

**Integrated Summary
of Efficacy**



VOLUME 2

11 INTEGRATED SUMMARY OF EFFICACY

This section is a review of the evidence supporting the efficacy of ASA in the prevention of MI and cardiovascular events across the risk continuum. As such, an overview of the support for ASA efficacy in high-risk patients is presented, followed by the support for ASA efficacy in the lower risk patients, i.e., a review of the efficacy support from the 5 primary preventions studies. Additional efficacy-related information has also been provided to respond to FDA's and the Cardiovascular and Renal Drugs Advisory Committee's discussions regarding ASA resistance, silent MI, and support for the proposed 75-325 mg/day dosing recommendation.

11.1 ASA Prevents Cardiovascular Events Regardless of Risk

The extensive evidence supporting the efficacy of ASA includes more than 200 studies involving over 200,000 patients; including over 150,000 high-risk secondary prevention patients and over 55,000 lower risk primary prevention individuals.

While the ASA prevention database does not precisely meet the traditional new drug approval requirement of two pivotal trials demonstrating significant effects in the specific moderate-risk patient population indicated by the proposed labeling (Volume 1, Appendix 1), the available data are robust and consistent, adding rather than detracting from the reliability of the overall findings. Additionally, in contrast to traditional NDA development programs, the overall database for ASA is incredibly diverse, including studies exhibiting the following features:

- Broad age range;
- Patients with different underlying baseline CHD risk (low, moderate, and high-risk patients);
- Inclusion of wide array of co-morbid conditions (e.g., diabetes, hypertension)
- Patients using concomitant drugs;
- Different doses and formulations of ASA; and
- Geographical and ethnic/cultural diversity.

This diversity, coupled with consistent findings across the study populations, provides added reliability in the findings as well as confidence in their broad applicability. Taken as a whole, the data support the effectiveness of ASA in preventing MI in patients at all levels of CHD risk, regardless of whether patients experienced a previous cardiovascular event or not. In addition, based on the similar findings with respect to MI risk reduction across the low and high-risk patient groups studied, extrapolation to patients at moderate-risk is warranted. The appropriateness of extrapolation is strengthened by the demonstration of effectiveness in a substantial number of moderate-risk patients across the five low-risk studies that form the basis of the Bayer HealthCare Petition.

Because the relative risk reductions are similar in high-risk and low-risk patient populations, the results can be extrapolated to include moderate-risk populations as well. Likewise, the large and robust secondary prevention database can be used to address questions regarding effectiveness of ASA in subgroups, such as gender, age, and diabetics where the primary prevention database is either too small or not sufficient to address these issues statistically. Specifically, based on the relative risk reduction observed of 34%, one should be expected to prevent 14 MIs for every 1,000 patients with moderate or greater risk treated for 5 years.

To support the position that ASA is effective in patients at moderate or greater CHD risk independent of a history of a previous event, this section reviews the relevant efficacy data; first for high-risk populations (Section 11.2) and next for the lower risk group (Section 11.5). Finally, the evidence from patients at moderate-risk is reviewed (Section 11.6).

11.2 ASA Prevents Cardiovascular Events in High-Risk Populations

The efficacy of ASA as an antiplatelet drug in the prevention of cardiovascular events is well-established and recognized by the agency. The secondary prevention data that form the basis of currently approved ASA professional labeling are instructive in addressing questions that are not answerable with the low-risk primary prevention studies alone. In addition, studies in this population provide the “anchor point” for extrapolating the benefits to moderate-risk patients as a straight line can be drawn for the proportional MI risk reductions between the high-risk and the low-risk populations.

Because the populations in the high and low-risk studies are homogeneous with respect to a common pathophysiology, the evidence obtained in high-risk patients helps to confirm and extend the findings presented for low-risk patients and provide insight with respect to subgroups.

11.2.1 The Antithrombotic Trialists' Collaboration (ATT) Comprehensive High-Risk Population Overview

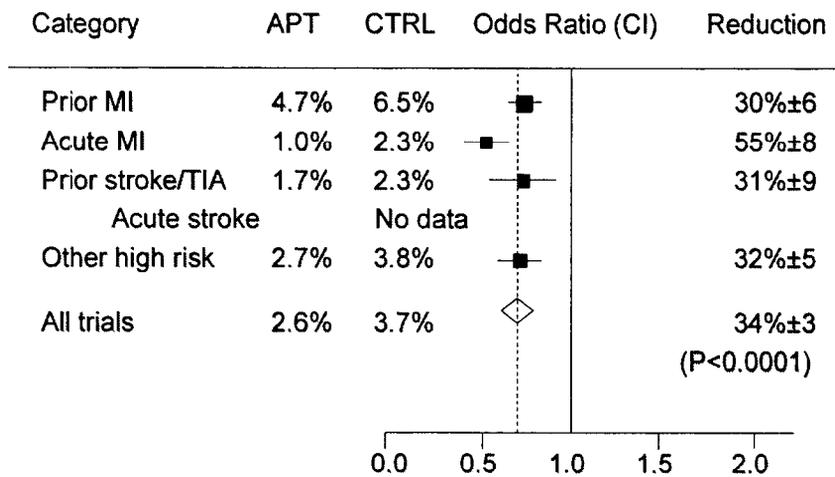
The systematic overview of the effects of antiplatelet therapy on vascular events conducted by the Antithrombotic Trialists' Collaboration (ATT) (2002) evaluated data from the following high-risk patient populations:

- Patients with Acute Evolving MI;
- Patients with Prior MI;
- Patients with Unstable Angina Pectoris;
- Patients with Prior Stroke or TIA;
- Patients with Chronic Stable Angina;
- Patients with Chronic Non-Valvular Atrial Fibrillation; and
- Patients Undergoing Revascularization Procedures and Those Requiring Establishment of Hemodialysis Access

This massive collection of data shows that in over 200 randomized trials, antiplatelet therapy (with ASA being the most widely studied antiplatelet therapy) is highly effective in reducing the incidence of nonfatal MI in a variety of patient types defined as being at high-risk at a similar rate (34%) as that observed in the low-risk population as included in the 5 pivotal primary prevention studies that form the basis of this submission.

Figure 6 below provides a summary of the reductions in nonfatal MI demonstrated across a variety of patient populations (ATT, 2002).

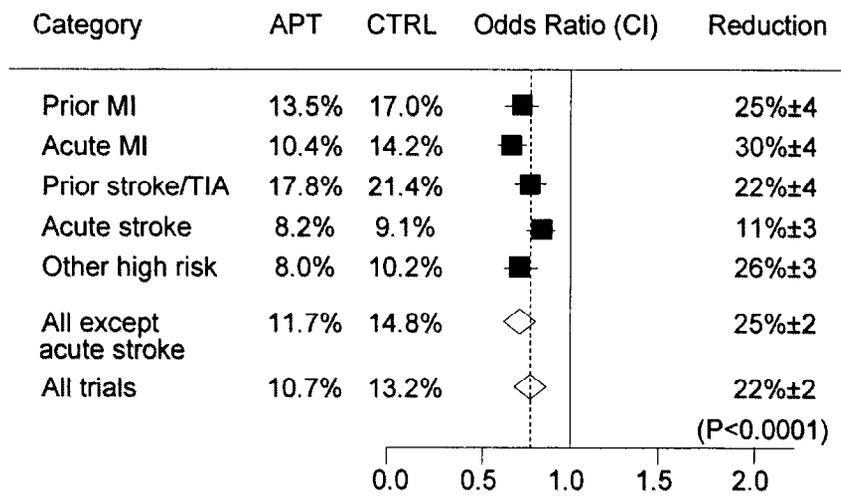
Figure 6: ATT Collaboration Data: Nonfatal MI



Adapted from ATT, 2002

In addition, antiplatelet therapy was also highly effective in reducing the number of vascular events across the range of high-risk patients studied. The risk reduction data are summarized in Figure 7 extracted from the ATT publication (ATT, 2002).

Figure 7: ATT Collaboration Data: Vascular Events



Adapted from ATT, 2002

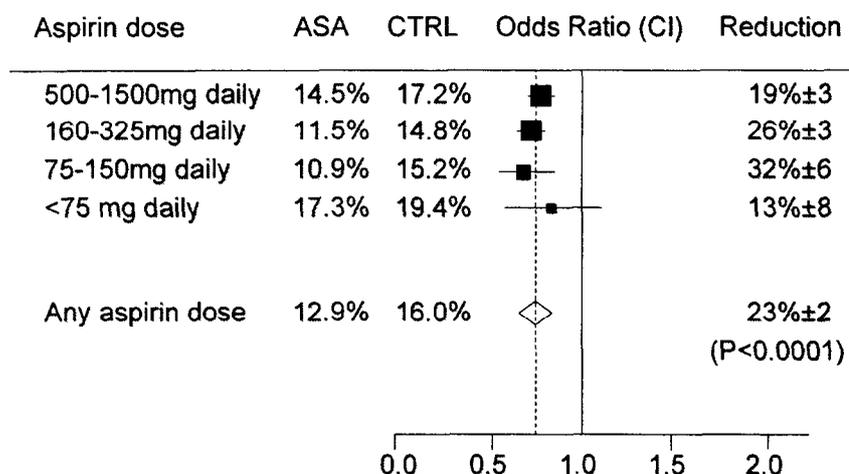
These findings demonstrate that the proportional risk reductions for nonfatal MI are similar regardless of the qualifying event warranting inclusion in the high-risk studies. The authors of the ATT publication conclude: “Our results suggest that among individuals at high-risk of occlusive vascular disease, the proportional risk reductions with antiplatelet therapy were roughly similar in most categories of patient (although they are smaller in acute stroke).”

Effect of ASA Dose on Vascular Events

The investigators reported a 26% – 32% reduction of the combined endpoints of MI, stroke, or vascular death by treatment with ASA alone at doses of 75 mg to 325 mg. Analysis of the overall data in high-risk individuals shows that low-doses of ASA (\leq 325 mg/day) exert at least as great a protective effect as higher doses (326 to 1500 mg/day).

These cardiovascular risk reductions in these patient populations exposed to ASA therapy are summarized in the Figure 8, below.

Figure 8: ATT Collaboration Data: Effect of Dose



Adapted from ATT, 2002

Based on these data, there does not appear to be a significant effect of ASA dose (in the range studied) on the prevention of vascular events in this high-risk patient population.

Relevant Subgroup Analysis

The analyses from the ATT have found that there was no significant effect of age, gender or diabetes status, on the ability of antiplatelet therapy to prevent vascular events in a variety of high-risk patients. With respect to diabetes, the reductions in vascular events were comparable between diabetics and nondiabetic patients, with a trend toward increased risk reductions with doses of ASA between 75 and 162 mg/day. It was estimated that 38 ± 12 vascular events per 1,000 diabetic patients would be prevented if they were treated with ASA for secondary prevention. Antiplatelet therapy was associated with a non-significant 7% proportional reduction in serious vascular events among diabetic patients (independent of history of MI or stroke). The authors do not interpret this lack of statistical finding as indicating a lack of worthwhile benefit for such patients, but rather as consistent with a benefit of antiplatelet therapy in this patient population. In fact, they specifically state that ASA “is likely to be effective for the primary prevention of vascular events among diabetic populations.”

This view is further supported by the Early Treatment Diabetic Retinopathy Study (ETDRS, 1992) results. Results of this study of type 1 and type 2 diabetic men and women, of which 48% having a history of cardiovascular disease, showed the relative risk for MI in the first 5 years in those randomized to ASA therapy was lowered significantly to 0.72 (CI 0.55-0.95). In fact, the American Diabetes Association (ADA, 2004) recommends ASA therapy as both primary and secondary prevention therapy for diabetic patients at increased cardiovascular risk.

With respect to the effect of antiplatelet therapy in specific subgroups generally, the ATT investigators state: “...these findings can reasonably be extrapolated to a far wider range

of high-risk patients than those studied...”, suggesting that studies in every subgroup of at-risk patients would not be warranted.

11.3 Meta-Analysis of Six High-Risk Trials (Secondary Prevention Trials)

To specifically address the effects of ASA in FDA-approved indications, Weisman and Graham (2002) identified a subset of studies in which secondary prevention patients were treated with low-dose ASA. Specifically, they identified all randomized, placebo controlled interventions with an ASA-only arm with low-dose ASA (defined as daily doses of 50 – 325 mg) for FDA-approved secondary prevention indications as summarized in the FDA’s 1998 rule (Federal Register, 1998). These uses included stroke in those with a previous history of stroke or TIA, and MI in those who had a previous MI or a history of angina.

Six studies were identified meeting these inclusion criteria (Elwood et al., 1974; Farrell et al., 1991; RISC Group, 1990; SALT Collaborative Group, 1991; Chen et al., 1991; Lewis, 1985). According to this analysis, among 6,300 patients, 2,427 experienced a previous MI and 1,757 had a history of TIA or stroke. Among the secondary prevention patients, there were 558 subsequent MIs, 424 strokes, and 91 other vascular events. All of the assessments demonstrated a trend in favor of ASA reducing the risks of cardiovascular events (MI) and cerebrovascular events (stroke) with relative risk reductions between 20% and 30%.

Risk ratio estimates from this meta-analysis are summarized in Table 10 below.

Table 10: Summary of Risk Ratio Estimates for 6 Studies Evaluating ASA for the Prevention of Stroke in High-Risk Patients

| Outcome | Risk Ratio (95%) | | Risk Reduction, % | Homogeneity P Value |
|-----------------------|---------------------|---------|-------------------|---------------------|
| | Confidence Interval | P Value | | |
| Death | 0.82 (0.7-0.99) | .03 | 18 | .7 |
| Vascular events | | | | |
| Vascular events* | 0.7 (0.6-0.8) | <.001 | 30 | <.001 |
| Myocardial Infarction | 0.7 (0.6-0.8) | <.001 | 30 | <.001 |
| Stroke | 0.8 (0.7-1.0) | .07 | 20 | >.99 |

Adapted from Weisman and Graham, 2002

**Myocardial Infarction, stroke and other vascular events, including vascular death (calculated).*

11.4 ASA Prevents Cardiovascular Events in Low to Moderate-Risk Populations

11.4.1 Description of Individual Randomized Studies Supporting the Effectiveness of ASA in the Prevention of a First MI

This Section summarizes the evidence that ASA prevents a first MI in apparently healthy individuals as well as in subjects selected for evaluation based on identified cardiovascular risk factors.

The effectiveness of low-dose ASA in the prevention of a first MI is supported by 5 prospective, randomized clinical trials conducted by independent researchers. These studies will be referred to throughout this document as follows:

- BDT: British Doctors' Trial (Appendix 9)
- HOT: Hypertension Optimal Treatment Trial (Appendix 10)
- PHS: Physicians' Health Study (Appendix 11)
- PPP: Primary Prevention Project (Appendix 12)
- TPT: Thrombosis Prevention Trial (Appendix 13)

The 5 primary prevention studies have been conducted in subjects with a variety of entry criteria, including elevated baseline cardiovascular risk in 3 of the studies. The data taken as a whole lend strong support to the view that ASA effectively prevents MI in low-risk populations and provide a critical anchor point for extrapolating the benefit of ASA to patients between this risk level and that of the high-risk group discussed above. Based on the considerable number of patients at intermediate levels of risk within these studies, it is possible to conclude with confidence that moderate-risk and high-risk patients do not differ in their response to ASA for MI prophylaxis (See Section 11.6 for discussion of evidence of effectiveness of ASA in patients at moderate CHD risk).

An overview of the above mentioned primary prevention studies, including their methodologies are summarized in the table below.

Table 11: Summary of Studies Evaluating ASA Prevention of First Cardiovascular Event

| Variable | BDT | PHS | TPT | HOT | PPP |
|-------------------------|---|------------------------------------|------------------------------------|---|---|
| Year | 1988 | 1989 | 1998 | 1998 | 2001 |
| Duration of therapy, † | 5.8 y | 5 y | 6.8 y | 3.8 y | 3.6 y |
| Patients (women), n | 5,139 (0) | 22, 071 (0) | 2,540 (0) | 18,790 (8,883) | 4,495 (2,583) |
| ASA therapy dose (N) | 500 mg/d 300 mg/d if later requested (3,429) | 325 mg qod (11,037) | 75 mg/d (cont. rel.) (1,268) | 75 mg/d (9,399) | 100 mg/d (2,226) |
| Control (N) | No placebo (1,710) | Placebo (11,034) | Placebo (1,272) | Placebo (9,391) | No placebo (2,231) |
| Additional therapies | None | β-Carotene (50% of patients) | Warfarin‡ | Felodipine with or without ACE inhibitor or β- blocker | Vitamin E |
| Subjects | Healthy males | Healthy males | Men at high-risk for CHD | Men and women with DBP 100-115 mm Hg | Men and women with >1 risk factors for CHD |
| Age | <60 y (46.9%); 60-69y (39.3%); 70-79 y (13.9%) | Mean, 53 y (range, 40-84 y) | Mean, 57.5 y (range, 45-69 y) | Mean, 61.5 y (range, 50-80 y) | <60 y (29%); 60-69 y (45%); 70-79 y (24%) |

BDT: British Doctors' Trial (Hennekens and Buring, 1994; Peto et al., 1988); HOT: Hypertension Optimal Treatment Trial (Hansson and Zanchetti, 1995); PHS: Physicians' Health Study (Steering Committee of the Physicians' Health Study, 1989); PPP: Primary Prevention Project (De Caterina, 2001; Collaborative Group of the Primary Prevention Project, 2001); TPT: Thrombosis Prevention Trial (FitzGerald and Charman, 1998; Medical Research Council's General Practice Research Framework, 1998).

† Values given are means except for the TPT value, which is the median.

‡ Data from patients who received warfarin are not included in this table.

It is important to note that these trials were conducted by independent researchers in different parts of the world as separate but related research initiatives. This explains the differences in study designs, populations, primary objectives, ASA doses, and other differences between trials.

Across these trials, a total of 2,402 CVD endpoints occurred among nearly 55,000 randomized participants, including 11,466 women. There was no significant evidence of heterogeneity among the trials.

The results from the individual studies evaluating the effectiveness of ASA in the prevention of MI will be presented, followed by analysis of the findings in aggregate from a number of comprehensive meta-analyses.

A brief description of each individual trial evaluating the effectiveness of ASA in the primary prevention of MI is provided in this section.

11.4.1.1 Physicians' Health Study (PHS)

The PHS was a randomized, double-blind, placebo controlled prevention trial of 22,071 healthy male U.S. physicians, using a factorial design to evaluate the role of low-dose ASA (325 mg every other day) in the prevention of cardiovascular mortality and beta-carotene in the reduction of cancer incidence. The study, initiated in 1982, was designed to test two primary prevention hypotheses in a population of healthy male physicians: (1) whether ASA in low-doses reduces mortality from CVD; and (2) whether beta-carotene decreases the incidence of cancer. Although the beta-carotene portion of the study continued, the ASA component was terminated on January 25, 1988 after approximately 5 years of study (3 years ahead of schedule).¹

Subjects were randomly assigned to one of four treatment groups: (a) ASA and beta-carotene; (b) ASA and beta-carotene placebo; (c) ASA placebo and beta-carotene; and (d) ASA placebo and beta-carotene placebo. Altogether 11,037 physicians were randomly assigned to receive ASA and 11,034 to receive ASA placebo.

After five years of follow-up, the reported use of ASA or other platelet-active drugs was 85.7% in the ASA group and 14.2% in the placebo group. At this time, the investigators reported 139 MIs among those taking ASA and 239 among those taking placebo. This represents a 44% reduction in risk (RR=0.56; 95% CI=0.45-0.70; $p<0.00001$). The incidence of fatal MI was also significantly lower with ASA therapy compared to placebo (10 vs. 26, respectively; RR=0.34; CI=0.15-0.75; $p=0.007$). Finally, the incidence of nonfatal MI was significantly reduced in those patients exposed to ASA by 41% (129 vs. 213, respectively; RR=0.59; CI=0.47-0.74). The relevant MI data are compiled in the table below.

¹ Several factors were considered by the Data Monitoring Board in the decision to terminate, including a cardiovascular mortality rate markedly lower than expected in both ASA and placebo subjects, precluding the evaluation of the primary ASA hypothesis, as well as the highly significant ($p<0.00001$) and impressive 44% reduction (relative risk 0.56; 95% CI 0.45 - 0.70) in the risk of first myocardial infarction in the ASA group.

Table 12: Confirmed Cardiovascular End Points in the ASA Component of the Physicians' Health Study, According to Treatment Group

| End Point | ASA Group | Placebo Group | Relative Risk | 95% Confidence Level | |
|-----------------------------|-----------|---------------|---------------|----------------------|----------|
| | | | | P Value | |
| Type of MI | | | | | |
| Fatal | 10 | 26 | 0.34 | 0.15-0.75 | 0.007 |
| Nonfatal | 129 | 213 | 0.59 | 0.47-0.74 | <0.00001 |
| Total | 139 | 239 | 0.56 | 0.45-0.70 | <0.00001 |
| Person-years of observation | 54,560.0 | 54,355.7 | -- | -- | -- |

Adapted from the Steering Committee of the Physicians' Health Study, 1989

* Additional events that could not be confirmed because records were not available included 17 myocardial infarctions (10 in the ASA group and 7 in the placebo group)

No reduction in mortality from all CV causes was associated with ASA use (RR=0.96; 95% CI=0.60; p=0.87). However, a combined endpoint consisting of nonfatal MI, nonfatal stroke and death from a CV cause yielded a statistically significant 18% reduction in those who were assigned to ASA (RR=0.82; 95 % CI=0.70-0.96; p=0.01).

After the ASA portion of the study was terminated in 1988 (following five years of study), the population was evaluated seven years later (Cook et al., 1999). At this time point, 99.7% of participants were providing morbidity information, and mortality information was complete for all but 1 of the 22,071 participants. At that time, 78.7% of participants were still taking beta-carotene or placebo.

In order to obtain information about the effect of ASA after the randomization period, the investigators questioned all participants about self-selected ASA use and obtained the following data:

- 59.5% reported taking ASA at least 180 days during the past year;
- 11.6% reported taking ASA 121 to 179 days during the past year;
- 8.1% reported taking ASA 14 to 120 days during the past year; and
- 20.8% reported taking ASA 0 to 13 days during the past year.

The investigators were able to use these data to evaluate the relationship between self-selected post-trial ASA use with subsequent CHD events and mortality in the period from 7 to 12 years of follow-up among those with no CHD before this time. During the five-year post-trial follow-up period, there were 311 reports of MI, 266 strokes (including 185 ischemic and 34 hemorrhagic), 205 cardiovascular-related deaths, and 782 total deaths.

During the five-year follow-up, there was a statistically significant 28% lower rate of MI

in self-reported frequent ASA users (≥ 180 d/y) compared with the nonusers (0-13 d/y) (RR = 0.72; 95% CI=0.55-0.95). This 28% reduction, therefore, confirms and extends the 44% reduction observed during the randomization period.

In the PHS, a significant reduction in CVD-related mortality with self-selected ASA use (RR = 0.65; 95% CI=0.4–0.89) was also observed, resulting in a benefit in total mortality (RR = 0.64; CI=0.54–0.77). These findings were not seen during the randomization period, suggesting that the original observation period was not sufficiently long to obtain a meaningful mortality benefit.

11.4.1.2 British Doctors' Trial (BDT)

In this study involving 5,139 physicians, ASA was administered for an average of 4 years. The study was randomized but not placebo controlled: 3,429 of the doctors were assigned ASA (500 mg/day ordinary, soluble or effervescent ASA or 300 mg enteric-coated ASA tablets), while the remaining 1,710 doctors were to avoid ASA. No differences in the incidences of MI or stroke were observed. However, total mortality was 10% lower in the ASA group than in the control group, but this difference was not statistically significant. The incidence of cerebral TIAs was significantly reduced to 15.9% in the ASA group compared to 27.5% in the control group.

The authors themselves attributed the lack of significance on their main objective to the fact that during the study period 30% of the participants in the ASA group ceased taking ASA whereas 12% in the control group abandoned their regimen and started taking ASA. The final evaluation, however, had to be based on the original assignment of the subjects to the two groups at the time of randomization. The fact that so many doctors changed from one group to the other meant that the results of ASA therapy were diluted while the control group results appeared to be better than they really were. Moreover, it is logical to assume that for healthy individuals, a much larger sample size is necessary to demonstrate any clinically relevant effect on the incidence of vascular events.

11.4.1.3 Thrombosis Prevention Trial (TPT)

The aim of the TPT was to evaluate low-dose ASA and low-intensity oral anticoagulation with warfarin in the primary prevention of ischemic heart disease (IHD) in a moderate-risk population. The primary endpoint was all IHD, defined as the sum of fatal and nonfatal events (i.e. coronary death, and fatal MI, and nonfatal MI). Treatment effects on fatal and nonfatal MI were also separately examined. Fatal IHD was defined as the sum of coronary death and fatal MI (death within a month), since there was often little distinction between the clinical and pathological characteristics of the two groups. Stroke was a secondary endpoint, with results for thrombotic and hemorrhagic events distinguished as far as possible, depending on whether appropriate imaging or necropsy findings were available.

A total of 5,499 men aged between 45 and 69 years were recruited from 108 practices in the UK that belonged to the Medical Research Council's General Practice Research Framework. Initially, warfarin or placebo was randomly allocated to 1,427 men; 1,013 of

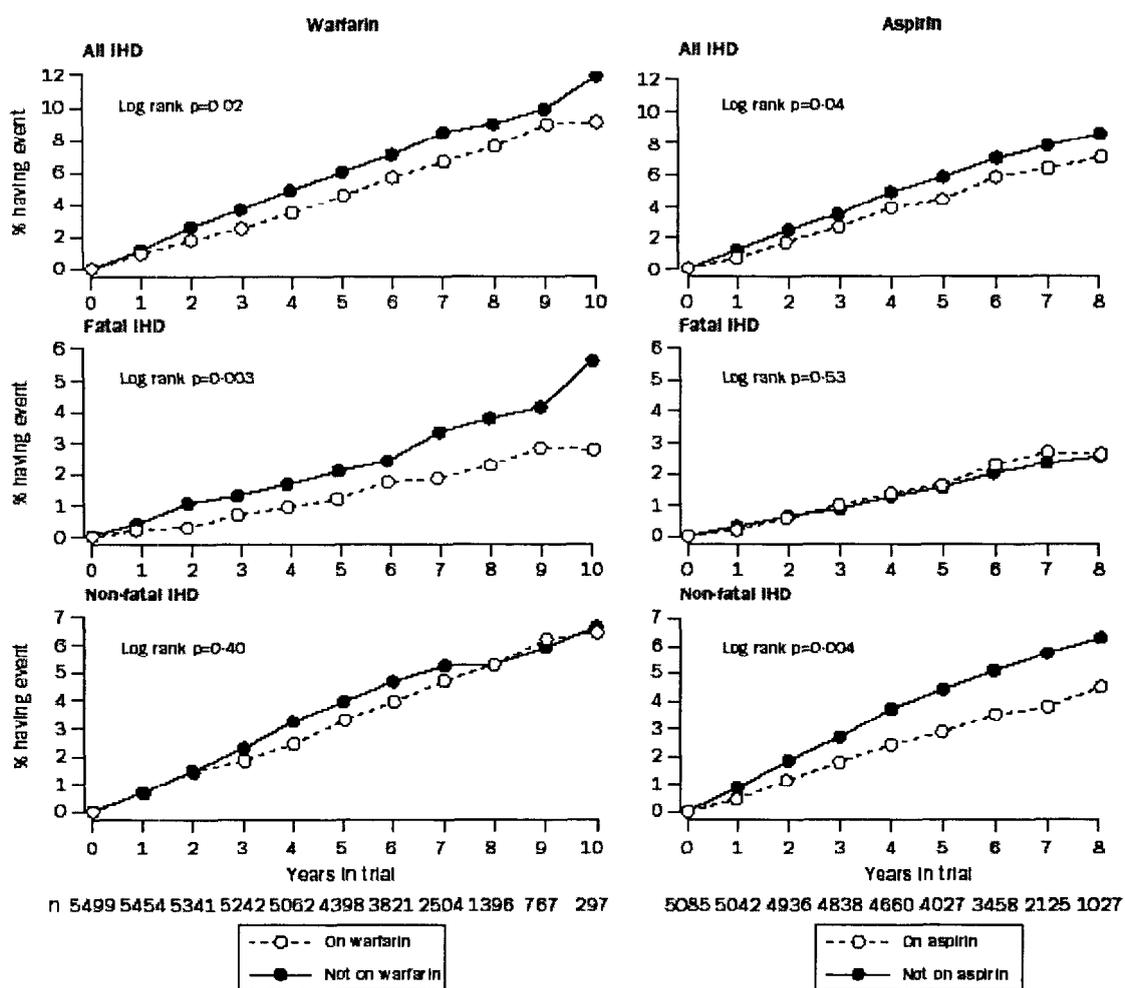
these men later moved to a factorial stage of the trial, retaining their warfarin or placebo-warfarin allocation and adding randomly allocated active or placebo ASA. Another 4,072 men entered directly into the factorial stage of the trial making a total of 5,085 men in the trial.

The four factorial treatment groups were: active ASA and active warfarin (WA; n = 1,277), active ASA and placebo warfarin (A; n = 1,268), active warfarin and placebo ASA (W; n = 1,268), and placebo warfarin and placebo ASA (P; n = 1,272). Subjects in this trial received 75 mg/day controlled release ASA.

The participants were regarded as being at moderate-high-risk of ischemic heart disease at entry, defined as the top 20% of a risk score distribution based on smoking history, blood pressure, body mass index, blood cholesterol, fibrinogen and factor VII activity. These variables were weighted according to their relationship with ischemic heart disease in the Northwick Park Heart Study (Meade et al., 1986). The observation period was 8 to 13 years with median participation 6.8 years.

The primary effect of low-dose ASA was a 32% reduction in nonfatal MI ($p=0.004$). This robust finding was largely responsible for the 20% reduction of all IHD ($p=0.04$). The findings are summarized in the figure below.

Figure 9: Cumulative Proportion (%) of Men with IHD, Main Effects (Figure 2 from TPT Study)



Adapted from the Medical Research Council's General Practice Research Framework, 1998

The results of the TPT Study clearly confirm the effectiveness of ASA in the prevention of MI in persons chosen based on a moderate-risk profile resulting from the presence of multiple cardiovascular risk factors. ASA had no effect on stroke or total mortality in this study.

11.4.1.4 Hypertension Optimal Treatment Study (HOT)

The main objectives of the Hypertension Optimal Treatment (HOT) Study were to evaluate the effects of antihypertensive and antiplatelet therapy on the incidence of adverse cardiovascular outcomes. The investigators aimed to assess the optimum target diastolic blood pressure and the potential benefit of low-dose ASA (75 mg daily) in addition to the medical treatment of hypertension.

In this trial, 18,790 patients (including 8,883 women) from 26 countries were randomly

assigned a target blood pressure of ≤ 90 mmHg, ≤ 85 mmHg or ≤ 80 mmHg. The average follow-up time was 3.8 years (range: 3.3 to 4.9 years) and the total number of patient-years was 71,051. The age of patients ranged from 50 to 80 years (mean: 61.5 years); 53% were male, 47% female. If necessary, felodipine was given as a baseline therapy plus other hypertensive agents, according to a five-step regimen. A total of 9,399 patients were randomly assigned low-dose ASA and 9,391 patients were assigned placebo.

ASA reduced the total MI endpoint (combined fatal and nonfatal MI) by 36% ($p=0.002$). It should be noted, however, that the effects of ASA on major cardiovascular events and on MI were no longer significant when silent MIs were included in the analysis. However, silent MIs were not included as endpoints in any of the other randomized controlled studies examining the role of ASA in the prevention of cardiovascular events in high-risk or low-risk patients with ASA. The consensus of investigators in the field is that the analysis is most appropriate without the inclusion of silent MI, as this endpoint represents a very different clinical picture than a documented clinical event.

ASA also exerted a statistically significant reduction in major cardiovascular events by 15% ($p=0.03$). It should be noted that there were no differences in antihypertensive therapy between the ASA and the placebo group. The relevant risk reductions are provided below. Importantly, many of the patients that reached their assigned target blood pressure in the study would be considered hypertensive by today's standards (JNC-7), further highlighting the utility of ASA in this population.

Table 13: Risk Reductions for Prevention of Cardiovascular Events in the HOT Study

| Events | Number of events | Events/1,000 patient-years | p | Relative risk (95% CI) |
|---|------------------|----------------------------|-------|------------------------|
| Major cardiovascular events | | | | |
| Acetylsalicylic acid | 315 | 8.9 | | |
| Placebo | 368 | 10.5 | 0.03 | 0.85 (0.73-0.99) |
| Major cardiovascular events, including silent MI | | | | |
| Acetylsalicylic acid | 388 | 11.1 | | |
| Placebo | 425 | 12.2 | 0.17 | 0.91 (0.79-1.04) |
| All MI | | | | |
| Acetylsalicylic acid | 82 | 2.3 | | |
| Placebo | 127 | 3.6 | 0.002 | 0.64 (0.49-0.85) |
| All MI, including silent cases | | | | |
| Acetylsalicylic acid | 157 | 4.4 | | |
| Placebo | 184 | 5.2 | 0.13 | 0.85 (0.69-1.05) |
| All stroke | | | | |
| Acetylsalicylic acid | 146 | 4.1 | | |
| Placebo | 148 | 4.2 | 0.88 | 0.98 (0.78-1.24) |
| Cardiovascular mortality | | | | |
| Acetylsalicylic acid | 133 | 3.7 | | |
| Placebo | 140 | 3.9 | 0.65 | 0.95 (0.75-1.20) |
| Total mortality | | | | |
| Acetylsalicylic acid | 284 | 8.0 | | |
| Placebo | 305 | 8.6 | 0.36 | 0.93 (0.79-1.09) |

Adaped from Hansson et al., 1998

Events in relation to acetylsalicylic acid (n=9,399) or placebo (n=9,391)

It must be emphasised that HOT is the first trial to demonstrate a beneficial effect of low-dose ASA in addition to antihypertensive therapy in the prevention of MI and major cardiovascular events in patients with treated high blood pressure. As the number of patients who had a previous cardiovascular event was small (1.6% had a previous MI, 1.2% had a previous stroke, and approximately 6% had other previous CHD), the HOT Study can be regarded as a major primary prevention study. In addition to high blood pressure, approximately 16% of the HOT Study population were smokers and 8% suffered from diabetes mellitus.

11.4.1.5 Primary Prevention Project (PPP)

The aim of the Primary Prevention Project (PPP) was to investigate the efficacy of 100 mg ASA per day provided as enteric-coated tablets and/or vitamin E (300 mg/day) in the primary prevention of cardiovascular events in addition to the treatment of specific risk factors. In this study, 4,495 subjects (57.4% women; mean age 64.4 years) with at least

one vascular risk factor (e.g., old age, hypertension, diabetes, obesity, hypercholesterolemia, and family history of premature MI) were included in an open, randomized, controlled 2x2 factorial design. The primary endpoint was the cumulative rate of cardiovascular death, nonfatal MI and nonfatal stroke. Secondary endpoints were each component of the primary endpoint, total deaths and other CVD events. Most of the participants were screened for eligibility by general practitioners.

The trial was prematurely stopped for ethical reasons because newly available evidence from the Thrombosis Prevention Trial and the HOT Study on the benefit of ASA in primary prevention was strictly consistent with the results of the second interim analysis after a mean follow-up of 3.6 years.

Specifically, ASA lowered the frequency of all endpoints, being significant for cardiovascular deaths (RR=0.56; 95% CI=0.31–0.99; p=0.049) and for any cardiovascular events including cardiovascular death, nonfatal MI, nonfatal stroke, TIA, angina pectoris, peripheral artery disease and revascularisation procedures (RR=0.67; 95% CI=0.62–0.95; p=0.014). Because vitamin E showed no effect on any pre-specified endpoint, it could be argued that the vitamin E group served as a “placebo control.”

The relevant risk reduction data are presented below in a copy of the table extracted from the publication.

Table 14: Relative Risk Reductions with ASA and Vitamin E Treatment

| | ASA (n=2,226) | No ASA (n=2,269) | Relative risk (95% CI) | Vitamin E (n=2,231) | No vitamin E (n=2,264) | Relative risk (95% CI) |
|--|------------------|---------------------|---------------------------|------------------------|---------------------------|---------------------------|
| Main combined endpoint (cardiovascular death, nonfatal MI, and nonfatal stroke) | 45 (2.0%) | 64 (2.8%) | 0.71 (0.48-1.04) | 56 (2.5%) | 53 (2.3%) | 1.07 (0.74-1.56) |
| Total cardiovascular events of diseases* | 141 (6.3%) | 187 (8.2%) | 0.77 (0.62-0.95) | 158 (7.1%) | 170 (7.5%) | 0.94 (0.77-1.16) |
| All deaths | 62 (2.8%) | 78 (3.4%) | 0.81 (0.58-1.13) | 72 (3.2%) | 68 (3.0%) | 1.07 (0.77-1.49) |
| Cardiovascular | 17 (0.8%) | 31 (1.4%) | 0.56 (0.31-0.99) | 22 (1.0%) | 26 (1.1%) | 0.86 (0.49-1.52) |
| Non-cardiovascular | 45 (2.0%) | 47 (2.0%) | 0.98 (0.65-1.46) | 50 (2.2%) | 42 (1.9%) | 1.21 (0.80-1.81) |
| All MI | 19 (0.8%) | 28 (1.2%) | 0.69 (0.38-1.23) | 22 (1.0%) | 25 (1.1%) | 0.89 (0.52-1.58) |
| Nonfatal MI | 15 (0.7%) | 22 (1.0%) | 0.69 (0.36-1.33) | 19 (0.8%) | 18 (0.8%) | 1.01 (0.56-2.03) |
| All stroke | 16 (0.7%) | 24 (1.1%) | 0.67 (0.36-1.27) | 22 (1.0%) | 18 (0.8%) | 1.24 (0.66-2.31) |
| Nonfatal stroke | 15 (0.7%) | 18 (0.8%) | 0.84 (0.42-1.67) | 20 (0.9%) | 13 (0.6%) | 1.56 (0.77-3.13) |
| Angina pectoris | 54 (2.4%) | 67 (3.0%) | 0.82 (0.58-1.17) | 66 (3.0%) | 55 (2.4%) | 1.22 (0.86-1.73) |
| Transient ischaemic attack | 28 (1.3%) | 40 (1.8%) | 0.71 (0.44-1.15) | 33 (1.5%) | 35 (1.5%) | 0.96 (0.60-1.53) |
| Peripheral-artery disease | 17 (0.8%) | 29 (1.3%) | 0.60 (0.33-1.08) | 16 (0.7%) | 30 (1.3%) | 0.54 (0.30-0.99) |
| Revascularisation procedure | 20 (0.9%) | 29 (1.3%) | 0.70 (0.40-1.24) | 27 (1.2%) | 22 (1.0%) | 1.25 (0.71-2.18) |

Adapted from the Collaborative Group of the Primary Prevention Project, 2001

All data are presented as, n (%) unless otherwise indicated. *Participants with one or more of the following events: cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, angina pectoris, transient ischaemic attack, peripheral-artery disease, revascularisation procedure.

In summary, the PPP adds to the evidence that low-dose ASA is effective in the prevention of cardiovascular events, especially MI, in persons at increased CHD risk. The risk factors investigated included hypertension, diabetes, hyperlipidemia, old age, family history and others. It must be emphasised that the beneficial effects of ASA occurred in addition to the treatment of these specific risk factors in individual patients.

The authors interpreted the study results as follows: "In women and men at risk of having a cardiovascular event because of the presence of at least one major risk factor, low-dose ASA given in addition to treatment of specific risk factors contributes an additional preventive effect, with an acceptable safety profile."

11.5 Description of Meta-Analyses Supporting the Effectiveness of ASA in the Prevention of First MI

11.5.1 Published Meta-Analysis of Low-Risk Trials

A number of meta-analyses have been conducted using data from the 5 primary prevention studies and have reached similar conclusions. The most recent of the published analyses, conducted by Eidelman and colleagues used a computerized search of the English literature from 1988 to 2002 to identify 5 published randomized trials of ASA in the primary prevention of CHD (Eidelman et al., 2003). To perform the meta-analysis, the investigators used the published data from the PHS, the BDT, the TPT, the HOT study, and the PPP. The outcomes examined were a combined endpoint of any important vascular event (nonfatal MI, nonfatal stroke, or vascular death), and each of these individual components separately.

The criteria for inclusion of trials were as follows: (1) ASA alone was used for the primary prevention of CHD, as opposed to combined interventions; (2) comparisons of outcomes were made between ASA groups and either placebo or open control groups; and (3) data were available on MI, stroke, and vascular deaths. Eidelman and colleagues' complete analysis report can be found in Appendix 14.

11.5.1.1 Meta-Analysis – Nonfatal MI

Eidelman and colleagues reported a statistically significant risk reduction of 32% for nonfatal MI associated with ASA therapy (RR=0.68; 95% CI=0.59-0.79). A tabular summary of the data making up this analysis is presented in the Table 15 below.

Table 15: Nonfatal Myocardial Infarction (MI) in the Randomized Trials of ASA in the Primary Prevention of Cardiovascular Disease

| Trial | ASA | | Control | |
|------------------------|--------------------|---------------------------|-------------------|---------------------------|
| | Nonfatal MI (No.) | Subjects Randomized (No.) | Nonfatal MI (No.) | Subjects Randomized (No.) |
| PHS | 129 | 11,037 | 213 | 11,034 |
| BDT | 80 | 3,429* | 41 | 1,710* |
| TPT | 94 | 2,545 | 137 | 2,540 |
| HOT | - | - | - | - |
| PPP | 15 | 2,226 | 22 | 2,269 |
| Total | 318 | 19,237 | 413 | 17,553 |
| Relative Risk (95% CI) | 0.68 (0.59 – 0.79) | | | |

Adapted from Eidelman, 2003

* A 2:1 randomization of ASA to control was used

11.5.1.2 Meta-Analysis: Any Important Vascular Event

The meta-analysis also reported a statistically significant 15% reduction in the risk of any important vascular event associated with ASA therapy (RR=0.85; 95% CI=0.79-0.93), driven in large part by the statistically extreme finding of reduced MI risk. A tabular summary of the important data contributing to this analysis is presented below.

Table 16: Any Important Vascular Event in the 5 Randomized Trials of ASA in the Primary Prevention of Cardiovascular Disease

| Trial | ASA | | Control | |
|------------------------|------------------------------------|----------------|------------------------------------|----------------|
| | Any Important Vascular Event (No.) | Subjects (No.) | Any Important Vascular Event (No.) | Subjects (No.) |
| PHS | 307 | 11,037 | 370 | 11,034 |
| BDT | 289 | 3,429 | 147 | 1,710 |
| TPT | 228 | 2,545 | 260 | 2,540 |
| HOT | 315 | 9,399 | 368 | 9,391 |
| PPP | 47 | 2,226 | 71 | 2,269 |
| Total | 1,186 | 28,636 | 1,216 | 26,944 |
| Relative Risk (95% CI) | 0.85 (0.79 – 0.93) | | | |

Adapted from Eidelman, 2003

11.5.1.3 Meta-Analysis: Vascular Death

For vascular deaths, there was no significant reduction in risk, although the confidence intervals were wide and included the plausible decrease seen in the trials of secondary prevention, as well as a small increase (RR=0.98; 95% CI=0.85-1.12).

11.5.1.4 Meta-Analysis: Stroke

It is difficult to interpret the overall effect of ASA on stroke because the effect differs for different types of stroke. Overall stroke rates were lower than expected (based on age and risk factors) in all 5 low-risk trials. In each trial, control participants who had not been given ASA had a less than 2% incidence of total strokes over 5 years. Because of the lower-than-expected stroke rates, the individual trials had a limited statistical power to reliably detect the true effect of ASA on stroke. Summary estimates showed no statistically significant reduction in total stroke overall (OR =1.02; 95% CI=0.85-1.23).

11.5.2 ATT Collaboration Primary Prevention Subgroup Meta-Analysis

Under the auspices of the Clinical Trial Service Unit (CTSU) of the University of Oxford, the Antithrombotic Trialists' Primary Prevention Group (ATT) was assembled in February 2001 to conduct a comprehensive meta-analysis based on individual patient data from the 5 available primary prevention trials. The principal investigators of each of the major trials agreed to collaborate in this meta-analysis in order to address additional questions that could not be answered by meta-analyses based on data derived from

publications alone. The meta-analysis was designed to assess the proportional effects of ASA on major cardiovascular outcomes (vascular events [as defined by nonfatal MI, nonfatal stroke, or vascular death], CHD events [nonfatal MI or CHD death], presumed ischemic stroke, hemorrhagic stroke, vascular or non-vascular causes of death, and major extracranial bleeds) and to compare these effects with the analogous results from long-term trials of ASA involving high-risk patients (secondary prevention). As individual primary prevention trials have suggested that the net effects of ASA might be different in certain populations, the effects of ASA on pre-specified subgroups (as defined by age, gender, smoking history, blood pressure, etc) were to be considered.

A particular goal of the collaboration was to assess whether there might be selected patients within the primary prevention studies that could be identified as being at moderate-risk (annual risk of 1-2%) of a CHD event, and to compare the effects of ASA in these individuals to that observed in a high-risk setting. The intent of this analytical approach was to determine if the benefit to risk relationship might be enhanced by restricting use to a group with risk of a CHD event greater than that generally observed in the primary prevention trials.

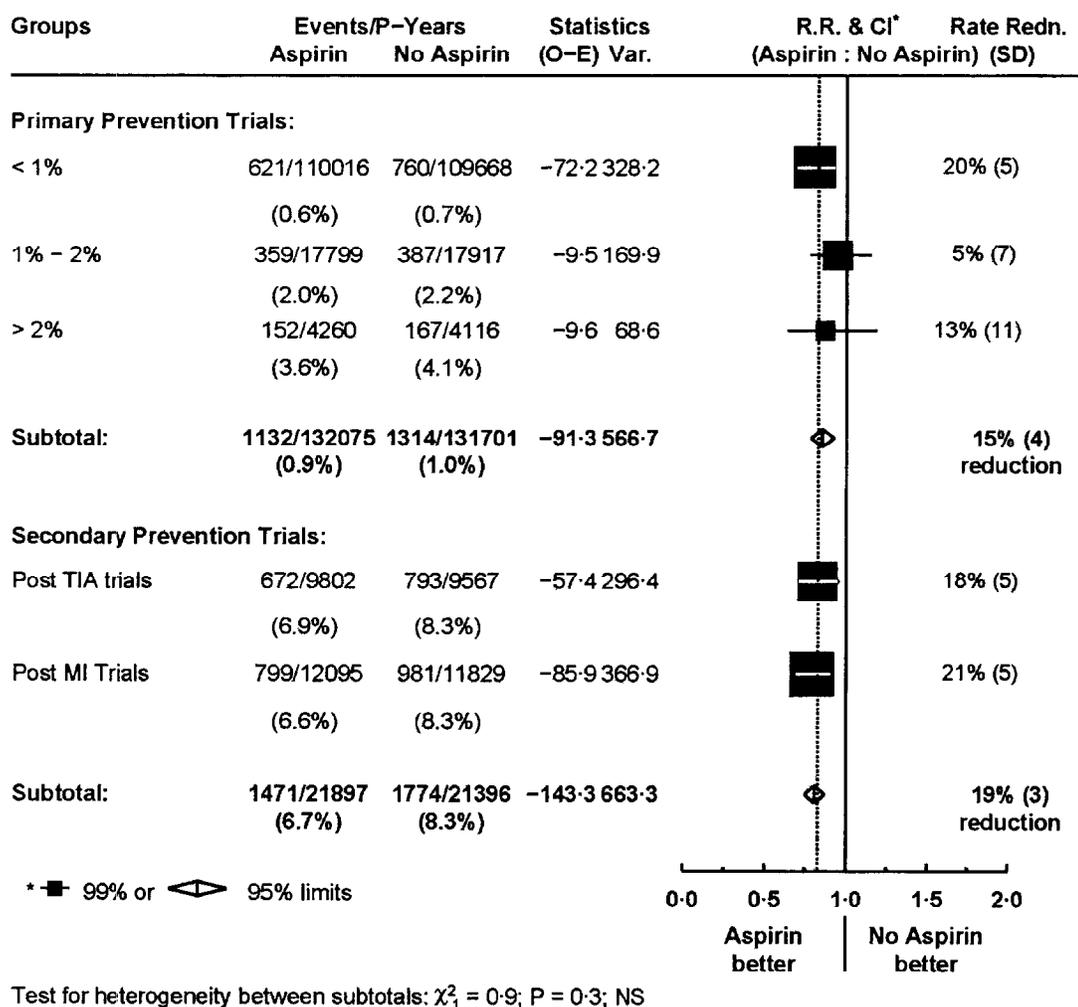
The ATT Primary Prevention Group recently met to discuss the implications for broader use of ASA based on the preliminary findings of the analyses set forth above. It is important to note that this analysis is based on the same 5 studies included in the literature-based meta-analysis under review by the FDA. While this work is still underway and not yet subjected to peer review, this collaborative work by the principal investigators of the primary prevention trials has helped to define the effects of ASA across different populations. It therefore clarifies the findings of the previously conducted meta-analysis (and other published analyses) submitted in consideration of the requested indication for the use of ASA in patients at increased risk of CHD events (as defined by a 10-year risk of at least 10%).

The complete report of the ATT Primary Prevention Group's meta-analysis will be submitted for publication shortly and simultaneously submitted to the FDA for review. In addition, the investigators have agreed to make raw data available to the agency as needed, utilizing the CTSU as a central clearing house for these data. While the data from the ATT analysis and commentary will be submitted separately to assure independence, this section provides a top line review of their findings.

11.5.2.1 Efficacy Overview

Overall, the ATT Primary Prevention Group analyses, which include 55,580 patients, demonstrate a statistically significant $15\% \pm 4$ reduction in vascular events (Figure 10) that was largely driven by a $23\% \pm 5$ reduced risk of CHD events.

Figure 10: ATT Primary Prevention – Effects on Vascular Events

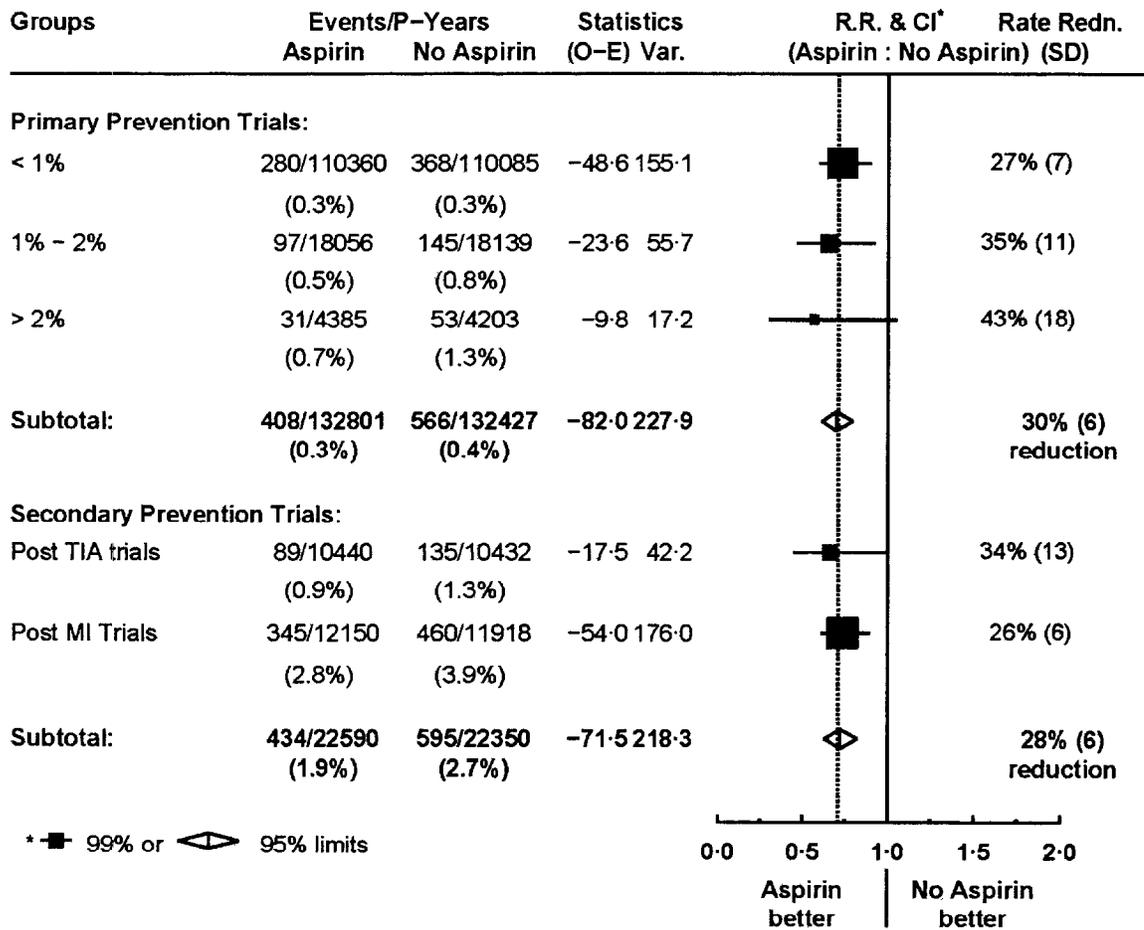


Adapted from FDA AC Presentation, December 8, 2003

As each of the studies included patients at a variety of baseline CHD risk levels, the data were further stratified to examine whether this the benefit accrued disproportionately to a particular risk strata. Specifically, patients whose annual risk was less than 1%, 1-2%, and greater than 2% were evaluated for each endpoint. Not surprisingly, the greatest number of patients was in the lowest risk group (corresponding to a less than 10% 10-year baseline risk), with over 100,000 person years of exposure to ASA. This is in contrast to the moderate-risk group (1-2% per annum) with approximately 18,000 person

years and roughly 4,000 patient-years in the high-risk (greater than 2% per annum) group. In spite of the difference in exposure, and hence the corresponding number of events, the benefits of ASA were not different for any of the endpoints as a function of underlying risk (Figure 11).

Figure 11: ATT Primary Prevention – Effects on Nonfatal MI

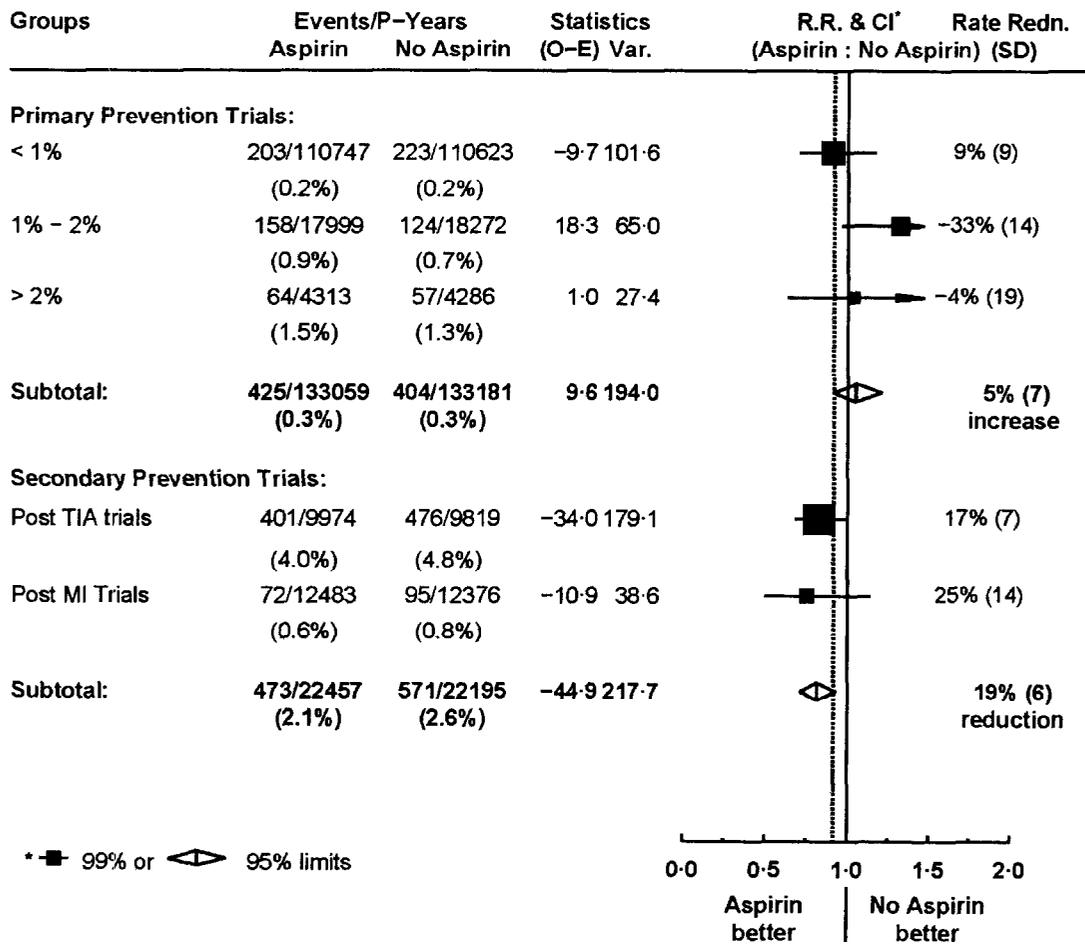


Test for heterogeneity between subtotals: $\chi^2_1 = 0.1$; $P = 0.7$; NS

Adapted from FDA AC Presentation, December 8, 2003

In contrast to the secondary prevention database, there was no net reduction in the risk of stroke (non-significant 5% increase) (Figure 12), and no reduction in vascular death (2% non-significant reduction) (Figure 13).

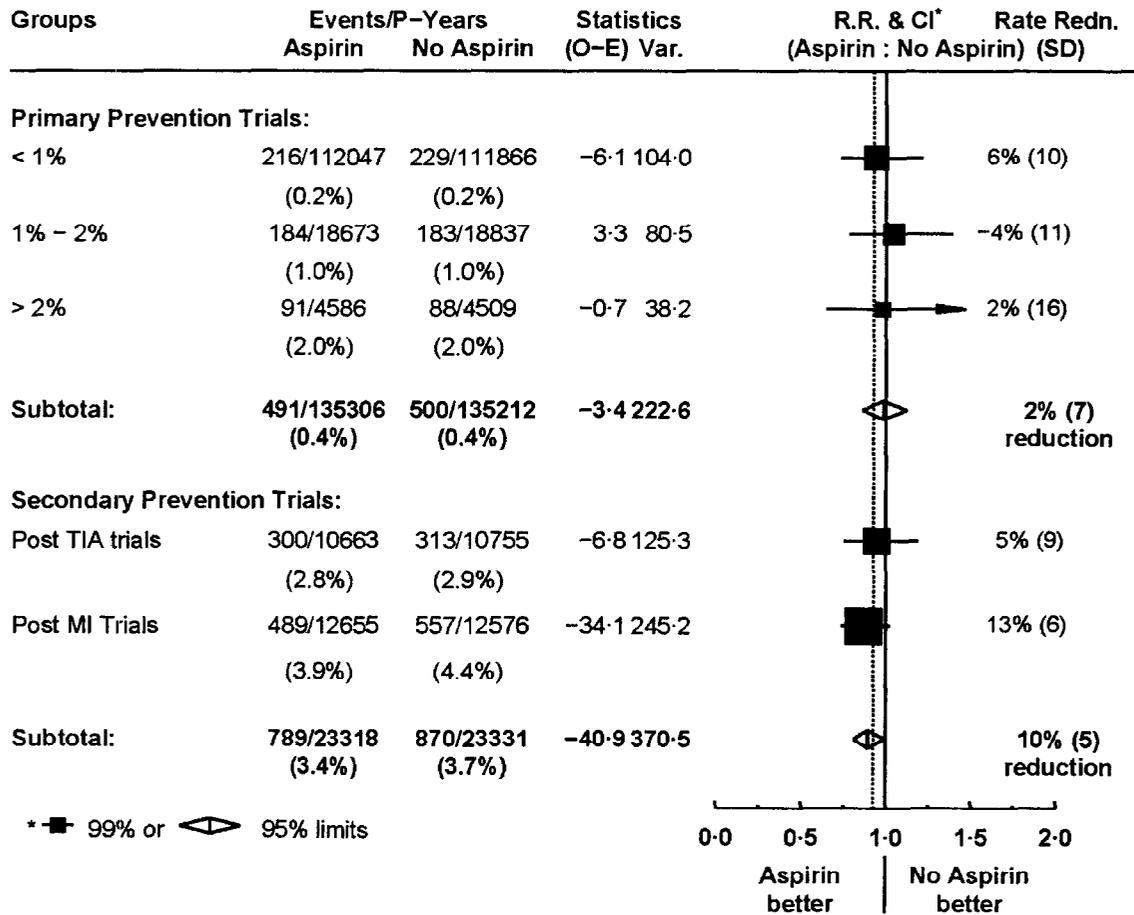
Figure 12: ATT Primary Prevention – Effects on Any Stroke



Test for heterogeneity between subtotals: $\chi^2_1 = 6.7$; $P = 0.01$

Adapted from FDA AC Presentation, December 8, 2003

Figure 13: ATT Primary Prevention – Effects on Vascular Death

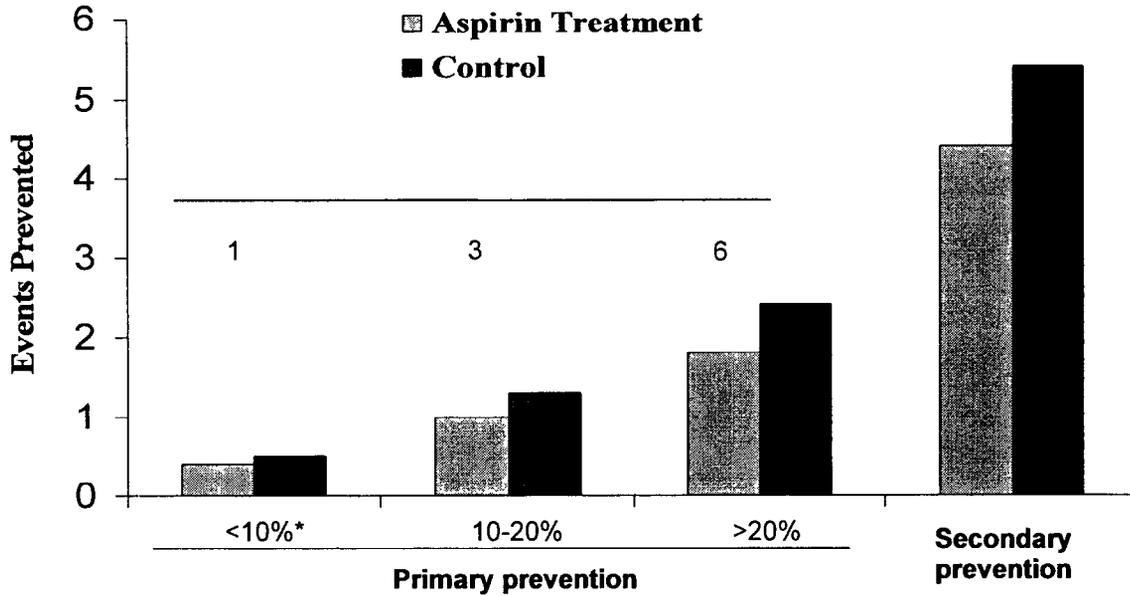


Test for heterogeneity between subtotals: $\chi^2_1 = 1.3$; $P = 0.3$; NS

Adapted from FDA AC Presentation, December 8, 2003

Based on this analysis, it might be expected that, among healthy low-risk individuals such as those generally studied in the 5 primary prevention trials, ASA would prevent approximately 5 CHD events for every 1,000 patients treated for 5 years. The actual number of MI events prevented increases to 14 per thousand patients treated for 5 years for moderate-risk patients and to more than 25 in patients at high-risk (20% or greater 10-year risk) (Figure 14).

Figure 14: Absolute Benefits of ASA on CHD Events in Primary and Secondary Prevention



*10 year baseline risk
 Adapted from FDA AC Presentaiton, December 8, 2003

The proportional, or relative risk reduction of about one quarter in CHD events appeared to be similar regardless of age, gender, history of hypertension, diabetes or atrial fibrillation, smoking, cholesterol levels, body mass index, or baseline risk of CHD. In addition, the one-quarter reduction in CHD events also appeared similar to that observed in previous trials for the secondary prevention of MI or of stroke among high-risk patients.

11.5.2.2 Subgroup Analysis

Gender

The initial 3 primary prevention trials were initiated in the early 1980's, while the HOT and PPP trials were initiated in the 1990's. The gender enrollment differences between the early vs. the later studies were reflective of the general regulatory policy in place at the time each study was conducted. Therefore, the vast majority of the subjects in the 5 primary prevention trials were men (41,569 participants) and thus the observed benefits are most easily generalizable to men.

Despite the preponderance of male subjects in the 5 trials, there were a substantial number of women represented across the trials. Two of the 5 primary prevention trials included women in the trials; HOT randomized 8,883 women and the PPP 2,583, for a total of 11,466 women. In HOT, subgroup analyses were presented for women and there was a possible but non-significant 19% reduction in risk of a first MI. In PPP, the authors reported that the magnitude of benefit in women and men equaled the overall

31% reduction in risk of a first MI. Thus, the overall point estimate of the reduction in risk of a first MI for women is about 22% (consistent with the overall benefits observed among the trials).

Age

The 5 primary prevention trials evaluated subjects over a variety of ages. A summary of the age ranges in each of the trials is provided below.

Table 17: Ages of Subjects

| Trial | Age Range |
|-------|---------------|
| BDT | < 60 y – 79 y |
| PHS | 40 – 84 y |
| TPT | 45 – 69 y |
| HOT | 60 – 80 y |
| PPP | < 60 y – 79 y |

BDT: *British Doctors' Trial* (Hennekens and Buring, 1994; Peto et al., 1988); HOT: *Hypertension Optimal Treatment Trial* (Hansson and Zanchetti, 1995); PHS: *Physicians' Health Study* (Steering Committee of the Physicians' Health Study, 1989); PPP: *Primary Prevention Project* (De Caterina, 2001; Collaborative Group of the Primary Prevention Project, 2001); TPT: *Thrombosis Prevention Trial* (FitzGerald and Charman, 1998; Medical Research Council's General Practice Research Framework, 1998).

It is evident from the Table that a broad range of ages were studied in these trials (through an upper range of 84 years old in the PHS) and therefore the results should be generalizable for individuals over 40 years of age.

Diabetes

The proportion of patients with diabetes mellitus was small in each trial (PPP: 17%; HOT: 8%; PHS: 2%; BDT: 2%; TPT: 2%). In PHS, patients with diabetes derived greater benefit from ASA than those without diabetes (RR=0.39 vs. 0.60) (Guise et al., 2002).

Hypertension

The influence of hypertension on the effectiveness of ASA therapy has been examined in subgroup analyses. In TPT, Meade et al., (1986) found that ASA reduced total cardiovascular events in patients whose systolic blood pressure (SBP) was less than 130 mmHg (RR=0.59) but not in patients whose SBP was greater than 145 mmHg (RR=1.08). Patients with SBP between 130 and 145 mmHg also had reduced risk (RR=0.68). In PHS, patients who were taking ASA and had SBP greater than 150 mmHg had a relative risk of 0.65 for MI, compared with relative risks of 0.55 for those with SBP between 130 and 149 mmHg and 0.52 for those with SBP between 110 and 129 mmHg. The largest study involving patients with hypertension, the HOT trial, found significant reductions in CHD events among patients with controlled hypertension. Importantly, many of the patients that reached their assigned target blood pressure in the study would be considered hypertensive by today's standards (JNC-7), further highlighting the utility of ASA in this population.

11.6 Inter- and Intra- Studies Breakdown by Risk

Evidence from 4 studies evaluating low-risk patients (BDS, PHS, HOT, and PPP), and one study evaluating *moderate-risk* patients (TPT), along with the secondary prevention database, confirms that ASA reduces the risk of MI at all risk levels, albeit driven largely by reductions in the more common form – nonfatal MI (2/3 of all MIs).

There is substantial evidence of safety and efficacy in the intended moderate-risk population and both intra- and inter- study analyses confirm that equivalent benefits (e.g., risk reductions) are seen regardless of baseline global risk. Over 36,000 patient-years of evaluation are included in the primary prevention database, including patients from a large study (TPT) that had as its specific aim inclusion of patients at baseline moderate-risk.

While the patients' average risk level in 4 of the 5 studies was deemed to be low, all 5 studies included patients at various levels of risk (see Table 18).

Table 18: Patient Enrollment by Underlying CHD Risk Per Year

| | <1% | 1-2% | >2% | TOTAL | <1% | 1-2% | >2% | TOTAL |
|--------------|---------------|--------------|--------------|---------------|------------|------------|-----------|-------------|
| BDS | 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% |

The request for an indicated use in patients whose CHD risk is at least moderate is based on the desire to enhance the benefit to risk relationship by restricting use to those where this relationship is appropriately favorable. It is not based on lack of effectiveness in the low-risk study population as defined by the 5 primary prevention studies.

Specific evaluation of moderate-risk patients confirms a reduced risk of nonfatal MI of 35% (Table 19).

Table 19: Risk Reductions Compared to Global Risk

| Global Risk | ASA | | Placebo | | RR |
|-------------|--------|-----------------|---------|-----------------|----------|
| | 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) |

The TPT trial, which specifically included patients deemed to be at moderate-risk or greater (>10%), demonstrates nonfatal MI risk reductions equivalent to the other 4 primary prevention studies (32%).

- Based on its size and design, TPT should be viewed as pivotal and supported by the other four studies for the use of ASA to prevent MI in moderate-risk patients.
- The statistical review of TPT undertaken by the FDA appears to contain a number of inaccuracies, which has led to an apparent erroneous conclusion regarding the benefit to risk findings of this study. A more thorough review of this study appears to be warranted.
- A single study has been used to support other approved ASA indications. Most recently, the single Swedish Angina Pectoris Aspirin Trial (SAPAT) formed the basis of the FDA approval of aspirin for chronic stable angina in 1998.

The final decision as to which patients should be considered for ASA preventative therapy based on their particular level of risk requires a benefit-risk evaluation.

11.7 ASA Resistance

As there has been recent discussion on the potential for certain patients to be “resistant” to the cardioprotective effects of ASA that could adversely impact the review of the efficacy of ASA for the primary prevention of MI, a review of this issue is provided. It is important to be aware that the issue of variable response is not unique to ASA, and that the available evidence is in no way indicative of a diminution of therapeutic effectiveness over time, as has been observed for antibiotics. As such the term “resistance” is a misnomer and is better described as variable response. As outlined below, concerns related to lack of effectiveness of ASA should in no way impact the broadening of the indications for ASA to reduce the risk of MI in patients at moderate-risk or greater.

11.7.1 Defining ASA Resistance

The term “ASA resistance” has been loosely defined as the occurrence of cardiovascular events despite regular ASA intake at recommended doses (Weber et al., 2002). This definition also applies to treatment failures that occur with a myriad of other cardiovascular drugs such as beta-blockers, angiotensin converting enzyme inhibitors, statins, as well as other antiplatelet agents (Hennekens et al., 1996). In terms of secondary prevention, the clinical effectiveness of ASA has been clearly demonstrated and is comparable to the aforementioned drugs, in that they all reduce nonfatal CVD events between 25-30% and fatal events by about 15-20% in randomized trials (Hennekens et al., 1996). On the other hand, these results suggest that 70-75% of nonfatal and 80-85% of fatal events are not prevented by any of these drugs (Hankey et al., 2004). Thus the results of the previously mentioned drugs correspond to a slight reduction in risk that can be regarded as clinically useful.

Currently, biochemical laboratory evaluations of platelet function have been the most commonly utilized methods of determining “ASA resistance” or variable response.

While thrombosis is the usual cause of nearly all occlusive vascular events, other relevant factors, such as interactions with monocytes and vascular function could also potentially contribute to a cardiovascular event (Davies, 1996; Halcox et al., 2002; Sarma et al., 2002). The impact of testing platelet aggregation *ex vivo* gives little knowledge on its effectiveness in a clinical model. Thus, the term “ASA resistance” with respect to identification by means of platelet function is relatively inadequate in reference to offering a credible basis for either clinical diagnosis and/or decision-making.

11.7.2 Epidemiological Studies

The current epidemiological evidence for “ASA resistance” is derived from a case series and an observational analytic study (Gum et al., 2001; Halushka et al., 2003). In the observational analytic study, “ASA resistance” was looked at in reference to the incidence of cardiovascular events in a high-risk population (Eikelboom et al., 2002). The patients included were 970 of the subjects from the HOPE study whose baseline urinary 11-dehydro thromboxane B₂ was measured and recorded. Urinary 11-dehydro thromboxane B₂ was measured in order to determine the extent of the inhibition of thromboxane A₂ generation, which in this study was defined as “ASA resistance” (Eikelboom et al., 2002). After a five year follow-up, the patients with urinary 11-dehydro thromboxane B₂ levels in the highest quartile had a significantly greater risk for the composite endpoint which included nonfatal MI, nonfatal stroke, and cardiovascular death (OR=1.8; 95% CI=1.2-2.7), with significant increases in both MI and cardiovascular death compared to those in the lowest quartile (Eikelboom et al., 2002).

There are a number of issues that could explain the findings, independent of a lack of effectiveness. For instance, the compliance aspect of this study was addressed by physician questioning at each follow-up visit; however this was never confirmed by any type of objective measurement and therefore cannot be considered highly reliable. Additionally, the dose of the ASA being taken in this study was never specified, nor was any information obtained on possible drug-drug interactions, such as concurrent NSAID use, in the patients involved. There are multiple possible sources of bias in this study mainly stemming from the fact that this is an attempt to link an analysis of a pharmacological response to a clinical outcome after the initial study was already concluded.

In the case series, 325 patients with CVD were studied following an ASA treatment regimen of 325 mg daily for a minimum of 7 days, and platelet aggregation data was recorded in order to determine their ASA “resistance” (Gum et al., 2001). In this study ASA “resistance” was defined as having a normal aggregation response induced by either collagen and/or epinephrine. In this case series, it was reported that 6-10% of the patients appeared to be “resistant” to the antiplatelet effects of ASA with an additional 24% appearing to have a “reduced” response (Gum et al., 2001). However, the observations were not controlled for recognized factors that influence platelet aggregability, including the simultaneous use of other platelet active drugs. Additionally, this study lacked a comparison group of individuals treated with other various antiplatelet drugs, thereby making the study unreliable.

11.7.3 Measurement of ASA Resistance

Determination of “ASA resistance” has primarily relied on quantitative interpretations of the impact of ASA on either platelet aggregation, serum thromboxane B₂, bleeding time, or urinary 11-dehydro thromboxane B₂ excretion (Howard, 2002; Hart et al., 2003; Eikelboom et al., 2002; Hankey and Eikelboom, 2004). All of the aforementioned methods of testing have aided in determining the pharmacology of ASA, however none of them have proven effective in predicting clinical events in individuals, and in particular the relationship between the pharmacology and the clinical outcome. Therefore, the presumption that a quantitative response in one of these variables to ASA administration might predict the efficacy of ASA in preventing a cardiovascular event in an individual is presently unsubstantiated. It seems very unreliable to predict a clinical outcome of a patient who may be considered “ASA resistant” solely based upon a biochemical measurement, without any substantial clinical backup.

11.7.3.1 Possible Molecular Mechanisms of ASA Resistance

It is possible that molecular mechanisms may either contribute to or may possibly be the primary cause of treatment failure associated with ASA. These include genetic variability in the target cyclooxygenases, including COX-1, COX-2, or in the proteins relevant to ASA disposition such as thromboxane A₂-synthetase or various enzymes associated with the metabolism of arachidonate (Halushka et al., 2003; Hankey and Eikelboom, 2004). While COX polymorphisms have been noted, they have not at the present time been linked to any type of substantial clinical outcome (Cambria-Kiely et al., 2002). Additionally, drug-drug interactions may also be an explanation for the occurrence of a cardiovascular event despite chronic ASA intake. For example, nonsteroidal anti-inflammatory drugs (NSAID) may interact pharmacodynamically with ASA, leading to a decreased ASA bioavailability thereby compromising its ability to sustain inhibition of platelet thromboxane formation (Catella-Lawson et al., 2001; Patrono, 2002). There are some *ex vivo* studies that suggest that an increase in ASA dosage from 325 to 1300 mg a day reduce the rate of ASA resistance from 25% to 8%, however as previously mentioned this has yet to be substantiated (Wong et al., 2004).

11.7.3.2 Conclusion

The current usage of the term “ASA resistance” implies a linkage between a laboratory test and a clinical outcome that cannot be substantiated through the current studies at this time. The data currently available is either analytical or descriptive in nature and numerous biases are found, thereby making it essentially unreliable. There are both environmental and genetic factors that may or may not contribute alone or in combination to the incidence of cardiovascular events in patients taking ASA. Currently, serum thromboxane, bleeding time, urinary thromboxane metabolites, and platelet aggregation are the most common tools for explaining the pharmacologic effect of ASA in an individual. Unfortunately, they carry little to no weight in assessing the clinical outcome in a particular patient. As such, a biochemically verifiable mechanism for ASA variable response needs to be defined before concerns regarding such a phenomenon are

warranted. Therefore, discussions at this time regarding the potential for “ASA resistance”/variable response should not interfere with the adoption of labeling to broaden the approved uses of ASA.

11.8 Silent MI

11.8.1 Clinical Overview of Silent MI

The ischemic process of silent MI, including abnormalities of left ventricular function and ECG changes, is an asymptomatic event in patients with coronary artery disease. Patients such as those with a high threshold for pain (Droste and Roskamm, 1983; Falcone et al. 1988; Droste et al., 1986), diabetics with damaged nerves (Caracciolo et al., 1996), and older individuals with coronary artery disease and reduced sensitivity to pain (Aronow, 2003) may fail to recognize the symptoms associated with MI. It is estimated that 25-40% of acute MIs go unrecognized (Sigurdsson et al. 1995; Sheifer et al., 2000; Medalie and Goldbourt, 1976; Yano and Maclean, 1989). While clinically meaningful (Rogers et al., 1995), because of methodological difficulties in their evaluation, it is not practical or necessary to evaluate silent MI in outpatient clinical trials where the beneficial effects of a pharmacological treatment have been demonstrated for symptomatic events.

11.8.2 Silent MI in Clinical Studies

A discussion of the relevance of the failure of the primary prevention studies to adequately assess the impact of silent MI on their conclusions is included based on questions raised by the agency. It is Bayer HealthCare’s position that these studies are indeed meaningful without this inclusion based on the consensus of the clinical research community that the efficacy analysis of a preventive measure for MI is most appropriate without the inclusion of silent MI data, as this endpoint is difficult to record with accuracy in outpatient studies, and has similar pathophysiology to a documented MI.

Silent MI is defined by only one criterion (ECG) and, as a result its diagnosis is easily overlooked. This is in contrast to nonfatal MI which is defined by two or three criteria (clinical, ECG, or enzymes). Since the clinical outcomes are similar in both clinically manifested and silent MI (Cohn, 1988; Hedblad et al., 1989; Kannel et al., 1990; Bertolet and Hill, 1989), many clinical trials which formed the basis for approval of drugs for MI risk reduction do not systematically include the evaluation of silent MI as a main outcome when evaluating data on the primary prevention of myocardial infarction, including the studies evaluating the efficacy of ASA (PHS, BDT, TPT, HOT, and PPP). Likewise, the majority of the secondary prevention studies involving ASA and most other interventions fail to consider silent events. For example, the Antithrombotic Trialists’ Collaboration that has systematically reviewed the evidence for all antithrombotic trials conducted (over 200 studies involving more than 200,000 subjects) has prospectively excluded silent MI from their analyses for over 20 years. The following examines the rationale for the handling of silent MI in the various ASA primary prevention studies.

The HOT trial investigators, while originally intending to include silent MI data in their analysis, excluded silent events from the final principal efficacy analysis on the basis that silent MIs could only be adjudicated by a single criterion, while fatal and nonfatal MI could be evaluated on two of three criteria. Additionally, since ECGs were only performed at baseline and study end there was a lack of time dependent information, an essential component of the efficacy analysis. The fact that the effect of ASA on major cardiovascular events and on MIs was no longer significant when silent MIs were included in a secondary analysis of this study most likely reflects the poor diagnostic specificity of this endpoint.

Silent MI data were collected in the TPT with the intention of including a brief reference to the results due to an interest expressed by colleagues of the investigators. However, these evaluations were not collected with the intention of including the data in the combined analyses of the major clinical endpoints. While ECG information was collected at entry and at each annual follow-up exam, the findings are not sufficient for a stand-alone analysis nor adequate to be combined with the major events.

The other primary prevention studies did not include silent MI observations since it was either not feasible to collect ECGs at baseline and at the end of the trial for each patient (PPP) or simply was not a concern of the investigators at the time of the trial design. Importantly, the two physician studies (BDT and PHS) relied on the reports from physicians themselves and did not require ECG data.

It is important to note that the systematic review of the 5 ASA primary prevention studies by the Antithrombotic Trialists' Collaboration prospectively excluded silent MI, eliminating the potential for bias. It is also worth noting that other studies that have formed the basis of approval for other MI prophylactic agents in the U.S. have excluded silent MI from their analyses (e.g., HOPE Study [Arnold et al., 2003]).

11.8.3 Conclusions

The 5 ASA primary prevention studies described above effectively demonstrate the beneficial effect of ASA in the prevention of symptomatic MI. Combined with the evidence that silent and recognized MI exhibit similar prognosis, risk factors, and health implications (Cohn, 1988; Hedblad et al., 1989; Kannel et al., 1990; Bertolet and Hill, 1989; Kannel and Abbott 1984; Nadelmann et al., 1990; Sigurdsson et al., 1995; Sheifer et al., 2000; Aronow, 1989) it is reasonable to assume that ASA use would not adversely impact patients presenting with this diagnosis. As an effective means to collect data on silent MI in a clinical trial setting has yet to be developed, it is appropriate to assess the efficacy of ASA in the primary prevention of myocardial infarction based upon symptomatic MI data.

11.9 Support for Proposed 75-325mg/day Dosing Recommendation

Significant attention has been directed toward determining the optimal ASA dose for cardioprotection, with many advocating the use of the lowest effective dose. Since trials supporting the use of ASA in the management of cardiovascular disorders have utilized

doses optimized for other pharmacologic effects (e.g., pain and inflammation) (Kong, 2004), it is difficult to conclude with certainty a single specific dose that would be appropriate for the proposed primary MI prophylaxis indication. It is clear however, as reviewed below, that low doses in the range of 75-325 mg/day offer a favorable benefit to risk relationship and should therefore be acknowledged in approved labeling. Such an approach would be responsive to the available data, as well as ensure consistency with the currently approved ASA labeling for secondary MI prophylaxis.

ASA is currently marketed in 81 mg, 325 mg, and 500 mg doses, reflecting the historical use of ASA in the management of pain and fever in children and adults. The FDA's guidelines for ASA dosing for vascular indications, revascularization procedures and rheumatologic disease indications are provided in the Regulatory Overview Section (Section 4). The current Final Rule for the professional labeling of ASA recognizes a range of doses from 75-325 mg/day for the prevention of recurrent MI (FDA, 1998). Higher doses are indicated for treatment of an acute MI (minimum of 160 mg) and for a variety of vascular procedures (e.g., PTCA and CABG, 325 mg). Likewise, doses up to 650 mg BID are recognized for carotid endarterectomy.

There is broad support for a range of doses for MI prophylaxis. In the marketplace, dose selection is largely driven by commercial availability, cost, physician preference and perceptions regarding safety. Interestingly, in the most recent survey published, it indicates that the 300-325 mg dose is the most prescribed (Hart and Harrison, 1996). However, more recent information from a survey of 303 physicians (Bayer HealthCare Data on File, 2003) indicates that the dose most often recommended for primary prevention is the 81 mg dose (87%), while for recommendations made for secondary prevention recommendations are comparable between the 81 mg dose (49%) and for the 325 mg dose (42%). The interest in lower doses emanates from *in vitro* and *in vivo* analyses that suggest that doses as low as 30 mg/day have clinically meaningful antiplatelet effects (Kong, 2004). This, coupled with the belief that lower doses have the potential of improved tolerability, has led many to advocate their use.

Unfortunately, the evidence is scant, with few direct comparisons between ASA doses. The evaluations that have been touted as meaningful in support of lower doses in the approved range are based on either indirect comparisons across diverse studies or findings from observational components of clinical trials, such as CURE (Peters et al., 2003) and BRAVO (Topol et al., 2003), where the ASA dose allocation was not randomly assigned.

11.9.1 Pharmacology

A number of pharmacokinetic (PK) and pharmacodynamic (PD) differences between ASA doses with respect to platelet aggregation have been observed, suggesting that they may underlie differences in therapeutic outcomes. A recent study by Cerletti and colleagues (2003) evaluated the PK/PD effects of two doses of ASA, 80 or 160 mg/day, randomly assigned to 16 healthy volunteers, and found that the inhibition of serum and urinary thromboxane levels by the lower dose, while substantial, appeared incomplete compared to the higher dose. Thromboxane levels, not surprisingly, were inversely

correlated with increased ASA and salicylate levels. Likewise, Gan et al (2002) demonstrated the dose-dependent inhibition by ASA of platelet aggregation induced by adenosine diphosphate (ADP) up to 1,300 mg/day in post-stroke patients.

While its antiplatelet effect is widely accepted as an important contributor to the clinical effectiveness of ASA in the prevention of MI, there are other mechanisms that have been postulated to contribute to this clinical effect. There is evidence that at higher doses, ASA can acetylate a number of proteins besides COX, including fibrinogen (Bjornsson et al., 1989) and prothrombin (Szczeplik et al., 1992), as well as findings to suggest that ASA may decrease the atherosclerotic process by protecting low-density lipoproteins (LDL) from oxidative changes (Steer et al., 1997), and reducing the inflammatory response in patients with CHD. Other evidence supports the view that ASA may also improve endothelial cell functioning in atherosclerotic vessels (Husain et al., 1998). Such findings are suggestive of a similar mechanism to that postulated for the pleiotropic effects of statins in modifying CHD risk. While additional research is needed to establish the relevance of these findings to the antithrombotic effects of ASA in the clinical setting, the initial findings are promising and suggest that higher doses than those necessary to simply inhibit thromboxane generation by platelets may prove beneficial.

11.9.2 Clinical Trials – Dose Review

Clinical trials have evaluated doses ranging from 30 to 1500 mg/d and have demonstrated effectiveness in preventing thromboembolic events throughout this range (Klimt et al., 1976; Canadian Cooperative Study Group, 1978; Steering Committee of the Physicians' Health Study Research Group, 1989; Hennekens and Eberlein, 1985; Patrono, 1989; Libretti and Bertele, 1989). As there have only been three controlled investigations that specifically have compared doses, all three in TIA patients (European Stroke Prevention Study II (ESPSII), Dutch TIA and UK TIA), it is impossible to say with confidence whether one dose is superior to another in MI prophylaxis. Rather, it is likely that the optimal dose will vary by patient, suggesting that the full range of low-dose options (75-325 mg/day) should be considered by the clinician.

- In the ESPSII, the 25 mg BID ASA dose was as effective in reducing the risk of recurrent stroke or death in patients with prior strokes or TIA as the higher dose (Sivenius et al., 1991; Sivenius et al., 1992; Sivenius et al., 1999). In this study of over 30,000 patients, ASA 25 mg/d was compared with ASA 285 mg/d. There was no significance difference in the outcome of vascular stroke, MI, or death.
- The Dutch TIA Trial evaluated two ASA doses and found no difference between 30 and 283 mg of ASA daily (Dutch TIA Trial Study Group, 1991). Likewise, the UK TIA study (Farrell et al., 1991) provides evidence that a 1,200 mg daily dose is not superior to a dose of 300 mg/day.

There have only been two small studies that have directly compared ASA doses in ACS patients: the Duke University Clinical Cardiology Group Study II (DUCCS-II) (O'Connor et al., 1996) comparing 81 mg/day with 325 mg/day and the unpublished ASA at Low-dose in Unstable Angina (ALDUSA) pilot that compared 40 mg/day with

325 mg/day. Neither trial demonstrated a difference in outcome or adverse effects, but was considered underpowered to do so.

The ATT Collaboration meta-analysis (discussed in Section 11.2.1), that reviewed over 200 studies, suggests that the benefits of ASA are not significantly different between high-dose (≥ 500 mg/day) and low-dose (≤ 325 mg/day) in the prevention of secondary vascular events (Antithrombotic Trialists' Collaboration, 2002; Sze et al., 1988).

The risk of GI bleeding, the most common adverse event associated with ASA use, should also be considered in dose selection. While there is no ASA dose where antithrombotic effectiveness is achieved without an increased risk of bleeding, the available evidence suggests that doses equal to or less than 325 mg/day are preferable to higher doses (de Abajo and Garcia Rodriguez, 2001; Hawkey, 1994). While this is the case, it is important to note that no meaningful differences in GI bleeding risk have been established between the low-dose forms, e.g., 81 mg and 325 mg daily doses. This point is best exemplified by the meta-analysis of long-term ASA use conducted by Derry and Loke (2000). This analysis evaluated 24 randomized, controlled trials with almost 66,000 participants comparing ASA with placebo or no treatment for a minimum of 1 year (average duration of use was 28 months). GI hemorrhage occurred in 2.47% of patients taking ASA compared with 1.42% taking placebo (OR=1.68; 95% CI=1.51-1.88, $p < 0.0001$). At doses below 163 mg/day, GI hemorrhage occurred in 2.30% of patients taking ASA compared with 1.45% taking placebo (OR =1.59; CI=1.40-1.81, $p < 0.0001$). Meta-regression showed no correlation between GI hemorrhage and dose.

The ASA dose question has been heightened by the recent publication and promotion of two studies, the Clopidogrel in Unstable angina to prevent Recurrent Event trial (CURE) (Peters et al., 2003) and the Blockade of the glycoprotein IIb/IIIa Receptor to Avoid Vascular Occlusion Trial (BRAVO) (Topol et al., 2003). These trials had as their primary goal the evaluation of the effectiveness of antithrombotic agents other than ASA. As a result, the allocation to ASA was not randomly assigned, but rather left to the discretion of the investigator in discussions with his/her patient. As a result, the findings must be viewed with extreme caution since a variety of confounding factors could influence their interpretation. For instance, if a physician, as many do, chose to put a higher risk person on a higher ASA dose, it may not be surprising to see a higher rate of adverse events associated with that dose. Nonetheless, for completeness, these two trials are reviewed below.

In the case of CURE, the trial was specifically designed to assess the benefits and risks of adding clopidogrel to ASA in the treatment of patients with acute coronary syndrome (ACS). In this study, 12,562 patients with ACS already on ASA, 75-325 mg daily, were randomized to either clopidogrel or placebo for up to one year. In the analysis, patients were divided into three groups based on their current ASA use at study entry: ≤ 100 mg, 101-199 mg, and ≥ 200 mg. The findings suggest that the incidence of major bleeding complications increases significantly with increasing ASA dose (with or without the addition of clopidogrel), with an apparent doubling of the risk of bleeding from the lowest to the highest dose groups (1.9% vs. 3.7%). While the actual rate of GI bleeding was low in the study as a whole, the authors assert that by lowering the dose of ASA, the

risk of major bleeding can be substantially lowered without loss of efficacy. Importantly, they also acknowledge the significant limitations of their study and indicate that the findings are based on a post hoc observational analysis and should therefore only be considered exploratory.

Similarly, BRAVO was a large-scale evaluation of an orally administered IIb/IIIa inhibitor, lotrafiban, in coronary and cerebrovascular disease that also relied on post hoc analyses to comment on the relative risks and benefits of different ASA doses. In this case, the investigators chose to examine the data based on two ASA dose cutoffs, low-dose (between 75 and 162 mg/day) and high-dose (> 162 mg/day). Not surprisingly, the investigators noticed significant geographical differences in the use pattern of ASA, with 81 mg being the low-dose of choice in the U.S., whereas 100 mg was more likely to be used outside of the U.S. It is not clear if the investigators controlled for the fact that enteric formulations were preferentially used at certain dose levels, as the 100 mg does is widely utilized as an enteric formulation throughout Europe and not available in the U.S. Nonetheless, the investigators note that in spite of the potential for international differences and other confounding factors, there appears to be an increased risk of bleeding (approximate doubling) with the use of the higher dose ASA. Another major shortcoming of the study is the failure to collect data pertaining to ASA dose during follow-up. Only the dose used at study entry was available, suggesting that there could have been changes in dose utilization throughout the study. Interestingly, this study demonstrated a lower risk of mortality in the high-dose ASA group compared to the low-dose group when this endpoint is evaluated independently. Based on this finding, one must question the author's recommendation for use of lower doses based on this study. In fact, this study could be interpreted as supportive of a basis for use of the 325 mg dose and suggestive of the possibility of mechanistic advantages contributing to differential effects of higher ASA doses, and therefore its findings should be viewed solely as hypothesis generating.

11.9.3 Dosing Recommendations

Dosing recommendations for the use of ASA in the primary and secondary prevention of MI, in the interest of consistency, should be the same. The available data suggest that comparable relative risk reductions are observed regardless of the presence or absence of a previous event and demonstrate no major differences between the two with respect to the risk for hemorrhagic complications. While some advocate higher ASA doses for protection against recurrent events and lower doses in apparently healthy individuals, the currently FDA approved range of 75 mg to 325 mg/day represents a favorable benefit to risk ratio for both populations.

As mentioned in a previous section (Section 11.5), there are some data to suggest that there is a small subset of patients who have new or recurrent thrombosis in spite of adequate ASA intake. These patients have been referred inappropriately to as "ASA resistant" (Gum et al., 2001; Helgason et al., 1994; Helgason et al., 1993). While it is not clear whether this phenomenon represents a distinct phenotype, or rather treatment failure due to a variety of other causes, there is some evidence that higher doses (e.g., 325 mg of ASA) may be sufficient to successfully overcome the resistance, providing an additional

basis for including 325 mg dose in the approved range for MI prevention (Refer to Section 11.7- ASA Resistance)

11.9.3.1 Primary Prevention of MI

A number of different aspirin doses and formulations have been evaluated in the 5 primary prevention studies. In these studies, the dose of ASA ranged from 75 mg to 500 mg/day, with the duration of ASA treatment ranging from a few months to many years (see Table 20). The diversity of design and consistency of findings reflect the strength of the database to provide meaningful conclusions.

Table 20: Summary of Studies Evaluating ASA Prevention of First Cardiovascular Event

| Variable | BDT | PHS | TPT | HOT | PPP |
|------------------|--|------------|-------------------------|---------|----------|
| ASA therapy dose | 500 mg/d | 325 mg qod | 75 mg/d | 75 mg/d | 100 mg/d |
| (N) | 300 mg/d if later requested (3,429) | (11,037) | (cont. rel.) (1,268) | (9,399) | (2,226) |

BDT: British Doctors' Trial (Hennekens and Buring, 1994); HOT: Hypertension Optimal Treatment Trial (Hansson and Zanchetti, 1995); PHS: Physicians' Health Study (Steering Committee of the Physicians' Health Study, 1989); PPP: Primary Prevention Project (De Caterina, 2001); TPT: Thrombosis Prevention Trial (FitzGerald and Charman, 1998).

A meta-analysis of all 5 studies by Eidelman (2003) demonstrated a statistically significant 32% reduction in the risk of MI. Furthermore, the overview analysis confirmed that there were no meaningful differences with respect to outcome as a function of dose across the range studied (75-500 mg/day).

With an appreciation of the fact that the benefits of ASA in primary prevention largely accrue from reductions in nonfatal MI events, the decision regarding dose selection must be weighed against this benefit as well as the potential for side effects, specifically GI bleeding and increased risk of hemorrhagic stroke (refer to ISS Volume 3). The available data demonstrate, as reviewed below, that this ratio is favorable for patients whose CHD risk is moderate or greater across the low-dose range (75-325 mg/day) and that there are no meaningful safety differences across this range of doses.

11.9.3.2 Secondary Prevention of MI

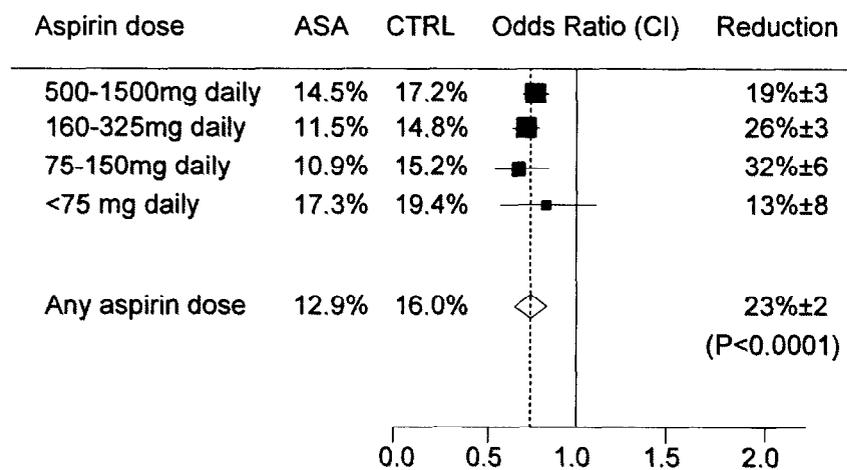
Many thousands of patients have been studied to evaluate the effect of ASA in the secondary prevention of MI (Borghi and Ambrosioni, 1996; Libretti and Bertele, 1989; SALT Collaborative Group, 1991; Hennekens, 1997; Hennekens et al., 1989; Ketterer, 1993; Krumholz et al., 1996; Merz et al., 1997; Rubowitz and Porath, 1992; Stein and Fuster, 1989; Tisdale, 1998). Not surprisingly, there is also great diversity in the patients, underlying diseases, doses and frequency of dosing, duration of therapy, controls, and other concurrent therapy in the secondary prevention database similar to that observed in primary prevention of MI. Despite these differences and variations in results, there is

incontrovertible evidence that ASA reduces the risk of reinfarction and death in patients with a history of MI. ASA is also effective in reducing the event rate in a wide range of patients undergoing coronary interventions such as bypass surgery and percutaneous angioplasty. There is also highly significant support for the benefits of ASA in reducing the rate of reinfarction and death when administered at the sign of a suspected evolving MI and continued for 30 days (Kong, 2004).

In a meta-analysis by Derry and Loke (2000), 24 randomized, controlled trials with almost 66,000 participants comparing ASA with placebo or no treatment for a minimum of 1 year to assess GI hemorrhage was undertaken. GI hemorrhage occurred in 2.47% of patients taking ASA compared with 1.42% taking placebo (odds ratio 1.68; 95% CI=1.51-1.88). At doses below 163 mg/day, GI hemorrhage occurred in 2.30% of patients taking ASA compare with 1.45% taking placebo (odds ratio 1.59; CI=1.40-1.81). Importantly, meta-regression showed no correlation between GI hemorrhage and dose.

In the Antiplatelet Trialists' meta-analysis (2002) based on 287 trials of antiplatelet therapy involving over 135,000 patients with a history of previous myocardial or cerebrovascular ischemia (Antithrombotic Trialists' Collaboration, 2002) which includes doses of ASA from 30 to 1500 mg allows for indirect comparisons of the effect of ASA in high-risk patients stratified by dose. In this analysis, patients receiving ASA 75-150 mg/day had the greatest reduction in cardiovascular events, while patient receiving less than 75 mg/day or more than 500 mg/day tended to have less benefit. However, none of these differences were statistically significant in spite of the large number of subjects evaluated.

Figure 15: Effect of ASA Dose on Vascular Events in the ATT Trial



Adapted from ATT, 2002

11.9.3.3 Dose Conclusions

The effectiveness of ASA in certain indications is based on studies at specific doses, and hence the FDA approvals for these uses have specific doses associated with them. For instance, the approval for acute MI is largely based on ISIS-2 (ISIS-2 Collaborative Group, 1988), which specifically studied a dose of 160 mg, chewed at the time of presentation with MI symptoms. Based on the lack of apparent differences in safety risk, the use of doses from 75 to 325 mg appear indicated, with some evidence of potential benefit of higher dose in the range.

As ASA may demonstrate other modes of action that may contribute to inhibition of platelet activity and to decrease in cardiac morbidity and mortality (Cazenave and Gachet, 1997; Tanasescu et al., 2000; Ghooi et al., 1995; Oberle et al., 1998; Podhaisky et al., 1997; Rumore et al., 1987), such as antioxidant activity, enhanced fibrinolysis, and suppression of plasma coagulation and platelet-dependent inhibition of thrombin generation with differing dose response curves, it may not be wise to cap the maximum dose based on *in vitro* platelet aggregation findings (Podhaisky et al., 1997; Rumore et al., 1987). As discussed, ASA may, in part, induce its cardioprotective effects through a reduction in inflammation (Ridker et al., 1997; Ridker et al., 1998), where higher doses are needed. There is sufficient evidence to demonstrate the association between inflammation and CHD, either as a pathogenic process or in response to injury (Tanasescu et al., 2000; Ghooi et al., 1995; Oberle et al., 1998; Podhaisky et al., 1997; Rumore et al., 1987; Haught et al., 1996; Mehta and Li, 1999; Mehta and Romero, 2000; Mehta et al., 1998; Ridker et al., 1997). ASA has been shown in numerous studies to directly affect neutrophils, erythrocytes, and platelets. In addition, it can protect the endothelium from oxidative stress and reduces endothelial dysfunction (Podhaisky et al., 1997; Oberle et al., 1998; Mullane and Pinto, 1987).

The pursuit of the optimal dose of ASA should not interfere with the broader appropriate use of ASA, as the majority of people can be effectively managed with ASA doses in the range of 75-325 mg/day. Physicians should be offered the option of offering a patient at an increased risk of GI upset and hemorrhagic complications the lower end of the dose range, while those patients who do not exhibit GI sensitivity might best be started on a higher dose (e.g., 325 mg/day), which might provide added mechanistic benefits and ensure broader platelet coverage with missed dosing. The physician's evaluation of the benefit-risk profile of the therapy for each patient warrants the choice of a range to consider.

Since the hemorrhagic potential does not appear to be affected across the proposed dose range of 75-325 mg/day the high end of the low-dose range may prove to be the most appropriate. Additional research in the form of well-designed randomized controlled trials will be required to better refine this recommendation.

11.10 ASA Effectiveness in Preventing Cardiovascular Events Across a Variety of Patient Populations: Conclusions

The following clear and compelling factors support the broadening of the labeling for ASA to include moderate-risk individuals:

- The database clearly supports the efficacy of ASA in preventing thromboembolic MI in patients at increased risk as well as “healthy” patients;
- The database is extremely robust with strong consistent findings in a large number of studies; and
- 14 MIs can be prevented for every 1,000 moderate-risk patients treated for 5 years.