Docket 77N-0094

Proposed Amendment to Final Rule for Professional Labeling of Aspirin

Primary Prevention of Myocardial Infarction in those Individuals at Sufficient Risk

Briefing Book

November 5, 2003

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LIST OF ABBREVIATIONS

ACC – American College Of Cardiology

ADA – American Diabetes Association

AHA – American Heart Association

ANPR – Advanced Notice Of Proposed Rulemaking

ASA – Acetylsalicylic Acid

ATT – Antithrombotic Trialists' Collaboration

BDT – British Doctors' Trials

CAD – Coronary Artery Disease

CHD – Coronary Heart Disease

COX – Cyclooxygenase

CV – Cardiovascular

CVD – Cardiovascular Disease

FDA – Food And Drug Administration

GI – Gastrointestinal

HDL – High Density Lipoprotein

HOT – Hypertension Optimal Treatment Trial

IHD – Ischemic Heart Disease

JNC – Joint National Commission

LDL – Low Density Lipoprotein

MI – Myocardial Infarction

NCEP – National Cholesterol Education Program

NDA– New Drug Application

NHLBI – National Heart, Lung, And Blood Institute

NHBPEP – National High Blood Pressure Education Program

NSAID – Non–Steroidal Anti–Inflammatory Drug

OTC – Over–The–Counter

PHS – Physicians' Health Study

PPP – Primary Prevention Project

SALT – Swedish Aspirin Low–Dose Trial

TFM – Tentative Final Monograph

TIA – Transient Ischemic Attack

TPT – Thrombosis Prevention Trial

UK–TIA – United Kingdom Transient Ischemic Attack Trial

USPSTF – U.S. Preventive Services Task Force

EXECUTIVE SUMMARY

This briefing book is provided to assist the Committees in their review of the appropriateness of aspirin (ASA) for preventing a first myocardial infarction (MI) in patients at sufficiently elevated risk. It specifically advocates **Bayer HealthCare's position that the benefits of low dose (75 – 325 mg) ASA can be extended to patients at "Moderate Risk", defined as a 10 year risk of coronary heart disease (CHD) that exceeds 10%, where the benefits of therapy would be expected to outweigh the risks.**

Statement of Purpose

Cardiovascular disease is the leading cause of death and disability in this country and strategies to reduce its impact must actively be embraced. ASA is highly effective in reducing the risk of MI and its broader use in appropriate patients can significantly reduce the tremendous personal and societal impact of this disease. For this benefit to be realized there is a need to align ASA labeling with current scientific knowledge and clinical practice guidelines as this is a critical and essential step in encouraging patients and physicians to discuss and appropriately manage cardiovascular risk. Because underlying cardiovascular risk is the single most important determinant of an individual's likelihood of experiencing an MI, labeling that reflects and endorses treatment based on a patient's global risk will have significant public health benefit. As there is no question that the absolute benefits of ASA accrue to those at Moderate to High Risk, effort should focus on how best to ensure that all individuals falling into these groups have access to this important therapeutic option. An approved indication is essential to this goal.

Rationale

Because absolute benefit of intervention is enhanced by ensuring that those who are at greatest CHD risk are the ones who receive treatment, strategies that define appropriate patient populations for intervention with ASA by risk would be expected to be most successful in reducing the burden of MI. The current FDA labeling paradigm that mandates the presence of a previous cardiovascular event is not a sufficient indicator of who should be a candidate for ASA treatment. This is because it fails to acknowledge that patients who may have not suffered a previous cardiovascular event could be at equal or greater risk compared to patients who have suffered such an event. Adoption of ASA labeling that focuses on underlying global risk and its management would better define appropriate populations for ASA intervention and would therefore be expected to have a major public health impact.

The Benefits of ASA Are Well Established Across the Underlying Risk Continuum

ASA has been shown to be effective in preventing MI in a large array of patient groups. The available evidence of benefit is derived from two distinct risk populations (Low and High) and consists of studies including over 55,000 Low Risk patients that have not experienced a previous cardiovascular event (i.e., the primary prevention database) as well as over 150,000 High Risk patients. The consistency of findings across these populations highlights the reliability and homogeneity of these findings and supports the view that Moderate Risk patients, although not specifically studied would also benefit from ASA therapy. A clinically important reduction of 14 MIs can be avoided for every 1000 patients treated in this population.

The Risks of ASA Are Low and Constant Across the Underlying Risk Continuum

Numerous controlled clinical trials and tens of millions of patients exposed to ASA a year for cardiovascular indications provide a clear picture regarding the potential risks associated with chronic low dose ASA use and highlight that these risks do not vary as a function of underlying cardiovascular risk. From the clinical trials and postmarketing adverse event tracking experience, it is clear that the most clinically important adverse events associated with the long-term cardiovascular use of ASA are related to bleeding complications. The data reveal that while gastrointestinal (GI) bleeding is a clinical concern, its rate of occurrence in clinical trials is relatively low (2.3% compared to a rate of 1.45% among patients taking placebo). Hemorrhagic stroke, which has also been reported to be associated with ASA, occurs at rates far lower (75 hemorrhagic strokes per 28,570 individuals or 0.26%) than that of GI bleeding. Clear and precise professional labeling will assist physicians in evaluating these risks and ensure that patients at elevated risk from such injuries are selectively excluded from ASA use.

The Benefit to Risk Relationship Is Clearly Favorable in Moderate Risk Patients

Selecting patients for ASA treatment at Moderate Risk based on global risk will enhance the benefit to risk relationship. While the benefits of ASA in preventing non-fatal MI were observed in the Low Risk trials, the selection of Moderate Risk patients in the proposed labeling for ASA was conservatively chosen to further enhance the benefit to risk relationship. Treating a thousand Moderate Risk Patients, i.e. those who have a 10-year risk of CHD greater or equal to 10%, with ASA for 5 years would be expected to prevent 14 MIs per 1000 patients treated. In this population, the same rate of serious adverse effects as observed in the High Risk and Low Risk studies would be expected (0-2 hemorrhagic strokes and 2-4 major GI bleeds per 1000 patients treated), resulting in a favorable benefit to risk relationship. The adoption of risk based labeling and a recognition of the benefits of ASA in Moderate Risk patients would be expected to enhance appropriate utilization of this effective therapy, as it would clarify those patients who should be on ASA and those who should not.

ASA Use in Moderate Risk Patients Is Consistent With Recommendation by the Medical Community

The use of ASA in a wider population of appropriate patients based on underlying cardiovascular risk is supported by recent publication of clinical guidelines by the American Heart Association (AHA) and the U.S. Preventive Services Task Force (USPSTF). These organizations recommend that individuals with a 10-year risk of CHD in the range of 6-10% be considered as candidates for ASA therapy. Their guidelines are based on their finding that clinically meaningful MI risk reduction will be achieved at this Moderate Risk level.

Bayer HealthCare looks forward to a partnership with the Food and Drug Administration (FDA), the medical community and patient advocacy groups to better communicate the importance of cardiovascular risk evaluation and management and the appropriate use of ASA. An approved expanded professional indication will provide clarity of communication to help ensure that the right patients are on ASA therapy and the wrong ones are not. Bayer Healthcare is committed to responsible marketing of this important therapeutic agent and looks forward to the input of the Committees with respect to how best to label ASA in the interest of improving public heath.

1 INTRODUCTION

1.1 Rationale for Approval of ASA for the Prevention of MI in Moderate Risk Individuals

This section provides the rationale for Bayer HealthCare's request that ASA be approved for the prevention of MI in individuals at "Moderate Risk" of CHD. The support for this request is highlighted by the following well-substantiated findings:

- ASA has been clearly shown to be effective in the prevention of MI in a wide variety of patient populations, including "Low Risk" and "High Risk" populations, with similar proportional risk reductions observed across the studies.
- Patients can be at sufficient risk of CHD to warrant treatment in spite of the absence of a previous event. Global, or underlying CHD risk is the more appropriate determinant of the type and intensity of intervention.
- The adverse event risks associated with chronic low-dose (75mg-325 mg/d) ASA therapy are the same regardless of underlying cardiovascular risk.
- Labeling can define a Moderate Risk population where the benefits of treatment far outweigh the risks.

Underlying Cardiovascular Risk Should Define Eligible Candidates for Treatment

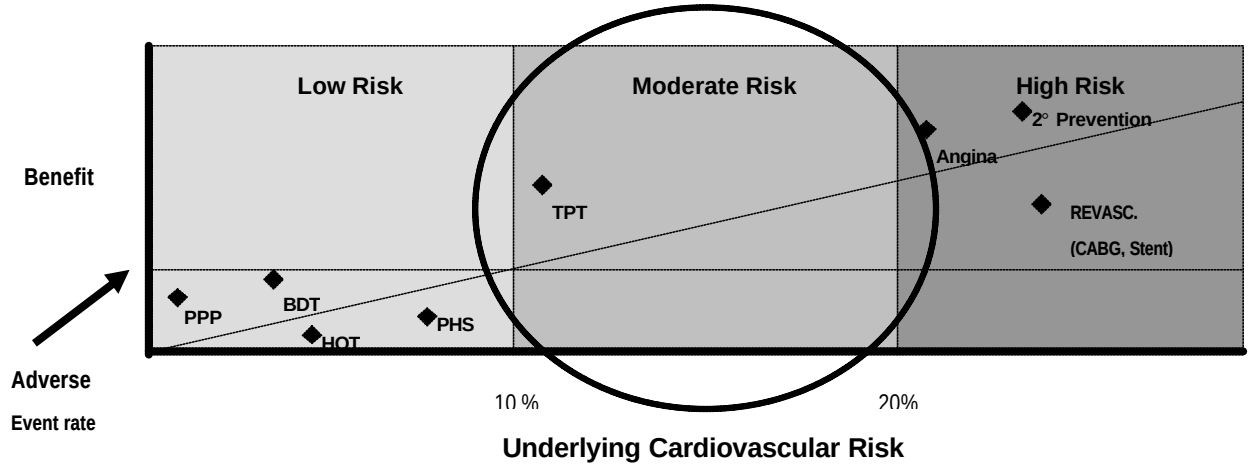
It is well accepted within the medical community that an understanding of an individual's cardiovascular risk profile (global risk), defined by number and severity of risk factors, is the key determinant in assessing that patient's likelihood of developing CHD. A major component of the risk assessment is the presence or absence of symptomatic disease. Patients who have a history of cardiovascular events – specifically, who have experienced an acute myocardial infarction (MI) or have a history of previous MI, stroke, transient ischemic attack (TIA), stable or unstable angina pectoris, chronic non-valvular atrial fibrillation, or peripheral vascular disease, as well as those requiring revascularization procedures or hemodialysis – are at substantially increased risk of experiencing subsequent occlusive vascular events and would be considered High Risk. At the other extreme of this spectrum would be patients who have no history of cardiovascular disease and who do not have cardiovascular risk factors and would be appropriately classified as "Low Risk."

While the risk paradigm described above assumes the presence or absence of a previous cardiovascular event as the defining factor in establishing level of risk, recent advances in risk assessment have suggested that a more appropriate model should be one based on global risk. With a thorough understanding of an individual's risk profile, the clinician can guide therapy appropriately and, more importantly accurately evaluate the likely benefit and compare it to potential for harm. In fact, 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. Encouraging broader treatment of patients where the benefit is expected to be greatest (i.e., those at elevated risk) will have significant public health impact.

Considering risk as a continuum, a third group can be defined that is intermediate between the High and Low Risk populations described above. This Moderate Risk population can be described as having no history of cardiovascular disease; however, they do have an increased level of underlying CHD risk as a result of a combination of factors. Importantly, the level of risk in this population can vary greatly, and while asymptomatic, many of these patients could be at a significantly high risk of an event, which in some cases could exceed the rate in the High Risk group addressed above. The following factors can affect risk appreciably, highlighting the importance of a detailed risk assessment as part of a patient's annual physical exam: hypercholesterolemia, smoking, diabetes, hypertension, age, obesity, and family history. Importantly, both lifestyle modifications and pharmacologic interventions have been shown to effectively reduce the risk of MI in this Moderate Risk population.

To illustrate the utility of a global risk based approach for evaluating at what level of underlying risk ASA therapy may be appropriate, a model addressing underlying cardiovascular risk is depicted in Figure 1.

Figure 1: ASA Should Be Indicated for All Populations Where Benefits Outweigh the Risks (Including Moderate Risk)



Basis for Including Moderate Risk Patients in ASA labeling

ASA is indicated in numerous countries 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 towards "event based" labeling, suggesting that a candidate must have a history of a cardiovascular event or symptomatic disease. In spite of these approvals, there are many more patients who are at sufficiently high risk to warrant treatment whom could benefit from the cardio-protective effects of ASA and for who the benefits outweigh the risks. Extending the labeling to these patients will result in significant reductions in morbidity.

It is clear that there are many Moderate Risk patients – i.e., people who are at increased risk for serious cardiovascular events – who are not included in the current ASA labeling. Because of

the common pathophysiology of coronary events across the disease continuum, there is sufficient evidence to support the view that the same preventive interventions (e.g., behavioral and pharmacological) would be effective in this population.

The Benefits and Risks of ASA Therapy can be Appropriately Extended to Moderate Risk Patients

The available scientific evidence clearly supports the utility of ASA in preventing MI across the risk spectrum, including patients at Moderate Risk. The data conclusively demonstrate that ASA prevents cardiovascular events (most notably and consistently MI) across the risk continuum (i.e., high risk, moderate risk, and low risk patients) as summarized below.

- High Risk Populations: Clinical studies and meta-analyses have provided conclusive evidence that low-dose ASA can prevent subsequent cardiovascular events (e.g., MI, stroke, and vascular death) in High Risk patient groups (i.e., MI relative risk reductions of 30%).
- Low Risk Populations: More recent 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) (MI relative risk reductions of 32%).
- Moderate Risk Populations: While not specifically studied in controlled trials, the available evidence suggests that the benefit to risk relationship is favorable for the use of aspirin in this population.

The diversity of the data (approximately 150 studies involving over 200,000 patients, including over 55,000 apparently healthy Low Risk individuals and over 150,000 High Risk patients), coupled with robust and consistent findings across the studies, provides confidence in the broad applicability of the observed benefits with respect to the ability of ASA to prevent MI in all at risk patients.

Extrapolation Across Risk Strata

The fact that the proportional risk reductions are essentially identical for the High Risk and Low Risk studies (as outlined in Table 1 below) highlights the homogeneous population across the risk continuum and the ability to extrapolate findings to intermediate groups that have not been specifically evaluated.

Table 1: Relative Risk Reductions of MI in High Risk and Low Risk Patient Populations are Similar

Trial	Underlying Risk of Patient Population	Relative Risk Reduction for MI
PHS	Low Risk	40%
BDT		3%
TPT		32%
HOT		--
PPP		31%
Overall		32%
Weisman and Graham meta-analysis	High Risk	30%

While comparable proportional risk reductions are observed across the risk continuum, very different absolute benefits would be expected in distinct risk strata based on the differing levels underlying risk of CHD. As noted in Figure 1 (diagonal line), the absolute benefit increases as a function of underlying risk. Such a relationship would be expected for any effective intervention. The point is further exemplified when the baseline risks for each of the five primary prevention studies and the mean of the High Risk (secondary) prevention studies are included. The fact that a line can be drawn between these databases highlights that an extrapolation can be made to other groups between the two studied extremes, suggesting that a predictable benefit can be achieved in Moderate Risk patients as well.

To complete the evaluation as to the appropriateness of treating Moderate Risk patients with ASA, it is important to also consider the potential hazards of treatment. Unlike benefit (which increases linearly with underlying risk), the well-documented adverse event rate (primarily gastrointestinal bleeding and hemorrhagic stroke) associated with ASA therapy would be conservatively expected to be constant across the risk continuum (lower risk patients could theoretically be healthier and at lower risk of adverse events) (Figure 1 – horizontal line).

In reviewing the model depicted above, it is clear that at global risk levels exceeding 10%, the absolute benefit of treatment outweighs the risk, highlighting the need for recognition of the need to treat patients with this risk level and above.

ASA Should Be Indicated for Prevention of MI in Moderate Risk Populations

Based on the construct presented above, it is clear that a broader group of patients than currently included in the professional labeling for ASA should be candidates for ASA therapy. Likewise, in any revisions to the labeling for aspirin, attention should be paid to the fact that there is significant utilization in all "at risk" populations. To that end, the following points should be considered:

- Low Risk Population (<10% risk): ASA use would not be appropriate because the benefits of treatment may not exceed the potential for adverse effect.
- Moderate Risk Population (10-20% risk): As with High Risk populations, ASA should be used for prevention in this population as it can be predicted that the benefit will consistently exceed the potential for an adverse outcome.
- High Risk Population (>20% risk): While this level of risk is comparable to the level of risk in the secondary prevention studies, the current labeling of ASA does not acknowledge that such a level of risk can exist in the absence of a previous event. Amendments to the labeling to reflect the impact of global risk will ensure that ASA is prescribed in all patients with a 20% or greater 10- year risk regardless of whether a previous event has been experienced.

Labeling Can Effectively Guide Appropriate Treatment

Because the underlying cardiovascular risk can be reliably predicted through clinical judgment supported by a variety of risk evaluation tools (Discussed in Section 2.3) the population in which the benefit of ASA treatment is likely to outweigh the risks can be adequately defined. Importantly, effective labeling can be developed that clearly communicates the appropriate patient populations for using ASA in patients at sufficiently high risk of a first MI. Both the U.S. Preventive Services Task Force [1] and the American Heart Association [2] have developed an effective risk/benefit approach that recommends use of low-dose ASA for primary prevention of CVD in appropriate patient populations. Earlier recommendations were issued by the American Diabetes Association in 1997 [3] (latest update in 2003 [4]) and by the Second Joint Task Force of European and Other Societies on Coronary Prevention in 1998 [5].

1.2 The Role of Aspirin in Coronary Heart Disease

The information presented below provides the reviewer with background on ASA, including its pharmacology, marketing and regulatory history.

1.2.1 ASA's pharmacology explains its cardiovascular benefits

The role of platelets, platelet-derived products, and thrombosis in the pathogenesis of vascular disease, particularly atherothrombotic disorders, is well documented [6]. The principle mechanism of ASA involves inhibition of platelet activation and resulting aggregation in the early stages of thrombus formation, occurring as a result of the irreversible inhibition of

cyclooxygenase. ASA has powerful antithrombotic effects and has been studied in various categories of patients at risk of occlusive thromboembolic events.

The initial phase of arterial thrombus formation is postulated to result from aggregation of platelets to a damaged endothelial surface. Other clotting mechanisms then complete the process of thrombus formation. Platelet aggregation appears to be mediated mainly by an increase in cytoplasmic calcium caused by the release of platelet granule contents, mainly ADP, by the synthesis and release of thromboxane A_2 and by various external stimuli [7]. Within this pathway, the enzyme cyclooxygenase converts arachidonic acid to the unstable endoperoxide prostaglandin G_2. Prostaglandin G_2 is reduced to prostaglandin H_2 and this compound is then metabolized to thromboxane A_2 by thromboxane synthase within the platelets or to prostacyclin (prostaglandin I_2) by prostacyclin synthase in the vascular endothelium [8]. Thromboxane A_2 also constricts vascular smooth muscle [7], and the prevention of thromboxane A_2-induced vasospasm may be an additional benefit of ASA in patients at high risk of occlusive vascular disease.

ASA is the prototype of a class of drugs that decrease platelet aggregation via inhibition of the production of the principal platelet pathway product, thromboxane A_2 [9]. The molecular mechanism of the antiplatelet action of ASA is the irreversible acetylation and thus permanent inactivation of the key-enzyme cyclooxygenase (COX) or prostaglandin G/H synthase [10], which catalyses the first step of prostaglandin synthesis by the so-called arachidonic acid cascade. ASA selectively acetylates the hydroxyl group of a single serine residue at position 529 [11, 12] within the polypeptide chain of human platelet prostaglandin G/H synthase-1, causing the irreversible loss of its cyclooxygenase activity by blocking the active centre of this enzyme [13, 14]. This blockade results in the suppression of the main product of the arachidonic acid cascade in the platelet, thromboxane A_2 that exhibits pronounced aggregating and vasoconstricting effects. Its counterpart, prostacyclin (PGI_2), is produced by endothelial cells of the vessel wall, acting as an antiaggregant and vasodilator.

Thus, by inhibiting the COX enzyme and subsequently inhibiting thromboxane formation in platelets, ASA reduces the tendency of platelets to clot, decreasing platelet aggregation and ultimately decreasing the risk of coronary artery thrombosis. Thus, the cardiovascular benefits of ASA are clearly understood from its pharmacological action on the COX enzyme.

1.2.2 ASA is widely used as a safe and cost effective treatment for cardiovascular disease prophylaxis

ASA is indicated for both consumer (OTC) and professional uses. As a highly effective pain reliever and antipyretic agent, ASA can be used safely and effectively under OTC-compliant short-term dosing conditions. Under a physician's guidance, ASA is indicated for preventing cardiovascular events, as well as to treat a variety of inflammatory conditions. Today, over 10 billion tablets are consumed a year [15], with a total 6 billion tablets consumed as a cardiovascular therapy. The FDA has recognized this use for over a decade.

The analgesic effects of ASA-like substances have been known since the ancient Romans prescribed the bark and leaves of the willow tree (rich in salicin) to relieve pain and fever. In 1897, a Bayer chemist named Felix Hoffman chemically synthesized a stable form of

acetylsalicylic acid powder. Bayer introduced ASA powder in 1899, and it soon became the number one drug worldwide.

In 1948, Dr. Lawrence Craven, a California general practitioner, noted that the 400 men to whom he provided ASA hadn't suffered any heart attacks. Prompted by this observation, he recommended to all patients and colleagues that "an aspirin a day" could dramatically reduce the risk of heart attack. With further scientific study, FDA recognized ASA as an effective preventive tool in reducing the risk of stroke in 1980 and recurrent myocardial infarction in 1985.

With over 100 years of history of use, ASA is one of the most extensively studied drugs in the history of medicine and is still the focus of current research efforts. Bayer HealthCare is the proud marketer of Bayer® Aspirin and is a leader in the scientific advancement of ASA. It has also had a major role in the creation of programs to ensure that appropriate patients have access to ASA with dedicated focus on healthcare professional programs, as well as public education programs urging patients to speak to their doctor. Bayer has worked extensively with the FDA and is committed to continuing to work with the Agency to ensure appropriate use and labeling of ASA.

1.2.3 Regulatory History of ASA

ASA is unique among the cardiovascular drugs and differs in many ways from other products with similar pharmacological properties marketed as prescription drugs. Most noteworthy, is its extensive worldwide history of consumer use extending over 100 years, with a significant scientific body of evidence supporting the safety and efficacy of the product as a cardiovascular agent. In addition, it is unique with respect to the regulatory process of review and approval. It is a product reviewed as part of the FDA's Over-the-Counter Monograph process, both as an internal analgesic/antipyretic OTC drug product and as a cardiovascular and antirheumatic drug product labeled for professional use.

The Internal Analgesic, Antipyretic and Antirheumatic Drug Products for Over-the-Counter Human Use; Tentative Final Monograph (TFM), issued by the FDA (1988) [16] establishes proposed conditions under which over-the-counter analgesic, antipyretic, and antirheumatic drug products are generally recognized as safe and effective. It provides for approved active ingredients, dosing regimens, and permissible combinations of active ingredients, as well as labeling requirements for such products. The Monograph process allows for the evaluation of information from a variety of sources and scientific agreement in determining indications and claims. While the TFM details use conditions for a variety of OTC analgesic ingredients, the focus of this briefing book is the review of professional rulemakings pertinent to ASA.

The monograph process for OTC analgesics was initiated with a July 21, 1972 Federal Register notice requesting the submission of data and information on OTC internal analgesic and antirheumatic drugs. Data submitted for review included that for Bayer® Aspirin supporting its use as a safe and effective ingredient for the temporary relief of self-limited symptoms. At the time, ASA was the most widely used single drug in the U.S.; with its extensive use, long marketing history, and a relatively low incidence of serious side effects associated with short-term use, the safety was considered well-established for the majority of the population and the risk-benefit ratio is favorable. Following review of the data by the Advisory Review Panel on

Over-the-Counter Internal Analgesic and Antirheumatic Products (the Panel), a report was submitted to FDA. The Advanced Notice of Proposed Rulemaking (ANPR) was issued on July 8, 1977, followed by issuance of the TFM on November 16, 1988.

The Panel recommended the use of ASA as an antirheumatic drug product to be considered only under the advice and supervision of a physician, i.e., professional labeling. The professional labeling indications in the 1977 ANPR included: rheumatoid arthritis, juvenile rheumatoid arthritis, systemic lupus erythematosus, osteoarthritis (degenerative joint disease), ankylosing spondylitis, psoriatic arthritis, Reiter's syndrome, and fibrositis.

The TFM proposed to expand the professional labeling recommendations to include the preliminary cardiovascular indications for ASA. Based upon the data submitted [17, 18] and the August 28, 1979 Peripheral and Central Nervous System Drugs Advisory Committee recommendation [19], the use of ASA for reducing the risk of recurrent transient ischemic attacks or stroke in men was included; based upon data submitted and reviewed by FDA, the use of ASA was determined to be effective in reducing the risk of death and/or non-fatal myocardial infarction in patients with a previous infarction [20, 21, 22, 23, 24, 25] or unstable angina pectoris [26]. Thus, the professional labeling proposed reflected these indications. The following cardiovascular statements were added to the proposed professional labeling:

> *For reducing the risk of recurrent transient ischemic attacks (TIA's) or stroke in men who have had transient ischemia of the brain due to fibrin platelet emboli. There is inadequate evidence that ASA or buffered ASA is effective in reducing TIA's in women at the recommended dosage. There is no evidence that ASA or buffered ASA is of benefit in the treatment of completed strokes in men or women.*
>
> *To reduce the risk of death and/or non-fatal myocardial infarction in patients with a previous myocardial infarction or unstable angina pectoris*

The indication for use of ASA as a prophylaxis for primary myocardial infarction has been the subject of scientific and regulatory consideration in the past. On October 6, 1989, the FDA's Cardiovascular and Renal Drugs Advisory Committee considered the claim for ASA for the prevention of primary (first) heart attack based upon the Physicians' Health Study [27]. The Committee recommended (voting 5 to 3) that, although an indication should be considered for some high-risk group of patients, ASA should not be used routinely in patients without risk factors or in women, until such patients had been studied. The Committee minority was concerned about the toxicity of ASA and the number of normal individuals at low risk of having a heart attack who would be treated long-term.

The prophylaxis indication was again the subject of discussion at a joint meeting of the Cardiovascular and Renal Drugs and Nonprescription Drugs Advisory Committees on January 23, 1997 in response to a petition. At that time, the Committee recommended that ASA be labeled for primary prevention of myocardial infarction based upon the data submitted in the form of a Citizen Petition from the Physicians' Health Study [27].

The FDA published the Final Rule for professional labeling on October 23, 1998. The final rule, which includes full prescribing information for the professional uses of ASA was established. The submission of two Citizen's Petitions provided support to amend the professional labeling section of the TFM to include an indication for aspirin for suspected acute MI. Data from published reports [28, 29, 30, 31, 32] was used to support the use of aspirin for cardiovascular uses in women. The rule also recommended that aspirin at low-dose levels (e.g., 50 - 325 mg) be

used based upon positive study findings [28, 33, 34, 35, 36]. Based upon data [36, 37, 38, 27] reviewed and the January 23, 1997 Cardiovascular and Renal Drugs Advisory Committee recommendation, the indication for aspirin for subjects to 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 emboli, and to reduce the combined risk of MI and sudden death in subjects with chronic stable angina pectoris was approved. In addition, aspirin use in subjects who have had specific arterial revascularization procedures [39, 40, 41, 42, 43] (i.e., coronary artery bypass graft [CABG], primary percutaneous transluminal cardiac angioplasty [PTCA], or carotid endarterectomy) was also included. The FDA did not find data from the PHS [27] and BDT [44] trials sufficient to support the primary prevention indication.

Since the FDA's review of the PHS and BDT trials, new data has been published that supports the re-review of use of ASA in patients at lower cardiovascular risk than currently approved. The data to be considered include the PHS, the BDT, and the three new published reports: Thrombosis Prevention Trial [45], Hypertension Optimal Treatment Trial [46], and the Primary Prevention Project [47]. The diverse make up of these studies and consistent findings has led to a discussion of recommendations for ASA use based on risk rather than event-based considerations.

Following the publication of the three additional primary prevention trials (TPT and HOT in 1998, and PPP in 2001), and the subsequent United States Preventive Services Task Force (USPSTF) and American Heart Association recommendations [1, 2] for an expanded use of ASA for men and women at risk of a first coronary event, Bayer HealthCare filed a Citizen's Petition on February 11, 2003 requesting approval for "expanded cardiovascular indications and professional labeling for the use of ASA to reduce the risk of a first myocardial infarction in at-risk patients" based on this scientific consensus.

1.2.3.1 U.S. Aspirin OTC Labeling

ASA is labeled for OTC use as an analgesic and antipyretic ingredient in accordance with FDA's 1988 TFM. The recommended analgesic/antipyretic OTC treatment encompasses a broad dosing margin, with single doses ranging from 325 mg to 1000 mg, with a 4,000 mg maximum daily limit. Bayer ASA is available as 500 mg, 325 mg, as well as the 81 mg tablets. The products contain warnings in accordance with the TFM.

1.2.3.2 U.S. Aspirin Professional Labeling

Table 2 provides the professional labeling indications and dosing currently approved for aspirin. For full professional labeling for aspirin, refer to Appendix 1.

Table 2: Professional Labeling Indications/Dosing

Indications	Recommended Daily Dosing (Duration)
Vascular Indications:	
Ischemic Strokes and TIA	50-325 mg daily (Indefinitely)
Suspected Acute MI	160-162.5 mg taken as soon as infarction is suspected; then once daily (For 30 days post infarction - after 30 days consider further treatment based on indication for previous MI)
Prevention of Recurrent MI	75-325 mg daily (Indefinitely)
Unstable Angina Pectoris	75-325 mg daily (Indefinitely)
Chronic Stable Angina Pectoris	75-325 mg daily (Indefinitely)
Revascularization Procedures:	
Coronary Artery Bypass Graft	325 mg daily starting 6 hrs. postprocedure (1 year)
Primary Percutaneous Transluminal Cardiac Angioplasty	325 mg 2 hrs. pre-surgery; Maintenance therapy: 160-325 mg daily (Indefinitely)
Carotid Endarterectomy	80 mg daily to 650 mg twice a day started pre-surgery (Indefinitely)
Rheumatologic Disease Indications:	
Rheumatoid Arthritis	Initial dose 3 g daily. Target plasma salicylate levels 150-300 µg/mL (As indicated)
Juvenile Rheumatoid arthritis	Initial dose 90-130 mg/kg/day. Target plasma salicylate levels 150-300 µg/mL (As indicated)
Spondylarthropathies	Up to 4 g daily (As indicated)
Osteoarthritis	Up to 3 g daily (As indicated)
Arthritis and Pleurisy of Systemic Lupus Erythematosus	Initial dose 3 g daily. Target plasma salicylate levels 150-300 µg/mL (As indicated)

1.2.3.3 Worldwide Approvals Overview

ASA is currently approved for primary and secondary prevention in the following countries outside the United States: Argentina, Belgium, Belo Russia, Brazil, Canada, Chile, Columbia, Ecuador, Denmark, Georgia, Greece, Italy, Kazakhstan, Korea, Mexico, Norway, Peru, Philippines, Poland, Portugal, Russia, Slovenia, Switzerland, Turkey, Ukraine, Uzbekistan, Venezuela. Approved doses vary and range from 75 mg to 325 mg per day use.

For an overview of ASA worldwide cardiovascular indications, refer to Appendix 2.

2 CARDIOVASCULAR DISEASE HAS A MAJOR PUBLIC HEALTH IMPACT

Coronary heart disease (CHD) is a significant and growing public health concern impacting all populations, with broad personal and economical implications. The risks associated with CHD are well established and should be evaluated with regard to behavioral and therapeutic options to reduce the overall incidence of CHD and CHD events through regulatory action.

2.1 Cardiovascular Disease is a Serious Public Health Threat

Cardiovascular disease affects over 60 million Americans and results in substantial disability, loss of productivity, and a marked reduction in quality of life [48]. The American Heart Association reports CVD as the primary cause of death in the U.S., accounting for approximately one million deaths annually [49]. This year an estimated 650,000 Americans will experience a first MI while 450,000 will have a recurrent attack.

Table 3: Prevalence, Mortality, Hospital Discharges and Cost of CVD in the U.S. population.

Population Group	Prevalence	Mortality	Hospital Discharges	Cost
Total population	61,800,000	945,836	6,294,000	$351.8 billion
Total males	29,700,000	440,175	3,115,000	--
Total females	32,100,000	505,661	3,179,000	--
White males	30.0%	382,516	--	--
White females	23.8%	440,903	--	--
Black males	40.5%	48,708	--	--
Black females	39.6%	57,063	--	--
Mexican-American males	28.8%	--	--	--
Mexican-American females	26.6%	--	--	--

*Sources: **Prevalence**: NHANES III (1988-94), CDC/NCHS; data for white and black males and females are for non-Hispanics. Total population data include children; percentages for racial/ethnic groups are age-adjusted for Americans age 20 and older. **Mortality:** CDC/NCHS; data for white and black males and females include Hispanics; data include congenital cardiovascular disease. **Hospital discharges:** CDC/NCHS; data include people both living and dead. **Cost:** NHLBI*

CVD risk is prevalent in all populations and interventions are necessary to reduce the numbers of associated deaths. CVD has claimed the lives of more females than males, with the gap between male and female deaths increasing dramatically. Heart disease in women often goes untreated and undetected until it has progressed to a severe state, resulting in a high rate of fatal first cardiovascular events or expensive intensive medical treatment [49, 50]. Intervention is imperative to reduce a first MI in this population. The prevalence in racial and ethnic minority populations is a significant and growing public health concern, particularly for African-Americans, Asian/Pacific Islanders, Hispanics/Latinos, and American Indian/Alaska natives. Compared to other sex/race groups, coronary heart disease mortality rates are particularly high in

middle-aged African-American men, and stroke mortality rates are relatively high for African-American men in general [51].

2.2 Economic Costs of Cardiovascular Disease

The CVD-associated cost in the U.S. in 2003 is estimated at $351.8 billion, which exceeds that of all cancers and HIV infections [49]. The estimate includes health expenditures and lost productivity resulting from morbidity and mortality. The costs associated with non-fatal MI are associated with direct medical costs, costs of medicines, lost work time, as well as rehabilitation costs. In fact, the first-year incidence cost in the U.S. was approximately $16.3 billion (1996 dollars); the adjusted estimates for 2003 for per patient non-fatal MI costs would be approximately $19,000 and a 5-year per patient estimate for direct medical costs at nearly $100,000. This is a growing problem, especially with the prevalence of U.S. heart disease expected to double in the next half century [52, 2], thus the need for education on the changes in behavior modification and ready availability of effective therapeutic agents such as ASA, statins and antihypertensive agents will have a significant impact on public health as it relates to CVD.

Preventing a greater number of first heart attacks in the U.S. population would result in a substantial reduction in the associated personal and national health economic costs. The significant costs for follow-up treatment from a non-fatal MI includes diagnostic costs, and premature, permanent disability in the U.S. labor force and disability allowances costs, as well as the treatment of associated depression. The reduction in the occurrence of these events, across patients of any risk of having a heart attack, will have significant public health consequences.

In addition to the direct costs of hospitalization, diagnostics and drug therapy associated with a myocardial infarction in the acute and peri-infarction period, the indirect costs of managing the sequelae and the cost attributed to diminished quality of life must be considered when assessing the healthcare burden. In individuals who have suffered an MI, the risk of another heart attack or stroke is substantial; it is estimated that 18% of men and 35% of women will have a second MI. The most debilitating illness resulting from myocardial ischemia and cell death is decreased ventricular contractility leading to congestive heart failure (CHF), seen in about 22% of men and 46% of women in the years following a heart attack. CHD is the leading cause of premature, permanent disability in the U.S. labor force, accounting for 19% of disability allowances by the Social Security Administration. Patients experiencing CHF have varying degrees of physical limitation secondary to the limited ability of the heart to deliver oxygen to tissues, and are at risk of serious complications including pulmonary edema. Also, various long-term drug therapies are typically required to manage this disorder. Another consideration in patients who survive a myocardial infraction, particularly those who have subsequent disability, is depression. It is estimated that up to 25% of patients with a chronic medical condition will develop a major depressive episode during the course of the condition, and medical management of this depression also has an impact on health care costs.

2.3 Cardiovascular Risk is Definable

2.3.1 Individual Risk and Global Risk Assessment

Based on the advancements in our understanding of the risk factors for CVD, it is now possible to better define an individual's CVD risks and thus define populations at sufficient risk to warrant intervention. The estimates of absolute risk usually require that the contribution of each risk factor be identified and be evaluated as a global risk assessment (i.e., the global risk is a summation of individual risks to assess the progression of CVD). The data supporting these principles largely originate with the Framingham Study.

The Framingham Study [53], using an epidemiologic approach, has successfully identified or documented major contributors (or risk factors) of CVD; they include atherogenic personal attributes, living habits that promote these, signs of preclinical disease and host susceptibility to these influences. Established atherogenic traits include blood lipids, blood pressure and blood sugar. Elevated LDL has been shown to be positively related and increased HDL inversely related to the subsequent rate of occurrence of coronary disease. The total/HDL cholesterol ratio was established as an efficient lipid risk profile. Hypertension was shown to be powerfully and independently related to the occurrence of CVD. The importance of isolated systolic hypertension was established. Diabetes was shown to make a unique contribution to risk of atherosclerotic CV events with a greater relative impact on women than men.

The Framingham data provide a realistic picture of a given individual's true absolute and relative risks. Therefore, they can be helpful in identifying patients where risk factor management is appropriate. The National Cholesterol Education Program (NCEP) [54, 55] used Framingham data to link recommended intensity of cholesterol management to absolute risk. The paradigm of matching intensity of therapy to absolute risk was further endorsed and developed in a consensus conference sponsored by the American College of Cardiology (ACC) [56]. The National High Blood Pressure Education Program Joint National Commission (JNC), which sets forth guidelines for treatment of hypertension, also adjusted intensity of antihypertensive therapy to absolute risk in its guidelines [57]. Matching intensity of preventive regimens to absolute risk is attractive because it offers a way to achieve an appropriate balance of efficacy, safety, cost of therapy and professional time commitment. The effort to quantify each component of this balance requires an estimate of absolute risk. Because estimates of absolute risk require that the contribution of each risk factor be summed, the summation has been called global risk assessment.

As previously described, the Framingham Study provides a model for quantitative estimate of risk based on the contribution of each risk factor. Framingham data therefore can be used as the foundation of a risk-assessment program. Framingham investigators [58] have proposed an approach to global risk assessment. Because of the continuous relationship between intensity of risk factors and risk for CHD, Framingham researchers have delineated a risk scoring technique founded on the summation of graded risk factors. This technique is based on the theory that the relation between risk factors and the likelihood of developing CHD is continuous rather than threshold. The advantage of continuous risk factors over the use of categorical risk factors is that the former should provide more quantitative estimates of global risk. For example, by combining multiple marginal risk factors, the estimate of total risk should be more accurate in circumstances

in which categorical risk factors are absent but multiple risk factors are present. Adoption by FDA of this risk paradigm in the labeling for ASA will ensure that appropriate patients are prescribed an ASA regimen.

2.3.2 Tools and Calculators

Several Framingham-based risk calculators are available. These tools are published in several forms including risk charts and computerized calculators for personal digital assistants, personal computers, and web-based use. They require information on age, smoking status, blood pressure, total and HDL cholesterol, and the presence or absence of diabetes. These tools include: the National Cholesterol Education Program (NCEP) calculator; the American Heart Association calculator; the Med-decisions.com calculator; the Medical College of Wisconsin calculator. A recent review [59] of several of these tools concludes that, compared to the full Framingham equations, accuracy for identifying patients at increased risk was generally quite high.

The AHA recommends in their 2002 update [2] that risk factor screening should begin at age 20 and global risk estimation be done every 5 years on healthy adults age 40 and older. In addition, AHA offers guidance with respect to specific risk factors and the goals of treatment. Specifically, low-dose ASA is recommended for persons at higher CHD risk (especially those with 10-year risk of CHD greater than or equal to 10%).

Currently available Framingham-based risk prediction tools can be used as an aid to clinical judgment in the identification of appropriate patients and guide primary prevention strategies. The use of these tools along with proper management of risk factors provides the best opportunity for reducing the incidence of CHD.

The Coronary Risk Prediction Score Sheets for men and women based on total cholesterol level are included in Appendix 3.

2.4 Cardiovascular Events are Preventable

Preventive strategies aimed at the first cardiovascular events are immensely valuable in lowering morbidity, mortality, and economic cost. Considering the magnitude of CHD as a health problem, more should and can be done for population-wide primary prevention.

The causes of CHD are mostly known and modifiable. Except in patients with congenital heart defects and other cardiovascular ailments, heart disease is the end result of a combination of lifestyle and environmental factors [49]. It has been demonstrated in the Nurses Health Study for example, that managing these risk factors – controlling body weight, maintaining good nutrition, exercising regularly, not smoking, limiting alcohol intake – dramatically reduces the risk of developing CVD (by 84% in the women studied) [60]. More people need to be aware of these risk factors and educated on behavior modification, and physicians need guidance with respect to which patients to treat and aggressively manage. The AHA Guidelines provide a framework for primary care physicians to reinforce the public health recommendations of healthy lifestyle habits and drug interventions for primary prevention of CVD for at-risk patients [2].

Existing effective therapeutic agents such as ASA, statins, and antihypertensive agents should be made available to appropriate at-risk populations. Wald & Law collectively present the results of several published studies on these therapeutic agents [61]. (Refer to Table 4, below)

Widespread appropriate use of available treatments would have a profound impact on public health.

Appropriate patients for ASA therapy can be identified with confidence based on Framingham risk assessment models. The use of risk assessment and the appropriate intensity of treatment that follows is the basis for current hyperlipidemia and hypertension guidelines. The same strategy can be put in place for ASA and is supported by AHA guidelines. Patients deemed at sufficient risk should be offered ASA along with all other applicable risk modifying strategies (i.e., diet and exercise regimen, lipid and blood pressure lowering therapies, smoking cessation, etc).

Table 4: Effects of the Multiple Therapies on the Risks of Ischemic Heart Disease and Stroke After Two Years of Treatment at Age 55-64

Risk Factor	Agent	Reduction in risk factor	% reduction in risk (95% CI) *		Source of evidence
			IHD event	Stroke	
LDL cholesterol	Statin †	1.8 mmol/l (70mg/dl) reduction in LDL cholesterol	61 (51 to 71)	17 (9 to 25)	Law et al [1]
Blood pressure	Three classes of drug at half standard dose	11 mm Hg diastolic	46 (39 to 53)	63 (55 to 70)	Law et al [2]
Serum homocysteine	Folic acid (0.8mg/day)	3 µmol/l	16 (11 to 20)	24 (15 to 33)	Wald et al [3]
Platelet function	Aspirin (75 mg/day)	Not quantified	32 (23 to 40)	16 (7 to 25)	ATT[4]
Combined effect	All		88 (84 to 91)	80 (71 to 87)	

LDL = low density lipoprotein

* 95% confidence intervals include imprecision of the estimates of both the agent reducing the risk factor and the risk factor reducing risk

† Atorvastatin 10 mg/day, or simvastatin or lovastatin 40 mg/day taken in the evening or 80mg/day taken in the morning

To obtain the highest possible level of CV risk reduction in the U.S., it is important for the FDA to approve the indications in accordance with the supporting data. Furthermore, it is necessary for patients, clinicians, and health delivery systems alike to be knowledgeable about the benefit of applicable prevention guidelines [62, 57]. In line with FDA's approval and preventive guidelines, the keys to preventing CVD are education, access to treatment, and behavioral change.

[1] Law MR, et al. BMJ 2003;326:1423-7.

[2] Law MR et al. BMJ 2003;326:1427-31.

[3] Wald DS et al. BMJ 2002;325:1202-6.

[4] Antithrombotic Trialists' Collaboration. BMJ. 2002; 324:71-86.

3 EFFICACY: ASA PREVENTS MI AND CARDIOVASCULAR EVENTS

This section reviews the available evidence supporting the efficacy of ASA in the prevention of MI and cardiovascular events across the risk continuum. The extensive evidence includes a totality of 150 studies involving over 200,000 patients. These trials have studied over 55,000 Low Risk individuals and over 150,000 High Risk patients.

In contrast to other development programs, the overall database for ASA is incredibly diverse, including studies with the following factors:

- Broad continuum of age
- Patients with different underlying baseline risk (Low, Moderate, and High Risk patients)
- Different doses and formulations of ASA studied
- Geographical and ethnic/cultural diversity

This diversity, coupled with consistent findings across the studies provides added reliability of the findings as well as confidence in the broad applicability of the observed benefits. Thus, despite the fact that the ASA prevention database does not precisely meet the new drug approval requirement of two pivotal trials demonstrating significant effects in Moderate Risk patients, the available data are robust and consistent, adding, rather than detracting from the reliability of the overall findings and allowing an extrapolation from patients at Low and High Risk to patients at Moderate Risk.

Taken as a whole, the data support the effectiveness of ASA in preventing MI and cardiovascular events in patients at all levels of underlying risk.

The relevant efficacy prevention data are described first for Low Risk populations (Section 3.1) and next for the High Risk populations (Section 3.2).

3.1 ASA Prevents Cardiovascular Events in Low Risk Populations

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 myocardial infarction is supported by five prospective, randomized clinical trials conducted by independent researchers. These studies will be referred to throughout this document as follows:

- BDT: British Doctors' Trial (Appendix 4)
- HOT: Hypertension Optimal Treatment Trial (Appendix 5)
- PHS: Physicians' Health Study (Appendix 6)
- PPP: Primary Prevention Project (Appendix 7)
- TPT: Thrombosis Prevention Trial (Appendix 8)

These studies have been conducted in subjects with a variety of entry criteria, including elevated baseline cardiovascular risk in three 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 ASA's role in preventing MI across the risk continuum.

An overview of these studies, including their methodologies is summarized in the table below.

Table 5: 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	5139 (0)	22 071 (0)	2540 (0)	18 790 (8883)	4495 (2583)
ASA therapy dose (N)	500 mg/d 300 mg/d if later requested (3429)	325 mg qod (11 037)	75 mg/d (cont. rel.) (1268)	75 mg/d (9399)	100 mg/d (2226)
Control (N)	No placebo (1710)	Placebo (11 034)	Placebo (1272)	Placebo (9391)	No placebo (2231)
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; HOT: Hypertension Optimal Treatment Trial; PHS: Physicians' Health Study; PPP: Primary Prevention Project; TPT: Thrombosis Prevention Trial.
† 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 must be noted at the outset that these trials were not conducted as part of a clinical trial program initiated by a pharmaceutical company. Rather, they 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.

In these studies, a total of 2402 CVD end points occurred among nearly 55,000 randomized participants, including 11,466 women. There was no significant evidence of heterogeneity among the trials.

The results from these studies supporting the effectiveness of ASA in the prevention of MI will first be presented individually. Following a description of each individual study, they will be considered in aggregate and evaluated by meta-analyses.

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

A brief description of each individual trial demonstrating the effectiveness of ASA in preventing cardiovascular events in Low Risk populations is provided in this section.

3.1.1.1 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).[5]

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 consumption 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 percent reduction in risk (relative risk, 0.56; 95% CI, 0.45 to 0.70; $p<0.00001$). The risk reduction was limited to those 50 years of age or older ($p=0.02$). The incidence of fatal MI was also significantly lower with ASA therapy as compared to placebo (10 vs. 26, respectively; relative risk 0.34; CI 0.15 - 0.75; $p=0.007$). Finally, the incidence of non-fatal MI was also significantly reduced in those patients exposed to ASA by 31% (129 vs. 213, respectively; RR=0.59; CI = 0.47-0.74). The relevant MI data are compiled in the table, below.

[5] 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 6: **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	--	--	--

** 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 (relative risk, 0.96; 95% CI, 0.60 to 1.54; p=0.87). A combined endpoint consisting of non-fatal MI, non-fatal stroke and death from a CV cause yielded a statistically significant 18% reduction in those who were assigned to ASA (relative risk, 0.82; 95 % CI, 0.70 to 0.96; p=0.01).

7-Year Follow Up of PHS

After the ASA portion of the study was terminated in 1988 (following five years of study), the population was evaluated seven years later [63]. 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 then able to use these data to evaluate the relationship between self-selected post-trial ASA use with subsequent CVD and mortality in the period from 7 to 12 years of follow-up among those with no CVD before this time. During the five-year post-trial follow-up period, there were 311 unrefuted 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.

The investigators also observed a significant reduction in CVD-related mortality with self-selected ASA use (RR = 0.65; 95% CI = 0.47 – 0.89) and, as a result, in total mortality (RR = 0.64; CI = 0.54 – 0.77), findings that were not seen during the randomization period, suggesting that the original observation period was not sufficiently long to obtain meaningful mortality benefit.

3.1.1.2 British Doctors' Trial (BDT)

In this open 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. Regarding the incidence of myocardial infarction or stroke, no difference was observed in the study; 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 transient ischemic attacks (TIAs) was significantly reduced to 15.9% in the ASA group as compared to 27.5% in the control group.

The authors themselves attributed the lack of significance regarding 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 on the one hand the results of ASA therapy were diluted while on the other hand the control group results appeared to be better than they really were. Moreover, it might be speculated that concerning healthy individuals a much larger study population is necessary in order to demonstrate any clinically relevant effect on the incidence of vascular events.

3.1.1.3 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). The primary endpoint was all IHD defined as the sum of fatal and non-fatal events (i.e. coronary death, and fatal MI, and nonfatal MI). Treatment effects on fatal and non-fatal 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.

5499 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

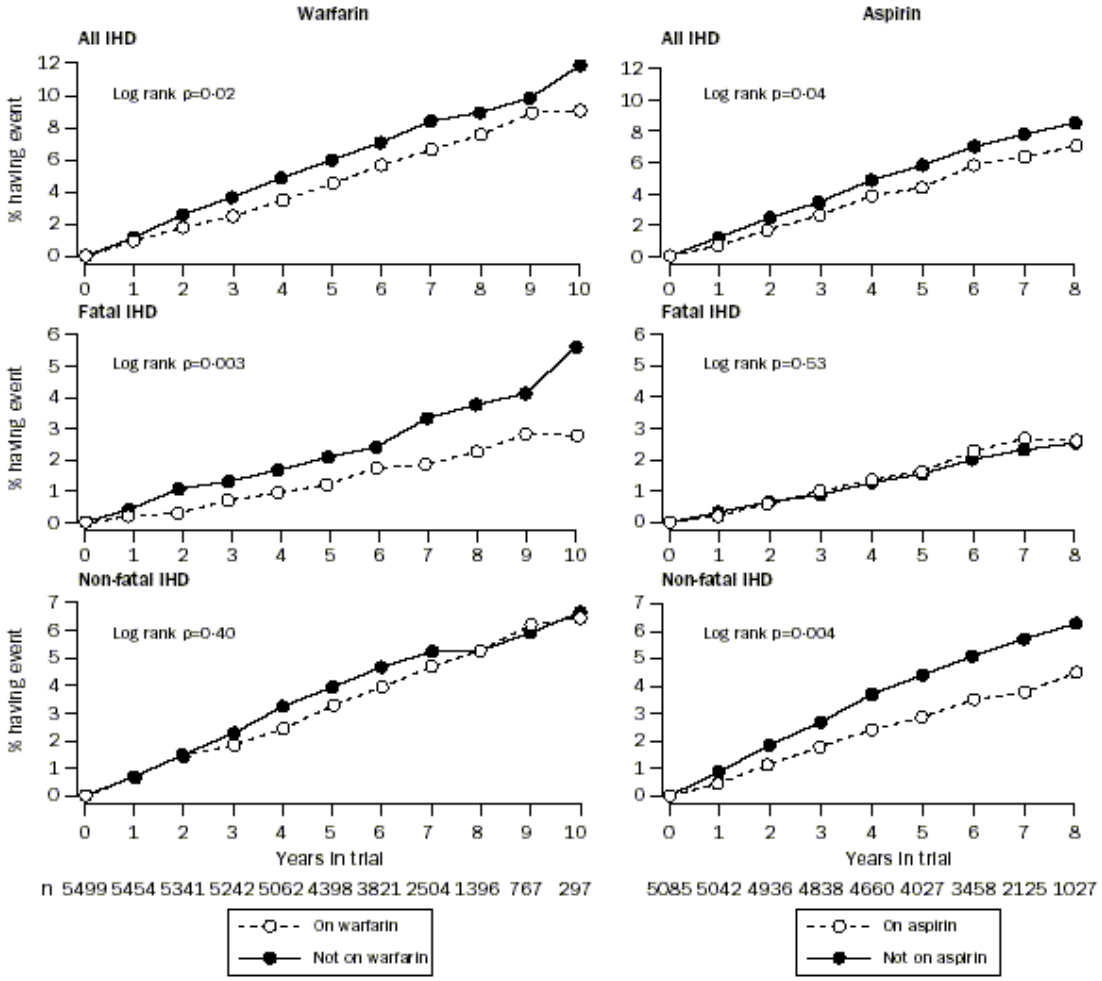
randomly allocated active or placebo ASA. Another 4072 men entered directly into the factorial stage of the trial making a total of 5085 men in the trial.

The four factorial treatment groups were: active ASA and active warfarin (WA; n = 1277), active ASA and placebo warfarin (A; n = 1268), active warfarin and placebo ASA (W; n = 1268), and placebo warfarin and placebo ASA (P; n = 1272). Subjects in this trial were given 75 mg/d of controlled release ASA.

The participants were regarded as being at a 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 [64]. The observation period was 8 to 13 years, median participation 6.8 years.

The primary effect of low-dose ASA was a 32% reduction in non-fatal 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 2: Cumulative proportion (%) of men with IHD, main effects (Figure 2 from TPT Study)



The results of the TPT Study clearly confirm the effectiveness of ASA in the prevention of MI in persons having cardiovascular risk factors. ASA had no effect on stroke or total mortality.

3.1.1.4 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 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 hypertensives, according to a five-step regimen. 9399 patients were randomly assigned low-dose ASA and 9391 patients were assigned placebo.

ASA reduced all MI (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 MIs were no longer significant when silent myocardial infarctions were included in the analysis. However, silent myocardial infarctions 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 on major cardiovascular events by 15% (p=0.03). Finally, it should be noted that there were no differences in antihypertensive therapy between the ASA and the placebo group. The data demonstrating the relevant risk reductions are provided below.

Table 7: Risk Reductions for Prevention of Cardiovascular Events in the HOT Study

Events	*Number of events*	*Events/1000 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 myocardial infarction				
Acetylsalicylic acid	388	11.1		
Placebo	425	12.2	0.17	0.91 (0.79-1.04)
All myocardial infarction				
Acetylsalicylic acid	82	2.3		
Placebo	127	3.6	0.002	0.64 (0.49-0.85)
All myocardial infarction, 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)

Events in relation to acetylsalicylic acid (n=9399) or placebo (n=9391)

It must be emphasised that the HOT Study is the first to demonstrate a beneficial effect of low-dose ASA in addition to antihypertensive therapy in the prevention of myocardial infarction 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, approximately 6% had other previous coronary heart disease), 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.

3.1.1.5 Primary Prevention Project (PPP)

The aim of the Primary Prevention Project (PPP) was to investigate the efficacy of 100 mg ASA per day given 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, 4495 subjects (57.4% women; mean age 64.4 y) with at least one vascular risk factor (e.g., old age, hypertension, diabetes, obesity, hypercholesterolemia, and family history of premature myocardial infarction) were included in an open, randomised, controlled 2x2 factorial design. The primary endpoint was the cumulative rate of cardiovascular death, non-fatal MI and non-fatal stroke. Secondary endpoints were each component of the primary endpoint, total deaths and other CVDs or 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, non-fatal MI, non-fatal 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 8: Relative Risk Reductions with Aspirin and Vitamin E Treatment

	Aspirin (n=2226)	*No aspirin (n=2269)*	*Relative risk (95% CI)*	*Vitamin E (n=2231)*	*No vitamin E (n=2264)*	*Relative risk (95% CI)*
Main combined endpoint (cardiovascular death, non-fatal myocardial infarction, and non-fatal 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 myocardial infarction	19 (0.8%)	28 (1.2%)	0.69 (0.38-1.23)	22 (1.0%)	25 (1.1%)	0.89 (0.52-1.58)
Non-fatal myocardial infarction	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)
Non-fatal 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)

All data are n (%) unless otherwise indicated. *Participants with one or more of the following events: cardiovascular death, non-fatal myocardial infarction, non-fatal stoke, 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 myocardial infarction, in persons at increased vascular 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 PPP was the first primary prevention trial showing a beneficial and significant effect of low-dose ASA on cardiovascular death. The lack of a placebo control is practically compensated by the fact that vitamin E did not show an effect on any pre-specified endpoint.

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.”

3.1.2 Meta-Analysis of Low Risk Trials

Eidelman and colleagues conducted a computerized search of the English literature from 1988 to 1998 and identified 4 published randomized trials of ASA in the primary prevention of CHD [65]. In a previous meta-analysis of these trials, ASA therapy was shown to significantly reduce the risk of a first MI by 32% and the risk of any important vascular event (nonfatal MI, nonfatal

stroke, or vascular death) by 13%. From 1998 to the present, a subsequent review of the English literature revealed 1 additional primary prevention trial of aspirin as well as new guidelines on the use of aspirin in the primary prevention of CHD. The fifth and most recently published trial of aspirin in the primary prevention of MI is the PPP. These investigators therefore updated their meta-analysis to include all five primary prevention trials.

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 end point of any important vascular event (non-fatal MI, nonfatal stroke, or vascular death), and each of these individual components separately.

The criteria for inclusion of trials were as follows: (1) aspirin alone was used for the primary prevention of CHD, as opposed to combined interventions; (2) comparisons of outcomes were made between aspirin 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 9.

3.1.2.1 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 below.

Table 9: Nonfatal Myocardial Infarction (MI) in the Randomized Trials of ASA in the Primary Prevention of Cardiovascular Disease

	ASA		Control	
Trial	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)			

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

3.1.2.2 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 10: Any Important Vascular Event in the 5 Randomized Trials of ASA in the Primary Prevention of Cardiovascular Disease

	ASA		Control	
Trial	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)			

3.1.2.3 Meta-Analysis: Vascular Death

For vascular deaths, there was no significant reduction in risk although the CIs 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).

3.1.2.4 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 aspirin on stroke. Summary estimates showed no statistically significant reduction in total stroke overall (OR =1.02; 95% CI = 0.85-1.23).

3.1.3 A Range of Doses Are Effective

The doses of ASA used in the five primary prevention trials ranged from 75 mg per day (in TPT and HOT) to 500 mg/day (in the BDT). While the BDT did not report a significant effect of 500 mg/day ASA on the prevention of nonfatal MI, the consensus view is that this trial was too small to detect a significantly meaningful benefit. The PHS did report a robust and statistically significant reduction in prevention of nonfatal MI of 44% at a dose of 325 mg every other day (details of this study are provided in Section 1.2.6.1). Studies in higher risk populations confirm that a wide range of ASA doses are effective in preventing cardiovascular events and support the proposed labeling to include doses of 75 mg – 325 mg/day [66].

3.1.4 Relevant Subgroup Analyses

Gender

The vast majority of the subjects in the five primary prevention trials were men (41,569 participants) and therefore the observed benefits are most easily generalizable to men.

Despite the preponderance of male subjects in the five trials, there were a substantial number of women represented across the trials. Of the five primary prevention trials, HOT randomized 8883 women and the PPP 2583, for a total of 11,466 women. In HOT, subgroup analyses were presented for women and there was a possible but nonsignificant 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 five 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 11: 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

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) [67].

Hypertension

The influence of hypertension on the effectiveness of ASA chemoprevention has been examined in subgroup analyses. In TPT, Meade et al., [64] found that ASA reduced total cardiovascular events in patients whose systolic blood pressure (SBP) was less than 130 mm Hg (RR = 0.59) but not in patients whose SBP was greater than 145 mm Hg (RR = 1.08). Patients with SBP between 130 and 145 mm Hg also had reduced risk (RR = 0.68). In PHS, patients who were taking ASA and had SBP greater than 150 mm Hg had a relative risk of 0.65 for MI, compared with relative risks of 0.55 for those with SBP between 130 and 149 mm Hg and 0.52 for those with SBP between 110 and 129 mm Hg. The HOT trial found significant reductions in CHD events among patients with treated hypertension, but did not have a comparison group without hypertension.

3.1.5 Other Relevant Meta Analyses

CTSU 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 five 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 aspirin on major cardiovascular outcomes (vascular events [as defined by non-fatal MI, non-fatal stroke, or vascular death], CHD events [non-fatal 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 aspirin involving high-risk patients (secondary prevention). As individual primary prevention trials have suggested that the net effects of aspirin 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%) of a CHD event, and to compare the effects of aspirin 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 aspirin based on the preliminary findings of the analyses set forth above. It is important to note that this analysis is based on the same five 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 aspirin 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 aspirin 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 can be found in Appendix 10.

Overall, in the ATT Primary Prevention Group analyses, which include 55,580 patients, there was a statistically significant 15% $\pm$ 4 reduction in vascular events that was largely driven by a 23% $\pm$ 5 reduced risk of CHD events. In contrast to the secondary prevention database, there was no net reduction in the risk of presumed ischemic stroke, and no reduction in vascular death. Based on this analysis, it might be expected that, among healthy individuals such as those generally studied in the 5 primary prevention trials, aspirin would prevent approximately 4-5 CHD events for every 1000 patients treated for 5 years.

The proportional reduction of about one quarter on 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.

While additional analyses are underway to further evaluate the absolute benefits and risks of ASA treatment based on underlying cardiovascular risk, the analyses suggest that there may be selected individuals at Moderate risk of a CHD event (i.e., greater than 1% per annum) who would be possible candidates for long-term ASA therapy. However, the analyses also highlight a relative lack of information from randomized trials concerning the effects of aspirin among moderate-risk individuals (such as those with "metabolic syndrome", for example), and suggest that the decision regarding the appropriateness of long-term aspirin in a given patient should give due consideration to these uncertainties as well as the underlying risk of CHD.

Finally, it should be noted that two other meta-analyses [68, 67] arrived at a similar findings to the CTSU and Eidelman and colleagues' analyses.

3.2 ASA Prevents Cardiovascular Events in High Risk Populations

As stated above, the efficacy of ASA as an antiplatelet drug in the prevention of cardiovascular events has been demonstrated in a large number of trials in a diversity of patient populations. The data obtained from patients that have already experienced a cardiovascular event (High Risk populations) are instructive in addressing questions that are not answerable with the Low Risk studies. In addition, studies in these High Risk populations provide the "anchor point" for the benefits of ASA for the high end of the risk continuum establishing the basis for extrapolating the benefits to Moderate Risk patients.

To provide support for the appropriateness of broadening the labeling of ASA to include Moderate Risk patients, the evidence from the secondary prevention database (i.e., High Risk patients) is described below. Because the populations in the High Risk and the Low Risk studies are homogeneous, 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.

3.2.1 The Antithrombotic Trialists' Collaboration (ATT)

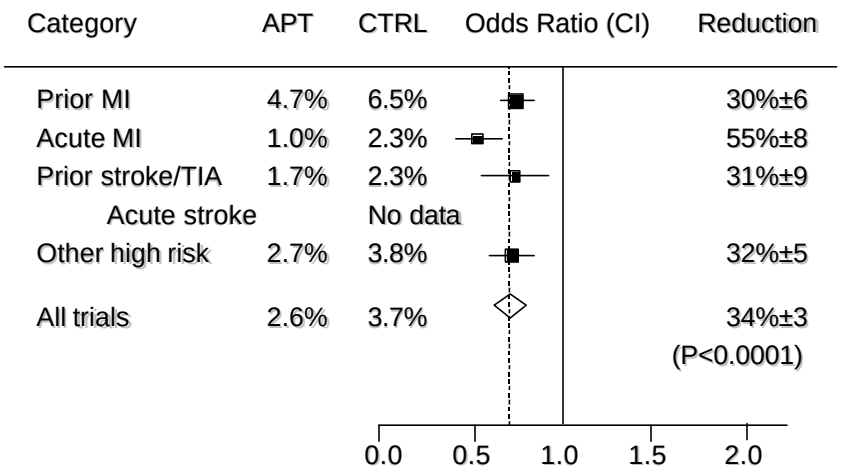
The systematic overview of the effects of antiplatelet therapy on vascular events conducted by the Antithrombotic Trialists Collaboration (ATT) [66] evaluated data from the following high risk patient populations:

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

This massive collection of data shows that, in approximately 200 randomized trials, antiplatelet therapy (with ASA being the most widely studied antiplatelet therapy) is highly effective in reducing the incidence of non-fatal MI in High Risk patients, at a similar rate (34%) as that observed in the Low Risk populations described above.

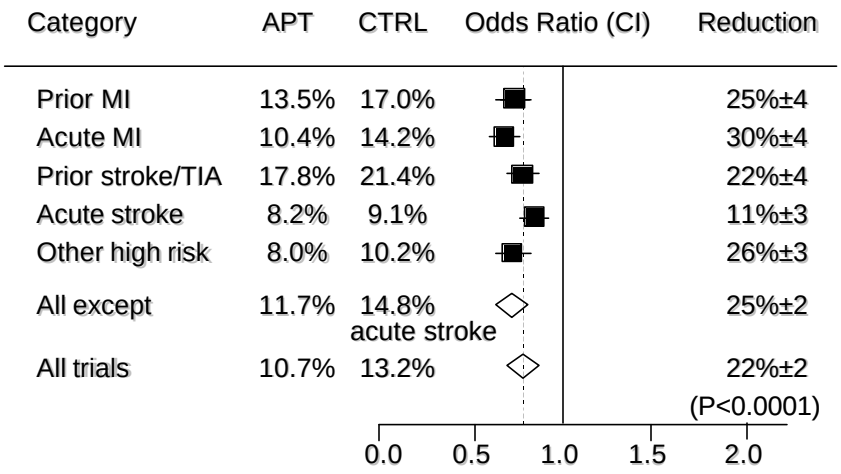
Figure 3 below provides a summary of the reductions in non-fatal MI demonstrated across a variety of patient populations.

Figure 3: ATT Collaboration Data: Non-Fatal Myocardial Infarction



In addition, antiplatelet therapy was also highly effective in reducing the number of vascular events across a wide range of High Risk patients. The risk reduction data are summarized in the following figure extracted from the ATT publication.

Figure 4: ATT Collaboration Data: Vascular Events



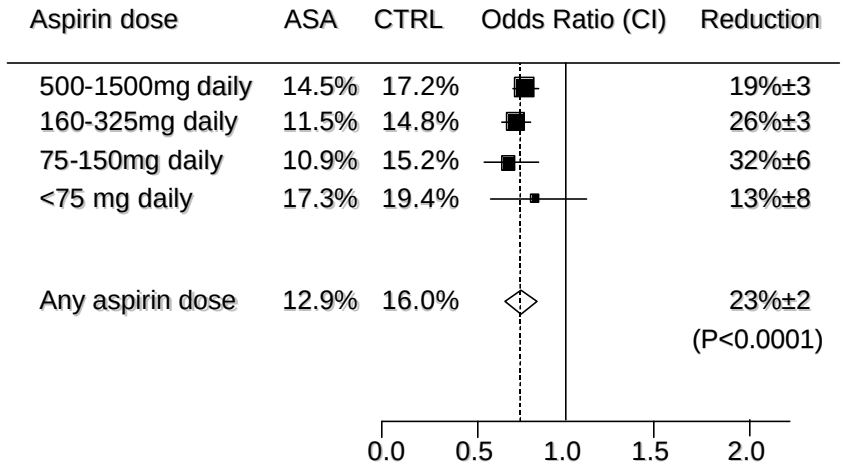
These studies in a variety of High Risk patient populations demonstrated that the proportional risk reductions for both non-fatal MI as well as for any vascular events are similar across populations. The authors of the ATT conclude: "Our results suggest that among individuals at high risk of occlusive vascular disease, the proportional risk reductions with antiplatelet therapy were roughly similar in most categories of patient (although they are smaller in acute stroke)."

3.2.2 Effect of ASA Dose on Vascular Events

The investigators reported a 26% – 32% reduction of the combined end points 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) exerts 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, below.

Figure 5: ATT Collaboration Data: Effect of Dose



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.

3.2.3 Relevant Subgroup Analysis

The analyses from the ATT have found that there was no significant effect of age or gender on the ability of antiplatelet therapy to prevent vascular events in a variety of High Risk patients. With respect to diabetes, according to these analyses, antiplatelet therapy was associated with a nonsignificant 7% proportional reduction in serious vascular events among patients with diabetes (but predominantly, no history of MI or stroke). The authors do not interpret this lack of statistical finding as indicating a lack of worthwhile benefit in such patients. Rather, taken as a whole, the ATT investigators interpret this finding as consistent with a benefit of antiplatelet therapy in this patient population. They specifically state that ASA "is likely to be effective for the primary prevention of vascular events among diabetic populations."

With respect to the effect of antiplatelet therapy in specific subgroups generally, the investigators state: "…these findings can reasonably be extrapolated to a far wider range of high risk patients than those studied…"

3.2.4 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 [69]. 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 and updated professional labeling for ASA. These uses included stroke in those who had a previous event or a TIA and MI in those who had a previous MI or a history of angina.

Six studies were identified meeting these inclusion criteria: [23, 85, 70, 36, 71, 72]. According to this analysis, among 6300 patients, 2427 experienced a previous MI and 1757 had a history of TIA or stroke. Among these 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 obtained from this meta-analysis are summarized in Table 12 below.

Table 12: Summary of Risk Ratio Estimates for 6 Studies Evaluating ASA For the Prevention of Stroke in High Risk Patients (adapted from Weisman and Graham, 2002).

Outcome	Risk Ratio (95%) Confidence Interval)	P Value	Risk Reduction, %	Homogeneity 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

3.2.5 High Risk Patients Provide Insight Regarding Effectiveness in Moderate Risk Populations

As mentioned previously, the available data confirm that similar proportional risk reductions for MI are obtained from patients that have experienced a previous serious cardiovascular event (High Risk populations) compared to risk reductions obtained from apparently healthy individuals that did not experience a previous cardiovascular event (Low Risk populations). This finding is evident from a review of the relative risk reductions for MI in the various groups of high risk and low risk patient populations studied, as shown below.

Table 13: Relative Risk Reductions of MI in High Risk and Low Risk Patient Populations are Similar

Trial	Underlying Risk of Patient Population	Relative Risk Reduction for MI
PHS	Low Risk	40%
BDT		3%
TPT		32%
HOT		--
PPP		31%
Overall		32%
ATT*	High Risk	34%
Weisman and Graham meta-analysis		30%

* Includes data for other antiplatelet studies in addition to ASA

Because the relative risk reductions are similar in High Risk and Low Risk patient populations, the results can be extrapolated across these risk strata to include Moderate Risk populations. They also highlight that the large and robust secondary prevention database can be used to address questions regarding effectiveness of ASA in subgroups such as gender, age, and diabetes subjects where the primary prevention database is either too small or not sufficient to address these issues statistically. Specifically, the relative risk reduction of 34% should be expected to prevent over 20 MIs for every 1000 patients treated for 10 years.

The final decision as to which patients should be considered for ASA preventative therapy based on their particular level of risk then becomes a risk benefit evaluation that will be discussed in Section 5, below.

3.3 ASA's 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;
- 14 MIs can be prevented for every 1000 Moderate-Risk patients treated for 5 years

4 SAFETY: THE EVIDENCE FOR ASA SAFETY

4.1 4.1 Safety Profile Overview

ASA is one of the most extensively studied drugs and its adverse event profile is well understood. The safety profile has been established largely from experience with analgesic and anti-inflammatory use. As is the case for most drugs, adverse events associated with the use of ASA are dose and duration dependent. With short-term, episodic, OTC labeled use, the rate of adverse events does not significantly differ from other OTC analgesics, including acetaminophen. In fact, a retrospective meta-analysis of 3700 patients in 54 single-dose ASA (325-1300 mg) dental pain studies found that occurrences of adverse events did not differ from placebo [73].

Several factors distinguish the use of ASA in cardiovascular prevention from its use for analgesic and anti-inflammatory indications. Cardiovascular dosing is typically lower than that used for analgesia and inflammation, but the duration of use is long-term rather than episodic. In addition, patients at risk for cardiovascular events are more likely to have underlying disease (e.g., diabetes mellitus, hypertension, hyperlipidemia) and are likely to be using other medications. For these reasons, the large, controlled clinical trials evaluating ASA for the prevention of cardiovascular events (i.e., the primary and secondary prevention trials) and the extensive postmarketing experience are used to evaluate the potential risks of treatment.

Due to the multitude of studies with large numbers of patients in secondary prevention of cardiovascular events it has been possible to obtain information on the risk of ASA associated with its use as a platelet aggregation inhibitor in lower doses for a time period of up to 7 years. In these clinical trials, the most important adverse events due to ASA are gastrointestinal side effects and intracerebral hemorrhage.

Based on the totality of the cardiovascular use evidence, it is reasonable to estimate that for every 1000 patients treated for a 5-year period, ASA therapy would be expected to cause an average of 3 significant gastrointestinal episodes and 1 case of hemorrhagic stroke. In contrast to other drugs, clinically relevant hazards of aspirin (bleeding) are related to the mechanism of action underlying its therapeutic utility.

4.2 4.2 Mechanism Of Action

As described above (section 1.3.1), ASA's beneficial mechanism of action is mediated by its ability to inhibit prostaglandin synthesis through an inhibitory effect on the cyclooxygenase enzyme (COX). The mechanism of action responsible for its analgesic and anti-inflammatory effect also has safety-related impact that is affected by dose and duration.

Inhibition of prostaglandin synthesis by ASA has been implicated in its tendency to cause gastrointestinal (GI) adverse reactions [74], including, in rare cases, gastric perforations, ulcers and bleeding. This effect is largely due to the inhibitory effects on a normally gastroprotective substance. ASA has been shown to affect neutrophil adherence, thus increasing the risk of mucosal injury. In addition, at the superficial mucosal level, ASA is a weak acid. In the highly acidic environment of the stomach, however, ASA is non-ionized and able to migrate across cell membranes into the superficial epithelium where it is metabolized. In its ionized form, ASA

traps hydrogen ions and can attenuate the protective effects of gastric mucosa, leading to epithelial damage [75].

Through its inhibitory role in thromboxane synthesis, and its subsequent inhibitor effects on platelet aggregation, ASA has been associated with the rare but unwanted side effect of increasing the risk of unintended bleeding, leading to an increased risk of intracerebral hemorrhage (i.e., hemorrhagic stroke). As such, the risk of hemorrhagic side effects is not likely to be separated from the antithrombotic effect, even by low doses of ASA.

Renal blood flow is prostaglandin mediated, and thus can be affected by analgesic ingredient use.

4.3 4.3 Safety by Body System

The evidence for the safety of ASA is reviewed in the sections below, with an emphasis on gastrointestinal effects, intracerebral effects and renal effects.

4.3.1 Gastrointestinal Effects

4.3.1.1 Overall Rate of GI Effects

GI adverse effects are by far the most important and consistently reported safety concern with ASA therapy. Serious adverse GI reactions have been reported to occur at an annual rate of 1-2% in individuals who take prescription strength NSAIDs and ASA regularly [76]. Nonetheless, recent data suggest that the suspected risk of ASA-induced GI injury, even under such use conditions, has been overestimated.

The risk of developing GI injury due to ASA is influenced by several factors, including dose and duration of use, use of concomitant medication, increasing age, co-morbid conditions, presence of *H. pylori* infections, and prior history of ulcers or stomach irritation [77, 78].

In addition to GI bleeding, endoscopic studies have implicated ASA use in the development of acute superficial lesions suggestive of mucosal injury [79, 80]. However, the clinical significance of these superficial lesions is uncertain, and no correlation to clinical outcome has been demonstrated. Specifically, acute endoscopic changes have not been shown to correlate with risk of bleeding, ulceration, or other untoward effects As such, endoscopic findings have very limited value in predicting the frequency or severity of chronic gastric ulcers or gastrointestinal bleeding. In fact, endoscopic findings were not accepted as a meaningful predictor of GI events when the FDA reviewed the approval of COX-2 inhibitors [81].

4.3.1.2 GI Data From Controlled Trials

Data relevant to the GI side effects of ASA derived from the five primary prevention trials are summarized in Table 14.

Table 14: ***Major Gastrointestinal Events in Primary Prevention Trials***[1]

	TYPE OF EVENT	% SUBJECTS WITH EVENT (NUMBER OF FATALITIES)		SIGNIFICANCE	EVENTS CAUSED PER 1000 PATIENTS TREATED WITH ASA PER YR
		ASA	control		
PHS	Upper GI ulcer	1.5 (1)	1.3 (0)	p=0.08	0.4
BDT	Peptic ulcer	2.6 (3)	1.6 (3)	P<0.05	1.7
TPT	Serious GI bleeding	1.7 (0)	0.8 (1)	Not significant	1.3
HOT	Major GI bleeding	0.8 (5)	0.4 (3)	Not reported	1.1
PPP	Severe GI bleeding	0.8 (0)	0.2 (0)	Not reported	1.5

Types of events captured and reported for each trial are different, but are the best estimates available for estimating overall gastrointestinal safety in this Low Risk population. Nonetheless, the much larger secondary prevention database provides more precise estimates of the hazards (summarized below).

4.3.1.3 GI Data from Meta-Analyses

In the meta-analysis conducted by Hayden and colleagues [82] of the Low Risk studies, the focus was on major extracranial bleeding. An odds ratio for ASA therapy was estimated to be 1.7 (CI 1.4 to 2.1), or an excess risk for major (mostly gastrointestinal) bleeding events of 0.7 (CI, 0.4 to 0.9) per 1000 patient-years. The estimates regarding excess GI bleeding events per 1,000 patients treated per year ranged from 0.4 (Physicians' Health Study) to 1.7 (British Doctors' Trial). The total numbers of fatal GI bleeding events across the studies were few; 9 in the ASA groups and 7 in the control group across the trials.

[1] Adapted from USPSTF, 2002

*Table 15: Estimates of the Role of ASA in Gastrointestinal Bleeding**

Trial (Reference)	*Type of Gastrointestinal Bleeding*	*Cumulative Incidence*		*P Value*	*Excess Bleeding Events per 1000 Patients Treated per Year*	*Fatal Gastrointestinal Bleeding Events*	
		Aspirin Group	*Control Group*			*Aspirin Group*	*Control Group*
		%				*n*	
BDT (5)	Self-reported peptic ulcer disease	2.6	1.6	<0.05	1.7	3	3
PHS (4)	Upper gastrointestinal ulcers	1.5	1.3	0.08	0.4	1	0
TPT (7)	Major or intermediate bleeding†	1.7	0.8	NR	1.3	0	1
HOT (8)	Fatal and nonfatal major gastrointestinal bleeding events‡	0.8	0.4	NR	1.1	5	3
PPP (9)	Gastrointestinal bleeding§	0.8	0.2	NR	1.5	0	0

*BDT = British Male Doctors' Trial; HOT= Hypertension Optimal Treatment Trial; NR = not reported; PHS = Physicians Health Study; PPP = Primary Prevention Project; TPT = Thrombosis Prevention Trial
†Major bleeding included fatal and life-threatening hemorrhages that required transfusion, surgery, or both. Intermediate episodes were bleeding events that prompted patients to notify research coodinators separately from routine questionnaires
‡Major bleeding was not defined.
§Described as severe but nonfatal.

The findings by Hayden and colleagues were similar to the findings of the meta-analyses of secondary prevention trials conducted by Roderick and colleagues [83]. They conducted an overview analysis of 21 placebo-controlled, randomized clinical trials, representing 70,000 person years of ASA exposure and found that ASA increased the pooled odds ratio for gastrointestinal bleeding (including non major bleeding, e.g., melena) (OE 1.5 to 2.0). The risk of subjective gastrointestinal symptoms was reported to be 1.7 and peptic ulcer 1.3 [83].

The risk of gastrointestinal hemorrhage with long-term use of ASA across a variety of uses (including both Low Risk and High Risk patient populations) was assessed in a meta-analysis by Derry and Loke [84]. They evaluated 24 randomized, controlled trials with almost 66,000 participants comparing ASA with placebo or no treatment for a minimum of 1 year. As expected, gastrointestinal 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, gastrointestinal hemorrhage occurred in 2.30% of patients taking ASA compared with 1.45% taking placebo (1.59; 1.40 - 1.81). Meta-regression showed no correlation between gastrointestinal hemorrhage and dose. For modified release formulations of ASA the odds ratio was 1.93 (1.15 - 3.23). According to the authors, these data suggest a number needed to harm of 248 per year.

Weisman and Graham evaluated the gastrointestinal risks of low dose ASA ($\leq$ 325 mg/d) when used in FDA-approved secondary prevention of cardiovascular events [69]. Using a computerized literature technique, the investigators reviewed the worldwide published literature to perform a meta-analysis of 6 trials (6300 patients) using ASA in approved secondary

prevention indications. The investigators reported that GI bleeding was a rare finding with only 58 reports across the 6 studies (41 in the ASA groups; 17 in the placebo groups). Only about half of the cases of GI bleeding were deemed severe enough to require treatment withdrawal. There were no reported deaths related to GI bleeding and GI bleeding led to almost no permanent morbidity (i.e., morbidity reported by the investigators of the studies). Only one report, the United Kingdom Transient Ischemic Attack (UK-TIA) trial [85] demonstrated a statistically significant increased risk of GI bleeding as a result of ASA intake. An analysis of GI bleeding across all studies suggests a common risk ratio of 2.5 (95% CI, 1.4-4.7; P=.001). Calculation revealed an absolute risk range for GI bleeding of 0% to 2.0% $\pm$1.4% (52-month follow-up).

The Antithrombotic Trialists' Primary Prevention Group also conducted a comprehensive meta-analysis based on individual patient data from the five available Low Risk primary prevention trials [66]. In their analysis, ASA use was associated with a nonstatistically significant increased risk of major bleeds (67%), suggesting that ASA might cause 4 - 5 major extracranial bleeds per 1000 patients treated for 5 years.

4.3.1.4 Labeling for GI Warnings

The professional labeling for ASA includes the following warning information associated with the risk of adverse GI effects in susceptible individuals. As the rate of adverse GI events are similar in the low risk studies, this warning should be sufficient to include the risks associated with broadened labeling.

> ***GI Side Effects:*** GI side effects include stomach pain, heartburn, nausea, vomiting, and gross GI bleeding. Although minor upper GI symptoms, such as dyspepsia, are common and can occur anytime during therapy, physicians should remain alert for signs of ulceration and bleeding, even in the absence of previous GI symptoms. Physicians should inform patients about the signs and symptoms of GI side effects and what steps to take if they occur.

4.3.2 Intracerebral Bleeding (Hemorrhagic Stroke)

4.3.2.1 Overall Rate of Intracerebral Bleeding

Based upon the available evidence, a reasonable approximation of the risk of hemorrhagic stroke associated with the use of ASA therapy in Low Risk patients is 0.2 events per 1000 patient-years. That is, for every 1000 patients treated for a 5-year period, ASA therapy would be expected to result in 1 excess hemorrhagic stroke.

4.3.2.2 Intracerebral Bleeding Data from Controlled Trials

Data relevant to hemorrhagic stroke from all five trials in Low Risk patients are summarized in the following Table:

Table 16: Hemorrhagic Stroke / Intracranial Hemorrhage in Primary Prevention Trials[1]

	% patients with event		Odds ratio (95%CI)	Events caused (or avoided) per 1000 patients treated with ASA per year
	ASA	Control		
PHS	0.21	0.11	1.92 (0.95 – 3.86)	0.20
BDT	0.38	0.35	1.08 (0.41 – 2.85)	0.05
TPT	0.24	0.16	1.51 (0.25 – 9.03)	0.12
HOT	0.15	0.16	0.93 (0.45 – 1.93)	(0.03)
PPP	0.09	0.13	0.67 (NR)	(0.12)

The estimates of the role of ASA in hemorrhagic stroke and intracranial haemorrhage showed 0.05, 0.12 and 0.2 approximate excess bleeding events per 1,000 patients treated per year in the British Doctors' Trial, the Thrombosis Prevention Trial and the Physicians' Health Study, respectively. In the Hypertension Optimal Treatment Trial and the Primary Prevention Project, the approximate bleeding events avoided per 1,000 patients treated per year were 0.03 and 0.12, respectively. These adverse event rates in the primary prevention trials do not differ appreciably from those seen in the secondary prevention trials, suggesting that the much larger database should be used in developing the Contraindications and Warnings sections of the professional label.

The effect of blood pressure on the occurrence of hemorrhagic stroke was not consistently demonstrated in these trials. Interestingly, in the HOT trial, where blood pressure was controlled, no difference in the occurrence of hemorrhagic stroke between the treatment and control groups was seen. In all studies, the difference in the percent of patients experiencing a hemorrhagic stroke or intracranial bleed (ASA vs. placebo) did not reach statistical significance, due to the very rare occurrence of these events.

4.3.2.3 Intracerebral Bleeding Data from Meta-Analyses

A number of meta-analyses have examined the effect of ASA on the incidence of hemorrhagic stroke in Low Risk patients [86, 65, 87].

Hart and colleagues pooled the results of the first four Low Risk studies (excluding PPP) and estimated that the relative risk for hemorrhagic stroke due to long-term ASA use was 1.36 (95% CI = 0.88 – 0.21). Sudlow's analysis reached a similar estimate (OR = 1.4; 95% CI = 0.9 to 2.0). Eidelman and colleagues calculated a slightly higher statistically non-significant elevated relative risk for hemorrhagic stroke (RR = 1.56; 95% CI = 0.99 – 2.46).

A comprehensive meta-analysis of hemorrhagic stroke has been conducted by He and colleagues (1998) across a wide variety of trials (including two Low Risk populations) [86]. These

[1] Adapted from USPSTF, 2002

investigators performed a meta-analysis of 16 trials (including 14 secondary prevention trials) that reported stroke subtypes involving more than 55,000 participants. The summary RR for hemorrhagic stroke with ASA use was 1.84 (CI, 1.24-2.74), or an increased absolute risk of 12 events (CI, 5-20) per 10,000 persons over about 3 years, or about 0.4 excess event per 1000 users annually ($p<0.001$). The number needed to cause 1 excess hemorrhagic stroke event was 833.

Finally, the Antithrombotic Trialists' Primary Prevention Group meta-analysis based on individual patient data from the five available primary prevention trials found that ASA use was associated with a 32% non-statistically significant increased risk of hemorrhagic stroke.

4.3.2.4 Labeling for Intracerebral Bleeding Warnings

The professional labeling for ASA includes the following adverse reaction information associated with the risk of intracerebral bleeding.

ADVERSE REACTIONS

Many adverse reactions due to aspirin ingestion are dose-related. The following is a list of adverse reactions that have been reported in the literature. (See **Warnings.**)

Central Nervous System: Agitation, cerebral edema, coma, confusion, dizziness, headache, subdural or intracranial hemorrhage, lethargy, seizures.

4.3.3 Renal Effects

4.3.3.1 Overall Rate of Renal Effects

The risk of analgesic-induced renal toxicity is low; however, some pre-existing conditions may increase the risk. Patients with diabetes [88], concomitant diuretic therapy, renal or hepatic impairment, cardiac failure, or old age, should use caution with non-prescription analgesic self-therapy. Elevations in blood urea nitrogen or serum creatinine levels have been reported with long-term high dose ASA [89], as well as short-term use in patients with underlying renal impairment [90]. Cessation of ASA use, however, typically results in a reversal of drug-induced effects on renal function [90, 89].

Analgesic nephropathy, a unique type of renal toxicity, has been reported with ASA; however, such toxicity occurs most often only after years of exposure to high therapeutic doses or mixtures containing at least two analgesics with caffeine or codeine [91]. Additionally, many early reports of analgesic nephropathy were reported in patients taking large amounts of products containing phenacetin [91], an ingredient that has been taken off the U.S. market due to toxicity.

4.3.3.2 Labeling for Renal Warnings

The professional labeling for ASA includes the following precaution information associated with the renal effects.

> ***Renal Failure:*** Avoid aspirin in patients with severe renal failure (glomerular filtration rate less than 10 mL/minute).

4.4 ASA Drug Interactions

4.4.1 Interactions with prescription medications

While ASA has been implicated in a number of drug interactions, physicians consider only a few such interactions to be clinically significant. Among the noteworthy drug interactions with ASA are those associated with concomitant oral anticoagulant, thrombolytic, uricosuric agent, sulfonylurea, corticosteroid, or methotrexate use [92].

Table 17: Drug-Drug Interactions with ASA that Warrant Caution

Prescription Drug	ASA
Oral Anticoagulants and Heparin	+*
Anti-thrombotics	+
Anti-convulsants	+
Uricosuric Agents	+
Corticosteroids	+
Methotrexate	+**
Sulfonylureas	+***

+ = Drug-drug interaction requires caution due to inherent risk of adverse event

*Despite the interaction between ASA and heparin use, the American College of Cardiology and American Heart Association promotes the use of ASA and heparin for management of patients with acute coronary syndrome (unstable angina) (Ryan, 1999)

**ASA administration to patients receiving low dose methotrexate therapy for treatment of rheumatic conditions is of little safety concern (Haas, 1999).

***Despite potential interactions between some anti-diabetic drugs and ASA, the American Diabetes Association (ADA) advocates the benefits of ASA, particularly for use as a primary prevention strategy in men and women with diabetes who are at high risk for cardiovascular events (American Diabetes Association, 2002).

4.4.2 Interactions with other Analgesics

Concomitant use of ASA with other OTC analgesic ingredients, including the NSAIDs, may increase risk of gastrointestinal [93, 94] or renal disorders [92]. The potential increased risk for GI and renal adverse events warrant caution with concomitant use of ASA with ibuprofen, naproxen sodium or ketoprofen.

Importantly, the efficacy of low-dose ASA used for cardiovascular benefit may be compromised by concomitant use of ASA with other NSAIDs. Treatment with ibuprofen in patients with increased cardiovascular risk may limit the cardio-protective effects of ASA [95].

4.5 Post Market Surveillance

4.5.1 Published ASA Safety Evaluations

It is important to evaluate ASA's safety profile from a postmarketing perspective. A review of reported adverse effects can assist in the development of warnings and contraindications for use, as well as areas for further investigation.

A number of published case analyses have specifically evaluated the gastrointestinal tolerability of chronic low dose ASA for cardiovascular prophylaxis and are instructive in assessing the potential hazards of broader ASA use. These analyses are based on findings from observational studies of a variety of types, and hence have differing degrees of reliability. Nonetheless, to provide the Committees with a complete understanding of the overall safety picture of ASA they are included herein for completeness.

Three relevant case-control observational studies have also been conducted [96, 97, 98]. These three studies specifically evaluated hospitalization for gastrointestinal bleeding and evaluated the effects of ASA.

Weil and Colleagues [96] evaluated hospitalization for bleeding peptic ulcer with prophylactic ASA regimens of 300 mg or less per day. This case control study was conducted with 1121 patients presenting with gastric or duodenal ulcer bleeding and age and gender matched hospital and community controls (989 subjects). Prior drug use was assessed by questioning patients who were admitted to selected hospitals in the UK with a report of hematemesis or melena secondary to gastric or duodenal ulcer. Only patients 60 or older were included in this evaluation. The number of cases reporting exposure to any dose of ASA at any time during the month before admission was 126 compared to 60 for the hospital and 57 for the community controls respectively, resulting in an odds ratio of 4.0 (2.8 – 5.8 CI). Rates varied appreciably by formulation.

Kelly [97] evaluated 550 incident cases admitted to 28 Massachusetts hospitals because of acute upper gastrointestinal bleeding. Cases as well as 1202 population controls were interviewed regarding their use of ASA and other nonsteroidal anti-inflammatory drugs during the seven days before presenting with a bleed. The odds-ratios for risk of bleeding varied between 2.6 and 3.1 based on various demographic groupings.

The study by de Abajo [98] represents a retrospective, population-based case control evaluation. Identified incident cases of upper gastrointestinal bleeding or perforation were from the General Practice Research Database (UK). Controls were randomly selected from the source population. A total of 2105 cases and 11500 controls were selected. Among them, 287 (13.6%) cases and 837 (7.3%) controls were exposed to ASA, resulting in a relative risk of 2.0 (1.7 –2.3).

4.5.2 Bayer Sponsored Post Marketing Study

To further evaluate the tolerability of low dose ASA, Bayer HealthCare conducted an open label post marketing surveillance study enrolling 2739 patients recruited from 577 physician practices. Patients were prescribed 100 mg enteric-coated aspirin tablets for prevention of cardiovascular or cerebrovascular events and followed for a period of two years, with 8 visits scheduled over this period. The mean age of participants was 65.4 years (23-97), 40.6% were women, and 57.3% were previously taking another ASA containing product. Interestingly, the main reason many entered the study was because of previous gastrointestinal complaints (42.2%) or heartburn (19.5%) with previously used ASA formulations.

The mean duration of treatment was 30.2 months. At baseline and at 3-month intervals, patients were evaluated by questionnaire regarding 8 gastrointestinal symptoms (heartburn, sensation of fullness, gastrointestinal complaints, nausea, vomiting, constipation, diarrhea, melena). In addition, bleeding events and other adverse events were collected.

A total of 460 (16.8%) patients did not complete the study. Reasons were lack of compliance, death (none related to study medication), non-medical reasons and others. Only thirty-four patients (1%) discontinued study medication due to intolerance.

Adverse events (Table 18) were largely (2.3%) non-specific gastrointestinal complaints. Gastrointestinal hemorrhage and gastric ulcer were reported in 0.2% and 0.6% respectively. Overall 10.6% of patients reported at least one adverse event.

Table 18: Adverse Event Rates in Post Marketing Surveillance Study

Adverse Effect	Patients (n)	Patients (%)	Number of Events	% Of Total Number
GI Complaints	64	2.3	68	19.2
Micro-hemorrhage	2	0.1	2	0.6
GI hemorrhage	6	0.2	6	1.7
Gastric Ulcer	17	0.6	17	4.8
Nausea	5	0.2	5	1.4
Vomiting	2	0.1	2	0.6
Diarrhea	3	0.1	3	0.9
Hypersensitivity Reactions	2	0.1	2	0.6
Other	190	6.9	249	70.3
TOTAL	291	10.6	354	100

4.5.3 Bayer Post Marketing Experience

All U.S. serious adverse events reported to Bayer HealthCare for ASA are captured in the Bayer Global Drug Safety database. Data in this database from 1999-mid 2003 was searched for all U.S. cases where a serious gastrointestinal event or a serious bleeding event was reported while

the patient was using aspirin. Importantly, during this time period, 10 billion Bayer aspirin tablets were sold in the U.S.

A total 79 cases meeting these criteria were identified. Forty cases (50%) were reported by consumers, sixteen (20%) were from clinical trials, seven (9%) were found in the scientific literature and four (5%) were reported by healthcare professionals. Fifty-six reports (71%) involved the gastrointestinal body system. Forty-three cases (54%) involved daily aspirin doses greater than 325 mg, including 12 cases from a clinical trial using 650 mg daily. Twenty-six reports (33%) involved doses between 325 and 81mg, and ten (13%) involved aspirin doses of less than or equal to 81 mg daily. Fifty (63%) of the patients identified in these cases were female, and the average patient age was 62 years. Approximately 58% of patients were taking ASA for cardiovascular prevention, which corresponds to estimates of the percent of total ASA sales in the U.S. for cardiovascular use.

Using sales volume as a surrogate for exposure, one can calculate a reporting rate for combined serious GI and bleeding events at 0.008 per million tablets sold, demonstrating that reports of these events are exceedingly rare.

4.5.4 FDA Office of Drug Safety Postmarketing Safety Review

The FDA Office of Drug Safety conducted a review of the postmarketing experience of ASA-containing products relating to gastrointestinal hemorrhage, ulceration, or perforation to better understand the circumstances that may result in these events. The review was conducted for the NDAC review of OTC analgesics September 2002. The review was limited to events reported to the FDA from January 1, 1998 through December 31, 2001 [99].

The analysis was based on the review of 541 cases of GI hemorrhage, ulceration or perforation reported for ASA-containing products. Most reports did not contain complete information related to the patients' prior medical history, medication use, and course of the GI event. The majority of patients in this analysis were taking low dose ASA (less than or equal to 325 mg per day) for cardio- or cerebrovascular indications. Use for cardiovascular disease prophylaxis was specifically mentioned in 181 of the cases. Use of multiple preparations containing aspirin was reported in only 10 cases (1.9%).

The mean age of patients in this analysis was 69.3 years. For the subset for which gender was reported, 63% (319/503) of the cases were male. The duration of aspirin use, while not reported in the majority of the cases, ranged from less than 1 day (after one dose) to 25 years. The median duration, for those cases reporting duration, was 42 days. The median daily dose and the dose most commonly reported was 325 mg per day.

Eighty six percent of the reports (468) involved hospitalization and 5% (29) died. Medical treatment was indicated in most of the reports, with only 24 patients requiring surgical intervention.

Table 19: Number of GI Events

GI Event or Finding	Number
Bleed	361
Ulceration	197
Perforation	9
Melena	101
Hematemesis	52
Gastritis	29
Hematochezia	20
Erosion	10
Duodenitis	6
Esophagitis	5
Colitis	3
Other GI	4
TOTAL	797

Remarkably, 485 patients (approximately 90%) had one or more risk factors or other possible causes for their GI event. Risk factors included a significant GI medical history (111 cases), concurrent medication that may have increased risk of a GI bleed (366 cases), a concurrent smoking or drinking history that may have increased risk (75 cases). Sixty-seven percent of the 347 patients listed age greater than 65 as the only risk factor. Additionally, although not quantified, many patients had other significant intercurrent illness or past medical history that might put them at increased risk of a GI event. These findings are suggestive that with appropriate warnings and effective physician evaluation the benefit-to-risk relationship for aspirin can be enhanced.

4.7 Conclusion

The safety profile of ASA is well characterized, and toxicity is generally dose-related and adverse events are extremely rare, especially at lower doses. Based upon the data, the most important adverse events due to ASA when used for cardiovascular therapy, include the GI effects and intracerebral hemorrhage.

5 PATIENTS CAN BE IDENTIFIED FOR WHOM THE CARDIOVASCULAR BENEFITS OF ASPIRIN OUTWEIGH THE RISKS

5.1 Overview of the Risk/Benefit Analysis

ASA has clear therapeutic benefits in the prevention of MI in patients in a variety of underlying risk categories ranging from Low Risk to High Risk as summarized in Section 3. However, ASA is also associated with specific, well-defined risks (summarized in Section 4) that must be taken into account before a clear recommendation for ASA therapy can be made in any given individual.

In patients with high underlying cardiovascular risk (i.e., patients with a greater than 20% 10 year CHD risk), the benefits of ASA therapy clearly outweigh the risks for prevention of MI and therefore ASA has been recommended by numerous professional bodies for treatment in this population. However, the current FDA approvals for ASA limit its use to patients who have suffered a previous event (a High Risk group), failing to recognize that many individuals may be at sufficient risk of MI to warrant treatment in spite of not having had a previous event (a Moderate Risk group). The available data also clearly demonstrate that the benefits of ASA in the prevention of MI can be appropriately extended to individuals at Moderate Risk (i.e., individuals with a greater than 10% risk of CHD over 10 years). A clear understanding of the number of MIs that can be prevented in this population can be easily determined by applying the proportional risk reductions observed across the risk continuum to the underlying 10% 10 year risk. The known hazards of chronic low dose ASA can then be compared to these benefits to demonstrate that a favorable benefit to risk relationship can be achieved. In fact, in the Moderate Risk population, 2-3 CHD events can be prevented for every adverse event caused.

Of course, for individuals with a 10-year risk that is <10% (a Low Risk individual), the absolute number of coronary heart disease events that would be avoided in treating 1000 patients over a 5 year period, is 4 (1 - 12), compared to the absolute number of hemorrhagic strokes 1 (0 - 2) and major GI bleeding events 3 (2 - 4) that would be caused. Because this differential is not great, the risk-benefit analysis might reject the recommendation of ASA for cardiovascular disease prevention in these individuals. Of course, the severity of the risk (i.e., GI bleeds) must also be weighed in relation to the magnitude of the benefit (i.e., preventing a potentially life-threatening MI).

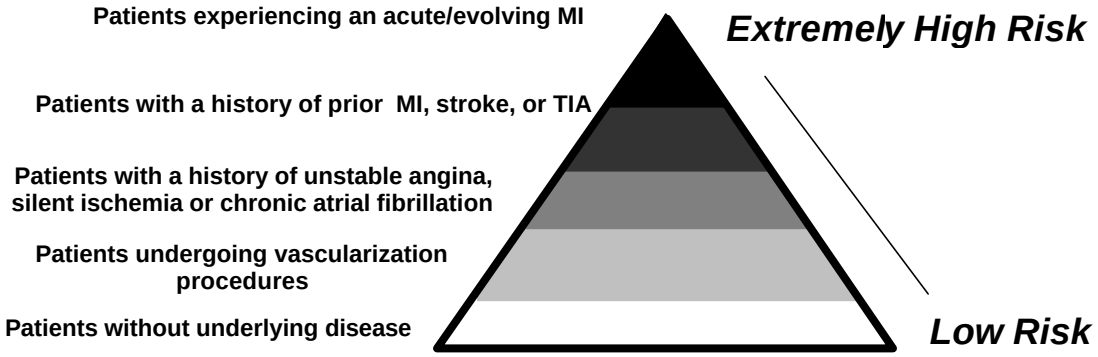
5.1.1 Extrapolation to Broad Patient Groups is Appropriate

A comprehensive cardiovascular risk assessment is of critical importance in assessing whether an individual patient should be considered a candidate for treatment, as it determines the goals of therapy and the intensity of the intervention. As in all areas of medical practice, the risk assessment guides the clinical judgement of the physician as it relates to the management of the individual patient. Today, the physician can draw on many resources to make informed decisions regarding treatment options. These include a large body of evidence from epidemiological studies and from prospective clinical trials toguide therapeutic decision-making.

With respect to ASA, the database is large and robust and provides significant insight regarding the benefits and hazards of preventative therapy that exceed other therapeutic interventions. Nonetheless, in spite of its size, the ASA database does not include every single permutation of the risk continuum and therefore requires an understanding of the pathophysiology of the underlying disease process and the pharmacology of the agent to make appropriate extrapolations relative to a decision regarding a specific patient.

Importantly, an appropriate risk evaluation is necessary in the selection of the appropriate type and intensity of treatment, including whether or not drug treatment is appropriate. Such an assessment will identify those patients in which the risk of an event is significantly great enough to necessitate intervention.

Figure 6: Vascular Event Risk



There is no question that risk is enhanced as a consequence of having suffered a previous serious vascular event. As highlighted in Figure 6 above, persons experiencing an acute, evolving MI are at greatest risk of a nonfatal or fatal vascular event. Those with unstable angina, a history of prior MI, stroke, TIA, chronic stable angina or atrial fibrillation, as well as patients undergoing a revascularization procedure or haemodialysis, are also at substantially elevated risks of occlusive vascular events. However, those without clinically evident vascular disease, but with underlying pathology/multiple risk factors (including high cholesterol level, high blood pressure, diabetes or a history of smoking) are at intermediate risk, a group referred to in this document as Moderate Risk. And, finally, those without overt manifestations of vascular disease or risk factors are at much lower risk.

If one considers cardiovascular risk as a continuum, with individuals who experienced a previous cardiovascular event at one end (i.e., the group with the highest underlying risk) and those with underlying risk factors who are otherwise "healthy" at the other end (i.e., the group with lower underlying risk) a logical risk model can be established. Of course, healthy individuals with no underlying risk factors would be the group with the lowest underlying risk. The expected benefits of an intervention along this continuum depend on the risk/benefit analysis, with the clearest benefit being conferred to those at the higher levels of underlying risk.

Today ASA is indicated in individuals who have suffered a previous vascular event (MI, TIA, stroke, angina). The suggestion that many patients exist who could benefit from ASA in spite of the fact that they have not experienced a previous event necessitates revision of the labeling to include those at elevated risk (Moderate Risk), defined as those with a 10% or greater risk of a

CHD event over the next 10 years (or 1% per annum). Risk-based strategies are currently recognized as effective in selecting patients for a variety of interventions, including cholesterol and blood pressure lowering agents.

5.1.2 Risk Assessment Can be Guided With Appropriate Tools

There is a large gap between which evidence-based interventions are recommended and what is actually carried out in clinical practice. The challenge for healthcare professionals is to engage greater numbers of patients at an earlier stage of their disease, so that many more individuals may realize the benefits that primary prevention can provide. Guidelines, even when based on the best available evidence from randomized, controlled trials, cannot be successfully implemented without broad understanding by the healthcare team. In other words, a physician-patient partnership must be forged. As part of this partnership, the physician must assess and effectively communicate to the patient information pertaining to underlying CHD risk as well as benefits and risks of therapy and must develop, with the patient, a plan of preventive action.

Risk for future CHD events can be predicted from coronary risk algorithms. Factors used to estimate risk include sex, age, blood pressure, serum total cholesterol level, diabetes mellitus and cigarette smoking. These established risk factors allow physicians to accurately assess an individual patient's 10-year risk of having a cardiovascular event, allowing the determination as to the appropriateness of a variety of interventions. Several easy-to-use risk assessment tools, most based on risk equations derived from the Framingham Heart Study, are available and can be used to facilitate clinical decision-making. Framingham data have recently been shown to generalize adequately to other populations.

The natural response when confronted with the utility of tools to assist in clinical decision-making is to ask whether they have been adequately validated. While a reasonable question, it is clear that these are only tools to assist physicians in their clinical evaluation and should not be viewed as definitive "diagnostic tests" requiring specific performance standards. As there are not fine lines between patient groups who should be treated and those who should not, such precision is not required.

Based upon the available risk calculators and working backwards, Moderate Risk for CHD can be defined as an individual that meets any one of the following four criteria:

1. presence of one risk factor of severe degree sufficient to warrant intervention (e.g., a middle aged man who smokes a pack a day);
2. presence of two risk factors of moderate degree (e.g., a middle aged man with a plasma cholesterol of 200-300 mg/dL plus HDL-cholesterol less than 40 mg/dL or obesity);
3. a quantitative risk assessment that exceeds 1% per year; or
4. presence of type 1 or type 2 diabetes mellitus without microvascular complications.

In quantitative terms, a High Risk individual presents with a CHD risk of 2% per annum or greater (i.e., 20% over 10 years). In contrast, a Low Risk individual would have less than 1% per annum risk (i.e., 10% over 10 years). The Moderate Risk individual falls in between these two extremes.

To provide a sense of the ease in which global risk can be evaluated, the following examples are presented below.

Example 1. Solitary elevated LDL-cholesterol (180 mg/dL)

A 45 year-old man with systolic blood pressure 130 mmHg, HDL-cholesterol 49 mg/dL, triglycerides 90 mg/dL, LDL-cholesterol 180 mg/dL, total cholesterol 247 mg/dL, smoker, non-diabetic. *This patient's CHD risk is 13% over 10 years, i.e. "moderate risk".*

Example 2. Multiple risk factors including elevated LDL-cholesterol (180 mg/dL)

A 45 year-old man with systolic blood pressure 180 mmHg, HDL-cholesterol 30 mg/dL, triglycerides 250 mg/dL, LDL-cholesterol 180 mg/dL, total cholesterol 260 mg/dL, smoker, non-diabetic. *This patient's CHD risk is 31% over 10 years, putting him in the highest risk group.*

Example 3. Multiple risk factors, normal LDL-cholesterol (100 mg/dL)

A 45 year-old man with systolic blood pressure 180 mmHg, HDL-cholesterol 30 mg/dL, triglycerides 250 mg/dL, LDL-cholesterol 100 mg/dL, total cholesterol 180 mg/dL, smoker, non-diabetic. *This patient's CHD risk, despite the normal LDL-cholesterol level is 20% over 10 years, also putting him in the highest group.*

As the available evidence strongly supports the effectiveness of ASA in reducing the MI risk in both Low Risk and High Risks groups, it is intuitive that it would also be of benefit in Moderate Risk individuals. It is also logical and appropriate to conclude that the absolute benefit would be proportionate to the underlying risk and therefore greater in Moderate Risk patients than in Low Risk patients. To make an appropriate decision as to whether ASA is appropriate in this Moderate Risk group one needs to understand the hazards of treatment as well. With this information, the risk-benefit relationship can be established.

5.2 The Risk-Benefit Relationship of ASA in Moderate Risk Patients

5.2.1 Benefits of ASA Treatment in Moderate Risk Patients

There is compelling evidence that ASA reduces the risk of a first MI appreciably in Low Risk patients. The analysis by Eidelman, *et. al.* [56], which was published in the September 2003 issue of *Archives of Internal Medicine* and serves as the basis of our petition, demonstrates a highly significant 32% risk reduction in nonfatal MI. The USPSTF systematic review of the pooled data from the five primary prevention studies came up with a comparable estimate, concluding that ASA therapy reduced the risk of coronary heart disease by 28% (summary odds ratio 0.72, 95% CI 0.60 to 0.87) [1], as did the Antithrombotic Trialist Primary Prevention Group that found a 23% risk reduction. While these estimates appear different, because of slight variations in how the data were handled, they are suggestive of the same clinical impact.

In light of the clear and consistent evidence that ASA reduces the risk of MI in Low and High Risk trials combined with the fact that these two databases represent a homogeneous group of patients with the same underlying pathologic basis for cardiovascular events, it is reasonable and appropriate to use these data to develop an integrated model for the expected relative and absolute benefits in MI. As the absolute benefits in terms of MI reduction increase as one moves

from a healthy to a more "at risk" population, there is no question that the benefits of ASA therapy will be enhanced.

In patients at particularly High Risk of vascular events, the benefits of antiplatelet therapy are evident. For example, among 1,000 patients with acute MI who are given one month of ASA (ASA) and then continue to take low-dose ASA for some years, about 40 would avoid a serious vascular event during the first month and a roughly equivalent number of patients would avoid a vascular event in the next couple of years. Even in patient populations at a 2-3% annual risk of serious occlusive vascular events (e.g., patients with stable angina who have not had a previous vascular event), antiplatelet therapy for one to two years would be expected to prevent about 10-15 vascular events for every 1,000 patients treated. As a consequence, there is no question that if underlying risk of MI is sufficiently high, the benefits increase, regardless of the intervention.

5.2.2 Risks of ASA in Moderate Risk Patients

To fairly assess whether a patient at a certain cardiovascular risk should be considered a candidate for ASA therapy, it is important to know the "cost" of the benefit (in terms of side effects). It is possible to address this question by evaluating the totality of safety evidence derived from a variety of sources. As the hazards of treatment are not expected to be affected by underlying cardiovascular risk (if anything, candidates for primary prevention would presumably be healthier and therefore at a lower risk of adverse bleeding events), it is prudent to be conservative and assume that the same risks accrue to all chronic users of ASA. By doing so, it is possible to utilize the complete ASA database, including high-risk studies and post marketing experience to address the hazard side of the risk benefit analysis.

The side-effect profile of ASA has been well established. Much is known about the pharmacology of ASA and its anticipated adverse effects from over 100 years of use as well as hundreds of controlled clinical trials. As specified in the safety summary (Section 4), the primary safety concerns associated with chronic ASA use are GI bleeding and hemorrhagic stroke. As expected, the safety data demonstrate that adverse event rates are constant across the cardiovascular risk strata and suggest that the risk of injury can be projected to be the same in patient groups not necessarily included in the current database.

The findings with respect to the adverse effects of greatest interest suggest that chronic low dose ASA use can increase the risk of GI bleeding 2-3 fold and hemorrhagic stroke risk by about one-third. This would result in approximately 1 excess major extracranial bleed for every 1000 patients and 1 hemorrhagic stroke for every 10,000 patients exposed to ASA. Such risks would be expected to be equivalent whether one evaluates Low, Moderate, or High Risk patients.

5.2.3 The Benefit to Risk Relationship is Favorable in Moderate Risk Patients

The benefit to risk evaluation with respect to the use of ASA in Moderate Risk patients must therefore compare the expected absolute benefits and risks of treatment. As outlined above, the risks of treatment across the cardiovascular risk continuum are well established. Likewise, the benefits of treatment in reducing the risk of MI across the continuum are supported by equivalent proportional risk reductions in both the low and high-risk databases. The only additional variables that affect the risk-benefit analysis are the clarity of understanding of an individual's

underlying cardiovascular risk profile and an appreciation of individual history that may alter the risk, such as a history of gastric ulcer.

Clinicians can effectively assess cardiovascular risk and counsel patients with respect to the benefits and risks of treatment options. This, coupled with clear and consistent evidence that significant benefits can be achieved, safely mandates the need for broader labeling to include patients at Moderate Risk of CHD. The broader use in this population would be expected to prevent 2-3 CHD events for every extracranial bleed. As highlighted in the Safety section, the vast majority of bleeds are not life threatening and are appropriately managed through standard medical care. A therapeutic margin of this magnitude is consistent with other interventions of this type and should therefore lead to more broad scale appropriate use.

5.3 Recommendations

To ensure that appropriate candidates are not denied the benefits of ASA, while ensuring an appropriate therapeutic margin, numerous guidelines have been developed that have specifically set the point at which ASA therapy is appropriate at an underlying risk level that is higher than that in the five studies that comprise the primary prevention database. Our proposal to include individuals at Moderate Risk of MI in the professional labeling for ASA is consistent with the views of these major public health organizations, which have independently reviewed the evidence in development of guidelines for reducing the burden of cardiovascular disease in this country. The promulgation of guidelines by the United States Preventive Services Task Force and the American Heart Association highlights that significant scientific consensus exists regarding the public health importance of broadening the aspirin labeling to include patients "at risk" who have not suffered a previous cardiovascular event.

5.3.1 The U.S. Preventive Services Task Force Recommendations

The favorable benefit to risk relationship for the use of ASA in Moderate Risk patients is clearly demonstrated by the recent U.S. Preventive Services Task Force recommendations (2002) [1]. Furthermore, the taskforce acknowledges the importance of global risk assessment, including asking about 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 (in younger adults), and smoking in determining whether an individual patient should be a candidate for ASA therapy.

The taskforce estimated the benefits and harms of ASA administered for 5 years to 1000 persons with various levels of baseline risk for coronary heart disease, basing their estimates on a clearly supportable relative risk reduction of 28% for coronary heart disease events in ASA-treated patients derived from the five primary prevention studies in Table 20 below. 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 20: Estimates of Benefits and Harms of Aspirin Given for 5 years to 1000 Persons with 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 aspirin-treated patients and assume that risk reductions do not vary significantly by age.
†Nonfatal acute myocardial infarction and fatal coronary heart disease. Five-year risks of 1%, 3%, and 5% are equivalent to 10-year risks of 2%, 6% and 10% respectively.
‡Data from secondary prevention trials suggests that increases in hemorrhagic stroke may be offset by reduction in other types of stroke in patients at very high risk for cardiovascular disease. (≥10% 5-year risk).
§Rates may be two to three times higher in persons older than 70 years of age.
**Based on an analysis of secondary prevention studies

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 5-year risk that is greater than 3% (a 6% risk over 10 years). In this population, 4 - 12 coronary heart disease events would be avoided, while only 0 - 2 hemorrhagic strokes and 2 - 4 major GI bleeding events would be caused when treating 1000 patients for a 5-year period. Thus, the risk-benefit analysis clearly works in favor of recommending ASA for cardiovascular disease prevention in this Moderate Risk individual.

5.3.2 The AHA Recommendations

Using the meta-analysis by Hayden and co-workers [82] as a basis, the American Heart Association arrived at a more conservative recommendation than the U.S. Preventive Services Task Force [1]. According to the latest AHA guidelines for primary prevention [2], 75 to 160 mg ASA per day should be considered for persons at higher risk, especially those with a 10-year risk of coronary heart disease of ≥10%. Treating such patients would further enhance the benefit to risk relationship and prevent 14 events (range: 6 to 20), a benefit of cardiovascular risk reduction which outweighs possible harms estimated to result in an excess of 1 hemorrhagic stoke (range: 0 to 2) and 3 major gastrointestinal bleeding events (range: 2 to 4) among 1,000 persons treated over a 5-year period.

5.3.3 Bayer HealthCare Recommendations

This Citizen's Petition follows the more conservative recommendation by the American Heart Association of defining only patients at Moderate Risk (those with a 10-year risk of coronary heart disease of ≥10%) as eligible for treatment in order to make sure that the patients' benefit of treatment clearly outweighs potential risks. If appropriate patients are selected, many more heart attacks can be prevented for the small number of adverse events caused.

5.4 Conclusions: ASA Therapy Should Be Recommended for Those Individuals for Whom the Benefit Outweighs the Risk

The available data support the following specific guiding principles for arriving at a risk assessment as to whether an individual patient should be considered appropriate for ASA for the prevention of MI:

- The risk of experiencing a first MI increases proportionally with an individual's overall underlying, measurable, cardiovascular risk.
- The appropriateness of any intervention for MI (including ASA therapy) should be evaluated in the context of that individual's global risk of experiencing an MI (first MI or subsequent MI).
- The proportional benefits and risks of ASA therapy are similar in individuals who are at High, Moderate, or Low Risk and are known and predictable
- Because the proportional risk reductions of ASA are consistent across the studied Low Risk and High Risk populations, the benefits can reasonably be expected to extend to a Moderate Risk population where the absolute benefits will be greater than the benefits in the Low Risk population.
- The benefits of ASA therapy should be offered to those who might accrue the greatest benefit.
- A large number of patients exist who are at sufficiently high risk of MI to warrant intervention even if they have not had a previous event.
- To maximize the benefit-risk relationship, patients at Moderate Risk (e.g., 10% or greater 10 year risk) where the benefit would be expected to far exceed the risk should be specifically included in the labeling.

Some might suggest that it would be inappropriate to approve the use of ASA in Moderate Risk patients without additional study. However, this is an overly cautious point of view. The label will clearly and appropriately limit exposure to those at sufficiently elevated risk (based on all the available scientific evidence) and, as set forth here, will greatly improve the benefit-to-risk relationship. Furthermore, such an approach validates the view that decisions are based on the totality of the evidence, including the pathophysiology of the underlying condition. Finally, this approach is consistent with previous precedent in restricting access to a more limited population than specifically studied in the pivotal clinical trials.

Based on this recommendation, the routine use of ASA by Moderate Risk patients would be expected to result in 6 – 20 CHD events prevented at an appropriate level of risk of side effects per 1000 patients treated in a 5-year period. Based on these findings ASA represents a worthwhile intervention that should be used more broadly in this population.

6 GOALS OF LABELING ASA FOR PRIMARY PREVENTION

The FDA is charged with assuring that drugs are safe and effective for their intended use and that their labeling provides adequate information for such use and is not false or misleading. Informing physicians about uses and necessary precautions is an important element in fulfilling that responsibility. As new information becomes available to the agency, the labeling of drug products should reflect the new information after scientific and regulatory review.

Based on the body of evidence available showing a favorable benefit to risk relationship and the issuance of the AHA and USPSTF recommendations, along with the underutilization of ASA, it is important to consider swift revisions to the professional labeling for ASA.

6.1 Benefit-Risk Assessment

The labeling for a product serves as the tool to communicate the appropriateness of therapy and necessary precautions associated with therapy. The labeling for ASA should define the appropriateness of therapeutic intervention based upon the evaluation of benefit-to-risk relationship. Since the side effect profile of ASA is well established, with the primary concerns of chronic use being GI bleeding and hemorrhagic stroke, the focus of changes in labeling should be to delineate the benefit to risk relationship associated with treatment of ASA in a broader at risk population.

The currently approved professional labeling for ASA and the proposed labeling to be considered can be found in Appendix 1. The expanded labeling approved must adequately define the “moderate” risk population (CHD risk of 10% over 10 years or in patients for whom there is a positive benefit-risk as assessed by their health care provider), to ensure a positive therapeutic margin where the benefits of treatment would outweigh the risks. The recommended level of adverse event risk is greater than the baseline cardiovascular risk in the Low Risk population studies. This 10% over 10 years was conservatively chosen to ensure a positive therapeutic margin where the benefits of treatment would significantly outweigh the risks and is consistent with the current guidelines of the AHA based on their evaluation of the benefit-to-risk relationship.

6.2 Underutilization of Treatment

A survey [63] was conducted to determine the prevalence of use of ASA or other OTC analgesics to prevent or treat CVD. The survey participants included 23,158 persons aged 40 or over with no prior CVD and 3818 that reported prior CVD. Results demonstrate that 10% of the respondents reported regular use of any analgesic for primary prevention; 8% specified reporting using ASA. Only 43% of the participants that reported prior CVD used ASA. Based upon the results of the survey, there is a need from a public health standpoint to address this underutilization of therapy and to ensure appropriate product use. Professional labeling of ASA and educational programs to support the appropriate use of ASA in a population at risk for CVD would have a significant positive public health impact.

7 EDUCATION

Directing cardiovascular health associated information to both the patient and the physician are necessary to ensure appropriate ASA use. The patient must be a part of the decision-making process with regard to their health choices and must be directed to seek medical input and advice, while the physician must have the labeling and risk assessment tools to appropriately evaluate the patient. The process whereby this will be achieved is through responsible educational healthcare communications from a variety of sources, including, but not limited to the FDA, industry, and professional organizations such as the American Heart Association.

7.1 Patient/Consumer Education

The importance of having the patient participate in the decision-making process as it relates to their health is necessary from a public health perspective. The patient needs to understand how risks associated with cardiovascular disease (among others) impact their health, and how behavior modification can reduce those risks. In order for this to be a success, the public must have ready access to important healthcare information. The responsibility for the communication of accurate healthcare information lies with all parties concerned with public health.

Bayer HealthCare takes its role seriously and has helped to educate the public on the risks associated with cardiovascular disease and the behaviors known to mitigate these risks, with the goal of encouraging individuals to visit a physician and have their personal risk assessed. Brochures have been distributed through Bayer HealthCare Consumer Relations, physicians and in retail outlets on such topics as how to recognize the symptoms of a heart attack, steps to better heart health and heart health for women. In 2003, over 3 million brochures have been distributed to consumers. In addition, Bayer has provided tools to consumers with cardiovascular disease risk factors, such as high blood pressure, diabetes and high cholesterol, through the sponsorship of blood pressure kiosks, educational booklets and distribution of information on responsible aspirin use. Individuals can also obtain additional information by calling the toll-free number, which is listed on all Bayer Aspirin products (1-800-331-4536), or by visiting Bayeraspirin.com. Bayer plans to continue to expand these information resources over time.

The broadest approach to reaching individuals at risk of a cardiovascular event is via media (television, magazines, radio, internet). Direct-to-Consumer (DTC) advertising has increased consumer's knowledge about the availability of various drug products, with the focus on speaking to their doctor. In 1999 the FDA conducted a national telephone survey [100] of adults (with a follow-up mail survey) to ask their views on DTC promotion of prescription drugs. Although aspirin is not a true "prescription" drug, the results from the FDA's survey highlight some areas that are applicable to ASA as a drug product with professional labeling. The FDA's Survey demonstrates that more consumers need to consider seeing their physician. The results of the survey showed that there were a significant group of respondents that had not seen a doctor in more than a year (28% of those patients categorized as not having seen a doctor in the last 3 months responded that they had not seen a doctor for their own health condition or health concern for "more than 1 year").

The public health impact of ASA "DTC" advertising is aimed at communicating the importance of CV health and the importance talking to their doctor before starting an ASA regimen.

7.2 Physician Education

Physicians are provided with new information from a wide variety of sources. New information comes in numerous ways, e.g., guidelines, new publications, new drug products, changes in drug products, CME topics, industry detailing. The importance of keeping up with new medical/scientific information for all drug products continues as new information emerges. This is especially relevant to emerging information on the cardiovascular medicine front. Physicians need to increase the consumer/physician interactions to stem the underutilization of therapy and behavior modification needed to treat the growing CVD problem. Physician directed educational programs help to encourage the medical community to recognize the importance of their role in assessment and treatment of patients' cardiovascular risks. Bayer HealthCare has a wide range of medical communication initiatives to inform, educate and assist physicians and other healthcare providers implement the appropriate use of aspirin in their patient populations. In 2003, 180,000 physician office visits have been made and Bayer Aspirin-sponsored CME programs have reached over 100,000 physicians and pharmacists.

In addition, Bayer has developed physician tools and patient materials to help facilitate the discussion between doctors and their patients about their risk for cardiovascular disease and to help determine if aspirin therapy is right for them. Physicians can download cardiovascular risk assessment guides by logging on to www.bayeraspirin.com/savinglivesASAP. Electronic versions are also being made available for physicians to download onto their personal digital assistants (PDAs). Additionally, copies are to be distributed to physicians via the Bayer sales force and at major medical meetings.

7.3 Professional Associations

To further enhance the communication of credible cardiovascular risk reduction information, Bayer HealthCare partners with a number of leading health authorities, such as The American Stroke Association, The American College of Obstetricians & Gynecologists, and the American College of Emergency Physicians. Bayer is also a major sponsor of the American Heart Association (AHA) to help raise awareness of the risks of cardiovascular disease and ways to help control risk factors. An AHA partner for more than a decade, Bayer provides particular support to initiatives supporting healthcare professional education. These AHA initiatives include:

- Healthcare Professional AHA Guidelines Distribution: Bayer HealthCare will continue to aid AHA in disseminating primary and secondary prevention guidelines, to provide the latest science and education on this topic to multiple professional audiences;
- Underwriting of related scientific conferences on this topic;
- Distribution of Healthcare Professional Tool Kit Materials;

Bayer has also expanded its nationwide partnership with VHA Inc, the largest cooperative of not-for-profit hospitals in the U.S., comprising 2,200 healthcare organizations, in support of the Women's HeartAdvantage program. The goals of this educational program are to raise cardiovascular disease awareness among women, and to encourage and enhance communication between physicians and patients. The program strives to change women's heart health behavior through the prevention, detection and treatment of risk factors. Bayer HealthCare through this program provide more than 100 hospitals with aspirin compliance packs, which are provided by the physician to appropriate patients upon discharge from the hospital. The compliance packs are designed to help patients new to an aspirin regimen follow their physician-prescribed therapy. In 2003, 100,000 discharge kits have been distributed through this program.

Bayer HealthCare looks forward to continuing to improve and expand its outreach to doctors and patients through its own efforts as well as through partnerships with organizations dedicated to improving cardiovascular health.

8 CONCLUSION

Bayer HealthCare has provided compelling evidence supporting the urgency for the expanded use of ASA in a broader “at risk” population, i.e., moderate risk (10% 10-year CHD risk). The totality of the efficacy and safety evidence supports the utility of ASA in preventing MI in this population. Based on this evidence, regulatory action is necessary to align the FDA approved ASA labeling with current practice guidelines that define the current appropriateness of therapeutic intervention based upon the evaluation of benefit-to-risk in all patients at increased risk for CHD.

9 LIST OF APPENDICES

Appendix 1. Aspirin Professional Labeling / Proposed Labeling

Appendix 2. Aspirin Worldwide Cardiovascular Indications

Appendix 3. Coronary Disease Risk Prediction Score Sheets for Women and Men Based on Total Cholesterol Level

Appendix 4. British Doctors' trial (BDT): Peto, R.; Gray, R.; Collins, R.; Wheatley, K.; Hennekens, C.; Jamrozik, K.; Warlow, C.; Hafner, B.; Thompson, E.; Norton, S.; Gilliland, J.; Doll, R. Randomised trial of prophylactic daily aspirin in British male doctors. BMJ 1988; 296: 313-316.

Appendix 5. Hypertension Optimal Treatment trial (HOT): Hansson, L.; Zanchetti, A.; Carruthers, S.G.; Dahlöf, B.; Elmfeldt, D.; Julius, S.; Ménard, J.; Rahn, K.H.; Wedel, H.; Westerling, S. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. Lancet 1998; 351: 1755-1762.

Appendix 6. Physicians' Health Study (PHS): Steering Committee of the Physicians' Health Study Research Group. Final report on the aspirin component of the ongoing Physicians' Health Study. N.Engl.J.Med. 1989; 321: 129-135.

Appendix 7. Primary Prevention Project (PPP): Collaborative Group of the Primary Prevention Project (PPP). Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general practice. Lancet 2001; 357: 89-95.

Appendix 8. Thrombosis Prevention Trial (TPT): Medical Research Council's General Practice Research Framework. Thrombosis Prevention Trial: randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischemic heart disease in men at increased risk. Lancet 1998; 351: 233-241.

Appendix 9. Eidelman, R.S.; Hebert, P.R.; Weisman, S.M.; Hennekens, C.H. An Update on Aspirin in the Primary Prevention of Cardiovascular Disease. Arch Intern Med. 2003; 163: 2006-10.

Appendix 10. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomized trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002; 324: 71-86.

10 REFERENCES

1 U.S. Preventive Services Task Force. Aspirin for the Primary Prevention of Cardiovascular Events: Recommendation and Rationale. Annals of Internal Medicine. 2002 Jan 15; 136(2):157-160.

2 Pearson. AHA Guidelines for Primary Prevention of Cardiovascular Disease and Stroke: 2002 Update. Circulation. 2002; 106:388-91.

3 American Diabetes Association. Aspirin therapy in diabetes. Diabetes Care. 1997 Nov; 20(11):1772-3.

4 American Diabetes Association. Position Statement: Aspirin Therapy in Diabetes. Diabetes Care. 2002; 25(1):213-229.

5 Wood D, De Backer, G, Faergeman O, Graham I, Mancia G, Pyörälä K together with members of the Task Force. Prevention of coronary heart disease in clinical practice. Recommendations of the 2nd Joint Task Force of European and other Societies on Coronary Prevention. Eur.Heart J. 1998; 19:1434-1503.

6 Fuster, V.; Dyken, M. L.; Vokonas, P. S., and Hennekens, C. Aspirin as a therapeutic agent in cardiovascular disease. Special Writing Group. Circulation. 1993 Feb; 87(2):659-75.

7 Fuster, V.; Adams, P. C.; Badimon, J. J., and Chesebro, J. H. Platelet-inhibitor drugs' role in coronary artery disease. Prog Cardiovasc Dis. 1987 Mar-1987 Apr 30; 29(5):325-46.

8 Kerins, D. M. and FitzGerald, G. A. The current role of platelet-active drugs in ischemic heart disease. Drugs. 1991 May; 41(5):665-71.

9 O'Reilly, R.A. Drugs used in disorders of coagulation. In: Katzung, B.G., Ed. Basic and Clinical Pharmacology, 3rd Ed. Norwalk, Conn: Appleton & Lange; 1987:372-383.

10 Roth, G. J.; Stanford, N., and Majerus, P. W. Acetylation of prostaglandin synthase by aspirin. Proc Natl Acad Sci U S A. 1975 Aug; 72(8):3073-6.

11 DeWitt, D. L. and Smith, W. L. Primary structure of prostaglandin G/H synthase from sheep vesicular gland determined from the complementary DNA sequence. Proc Natl Acad Sci U S A. 1988 Mar; 85(5):1412-6.

12 Funk, C. D.; Funk, L. B.; Kennedy, M. E.; Pong, A. S., and Fitzgerald, G. A. Human platelet/erythroleukemia cell prostaglandin G/H synthase: cDNA cloning, expression, and gene chromosomal assignment. FASEB J. 1991 Jun; 5(9):2304-12.

13 Smith, W.L. Molecular Mechanisms of aspirin action. DN&P. 1991; 4:362-366.

14 Shimokawa, T. and Smith, W. L. Prostaglandin endoperoxide synthase. The aspirin acetylation region. J Biol Chem. 1992 Jun 15; 267(17):12387-92.

15 Mediscope, The Health Information Company. **www.mediscope.org**. Accessed October 2003.

16 Food and Drug Administration. Over-the-Counter Drug Products Containing Analgesic/Antipyretic Active Ingredients for Internal Use: Proposed Rule. Federal Register. 1988 Nov 16; 53(221):46204-46260.

17 The Canadian Cooperative Study Group. A randomized trial of aspirin and sulfinpyrazone in threatened stroke. The Canadian Cooperative Study Group. N Engl J Med. 1978 Jul 13; 299(2):53-9.

18 Fields, W. S.; Lemak, N. A.; Frankowski, R. F., and Hardy, R. J. Controlled trial of aspirin in cerebral ischemia. Stroke. 1977 May-1977 Jun 30; 8(3):301-14.

19 Minutes of the FDA Peripheral and CNS Drugs Advisory Committee, August 28, 1979, OTC Volume 03BTFM.

20 Aspirin Myocardial Infarction Study (AMIS) Team. A randomized, controlled trial of aspirin in persons recovered from myocardial infarction. JAMA. 1980 Feb 15; 243(7):661-9.

21 The Coronary Drug Project Research Group. Aspirin in coronary heart disease. The Coronary Drug Project Research Group. J Chronic Dis. 1976 Oct; 29(10):625-42.

22 The Persantine-Aspirin Reinfarction Study Research Group.Persantine and aspirin in coronary heart disease. Circulation. 1980 Sep; 62(3):449-61.

23 Elwood, P. C.; Cochrane, A. L.; Burr, M. L.; Sweetnam, P. M.; Williams, G.; Welsby, E.; Hughes, S. J., and Renton, R. A randomized controlled trial of acetyl salicylic acid in the secondary prevention of mortality from myocardial infarction. Br Med J. 1974 Mar 9; 1(905):436-40.

24 Breddin, K.; Loew, D.; Lechner, K.; Uberla, K., and Walter, E. Secondary prevention of myocardial infarction. Comparison of acetylsalicylic acid, phenprocoumon and placebo. A multicenter two-year prospective study. Thromb Haemost. 1979 Feb 28; 41(1):225-36.

25 Elwood, P. C. and Sweetnam, P. M. Aspirin and secondary mortality after myocardial infarction. Lancet. 1979 Dec 22-1979 Dec 29; 2(8156-8157):1313-5.

26 Lewis, H. D. Jr; Davis, J. W.; Archibald, D. G.; Steinke, W. E.; Smitherman, T. C.; Doherty, J. E. 3rd; Schnaper, H. W.; LeWinter, M. M.; Linares, E.; Pouget, J. M.; Sabharwal, S. C.; Chesler, E., and DeMots, H. Protective effects of aspirin against acute myocardial infarction and death in men with unstable angina. Results of a Veterans Administration Cooperative Study. N Engl J Med. 1983 Aug 18; 309(7):396-403.

27 Steering Committee of the Physicians' Health Study Research Group. Final report on the aspirin component of the ongoing Physicians' Health Study. N Engl J Med. 1989 Jul 20; 321(3):129-35.

28 ISIS-2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction. Lancet. 1988 Aug 13; 2(8607):349-60.

29 UK-TIA Study Group. United Kingdom transient ischemic attack (UK-TIA) aspirin trial: interim results. Br Med J (Clin Res Ed). 1988 Jan 30; 296(6618):316-20.

30 Bousser, M. G.; Eschwege, E.; Haguenau, M.; Lefaucconnier, J. M.; Thibult, N.; Touboul, D., and Touboul, P. J. "AICLA" controlled trial of aspirin and dipyridamole in the secondary prevention of athero-thrombotic cerebral ischemia. Stroke. 1983 Jan-1983 Feb 28; 14(1):5-14.

31 Sivenius, J.; Laakso, M.; Penttila, I. M.; Smets, P.; Lowenthal, A., and Riekkinen, P. J. The European Stroke Prevention Study: results according to sex. Neurology. 1991 Aug; 41(8):1189-92.

32 The American-Canadian Co-Operative Study group. Persantine Aspirin Trial in cerebral ischemia. Part II: Endpoint results. Stroke. 1985 May-1985 Jun 30; 16(3):406-15.

33 Antiplatelet Trialists' Collaboration. Secondary prevention of vascular disease by prolonged antiplatelet treatment. Br Med J. 1988; 296:320-31.

34 Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy--I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. Antiplatelet Trialists' Collaboration. BMJ. 1994 Jan 8; 308(6921):81-106.

35 Boysen, G.; Sorensen, P. S.; Juhler, M.; Andersen, A. R.; Boas, J.; Olsen, J. S., and Joensen, P. Danish very-low-dose aspirin after carotid endarterectomy trial. Stroke. 1988 Oct; 19(10):1211-5.

36 The SALT Collaborative Group. Swedish Aspirin Low-Dose Trial (SALT) of 75 mg aspirin as secondary prophylaxis after cerebrovascular ischemic events. Lancet. 1991 Nov 30; 338(8779):1345-9.

37 Diener, H. C.; Cunha, L.; Forbes, C.; Sivenius, J.; Smets, P., and Lowenthal, A. European Stroke Prevention Study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. J Neurol Sci. 1996 Nov; 143(1-2):1-13.

38 Juul-Möller, S.; Edvardsson, N.; Jahnmatz, B.; Rosen, A.; Sorensen, S., and Omblus, R. Double-blind trial of aspirin in primary prevention of myocardial infarction in patients with

stable chronic angina pectoris. The Swedish Angina Pectoris Aspirin Trial (SAPAT) Group. Lancet. 1992 Dec 12; 340(8833):1421-5.

39 Goldman, S.; Copeland, J.; Moritz, T.; Henderson, W.; Zadina, K.; Ovitt, T.; Doherty, J.; Read, R.; Chesler, E.; Sako, Y., and et. al. Improvement in early saphenous vein graft patency after coronary artery bypass surgery with antiplatelet therapy: results of a Veterans Administration Cooperative Study. Circulation. 1988 Jun; 77(6):1324-32.

40 Goldman, S.; Copeland, J.; Moritz, T.; Henderson, W.; Zadina, K.; Ovitt, T.; Doherty, J.; Read, R.; Chesler, E.; Sako, Y., and et. al. Saphenous vein graft patency 1 year after coronary artery bypass surgery and effects of antiplatelet therapy. Results of a Veterans Administration Cooperative Study. Circulation. 1989 Nov; 80(5):1190-7.

41 Lorenz, R. L.; Schacky, C. V.; Weber, M.; Meister, W.; Kotzur, J.; Reichardt, B.; Theisen, K., and Weber, P. C. Improved aortocoronary bypass patency by low-dose aspirin (100 mg daily). Effects on platelet aggregation and thromboxane formation. Lancet. 1984 Jun 9; 1(8389):1261-4.

42 Brown, B. G.; Cukingnan, R. A.; DeRouen, T.; Goede, L. V.; Wong, M.; Fee, H. J.; Roth, J. A., and Carey, J. S. Improved graft patency in patients treated with platelet-inhibiting therapy after coronary bypass surgery. Circulation. 1985 Jul; 72(1):138-46.

43 Kretschmer, G.; Pratschner, T.; Prager, M.; Wenzl, E.; Polterauer, P.; Schemper, M.; Ehringer, H., and Minar, E. Antiplatelet treatment prolongs survival after carotid bifurcation endarterectomy. Analysis of the clinical series followed by a controlled trial. Ann Surg. 1990 Mar; 211(3):317-22.

44 Peto, R.; Gray, R.; Collins, R.; Wheatley, K.; Hennekens, C.; Jamrozik, K.; Warlow, C.; Hafner, B.; Thompson, E.; Norton, S., and et. al. Randomised trial of prophylactic daily aspirin in British male doctors. Br Med J (Clin Res Ed). 1988 Jan 30; 296(6618):313-6.

45 The Medical Practice Council's General Practice Research Framework. Thrombosis prevention trial: randomised trial of low-intesity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. 1998 Jan 24; 351, 233-41.

46 Hansson, L.; Zanchetti, A.; Carruthers, S. G.; Dahlof, B.; Elmfeldt, D.; Julius, S.; Menard, J.; Rahn, K. H.; Wedel, H., and Westerling, S. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. Lancet. 1998 Jun 13; 351(9118):1755-62.

47 Collaborative Group of the Primary Prevention Project. Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general practice. Collaborative Group of the Primary Prevention Project. Lancet. 2001 Jan 13; 357(9250):89-95.

48 Hennekens, C.H.; Dyken, M.L., and Fuster, V. Aspirin as a therapeutic agent in cardiovascular disease: A statement for healthcare professionals from the American Heart Association. Circulation: American Heart Association. 1997 Oct 21; 96(8):2751-3.

49 American Heart Association. Heart Disease and Stroke Statistics-2003 Update. Dallas, TX: American Heart Association; 2002.

50 American Medical Association Council on Scientific Affairs. Women's Health: Sex- and Gender-based Differences in Health and Disease. 2000 Dec; 4 (I-00):30 pp.

51 Cooper, R.; Cutler, J.; Desvigne-Nickens, P.; Fortmann, S. P.; Friedman, L.; Havlik, R.; Hogelin, G.; Marler, J.; McGovern, P.; Morosco, G.; Mosca, L.; Pearson, T.; Stamler, J.; Stryer, D., and Thom, T. Trends and disparities in coronary heart disease, stroke, and other cardiovascular diseases in the United States: findings of the national conference on cardiovascular disease prevention. Circulation. 2000 Dec 19; 102(25):3137-47.

52 National Institutes of Health, National Heart, Lung, and Blood Institutes. Morbidity & Mortality: 2002 Chartbook on Cardiovascular, Lung, and Blood Diseases. U.S. Department of Health and Human Services; 2002 May:88 pp.

53 Kannel, W.B.; Dawber, T. R.; Kagan, A.; Revotskie, N., and Stokes, J. 3rd. Factors of risk in the development of coronary heart disease--six year follow-up experience. The Framingham Study. Ann Intern Med. 1961 Jul; 55:33-50.

54 National Cholesterol Education Program. Second Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). Circulation. 1994 Mar; 89(3):1333-445.

55 Summary of the second report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). JAMA. 1993 Jun 16; 269(23):3015-23.

56 27th Bethesda Conference. Matching the Intensity of Risk Factor Management with the Hazard for Coronary Disease Events. September 14-15, 1995. J Am Coll Cardiol. 1996 Apr; 27(5):957-1047.

57 Chobanian, A. V.; Bakris, G. L.; Black, H. R.; Cushman, W. C.; Green, L. A.; Izzo, J. L. Jr; Jones, D. W.; Materson, B. J.; Oparil, S.; Wright, J. T. Jr, and Roccella, E. J. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA. 2003 May 21; 289(19):2560-72.

58 Wilson, P. W.; D'Agostino, R. B.; Levy, D.; Belanger, A. M.; Silbershatz, H., and Kannel, W. B. Prediction of coronary heart disease using risk factor categories. Circulation. 1998 May 12; 97(18):1837-47.

59 Sheridan *et.al.* Framingham-Based Tools to Calculate the Global Risk of Coronary Heart Disease: A Systematic Review of Tools for Clinicians. In press.

60 Stampfer, M. J.; Hu, F. B.; Manson, J. E.; Rimm, E. B., and Willett, W. C. Primary prevention of coronary heart disease in women through diet and lifestyle. N Engl J Med. 2000 Jul 6; 343(1):16-22.

61 Wald, N. J. and Law, M. R. A strategy to reduce cardiovascular disease by more than 80%. BMJ 2003; 326:1419.

62 Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA. 2001 May 16; 285(19):2486-97.

63 Cook, N. R.; Chae, C.; Mueller, F. B.; Landis, S.; Saks, A. M., and Hennekens, C. H. Mis-medication and Under-utilization of Aspirin in the Prevention and Treatment of Cardiovascular Disease. MedGenMed 1999; E1.

64 Meade, T. W.; Mellows, S.; Brozovic, M.; Miller, G. J.; Chakrabarti, R. R.; North, W. R.; Haines, A. P.; Stirling, Y.; Imeson, J. D., and Thompson, S. G. Haemostatic function and ischaemic heart disease: principal results of the Northwick Park Heart Study. Lancet. 1986 Sep 6; 2(8506):533-7.

65 Eidelman, R. S.; Hebert, P. R.; Weisman, S. M., and Hennekens, C. H. An update on aspirin in the primary prevention of cardiovascular disease. Arch Intern Med. 2003 Sep 22; 163(17):2006-10.

66 Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ. 2002 Jan 12; 324(7329):71-86.

67 Guise, J.M.; Mahon, S.M.; Aicken, M.; Helfand, M.; Peipert, J.F., and Westhoff, C. Aspirin for the primary prevention of cardiovascular events: Summary of the evidence. Ann Intern Med 2002; 136:161-172.

68 Sanmuganathan, P. S.; Ghahramani, P.; Jackson, P. R.; Wallis, E. J., and Ramsay, L. E. Aspirin for primary prevention of coronary heart disease: safety and absolute benefit related to coronary risk derived from meta-analysis of randomised trials. Heart. 2001 Mar; 85(3):265-71.

69 Weisman, S. M. and Graham, D. Y. Evaluation of the benefits and risks of low-dose aspirin in the secondary prevention of cardiovascular and cerebrovascular events. Arch Intern Med. 2002 Oct 28; 162(19):2197-202.

70 The RISC Group. Risk of myocardial infarction and death during treatment with low dose aspirin and intravenous heparin in men with unstable coronary artery disease. Lancet 1990; 336:827-30.

71 Chen, Z.; Xu, Y.; Yu, Q.; Kou, W.; Lu, Z.; Yao, K., and et.al. Secondary prevention of myocardial reinfarction with low dose aspirin. Chin Med Sci J. 1991; 6:141-4.

72 Lewis, H.D. Jr. Unstable angina: status of aspirin and other forms of therapy. Circulation. 1985; 72:V155-60.

73 Cooper, S.A., and Press, K. Review of side effects-ten years of experience with dental pain model. Adv Ther. 1985; 2:20-29.

74 Stiel, D. Exploring the link between gastrointestinal complications and over-the-counter analgesics: current issues and considerations. Am J Ther. 2000 Mar; 7(2):91-8.

75 Green, G. A. Understanding NSAIDs: from aspirin to COX-2. Clin Cornerstone. 2001; 3(5):50-60.

76 Cryer, B. Nonsteroidal anti-inflammatory drug gastrointestinal toxcity. Curr Opin Gastroenterol. 1999; 15:473-480.

77 Halverson, P. B. Nonsteroidal antiinflammatory drugs: benefits, risks, and COX-2 selectivity. Orthop Nurs. 1999 Nov-1999 Dec 31; 18(6):21-6; quiz 27-8.

78 Bazzoli, F.; De Luca, L., and Graham, D. Y. Helicobacter pylori infection and the use of NSAIDs. Best Pract Res Clin Gastroenterol. 2001 Oct; 15(5):775-85.

79 Lanza, F.; Royer, G., and Nelson, R. An endoscopic evaluation of the effects of non-steroidal anti- inflammatory drugs on the gastric mucosa. Gastrointest Endosc. 1975 Feb; 21(3):103-5.

80 Lanza, F. L. Endoscopic studies of gastric and duodenal injury after the use of ibuprofen, aspirin, and other nonsteroidal anti-inflammatory agents. Am J Med. 1984 Jul 13; 77(1A):19-24.

81 Arthritis Advisory Committee (Food and Drug Administration). Summary of Minutes Arthritis Advisory Committee; 1998 Dec 1.

82 Hayden, M.; Pignone, M.; Phillips, C., and Mulrow, C. Aspirin for the Primary Prevention of Cardiovascular Events: A Summary of the Evidence. Ann Intern Med. 2002; 136(2):161-172.

83 Roderick, P.J.; Wilkes, H.C., and Meade, T.W: The gastrointestinal toxicity of aspirin. An overview of randomized controlled trials. Br. J Clin Pharmac. 1993; 35:219-226.

84 Derry, S. and Loke, Y. K. Risk of gastrointestinal haemorrhage with long term use of aspirin: meta-analysis. BMJ. 2000 Nov 11; 321(7270):1183-7.

85 Farrell, B.; Godwin, J.; Richards, S., and Warlow, C. The United Kingdom transient ischaemic attack (UK-TIA) aspirin trial: final results. J Neurol Neurosurg Psychiatry. 1991 Dec; 54(12):1044-54.

86 He, J.; Whelton, P. K.; Vu, B., and Klag, M. J. Aspirin and risk of hemorrhagic stroke: a meta-analysis of randomized controlled trials. JAMA 1998; 280:1930-5.

87 Hart, R.G.; Halperin, J.L.; McBride, R.; Benavente, O.; Man-Son-Hing, M.; Kronmal, R.A. Aspirin for the primary prevention of stroke and other major vascular events: meta-analysis and hypotheses. Arch Neurol. 2000 Mar; 57(3):326-32.

88 Whelton, A. and Hamilton, C. W. Nonsteroidal anti-inflammatory drugs: effects on kidney function. J Clin Pharmacol. 1991 Jul; 31(7):588-98.

89 Bonney, S. L.; Northington, R. S.; Hedrich, D. A., and Walker, B. R. Renal safety of two analgesics used over the counter: ibuprofen and aspirin. Clin Pharmacol Ther. 1986 Oct; 40(4):373-7.

90 Whelton, A.; Stout, R. L.; Spilman, P. S., and Klassen, D. K. Renal effects of ibuprofen, piroxicam, and sulindac in patients with asymptomatic renal failure. A prospective, randomized, crossover comparison. Ann Intern Med. 1990 Apr 15; 112(8):568-76.

91 De Broe, M. E. and Elseviers, M. M. Analgesic nephropathy. N Engl J Med. 1998 Feb 12; 338(7):446-52.

92 McEvoy, G.K. American Hospital Formulary Service (AHFS) Drug Information. Bethesda, MD: American Society of Health System Pharmacists; 2000.

93 Garcia Rodriguez, L. A. and Hernandez-Diaz, S. Relative risk of upper gastrointestinal complications among users of acetaminophen and nonsteroidal anti-inflammatory drugs. Epidemiology. 2001 Sep; 12(5):570-6.

94 Rahme, E.H.; Pettitt, D., and LeLorier, J. Dose Response Curves with Time Dependent Exposure – The Case of Acetaminophen Gastrointestinal Sides Effects. Pharmacoepidemiology and Drug Safety. 2000; 9:S104.

95 Catella-Lawson, F.; Reilly, M.; Kapoor, S.; Cucchiara, A.; DeMarco, S.; Tournier, B.; Sachin, V., and FitzGerald, G. Cyclooxygenase Inhibitors and the Antiplatelet Effects of Aspirin. N Engl J Med. 2001 Dec 20; 345(25):1809-1817.

96 Weil, J.; Colin Jones, D., and et. al. Prophylactic aspirin and risk of peptic ulcer bleeding. Br Med J. 1995; 310:827-830.

97 Kelly, J. P.; Kaufman, D. W.; Jurgelon, J. M.; Sheehan, J.; Koff, R. S., and Shapiro, S. Risk of aspirin-associated major upper-gastrointestinal bleeding with enteric-coated or buffered product. Lancet 1996; 348:1413-6.

98 de Abajo, F. J. and Garcia Rodriguez, L. A. Risk of upper gastrointestinal bleeding and perforation associated with low-dose aspirin as plain and enteric-coated formulations. BMC Clin Pharmacol 2001; 1:1.

99 Karwoski C., FDA Report July 15, 2002.

100 Attitudes and Behaviors Associated with Direct-to-Consumer (DTC) Promotion of Prescription Drugs, Office of Medical Policy, Division of Drug Marketing, Advertising, and Communications, 1999.