the likelihood of continuation of aspirin during surgical procedures when it is not indicated, compared to the rate at which this occurs when the patient is taking aspirin as a separate medication. This will depend heavily on how clearly the combination product is packaged and labeled. If both the physician *and* the patient fail to realize that the combination product contains low-dose aspirin, it might be continued preoperatively; the possible consequences of this are summarized below.

However, another possibility is at least as likely, if not more so. That is that this problem may be *less* likely to occur with such a combination product, appropriately packaged and available by prescription only, than with OTC products. The combination product would be within the immediate prescribing control of the physician, as OTC aspirin is not. In addition, if adequately packaged and labeled at the point of sale, such a combination could be *more* likely to be recognized as containing aspirin than an OTC product with a product name (e.g., Excedrin, Anacin) that the patient may not recognize as denoting that it is an aspirin-containing product.

Despite these factors, it is nonetheless important to consider the possible outcomes of continuation of aspirin during surgery. This will vary depending upon patient characteristics and the nature of the operative procedure.

Traditionally, any agents that could compromise platelet function or the coagulation cascade were generally discontinued during the perioperative period (except for DVT/PE prevention purposes) to avoid bleeding complications. However, more recently several studies have questioned this practice, or have even reported favorable outcomes with continuation of perioperative ASA use for certain surgical procedures.

Coronary artery bypass graft procedures

Effect on Graft Patency

Goldman et al compared 4 different antiplatelet drug regimens (aspirin 325 mg daily, aspirin 325 mg three times a day, aspirin 325 mg plus dipyridamole 75 mg three times a day, and sulfinpyrazone 267 mg three times a day) with placebo to assess the graft patency rate in 555 patients undergoing coronary artery bypass surgery (1781 grafts).[19],[20] Aspirin was started 12 hours before surgery. In the early postoperative period (within 60 days of operation), all patients with aspirin-containing regimens showed an improved patency rate (>90%) compared with placebo (85.2%, $p<0.05$), but they also experienced more chest tube drainage ($p<0.02$), more red blood cells and platelet transfusions ($p<0.005$), and a higher reoperation rate ($p<0.01$). There was no significant difference in mortality rate. At 1 year, 406 patients (1315

grafts) remained qualified for the analysis, and patients on aspirin-containing regimens were found to have a better patency rate (84.2%) than the placebo group (77.4%, p=0.03). Similarly, the regimen of aspirin 325 mg daily resulted in a better patency rate (86.8%) than placebo (p=0.05). There were no differences between aspirin-containing regimen groups and the placebo group in cardiac events (myocardial infarction, p=0.347) and mortality (p=0.627). There were no data presented regarding blood loss or drainage, but it was reported that none of the deaths in the aspirin group was related to bleeding.

Comparable favorable results for an effect of aspirin on graft patency were observed in a randomized controlled study in Australia.[21] In this study, aspirin was started within 1 hour of CABG. Gaveghan et al compared 1 week and 1 year graft patency rates between patients randomized to aspirin (324 mg/day) vs. placebo. The early and late graft occlusion rates were 1.6% and 5.8% in the aspirin group respectively, as opposed to 6.2% and 11.6% in the placebo group (p=0.004, p=0.01). The two groups did not differ in their mean chest tube drainage in the first 24 hours after operation, but the aspirin group underwent reoperation more often (4.8%) than the placebo group (1%), though the difference was not significant (p=0.1).

Another Australian study comprised a randomized controlled trial with enteric coated aspirin (100 mg daily) given perioperatively, and assessed the bypass graft patency rate.[22] The study did not find a statistically significant difference in patency rate or in postoperative blood loss between the placebo and treatment groups.

To assess the effect of timing of aspirin administration on graft patency and the risk of bleeding, Goldman et al directly compared two groups of patients; one with aspirin given preoperatively and the other with aspirin given 6 hours after operation.[23] The preoperative aspirin group received more transfusions (median 900ml versus 725ml, p=0.006) and had a higher reoperation rate for bleeding (6.3% versus 2.4%, p=0.036) with no additional benefit in graft patency.

Overall mortality

A few studies have begun to appear in the literature that shift the focus from graft patency and bleeding after CABG to the avoidance of major adverse events postoperatively. Dacey et al performed a case-control study of 8,641 consecutive CABG procedures. Cases were those who died in hospital; controls were those who survived. The exposure of interest was aspirin use in the 7 days prior to surgery. Those who had used aspirin in the week prior to CABG had a lower risk of death than those who did not, after controlling for a wide variety of potential confounders (odds ratio 0.73, 95% confidence interval 0.54 – 0.97).[24] These same authors a year later reported the experience of an additional 13,350 CABG patients who underwent surgery between 1995 and 2000. The lower odds ratio for death persisted (0.78, 95% CI 0.61 – 0.99). They noted, "Inasmuch as aspirin is known to decrease the incidence of myocardial ischemic events, discontinuing it in patients with known critical coronary stenosis before operation may indeed contribute to preoperative or intraoperative instability."[25]

Peripheral vascular surgery

Perioperative Use of ASA/Dipyridamole

Studies with small numbers of patients have found a favorable effect of antiplatelet drugs on graft patency in peripheral vascular surgery, although a larger scale multicenter trial in Great Britain did not observe the same effect. Goldman et al conducted a prospective randomized study to assess the effect of aspirin plus dipyridamole on the patency of prosthetic femoro-popliteal bypass grafts.[26] Compared to a cumulative patency rate of 36% seen in the placebo group, patients taking aspirin and dipyridamole had a 67% cumulative patency rate at 12 months. Clyne et al also reported that perioperative use of dipyridamole and aspirin made the patency of prosthetic grafts almost comparable to that seen with autogenous grafts.[27]

In a multicenter trial in the UK[28], 549 patients were randomized to placebo (263 patients) or 300 mg aspirin plus 150 mg dipyridamole (286 patients) two days before surgery and continued indefinitely. Although the trial failed to show a significant difference in graft patency during the 3-year follow-up period, there was a significantly lower incidence of MI among patients treated with the antiplatelet drugs (39.7/1000 patient-years vs 84.4/1000 person-years, p=0.004). There was twice the rate of serious bleeding complications among treated patients (6.4% vs 3.5%, p=0.13).

Neilipovitz et al, using a decision tree model, calculated the perioperative mortality rate and the projected crude and quality-adjusted life expectancy for two strategies (with or without continuous ASA use during the perioperative period).[29]

The model projected a decrease in perioperative mortality rates from 2.78% to 2.05%, a predicted increase in hemorrhagic complications of 2.46% related to an increased incidence of non-life-threatening complications, an increase in crude life expectancy from 14.83 to 14.89 per year, and an increase in quality-adjusted life-years from 14.72 to 14.79.

Several studies indicate that long-term and regular use of aspirin has a positive effect in reducing the risk of graft occlusion, but not the risk of stroke, MI or death following peripheral vascular surgery.[30] In one study, the relative risk of graft occlusion in aspirin users was 0.78 (95% CI, 0.64-0.95) compared to non-users.

0rthopedic surgery

Effect of perioperative use of aspirin for DVT/PE prevention

Patients undergoing orthopedic surgery (hip replacement, knee replacement) are at greater risk to develop DVT/PE. The PEP trial was a randomized controlled trial that examined the effect of preoperative aspirin therapy for DVT/PE prevention in patients undergoing hip surgery.[31] Aspirin was given for 35 days starting before hip replacement or arthroplasty. The study found a reduction in pulmonary embolus of 43% (95% CI 18-60; p=0.002) and in DVT of 29% (95% CI 3-48; p=0.03). Aspirin prevented 4 fatal PE events per 1000 pts compared to placebo (with no effect on death from any other vascular cause), but with 6 more postoperative transfusion episodes for bleeding per 1000 patients (p=0.04). (Despite this finding, low molecular weight heparin is the more effective and standard preventive measure for this population .[32])

Carotid endarterectomy

Restenosis

Perioperative aspirin use seems to have no effect on recurrent stenosis after carotid endarterectomy, a complication that occurs in 7-20% of patients. Patients were started on low-dose aspirin (74 mg/d) the day before surgery and continued for 6 months. There was no difference in incidence of recurrent stenosis between the treatment group and the placebo group.[33]

Perioperative morbidity and mortality

In the same cohort of patients, the risk of intraoperative or postoperative stroke was assessed.[34] Stroke events were significantly lower in the low-dose aspirin (75 mg/d) group at 30 days (0) and 6 months (2), compared to the control group at 30 days (7) and 6 months (11). Neither mortality nor intraoperative bleeding differed between the two groups.

Dose seems to be an important factor in influencing perioperative morbidity and mortality, though controversy persists in this area. Taylor et al randomized patients to 4 different regimens of aspirin (81 mg, 325 mg, 650 mg, or 1300 mg) and examined the combined rates of stroke, myocardial infarction and death.[35] At three months, the combined outcome rate was significantly lower in the low-dose groups (81 mg or 325 mg) than in the high-dose groups (6.2 vs 8.4%, p=0.03).

Risk of wound hematoma

Although the number in their study was too small to draw definitive conclusions, Kunkel at al concluded that antiplatelet therapy such as ASA may be a

predisposing factor to development of wound hematomas after carotid endarterectomy. They observed 15 cases of wound hematoma after carotid endarterectomy which required an evacuation procedure (total 596 cases). Among those who required evacuation, 10 patients were taking aspirin until the time of operation and two had discontinued it 3 days or more prior to the operation.[36]

Urological procedures

Perioperative ASA use and risk of bleeding

Nielsen et al conducted a randomized controlled study in which patients were randomized to aspirin or placebo 10 days before transurethral prostatectomy. They found no difference in intraoperative blood loss and in transfusion requirements, but postoperative blood loss in the ASA group was significantly higher than in the placebo group (median 284 ml vs. 144 ml, p=0.011).[37] A similar outcome was reported in a case-control study in 1998, in which Wierod et al observed significantly smaller units of blood transfusion in non-ASA/NSAIDs users compared to ASA/NSAIDs users (p=0.04).[38] The same journal in 1998 concluded that NSAIDs and ASA increased the risk of bleeding during and after TURP and recommended ASA withdrawal one week prior to surgery.

It was noted that aspirin's antithrombotic effect might improve graft patency in both peripheral and cardiovascular surgery. Murphy et al, following the same theory, compared 105 patients who received cadaveric renal transplants and were treated with daily aspirin (150mg) for three months starting the day after surgery with

a historical comparison group of comparable patients who had not received aspirin.[39] They found lower allograft thrombosis cases among aspirin group (p=0.03), though two groups did not differ in terms of allograft survival at 2 years.

General and other surgery

Perioperative aspirin use and complications

Scher at al examined the postoperative incidence of diffuse bleeding as opposed to site-specific bleeding. Study patients were those who underwent non-cardiac and peripheral vascular surgery. They reported that 19 (95%) of the 20 patients with diffuse bleeding were taking either aspirin alone or aspirin in combination with other NSAIDs; none of the patients with site-specific bleeding was taking any of these products before surgery.[40]

In cutaneous surgery, the risk of severe bleeding complication is generally very low. Despite the common practice of withholding antiplatelet/anticoagulation agents prior to cutaneous surgery, Otley et al found no significant difference in the risk of severe bleeding complications in patients who were taking aspirin or NSAIDs vs. those who were not (RR=1.6, 95% CI 0.38-10.05).[41]

According to a survey done among neuroanesthesiologists in the UK[42], 44% of respondents considered that patients taking low-dose ASA were at increased risk of excessive perioperative hemorrhage associated with intracranial procedures. The mean time suggested for discontinuation of ASA preoperatively was 11.3 days (range 1- 42 days).

Regional anesthesia

Perioperative ASA use and bleeding complications related to regional anesthesia

Horlocker et al assessed the effect of antiplatelet drug use in patients who required regional anesthesia (spinal or epidural) for various orthopedic operations.[43] They found no significant difference in minor hemorrhagic complications related to anesthesiologic procedures between patients who had a history of preoperative antiplatelet use and those who did not.

Other studies of bleeding complications

The effect of perioperative aspirin use on perioperative bleeding complications is marked by inconsistent outcomes from several studies. In one randomized controlled trial, patients were randomized to a 2-week course of aspirin 300 mg daily until the day of operation, vs. placebo. Total blood loss was significantly higher in the aspirin group compared to the placebo group (1185 ml vs 791 ml, $p=0.001$) as well as units of blood and FFP transfused ($p<0.05$).[44]

Reich et al conducted a case control study of patients who underwent elective CABG during 1991-1992.[45] They defined a positive history of aspirin use as any aspirin use within 7 days prior to the operation. Though they found no significant differences between ASA and control group in homologous transfusion requirements, patients with a history of aspirin use experienced larger volumes of postoperative mediastinal tube drainage (500ml vs 400ml, $p=0.03$) which was autotransfused back to patients.

Tuman et al looked at the effect of perioperative aspirin use among patients who underwent reoperative CABG operations and therefore were at high risk for bleeding complications.[46] They used the same definition as Reich et al, and found no difference in the total mediastinal drainage or in the total amount of allogenic blood product transfused. According to a study conducted in New England between the period 1992 - 1994 and the period 1995 - 1997, the proportion of surgeons using preoperative aspirin up until the time of surgery increased from 22% to 78% ($p<0.001$). [47]

Compliance and dosing schedules

Conventional wisdom has long held that the more medications a patient is prescribed, the greater the risk for noncompliance. A very recent meta-analysis has reviewed the literature in this area for antihypertensive drugs, and reached a similar conclusion. In studies comparing compliance rates with various daily regimens, the authors reported that compliance rates with once-a-day dosing were significantly higher than those found with twice-a-day ($p = .026$) or other multiple-dose regimens ($p < .001$) for comparable therapies.[48]

SUMMARY

The net benefit-risk profile of any drug (or drug combination) must take into account the sum of numerous factors. No single agent can promise pure efficacy with no risk, but must be judged in terms of the balance between the two; the same applies to the incremental benefit and incremental risk that occur when two agents are

combined. Emerging concepts of "risk management" at FDA have emphasized that the way medications are actually used in practice is a vitally important aspect of their safety and efficacy. Although earlier risk management programs have focused more on containing risk (e.g., clozapine, thalidomide, Accutane), this concept also has important implications for maximizing effectiveness as well. In the case of the proposed pravastatin-aspirin combination product, the following conclusions seem reasonable:

1.The most prominent fact about drugs used for the prevention of cardiovascular disease is the unacceptably low rate of utilization by physicians and patients, despite compelling data on their efficacy and safety;

2. It is likely that a combination of statin and aspirin would help address this problem in several ways:

a. by making it more likely that aspirin will be prescribed systematically for patients who require it, and in the proper dose;
b. by simplifying the regimen for secondary-prevention patients, who may already be taking multiple medications and be at greater risk for poor compliance.

3. In a pravastatin and aspirin combination product, the aspirin component of therapy would be integrated into the list of prescribed medications maintained in the patient's medical record. The presence of aspirin would also be prominently displayed on the packaging, making it more likely to be noted by all physicians caring for a patient than OTC aspirin use would be.

4. It is increasingly clear that for many types of vascular invasive procedures, appropriate care requires that aspirin be continued, not discontinued, perioperatively.

5. For procedures in which aspirin is to be stopped preoperatively, this should be no more problematic in a combination product than in an OTC form, and as noted above may in fact be more likely to be done correctly.

6. The aspirin in a combined pravastatin-aspirin combination product could on occasion be inadvertently continued perioperatively, just as errors can occur with any prescribed medicine, although there is no evidence to suggest this would occur more often than with OTC aspirin, and with appropriate labeling could occur less frequently.

7. It is likely that in patients with existing coronary artery disease, who would be the main users of such a product, the resulting risks would likely be more than offset on a population basis by the number of cardiac events prevented and life-years gained by increased use of aspirin in the target population. Although the literature is incomplete in this area, there is evidence to suggest that in individual patients, the benefit of preventing catastrophic events such as postoperative myocardial infarction or stroke would need to be considered alongside the risks of increased perioperative bleeding, which is usually much less devastating.

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