

44-111-1000

1 SUPPORT FOR THE USE OF ASPIRIN IN PRIMARY PREVENTION OF PATIENTS AT MODERATE OR GREATER RISK

1.1 Continued Efforts to Support the Petition

Cardiovascular disease (CVD) is the leading cause of death and disability in this country (AHA Heart Disease and Stroke Statistics, 2005). Aspirin (ASA) is widely recognized as a highly effective and affordable agent in reducing the risk of coronary heart disease (CHD) events. ASA has a well-established safety profile with over a century of use. In order to reduce the tremendous personal and societal impact of this disease, the Food and Drug Administration (FDA) should take action to align ASA professional labeling with current scientific knowledge and clinical practice guidelines (AHA, USPSTF, ADA). Underlying CHD risk is the single most important determinant of an individual's likelihood of experiencing a myocardial infarction (MI). Therefore, labeling that reflects and endorses treatment for patients at appropriate risk will have significant public health benefit. The absolute benefits of ASA accrue most meaningfully to those individuals at moderate or greater risk.

Subsequent to the submission of the Petition in February 2003, several events and communications have taken place including the December 8th 2003 Advisory Committee Meeting and a public meeting on April 30th 2004. Following these meetings Bayer provided information to address outstanding questions including the request to receive the study data from the Thrombosis Prevention Trial (TPT). Following this submission the FDA issued a letter noting that the silent MI data were not provided. As discussed previously, silent MI data were not part of the primary analysis of the TPT and were not part of the data sent to the Agency. Bayer did not conduct this study and does not have access to the data for TPT. However, Bayer has continued to work to facilitate the availability of the silent MI information. This effort was successful as evidenced by the submission by Dr. Thomas Meade to the Agency on May 27th 2005.

The following presents a summary of the support for the petition and a discussion of the ongoing issues. Also discussed is the pending communication plan following the decision and the potential ramifications.

1.2 Basis for Including Moderate-Risk Patients in ASA Labeling

ASA is currently indicated for the secondary prevention of MI and stroke, for the prevention of cardiovascular events after coronary bypass surgery and interventions, and for the primary prevention of MI in subjects with a history of angina pectoris. The approvals to date have reflected a bias toward event-based labeling, requiring that a candidate have a history of a cardiovascular event or symptomatic disease to be eligible

for ASA prophylaxis. Nonetheless, it is clear that there are many at-risk patients – i.e., people who are at increased risk for serious cardiovascular events – who are not currently recognized by the current ASA labeling. Many of these patients are at sufficient risk to warrant treatment. Such patients would benefit from the cardio-protective effects of ASA since, in these moderate risk patients, the benefit would clearly outweigh the risk. Extending the labeling to and increasing the appropriate use among these patients will result in significant reductions in morbidity.

There is a common pathophysiology of most coronary events (i.e. occlusive ischemic myocardial injury). The majority of these coronary events involve plaque rupture, thrombin formation via platelet recruitment and fibrin deposition (Circulation. 1995; 91:2844-2850. Circulation.2001;104:365-372. Lancet.1999;353 (suppl 2):SII5-SII9). This appears true regardless of whether it is a first or recurrent event, and supports the view that the same preventive interventions (e.g., behavioral and pharmacological) are effective in MI prophylaxis independent of previous event status.

In addition to the rational basis for extending the benefits of ASA to at-risk patients who have not suffered a previous event, there is sufficient evidence from randomized controlled trials demonstrating that the benefit of ASA in reducing the risk of MI extends to patients at low CHD risk (<10% 10-year risk)(Arch Intern Med. 2003;163:2006-2010). As such, the question is not whether ASA is effective in patients without a history of CHD, but rather, at what level of CHD risk does ASA therapy consistently demonstrate a significant reduction of the important end point of clinically overt, non-fatal MI, while resulting in a favorable benefit-to-risk relationship. Although it is reasonable to believe that the relative risk reduction remains fairly consistent even in the low risk groups (< 10%), it is clear that as very low risk populations (< 3%, such as in the Women's Health Study) are studied, detectability of the effect becomes reduced due to the infrequency of overall events, unfavorable signal-to-noise ratio and sample size requirements. At a level of risk (~10%) where the efficacy of ASA based upon existing data becomes clearly evident, a risk/benefit assessment is required.

1.2.1 Extrapolation Across Risk Strata

Based upon the observation of nearly identical relative risk reductions for MI in the secondary prevention and primary prevention studies, it is reasonable and appropriate to extrapolate findings to intermediate groups (10-20% risk) that have not been as thoroughly evaluated. The Petition seeks labeling for an intermediate risk group that is not based on an expectation of an improved relative risk reduction for MI, but rather on an increase in the absolute benefit which is observed in more than 36,000 patient-years of evaluation in moderate-risk patients in the primary prevention study database (Table 2). Data from within the studies highlight no heterogeneity in response based on baseline CHD risk.

The five ASA primary prevention studies that form the basis of the Petition included a portion of patients whose baseline CHD risk was at least moderate (>1% per annum, approximately equivalent to >10% ten year risk; See breakdown by CHD risk in Table 1 below, source: Colin Baigent, December 8th 2003 Advisory Committee Presentation) even though the overall level of risk for each of these studies was less than 1% per annum. Importantly, both intra- and inter- study analyses confirm equivalent proportional reductions in the risk of MI regardless of baseline global risk. Specific evaluation of moderate-risk patients confirms a reduced risk of nonfatal MI of approximately 35%.

Table 1: Patient Enrollment by Underlying CHD Risk Per Year

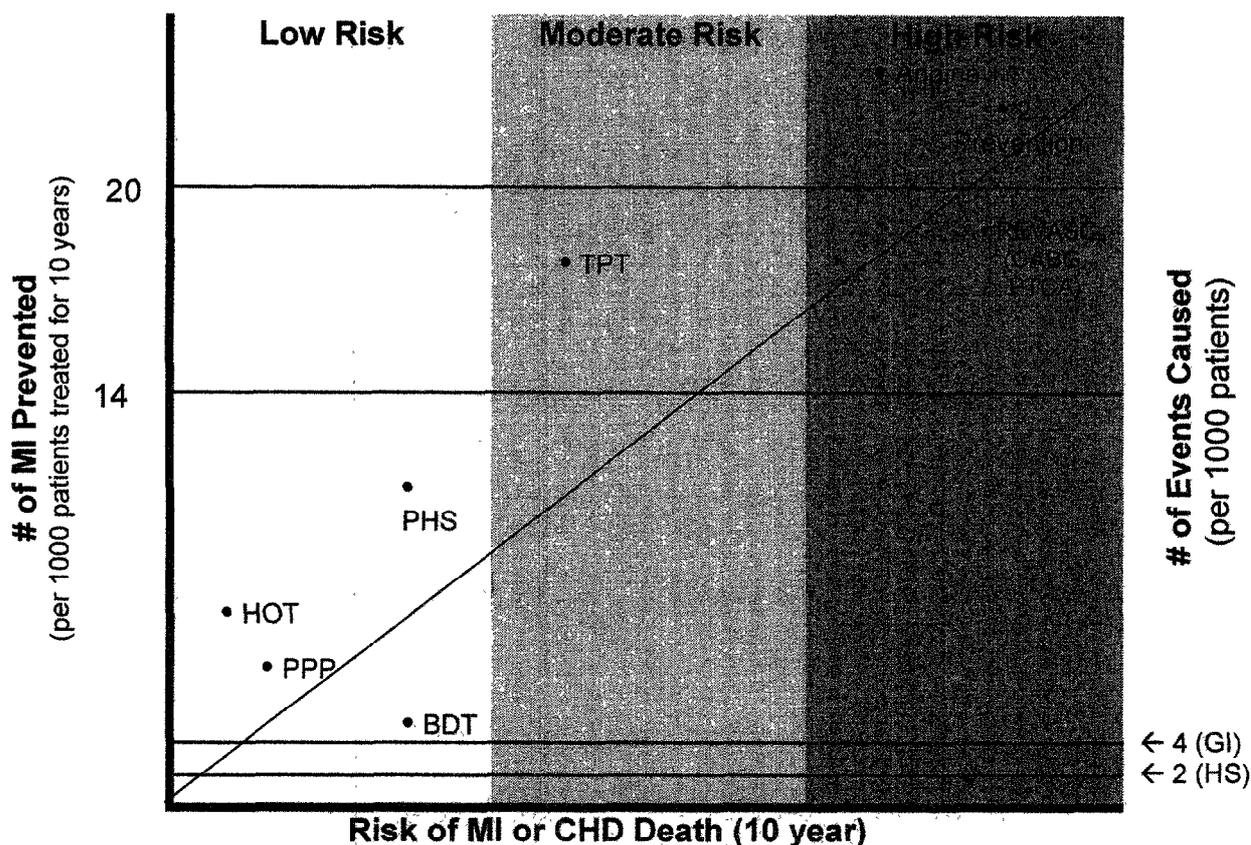
	<1%	1-2%	>2%	TOTAL		<1%	1-2%	>2%	TOTAL
BDT	3,584	1,136	419	5,139		70%	22%	8%	100%
HOT	15,179	2,870	741	18,790		81%	15%	4%	100%
PPP	3,230	935	330-	4,495		72%	21%	7%	100%
TPT	4,028	981	76	5,085		79%	19%	2%	100%
PHS	19,828	1,846	397	22,071		90%	8%	2%	100%
TOTAL	45,849	7,768	1,963	55,580		82%	14%	4%	100%

BDT: British Doctors' Trial; HOT: Hypertension Optimal Treatment Trial; PPP: Primary Prevention Project; TPT: Thrombosis Prevention Trial; PHS: Physicians' Health Study

Table 2: MI Risk Reduction by Baseline 10-year CHD Risk

CHD Risk	ASA		Placebo		RR (SE)
	Events	Patient-Years	Events	Patient-Years	
<10%	280	110,360	368	110,085	27% (7)
10% - 20%	97	18,056	145	18,139	35% (11)
>20%	31	4,385	53	4,203	43% (18)

Figure: Extrapolation Across Risk Groups



The figure represents the extension across CHD risk categories based upon the efficacy demonstrated in trials with patients at low (Hypertension Optimal Treatment Trial - HOT, Primary Prevention Project - PPP, British Doctors' Trial - BDT, Physicians' Health Study - PHS), moderate (Thrombosis Prevention Trial - TPT), and high baseline risk (such as those with a history of angina, CVD and coronary revascularization). Risk categories are defined as the following 10 year CHD estimates: low = <10%, moderate=10-20%, high=>20%.
 GI: gastrointestinal events, HS: hemorrhagic stroke events

Robust and consistent findings across the studies provide confidence in the broad applicability of the observed benefits with respect to the ability of ASA to reduce the risk of MI in high-risk, moderate-risk, and low-risk patients, as summarized below and in the figure above:

High-Risk (Secondary Prevention) Populations: Clinical studies and meta-analyses have provided conclusive evidence that low-dose ASA (75-325 mg) prevents subsequent cardiovascular events, e.g., MI (relative risk reductions of 30%), stroke, and vascular death.

Low-Risk Populations (<10% 10-year CHD risk): Evidence from clinical studies and meta-analyses demonstrates the effectiveness of ASA in preventing non-fatal MI in low-risk patients (i.e., patients that have not experienced a previous cardiovascular event), with MI relative risk reductions of 32%. The data is less certain in those at very low risk (<3% 10-year CHD risk).

Moderate-Risk Populations (10-20% 10-year CHD risk): While controlled trial data are more limited in this population, the available evidence (from TPT, where the patient enrollment criteria specified a moderate-risk status, as well as the moderate-risk patients from other primary prevention studies, accounting for over 36,000 patient-years of evaluation) suggests that the benefit-to-risk relationship is favorable for the use of ASA in this population. It is estimated that 14 CHD events could be prevented in 1,000 moderate risk patients over 5 years with use of ASA (USPSTF).

Based on the weight of the available evidence, the professional labeling for ASA should be broadened to include additional patient groups that can safely benefit from daily ASA use. This conclusion is based upon the extrapolation from the findings of studies in low- and high-risk populations, evidence from moderate-risk subsets of existing studies and ASA's lengthy in-market experience. All point to a benefit for ASA use among patients at moderate CHD risk. Furthermore, additional support from large-scale trials in a broad population is unlikely to be forthcoming. Revised professional labeling should be based upon the following considerations:

- **Low-Risk Population (<10% CHD risk)**: Although ASA could be considered for this patient population at the discretion of the physician, an indication is not being requested for this group, as additional data are needed to determine if the benefits of treatment exceed the potential for adverse effects. Given the large body of evidence in this group it would be valuable to provide communication of the experience in the clinical trial section of the professional labeling.
- **Moderate-Risk Population (10-20% risk)**: ASA use should be encouraged in this population, as the benefit of treatment will consistently exceed the potential for an adverse outcome. For this reason, the Petition is specifically requesting modification of the labeling to include moderate risk patients.
- **High-Risk Population (>20% risk)**: While this risk level is comparable to the level seen in secondary prevention patients, the current labeling of ASA does not recognize the use of ASA in patients at this level of risk who have not experienced a previous event. Adoption of CHD risk-based labeling will ensure that ASA is prescribed and highly encouraged in all appropriate patients with a 20% or greater 10-year risk regardless of a previous event history.

1.2.2 Adverse Events Do Not Differ Across CV Risk Groups

The safety profile of ASA is well described. From numerous clinical trials involving tens of thousands of patients, as well as post-marketing experience involving hundreds of millions of exposures, it is clear that the most common serious adverse events associated with ASA, while rare, are related to hemorrhage (largely GI and intracranial) and do not vary with regard to CHD risk. The U.S. Preventive Services Task Force assessment of the risks of ASA when used for primary prevention of MI predict that approximately 2-4 serious GI bleeds and 0-2 intracranial bleeds could be expected for every 1,000 patients exposed to ASA for 5 years. Comparing the absolute benefits of ASA in individuals at moderate CHD risk or greater to these hemorrhagic risks demonstrates a highly favorable benefit-to-risk relationship for this population.

1.3 Weight of Evidence Analysis is Different from Typical NDA Approach

1.3.1 Available Data are Substantial But Limiting

The primary prevention data for ASA are limited to the extent that the benefits in certain areas can be analyzed. The majority of patients studied has been at low risk for CV events and, therefore, does not provide direct evidence of the benefit exceeding the risk in a moderate-risk population. Despite the apparent limitations, a consistent reduction in non-fatal MI has been demonstrated. It is rational that this benefit should be extended to the populations at moderate risk for such events and included in the professional labeling of ASA.

Data for ASA in the primary prevention of cardiovascular events is now available from six randomized trials (BDT, PHS, TPT, HOT, PPP, WHS). Five of these trials have been previously described in detail in prior submissions. In general, these trials are limited for several reasons including but not limited to large simple designs lacking tight monitoring/control, self reporting of certain endpoints, and varied populations, dosage regimens and endpoints. Statistically, there are additional limitations when assessing the data as individual trials and in aggregate. For these reasons it is unsound to further dissect these trials and make attempts to gather anything but conclusions on primary endpoints and secondary endpoints of specific interest, such as a consistent reduction in nonfatal MI.

While these trials did not meet their predetermined primary endpoints, the consistent reduction in nonfatal MI is a compelling finding. Importantly, this observed reduction in MI is consistent with the well-described mechanism of action of ASA and the results seen in numerous trials in patients with a history of CVD. Questions regarding consistency across endpoints do arise when considering that effects on stroke and CV death are not observed although reasons remains uncertain, it may simply be that the population studied (relatively low risk) lacked the sensitivity to deliver sufficient endpoints. The results of these trials do not rule out profound and consistent benefits in a population at greater risk. Such benefits were observed in the subgroup of women \geq

65 years in the recent Women's Health Study (discussed below). Despite the apparent gap in primary prevention data in the moderate risk population, a study of adequate size may not be feasible for several reasons including ethical considerations.

The data under review have several limitations but remain sufficient to support the requested indication. It is requested that the evidence be considered in totality and be used as the foundation for a natural extension into the population which can benefit most.

1.3.2 Current Evidence Provides Validity

In earlier meetings with the FDA, it was agreed that there were different standards applicable to the totality of the evidence that ASA is effective and safe, based upon data from the five ASA primary prevention trials involving 55,000 apparently healthy individuals. The meta-analytical approach provides adequate evidence demonstrating that ASA is effective in prevention of a first MI. The approach was considered different yet acceptable compared to the evidentiary standards required for a NDA submission. In a NDA, the concept has been to usually require at least two independent cohorts to show statistical significance at the 0.05 level (ie, independent repetition of a significant outcome in a similar experiment). This has usually required meeting the primary endpoint twice in GCP-monitored trials. By virtue of this approach, internal validity of very well controlled experiments is established.

For an established chemical entity that has used large simple trial approaches, a different set of criteria should apply. The weight of the evidence approach takes into account the fact that:

- external validity exists in these trials by virtue of the number of different trials demonstrating the same result in the same endpoints, and
- these data are valid in assessing both efficacy and safety because the data are from randomized controlled trials rather than observational evidence. The results are consistent and reflect a reproducible finding.

1.3.3 Silent Myocardial Infarction as a Surrogate Endpoint

There has been a significant interest in the relationship between ASA and silent MI. By virtue of the varying methodologies by which the trials involving ASA were conducted, silent MI as an endpoint was collected in only two of the five trials. Given the meta

analytical approach being sought and the following points raised in this section, the utility of silent MI to assess the efficacy of ASA is considered questionable.

There is consensus that 25-40% of all MIs are clinically unrecognized. Due to improved recognition of MI, the lower number is the more contemporary point estimate (Am J Cardiol 2002;90:927-931). Most importantly, the assay sensitivity of this endpoint (silent MI) is unknown. To our knowledge, no clinical trial has demonstrated an effect in the moderate range, (i.e. 20-33% RRR) in both clinically overt MI and silent MI. Without such validation, it is unclear as to the utility of including silent MI in the analysis of total MI events.

1.3.3.1 Accepted Methodology for Surrogacy

The adoption of a valid surrogate endpoint requires that the effect of a given treatment on the surrogate endpoint allows the prediction of the effect on the outcome of interest (Fleming TR, DeMets DL. Surrogate end points in clinical trials: are we being misled? *Ann Intern Med* . 1996; 125: 605–613). Prentice proposes a formal definition of surrogate endpoints and outlines how potential surrogate endpoints could be validated using data from individual clinical trials and four operational criteria. To consider a paraclinical measure as a valid surrogate endpoint for a clinical endpoint of interest (this includes the support of a clinical finding by a paraclinical finding, in our view), these criteria require that a given treatment is effective on the surrogate endpoint (first criterion) and on the clinical endpoint of interest (second criterion), that the surrogate and the clinical endpoints are significantly correlated (third criterion), and, finally, that the effect of a given treatment on the clinical endpoint is mediated through an effect on the surrogate endpoint (fourth criterion). (Prentice RL. Surrogate markers in clinical trials: definition and operational criteria. *Stat Med* . 1989; 8: 431–440).

This set of criteria has already been used to test surrogacy in different medical conditions, however such a test has not been conducted for silent or clinically unrecognized MI.

In the ASCOT LLA trial, silent MI was studied as a tertiary endpoint and was found to not be significantly affected by the treatment. Therefore, it did not meet Prentice criteria in this high risk (>20% 10 yr risk of CVD) primary prevention population for surrogacy of effect. The data also reveals a very low estimate for the frequency of silent MI in this high risk population, comprising only 12% of all MIs, which is significantly lower than population-based data suggests, further demonstrating the high variability and poor predictive value of silent MI in particular populations. Therefore, in lower risk primary prevention populations, the sensitivity of this measure would be expected to perform even worse. (Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm (ASCOT-LLA): a

multicentre randomized controlled trial. Sever PS, et al, ASCOT investigators. Imperial College, London, UK. Lancet. 2003 Apr 5;361(9364):1149-58.)

The assay sensitivity of the silent MI endpoint may further be reduced by the lack of time-to-event data, especially when infrequent measures are taken, such as is the case with outpatient studies like Hypertension Optimal Treatment Trial (HOT) and The Thrombosis Prevention Trial (TPT).

Another argument that has been put forth regarding the assessment of silent MI relates to an analgesic effect of low dose ASA. It has been speculated that at sufficient dose, ASA may mask the acute MI chest pain and other pain to convert clinically apparent MIs into silent MIs. There is no evidence available in the overall understanding of the issue of pain, pain perception and analgesic effect of ASA and its relationship to silent MI to substantiate this hypothesis. Furthermore, low dose studies, such as The HOT Trial utilize a dose of ASA without appreciable pain relieving qualities.

1.3.3.2 Perspective from the Antiplatelet Trialists' Collaboration

The following section contains the point of view from Colin Baigent as submitted in a recent letter (April 20, 2005) to the Agency.

"When the Antiplatelet Trialists' Collaboration was set up in the 1980's, a deliberate decision was taken to exclude silent MI from the primary outcome, namely serious vascular event, defined as non-fatal myocardial infarction, non-fatal stroke, or vascular death. Of course, the vast majority of the 195 randomized trials among 135,000 high-risk patients considered in the 2002 cycle had not recorded silent MI in any case, but even if such data were available, they were not requested by our group."

"The reasons for excluding silent MI were chiefly methodological. Assessment of whether a silent MI occurred in a randomized patient can only be made if an EKG has been recorded. In those few trials where the protocol specifies that an EKG is to be measured, this most often occurs at the final visit, and so by definition this endpoint can only be evaluated in persons completing the trial. It cannot be determined whether silent MI occurred, for example, in any patient who is lost to follow-up, or who dies during the study. This creates the potential for serious biases. Moreover, the exact date of occurrence of a silent MI cannot be determined, so efficient statistical methods cannot be used to analyse this endpoint, increasing the probability that a treatment which truly prevented or delayed the occurrence of silent MI would be incorrectly judged to be ineffective."

"In its evaluation of the Citizen's Petition, the Agency has focussed on two trials in which EKGs were recorded: the Hypertension Optimal Treatment and the Thrombosis Prevention Trial. No such information was recorded in the other 3 primary prevention trials, so the effects of aspirin on silent MI can only be assessed on a small number of endpoints from just a subset of the available trials. In these circumstances, the Agency could not have expected to be able to determine without bias whether aspirin has any effect on silent MI, so it seems strange that this was a major rationale behind obtaining the data from our group."

1.3.3.3 Perspective from the TPT Trial

The report regarding silent MI in the Medical Research Council's Thrombosis Prevention Trial has been previously submitted to the Agency (May 27, 2005) and provides several important conclusions:

- "Among individual men, there is a considerable variability in the finding of silent MI. These are often not recorded consistently after an initial recording."
- "The data confirm that the finding of a silent MI significantly increases the risk of a major clinical event subsequently."
- "ASA does not appear to have an effect on the onset of silent MI."

1.3.3.4 SAVE Trial Discussion

As evidenced by the discussions in the literature (NEJM 1993;329:1204) the issue of silent MI has been raised in the SAVE trial (Survival and Ventricular Enlargement trial). In this clinical trial involving the use of captopril to prevent recurrent events, the overall benefit was deemed by the Agency only to be positive when the investigators removed silent MI from the analysis. However, the investigators put forth several reasons to support their analysis -- which excludes silent MI. The reasoning agreed by the investigators (below) is in line with Bayer HealthCare's position and reflects several of the points made above.

- Patients identified because of isolated Q-wave changed were not at increased risk for CV events
- The clinical definitions for MI were developed early, prior to the review of data
- Only clinical MI data were reviewed by the Data and Safety Monitoring Board

In conclusion, we respectfully disagree with the proposed usage of silent MI as a surrogate or supportive endpoint to assess the ability of ASA to reduce clinical MI incidence. In addition, we believe that the robust and consistent findings across five primary prevention studies with respect to the reduction in clinically manifest nonfatal MI is a sufficient basis for approval of the indication. To address Agency concerns regarding the lack of apparent impact of ASA on silent events, we suggest that the clinical trial section of the label clearly define that only clinically manifest events were positively affected by ASA.

1.4 The Women's Health Study Provides Additional Evidence

The most recently published primary prevention trial was conducted in women (NEJM 2005;352:1293-304). This trial studied 39,876 apparently healthy women over the age of 45. The participants were randomized to receive either 100 mg ASA or a placebo on alternate days, and were then monitored for an average of 10 years for a first major cardiovascular event (i.e. non-fatal MI, non-fatal stroke or death from a cardiovascular event). In the total population, ASA lowered the risk of stroke by 17% (RR: 0.83(0.69-0.99) P=0.04) without affecting the risk of MI (Table 3). The composite primary endpoint was reduced significantly in a subgroup of women 65 years of age or older.

Adverse effects (GI bleeding and peptic ulcer) were confirmed using a follow up questionnaire, and were significantly more common in the ASA group. There were 127 episodes of gastrointestinal bleeding requiring transfusion in the ASA group, compared to 97 in the placebo group (RR:1.4(1.07-1.43) P=0.02). Self-reported events (hematuria, easy bruising and epistaxis) were also significantly increased in the ASA group. The percentage of participants reporting gastric upset was almost identical in the ASA and placebo groups (59.5% vs 59.7%) and there were 5 fatal gastrointestinal hemorrhages (three in the placebo group and two in the ASA group).

The WHS enrolled a large number of female patients 65 years or older (n=4097). Results from this randomized subgroup suggest that these women benefited significantly from routine use of ASA. There was a 26% relative risk reduction in the primary endpoint (RR 0.74, 95% CI 0.59-0.92, p=0.008, 131 events in the ASA group vs. 175 in the placebo group). The authors also report that there were 16 more gastrointestinal hemorrhages requiring transfusion in the ASA group compared to placebo in elderly patients.

The 65 years and older subgroup in the WHS represents an important population. Among ASA users in the US, 48% are 65 or older and among female ASA users 49% are in this age group (Bayer HealthCare. Data on file.). Furthermore, hitherto there has

been a paucity of randomized controlled clinical data regarding ASA in elderly subjects. Thus a recent computer-generated analysis, which did not include WHS data, failed to confidently determine the benefit-risk ratio in ASA users age ≥ 70 years (BMJ 2005;330:1306). There remains no conclusive evidence to suggest that significantly increased bleeding risks outweigh the absolute CV risk reduction in this subgroup.

The participants in this subgroup had a CV event rate that approached the moderate risk threshold (8%). As described above, the use of ASA resulted in a significant reduction in the composite endpoint of stroke/MI/CV death as well as reductions in the individual endpoints of ischemic stroke (RR 0.70, 95 % CI 0.49-1.00, $p=0.005$) and MI (RR 0.66, 95% CI 0.44-0.97, $p=0.04$). These findings coupled with the baseline risk help to suggest that the benefits of ASA in a moderate risk population are likely to be considerable and also in women.

Additionally, there was an increase in serious GI bleeding events in this group. Despite the increase in GI risk, it appears that the CV benefits outweigh the risk by nearly 3 to 1. Therefore, it may be concluded that in apparently healthy women who are 65 years or older, the benefits of low dose ASA outweigh the risks.

The WHS provides ample evidence to gain an even better understanding of the long-term effects associated with routine ASA use and the benefits in older, moderate risk patients. The results suggest that while the risk for serious bleeding is increased, the absolute increase over placebo is very minor (0.6% vs. 0.5%) in the general population. Further, the use of ASA did not result in an increase in stomach upset or fatal bleeding events. Additionally, ASA use in an older population, which approached moderate risk, resulted in a substantial reduction in CV events and an acceptable benefit-to-risk ratio.

Table 3: Incidence and Relative Risk of Confirmed Cardiovascular End Points from the WHS

End Point	ASA	Placebo	Relative Risk (95% CI)*	P Value
	(N=19,934)	(N=19,942)		
Number of Events				
Major cardiovascular event	477	522	0.91 (0.80-1.03)	0.13
Stroke	221	266	0.83 (0.69-0.99)	0.04
Ischemic	170	221	0.76 (0.63-0.93)	0.009
Hemorrhagic	51	41	1.24 (0.82-1.87)	0.31
Fatal	23	22	1.04 (0.58-1.86)	0.90
Nonfatal	198	244	0.81 (0.67-0.97)	0.02
Myocardial infarction	198	193	1.02 (0.84-1.25)	0.83
Fatal	14	12	1.16 (0.54-2.51)	0.70
Nonfatal	184	181	1.01 (0.83-1.24)	0.90
Death from cardiovascular causes	120	126	0.95 (0.74-1.22)	0.68
Transient ischemic attack	186	238	0.78 (0.64-0.94)	0.01
Coronary revascularization	389	374	1.04 (0.90-1.20)	0.61
Death from any cause	609	642	0.95 (0.85-1.06)	0.32

*CI denotes confidence interval.

+ A major cardiovascular event was defined as a nonfatal myocardial infarction, a nonfatal stroke, or death from cardiovascular causes.

Abstracted from NEJM 2005;352:1293-304.

1.5 CV Risk Determination

The absolute benefits of ASA accrue most meaningfully to those individuals at moderate or greater risk. To define the appropriate moderate risk groups for the primary prevention of CHD events, a reasonable approach may be to utilize age as a surrogate. Recent studies have examined the prevalence of risk factors in older US adults. It appears that age may be an appropriate marker for additional risk based on the relatively high prevalence of CV risk factors among older US adults.

Support for age as a surrogate for additional risk was observed in an analysis performed by Vasan et al (Ann Intern Med. 2005;142:393-402.) based on data from The Third National Health and Nutrition Examination Survey (NHANES). For the purpose of this study, risk factors were considered to be elevated blood pressure, elevated LDL, low HDL, glucose intolerance and smoking. Additionally, this paper reported the

prevalence of borderline risk factors. Borderline risks were defined as suboptimal but below current treatment thresholds.

The investigators reported that among men age 55-64, 74.6% had at least one major risk and 39.7% have at least two major risk factors (Table 4). All men in both groups had at least one additional borderline risk as well. The prevalence of risk factors was similar in the age 65-74 male subgroup. In this group, 81% have at least one major risk and 45.3% have at least two major risk factors. Again, all men in this age group had at least one borderline risk factor in addition to the major risk factor(s). As expected, the prevalence of risk factors in women was reduced but still remains significant. Among women age 55-64, 59.9% had at least one major risk factor, and 22.6% had two or more risk factors. For women age 65-74, 71.4% had at least one risk factor and 35.6% have at least two. Borderline risk factors were also common among these women.

Further support was observed in a report (Arch Intern Med. 2004;164:181-188.) of data from the Behavioral Risk Factor Surveillance System (BRFSS). The BRFSS is a state-based telephone survey of adults 18 years or older. Data from five time points were available for review (1991, 1993, 1995, 1997, 1999). For the purpose of this particular study, risk factors were defined as self-reported high blood pressure, high blood cholesterol, diabetes, obesity, or current smoking.

This study reported an apparent age relationship to the prevalence of multiple risk factors (Table 5). In 1991, among patients age 18-34, the prevalence of two or more risk factors was 14.1% and for those ages 35-49, 26.0%. For those ages 50-64 and >65, the corresponding rates were 40.4% and 41.8%, respectively. Additionally, among patients who reported high blood cholesterol levels, 63.6% had at least one other risk factor. Over the five time points, there was a consistent increase in multiple risk factor prevalence beginning with 57.7% in 1991. The most prevalent individual risk factor in this group was high blood pressure over all five time points (36.8% in 1999). Hypercholesterolemics represent a key risk group as about half of all US adults have a total cholesterol level above 200 mg/dL (AHA Heart Disease and Stroke Statistics 2005). Based on the data above, it can be concluded that among adults age >50 and patients with high cholesterol, the presence of multiple risk factors is common.

The two studies above reported relatively consistent findings with respect to the prevalence of multiple risk factors and advancing age. Further, the trend over time suggests that in 2005 the prevalence is likely to have increased beyond what was reported in 1999. Vasan et al report consistent findings and additionally report the prevalence of borderline risk factors. While borderline risk factors do not require treatment, they do contribute to overall CV risk and the use of appropriate risk reduction methods.

Based upon the data provided from two large, national surveys, it can be concluded that the prevalence of multiple major CV risk factors is common among adults over age 50 and should be considered when evaluating population-based CV risk reduction strategies directed at patients in the moderate or near moderate CV risk range.

Table 4: Age-Specific Prevalence of Risk Factor Groups in the Third National Health and Nutrition Examination Survey*

Risk Factor Group	Men, %				Women, %			
	33-44 y	45-54 y	55-64 y	65-74 y	35-44 y	44-54 y	55-64 y	65-74 y
0	32.6	23.5	25.6	19.0	55.2	45.4	40.1	28.6
1	33.7	37.9	34.7	35.7	22.8	32.8	37.3	35.8
2	26.4	26.9	24.8	35.7	11.2	16.4	15.8	28.8
3	7.3	10.5	11.3	7.4	1.9	1.7	6.0	5.9

*Data from non-Hispanic white persons who were 35 to 74 years of age and had no vascular disease in their medical history (see text for details). The Third National Health and Nutrition Examination Survey includes several million men and women when weights are applied, so the 95% CIs around the estimates do not differ greatly from the estimates themselves.

Abstracted from *Ann Intern Med.* 2005;142:393-402.

Table 5: Prevalence of Multiple Cardiovascular Disease Risk Factors by Selected Characteristics, 1991-1999, Behavioral Risk Factor Surveillance System*

Characteristic	Percent \pm 95% Confidence Interval				
	1991	1993	1995	1997	1999
Age group, y					
18-34	11.7 \pm 0.82	12.1 \pm 0.78	13.3 \pm 0.92	13.2 \pm 0.73	14.1 \pm 0.77
35-49	22.7 \pm 0.98	22.7 \pm 0.82	23.3 \pm 1.00	24.1 \pm 0.75	26.0 \pm 0.77
50-64	35.1 \pm 1.31	35.9 \pm 1.14	38.4 \pm 1.37	38.3 \pm 1.02	40.4 \pm 0.98
\geq 65	33.2 \pm 1.23	35.5 \pm 1.08	37.2 \pm 1.16	38.3 \pm 0.98	41.8 \pm 1.02

* Percentage reporting 2 or more of the following risk factors: high blood pressure, high blood cholesterol level, diabetes, obesity and /or current smoking. Percentages are weighted to state population estimates. Percentages by sex, race/ethnicity, and education are also age adjusted to the 2000 US standard population. Abstracted from *Arch Intern Med.* 2004;164:1981-1988.

1.6 Importance of Consistency with Practice Guidelines

Bayer HealthCare believes it is essential for there to be consistency in messages communicated by the FDA via professional labeling of ASA and guideline recommendations by major health organizations. This is critical in order to maintain consumer, patient and physician confidence and not confuse important preventive health care strategies.

Bayer HealthCare's proposal to include individuals at moderate or greater risk of MI in the professional labeling for ASA is consistent with the views of the major public health organizations that have independently reviewed the evidence in development of their guidelines. The introduction of risk-based guidelines by the United States Preventive Services Task Force (Hayden, 2002) and the American Heart Association (Pearson, 2002), among other groups, highlights that significant scientific consensus exists regarding the public health importance of broadening the ASA labeling to include patients at moderate or greater CHD risk who have not suffered a previous cardiovascular event.

1.6.1 The US Preventive Services Task Force (USPSTF) Recommendations

The favorable benefit-to-risk relationship for the use of ASA in moderate-risk patients is clearly demonstrated by the recent US Preventive Services Task Force recommendations (2002). Furthermore, the Task Force acknowledges the importance of global risk assessment -- including evaluating the presence and severity of the following risk factors: age, sex, diabetes, elevated total cholesterol levels, low levels of high-density lipoprotein cholesterol, elevated blood pressure, family history (especially in younger adults), and smoking -- in determining whether an individual patient should be a candidate for ASA therapy.

The USPSTF estimated the benefits and harms of ASA administered for five years to 1,000 persons with various levels of baseline risk for coronary heart disease. Their estimates are based on a clearly supportable relative risk reduction of 28% for CHD events in ASA-treated patients derived from the five primary prevention studies (Table 6). For comparison purposes, it is important to note that the USPSTF estimates are based on 5-year event rates rather than the 10-year rates included in our submission and the recommendations of the American Heart Association.

Table 6: Estimates of Benefits and Harms of ASA at Various Levels of Baseline Risk for Coronary Heart Disease

Benefits and Harms	Baseline Risks for Coronary Heart Disease over 10 Years		
	Low-Risk (<10%)	Moderate-Risk (10%)	High-Risk (20%)
Coronary heart disease events, n	3 - 8 (1 - 12) avoided	14 (6-20) avoided	20+ avoided**
Hemorrhagic strokes, n‡	1 (0 - 2) caused	1 (0 - 2) caused	1 (0 - 2) caused
Major gastrointestinal bleeding events, n§	3 (2 - 4) caused	3 (2 - 4) caused	3 (2 - 4) caused

*Estimates are based on a relative risk reduction of 28% for coronary heart disease events in ASA-treated patients and assume that risk reductions do not vary significantly by age.

‡Data from secondary prevention trials suggests that increases in hemorrhagic stroke may be offset by reduction in other types of stroke in patients at high-risk for cardiovascular disease. (≥10% 5-year risk).

§Rates in persons older than 70 years of age are not clearly known

**Based on an analysis of secondary prevention studies

Adapted from Hayden, 2002

According to this analysis, estimates of the type and magnitude of benefits and harms associated with ASA therapy vary with an individual's underlying cardiovascular risk. The balance of benefit to risk is clearly favorable in individuals with a 10-year risk that is greater than 6%.

1.6.2 The American Heart Association (AHA) Recommendations

The latest AHA guidelines for primary prevention (2002) recommend that 75 to 160 mg ASA per day should be considered for persons at moderate risk, specifically, those with a 10-year risk of CHD of ≥10%. Treating such patients would further enhance the benefit-to-risk relationship and prevent 14 events (range: 6 to 20) in 1,000 patients treated for 5 years. This benefit outweighs possible harms, which are estimated to result in an excess of 1 hemorrhagic stroke (range: 0 to 2) and 3 major gastrointestinal bleeding events (range: 2 to 4) in the same treatment group.

1.6.3 Additional Organizational Support

In addition to the USPSTF and AHA recommendations, a number of other authoritative groups have come out in favor of the primary prevention indication for ASA, as demonstrated during the December 8, 2003 Advisory Committee meeting. During the Open Public Hearing, strong support was provided by representatives from the American Diabetes Association, the American Black Cardiologists, the American Academy of Family Physicians, the American College of Cardiology, and the Preventative Cardiovascular Nurses Association. The testimonies of these groups advocated alignment of the ASA labeling with current scientific knowledge and evidence

based clinical practice guidelines. They noted that revisions to the ASA labeling would provide an opportunity to raise awareness of appropriate ASA use and counter the underutilization of ASA.

1.7 Clear Public Health Benefit

Heart disease and stroke are the principal components of cardiovascular disease and are the first and third leading causes of death in the United States. About 62 million Americans have some form of cardiovascular disease, with CHD being the leading cause of premature, permanent disability among working adults.

With over 500,000 MIs occurring in this country each year, and significant associated morbidity and mortality, the need for strategies to prevent these events must be actively embraced. It is well accepted within the medical community that an understanding of an individual's cardiovascular risk profile, defined by number and intensity of risk factors, is the key determinant in assessing that person's likelihood of developing CHD. While a major component of the risk assessment is the presence or absence of symptomatic disease, a large number of individuals experience a first event, suggesting that they were at elevated risk at the time of the event. The current FDA approved professional labeling for ASA for MI prophylaxis requires the presence of a previous cardiovascular event or evidence of symptomatic CHD as the defining factor in establishing a level of risk sufficient for ASA exposure. Recent advances in risk assessment have suggested that a more appropriate model should be one based on CHD risk. With a thorough appreciation of an individual's risk profile, the clinician can guide ASA therapy appropriately and more importantly, accurately evaluate the likely benefit and compare it to potential for harm. In fact, with this knowledge, numbers of events prevented can be compared to the number of adverse events caused in a manner that will allow patients and physicians to evaluate the appropriateness of treatment on an individual patient basis. Encouraging broader treatment of patients where the absolute benefit is expected to be greatest (i.e., those at elevated risk) will significantly enhance the impact of treatment.

The Centers for Disease Control and Prevention (CDC) has identified several CVD-related goals. These include building a nationwide program to prevent heart disease and stroke, reducing disparities in cardiovascular health among high-risk populations, promoting secondary prevention of heart disease and stroke, and developing and assessing new methods for preventing heart disease and stroke. The CDC goals highlight the keys to reducing the societal and economic burden of CVD in the United States. Clearly, more extensive and appropriate use of ASA will help to achieve these goals, as well as the goals of many other healthcare organizations and initiatives. The Agency's endorsement of the benefits of ASA will solidify the role of ASA as an important risk reduction strategy.

1.8 Proposed Primary Prevention Labeling

With over 100 years of history of use, ASA is one of the most extensively studied drugs in the history of medicine and remains the focus of current research efforts. Bayer HealthCare is the proud maker of Bayer® Aspirin and is a leader in the scientific advancement of ASA. It has led the way in the creation of programs to ensure that appropriate patients have access to ASA, with a dedicated focus on healthcare professional programs, as well as public education programs urging patients to speak to their doctor about whether an ASA regimen is right for them. Bayer HealthCare has worked extensively with the FDA over many years to align the labeling of ASA with current scientific evidence and is committed to continuing to work with the agency to ensure that the use of ASA can be appropriately extended to an even broader at-risk population.

Following is the labeling proposed as part of the Petition:

CLINICAL STUDIES

Primary Prevention of Myocardial Infarction (MI): In a meta-analysis of five primary prevention trials involving 55,580 patients (11,466 women) with varying levels of baseline CHD risk, aspirin demonstrated a 15 percent reduction in the risk of combined outcome of any important vascular event (combined endpoint of vascular death, nonfatal MI or nonfatal stroke). It should be noted however, that the benefit was largely driven by the large, statistically significant 32 percent reduction in the risk of nonfatal MI. No apparent effect on stroke or mortality was observed. While the average CHD risk level in four of these five studies was considered low (less than 10 percent 10 year risk), all five studies included patients at higher risk, including over 36,000 patients at moderate risk (10 to 20 percent CHD risk). Intra- and inter-study analyses confirm equivalent benefits (e.g., risk reductions) regardless of baseline global CHD risk, with a 35 percent reduction of nonfatal MI in moderate risk patients. The rationale for restricting use to patients of at least moderate risk (a CHD risk greater than 10 percent over 10 years) is based on the favorable benefit to risk relationship. Three of the five clinical studies did not record silent MI events, thus, the meta-analysis of the studies excluded these events.

INDICATIONS AND USAGE

Vascular Indications (Ischemic Stroke, TIA, Acute MI, Prevention of Recurrent MI, Unstable Angina Pectoris, Chronic Stable Angina Pectoris, and Primary Prevention of MI in Patients of at Least Moderate CHD Risk): Aspirin is indicated to: (1) Reduce the combined risk of death and nonfatal stroke in patients who have had ischemic stroke or transient ischemia of the brain due to fibrin platelet emboli, (2) reduce the risk of vascular mortality in patients with a suspected acute MI, (3) reduce the combined risk of death and nonfatal MI in patients with a

previous MI or unstable angina pectoris, (4) reduce the combined risk of MI and sudden death in patients with chronic stable angina pectoris, and (5) reduce the risk of a first myocardial infarction in patients at moderate CHD risk, defined as a 10 year risk of coronary heart disease that exceeds 10 percent, where the benefits of therapy would be expected to outweigh the risks.

DOSAGE AND ADMINISTRATION

Each dose of aspirin should be taken with a full glass of water unless patient is fluid restricted. Anti-inflammatory and analgesic dosages should be individualized. When aspirin is used in high doses, the development of tinnitus may be used as a clinical sign of elevated plasma salicylate levels except in patients with high frequency hearing loss.

Primary Prevention of MI in Patients at Moderate Risk (10 percent or greater 10 year CHD risk):

75-325 mg once a day. Continue therapy indefinitely.

2 COMMUNICATION

2.1 Proper Communication of Benefit

The FDA has long held the view that its authority in regulating the sale of pharmaceutical drug products should not interfere with the practice of medicine. In fact, in Section 214 of FDAMA, "Practice of Medicine", Congress explicitly provides that "nothing in this Act shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed drug to a patient for any condition or disease within a legitimate healthcare practitioner-patient relationship." To this end, it is important that any FDA pronouncement regarding the utility of ASA in the primary prevention of MI not appear to negate current treatment guidelines recognizing the utility of ASA for such use.

In a number of recent official and public communications, the Agency has acknowledged the evidence in favor of the use of ASA for prevention of cardiovascular events in at-risk patients. Most recently, in the FDA's decision on June 15, 2005 requiring modifications to the approved labeling for NSAIDs to include a black box warning regarding the risk of adverse cardiovascular events, the Agency specifically exempted ASA from this action due to the evidence of a protective benefit of ASA in preventing such events in certain patient populations. Further evidence of FDA's stance on the utility of ASA in the prevention of cardiovascular events in individuals at risk who have not experienced a previous event comes from the IND authorization process, which has specifically authorized studies requiring ASA as a comparator or as baseline therapy in all patients at elevated MI risk.

Regardless of the rationale for the agency's conclusion regarding the adequacy of the ASA findings to support the petitioned label change, it is essential that the communication of the outcome of the review acknowledges current practice guidelines and does not adversely affect the patient and physician relationship as it relates to appropriate ASA use. Today, ASA is substantially underutilized in both secondary prevention of MI and stroke, as well as in acute evolving MI. As the lay person is not easily able to discern the differences between primary and secondary prophylaxis, Agency conclusions on the Petition may be misconstrued that the FDA is rethinking the utility of ASA in CV prophylaxis. As such, the FDA must assure that patients on a physician recommended ASA regimen not discontinue treatment. Furthermore, the Agency should reassure physicians who practice the guidelines, that this practice is both rational and appropriate, including an acknowledgment that there have been large-scale trials conducted in this area with significant, meaningful findings. This is particularly noteworthy based upon recent findings that suggest abrupt cessation of ASA therapy can result in a dramatic increase in the CV event rate with significant real world consequences (JACC 2005;45:456-9).

2.2 Rationale for Inclusion of Information in the Clinical Trial Section

There are a number of possible approaches that the Agency could consider that would acknowledge the presence of large-scale ASA primary prevention studies and treatment guidelines based on their results, differentiating this action from many others where data are either scant or nonexistent. A reasonable option involves a discussion of the strengths and limitations of the primary prevention clinical trial experience in the approved professional labeling. For instance, language simply acknowledging the number of studies and patients evaluated would provide physicians with a full disclosure of the available evidence that underlies the current treatment guidelines, as well as highlighting limitations of the database. This approach would prove to be the most informative and least confusing to physicians and their patients regarding the relevance of the action to previously approved uses of ASA.

Another option is to acknowledge in the labeling that the Agency recognizes that there are individuals under a physician's care who may be suitable candidates for ASA in spite of not having experienced a previous event. Such language will allow for the inclusion of information to guide physicians in assessing an individual patient's likely benefit and risk from ASA, and, thereby, ensure more appropriate ASA use than may be occurring presently in the absence of any guidance in the labeling.

The above-mentioned alterations to the labeling for ASA will add clarity around the use of ASA and diminish inappropriate use with a corresponding benefit to public health. This can be suitably achieved without going so far as to suggesting that the data meet current drug approval standards. In addition, such labeling will be consistent with clinical trial advice given to sponsors wishing to include an ASA comparator in a trial, providing a rationale for this FDA guidance.

2.3 Enhancing Patient and Physician Understanding of the FDA Action

Regardless of the communication options chosen and in the light of recent discussions regarding COX-2 inhibitors and NSAIDs, it is essential that the Agency carefully craft its communications regarding its actions on the Petition to ensure that the positive attributes of ASA are appropriately understood. Failure to do so, along with the expected media coverage, could adversely affect patient physician relationships where ASA has been prescribed. To avoid such an outcome, a number of approaches should be considered. A Talk Paper at the time of its ruling will help to clarify the issues. This important communication vehicle could be designed in a way that conveys that numerous studies have been conducted, yet highlights that additional questions need to be answered. It will be important to point out in this document that the action on the primary prevention indication in no way alters the Agency's support for the currently approved indications or individual physician recommendations. This could be supported by providing a link on the FDA web site to other authoritative bodies, such as the

American Heart Association, that can provide guidance to physicians and patients who have issues and concerns related to the ruling.

3 BAYER HEALTHCARE IS COMMITTED TO COLLABORATING WITH THE FDA IN THE MANAGEMENT OF THE IMPENDING DECISION

3.1 Additional Data

Based on the presence and acceptance of primary prevention guidelines, large-scale studies in this area will be difficult to conduct. Ethical concerns regarding equipoise might further hamper large-scale long-term studies in these populations. Nonetheless, Bayer HealthCare remains committed to working with the FDA and the academic medical community to design and conduct the necessary studies to answer any remaining questions. Studies that are ongoing largely focus on subgroups of interest, e.g., the elderly and diabetics, as questions around benefit and risk are reasonable in these largely unstudied groups.

Bayer HealthCare looks forward to an enhanced partnership with the Agency to improve the cardiovascular health of Americans by ensuring the appropriate utilization of this remarkably effective, safe and inexpensive drug.

4 CONCLUSION

To conclude, it must be remembered that unlike most other drugs, the use of ASA in the primary prevention of cardiovascular events has been extensively studied. With the inclusion of the Women's Health Study, nearly 100,000 patients have been studied for a total of approximately 700,000 person years. The database includes studies with a variety of doses, forms and approaches, and show remarkably consistent results. The fact that these studies were largely investigator-initiated independent investigations is responsible for both their strength and their inability to align with current NDA approval standards. They have been critically reviewed and are the basis of numerous published treatment guidelines supporting the use of ASA in primary prevention. For these reasons and others describe previously, it is again felt that the data available provides adequate support for the use of ASA for the prevention of non fatal MI in patients at moderate or greater risk.