

**ATTACHMENT 2**

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**Summary of Aspirin Safety Information**

**SUMMARY OF ASPIRIN SAFETY INFORMATION**

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## List of Abbreviations

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ACG	American College of Gastroenterology
ACS	acute coronary syndromes
AMIS	Aspirin Myocardial Infarction Study
ATC	Antithrombotic Trialists' Collaboration
BDT	British Doctors' Trial
BID	twice daily
BRAVO	Blockade of the Glycoprotein IIb/IIIa Receptor to Avoid Vascular Occlusion Trial
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CI	confidence interval
CNS	central nervous system
CURE	Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial
ECG	electrocardiogram
ESPS	European Stroke Prevention Study
ETDRS	Early Treatment of Diabetic Retinopathy Study
GI	gastrointestinal
FDA	Food and Drug Administration
GP IIb/IIIa	glycoprotein IIb/IIIa receptor
HOT	Hypertension Optimal Treatment
HR	hazard ratio
ISIS-2	Second International Study of Infarct Survival
MI	myocardial infarction
MRC-TPT	Medical Research Council's Thrombosis Prevention Trial
N	number
ns	not specified
NS	not significant
NSAIDs	non-steroidal anti-inflammatory drugs
OTC	over-the-counter
PAF	primary atrial fibrillation
PCI	percutaneous coronary intervention
PTCA	percutaneous transluminal coronary angioplasty
PVD	peripheral vascular disease
QOD	every other day
RR	relative risk
SALT	Swedish Aspirin Low-dose Trial
SAPAT	Swedish Angina Pectoris Aspirin Trial
TIA	transient ischemic attack
TIMI	Thrombolysis in Myocardial Infarction
UGIB	upper gastrointestinal bleeding
UGIC	upper gastrointestinal complications
USPHS	U.S. Physicians Health Study

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## 1. INTRODUCTION

### 1.1. Background

Aspirin for the treatment of acute myocardial infarction (MI) and for the secondary prevention of MI, chronic stable and unstable angina pectoris, transient ischemic attacks (TIA), and ischemic stroke is one of the most important therapies available to reduce cardiovascular morbidity and mortality. Since the initial proposed rule of November 16, 1988 [53 FR § 46204] for aspirin professional labeling, the Food and Drug Administration (FDA) has expanded the vascular indications and refined aspirin dosage instructions in the subsequent Federal Register notices of June 13, 1996 [61 FR § 30002] and the Final Rule of October 23, 1998 [63 FR § 56802]. Since the 1998 Final Rule, new data have become available that support the need to reconsider the safety profiles of the recommended doses of aspirin for these vascular indications.

Since 1988, the FDA has reviewed the safety experience associated with the use of aspirin over a broad range of effective doses (i.e., 50 to 1500 mg/day). In the 1988 Federal Register [53 FR § 46231], FDA concluded that aspirin at a dose of 1300 mg/day was safe and effective for reducing the risk of recurrent TIAs or stroke in men. For secondary MI prevention, the notice [53 FR § 46232] stated in part:

*“Dosage and Administration: Although most of the studies used dosages exceeding 300 milligrams, 2 trials used only 300 milligrams, and pharmacologic data indicate that this dose inhibits platelet function fully. Therefore, 300 milligrams, or a conventional 325 milligram aspirin dose is a reasonable, routine dose that would minimize gastrointestinal adverse reactions.”*

Furthermore, based on findings from the Aspirin Myocardial Infarction Study (AMIS Research Group, 1980) regarding adverse reactions [53 FR § 46231], in the 1988 Federal Register Notice, the FDA also stated in part:

*“Gastrointestinal Reactions: Doses of 1,000 milligrams per day of aspirin caused gastrointestinal symptoms and bleeding that in some cases were clinically significant.”*

On June 13, 1996, the FDA published a proposed amendment to the tentative final monograph [61 FR § 30002]. In this proposal, the FDA recognized the dose-relationship between aspirin dose and major bleeding events. Regarding bleeding events in the AMIS trial (1980), in which subjects received aspirin at a dose of 1000 mg/day, and the Second International Study of Infarct Survival (ISIS-2)(1988), in which subjects received aspirin at a dose of 162.5 mg/day, the Agency stated in part:

*“Bleeding: In the AMIS and other trials, aspirin-treated subjects had increased rates of gross gastrointestinal bleeding. In the ISIS-2 study, there was no significant difference in the*

*incidence of major bleeding (bleeds requiring transfusion) between 8,587 subjects taking 162.5 milligrams aspirin daily and 8,600 subjects taking placebo.”*

In the October 23, 1998 Final Rule [63 FR § 56802], the last professional labeling change for aspirin was made in which the FDA codified the acute MI indication and refined its evaluation of the dose needed for secondary prevention following the availability of new data and analyses. FDA considered data from the Antiplatelet Trialists' Collaboration (1994), the United Kingdom-TIA study (1988), the Danish Very Low Dose study (1988), the Swedish Aspirin Low-dose Trial (1991), European Stroke Prevention Study-2 (ESPS-2) for TIA or stroke prevention (1996), and the Swedish Angina Pectoris Aspirin Trial (SAPAT) in chronic stable angina (1992). The Agency provided the following summary [63 FR § 56806] regarding support for a lower dose of aspirin:

*“In summary, there is clinical trial support for a lower dose of aspirin for subjects with a history of TIA or cerebral ischemia and considerable evidence in patients with MI. It is also clear that the effect of aspirin on platelet functions is complete at lower doses. The positive findings at lower dosages (e.g., 50, 75 and 300 mg daily) along with the higher incidence of side effects expected at the higher dosage (e.g., 1300 mg daily) are sufficient reason to lower the dosage of aspirin for subjects with TIA and stroke.”*

Furthermore, in the 1998 Final Rule, FDA also stated in part:

*“...specific doses for specific uses of aspirin, supported by appropriate data, are necessary for an optimal benefit to the user and, in general, that a minimum effective dose established for a given indication should be used to minimize dose related adverse effects.”*

The FDA's statement thereby allows the opportunity for further refinement of the aspirin dose that provides optimal benefit for a given indication, while minimizing adverse effects.

Since the 1998 Final Rule notice, the approved monograph for professional labeling of aspirin was used to form the basis for the New Drug prescription labeling of buffered aspirin approved as an independent drug product co-packaged with PRAVACHOL<sup>®</sup> (pravastatin sodium). This product, PRAVIGARD<sup>™</sup> PAC (NDA 21-387), was approved by the FDA on June 24, 2003. The aspirin component of that labeling was consistent with the 1998 Final Rule and provides physicians with information appropriate to the use of buffered aspirin when used in conjunction with PRAVACHOL<sup>®</sup>. FDA's approval of PRAVIGARD<sup>™</sup> PAC was consistent with the monograph professional labeling of aspirin. However, the FDA review resulted in modification of the aspirin component of that labeling. McNeil's proposal includes a request to modify the current professional labeling to be consistent with FDA's aspirin evaluation during the PRAVIGARD<sup>™</sup> PAC review.

At the time of FDA's publication of the Final Rule in 1998, sufficient data regarding the safety of aspirin at doses within the range of 50–325 mg/day were not available. McNeil's Petition proposes to modify the current monograph professional aspirin labeling (21 C.F.R §

330.11) based on data that has become available since the 1998 Final Rule. Since that time, data from several key studies, particularly the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study (2003), the Blockade of the Glycoprotein IIb/IIIa Receptor to Avoid Vascular Occlusion (BRAVO) trial (2003), and the large meta-analyses by Serebruany et al., (2004) and (2005), have provided safety information within the dose range of 50–325 mg/day that support the concern that bleeding is increased at higher aspirin doses within this range. In addition, McNeil's proposed changes are also reflective of the NDA-approved labeling of the aspirin component of PRAVIGARD™ PAC under 21CFR § 314.54. The proposed aspirin labeling provides professional labeling information appropriate to the use of aspirin doses 75–150 mg/day for secondary cardiovascular prevention and 50–150 mg/day for secondary cerebrovascular prevention. An annotated version of the proposed professional labeling for aspirin is provided in Attachment 1.

McNeil considers that all the material and methods used by the FDA to reach the scientific and regulatory conclusions enunciated in the Federal Register notices of 1988, 1996, and 1998 (Section 2.1.1), as well as the NDA 21-387 approval of new labeling for buffered aspirin (Section 2.1.1), provide the critical background information for consideration of new post-1998 aspirin data, particularly safety data. Using the FDA process to establish the safe and effective dose of aspirin for secondary vascular prevention under 21 C.F.R. § 343.80 Professional Labeling and the new post-1998 aspirin data, McNeil requests that the professional labeling for aspirin specify the more favorable benefit/risk profile of aspirin dose of 75–150 mg/day for secondary cardiovascular prevention and 50–150 mg/day for secondary cerebrovascular prevention to provide effective treatment and minimize major bleeding events, particularly gastrointestinal (GI) bleeding.

These conclusions are reflected in the **Clinical Studies, Warnings, Adverse Reactions-Controlled Trials, and Dosage and Administration** sections of the new proposed labeling submitted in the subject Citizen's Petition for FDA's review. The scientific basis regarding the benefit/risk profile of aspirin at doses  $\leq 150$  mg/day versus  $> 150$  mg/day follows.

## 1.2. Safety Conclusions Supported

Data from the publications discussed in the safety summary substantiate the following safety claims for aspirin:

- Although adverse events have been reported at low aspirin doses, within the dose range of 50–325 mg/day, more bleeding events occur at higher doses (i.e.,  $> 150$  mg daily) than at lower doses (i.e., 75–150 mg daily).
- The recommended aspirin dose for chronic administration is 75–150 mg daily, which is safe and effective for prevention of recurrent MI, and for treatment of unstable angina pectoris or chronic stable angina pectoris, and 50–150 mg daily for treatment of ischemic stroke and TIA. Aspirin is recommended for patients who undergo revascularization

procedures, such as coronary artery bypass grafting (CABG), angioplasty, or carotid endarterectomy, if there is a pre-existing condition for which aspirin is already indicated. Therapy should be continued indefinitely.

## **2. DESCRIPTION OF THE SAFETY SUMMARY FORMAT**

A discussion of the general methodology that was used to identify articles included in this safety summary is presented in Section 3. This includes a description of the initial literature search that was performed and a description of criteria that were developed to identify and group articles containing relevant bleeding data. Section 3 also includes a brief description of the articles in each publication grouping. For the remaining sections of the safety summary, each publication grouping has been organized such that data from individual clinical trials or other studies are presented first, followed by data from meta-analyses. No pooling of data across any of the publications was performed.

In Section 4, information related to study design, including patient population characteristics (e.g., age, sex, and relevant medication conditions at study entry), study objectives, key inclusion and exclusion criteria, bleeding endpoints, and a brief description of statistical methodology are presented. Section 5 discusses the numbers of patients in each treatment group and the extent of exposure to aspirin.

Bleeding data for the three publication groupings are presented in Section 6. Finally, Section 7 provides a summary of the bleeding data presented and a discussion of overall conclusions; Section 8 provides a bibliographical list of references.

## **3. METHODOLOGY**

### **3.1. Literature Search Methodology**

Three literature searches were conducted for aspirin-related publications for the time period from 1996 through 2004 and included both the MEDLINE™ and EMBASE™ databases. The following search strategies were used:

**Search #1:**

Set	Items	Description
S1	24401	ASPIRIN/DE
S2	35847	ACETYLSALICYLIC ACID/MAJ
S3	314831	(CEREBROVASCULAR DISEASE OR CEREBROVASCULAR ACCIDENT OR CEREBROVASCULAR()DISORDERS OR BRAIN ISCHEMIA OR ISCHEMIC ATTACK TRANSIENT OR MYOCARDIA INFARCTION OR ANGINA PECTORIS OR HEART INFARCTION)/DE
S4	906698	(SECONDARY PREVENTION OR PROPHYLAXIS OR PROPHYLACTIC OR PRIMARY PREVENTION OR PREVENTION OR HEART PROTECTION)/DE
S5	380338	DT=(CLINICAL TRIAL OR MULTICENTER STUDY OR META-ANALYSIS OR RANDOMIZED CONTROLLED TRIAL OR CONTROLLED CLINICAL TRIAL)
S6	279193	(MULTICENTER OR CONTROLLED STUDY OR CLINICAL TRIAL OR CLINICAL STUDY OR META ANALYSIS OR DOUBLE BLIND OR SINGLE BLIND)/DE
S7	1339	(S1 OR S2) AND S3 AND S4 AND (S5 OR S6)
S8	1193	S7 NOT REVIEW/DE
S9	986	S8/ENG
S10	969	S9/HUMAN
S11	495	S10/1996:2003
S12	452	RD (unique items)

DE = descriptor; MAJ = major descriptor; DT = document type; ENG = English language;RD = remove duplicates

**Search #2:**

Set	Items	Description
S1	24428	ASPIRIN/DE
S2	35858	ACETYLSALICYLIC ACID/MAJ
S3	375012	(CEREBROVASCULAR DISEASE! OR CEREBROVASCULAR ACCIDENT OR CEREBROVASCULAR DISORDERS OR BRAIN ISCHEMIA OR HEMORRHAGE OR GASTROINTESTINAL SYSTEM OR GASTROINTESTINAL DISEASES OR ULCER)/DE
S4	214088	(GASTROINTESTINAL SYSTEM OR GASTROINTESTINAL DISEASES OR CEREBROVASCULAR DISEASE OR DYSPEPSIA OR BLEEDING! OR DIGESTIVE SYSTEM DISEASE!)/DE
S5	19638	(DIGESTIVE SYSTEM INJURY OR GASTROINTESTINAL TOXICITY)/DE
S6	617809	(GASTROINTESTINAL OR DIGESTIVE SYSTEM OR STOMACH OR MUCOS OR GASTRODUODEN OR DUODEN)/DE
S7	381022	DT=(CLINICAL TRIAL OR MULTICENTER STUDY OR META-ANALYSIS OR RANDOMIZED CONTROLLED TRIAL OR CONTROLLED CLINICAL TRIAL)
S8	279655	(MULTICENTER OR CONTROLLED STUDY OR CLINICAL TRIAL OR CL INICAL STUDY OR META ANALYSIS OR DOUBLE BLIND OR SINGLE BLIND)/DE
S9	315253	(CEREBROVASCULAR DISEASE OR CEREBROVASCULAR ACCIDENT OR CEREBROVASCULAR DISORDERS OR BRAIN()ISCHEMIA OR ISCHEMIC ATTACK TRANSIENT OR MYOCARDIAL INFARCTION OR ANGINA PECTORIS OR HEART INFARCTION)/DE
S10	908158	(SECONDARY PREVENTION OR PROPHYLAXIS OR PROPHYLACTIC OR PRIMARY PREVENTION OR PREVENTION OR HEART PROTECTION)/DE
S11	2743	(S1 OR S2) AND (S3 OR S5 OR S6) AND (S7 OR S8)
S12	5405	(S1 OR S2) AND (S9 OR S10) AND (S7 OR S8)
S13	1381	S11 NOT S12
S14	1338	S13 NOT REVIEW/DE
S15	1117	S14/ENG
S16	1019	S15/HUMAN
S17	249	S16/1996:2003
S18	215	RD (unique items)
S19	82	S18 FROM 155

DE = descriptor; MAJ = major descriptor; DT = document type; ENG = English language RD = remove duplicates

**Search #3:**

Set	Items	Description
S1	24428	ASPIRIN/DE
S2	35858	ACETYLSALICYLIC ACID/MAJ
S3	375012	(CEREBROVASCULAR DISEASE! OR CEREBROVASCULAR()ACCIDENT OR CEREBROVASCULAR DISORDERS OR BRAIN ISCHEMIA! OR HEMORRHAGE OR GASTROINTESTINAL SYSTEM OR GASTROINTESTINAL DISEASES! OR ULCER)/DE
S4	214088	(GASTROINTESTINAL SYSTEM OR GASTROINTESTINAL DISEASES OR CEREBROVASCULAR DISEASE OR DYSPEPSIA OR BLEEDING! OR DIGESTIVE SYSTEM DISEASE!)/DE
S5	19638	(DIGESTIVE SYSTEM()INJURY OR GASTROINTESTINAL TOXICITY)/DE
S6	617809	(GASTROINTESTINAL OR DIGESTIVE SYSTEM OR STOMACH OR MUCOS? OR GASTRODUODEN? OR DUODEN?)/DE
S7	381022	DT=(CLINICAL TRIAL OR MULTICENTER STUDY OR META-ANALYSIS OR RANDOMIZED CONTROLLED TRIAL OR CONTROLLED CLINICAL TRIAL)
S8	279655	(MULTICENTER OR CONTROLLED STUDY OR CLINICAL TRIAL OR CL INICAL
	4	STUDY OR META ANALYSIS OR DOUBLE BLIND OR SINGLE BLIND)/DE
S9	315253	(CEREBROVASCULAR DISEASE OR CEREBROVASCULAR ACCIDENT OR CEREBROVASCULAR()DISORDERS OR BRAIN ISCHEMIA OR ISCHEMIC ATTACK TRANSIENT OR MYOCARDIAL INFARCTION OR ANGINA PECTORIS OR HEART INFARCTION)/DE
S10	908158	(SECONDARY PREVENTION OR PROPHYLAXIS OR PROPHYLACTIC OR PRIMARY PREVENTION OR PREVENTION OR HEART PROTECTION)/DE
S11	2743	(S1 OR S2) AND (S3 OR S5 OR S6) AND (S7 OR S8)
S12	5405	(S1 OR S2) AND (S9 OR S10) AND (S7 OR S8)
S13	1381	S11 NOT S12
S14	1338	S13 NOT REVIEW/DE
S15	1117	S14/ENG
S16	1019	S15/HUMAN
S17	249	S16/1996:2003
S18	215	RD (unique items)
S19	82	S18 FROM 155

DE = descriptor; MAJ = major descriptor; DT = document type; ENG = English language; RD = remove duplicates

Of note, three additional publications that did not meet the criteria defined in the above searches were identified and are also included in this submission for safety information purposes (Serebruany et al., 2004; Serebruany et al., 2005 [in press]; Blot and McLaughlin, 2000). A total of 850 articles were reviewed in detail for relevant content.

The 850 articles were classified as follows. Articles were separated into groups according to whether or not they described the use of aspirin in a cardiovascular and/or cerebrovascular indication. Articles that described the use of aspirin in a cardiovascular and/or cerebrovascular indication were further classified into those that presented primary data from a clinical trial, meta-analysis, or other study and those that were considered to be review articles, editorials, letters, commentaries, etc.

For articles that described the use of aspirin in a cardiovascular and/or cerebrovascular indication and presented primary data from a clinical trial, meta-analysis or other study, the following information was summarized:

- Type of article (i.e., clinical trial, meta-analysis, etc.)
- Indication(s) being addressed by the publication
- Patient population
- Number of patients
- Mean age (or median age)
- Sex breakdown
- Treatment groups investigated (including non-aspirin treatment groups)
- Treatment duration
- Endpoints
- Efficacy data
- Safety data
- Conclusions
- Comments
- Article keywords

Articles describing studies that used aspirin in a non-cardiovascular and/or cerebrovascular indication were also summarized in the same way if they captured data on bleeding events associated with aspirin use. Otherwise, these articles were considered not relevant and were not summarized.

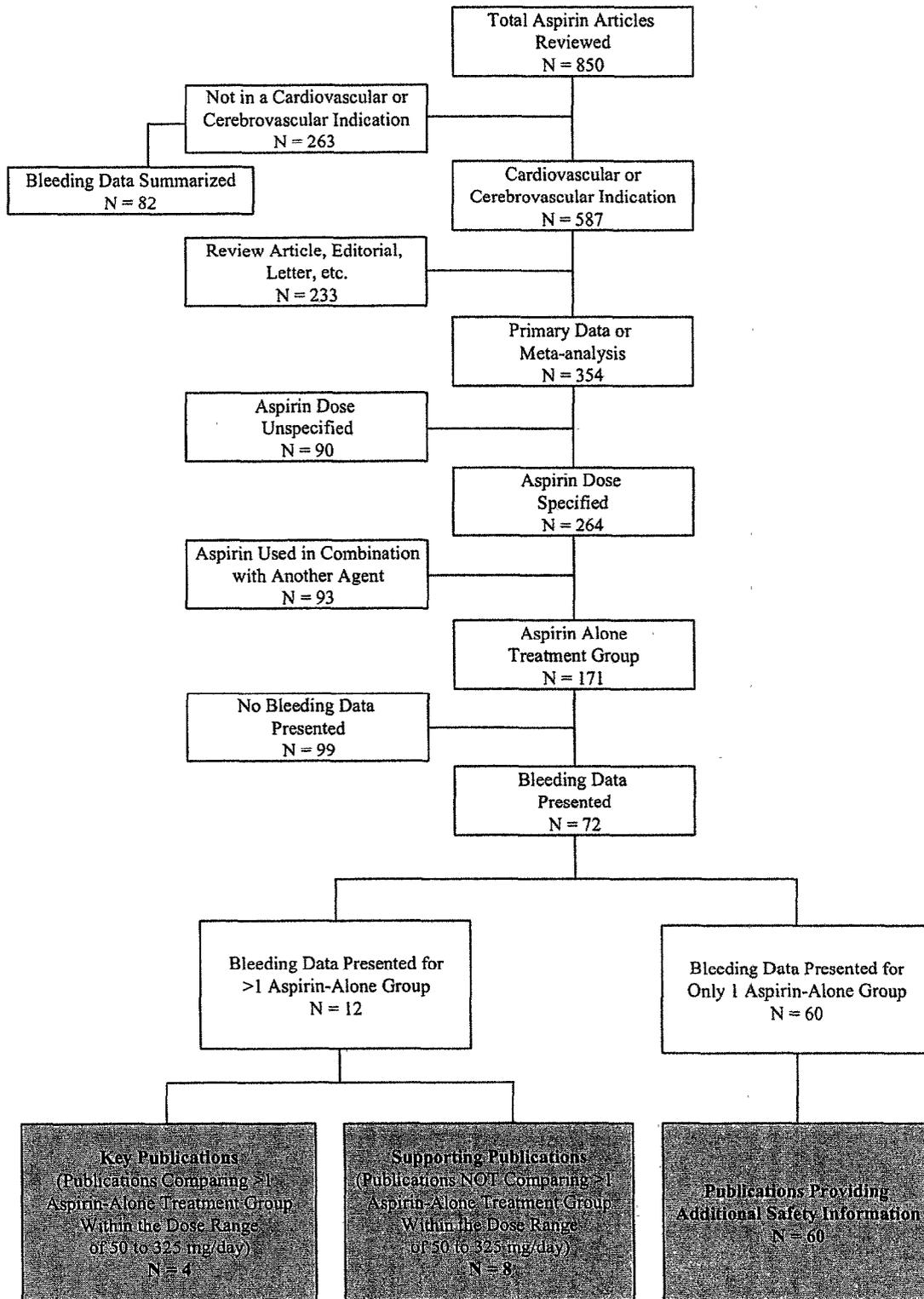
For articles that described the use of aspirin in a cardiovascular and/or cerebrovascular indication that were considered to be review articles, editorials, letters, and commentaries, etc., the following information was summarized:

- Type of article (i.e., review, letter, etc.)
- Conclusions
- Comments
- Keywords

### **3.2. Safety Summary Methodology**

Figure 1 represents a flowchart of the process used for categorizing articles for the purposes of this safety summary.

Figure 1. Flowchart of Literature Search Methodology – Safety Data



Of the 850 articles reviewed, a total of 587 involved the use of aspirin in a cardiovascular and/or cerebrovascular indication. Of these 587 articles, 354 presented primary data from a clinical trial, meta-analysis, or other study. These 354 articles were categorized based on whether the aspirin dose was specified (264 articles) or unspecified (90 articles). Articles in which the aspirin dose was specified were further categorized based on whether or not they reported data when aspirin was administered alone (171 articles) or in combination with other agents (93 articles). Finally, the 171 articles that included an aspirin-alone treatment group were categorized based on whether they presented clinically relevant bleeding event information, resulting in a total of 72 articles.

Per the FDA's 1998 Final Rule for the Professional Labeling of Aspirin, the current Dosage and Administration recommendations identify aspirin doses within the range of 50–325 mg/day for the following cardiovascular and cerebrovascular indications: ischemic stroke and TIA, suspected acute MI, prevention of recurrent MI, unstable angina pectoris, chronic stable angina pectoris, CABG, and percutaneous transluminal coronary angioplasty (PTCA). For the purposes of this safety summary, we sought to further identify the aspirin dose(s) within the range of 50–325 mg/day that confer the most favorable benefit/risk profile for aspirin in terms of bleeding complications, particularly gastrointestinal bleeding.

The 72 articles included in this safety summary are classified into three major groupings. The first two groupings include articles that reported bleeding outcome information for more than one aspirin-alone treatment group, allowing for a dose-by-dose comparison of safety. The first of these two groupings is comprised of four articles summarizing the results of clinical trials or meta-analyses in which direct comparisons of bleeding outcome data were made between at least two aspirin-alone treatment groups that fell within the dose range of 50–325 mg/day (i.e., Key Publications). This grouping forms the basis of this Petition and the proposed labeling change in the recommended aspirin dose from 75–325 mg/day to 75–150 mg/day for cardiovascular prevention and from 50–325 mg/day to 50–150 mg/day for cerebrovascular prevention.

The second grouping comprises eight articles summarizing the results of clinical trials, meta-analyses, or other studies that either compared bleeding outcome data for one aspirin-alone treatment group outside the dose range of interest, or compared bleeding outcome data for aspirin-alone treatment groups that all fell outside the dose range of interest. The third grouping comprises 60 articles summarizing the results of clinical trials, meta-analyses, or other studies in which bleeding outcome data were presented for a single aspirin-alone treatment group, thereby not allowing for direct comparisons between aspirin doses. The inclusion of this third publication grouping in this Petition serves to ensure that all aspirin-related safety data in cardiovascular and/or cerebrovascular indications published since 1996 are presented. However, these studies were conducted in a wide variety of indications, many of which are not directly relevant for this Petition.

### 3.2.1. Key Publications

The Key Publications include clinical trials or meta-analyses in which direct comparisons of bleeding outcome data were made between at least two aspirin-alone treatment groups that fell within the dose range of 50–325 mg/day. This grouping is comprised of two large clinical trials (a post-hoc analysis of the CURE trial [Peters et al. 2003] and the BRAVO trial [Topol et al., 2003]) and two large-scale meta-analyses (Serebruany et al., 2004; Serebruany et al., 2005 [in press]). The general characteristics of these four publications are presented in Table 1.

**Table 1. Table of Studies – Key Publications**

Reference	Total Subjects (N)	Patient Population	Treatment Groups (N)	Treatment Duration	Type of Article
Peters RJG, Mehta SR, Fox KAA, et al. Effects of aspirin dose when used alone or in combination with clopidogrel in patients with acute coronary syndromes: observations from the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study. <i>Circulation</i> . 2003;108 (14):1682-1687.	12,562	Patients with symptoms of ACS without ST-segment elevation >1 mm on the ECG	Aspirin ≤100 mg/day <sup>1</sup> alone or with 75 mg/day clopidogrel (5320) <sup>2</sup> Aspirin 101–199 mg/day <sup>1</sup> alone or with 75 mg/day clopidogrel (3109) <sup>2</sup> Aspirin ≥200 mg/day <sup>1</sup> alone or with 75 mg/day clopidogrel (4110) <sup>2</sup>	Mean: 9 months	Clinical Trial
Topol EJ, Easton D, Harrington RA, et al. Randomized, double-blind, placebo-controlled, international trial of the oral IIb/IIIa antagonist lotrafiban in coronary and cerebrovascular disease. <i>Circulation</i> . 2003;108 (4): 399-406.	9190	Patients with vascular disease	Aspirin 75–162 mg/day <sup>1</sup> + placebo (2410) Aspirin >162 mg/day <sup>1</sup> + placebo (2179) Aspirin 75–325 mg/day <sup>1</sup> + lotrafiban 30 or 50 mg <sup>3</sup> BID (4600)	Up to 2 years	Clinical Trial
Serebruany VL, Malinin AI, Eisert RM, Sane DC. Risk of bleeding complications with antiplatelet agents: Meta-analysis of 338,191 patients enrolled in 50 randomized clinical trials. <i>American Journal of Hematology</i> . 2004;75:40-7.	338,191	Patients with multiple cerebrovascular/ cardiovascular conditions	Aspirin <100 mg/day <sup>4</sup> Aspirin 100 to 325 mg/day <sup>4</sup> Aspirin >325 mg/day <sup>4</sup> Dipyridamole <sup>4</sup> ADP-receptor blockers <sup>4</sup> Glycoprotein IIb/IIIa inhibitors, i.v. <sup>4</sup> Glycoprotein IIb/IIIa inhibitors, oral <sup>4</sup>	ns <sup>5</sup>	Meta-analysis of clinical trials
Serebruany VL, Steinhubl SR, Berger PB, Malini AI, Oshrine BR, Baggish JS, Bhatt DL, Topol EJ. Analysis of risk of bleeding complications after different doses of aspirin in 192,036 patients enrolled in 31 randomized controlled trials. <i>Am J Card</i> . 2005 (in press)	192,036	Patients with multiple cerebrovascular/cardiovascular conditions	Aspirin < 100mg/day Aspirin 100–200 mg/day Aspirin >200 mg/day	ns <sup>5</sup>	Meta-analysis of clinical trials

Abbreviations: ACS: acute coronary syndrome; ADP: adenosine diphosphate; BID: twice daily; ECG: electrocardiogram; ns: not specified.

1. The choice of aspirin dose was determined by the Investigator.
2. The numbers of patients exposed to aspirin-alone were not specified in this publication.
3. The dose of lotrafiban was dependent on creatinine clearance.
4. The number of patients in each treatment group were not specified.
5. Only trials in which patients had a clinical follow-up for at least 1 month were included in the analysis.

Peters et al. (2003) performed a post-hoc analysis of 12,539 patients enrolled in the CURE study to examine the relationship between the dose of aspirin ( $\leq 100$ , 101–199, and  $\geq 200$  mg/day) and the risk of bleeding when used alone or in combination with clopidogrel. Patients with symptoms of acute coronary syndrome (ACS) were treated for an average of nine months.

The BRAVO clinical trial (Topol et al., 2003) compared the effect of adding lotrafiban or placebo to different doses of aspirin (75–162 and  $>162$  mg/day) in 9190 patients with vascular disease for a duration of up to two years.

The meta-analysis by Serebrauany et al. (2004) included 338,191 patients from 50 trials and evaluated the hemorrhagic risk associated with six different classes of antiplatelet agents. One of the classes of compounds included in this study was aspirin at doses  $<100$ , 100–325, and  $>325$  mg/day in patients with cardiovascular or cerebrovascular disease. Of note, this meta-analysis included patients from the CURE study (2001).

The second meta-analysis by Serebrauany et al. (2005, in press) included 192,036 from 31 trials and evaluated the hemorrhageis risk associated with low ( $<100$  mg), moderate (100–200 mg), and high ( $>200$  mg) doses of aspirin.

### **3.2.2. Supporting Publications**

The Supporting Publications grouping comprises eight articles summarizing the results of clinical trials, meta-analyses, or other studies that compared bleeding outcome data for one aspirin-alone treatment group in the dose range of interest versus a second aspirin-alone treatment group outside the dose range of interest, or compared bleeding outcome data for aspirin-alone treatment groups that all fell outside the dose range of interest (i.e., 50–325 mg/day). Table 2 summarizes the general characteristics of the eight articles comprising this grouping.

<b>Table 2. Table of Studies – Supporting Publications</b>					
<b>Reference</b>	<b>Total Subjects (N)</b>	<b>Patient Population</b>	<b>Treatment Groups (N)</b>	<b>Treatment Duration</b>	<b>Type of Article</b>
Posada IS, Barriaes V. Alternate-day dosing of aspirin in atrial fibrillation. American Heart Journal. 1999;138 (1 pt. 1): 137-143.	285	Patients with primary atrial fibrillation	Aspirin: 125 mg/day (104) 125 mg on alternate days (90) Placebo (91)	Mean follow-up period was 550 days	Clinical Trial
Taylor DW, Barnett HJM, Haynes RB, Ferguson GG, Sackett DL, Thorpe KE, Simard D, Silver FL, Hachinski V, Clagett GP, Barnes R, Spence JD. Low-dose and high-dose acetylsalicylic acid for patients undergoing carotid endarterectomy: a randomised controlled trial. ASA and Carotid Endarterectomy (CEA) Trial Collaborators Lancet. 1999;353 (9171): 2179-2184.	2804	Patients undergoing carotid endarterectomy	Aspirin 81 mg/day (698) Aspirin 325 mg/day (697) Aspirin 650 mg/day (703) Aspirin 1300 mg/day (706)	3 months	Clinical Trial
Blot WJ, McLaughlin JK Over the counter non-steroidal anti-inflammatory drugs and risk of gastrointestinal bleeding. Journal of Epidemiology and Biostatistics. 2000; 5 (2): 137-142.	1217	From the American College of Gastroenterology Bleeding Registry: Patients with (cases) or without (controls) GI bleeding	Cases (627): Aspirin (169) Other OTC analgesics (458) Controls (590): Aspirin (71) Other OTC analgesics (519)	ns <sup>1</sup>	Case-Control
Kelly JP, Kaufman DW, Jurgelon JM, Sheehan J, Koff RS, Shapiro S. Risk of aspirin-associated major upper-gastrointestinal bleeding with enteric-coated or buffered product. Lancet. 1996;348: 1413-1416.	1752	Patients with UGIB or controls	Plain aspirin: Cases/Controls ≤325 mg/day (45/71) ≥325 mg/day (81/54) Enteric-coated aspirin: ≤325 mg/day (17/25) ≥325 mg/day (2/10) Buffered aspirin: ≤325 mg/day (10/12) ≥325 mg/day(18/9)	ns <sup>2</sup>	Case-Control
Serrano P, Lanas A, Arroyo MT, Ferreira IJ. Risk of upper gastrointestinal bleeding in patients taking low-dose aspirin for the prevention of cardiovascular diseases. Alimentary Pharmacology and Therapeutics. 2002;16 (11): 1945-1953	903	Patients with cardiovascular diseases	Aspirin: 75 mg/day (3) 100 mg/day (27) 125 mg/day (341) 150 mg/day (89) 200 mg/day (416) 250 mg/day (8) 300 mg/day (19)	Mean follow-up period was 45 months	Case Study

Reference	Total Subjects (N)	Patient Population	Treatment Groups (N)	Treatment Duration	Type of Article
Derry S, Loke YK. Risk of gastrointestinal haemorrhage with long-term use of aspirin: meta-analysis. <i>British Medical Journal</i> . 2000;321 (7270): 1183-1187.	65,987	Patients taking aspirin for cardiovascular prophylaxis (primary prevention) and stroke patients taking aspirin for secondary prevention	Aspirin 50 to 1500 mg/day <sup>3</sup>	Minimum treatment of 1 year; mean of 28 months	Meta-analysis
Hart RG, Halperin JL, McBride R, Benavente O, Man-Son-Hing M, Kronmal RA. Aspirin for the primary prevention of stroke and other major vascular events: meta-analysis and hypotheses. <i>Archives of Neurology</i> . 2000;57 (3): 326-332.	52,251	Patients without manifest vascular disease	Aspirin (26,989): 75 mg/day (10,667) 325 mg QOD (11,037) 500-650 mg/day (5285) Placebo (25,262)	Mean follow-up: 4.6 years	Meta-analysis
Garcia Rodriguez LA, Hernandez-Diaz S, de Abajo FJ. Association between aspirin and upper gastrointestinal complications: systematic review of epidemiologic studies. <i>British Journal of Clinical Pharmacology</i> . 2001;52 (5): 563-571.	ns <sup>4</sup>	Patients with UGIC	Aspirin 75 to >600 mg/day <sup>3</sup>	ns <sup>5</sup>	Meta-analysis

Abbreviations: OTC: over-the-counter; UGIC: upper gastrointestinal complications; UGIB: upper gastrointestinal bleeding; QOD: every other day; ns: not specified.

1. Information on current or within the past week analgesic use was obtained.
2. Information on aspirin use in the 7 days before the onset of UGIB (cases) or the day of the interview (controls) was collected.
3. The numbers of patients in each aspirin treatment group were not specified.
4. The total number of patients from the 17 studies was not specified.
5. The treatment duration was not specified in this article but can be obtained from the 17 studies included in this analysis.

In this grouping, bleeding data from two clinical trials are presented first followed by three case studies (two case-control studies and one case study without controls) and three meta-analyses.

The first clinical trial is a placebo-controlled study by Posada et al. (1999) which compared bleeding events at an aspirin dose of 125 mg given daily or every other day in patients with primary atrial fibrillation (PAF). This publication is followed by a randomized clinical trial by Taylor et al. (1999) which compared the effect of low- (defined in this study as 81 and 325 mg/day) and high-dose (defined in this study as 650 and 1300 mg/day) aspirin on bleeding complications in patients undergoing carotid endarterectomy.

The first case-control study, published by Blot and McLaughlin (2000), is a further analysis of a previous case-control study (Peura et al., 1997). Peura et al. created a bleeding registry based on data compiled from questionnaires completed by fellows of the American

College of Gastroenterology (ACG) regarding patients' bleeding complications (in addition to information on controls without bleeding complications). Using this database, Blot and McLaughlin (2000) assessed the risk of gastrointestinal (GI) bleeding in these patients and controls in relation to the use of specific analgesics (including aspirin at doses <325, 325–974, and >974 mg/day). The second case-control study, published by Kelly et al. (1996), examined the effect of different aspirin formulations (plain, enteric-coated, or buffered) and doses ( $\leq 325$  and  $> 325$  mg/day) in subjects with or without upper GI bleeding (UGIB). The third study, presented by Serrano et al. (2002), was a case study examining the risk of GI bleeding in patients taking different doses of aspirin (75–300 mg/day) for secondary prevention of cardiovascular disease.

The first meta-analysis (Derry and Loke, 2000), comprised of patients from 24 randomized controlled trials, evaluated the risk of GI hemorrhage in patients taking 50–1500 mg/day aspirin for primary or secondary prevention of cardiovascular events. Hart et al. (2000) conducted a meta-analysis of 5 randomized trials: Early Treatment of Diabetic Retinopathy Study (ETDRS), Medical Research Council's Thrombosis Prevention Trial (MRC-TPT), Hypertension Optimal Treatment (HOT), US Physicians' Health Study (USPHS), and the British Doctors' Trial (BDT) to assess the effect of aspirin (75 mg/day, 325 mg QOD, or 500–650 mg/day) on hemorrhagic and ischemic stroke in patients without clinically manifest vascular disease. A meta-analysis by Garcia Rodriguez et al. (2001) of 17 epidemiological studies evaluated the association between aspirin dose (75 to  $> 600$  mg/day) and aspirin formulation (plain, buffered, or enteric-coated) on upper gastrointestinal complications (UGIC). Of note, this meta-analysis included the case study by Kelly et al. (1996), which is also included in this grouping.

### **3.2.3. Publications Providing Additional Safety Information**

A total of 60 articles are included in the Publications Providing Additional Safety Information grouping. This grouping is comprised of articles summarizing the results from a clinical trial, meta-analysis, or other study in which bleeding data were presented for a single aspirin-alone treatment group. A summary of study and patient characteristics for the publications included in this grouping is presented in the Table of Studies in Appendix 1.

A discussion of the bleeding data from the studies included in this grouping is provided in Section 6.3, and a tabular presentation of the bleeding data is provided in Appendix 2 of this aspirin safety summary. However, it is important to note that meaningful comparisons across the different publications are difficult, primarily due to differences in the methods of deriving and presenting bleeding data across studies (e.g., incidence rates, relative risks, annualized event rates, risk ratios, odds ratios, hazard ratios, etc.), differences in study-specific endpoints (e.g., differences in definitions of 'major' bleeding), and differences in treatment durations. Because of the wide variation in the characteristics of these studies, the 60 publications in this grouping are discussed in more general terms in this aspirin safety summary and not by individual publication.

The inclusion of this publication grouping in this submission serves to ensure that all aspirin-related safety data in cardiovascular and/or cerebrovascular indications published since 1996 are presented; however, it is important to note that these studies were conducted in a wide variety of indications, many of which are not directly relevant for this submission.

#### 4. OVERVIEW AND STUDY POPULATION CHARACTERISTICS OF RELEVANT PUBLISHED STUDIES

This section provides a brief overview of publications included in this aspirin safety summary regarding study design characteristics (study objectives, inclusion and exclusion criteria, treatment groups) safety endpoints, and statistical methodology. In addition, this section includes relevant study population characteristics such as indication for aspirin use, age, and sex. All descriptions were derived from the methods section of each publication.

##### 4.1. Key Publications

A description of the patient population characteristics for studies included in this grouping is presented in Table 3. The data presented in Table 3 represent patients exposed to aspirin-alone unless otherwise noted.

**Table 3. Summary of Patient Characteristics – Key Publications**

Reference	N	Patient Population	Age	Sex (%M/%F)
Peters et al., 2003	6303 <sup>1,2</sup>	Patients with symptoms of ACS without ST-segment elevation >1 mm on the ECG	64.2 years <sup>1</sup>	Aspirin: ≤100 mg/day: 58.8/41.2 <sup>3</sup> 100–199 mg/day: 61.1/38.9 <sup>3</sup> ≥200 mg/day: 65.4/34.6 <sup>3</sup>
Topol et al., 2003	4589	Patients with coronary or cerebrovascular disease	62.2 years	71.2/28.8
Serebruany et al., 2004	179,524 <sup>4</sup>	Patients with multiple cardiovascular/cerebrovascular indications	ns <sup>5</sup>	ns <sup>5</sup>
Serebruany et al., 2005 (in press)	192,036	Patients with multiple cardiovascular/cerebrovascular indications	ns <sup>5</sup>	ns <sup>5</sup>

Abbreviations: ACS: acute coronary syndromes; ECG: electrocardiogram; ns: not specified.

- Information obtained from the original publication of the CURE trial: CURE Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *New England Journal of Medicine*. 2001;345(7):494-502.
- Represents the total number of patients randomized to the placebo (i.e., aspirin-alone) treatment group per the original publication of the CURE trial.
- Includes both patients randomized to aspirin plus placebo or aspirin plus clopidogrel.
- The total number of patients exposed to aspirin in this meta-analysis was not specified, but was derived from a table in the publication.
- The age and sex of patients exposed to aspirin in this meta-analysis were not specified.

##### 4.1.1. Peters et al., 2003 (CURE Study)

Peters et al. (2003) conducted a post-hoc observational analysis of the CURE study, a randomized, double-blind, placebo-controlled study that was designed to evaluate the

benefits and risks of adding clopidogrel to different doses of aspirin in patients with ACS. The risk of major and minor bleeding at various aspirin doses was assessed.

A total of 12,562 patients from 28 countries were enrolled in the study, with 6303 patients randomized to placebo plus aspirin (i.e., aspirin alone) (CURE, 2001). To be included in the study, patients had to have symptoms indicative of ACS within 24 hours of study entry without ST-segment elevation  $>1$  mm on the electrocardiogram (ECG). In addition, ECG evidence of new ischemia or concentrations of cardiac enzymes (including troponin) at two times the upper limit of normal (ULN) was required. Patients were excluded if they had New York Heart Association class IV heart failure, if they had undergone percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) in the previous three months, if they had contraindications to antithrombotic or antiplatelet therapy, if they had previous disabling or hemorrhagic stroke or intracranial hemorrhage, if they had clinically severe thrombocytopenia, if they used or required oral anticoagulants or nonstudy antiplatelet agents, or if they had received a glycoprotein (GP) IIb/IIIa receptor inhibitor fewer than three days prior to randomization.

Patients were assigned to receive clopidogrel or placebo. A loading dose of 300 mg oral clopidogrel or placebo was given, followed by 75 mg/day clopidogrel or placebo. Aspirin was coadministered with both clopidogrel and placebo. The dose of aspirin was left to the discretion of the Investigator, but a 75–325 mg/day dose was recommended per the protocol. Patients were treated for an average of 3 to 12 months (mean: 9 months).

For analysis, patients were divided into three groups based on daily aspirin dose at the time of randomization ( $\leq 100$ , 101–199, or  $\geq 200$  mg/day). The percentage of males in the three aspirin dose groups ranged from 58.8 to 65.4% and mean age was 64.2 years. Over 50% of patients had hypertension. In each dose group, approximately one-third of patients had a previous MI and 9 to 14% had a history of CABG. Of note, data presented in Table 3 for each aspirin dose group represent patients taking aspirin (either alone or plus clopidogrel).

Bleeding endpoints measured included major bleeding, which was defined as significantly disabling, intraocular bleeding leading to significant loss of vision, or bleeding requiring transfusion of two or three units of red blood cells or equivalent whole blood. Major bleeding was subclassified as life-threatening or other major bleeding. Life-threatening bleeding complications were defined as fatal or leading to a drop in hemoglobin of  $\geq 5$  g/dL or significant hypotension with the need for inotropes, requiring surgery (other than vascular site repair) or symptomatic intracranial hemorrhage, or requiring transfusion of four or more units of red blood cells or equivalent whole blood. Minor bleeding was defined as any other bleeding requiring modification of the drug regimen.

For bleeding events, a logistic regression model was used. Hazard ratios (HR) for bleeding events were adjusted for sex, weight, hypertension, components of the Thrombolysis in Myocardial Infarction (TIMI) risk score (Rao et al., 1988), rates of angiography,

percutaneous coronary intervention (PCI), and CABG, and the use of non-steroidal anti-inflammatory drugs (NSAIDs), heparin, GP IIb/IIIa inhibitors, oral anticoagulants, open-label ticlopidine, or clopidogrel at any time during the study period. In addition, a stratified analysis of the risk of bleeding at various doses of aspirin was performed in selected patient subgroups.

#### **4.1.2. Topol et al., 2003 (BRAVO Study)**

The BRAVO study was a randomized, double-blind, placebo-controlled, study of lotrafiban, an oral GP IIb/IIIa antagonist, in patients with coronary and/or cerebrovascular disease. Safety endpoints included the incidence of serious bleeding, any bleeding, or any transfusion.

A total of 9190 patients from 23 countries were enrolled in the study. Patients were included if they had a prior MI or unstable angina within 14 days of Baseline, ischemic stroke 5-30 days after the acute event, a TIA within 30 days, or "double bed" vascular disease defined as documented peripheral vascular disease (PVD) combined with either coronary or cerebrovascular disease. Patients were not eligible for the study if they had a predisposition to bleeding, suboptimal blood pressure control, intolerance or allergy to aspirin, recent use of an intravenous GP IIb/IIIa antagonist, or need for therapy with warfarin or a thienopyridine drug. At the time of enrollment, almost 50% of patients had cardiovascular disease (MI or unstable angina), approximately 36% had cerebrovascular disease (TIA or stroke), about 11% had PVD and cardiovascular disease, and 5% had PVD and cerebrovascular disease.

The majority of patients who participated in the study were Caucasian (93.5%) and 71.2% were male. Mean age was approximately 62 years. Patients were randomly assigned to receive lotrafiban or placebo. Aspirin at doses of 75–325 mg/day was administered concomitantly, with the exact dose determined by the Investigator. Follow-up was for up to two years.

Odds ratios (OR) and 95% confidence intervals (CI) were calculated for the lotrafiban and placebo (aspirin-alone) groups for each of the following bleeding endpoints: serious bleeding, anemia, transfusion (any), transfusion of packed red blood cells/whole blood, platelet count <100,000, and platelet count <50,000. The percentage of patients experiencing serious bleeding, any bleeding, and transfusion in the low-dose (defined in this study as 75–162 mg/day) and higher dose (defined in this study as >162 mg/day) aspirin groups were also calculated. The type of bleeding in the lotrafiban and placebo groups was also evaluated.

#### **4.1.3. Serebruany et al., 2004**

Serebruany et al. (2004) conducted a meta-analysis of 50 randomized clinical trials to assess the risk of hemorrhage associated with various antiplatelet agents: aspirin <100 mg/day (3 trials), aspirin ≥100 mg/day (9 trials), dipyridamole (3 trials), thienopyridines

(10 trials), and intravenous (18 trials) and oral (7 trials) glycoprotein IIb/IIIa inhibitors. Data from clinical trials published between 1988-2002 retrieved from MEDLINE™, OVID™, and CARDIOSOURCE™ included patients with a follow-up of at least one month and a full description of hemorrhagic complications were included in the analysis. Information on sample size, study design, duration, agents used, patient characteristics, and bleeding severity was independently and blindly reviewed. The 50 clinical trials contributed a total of 338,191 patients, approximately 85% of whom were enrolled in the U.S. Most of the patients had ACS, unstable angina or MI. A few trials involved hypertensive patients, and about 40% of trials included patients with PCI. Hemorrhagic events were classified by the publication authors. The most common criteria used to assess bleeding severity were those by the TIMI study group (Rao et al., 1988) and, to a lesser extent, the Global Use of Strategies To Open Coronary Arteries (GUSTO) study group (1993). The mean age and sex ratios were not specified in this meta-analysis but can be obtained from the 50 clinical trials comprising this analysis and referenced in this publication. The weighted combination of major, minor, GI, and total bleeding rates and hemorrhagic stroke rates with 95% CI were calculated for each of the six categories of antiplatelet agents; however, only data related to aspirin use will be presented and discussed in this aspirin safety summary.

#### **4.1.4. Serebruany et al., 2005 (in press)**

Serebruany et al. (2005) conducted a meta-analysis of 31 randomized clinical trials to compare the risk of hemorrhage for the low (<100 mg) (9 trials), moderate (100–200 mg) (8 trials) and high (>200 mg) (21 trials), doses of aspirin in 192,036 patients enrolled in 31 clinical trials. Searching MEDLINE™, OVID™, and CARDIOSOURCE™, 31 clinical trials reported in English between 1988 and 2003 meet the required standards. These trials had clinical follow-up of at least one month and contained a detailed description of hemorrhagic complications. Hemorrhagic events were classified by the publication authors. The most common criteria used to assess bleeding severity were those by the TIMI study group (Rao et al., 1988) and, to a lesser extent, the Global Use of Strategies To Open Coronary Arteries (GUSTO) study group (1993). The mean age and sex ratios were not specified in this meta-analysis but can be obtained from the 50 clinical trials comprising this analysis and referenced in this publication. The weighted combination of major, minor, GI, and total bleeding rates and hemorrhagic stroke rates with 95% CI were calculated for each of the aspirin doses, low (<100 mg), moderate (100–200 mg) and high (>200 mg).

#### **4.2. Supporting Publications**

A description of patient characteristics including patient population, age, and sex are summarized in Table 4. The data presented in Table 4 represent patients exposed to aspirin-alone unless noted otherwise.

**Table 4. Summary of Patient Characteristics – Supporting Publications**

Reference	N	Patient Population	Age	Sex (%M/%F)
Taylor et al., 1999	2804	Patients scheduled to undergo carotid endarterectomy	69 years <sup>1</sup>	Aspirin 81 mg/day: 68/32 Aspirin 325 mg/day: 71/29 Aspirin 650 mg/day: 71/29 Aspirin 1300 mg/day: 70/30
Posada et al., 1999	194	Patients with PAF	66 years <sup>2</sup>	Aspirin 125 mg/day: 55/45 Aspirin 125 mg QOD: 49/51
Blot and McLaughlin, 2000	240	From the American College of Gastroenterology Bleeding Registry: Patients with (cases) or without (controls) GI bleeding	Cases: 60.1 years <sup>3</sup> Controls: 55.0 years <sup>3</sup>	Cases: 62.7/37.0 <sup>4</sup> Controls: 49.3/50.3 <sup>4</sup>
Kelly et al., 1996	649	Patients with UGIB admitted to the hospital with melena or hematemesis and controls	Cases: Gastric bleeding: 61 years <sup>5</sup> Duodenal bleeding: 60 years <sup>5</sup> Bleeding at both sites: 55 years <sup>5</sup> Controls: 60 years <sup>5</sup>	Cases: Gastric bleeding: 54.5/45.5 Duodenal bleeding: 75.6/24.4 Bleeding at both sites: 76/24 Controls: 61.4/38.6
Serrano et al., 2002	903	Patients diagnosed with cardiovascular diseases who were discharged on aspirin regimens.	65 years for all groups	73.9/26.1 <sup>6</sup>
Derry and Loke, 2000	65,987	Ranged subjects taking aspirin for primary prevention to patients who had experienced a stroke	ns	74/26 <sup>6</sup>
Hart et al., 2000	26,989 <sup>7</sup>	Patients at high-risk (HOT, MRC-TPT, ETDRS) or low-risk (USPHS, BDT) for vascular disease	57 years <sup>7</sup>	80/20 <sup>7</sup>
Garcia Rodriguez et al., 2001	ns	Patients from case-control or cohort studies with UGIC	ns	ns

Abbreviations: CE: carotid endarterectomy; PAF: primary atrial fibrillation; GI: gastrointestinal; UGIC: upper GI bleeding complications; UGIB: upper GI bleeding; ns: not specified.

1. Median age was 69 years in all 4 treatment groups.
2. Mean age across all aspirin treatment groups.
3. The age represents the entire number of cases or controls whether taking aspirin-alone, other analgesics, or a combination of both aspirin and analgesics.
4. The sex was unknown for 0.3% of cases and controls.
5. Median age.
6. Percentages of males/females across all aspirin treatment groups.
7. Represents information for all treatment groups (aspirin, placebo, or no treatment).

#### **4.2.1. Posada et al., 1999**

The study by Posada et al. (1999) was a multi-center, randomized, placebo-controlled study of open-label aspirin in adult patients with PAF. Patients were evaluated over a mean period of 550 days. The primary objective of the study was to evaluate the cardiovascular and cerebrovascular protective effects of low-dose aspirin (125 mg) administered daily versus on alternate days. Patient withdrawals due to bleeding events or other GI complications were also recorded.

There were a total of 285 patients enrolled in the study. Not included were patients who had general contraindications to the use of aspirin (peptic ulcer, symptomatic hiatus hernia, aspirin hypersensitivity), an accepted indication for the use of oral anticoagulants (vascular prosthesis, cardiac intracavity thrombus, spontaneous echoes), or an indication for antiplatelet treatment before entry into the study, such as previous episodes of angina, MI, or TIA.

Patients were randomly assigned to one of three treatment groups and received 125 mg aspirin daily, 125 mg on alternate days, or placebo. There was a slightly higher percentage of males than females among patients taking 125 mg of aspirin daily compared to those taking 125 mg every other day (QOD) or placebo. Mean age was approximately 66 to 67 years across the treatment groups. As expected, 80% or more of patients in all treatment groups had constant atrial fibrillation and approximately 50% had arterial hypertension. Approximately 7–11% of patients in each group had an implanted pacemaker.

No statistical methods from this publication are included in this aspirin safety summary since the only bleeding data discussed are the numbers of subjects who withdrew from the study due to mild bleeding.

#### **4.2.2. Taylor et al., 1999**

The study by Taylor et al. (1999) was a multi-center, randomized, double-blind, controlled trial of aspirin at doses of 81, 325, 650, and 1300 mg/day in adult patients who were scheduled to undergo carotid endarterectomy for arteriosclerotic disease. Patients were treated with aspirin prior to and for three months following surgery. The primary objective of the study was to evaluate differences in the occurrence of perioperative complications (stroke, MI, and death) at 30 days and three months after surgery among patients receiving four different doses of aspirin. Although the primary objective of this study was to evaluate the effect of aspirin on efficacy measures, this study did assess the relative risk (RR) of hemorrhagic stroke in patients on low (defined as 81 and 325 mg/day) vs. high-dose (defined as 650 and 1300 mg/day) aspirin. Other bleeding complications (e.g., wound hematoma, melena, hematemesis, etc.), were also assessed.

A total of 2804 patients were enrolled (2800 patients planned) at 74 centers in the United States (48), Canada (19), Australia (4), Italy (1), Argentina (1), and Finland (1). Patients who were taking aspirin or any other antiplatelet medication that could not be stopped, had had a recent disabling stroke, or had undergone cardiac surgery in the previous 30 days were excluded from the study. Prior to randomization, a medical history was taken and patients underwent physical, neurological, and functional-status assessments. A randomization schedule stratified by center and balanced every 12 patients was used to assign patients to one of four aspirin treatment groups. Patients received 81, 325, 650, or 1300 mg/day aspirin, plus placebo. Almost all patients in each of the four aspirin treatment groups were Caucasian (95%) and approximately 70% of patients were male. The median age in all treatment groups was 69 years. Approximately 46% of patients (1292 of 2804) in each dose group had had ischemic carotid-territory symptoms in the preceding 6 months and 54% (1512 of 2804 patients) were symptom-free.

The primary analysis compared the two high-dose groups (650 and 1300 mg/day) with the two low-dose groups (81 and 325 mg/day) with Pearson's  $\chi^2$  test. Because no comparisons were made between the 81 and 325 mg/day dose groups (which includes the dose range of interest), this publication is in the supporting publications grouping.

#### **4.2.3. Blot and McLaughlin, 2000**

Blot and McLaughlin (2000) conducted an independent analysis of a case-control study by Peura et al. (1997). In the Peura et al. (1997) study, preliminary findings regarding the risk of GI bleeding among users of aspirin and other NSAIDs were reported. The purpose of the Blot and McLaughlin (2000) study was to assess the risk of GI bleeding in relation to the use of specific analgesics at over-the-counter (OTC) doses in addition to other factors (e.g., alcohol and tobacco use). In the Peura et al. (1997) study, a mail survey of all members and fellows of the ACG was conducted. The survey was used to obtain information on patients with GI bleeding (cases) and procedure-matched patients without GI bleeding (controls). Thus, a Bleeding Registry was created based upon these data. Each gastroenterologist was asked to complete the survey for up to 10 recent cases and 10 subsequent controls. The cases typically included patients hospitalized for bleeding associated with esophagitis, esophageal/gastric varices, gastric or duodenal ulcer, other upper GI conditions, and diverticular and other lower GI conditions. Approximately three-quarters of cases had an upper and one-quarter a lower GI bleeding source. The controls were endoscopy patients without GI bleeding, matched by whether the procedure concerned the upper or lower GI tract.

The survey sought information on demographics, symptoms and conditions, recent (described as "current" or "within the last week") OTC and prescription analgesic and other drug use, and tobacco and alcohol consumption. The mean ages were similar between the cases (60.1 years) and controls (55.0 years). Mean ages were calculated from the entire number of cases and controls, some of whom were on other analgesics besides aspirin or

combinations of aspirin and other analgesics (e.g., acetaminophen, NSAIDs). There were more males in the cases compared to the controls (62.7% vs. 49.3%, respectively). Similar to the data on mean age, the percentages of each sex in the two groups included patients other than those on aspirin-alone.

The risk of GI bleeding among cases and controls associated with analgesic use and other factors was evaluated. Odds ratios and corresponding 95% CI were calculated per logistic regression analysis.

#### **4.2.4. Kelly et al., 1996**

In a multi-center case-control study, Kelly et al. (1996) assessed the risk of major UGIB with different aspirin formulations. A total of 550 incident cases of UGIB hospital admissions and 1202 controls identified per population census lists were included in the study. Cases and controls were interviewed by phone regarding their use of aspirin and other NSAIDs. Cases were defined as patients admitted to the hospital with a first episode of major UGIB due to gastric or duodenal ulcer or gastritis characterized by melena or hematemesis confirmed by endoscopy. Patients were excluded if they had any of the following: previous episode of UGIB, history of ulcer disease, GI symptoms lasting more than 30 days, present cancer, history of gastric cancer, cirrhosis or alcoholic liver disease, other sites or cause of major UGIB such as Mallory-Weiss tear or esophageal varices, disorders of the lower GI tract, bleeding disorder or other conditions that predispose to UGIB, or current therapy with anticoagulants, antineoplastic drugs, or histamine antagonists. Controls were selected to match cases by residence, sex, and half-decade of age. Exclusion criteria were the same as for cases.

Aspirin use was defined as use in the seven days before the index day (i.e., day on which melena or hematemesis first occurred). For the controls for whom no comparable event existed, the index day was the day of the interview. Aspirin use was categorized according to formulation (plain, buffered, or enteric-coated), dose, ( $\leq 325$  mg/day or  $> 325$  mg/day), and frequency (regular [taken at least every other day] or occasional [use on 1–3 days during the week]).

For cases, the type of bleeding was categorized by median age and sex and not by the aspirin dose or formulation. The median ages for cases with gastric, duodenal, or bleeding at both sites was 61, 60, and 55 years, respectively. For controls, the median age (60 years) was comparable to cases. The majority of the three bleeding types in the cases occurred in males. Duodenal bleeding or bleeding at both sites (75.6% and 76%, respectively), had the higher percentage of male cases. The majority of controls were also males (61.4%).

Relative risks of UGIB and 95% CI were estimated by multiple logistic regression for drug categories in which at least five cases and controls were exposed.

#### **4.2.5. Serrano et al., 2002**

Serrano et al. (2002) studied a cohort of patients taking low-dose aspirin for cardiovascular prophylaxis to assess the risk of GI bleeding in this population. A total of 903 consecutive patients diagnosed with cardiovascular disease who were discharged from the hospital on low-dose (75–325 mg) aspirin regimens were included. Structured telephone interviews using a standardized questionnaire were employed to collect data from patients concerning the reason for aspirin use, other medical history besides UGIB, other medications, and details concerning the UGIB if applicable. UGIB was defined as the presence of melena and/or hematemesis confirmed by hospital staff and requiring hospital admission.

The mean age across all aspirin treatment groups was 65 years and the majority of patients were male (73.9%). The most common cardiovascular events reported at baseline were prior angina (52.4%) and prior Q-wave MI (46.4%). Nearly 40% of the patients had hypertension. Patients were followed for a mean of 45 months.

A multivariate (Cox regression) analysis was used to assess the RR (and 95% CI) of suffering a UGIB in patients with and without various risk factors.

#### **4.2.6. Derry and Loke, 2000**

To assess the risk of GI hemorrhage with long-term aspirin use, Derry and Loke (2000) conducted a meta-analysis of 24 randomized, double-blind, placebo-controlled trials (N=65,987). Trials were included in the analysis if patients in one treatment arm were allocated to aspirin-alone and patients in the control arm to placebo or no treatment, provided that the scheduled duration of treatment was a minimum of 12 months. Only trials that provided numerical data on GI hemorrhages in both treatment arms were included. For bleeding complications, only the terms "hematemesis" or "melena" were accepted. Trials were excluded if the term "randomized" was not specifically mentioned in the publication or if the trials clearly used non-random allocation. In addition, trials with fewer than 50 patients in each arm, crossover studies, and studies in which aspirin was used in conjunction with other antiplatelet agents or anticoagulants without a placebo or "no treatment" control arm, were also excluded.

Across the 24 trials, indications for aspirin use extended from primary prevention in healthy individuals to secondary prophylaxis after stroke. The dosage of aspirin ranged from 50–1500 mg/day.

Most participants were middle-aged, although the article did not specify the age range for subjects from the 24 trials included in the analysis. The majority of participants across all aspirin doses, placebo, or no treatment were male (74%).

Pooled ORs and heterogeneity were analyzed for the incidence of GI hemorrhage in patients taking aspirin vs. placebo in addition to a calculation of the number needed to harm (with 95% CI). A meta-regression analysis was used to test for a linear relation between the

daily dose of aspirin and the risk of GI hemorrhage. Data from the eight trials that used doses of 50 to 162.5 mg/day (N=49,927) were analyzed separately to evaluate the incidence of GI hemorrhage in this population.

#### **4.2.7. Hart et al., 2000**

To assess the effect of aspirin on the incidence of stroke and other major vascular events in persons without clinically recognized cardiovascular disease, Hart et al. (2000) performed a search of medical databases from 1980–1988. The Cochrane Collaboration Registry and published lists of the ATC were also reviewed. Clinical trials in which all participants had major atherosclerotic risk factors (e.g., advanced age, hypertension, diabetes mellitus) were included, but considered separately in secondary analyses. Clinical trials in which >20% of the participants had clinically diagnosed vascular disease, those who did not report stroke outcomes, and those without observed strokes were not analyzed. Clinical trials in which aspirin was combined with another antiplatelet agent were also excluded.

This search yielded five randomized trials (USPHS, ETDRS, MRC-TPT, HOT, and BDT) which were used for the meta-analysis. For three of these trials the patients included had vascular risk factors: ETDRS patients had diabetes mellitus; MRC-TPT patients had coronary risk factors; and HOT study patients had hypertension. The remaining two trials (USPHS and BDT) employed healthy male physicians of whom only a minority had vascular risk factors. Aspirin doses ranged from 75–650 mg/day, and the mean follow-up period was 4.6 years. The mean age of participants across all five trials was 57 years; the majority of participants were male (80%).

The RR of hemorrhagic stroke from a pooled analysis of all five trials was assessed. Indirect comparisons of the RR of hemorrhagic stroke were also performed in the three trials testing aspirin doses of 75 mg/day to 325 mg QOD. In addition, the RR of ischemic stroke was assessed from a pooled analysis of the four trials that separated hemorrhagic from ischemic stroke (BDT, USPHS, MRC-TPT, and HOT).

#### **4.2.8. Garcia Rodriguez et al., 2001**

The main objective of the meta-analysis by Garcia Rodriguez et al. (2001) was to examine the association between aspirin and UGIC. To be included in this analysis, studies had to be case-control or cohort studies investigating the relationship between aspirin use and UGIC (defined as bleeding, perforation, or other serious upper GI event resulting in hospitalization or visit to a specialist), and the articles had to provide valid RR estimates or enough data to estimate a RR comparing aspirin users with nonusers. A total of 17 epidemiological studies (14 case-controls and three cohorts) published between 1990 and 2001 were included in the analysis. Aspirin doses ranged from 75 to >600 mg/day; however, the treatment duration was not specified. Information regarding age and sex were not presented in this meta-analysis but can be obtained for the 17 studies comprising this analysis and referenced in this publication.

The RR (with 95% CI) of UGIC associated with aspirin use was analyzed separately for aspirin dose, aspirin formulation (plain, coated, or buffered), study design (case-control vs. cohort) and other factors (e.g., sex, age, frequency of aspirin use, duration of use, site of the lesion, and type of lesion).

#### **4.3. Publications Providing Additional Safety Information**

A total of 60 studies included in this grouping describe a wide range of publications in a variety of patient populations. In general, the patient population consisted of males and females who were diagnosed with various cardiovascular and/or cerebrovascular conditions or who were considered to be at risk for such conditions. The studies also included patients in a wide array of age groups, ranging from 35.5 years to >90 years. Most of these publications are clinical trials and meta-analyses. Three of the publications are case studies and one each is an observational and a retrospective study. A summary of general study and patient characteristics for the publications included in this grouping is presented in the Table of Studies in Appendix 1.

### **5. SUMMARY OF SUBJECT ACCOUNTABILITY AND EXTENT OF EXPOSURE**

#### **5.1. Key Publications**

A brief description of subject accountability and exposure to aspirin is presented for the four key publications and summarized in Table 5.

**Table 5. Summary of Patient Exposure to Aspirin – Key Publications**

Reference	N	Aspirin Dose(s)	Number of Patients Exposed	Duration of Exposure
Peters et al., 2003	6303 <sup>1,2</sup>	≤100 mg/day <sup>3</sup> 101–199 mg/day <sup>3</sup> ≥200 mg/day <sup>3</sup>	5320 <sup>4</sup> 3109 <sup>4</sup> 4110 <sup>4</sup>	Mean 9 months <sup>1</sup>
Topol et al., 2003	4589	75–162 mg/day <sup>3</sup> >162 mg/day <sup>3</sup>	2410 2179	Up to 2 years
Serebruany et al., 2004	179,524 <sup>5</sup>	<100 mg/day 100–325 mg/day >325 mg/day	14,986 <sup>5</sup> 160,774 <sup>5</sup> 3764 <sup>5</sup>	ns <sup>6</sup>
ATC, 2002	29,652 <sup>7</sup>	<75 to 1500 mg/day	<75 mg/day: 1827 <sup>7</sup> 75–150 mg/day: 3370 <sup>7</sup> 160–325 mg/day: 13,240 <sup>7</sup> 500–1500 mg/day: 11,215 <sup>7</sup>	ns

Abbreviations: ns: not specified

- Information obtained from the original publication of the CURE trial: CURE Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *New England Journal of Medicine*. 2001;345(7):494-502.
- Represents the total number of patients randomized to the placebo (i.e., aspirin-alone) treatment group per the original publication of the CURE trial.
- The choice of aspirin dose was left to the discretion of the investigator.
- Includes both patients randomized to aspirin plus placebo or aspirin plus clopidogrel.
- The total numbers of patients exposed to aspirin in this meta-analysis were not specified, but were derived from a table in the publication.
- Only trials in which patients had a clinical follow-up for at least 1 month were included in the analysis.
- The total numbers of patients exposed to aspirin in this meta-analysis were not specified, but were derived from a figure in the publication. This number only includes patients exposed to aspirin in trials in which aspirin was compared to a control group. This number includes patients from trials that may have contributed to more than one aspirin-alone dose comparison group.

**5.1.1. Peters et al., 2003**

A total of 6303 patients were randomized to placebo plus aspirin (i.e., aspirin alone) in the CURE study (2001). Patients included in the post-hoc observational analysis of the CURE study data were exposed to a median aspirin dose of 150 mg/day. The CURE study recruited patients from 482 centers in 28 countries (2001). Aspirin dosing varied among regions with the highest dose (≥200 mg/day), which was most common in North and South America. Use of the medium dose (101–199 mg/day) was common in Australia and New Zealand, and use of the lowest dose (≤100 mg/day) was common in Eastern and Western Europe. Within each center, the variation in aspirin dose was small. An average of 89% of all patients per center used a dose of aspirin within 50 mg of the most frequently used dose. Aspirin dose per patient varied little during the course of the study. Only 14% of patients used a dose that differed by at least 50 mg from the initial dose for >50% of the duration of follow-up (mean: 9 months; CURE, 2001). As noted previously, data presented for each aspirin dose group in Table 5 represents patients taking aspirin-alone and aspirin plus clopidogrel.

### **5.1.2. Topol et al., 2003**

A total of 4589 patients in the placebo plus aspirin treatment groups of the BRAVO study were exposed to doses of aspirin that ranged from 75–325 mg/day for up to two years (75–162 mg/day: 2410 patients; >162 mg/day: 2179 patients). A dose reduction was required in 4.6% of patients in this treatment group and 22.9% of patients prematurely discontinued study medication. Reasons for premature discontinuation included major (1.6%) and minor (2.6%) bleeding. The length of follow-up was 366 days (median) (includes patients in both the placebo plus aspirin and Iloprost plus aspirin treatment groups; 25<sup>th</sup> and 75<sup>th</sup> percentiles, respectively, were 279 and 463 days in the placebo plus aspirin treatment groups).

### **5.1.3. Serebruany et al., 2004**

Patients in this meta-analysis were exposed to aspirin doses <100 mg/day, 100–325 mg/day, or >325 mg/day. A total of 14,986 patients were exposed to <100 mg/day aspirin. Most of the patients exposed to aspirin were taking between 100–325 mg/day (160,774). A total of 3764 patients were exposed to daily aspirin doses >325 mg. The duration of exposure was not specified, but can be obtained for the 50 individual clinical trials comprising this analysis and referenced in this publication. Only trials in which patients had a clinical follow-up for at least one month were included in the analysis.

### **5.1.4. Serebruany et al., 2005 (in press)**

Patients in this meta-analysis were exposed to aspirin doses <100 mg/day, 100–200 mg/day, or >200 mg/day. A total of 19,428 patients were exposed to <100 mg/day aspirin, 32,223 patients were exposed to 100–200 mg/day. Most of the patients exposed to aspirin were taking >200 mg/day (140,385). The duration of exposure was not specified, but can be obtained for the 31 individual clinical trials comprising this analysis and referenced in this publication. Only trials in which patients had a clinical follow-up for at least one month were included in the analysis.

## **5.2. Supporting Publications**

A brief description of subject accountability and exposure to aspirin is presented for each of the supporting publications and summarized in Table 6.

**Table 6. Summary of Subject Accountability and Exposure to Aspirin – Supporting Publications**

Reference	N	Aspirin Dose(s)	Number of Patients Exposed	Duration of Exposure
Posada et al., 1999	194	125 mg/day 125 mg QOD	104 90	Mean follow-up: 510 days Mean follow up: 600 days
Taylor et al., 1999	2804	81 mg/day 325 mg/day 650 mg/day 1300 mg/day	698 697 703 706	3 months <sup>1</sup>
Blot and McLaughlin, 2000	240 <sup>2</sup>	<325 mg/day to > 974 mg/day	<325 mg/day <sup>3</sup> : Cases/Controls: 30/11 325-974 mg/day <sup>3</sup> : Cases/Controls: 63/32 >974 mg/day <sup>3</sup> : Cases/Controls: 27/6	Current or within the past week
Kelly et al., 1996	649	Plain: ≤325 mg/day >325 mg/day Occasional use Enteric-coated: ≤325 mg/day >325 mg/day Occasional Buffered: ≤325 mg/day >325 mg/day Occasional Combination:	Plain: Cases/Controls: 45/71 81/54 70/139 Enteric-coated: Cases/Controls: 17/25 2/10 4/2 Buffered: Cases/Controls: 10/12 18/9 26/41 Combination: Cases/Controls: 10/3	Seven days before the index day <sup>4</sup>
Serrano et al., 2002	903	75 mg/day 100 mg/day 125 mg/day 150 mg/day 200 mg/day 250 mg/day 300 mg/day	3 27 341 89 416 8 19	Mean follow-up period was 45 mos.
Derry and Loke, 2000	832	50-1500 mg/day	50-162.5 mg/day: 574 162.5-1500 mg/day: 258	1 year
Hart et al., 2000	26,989	75 mg/day 325 mg/day 500 to 650 mg/day	10,667 11,037 5285	Mean follow-up was 4.6 years
García Rodríguez et al., 2001	ns	75 to >600 mg/day	ns	ns

Abbreviations: QOD: every other day; ns: not specified.

1. Aspirin started before surgery and continued for 3 months.
2. Subjects exposed to aspirin either alone or with other analgesics or prescription NSAIDs.
3. Excludes subjects with unknown aspirin doses.
4. The index day was the onset of bleeding (cases) or the day of the interview (controls).

**5.2.1. Posada et al., 1999**

Patients participating in the study were exposed to 125 mg aspirin daily (N=104) or on alternate days (N=90) for a mean evaluation period of 510 and 600 days, respectively.

**5.2.2. Taylor et al., 1999**

Patients were exposed to 81 mg (698 patients), 325 mg (697 patients), 650 mg (703 patients), or 1300 mg (706 patients) daily for a duration of 3 months. Compliance was >90% at the 30-day assessment and ranged from 86 to 89% at the 3-month assessment.

Approximately two-thirds of patients in each treatment group were taking <650 mg/day of aspirin prior to study entry and 11% to 14% of patients in each aspirin dose group were taking ≥650 mg/day.

**5.2.3. Blot and McLaughlin, 2000**

The analyses presented by Blot and McLaughlin (2000) were based on a previously published case-control study by Peura et al. (1997). In the latter study, cases and controls reported their use of OTC aspirin and other analgesics in addition to prescription NSAIDs. The use of these drugs was defined as "current" or "within the last week." Of the 627 cases, 30 were exposed to aspirin doses up to 324 mg/day; 63 cases used 325–974 mg/day aspirin, and 27 used aspirin >974 mg/day. Of the 590 controls, 11 were exposed to aspirin doses 325 mg/day; 32 used 325–974 mg/day aspirin, and six used aspirin >974 mg/day. Of note, the number of cases or controls exposed to different aspirin doses includes those using aspirin only in addition to those using aspirin plus other analgesics or prescription NSAIDs.

**5.2.4. Kelly et al., 1996**

In this case-control study, cases and controls reported taking plain, enteric-coated, or buffered aspirin at doses of ≤325 mg/day, >325 mg/day, or occasional use defined as use on 1–3 days during the week. Information on the use of aspirin was confined to use seven days before the index day. For cases, the index day was the onset of bleeding and for controls, the index day was the day of the interview. Most cases and controls used plain aspirin followed by buffered and enteric-coated formulations. The most commonly used dose by cases was plain aspirin >325 mg/day. The controls most commonly used plain aspirin occasionally.

**5.2.5. Serrano et al., 2002**

Patients in this study were exposed to aspirin doses ranging from 75-300 mg/day. Of the 903 patients exposed to aspirin, most were taking 200 mg (N=416) or 125 mg (N=341). The 75 mg/day dose was taken by only three patients. The duration of exposure was not specified; however, patients were followed for an average of 45 months.

**5.2.6. Derry and Loke, 2000**

In this meta-analysis, patients were exposed to 50–1500 mg/day aspirin for a minimum of one year (mean: 28 months). A total of 574 patients were exposed to 50–162.5 mg/day aspirin and 258 patients were exposed to 162.5–1500 mg/day aspirin.

**5.2.7. Hart et al., 2000**

Among the 26,989 patients from five randomized trials included in this meta-analysis, exposure to aspirin ranged from 75–650 mg/day. Similar numbers of patients were exposed to 75 (N=10,667) and 325 mg/day (N=11,037) aspirin. Fewer patients were exposed to 500-650 mg/day aspirin (N=5285). The duration of exposure to these aspirin doses was not specified; the mean follow-up period was 4.6 years.

**5.2.8. Garcia Rodriguez et al., 2001**

Patients in this meta-analysis used 75–600 mg/day aspirin. The number of patients exposed to each aspirin dose and the duration of exposure were not specified, but can be obtained for the 17 individual trials comprising this analysis and referenced in the publication.

**5.3. Publications Providing Additional Safety Information**

The Publications Providing Additional Safety Information included a wide range of study sizes and treatment durations. For the individual studies in this grouping, the total number of subjects exposed ranged from a small case study of eight patients (Derksen et al., 2003) to a large clinical trial of 21,106 patients (Chinese Acute Stroke Trial [CAST] Collaborative Group, 1997). For the meta-analyses included in this grouping, the total number of subjects ranged from 3298 patients in five trials (Taylor et al., 2001) to a large meta-analysis of 55,462 patients in 16 trials (He et al., 1998). Aspirin doses utilized in the individual studies or the meta-analyses ranged from 30 to 650 mg/day with a duration of treatment (when specified) ranging from 7–14 days to 12 years and follow-up periods ranging up to 8.9 years. Summaries of subject accountability and extent of exposure for the studies included in this grouping are presented in the Table of Studies in Appendix 1.

**6. SUMMARY OF SAFETY INFORMATION REGARDING BLEEDING COMPLICATIONS**

**6.1. Key Publications**

As noted previously, this aspirin safety summary is organized first by a presentation of the Key Publications (those publications that presented bleeding data comparing >1 aspirin-alone treatment group within the dose range of 50–325 mg/day).

**6.1.1. Peters et al., 2003**

The post-hoc analysis of the CURE study was designed to evaluate the benefits and risks of adding clopidogrel to a range of aspirin doses in the treatment of patients with ACS. It should be noted that the exact aspirin dose (75–325 mg/day) in either treatment group was left to the discretion of the Investigator.

As shown in Table 7, in the aspirin plus placebo group (i.e., aspirin-alone), the incidence of major bleeding increased significantly with increasing aspirin dose (1.9%, 2.8%, and 3.7% for aspirin doses of  $\leq 100$ , 101–199, and  $\geq 200$  mg/day, respectively; p-value for trend,  $<0.0001$ ). When bleeding complications were further classified as life-threatening, a similar trend was observed in bleeding incidence (1.3%, 1.9%, and 2.4%, for aspirin doses of  $\leq 100$ , 101–199, and  $\geq 200$  mg/day, respectively; p-value for trend, 0.004). The adjusted ORs of developing a major bleeding complication were higher when aspirin-alone doses of 101–199 mg/day (OR: 1.52; 95% CI: 1.00 to 2.31) and  $>200$  mg/day (OR: 1.70; 95% CI: 1.22 to 2.59) were compared to doses  $\leq 100$  mg/day. A similar pattern was observed for life-threatening bleeding complications.

**Table 7. Major and Life-Threatening Bleeding by Various Doses of Aspirin – Peters et al., 2003**

	<b>Aspirin-alone</b>	<b>Aspirin + Clopidogrel</b>
<b>Major Bleeding Complications</b>		
Aspirin $\leq 100$ mg/day (% incidence)	1.86	2.97
Aspirin 101–199 mg/day (% incidence)	2.82	3.41
Aspirin $\geq 200$ mg/day (% incidence)	3.67	4.86
P-value for trend	$<0.0001$	$<0.001$
Adjusted <sup>1</sup> OR for 101–199 mg/day vs. $\leq 100$ mg/day	1.52 (1.00 to 2.31)	1.20 (0.84 to 1.73)
Adjusted <sup>1</sup> OR for $> 200$ mg/day vs. $\leq 100$ mg/day	1.70 (1.22 to 2.59)	1.63 (1.19 to 2.23)
<b>Life-threatening<sup>1</sup> Bleeding Complications</b>		
Aspirin $\leq 100$ mg/day (% incidence)	1.26	1.75
Aspirin 101–199 mg/day (% incidence)	1.90	1.39
Aspirin $\geq 200$ mg/day (% incidence)	2.37	3.29
P-value for trend	0.004	0.0006
Adjusted <sup>2</sup> OR for 101–199 mg/day vs. $\leq 100$ mg/day	1.48 (0.89 to 2.46)	0.79 (0.47 to 1.32)
Adjusted <sup>2</sup> OR for $\geq 200$ mg/day vs. $\leq 100$ mg/day	1.64 (1.04 to 2.59)	1.82 (1.22 to 2.71)

1. Defined as fatal bleeding or bleeding leading to a decrease in hemoglobin of  $\geq 5$ g/dL or significant hypotension with the need for inotropes, requiring surgery (other than vascular site repair) or symptomatic intracranial hemorrhage, or requiring transfusion of 4 or more units of red blood cells or equivalent whole blood.

2. Adjusted for gender, weight, hypertension, components of the TIMI risk score, rates of angiography, PCI and CABG, and the use of NSAIDs, heparin, GP IIb/IIIa inhibitors, oral anticoagulants, open-label ticlopidine, or clopidogrel at any time during the study period.

For the aspirin + clopidogrel group, a similar proportionate increase in major bleeding complications (3.0%, 3.4%, and 4.9%, p-value for trend, <0.001) and life-threatening bleeding complications (1.8%, 1.4%, and 3.3%, p-value for trend=0.0006) was observed. Across both treatment groups, a trend for a higher risk of major bleeding with increasing aspirin dose was observed in patients undergoing PCI, CABG, or no revascularization (data not shown).

The dose of aspirin prescribed was at the discretion of the Investigator and strongly dependent on the center at which the patient was treated. The choice of dose by the center was associated with geographic location. That is, a patient was more likely to receive  $\geq 200$  mg/day aspirin at centers in North or South America than at centers in Australia/New Zealand/South Africa or Eastern/Western Europe where doses of 101–199 mg/day and  $\leq 100$  mg/day, respectively, were most commonly used.

In sum, the data show that the risk of major bleeding increased with increasing aspirin dose irrespective of whether it was used alone or in combination with clopidogrel. Patients with acute coronary syndromes taking aspirin doses between 75–100 mg/day demonstrated a lower risk associated with bleeding complications than in patients taking aspirin doses of 101–199 mg/day and aspirin doses of 200–325 mg/day, respectively.

#### **6.1.2. Topol et al., 2003**

The BRAVO study evaluated the effect of the platelet GP IIb/IIIa receptor antagonist, lotrafiban, when combined with aspirin in patients with coronary artery disease (CAD) or cerebrovascular disease. Patients were randomized to receive either lotrafiban plus aspirin or placebo plus aspirin (i.e., aspirin-alone). As in the CURE study, the exact aspirin dose (75–325 mg/day) in either treatment group was left to the discretion of the Investigator. The major bleeding endpoints measured included serious bleeding, any bleeding, and the need for a transfusion.

As shown in Table 8, when the safety endpoints were evaluated by aspirin dose (low: 75–162 mg/day vs. high: >162 mg/day), the incidence of serious bleeding (2.4% vs. 3.3%), any bleeding (11.1% vs. 15.4%), or any transfusion (1.0% vs. 2.0%) was lower among subjects receiving 75–162 mg/day aspirin compared to >162 mg/day aspirin, respectively. Serious bleeding was also more common among patients exposed to higher aspirin doses (>162 mg/day) than lower doses when given with lotrafiban (data not shown). The authors of this publication suggest that lower aspirin doses ( $\leq 162$  mg/day) may be the most practical way to lower bleeding risk in patients with cardiovascular or cerebrovascular disease.

**Table 8. Bleeding and Other Outcomes by Aspirin Dose in the Placebo (Aspirin-alone) Treatment Group – Topol et al., 2003**

<b>Event</b>	<b>75-162 mg/day (N = 2410)</b>	<b>&gt;162 mg/day (N = 2179)</b>
Serious Bleeding (% incidence)	2.4	3.3
Any Bleeding (% incidence)	11.1	15.4
Transfusion (% incidence)	1.0	2.0

Although the dose of aspirin was not randomly assigned in the BRAVO study, the finding of increased bleeding and doses >162 mg/day was noteworthy. Based on the BRAVO study, doses of aspirin of  $\leq 162$  mg/day are prudent to avoid bleeding complications.

**6.1.3. Serebruany et al., 2004**

The purpose of this meta-analysis was to determine the frequency of bleeding complications dependent on the class and dose of antiplatelet used. A total of 50 randomized controlled trials with a total of 338,191 patients were analyzed. Aspirin doses were divided into 3 groups: <100, 100–325, and >325 mg/day. Bleeding complications analyzed by this meta-analysis included major and minor bleeding events, hemorrhagic stroke, GI bleeding events, and total bleeding events. The weighted average bleeding rates across aspirin dose groups were analyzed as shown in Table 9.

**Table 9. Weighted Average Bleeding Rates by Aspirin Dose – Serebruany et al., 2004**

Aspirin Dose	Number of Trials Reported	Number of Patients	Bleeding Rate (%)	95% CI
<b>Major Bleeding</b>				
<100 mg/day	5	13,337	1.7	1.4 to 1.9
100–325 mg/day	11	43,489	1.7	1.5 to 1.8
>325 mg/day	2	1409	2.5	1.7 to 3.3
<b>Minor Bleeding</b>				
<100 mg/day	3	11,963	1.8	1.5 to 2.0
100–325 mg/day	5	13,588	6.5	6.1 to 6.9
>325 mg/day <sup>1</sup>	0	0	Not applicable	Not applicable
<b>Hemorrhagic Stroke</b>				
<100 mg/day	4	12,661	0.3	0.2 to 0.4
100–325 mg/day	15	152,955	0.3	0.2 to 0.3
>325 mg/day	3	2224	1.1	0.7 to 1.5
<b>GI Bleeding</b>				
<100 mg/day	5	13,337	1.1	0.9 to 1.3
100–325 mg/day	7	30,413	2.4	2.2 to 2.6
>325 mg/day	3	2224	2.5	1.8 to 3.1
<b>Total Bleeding</b>				
<100 mg/day	4	12,639	3.6	3.3 to 3.9
100–325 mg/day	6	22,745	9.1	8.7 to 9.4
>325 mg/day	1	1540	9.9	8.4 to 11.4

1. No trials reported minor bleeding events for this dose range.

With increased aspirin dose, the weighted average rate for major bleeding episodes increased from 1.7% at the <100 mg/day and 100–325 mg/day dose groups to 2.5% with aspirin doses >325 mg/day. A similar trend was observed for hemorrhagic stroke (0.3% at the <100 and 100–325 mg/day doses and 1.1% at doses >325 mg/day). A more pronounced dose-related increase was observed regarding the rates of GI and minor bleeding. The GI bleeding rates were 1.1, 2.4, and 2.5%, for aspirin doses <100, 100–325, and >325 mg/day, respectively, and the minor bleeding rates were 1.8 and 6.5% at the <100 mg and 100–325 mg/day dose groups, respectively. Of note, no trials reported minor bleeding events for the >325 mg/day dose. In toto, the rate for all bleeding events was 3.6%, 9.1%, and 9.9% for the low, middle, and high-dose aspirin groups, respectively.

In this analysis, low-dose aspirin therapy (defined in this meta-analysis as <100 mg/day), was associated with the lowest risk of total bleeding events of any antiplatelet used in the studies comprising this meta-analysis. These data demonstrate that higher doses of aspirin (≥100 mg/day) were associated with relatively higher hemorrhagic rates. Thus, based on the results of this meta-analysis, the risk of a patient developing bleeding episodes (e.g., GI and total) increases with increasing aspirin dose. Patients taking doses of <100 mg/day aspirin, have significantly lower rates of bleeding episodes than those patients taking doses

of 100–325 mg/day and both groups had lower rates of bleeding episodes than patients taking aspirin doses >325 mg/day.

**6.1.4. Serebruany et al., 2005 (in press)**

The objective of this study was to determine and compare the risk of hemorrhage for the low (<100 mg/day), moderate (100–200 mg/day), and high (>200 mg/day) doses of aspirin. As shown in Table 10, low dose aspirin (<100 mg/day) was associated with the lowest risk of bleeding (major –1.56%, minor – 4.9%, hemorrhagic stroke – 0.24%, GI – 0.97%, fatal/life threatening – 0.27%, total – 3.72%). Moderate daily dose of aspirin (100–200 mg/day) was associated with the low risk for major (1.54%), GI (0.39%), and fatal/life threatening (0.46%) bleeding complications, while the rate of minor (6.75%) and total (11.31%) hemorrhagic events was relatively high. The greatest rate of bleeding complications was associated with the higher aspirin doses (>200 mg/day), however the hemorrhagic stroke were significantly higher (p=0.007) in the 100–200 mg/day cohort.

**Table 10. Weighted Average Bleeding Rates by Aspirin Dose**

Aspirin Dose (mg/day)	Number of Trials Reported <sup>1</sup>	Number of Patients	Bleeding Rate (%)	95% CI
<b>Major Bleeding</b>				
<100 mg	8	17,202	1.56	1.2 to 1.8
100-200 mg	8	32,223	1.54	1.4 to 1.8
>200 mg	10	19,758	2.29	1.9 to 7.0
<b>Minor Bleeding</b>				
<100	5	14,179	4.9	1.4 to 2.1
100-200 mg	4	10,973	6.75	6.1 to 7.0
>200 mg	6	6,359	8.86	4.7 to 11.2
<b>Hemorrhagic Stroke</b>				
<100 mg	7	17,103	0.24	0.1 to 0.4
100-200 mg	5	21,527	0.647	0.2 to 0.5
>200 mg	15	136,122	0.21	0.7 to 1.5
<b>GI Bleeding</b>				
<100 mg	8	17,779	0.97	0.7 to 1.3
100-200 mg	1	3,311	0.39	Not applicable
>200 mg	7	28,378	2.69	1.8 to 3.1
<b>Fatal/Life Threatening</b>				
<100 mg	5	13,276	0.27	0.1 to 0.4
100-200 mg	3	16,222	0.46	0.3 to 0.8
>200 mg	5	7,233	1.59	0.7 to 2.2
<b>Total Bleeding</b>				
<100 mg	7	17,462	3.72	3.1 to 3.7
100-200 mg	2	6,385	11.31	8.9 to 13.2
>200 mg	6	15,472	9.8	7.2 to 10.8

1. Trials Analyzed – 31; Aspirin <100 mg = 9 trials (19,428 patients); Aspirin 100-200 mg = 8 trials (32,223 patients); Aspirin >200 mg = 18 trials (140,385 patients); Total patients analyzed = 192,036.

Despite substantial differences in the reporting patterns of bleeding complications, low dose (<100 mg/day) aspirin was associated with the lowest risk. Aspirin doses of less than or equal to 200 mg/day caused fewer major bleeding events, particularly GI bleeding events, when compared with doses greater than 200 mg (equivalent to 325 mg in the United States). Surprisingly, doses of aspirin between 100–200 mg/day caused a relatively high hemorrhagic event rate, especially with regard to minor, GI, hemorrhagic stroke, and total bleeding. Similar results were reported in previous studies (CURE, 2003; BRAVO, 2003; ATC, 2002) but Serebrauny et al., (2005, in press) extends the bleeding observations to a larger cohort, and refines the optimal dose of aspirin with respect to bleeding.

## **6.2. Supporting Publications**

The bleeding data from the second publication grouping in this aspirin safety summary is presented below. These publications did not compare >1 aspirin-alone treatment group within the specified aspirin dose range (50–325 mg/day).

### **6.2.1. Posada et al., 1999**

This placebo-controlled study examined the protective effects of low-dose aspirin therapy (125 mg) when taken daily or every other day in patients with PAF. The mean follow-up period was 550 days. A total of 15 patients treated with 125 mg/day aspirin withdrew from the study compared to 17 patients who were treated with 125 mg aspirin every other day. Gastrointestinal discomfort or mild bleeding was the cause of withdrawal in seven patients taking 125 mg/day aspirin and 6 patients treated with 125 mg aspirin every other day ( $p=NS$ ). Thus, in this study, aspirin 125 mg given daily or every other day did not result in significant differences in bleeding or other safety endpoints leading to study withdrawal.

It should be noted that although this study examined the effect of two dose regimens (every day vs. every other day), the 125 mg dose was used in both regimens. Furthermore, the primary endpoints were efficacy measures (e.g., TIA, stroke, cardiovascular death). A reporting of the numbers of patients who withdrew from each aspirin regimen due to bleeding events provides minimal information regarding the incidence or risk of bleeding events.

### **6.2.2. Taylor et al., 1999**

The objective of this study was to examine the relationship between low (defined in this study as 81 and 325 mg) and high (defined in this study as 650 and 1300 mg) daily doses of aspirin and perioperative complication rates in 2804 patients undergoing carotid endarterectomy. Aspirin treatment began prior to surgery and continued for three months. Safety endpoints (incidence of hemorrhagic stroke and other bleeding complications) were assessed at 30 days and three months. No patient was lost to follow-up before the 30-day assessment and only two patients were lost to follow-up before the final assessment at three months.

The safety analysis included 1395 patients in the low-dose (81 and 325 mg/day) and 1409 patients in the high-dose (650 and 1300 mg/day) aspirin groups. Hemorrhagic stroke occurred in four, six, nine, and eight patients (range: 0.6%-1.3%) in the 81, 325, 650, and 1300 mg/day aspirin dose groups, respectively. Comparing the 81/325 mg/day aspirin group vs. the 650/1300 mg/day aspirin group, the RR of hemorrhagic stroke was (1.68, 95% CI=0.77 to 3.68; p=0.18). Other bleeding complications were unrelated to aspirin dose.

Because aspirin doses in this study were grouped together (low: 81 and 325 mg/day; high: 650 and 1300 mg/day), no comparisons were made between the 81 and 325 mg/day dose groups (i.e., within the dose range of interest). Even if these dose comparisons had been performed, the number of hemorrhagic stroke events were too small to allow for meaningful comparisons (four vs. six in the 81 and 325 mg/day groups, respectively).

### 6.2.3. Blot and McLaughlin, 2000

Blot and McLaughlin (2000) performed independent analyses of data from a case-control study originally published by Peura et al. (1997). The purpose of the current study was to evaluate the risks of GI bleeding associated with the use of analgesics (e.g., aspirin, ibuprofen, acetaminophen, etc.) at OTC doses.

Table 11 presents the adjusted OR and 95% CI of GI bleeding according to aspirin dose (<325, 325-974, and >974 mg/day). Of note, the OR were adjusted for age, sex, alcohol intake, dyspepsia, use of corticosteroids or anticoagulants, and prior GI bleeding. In addition, aspirin use was further adjusted for use of ibuprofen and prescription NSAIDs. The OR for GI bleeding tended to increase with increasing aspirin dose (OR=2.4, 2.2, and 7.2 for the three dose groups described above, respectively). Of note, the increased bleeding risk with increasing aspirin dose included both upper and lower GI bleeding. Although aspirin doses <325 mg/day were associated with a 2-fold increase in the risk of an upper or lower GI bleeding episode, doses >974 mg/day were associated with a 7-fold increased risk.

**Table 11. Odds Ratio (OR) of GI Bleeding According to Aspirin Dose – Blot and McLaughlin, 2000**

Aspirin <sup>1</sup> Dose	Case	Control	OR <sup>2</sup>	95% CI
<325 mg/day	30	11	2.4	1.1 to 5.0
325-974 mg/day	63	32	2.2	1.3 to 3.6
>974 mg/day	27	6	7.2	2.6 to 19.5

1. Excludes subjects (49 cases and 22 controls) with unknown aspirin dose or frequency.

2. Adjusted for age, sex, alcohol intake, dyspepsia, use of corticosteroids, ibuprofen, prescription NSAIDs or anticoagulants and prior GI bleeding.

Without a comparison of specific aspirin doses within the range of 50–325 mg/day, no specific conclusions regarding dosing recommendations can be made from these study results. This results of this study do, however, suggest that with increased aspirin doses, there is an accompanying increased risk of GI bleeding.

**6.2.4. Kelly et al., 1996**

In this study, the risks of major UGIB associated with different aspirin doses ( $\leq 325$  and  $> 325$  mg/day ) and formulations (plain, enteric-coated, and buffered) were assessed.

As shown in Table 12, comparing across the same aspirin formulation and dose, plain aspirin doses  $> 325$  mg/day were associated with a higher RR (5.8) than plain aspirin doses  $\leq 325$  mg/day (2.6) with regard to UGIB complications. A similar pattern was observed for buffered aspirin formulations (RR of 7.0 for doses  $> 325$  mg/day vs. 3.1 for  $\leq 325$  mg/day).

**Table 12. Multivariant Relative Risk (RR) of Upper Gastrointestinal Bleeding Associated with Aspirin Products in One Week Before Index Day – Kelly et al., 1996**

Aspirin Formulation and Dose	Cases (N = 550)	Controls (N = 1202)	Multivariant Relative Risk	95% CI
Plain aspirin $\leq 325$ mg/day	45	71	2.6	1.7 to 4.0
Plain aspirin $> 325$ mg/day	81	54	5.8	3.9 to 8.6
Buffered aspirin $\leq 325$ mg/day	10	12	3.1	1.3 to 7.6
Buffered aspirin $> 325$ mg/day	18	9	7.0	3.0 to 16

As shown in Table 13, similar results were observed when the RR was evaluated according to bleeding site. Comparing across the same aspirin formulation and dose group, plain aspirin doses  $> 325$  mg/day resulted in a higher RR compared to plain aspirin at doses  $\leq 325$  mg/day (5.7 vs. 2.6, respectively), with regard to gastric bleeding. Similarly, buffered aspirin  $> 325$  mg/day was associated with a higher RR compared to buffered aspirin  $\leq 325$  mg/day (RR of 7.8 and 3.6, respectively). The RR of duodenal bleeding with plain aspirin  $> 325$  mg/day was higher than the RR of duodenal bleeding with plain aspirin  $\leq 325$  mg/day (RR of 5.1 and 2.4, respectively). Buffered aspirin  $> 325$  mg/day also resulted in a higher RR of duodenal bleeding vs. buffered aspirin  $\leq 325$  mg/day (RR of 7.0 vs. 2.6, respectively).

**Table 13. Multivariate Relative Risk (RR) of Upper Gastrointestinal Bleeding, by Bleeding Site Associated with Aspirin Products in One Week Before Index Day – Kelly et al., 1996**

Aspirin Formulation and Dose	Cases (N = 332)	Controls (N = 1202)	Multivariate Relative Risk	95% CI
<b>Gastric Bleeding</b>				
Plain aspirin ≤325 mg/day	26	71	2.6	1.5 to 4.3
Plain aspirin >325 mg/day	51	54	5.7	3.6 to 8.9
Buffered aspirin ≤325 mg/day	7	12	3.6	1.3 to 9.8
Buffered aspirin >325 mg/day	12	9	7.8	3.0 to 20
<b>Duodenal Bleeding</b>				
Plain aspirin ≤325 mg/day	14	71	2.4	1.2 to 4.6
Plain aspirin >325 mg/day	25	54	5.1	2.9 to 8.9
Buffered aspirin ≤325 mg/day	3	12	2.6	0.7 to 9.9
Buffered aspirin >325 mg/day	6	9	7.0	2.2 to 22

Because this study grouped patients according to aspirin doses of <325 or >325 mg/day, comparisons could not be made between patients taking different aspirin doses within the range 50–325 mg/day. The results of this study do support the conclusion that higher (>325 mg/day) aspirin doses are associated with a greater risk of UGIB than lower doses of aspirin (<325 mg/day), regardless of the aspirin formulation or site of GI bleeding.

**6.2.5. Serrano et al., 2002**

The purpose of this study was to assess the risk of GI bleeding in patients with cardiovascular disease and who were discharged on various aspirin doses (75–300 mg/day). Over the average 45 months of follow-up, a total of 41 of 903 patients (4.5%) presented with upper GI bleeding requiring hospitalization. The incidence of upper GI bleeding (1.2 upper GI bleeds per 100-patient years) was uniformly distributed during the follow-up period, indicating that the risk of complications associated with low-dose aspirin use does not decrease with time. The most important factor (in addition to prior peptic ulcer or upper GI bleeding) that increased the risk of GI bleeding in this study was aspirin dose (per 100 mg/day increase, RR=1.8; 95% CI=1.5 to 2.9; p=0.016).

This study did not perform a dose comparison of the risk of GI bleeding with aspirin doses between 50–325 mg/day. However, these study results underscore the conclusion that the higher the aspirin dose, the higher the risk of upper GI bleeding. Based on the results of this study, the authors concluded that the lowest effective aspirin dose for treatment of cardiovascular and/or cerebrovascular conditions be utilized.

#### **6.2.6. Derry and Loke, 2000**

This meta-analysis of 24 randomized, placebo-controlled trials was conducted to determine the incidence of GI hemorrhage associated with long-term aspirin therapy in stroke patients and in patients taking aspirin for primary prevention of cardiovascular disease. Aspirin doses ranged from 50–1500 mg/day and were taken for a minimum of one year. Combining all 24 trials, GI hemorrhage occurred in 2.47% of patients taking aspirin vs. 1.42% of patients taking placebo. When eight trials of patients using aspirin doses of 50–162.5 mg/day were analyzed separately, aspirin was associated with a significant increase in GI hemorrhage rate (2.30% and 1.45% for aspirin and placebo, respectively, [RR=1.59, p<0.0001]). A meta-regression analysis of the 24 trials indicated a trend toward a relative reduction in the incidence of GI hemorrhage of 1.5% per 100 mg reduction of dose, but this trend was not significant (p=NS).

The results of this meta-analysis support the well-established conclusion that aspirin doses even as low as 50 mg increased the risk of GI hemorrhage vs. placebo. However, comparisons between different aspirin doses within the range of 50–325 mg/day were not performed.

#### **6.2.7. Hart et al., 2000**

The objective of this study was to assess the effect of aspirin in those with and without clinically apparent vascular disease. In the five randomized trials used in the analysis (ETDRS, MRC-TPT, HOT, USPHS, and BDT), long-term use of aspirin therapy (doses ranging from 75–650 mg/day), increased the incidence of hemorrhagic stroke (RR=1.35, p=0.03) vs. placebo. Thus, even low aspirin doses are associated with a greater risk of hemorrhagic stroke vs. placebo.

These data support the accepted conclusion that aspirin administration increases the risk of hemorrhagic stroke relative to placebo; however, there were no comparisons of different aspirin doses in the recommended dose range of 50–325 mg/day.

#### **6.2.8. Garcia Rodriguez et al., 2001**

The purpose of this meta-analysis of 17 epidemiological studies was to assess the relationship between aspirin (including dose and formulation) and UGIC. Five of the studies included that assessed the effect of different daily aspirin doses all found greater risks of UGIC for aspirin doses >300 mg/day compared to lower doses. However, the risk was still elevated (approximately two-fold) for doses up to 300 mg/day. Aspirin formulation (plain, buffered, or enteric-coated) did not affect the risk of UGIC.

Because this publication compared aspirin doses <300 mg vs. >300 mg/day, specific dose comparisons within the range of 50–325 mg/day could not be performed. This publication adds to the body of evidence showing that the risk of UGIC increases with higher aspirin doses.

### 6.3. Publications Providing Additional Safety Information

A summary of bleeding data from the publications included in this grouping is presented in Appendix 2. As discussed in Section 3.2.3 of this aspirin safety summary, meaningful comparisons of safety across the different studies in this grouping are difficult, primarily due to differences in the methods of deriving and presenting safety data across studies (e.g., incidence rates, annualized event rates, odds ratios, etc.), differences in study-specific endpoints, differences in study populations, and differences in treatment durations. Even across studies using the same aspirin dose (e.g., 160 mg/day), the study characteristics were too discrepant to allow for meaningful comparisons.

For example, both Hurlen et al. (2002) and the Coumadin Aspirin Reinfarction Study (CARS) Investigators (1997) studied the effect of 160 mg/day aspirin on bleeding complications in patients taking aspirin for secondary prevention of MI. However, while the aspirin dose and study populations were comparable across these two studies, the studies differed in other respects. In the study by Hurlen et al. (2002), the bleeding endpoints were major and minor bleeding episodes and in the CARS (1997) study, bleeding endpoints measured included spontaneous major hemorrhage. Furthermore, these two studies differed in the way these bleeding endpoints were reported. Hurlen et al. (2002) measured the frequency of major and minor bleeding while the CARS (1997) study presented the one-year life-table estimates for spontaneous hemorrhage. In addition, the treatment durations were dissimilar between these two studies. In the Hurlen et al. (2002) study, aspirin was administered for up to six years (mean: 1445 days); in the CARS (1997) study, the mean follow-up period was 452 days. Thus, while these two studies assessed the effect of the same aspirin dose in similar patient populations, differences in the bleeding endpoints measured, analysis of bleeding endpoints, and treatment durations preclude comparisons among these two studies.

Other examples of disparities between the publications in this grouping that make it difficult to make comparisons across the studies include the publications by Chan et al. (2003) and the Stroke Prevention in Atrial Fibrillation (SPAF, 1996) Investigators. Both of these studies examined the effect of 325 mg/day aspirin on major bleeding events. However, the two studies differed in the criteria used to define a major bleeding event. Chan et al. (2003) defined major bleeding as intracranial bleeding, overt bleeding resulting in a decrease in hemoglobin  $\geq 20$  g/L or requiring blood transfusion, and bleeding into a confined space which caused severe morbidity (e.g., hematoma). In contrast, the SPAF Investigators defined major bleeding as involving the central nervous system (CNS), requiring hospitalization, blood transfusion and/or surgical intervention, or resulted in permanent dysfunction to any degree. Furthermore, major bleeding episodes were verified independently by two adjudicators and reanalyzed using a pre-defined severity scale.

As these examples demonstrate, even studies examining the effect of the same aspirin dose in this grouping are too disparate regarding other study details, thus preventing meaningful conclusions about the bleeding results across the publications.

In addition, the inclusion of this publication grouping in this submission serves to ensure that all aspirin-related safety data in cardiovascular and/or cerebrovascular indications published since 1996 are presented; however, it is important to note that these studies were conducted in a wide variety of indications, many of which are not directly relevant for this submission.

## **7. OVERALL SUMMARY AND CONCLUSIONS**

The proposed labeling changes in the recommended aspirin dose from 75–325 mg/day to 75–150 mg/day for secondary cardiovascular prevention, and from 50–325 mg/day to 50–150 mg/day for secondary cerebrovascular prevention is supported by published safety data (particularly bleeding data). These data demonstrate that low-dose aspirin results in fewer bleeding complications than higher aspirin doses (>150 mg/day) and published efficacy data demonstrate that doses of aspirin within the range of 50–150 mg/day are equally effective for the prevention of serious vascular events. Clinical studies as well as meta-analyses, substantiate the modifications to the professional labeling for aspirin. These benefit/risk data were identified following an extensive search and review of the literature published between 1996–2004.

Large clinical trials and meta-analyses have consistently shown that the risk and/or incidence of bleeding complications increase with increasing aspirin dose within the dose range of 50–325 mg/day. While lower doses of aspirin are associated with a lower risk of all bleeding complications, it is the opportunity to reduce the number of severe hemorrhages that provides the most forceful argument for limiting aspirin exposure. Rare but potentially devastating bleeding events, such as severe GI bleeding requiring transfusion or surgery, have profound implications for the affected patient and his or her community. Evidence reviewed in this Citizen's Petition shows that the risk of GI bleeding increases monotonically with increasing aspirin dose. By restricting the daily dose of aspirin to 75–150 mg/day for cardiovascular prevention and 50–150 mg/day for cerebrovascular prevention, patients can minimize their risk for severe bleeding, particularly GI bleeding. Four publications in particular (Peters et al., 2003; Topol et al., 2003; Serebrauny et al., 2004; Serebrauny et al., 2005[in press]) collectively show that aspirin doses less than or equal to 150 mg/day result in fewer bleeding complications or lower the risk of bleeding complications compared to aspirin doses greater than 150 mg/day.

**Overall safety conclusions:**

- Although adverse events have been reported at low aspirin doses, within the dose range of 50–325 mg/day, more bleeding events occur at higher doses (i.e., >150 mg daily) than at lower doses (i.e., 75–150 mg daily).
- The recommended aspirin dose for chronic administration is 75–150 mg daily, which is safe and effective for prevention of recurrent MI, and for treatment of unstable angina pectoris or chronic stable angina pectoris, and 50–150 mg daily for treatment of ischemic stroke and TIA. Aspirin is recommended for patients who undergo revascularization procedures, such as coronary artery bypass grafting (CABG), angioplasty, or carotid endarterectomy, if there is a pre-existing condition for which aspirin is already indicated. Therapy should be continued indefinitely.

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APPENDIX 1. TABLE OF STUDIES – PUBLICATIONS PROVIDING ADDITIONAL SAFETY INFORMATION					
Reference	Total Subjects	Patient Population	Treatment Groups (N)	Treatment Duration	Type of Article
<b>Low-Dose Aspirin (≤200 mg/day)</b>					
<p>SPIRIT Study Group. 1997. A randomized trial of anticoagulants versus aspirin after cerebral ischemia of presumed arterial origin. <i>Annals of Neurology</i> 42(6):857-865.</p>	N=1316	Patients with a TIA or minor ischemic stroke within the preceding 6 months.	<p>Aspirin group (Aspirin 30 mg/day [95% of patients], 75 mg/day [3% of patients], or 100 mg/day [2% of patients]) (N=665)</p> <p>Anticoagulant group (target INR value of 3.0 to 4.5 achieved with phenprocoumon, acenocoumarol, or warfarin; phenprocoumon was the preferred anticoagulant.) (N=651)</p>	Mean follow-up=14 months	Clinical Trial
<p>Diener HC, Cunha L, Forbes C, Sivenius J, Smets P, Lowenthal A. 1996. European Stroke Prevention Study 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. <i>Journal of the Neurological Sciences</i> 143(1-2):1-13.</p> <p>Forbes CD. 1997. European Stroke Prevention Study 2: dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. <i>International Journal of Clinical Practice</i> 51(4):205-208.</p>	N=6602	Patients with a TIA or ischemic stroke within the preceding 3 months.	<p>Aspirin 50 mg/day (N=1649)</p> <p>Dipyridamole 400 mg/day (N=1654)</p> <p>Aspirin 50 mg/day+Dipyridamole 400 mg/day (N=1650)</p> <p>Placebo (N=1649)</p>	Subjects were followed for 2 years	Clinical Trial

APPENDIX 1. TABLE OF STUDIES – PUBLICATIONS PROVIDING ADDITIONAL SAFETY INFORMATION					
Reference	Total Subjects	Patient Population	Treatment Groups (N)	Treatment Duration	Type of Article
FRISC Study Group (Fragmin During Instability in Coronary Artery Disease). 1996. Low-molecular-weight heparin during instability in coronary artery disease. Lancet 347(9001):561-568.	N=1506	Subjects with unstable CAD (unstable angina or non-Q-wave MI) (Fragmin During Instability in Coronary Artery Disease Study [FRISC]).	Placebo (Aspirin 75 mg/day [following 300 mg loading dose]) (N=760)	Subjects stayed in the hospital during the acute phase for at least 5 days. On Days 5-8, subjects were discharged on the lower dose of dalteparin for the home treatment phase. On Days 40-50, subjects attended the outpatient department and treatment was stopped. The final follow-up visit was 5-7 months after trial inclusion.	Clinical Trial
Hebert PR, Hennekens CH. 2000. An overview of the 4 randomized trials of aspirin therapy in the primary prevention of vascular disease. Archives of Internal Medicine 160(20):3123-3127.	N=55085	Aspirin 325 mg qod/500 mg/day vs placebo (healthy male physicians; PHS, BDT). Aspirin 75 mg/day-CR vs placebo (high risk men - top 20% of risk score distribution; TPT). Aspirin 75 mg/day vs placebo (men/women with hypertension and diastolic BP 100-115 mmHg; HOT).	Aspirin 75-500 mg/day (N not specified) Placebo (N not specified)	Mean duration of treatment and follow-up of 4 to 6 years	Meta-Analysis
Meade TW, Brennan PJ, Wilkes HC, Zuhrie SR. 1998. Thrombosis prevention trial: randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. Lancet 351(9098):233-241.	N=5085	Men identified as being in the top 20% on the IHD risk score derived from the Northwick Park Heart Study. Criteria based on smoking history, family history, BMI, BP, cholesterol and fibrinogen levels, and plasma factor VII coagulant activity.	Aspirin 75 mg/day (N= 1268) Warfarin (mean stable INR of 1.47) (N=1268) Aspirin 75 mg/day+Warfarin (mean stable INR of 1.47) (N=1277) Placebo (N=1272)	Median of 6.8 years	Clinical Trial

<b>APPENDIX 1. TABLE OF STUDIES – PUBLICATIONS PROVIDING ADDITIONAL SAFETY INFORMATION</b>					
<b>Reference</b>	<b>Total Subjects</b>	<b>Patient Population</b>	<b>Treatment Groups (N)</b>	<b>Treatment Duration</b>	<b>Type of Article</b>
Sanmuganathan PS, Ghahramani P, Jackson PR, Wallis EJ, Ramsay LE. 2001. Aspirin for primary prevention of coronary heart disease: Safety and absolute benefit related to coronary risk derived from meta-analysis of randomised trials. <i>Heart (British Cardiac Society)</i> 85(3):265-271.	N=48540	This meta-analysis included patients enrolled across 4 randomized primary prevention clinical trials. Three of the four trials did not include women. In the one trial that did enroll women (HOT Trial), all study participants (100%) also had well controlled hypertension.	Aspirin (75 mg/day, 162.5 mg/day and 500 mg/day) (N=25133)	Treatment duration across the 4 trials ranged from 4 to 6 years	Meta-Analysis
Taylor FC, Cohen H, Ebrahim S. 2001. Systematic review of long term anticoagulation or antiplatelet treatment in patients with non-rheumatic atrial fibrillation. <i>BMJ</i> 322(7282):321-326.	N= 3298	Meta-analysis of 5 randomized trials (AFASAK 1, AFASAK 2, SPAF II, SIFA, PATAF) in patients with non-rheumatic atrial fibrillation.	AFASAK 1 (Aspirin 75 mg/day vs. warfarin) (N=671) AFASAK 2 (Aspirin 300 mg/day vs. warfarin) (N=339) SPAF II (Aspirin 325 mg/day vs. warfarin) (N=1100) SIFA (Indoprofen 400 mg/day vs. warfarin) (N=916) PATAF (Aspirin 150 mg/day vs. warfarin) (N=272)	Follow-up periods across the 5 meta-analyses ranged from 12 to 42 months	Meta-Analysis
Derksen RHWM, de Groot PG, Kappelle LJ. 2003. Low dose aspirin after ischemic stroke associated with antiphospholipid syndrome. <i>Neurology</i> 61(1):111-114.	N=8	Patients with noncardioembolic ischemic stroke and medium to high levels of anticardiolipin antibodies (aCL) or lupus anticoagulant (LAC) (ischemic stroke was the first manifestation of antiphospholipid syndrome [APS]).	Low-dose aspirin, dose not specified during the treatment period. During the follow-up period, aspirin doses ranged from 38 to 80 mg/day. (N=8)	Median follow-up period of 8.9 years	Clinical Trial

APPENDIX 1. TABLE OF STUDIES – PUBLICATIONS PROVIDING ADDITIONAL SAFETY INFORMATION					
Reference	Total Subjects	Patient Population	Treatment Groups (N)	Treatment Duration	Type of Article
Brouwer MA, van den Bergh PJPC, Aengevaeren WRM, Veen G, Luijten HE, Hertzberger DP, van Boven AJ, Vromans RPJW, Uijen GJH, Verheugt FWA. 2002. Aspirin plus coumarin versus aspirin alone in the prevention of reocclusion after fibrinolysis for acute myocardial infarction: results of the Antithrombotics in the Prevention of Reocclusion In Coronary Thrombolysis (APRICOT)-2 Trial. <i>Circulation</i> 106(6):659-665.	N=274	Patients receiving aspirin and heparin who had a patent infarct-related artery (TIMI grade 3 flow) <48 hours after fibrinolysis for acute MI.	Aspirin 80 mg/day + heparin (discontinued after 48 hours) (N=139)	Treatment duration of 3 months	Clinical Trial
Chan FKL, Chung SCS, Suen BY, Lee YT, Leung WK, Leung VKS, Wu JC, Lau JYW, Hui Y, Lai MS, Chan HLY, Sung JYJ. 2001. Preventing recurrent upper gastrointestinal bleeding in patients with <i>Helicobacter pylori</i> infection who are taking low-dose aspirin or naproxen. <i>New England Journal of Medicine</i> 344(13):967-973.	N=896	Patients taking either low-dose aspirin (for cardio/cerebrovascular indications) or NSAIDs (for arthritis) admitted to the hospital with upper GI bleeding. Patients with <i>H. pylori</i> infection were included in the study.	After eradication of <i>H. pylori</i> infection, patients with coronary heart disease/ stroke were given 80 mg/day aspirin for six months. (N=482) Patients with arthritis were given 500 mg naproxen BID for six months (N=414) Patients were then randomly assigned to receive either 20 mg omeprazole daily for six months or one week of eradication therapy	Treatment duration was 6 months	Clinical Trial
Huynh T, Theroux P, Bogaty P, Nasmith J, Solymoss S. 2001. Aspirin, warfarin, or the combination for secondary prevention of coronary events in patients with acute coronary syndromes and prior coronary artery bypass surgery. <i>Circulation</i> 103(25):3069-3074.	N=135	Enrolled subjects had unstable angina or non-ST-segment elevation MI with prior CABG and were poor candidates for a revascularization procedure.	Aspirin 80 mg/day (N=46) Warfarin to INR of 2.0 to 2.5 (N=45) Aspirin (80 mg/day)+Warfarin (INR of 2.0 to 2.5) (N=44)	Following the 12-month treatment period with one of the 3 aforementioned paradigms, open-label aspirin (325 mg/day) was prescribed for all subjects. There was a 1-month follow-up after administration of the open-label aspirin.	Clinical Trial

APPENDIX 1. TABLE OF STUDIES – PUBLICATIONS PROVIDING ADDITIONAL SAFETY INFORMATION					
Reference	Total Subjects	Patient Population	Treatment Groups (N)	Treatment Duration	Type of Article
van Es RF, Jonker JJC, Verheugt FWA, Deckers JW, Grobbee DE. 2002. Aspirin and coumadin after acute coronary syndromes (the ASPECT-2 study): a randomised controlled trial. <i>Lancet</i> 360(9327):109-113.	N=993	Men and non-pregnant women who were admitted with acute MI or unstable angina within the preceding 8 weeks at 53 hospitals in the Netherlands.	Aspirin (100 mg/day of pulverized carbasalate calcium; equivalent to 80 mg/day aspirin) (N=336)	Median follow-up was 12 months	Clinical Trial
Yasue H, Ogawa H, Tanaka H, Miyazaki S, Hattori R, Saito M, Ishikawa K, Masuda Y, Yamaguchi T, Motomiya T, Tamura Y. 1999. Effects of aspirin and trapidil on cardiovascular events after acute myocardial infarction. Japanese Antiplatelets Myocardial Infarction Study (JAMIS) Investigators. <i>American Journal of Cardiology</i> 83(9):1308-1313.	N=723	Patients with acute myocardial infarction (AMI) admitted within 1 month of the onset of symptoms.	Aspirin 81 mg/day (N=250) Trapidil 300 mg/day (N=243) No antiplatelet therapy (N=230)	Mean follow-up period was 475 days	Clinical Trial
Collaborative Group of the Primary Prevention Project (PPP). 2001. Low-dose aspirin and vitamin E in people at cardiovascular risk: A randomised trial in general practice. <i>Lancet</i> 357(9250):89-95.	N=4495	Primary prevention of cardiovascular events (nonfatal MI, nonfatal stroke, and cardiovascular death) in subjects with at least one known cardiovascular risk factor.	Aspirin 100 mg/day (N=2226) No aspirin (N=2269) Within each group, subjects were also randomized to Vitamin E (300 mg/day) or no Vitamin E	Mean follow-up was 3.6 years for a total of 16,390 person years	Clinical Trial
Hop JW, Rinkel GJE, Algra A, Berkelbach van der Sprenkel JW, van Gijn J. 2000. Randomized pilot trial of postoperative aspirin in subarachnoid hemorrhage. <i>Neurology</i> 54(4):872-878.	N=50	Subjects with aneurysmal subarachnoid hemorrhage (SAH) who had undergone surgery within 4 days after the SAH.	Aspirin 100 mg (suppositories) (N=24) Placebo (N=26)	Treatment duration was 21 days	Clinical Trial

APPENDIX 1. TABLE OF STUDIES – PUBLICATIONS PROVIDING ADDITIONAL SAFETY INFORMATION					
Reference	Total Subjects	Patient Population	Treatment Groups (N)	Treatment Duration	Type of Article
Lee TK, Chan KWA, Huang ZS, Ng SK, Lin RT, Po HL, Yuan RY, Lai ML, Chang TW, Yan SH, Deng JC, Liu LH, Lee KY, Lie SK, Sung SM, Hu HH. 1997. Effectiveness of low-dose ASA in prevention of secondary ischemic stroke, the ASA Study Group in Taiwan. <i>Thrombosis Research</i> 87(2):215-224.	N=466	Patients who had a first non-cardiogenic stable ischemic stroke (including lacunar infarction) or reversible ischemic neurological deficit (RIND) and hospitalized in 1 of 13 participating hospitals in Taiwan from October 1992 to April 1995.	Aspirin 100 mg/day (initiated within 3 to 6 weeks after the onset of stroke) (N=222)	The mean follow-up period for the aspirin treatment group was 612 days, and for the nicametate citrate treatment group the mean follow-up period was 625 days	Clinical Trial
Moshfegh K, Redondo M, Julmy F, Willemin WA, Gebauer MU, Haerberli A, Meyer BJ. 2000. Antiplatelet effects of clopidogrel compared with aspirin after myocardial infarction: enhanced inhibitory effects of combination therapy. <i>Journal of the American College of Cardiology</i> 36(3):699-705.	N=30	Patients with stable coronary artery disease and a history of MI older than three months on chronic aspirin treatment.	All patients (N=30) received the following five consecutive treatment periods: Phase 1 (Aspirin 100 mg/day for 7 days) Phase 2 (Clopidogrel 75 mg/day+aspirin 100 mg/day for 7 days) Phase 3 (After a washout period for clopidogrel and aspirin treatment, clopidogrel treatment at 75 mg/day for 7 days) Phase 4 (After a washout period for clopidogrel, aspirin treatment at 300 mg/day for 14 days) Phase 5 (Aspirin 300 mg/day+clopidogrel 75 mg for 7 days) Washout periods for either drug consisted of 7 days between Phases 2 and 3 and 14 days between Phases 3 and 4	Overall treatment duration was 7-14 days	Clinical Trial

**APPENDIX 1. TABLE OF STUDIES – PUBLICATIONS PROVIDING ADDITIONAL SAFETY INFORMATION**

<b>Reference</b>	<b>Total Subjects</b>	<b>Patient Population</b>	<b>Treatment Groups (N)</b>	<b>Treatment Duration</b>	<b>Type of Article</b>
Julian DG, Chamberlain DA, Pocock SJ, Bernard R, Chamberlain D, Bothwick L, Irving J, Murdoch W, Pohl J, Wood D, Penny J, Millar-Craig M, Robson D, Vallance B, Hine K, Powell-Jackson J, Varma M, Joseph S, Greenwood T, et al. 1996. A comparison of aspirin and anticoagulation following thrombolysis for myocardial infarction (the AFTER study): A multicentre unblinded randomised clinical trial. British Medical Journal 313(7070):1429-1431.	N=1036	Patients with MI who received anistreplase thrombolysis.	Aspirin 150 mg/day (N=519)	Aspirin (Given immediately after anistreplase and then daily for 3 months)	Clinical Trial
Berge E, Abdelnoor M, Nakstad PH, Sandset PM. 2000. Low molecular-weight heparin versus aspirin in patients with acute ischaemic stroke and atrial fibrillation: a double-blind randomised study. HAEST Study Group. Heparin in Acute Embolic Stroke Trial. Lancet 355(9211):1205-1210.	N=449	Subjects with acute ischemic stroke and atrial fibrillation.	Aspirin 160 mg/day (N=225) Dalteparin 100 IU/kg BID SC (N=224)	Treatment was to begin as soon as possible following acute ischemic stroke and to continue for 14 days (range: 11-17 days) or until earlier discharge	Clinical Trial
Coumadin Aspirin Reinfarction Study (CARS) Investigators. 1997. Randomised double-blind trial of fixed low-dose warfarin with aspirin after myocardial infarction. Lancet 350(9075):389-396.	N=8803	Subjects who had had a myocardial infarction 3-21 days prior to enrollment.	Aspirin 160 mg/day (N=3393) Aspirin 80 mg/day+Warfarin (1 or 3 mg) (N=5410)	The median follow-up period was 14 months	Clinical Trial

APPENDIX 1. TABLE OF STUDIES – PUBLICATIONS PROVIDING ADDITIONAL SAFETY INFORMATION					
Reference	Total Subjects	Patient Population	Treatment Groups (N)	Treatment Duration	Type of Article
CAST (Chinese Acute Stroke Trial) Collaborative Group. 1997. CAST: Randomised placebo-controlled trial of early aspirin use in 20,000 patients with acute ischaemic stroke. Lancet 349(9066):1641-1649.	N=21106	The Chinese Acute Stroke Trial (CAST) was conducted in patients with suspected acute ischemic stroke in whom hospital treatment with aspirin or placebo was initiated within 48 hours of onset and continued in hospital for up to 4 weeks.	Aspirin 160 mg/day (N=10554)	Treatment duration was 4 weeks	Clinical Trial
Hurlen M, Abdelnoor M, Smith P, Erikssen J, Arnesen H. 2002. Warfarin, aspirin, or both after myocardial infarction. New England Journal of Medicine 347(13):969-974.	N=3630	Patients after acute myocardial infarction.	Aspirin 160 mg/day (N=1206) Warfarin to INR 2.8-4.2 (N=1216) Aspirin 75 mg/day+Warfarin to INR 2.0-2.5 (N=1208)	Treatment duration was up to 6 years, with a mean duration of 1445 days	Clinical Trial
Ivert T, Intonti M, Stain-Malmgren R, Dumitrescu A, Blomback M. 1998. Effects of aprotinin during cardiopulmonary bypass in patients treated with acetylsalicylic acid. Scandinavian Cardiovascular Journal 32(5):289-295	N=35	Subjects undergoing primary isolated coronary artery bypass surgery.	Aspirin 160 mg/day (N=10) High-dose aprotinin+Aspirin 160 mg/day (N=10) Low-dose aprotinin+Aspirin 160 mg/day (N=15)	Treatment duration was not specified in the publication	Clinical Trial
Second SYMPHONY Investigators. 2001. Randomized trial of aspirin, sibrifiban, or both for secondary prevention after acute coronary syndromes. Circulation 103(13):1727-1733.	N=6637	Patients within 7 days of an acute coronary syndrome who were stable for at least 12 hours without signs of active ischemia, hemodynamic instability, or Killip class greater than 2.	Aspirin 160 mg/day (N=2231) Aspirin 160 mg/day)+Low-dose sibrifiban (3.0, 4.5, or 6.0 mg/day based on weight and serum creatinine) (N=2232) High-dose sibrifiban (3.0, 4.5, or 6.0 mg/day based on weight and serum creatinine) (N=2174)	The mean follow-up period was approximately 95 days	Clinical Trial

APPENDIX 1. TABLE OF STUDIES – PUBLICATIONS PROVIDING ADDITIONAL SAFETY INFORMATION					
Reference	Total Subjects	Patient Population	Treatment Groups (N)	Treatment Duration	Type of Article
SYMPHONY Investigators. 2000. Comparison of sibrافiban with aspirin for prevention of cardiovascular events after acute coronary syndromes: a randomised trial. Lancet 355(9201): 337-345.	N=9233	Patients within 7 days of an acute coronary syndrome who were stable for at least 12 hours without signs of active ischemia, hemodynamic instability, or Killip class greater than 2.	Aspirin 160 mg/day (N=3089) Low-dose sibrافiban (Sibrافiban doses [3.0, 4.5, or 6.0 mg/day] were based on a model accounting for weight and serum creatinine and designed to achieve at least 25% steady-state inhibition of platelet aggregation) (N=3105)	Treatment duration was 90 days	Clinical Trial
Cook NR, Hebert PR, Manson JE, Buring JE, Hennekens CH. 2000. Self-selected post-trial aspirin use and subsequent cardiovascular disease and mortality in the Physicians' Health Study. Archives of Internal Medicine 160(7):921-928.	N=18496	Apparently healthy male physicians (no previously-reported cardiovascular disease) in a 2 X 2 factorial trial of aspirin and beta carotene.	0-13 days post-trial aspirin use/year (N=3849) 14-120 days post-trial aspirin use/year (N=1501) 121-179 days post-trial aspirin use/year (N=2136) ≥180 days post-trial aspirin use/year (N=11010)	Treatment duration up to 12 years	Clinical Trial
Fiore LD, Ezekowitz MD, Brophy MT, Lu D, Sacco J, Peduzzi P. 2002. Department of Veterans Affairs Cooperative Studies Program Clinical Trial comparing combined warfarin and aspirin with aspirin alone in survivors of acute myocardial infarction: primary results of the CHAMP study. Circulation 105(5):557-563.	N=5059	The "CHAMP" study was conducted at 78 Department of Veterans Affairs Medical Centers and involved long-term follow-up of patients who had a myocardial infarction within 14 days of original admission and who were not being treated with high-dose aspirin or NSAIDs.	Aspirin 162 mg/day (N=2537) Aspirin 81 mg/day+warfarin to INR 1.5-2.5 (N=2522)	Median patient follow-up period was 2.7 years. The study lasted a total of 6 years (1992-1997). Person-years of follow-up was 6940 years in the aspirin group and 6789 years in the aspirin+warfarin group.	Clinical Trial

APPENDIX 1. TABLE OF STUDIES – PUBLICATIONS PROVIDING ADDITIONAL SAFETY INFORMATION					
Reference	Total Subjects	Patient Population	Treatment Groups (N)	Treatment Duration	Type of Article
<b>High-Dose Aspirin (&gt;200 mg/day)</b>					
Hart RG, Benavente O, McBride R, Pearce LA. 1999a. Anti-thrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. <i>Annals of Internal Medicine</i> 131(7):492-501.	N=8856	A meta-analysis of six randomized trials testing long-term (>3 months) use of antithrombotic agents in patients with atrial fibrillation.	Aspirin (25-1300 mg/day) versus placebo (N=3119) Warfarin (mean INR 2.0-2.6) versus placebo (N=2900) Warfarin (mean INR 2.2-3.1) versus aspirin (75-325 mg/day) (N=2837)	Treatment duration was >3 months across the trials included in this meta-analysis	Meta-Analysis
Weisman SM, Graham DY. 2002. Evaluation of the benefits and risks of low-dose aspirin in the secondary prevention of cardiovascular and cerebrovascular events. <i>Archives of Internal Medicine</i> 162(19):2197-2202.	N=6300	A meta-analysis of 6 secondary prevention studies that were randomized, placebo-controlled interventions with an aspirin-only arm, with low-dose aspirin defined as daily doses of 50 to 325 mg.	Aspirin doses investigated in these 6 studies included 50, 75, 300 and 324 mg/day (N=3127) Placebo (N=3173)	Treatment duration varied across the 6 studies and was not specifically reported in this meta-analysis	Meta-Analysis
Evans A, Perez I, Yu G, Kalra L. 2001. Should stroke subtype influence anticoagulation decisions to prevent recurrence in stroke patients with atrial fibrillation? <i>Stroke</i> 32(12):2828-2832.	N=386	Ischemic stroke patients admitted to a district general hospital in the United Kingdom. Inclusion criteria were clinical ischemic stroke confirmed by CT scanning and atrial fibrillation confirmed on ECG.	Aspirin 75 to 300 mg/day (N=172) Warfarin to a target INR of 2.0 to 3.0 (N=214)	Patients were treated and followed for up to 2 years	Clinical Trial
Srinivasan AK, Grayson AD, Pullan DM, Fabri BM, Dihmis WC. 2003. Effect of preoperative aspirin use in off-pump coronary artery bypass operations. <i>Annals of Thoracic Surgery</i> 76(1):41-45.	N=340	Patients who underwent off-pump coronary artery bypass operation (OPCAB) for the first time between January 1998 and September 2001.	Patients who continued taking aspirin therapy within 7 days before OPCAB (aspirin users) (N=170) Propensity-matched patients who had OPCAB but whose aspirin therapy was stopped a week before operation (nonaspirin users) (N=170)	Treatment duration was not specified in the article	Clinical Trial

<b>APPENDIX 1. TABLE OF STUDIES – PUBLICATIONS PROVIDING ADDITIONAL SAFETY INFORMATION</b>					
<b>Reference</b>	<b>Total Subjects</b>	<b>Patient Population</b>	<b>Treatment Groups (N)</b>	<b>Treatment Duration</b>	<b>Type of Article</b>
Schmulling S, Rudolf J, Strotmann-Tack T, Grond M, Schneewis S, Sobesky J, Thiel A, Heiss W-D. 2003. Acetylsalicylic acid pretreatment, concomitant heparin therapy and the risk of early intracranial hemorrhage following systemic thrombolysis for acute ischemic stroke. Cerebrovascular Diseases 16(3):183-190.	N=300	Stroke patients (300 consecutive patients) who underwent systemic thrombolysis with recombinant tissue-type plasminogen activator (rt-PA).	Prior to stroke:	Follow-up period was 3 months	Clinical Trial
Mangano DT. 2002. Aspirin and mortality from coronary bypass surgery. New England Journal of Medicine 347(17):1309-1317.	N=5022	A prospective and longitudinal study of 5065 patients undergoing coronary bypass surgery, of whom 5022 survived the first 48 hours following surgery.	Aspirin up to 650 mg/day (N=2999) No aspirin (N=2023)	Duration of aspirin treatment not specified; the trial endpoints were collected during the hospitalization, lasting up to 30 days	Clinical Trial
He J, Whelton PK, Vu B, Klag MJ. 1998. Aspirin and risk of hemorrhagic stroke: a meta-analysis of randomized controlled trials. Journal of the American Medical Association 280(22):1930-1935.	N=55462	Patients from 16 clinical trials (identified by a MEDLINE search) who received aspirin or a control treatment.	Mean dosage of aspirin administered across the 16 trials: 273 mg/day	Mean duration of treatment across the 16 trials was 37 months	Meta-Analysis
Bath PM, Lindenstrom E, Boysen G, De Deyn P, Friis P, Leys D, Marttila R, Olsson J, O'Neill D, Orgogozo J, Ringelstein B, van der Sande J, Turpie AG. 2001. Tinzaparin in acute ischaemic stroke (TAIST): a randomised aspirin-controlled trial. Lancet 358(9283):702-710.	N=1486	Patients admitted to the hospital in 10 European countries with a clinical syndrome of a stroke if they were aged 18-90 years and could be treated within 48 hours of stroke onset.	Aspirin 300 mg/day (N=491) Tinzaparin high-dose (175 anti-Xa IU/kg daily) (N=487) Tinzaparin medium-dose (100 anti-Xa IU/kg daily) (N=508)	Treatment duration up to 10 days	Clinical Trial

<b>APPENDIX 1. TABLE OF STUDIES – PUBLICATIONS PROVIDING ADDITIONAL SAFETY INFORMATION</b>					
<b>Reference</b>	<b>Total Subjects</b>	<b>Patient Population</b>	<b>Treatment Groups (N)</b>	<b>Treatment Duration</b>	<b>Type of Article</b>
Chen ZM, Sandercock P, Pan HC, Counsell C, Collins R, Liu LS, Xie JX, Warlow C, Peto R. 2000. Indications for early aspirin use in acute ischemic stroke : A combined analysis of 40 000 randomized patients from the chinese acute stroke trial and the international stroke trial. Stroke 31(6):1240-1249.	N=40090	Patients with acute ischemic stroke who had been enrolled into the Chinese Acute Stroke Trial (CAST) or International Stroke Trial (IST).	CAST (Aspirin 160 mg/day. Placebo given to the control group.) (N=20655)	CAST (Treatment duration=4 weeks)	Meta-Analysis
Gullov AL, Koefoed BG, Petersen P, Pedersen TS, Andersen ED, Godtfredsen J, Boysen G. 1998. Fixed minidose warfarin and aspirin alone and in combination vs adjusted-dose warfarin for stroke prevention in atrial fibrillation: Second Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation Study. Archives of Internal Medicine 158(14):1513-1521.	N=677	Patients with nonvalvular chronic atrial fibrillation.	Aspirin 300 mg/day (N=169) Warfarin 1.25 mg/day (N=167) Warfarin 1.25 mg/day+aspirin 300 mg/day (N=171) Adjusted dose warfarin (INR 2.0 to 3.0) (N=170)	Treatment duration was approximately 3 years	Clinical Trial
Gullov AL, Koefoed BG, Petersen P. 1999. Bleeding during warfarin and aspirin therapy in patients with atrial fibrillation: the AFASAK 2 study. Atrial Fibrillation, Aspirin, and Anticoagulation. Archives of Internal Medicine 159(12):1322-1328.	N=677	Patients with nonvalvular chronic atrial fibrillation.	Aspirin 300 mg/day (N=169) Warfarin 1.25 mg/day (N=167) Warfarin 1.25 mg/day+aspirin 300 mg/day (N=171) Adjusted dose warfarin (INR 2.0 to 3.0) (N=170)	Treatment duration was approximately 3 years	Clinical Trial

APPENDIX 1. TABLE OF STUDIES – PUBLICATIONS PROVIDING ADDITIONAL SAFETY INFORMATION					
Reference	Total Subjects	Patient Population	Treatment Groups (N)	Treatment Duration	Type of Article
Cruz-Fernandez JM, Lopez-Bescos L, Garcia-Dorado D, Lopez Garcia-Aranda V, Cabades A, Martin-Jadraque L, Velasco JA, Castro-Beiras A, Torres F, Marfil F, Navarro E. 2000. Randomized comparative trial of triflusal and aspirin following acute myocardial infarction. European Heart Journal 21(6):457-465.	N=2275	Patients with confirmed acute MI, within 24 hours of onset of symptoms.	Aspirin 300 mg/day (N=1140) Triflusal 600 mg/day (N=1135)	Treatment duration was 35 days	Clinical Trial
IST Collaborative Group (International Stroke Trial). 1997. The International Stroke Trial (IST): A randomised trial of aspirin, subcutaneous heparin, both, or neither among 19 435 patients with acute ischaemic stroke. Lancet 349(9065):1569-1581.	N=19435	Subjects with evidence of an acute ischemic stroke with onset <48 hours of study entry, no evidence of intracranial hemorrhage, and no clear indications for, or contraindications to, heparin or aspirin.	Aspirin 300 mg/day Unfractionated heparin (5000 IU [low-dose] or 12500 IU [medium-dose] SC BID) Aspirin (300 mg/day)+Heparin (5000 IU [low-dose] or 12500 IU [medium-dose] SC BID) Using a factorial study design, approximately one-half of the subjects received aspirin (N=9720) and approximately one-half received no aspirin (N=9715). In addition, approximately one-half received heparin (N=9717), split approximately evenly between the low- and medium-dose heparin, and approximately one-half (N=9718) received no heparin.	Subjects assigned to heparin or aspirin, or both received the first dose(s) immediately after randomization, and treatment was to continue for 14 days or until prior discharge. At discharge, clinicians could consider giving all subjects long-term aspirin.	Clinical Trial

APPENDIX 1. TABLE OF STUDIES – PUBLICATIONS PROVIDING ADDITIONAL SAFETY INFORMATION					
Reference	Total Subjects	Patient Population	Treatment Groups (N)	Treatment Duration	Type of Article
Aronow WS, Ahn C, Kronzon I, Gutstein H. 2000. Effect of warfarin versus aspirin on the incidence of new thromboembolic stroke in older persons with chronic atrial fibrillation and abnormal and normal left ventricular ejection fraction. American Journal of Cardiology 85(8):1033-1035.	N=350	Patients with chronic atrial fibrillation in a long-term health care facility.	Aspirin 325 mg/day (N=209) Warfarin (INR 2.0-3.0, mean ratio 2.4) (N=141)	The mean follow-up period was 36 months	Observational Study
Chan K-L, Dumesnil Jean G, Cujec B, Sanfilippo Anthony J, Jue J, Turek Michele A, Robinson Trevor I, Moher D. 2003. A randomized trial of aspirin on the risk of embolic events in patients with infective endocarditis. Journal of the American College of Cardiology 42(5):775-780.	N=115	Patients with infective endocarditis between 16 and 80 years of age.	Aspirin 325 mg/day (N=60) Placebo (N=55)	Treatment duration was 4 weeks	Clinical Trial
CAPRIE Steering Committee (Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events). 1996. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet 348(9038):1329-1339. Harker LA, Boissel JP, Pilgrim AJ, Gent M. 1999. Comparative safety and tolerability of clopidogrel and aspirin: results from CAPRIE. CAPRIE Steering Committee and Investigators. Clopidogrel versus aspirin in patients at risk of ischaemic events. Drug Safety 21(4):325-335.	N=19185	Patients with symptomatic atherosclerosis manifested as recent ischemic stroke, MI, or peripheral artery disease.	Aspirin 325 mg/day (N=9586; N=3198 in the stroke subgroup; N=3159 in the MI subgroup; N=3229 in the PAD subgroup) Clopidogrel 75 mg/day (N=9599; N=3233 in the stroke subgroup; N=3143 in the MI subgroup; N=3223 in the PAD subgroup)	Treatment duration ranged from 1 to 3 years	Clinical Trial

<b>APPENDIX 1. TABLE OF STUDIES – PUBLICATIONS PROVIDING ADDITIONAL SAFETY INFORMATION</b>					
<b>Reference</b>	<b>Total Subjects</b>	<b>Patient Population</b>	<b>Treatment Groups (N)</b>	<b>Treatment Duration</b>	<b>Type of Article</b>
Creager MA. 1998. Results of the CAPRIE trial: efficacy and safety of clopidogrel. <i>Vascular medicine</i> 3(3):257-260.	N=19185	Patients with symptomatic atherosclerosis manifested as recent ischemic stroke, MI, or peripheral artery disease.	Aspirin 325 mg/day (N=9586; N=3198 in the stroke subgroup; N=3159 in the MI subgroup; N=3229 in the PAD subgroup) Clopidogrel 75 mg/day (N=9599; N=3233 in the stroke subgroup; N=3143 in the MI subgroup; N=3223 in the PAD subgroup)	Treatment duration ranged from 1 to 3 years	Clinical Trial
Bhatt DL, Hirsch AT, Ringleb PA, Hacke W, Topol EJ. 2000. Reduction in the need for hospitalization for recurrent ischemic events and bleeding with clopidogrel instead of aspirin. <i>American Heart Journal</i> 140(1):67-73.	N=19099	Patients with symptomatic atherosclerosis manifested as recent ischemic stroke, MI, or peripheral artery disease.	Aspirin 325 mg/day (N=9546) Clopidogrel 75 mg/day (N=9553)	Treatment duration ranged from 1 to 3 years	Clinical Trial
Bhatt DL, Marso SP, Hirsch AT, Ringleb PA, Hacke W, Topol EJ. 2002. Amplified benefit of Clopidogrel versus Aspirin in patients with diabetes mellitus. <i>American Journal of Cardiology</i> 90(6):625-628.	N=3866	In this retrospective subanalysis of CAPRIE study data, patients with a history of diabetes mellitus at enrollment were identified from the original CAPRIE study population.	Aspirin 325 mg/day (N=1952) Clopidogrel 75 mg/day (N=1914)	Treatment duration ranged from 1 to 3 years	Clinical Trial
Johnson WC, Williford WO. 2002. Benefits, morbidity, and mortality associated with long-term administration of oral anticoagulant therapy to patients with peripheral arterial bypass procedures: a prospective randomized study. <i>Journal of Vascular Surgery</i> 35(3):413-421.	N=831	Subjects who underwent peripheral arterial bypass surgery.	Aspirin 325 mg/day (N=413) Aspirin 325 mg/day+Warfarin INR 1.4-2.8 (N=418)	The mean follow-up period for patients undergoing prosthetic bypass was 36.6 months, and the mean follow-up period for those undergoing vein bypass was 39.3 months.	Clinical Trial

<b>APPENDIX 1. TABLE OF STUDIES – PUBLICATIONS PROVIDING ADDITIONAL SAFETY INFORMATION</b>					
<b>Reference</b>	<b>Total Subjects</b>	<b>Patient Population</b>	<b>Treatment Groups (N)</b>	<b>Treatment Duration</b>	<b>Type of Article</b>
Leon MB, Baim DS, Popma JJ, Gordon PC, Cutlip DE, Ho KK, Giambartolomei A, Diver DJ, Lasorda DM, Williams DO, Pocock SJ, Kuntz RE. 1998. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. <i>New England Journal of Medicine</i> 339(23):1665-1671.	N=1653	Patients enrolled were those with single-vessel or multivessel disease of native coronary arteries who were successfully treated with a high-pressure, balloon-expandable stent and then randomly assigned to receive 1 of 3 antithrombotic-drug regimens.	Aspirin 325 mg/day (N=557) Aspirin 325 mg/day+Heparin i.v. (dosed to an aPTT of 40 to 60 seconds) (N=550) Aspirin 325 mg/day+Ticlopidine 500 mg/day (N=546)	Treatment duration was 30 days	Clinical Trial
Matias-Guiu J, Ferro Jose M, Alvarez-Sabin J, Torres F. 2003. Comparison of triflusal and aspirin for prevention of vascular events in patients after cerebral infarction: the TACIP Study: a randomized, double-blind, multicenter trial. <i>Stroke</i> 34(4):840-848.	N=2107	Patients 40 years or older who had suffered a TIA or nondisabling stroke within the previous 6 months.	Aspirin 325 mg/day (N=1052) Triflusal 600 mg/day (N=1055)	Treatment duration ranged from 1 to 3 years with a mean follow-up of of 30.1 months	Clinical Trial
Mohr JP, Thompson JL, Lazar RM, Levin B, Sacco RL, Furie KL, Kistler JP, Albers GW, Pettigrew LC, Adams HP, Jackson CM, Pullicino P. 2001. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. <i>New England Journal of Medicine</i> 345(20):1444-1451.	N=2206	Eligible patients were 30 to 85 years old, were considered acceptable candidates for warfarin therapy, had an ischemic stroke within the previous 30 days.	Aspirin 325 mg/day (N=1103) Warfarin INR 1.4-2.8 (N=1103)	Treatment duration was 2 years	Clinical Trial
Sarac TP, Huber TS, Back MR, Ozaki CK, Carlton LM, Flynn TC, Seeger JM. 1998. Warfarin improves the outcome of infrainguinal vein bypass grafting at high risk for failure. <i>Journal of Vascular Surgery</i> 28(3):446-457.	N=56	Patients who had undergone infrainguinal arterial bypass grafting with autogenous vein who were at high risk for graft failure, defined as suboptimal venous conduit, poor arterial runoff, or redo infrainguinal bypass grafting.	Aspirin 325 mg/day (N=24) Aspirin: 325 mg/day + Warfarin INR 2 to 3 (N=32)	Treatment duration ranged from 3 to 5 years	Clinical Trial

<b>APPENDIX 1. TABLE OF STUDIES – PUBLICATIONS PROVIDING ADDITIONAL SAFETY INFORMATION</b>					
<b>Reference</b>	<b>Total Subjects</b>	<b>Patient Population</b>	<b>Treatment Groups (N)</b>	<b>Treatment Duration</b>	<b>Type of Article</b>
SPAF Investigators. 1996. Bleeding during antithrombotic therapy in patients with atrial fibrillation. Archives of Internal Medicine 156(4):409-416.	N=1100	Patients with atrial fibrillation.	Aspirin 325 mg/day (N=545) Warfarin (approximate INR=2.0 to 4.5) (N=555)	The mean follow-up was 3.1 years for the subset of patients $\geq$ 75 years and 2.0 years for those patients >75 years	Retropective Study
SPAF III Writing Committee (Stroke Prevention in Atrial Fibrillation). 1998. Patients with nonvalvular atrial fibrillation at low risk of stroke during treatment with aspirin: Stroke Prevention in Atrial Fibrillation III Study. Journal of the American Medical Association 279(16):1273-1277.	N=892	Patients with atrial fibrillation categorized as "low risk" based on the absence of 4 prespecified thromboembolic risk factors (recent congestive heart failure or left ventricular fractional shortening of 25% or less, previous thromboembolism, systolic blood pressure greater than 160 mmHg, or female sex of age older than 75 years).	Aspirin 325 mg/day (N=892)	Patients were treated and followed for a mean of 2 years	Clinical Trial
Obialo CI, Conner AC, Lebon LF. 2003. Maintaining patency of tunneled hemodialysis catheters - Efficacy of aspirin compared to warfarin. Scandinavian Journal of Urology and Nephrology 37(2):172-176.	N=63	Patients with cuffed tunneled hemodialysis catheters awaiting maturation of their arteriovenous fistulae (AVF).	Aspirin 325 mg/day (N=21) Warfarin (INR of 2-3) (N=11) Control (Subjects receiving neither aspirin or warfarin) (N=31)	Follow-up period was 120 days	Clinical Trial
WASID Study Group (Warfarin-Aspirin Symptomatic Intracranial Disease). 1998. Prognosis of patients with symptomatic vertebral or basilar artery stenosis. Stroke 29(7):1389-1392.	N=68	Patients with symptomatic stenosis (50% to 99%) of a major intracranial artery (carotid siphon; anterior, middle, or posterior cerebral artery; vertebral artery; basilar artery; or posterior inferior cerebellar artery).	Aspirin (dose not specified; 21 of 26 patients were treated with at least 325 mg/day) (N=26) Warfarin (dose not specified; warfarin therapy was typically adjusted to maintain prothrombin times in the range of 1.2 to 1.6 times control) (N=42)	Patients were treated and followed for a median of 13.8 months	Clinical Trial

APPENDIX 1. TABLE OF STUDIES – PUBLICATIONS PROVIDING ADDITIONAL SAFETY INFORMATION					
Reference	Total Subjects	Patient Population	Treatment Groups (N)	Treatment Duration	Type of Article
Gorelick Philip B, Richardson D, Kelly M, Ruland S, Hung E, et al. 2003. Aspirin and ticlopidine for prevention of recurrent stroke in black patients: a randomized trial. Journal of the American Medical Association 289(22):2947-2957.	N=1809	Black subjects who had recently had a noncardioembolic ischemic stroke.	Aspirin 650 mg/day (N=907) Ticlopidine 500 mg/day (N=902)	Treatment duration up to 24 months	Clinical Trial
Lanas A, Bajador E, Serrano P, Arroyo M, Fuentes J, Santolaria S. 1998. Effects of nitrate and prophylactic aspirin on upper gastrointestinal bleeding: A retrospective case-control study. Journal of International Medical Research 26(3):120-128.	N=2208	Patients admitted to the hospital with upper GI bleeding due to peptic lesions, and age-and sex-matched controls.	<u>Cases:</u> Non-aspirin NSAIDs (N=159) Aspirin ≥500 mg/day (N=134) Low-dose aspirin <500 mg/day (N=93; 76 of whom used 200 mg/day) Low-dose aspirin/nitrates (N=20) Nitrates (N=35) Anti-secretory drugs (N=79) <u>Controls:</u> Non-aspirin NSAIDs (N=68) Aspirin ≥500 mg/day (N=11) Low-dose aspirin <500 mg/day (N=84, 58 of whom used 200 mg/day) Low-dose aspirin+nitrates (N=28) Nitrates (N=85) Anti-secretory drugs (N=138)	Treatment duration not specified in the publication	Case-control

APPENDIX 1. TABLE OF STUDIES – PUBLICATIONS PROVIDING ADDITIONAL SAFETY INFORMATION					
Reference	Total Subjects	Patient Population	Treatment Groups (N)	Treatment Duration	Type of Article
Lanas A, Bajador E, Serrano P, Fuentes J, Carreno S, Guardia J, Sanz M, Montoro M, Sainz R. 2000. Nitrovasodilators, low-dose aspirin, other nonsteroidal antiinflammatory drugs, and the risk of upper gastrointestinal bleeding. New England Journal of Medicine 343(12):834-839.	N=3353	Patients with acute gastrointestinal bleeding (defined as hematemesis of melena accompanied by evidence of peptic lesions) admitted to the hospital and matched controls.	Patients (N=1122) Controls (N=2231) Collected as part of the results: Any nonsteroidal anti-inflammatory drug other than low-dose aspirin (46.3% of patients and 10.3% of controls) Low-dose (8300 mg/day) aspirin alone (10.7% of patients and 9.2% of controls) Nitrovasodilators (5.3% of patients and 6.1% of controls) Antisecretory medication (12.0% of patients and 9.2% of controls)	Treatment duration not specified in the publication; however, these drugs were used at any time during the 7 days before hospital admission or the day of the patient/control interview	Case-control

**APPENDIX 2. SUMMARY OF BLEEDING DATA – PUBLICATIONS PROVIDING ADDITIONAL SAFETY INFORMATION**

Reference	Type of Article	Aspirin Doses/Treatment Groups	Bleeding Data
<b>Low-Dose Aspirin (&lt;200 mg/day)</b>			
SPIRIT Study Group. 1997. A randomized trial of anticoagulants versus aspirin after cerebral ischemia of presumed arterial origin. <i>Annals of Neurology</i> 42(6):857-865.	Clinical Trial	Aspirin group (Aspirin 30 mg/day [95% of patients], 75 mg/day [3% of patients], or 100 mg/day [2% of patients]). Anticoagulant group (target INR value of 3.0 to 4.5 achieved with phenprocoumon, acenocoumarol, or warfarin. Phenprocoumon was the preferred anticoagulant.)	The primary outcome measure was a composite event of death from all vascular causes, nonfatal stroke, nonfatal MI, or nonfatal major bleeding complication. An excess of the primary outcome event occurred in 81/651 patients in the anticoagulant group vs. 36/665 patients in the aspirin group (Hazard Ratio [HR] 2.3; 95% CI: 1.6-3.5). This excess could be attributed to 53 major bleeding complications (27 intracranial, 17 fatal) during anticoagulant therapy versus 6 on aspirin (3 intracranial, 1 fatal).
Diener HC, Cunha L, Forbes C, Sivenius J, Smets P, Lowenthal A. 1996. European Stroke Prevention Study 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. <i>Journal of the Neurological Sciences</i> 143(1-2):1-13.  Forbes CD. 1997. European Stroke Prevention Study 2: dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. <i>International Journal of Clinical Practice</i> 51(4):205-208.	Clinical Trial	Aspirin 50 mg/day Dipyridamole 400 mg/day Aspirin 50 mg/day + Dipyridamole 400 mg/day Placebo	Total bleeding episodes were significantly more frequent and more often moderate or severe/fatal in the aspirin alone (135 subjects, 8.2%) and aspirin + dipyridamole (144 subjects, 8.7%) groups in comparison to the dipyridamole alone (77 subjects, 4.7%) and placebo (74 subjects, 4.5%) treatment groups.  Of these total bleeding events, the percentage of events considered to be severe or fatal was significantly higher in the aspirin (20 subjects, 14.8%) and aspirin + dipyridamole treatment groups (27 subjects, 18.8%) than in the dipyridamole alone (6 subjects, 7.8%) and placebo (7 subjects, 9.5%) treatment groups. Bleeding was most commonly reported as epistaxis, "other sites," proctorrhagia, melena, hematuria, hematemesis, and purpura (in descending order).

**APPENDIX 2. SUMMARY OF BLEEDING DATA – PUBLICATIONS PROVIDING ADDITIONAL SAFETY INFORMATION**

Reference	Type of Article	Aspirin Doses/Treatment Groups	Bleeding Data
FRISC Study Group (Fragmin During Instability in Coronary Artery Disease). 1996. Low-molecular-weight heparin during instability in coronary artery disease. <i>Lancet</i> 347(9001):561-568.	Clinical Trial	Placebo (Aspirin 75 mg/day [following 300 mg loading dose]) Dalteparin (120 IU/kg for 6 days followed by 7500 IU for the next 30-45 days) + Aspirin (75 mg/day [following 300 mg loading dose])	During the acute phase, there were very few major bleeding episodes and no differences between the dalteparin (6 subjects, 0.8%) and placebo (aspirin only) (4 subjects, 0.5%) treatment groups. However, during this phase the incidence of minor bleeding episodes was higher in the dalteparin treatment group (61 subjects, 8.2%) compared to the placebo (aspirin only) treatment group (2 subjects, 0.3%).
Hebert PR, Hennekens CH. 2000. An overview of the 4 randomized trials of aspirin therapy in the primary prevention of vascular disease. <i>Archives of Internal Medicine</i> 160(20):3123-3127.	Meta-analysis	Aspirin 75 - 500 mg/day Placebo	Based on a small number of events, there was an apparent 69% increase in the risk of hemorrhagic stroke associated with aspirin therapy that was statistically significant (risk ratio: 1.69; 95% CI: 1.06-2.69) relative to placebo
Meade TW, Brennan PJ, Wilkes HC, Zuhrie SR. 1998. Thrombosis prevention trial: randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. <i>Lancet</i> 351(9098):233-241.7	Clinical Trial	Aspirin 75 mg/day Warfarin (mean stable INR of 1.47) Aspirin 75 mg/day + Warfarin (mean stable INR of 1.47) Placebo	There was a greater number of hemorrhagic strokes in the combined warfarin group (9 events) and in the combined aspirin plus warfarin group (9 events), due largely to 7 events in the warfarin group, which, compared with placebo (0 events), gives a rate difference of 0.9 (95% CI: 0.2-1.5, p=0.009). For hemorrhagic stroke, an increase of 0.5 (95% CI: 0.1-0.9) attributable to aspirin treatment was statistically significant (p=0.01). There was a statistically significantly higher incidence of major upper gastrointestinal bleeding in the warfarin group (8 events) vs. placebo (1 event) (p<0.05), and significantly higher incidences of intermediate and minor bleeding in each active warfarin group versus placebo.
Sanmuganathan PS, Ghahramani P, Jackson PR, Wallis EJ, Ramsay LE. 2001. Aspirin for primary prevention of coronary heart disease: safety and absolute benefit related to coronary risk derived from meta-analysis of randomised trials. <i>Heart (British Cardiac Society)</i> 85(3):265-271.	Meta-analysis	Aspirin (75 mg/day, 162.5 mg/day and 500 mg/day) Placebo	Based on the results of this meta-analysis, aspirin treatment significantly increased bleeding complications by 69% (95% CI: 38% to 107%).

**APPENDIX 2. SUMMARY OF BLEEDING DATA – PUBLICATIONS PROVIDING ADDITIONAL SAFETY INFORMATION**

Reference	Type of Article	Aspirin Doses/Treatment Groups	Bleeding Data
Taylor FC, Cohen H, Ebrahim S. 2001. Systematic review of long term anticoagulation or antiplatelet treatment in patients with non-rheumatic atrial fibrillation. <i>BMJ</i> 322(7282):321-326.	Meta-analysis	AFASAK 1 (Aspirin 75 mg/day vs. warfarin) AFASAK 2 (Aspirin 300 mg/day vs. warfarin) SPAF II (Aspirin 325 mg/day vs. warfarin) SIFA (Indoprofen 400 mg/day vs. warfarin) PATAF (Aspirin 150 mg/day vs. warfarin)	Major bleeding events were more common among those treated with long term anticoagulation than on antiplatelet therapy (OR: 1.45; 95 % CI: 0.93 to 2.27). It should be noted that not all major bleeding event rates from AFASAK 1 could be included because of insufficient reporting. The PATAF trial was unusual in reporting a higher rate of major bleeding in the antiplatelet group compared with the anticoagulation group (OR: 0.18; 95% CI: 0.04 to 0.84).
Derksen RHW, De Groot PG, Kappelle LJ. 2003. Low dose aspirin after ischemic stroke associated with antiphospholipid syndrome. <i>Neurology</i> 61(1):111-114.	Clinical Trial	Low-dose aspirin, dose not specified during the treatment period. During the follow-up period, aspirin doses ranged from 38 to 80 mg/day.	None of the patients experienced bleeding episodes during therapy with aspirin or oral anticoagulants.
Brouwer MA, van den Bergh PJPC, Aengevaeren WRM, Veen G, Luijten HE, Hertzberger DP, van Boven AJ, Vromans RPJW, Uijen GJH, Verheugt FWA. 2002. Aspirin plus coumarin versus aspirin alone in the prevention of reocclusion after fibrinolysis for acute myocardial infarction: results of the Antithrombotics in the Prevention of Reocclusion In Coronary Thrombolysis (APRICOT)-2 Trial. <i>Circulation</i> 106(6):659-665.	Clinical Trial	Aspirin 80 mg/day + heparin (discontinued after 48 hours) Aspirin (starting dose of 160 mg/day followed by 80 mg/day) + heparin (continued until target INR = 2.0-3.0) + coumarin	Bleeding complications according to the TIMI criteria occurred in 7 patients (5%) in the aspirin + coumarin treatment group (2 major, 5 minor) and 4 (3%) in the aspirin alone group (2 major, 2 minor). This difference was not statistically significant. No cerebral bleeding was reported in either group. In each group, 1 patient (1%) underwent a blood transfusion.
Chan FKL, Chung SCS, Suen BY, Lee YT, Leung WK, Leung VKS, Wu JC, Lau JYW, Hui Y, Lai MS, Chan HLY, Sung JYJ. 2001. Preventing recurrent upper gastrointestinal bleeding in patients with Helicobacter pylori infection who are taking low-dose aspirin or naproxen. <i>New England Journal of Medicine</i> 344(13):967-973.	Clinical Trial	After eradication of H. pylori infection, patients with coronary heart disease/stroke were given 80 mg/day aspirin for six months. Patients with arthritis were given 500 mg naproxen BID for six months. Patients were then randomly assigned to receive either 20 mg omeprazole daily for six months or one week of eradication therapy.	Three patients in the aspirin group were confirmed to have recurrent bleeding: 2 received eradication therapy and 1 received omeprazole. The estimated probability of recurrent bleeding during the 6-month study was 1.9% for patients who received eradication therapy and 0.9% for patients who received omeprazole (absolute difference, 1.0%; 95% CI: -1.9 to 3.9%).

APPENDIX 2. SUMMARY OF BLEEDING DATA – PUBLICATIONS PROVIDING ADDITIONAL SAFETY INFORMATION			
Reference	Type of Article	Aspirin Doses/Treatment Groups	Bleeding Data
Huynh T, Theroux P, Bogaty P, Nasmith J, Solymoss S. 2001. Aspirin, warfarin, or the combination for secondary prevention of coronary events in patients with acute coronary syndromes and prior coronary artery bypass surgery. <i>Circulation</i> 103(25):3069-3074.	Clinical Trial	Aspirin 80 mg/day Warfarin to INR of 2.0 to 2.5 Aspirin (80 mg/day) + Warfarin (INR of 2.0 to 2.5)	Minor bleeds were more frequent among subjects receiving warfarin (p=0.02) either as single therapy (8.9%) or in combination (9.8%) than among subjects receiving aspirin alone (1.5%). Major bleeding occurred only in subjects receiving warfarin alone (7.4%) or with aspirin (2.4%). The addition of 80 mg of aspirin to warfarin treatment resulted in no excess bleeding.
van Es RF, Jonker JJC, Verheugt FWA, Deckers JW, Grobbee DE. 2002. Aspirin and coumadin after acute coronary syndromes (the ASPECT-2 study): a randomised controlled trial. <i>Lancet</i> 360(9327):109-113.	Clinical Trial	Aspirin (100 mg/day of pulverized carbasalate calcium; equivalent to 80 mg/day aspirin) Oral anticoagulants (phenprocoumon or acenocoumarol) with a target INR of 3.0 to 4.0 Aspirin 80 mg/day + Oral anticoagulants (target INR of 2.0 - 2.5)	Hemorrhagic stroke: 0 patients in the aspirin group, 0 patients in the coumadin group and 1 patient (0.3%) in the aspirin + coumadin group (no hazard ratio). Major bleeding (including intracranial): 3 patients (1%) in the aspirin group, 3 patients (1%) (Hazard ratio 1.03 [0.21-5.08]) in the coumadin group and 7 patients (2%) (Hazard ratio 2.35 [0.61-9.10]) in the coumadin + aspirin group. Blood transfusion/surgical intervention: 2 patients (1%) in the aspirin group, 2 patients (1%) (Hazard ratio 1.03 [0.15-7.30]) in the coumadin group and 4 patients (1%) (Hazard ratio 2.02 [0.37-10.98]) in the coumadin + aspirin group. Minor bleeding: 16 patients (5%) in the aspirin group, 26 patients (8%) (Hazard ratio 1.68 [0.92-3.07]) in the coumadin group and 50 patients (15%) (Hazard ratio 3.13 [1.82-5.37]) in the coumadin + aspirin group.
Yasue H, Ogawa H, Tanaka H, Miyazaki S, Hattori R, Saito M, Ishikawa K, Masuda Y, Yamaguchi T, Motomiya T, Tamura Y. 1999. Effects of aspirin and trapidil on cardiovascular events after acute myocardial infarction. Japanese Antiplatelets Myocardial Infarction Study (JAMIS) Investigators. <i>American Journal of Cardiology</i> 83(9):1308-1313.	Clinical Trial	Aspirin 81 mg/day Trapidil 300 mg/day No antiplatelet therapy	Of the adverse effects in the aspirin and the trapidil groups, gastrointestinal discomfort was observed in 4 and 6 patients, gastrointestinal hemorrhage in 1 and 1, bleeding disorder in 2 and 1, liver dysfunction in 0 and 5, and skin eruption in 0 and 3, respectively. The relative risk of adverse experiences in the aspirin group compared with the trapidil group was 0.425 (95% CI: 0.178 to 1.105).

**APPENDIX 2. SUMMARY OF BLEEDING DATA – PUBLICATIONS PROVIDING ADDITIONAL SAFETY INFORMATION**

Reference	Type of Article	Aspirin Doses/Treatment Groups	Bleeding Data
Collaborative Group of the Primary Prevention Project (PPP). 2001. Low-dose aspirin and vitamin E in people at cardiovascular risk: A randomised trial in general practice. <i>Lancet</i> 357(9250):89-95.	Clinical Trial	Aspirin 100 mg/day No aspirin Within each group, subjects were also randomized to Vitamin E (300 mg/day) or no Vitamin E.	No major differences were seen among subjects in the aspirin and no aspirin treatment groups regarding type of stroke. Of the 16 stroke cases in the aspirin group, 2 were hemorrhagic and 3 were deemed disabling. Of the 24 strokes in the no aspirin group, 3 were hemorrhagic and 4 were disabling. The rate of non-cardiovascular death was similar across the treatment groups (approximately 2%). VA large proportion of the excess of nonfatal events reported for aspirin was, as expected, due to bleeding complications (aspirin: 24 events [1.1%]; no aspirin: 6 events [0.3%]) (p=0.0008). Of the 4 deaths caused by hemorrhage, 3 were in the no aspirin group and 1 was in the aspirin group.
Hop JW, Rinkel GJE, Algra A, Berkelbach van der Sprenkel JW, van Gijn J. 2000. Randomized pilot trial of postoperative aspirin in subarachnoid hemorrhage. <i>Neurology</i> 54(4):872-878.	Clinical Trial	Aspirin 100 mg (suppositories) Placebo	Four subjects had a hemorrhagic complication. One subject in the placebo group died from an intracerebellar hematoma and another subject in this treatment group had an epidural hematoma with deterioration in clinical condition. In the aspirin group, one subject had a spontaneously resolving hematoma in the area of surgery without changes in neurological condition, and one subject developed a subcutaneous hematoma at the point of entry of an extraventricular drain.
Lee TK, Chan KWA, Huang ZS, Ng SK, Lin RT, Po HL, Yuan RY, Lai ML, Chang TW, Yan SH, Deng JC, Liu LH, Lee KY, Lie SK, Sung SM, Hu HH. 1997. Effectiveness of low-dose ASA in prevention of secondary ischemic stroke, the ASA Study Group in Taiwan. <i>Thrombosis Research</i> 87(2):215-224.	Clinical Trial	Aspirin 100 mg/day (initiated within 3 to 6 weeks after the onset of stroke) Nicametate citrate 50 mg/day (initiated within 3 to 6 weeks after the onset of stroke)	Incidence (%) of events related to safety: Aspirin vs. nicametate: Non-fatal cerebral hemorrhage: 0.5% vs. 0.8% Fatal cerebral hemorrhage: 0.9% vs. 0.0% Non-fatal subarachnoid hemorrhage: 0.0% vs. 0.4% Gastrointestinal disturbance (includes heart burn, upper GI bleeding, epigastralgia, and gastric ulcer): 7.7% vs. 6.1% Hematuria: 0.5% vs. 0.0%

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Reference	Type of Article	Aspirin Doses/Treatment Groups	Bleeding Data
<p>Moshfegh K, Redondo M, Julmy F, Wuillemin WA, Gebauer MU, Haeberli A, Meyer BJ. 2000. Antiplatelet effects of clopidogrel compared with aspirin after myocardial infarction: enhanced inhibitory effects of combination therapy. <i>Journal of the American College of Cardiology</i> 36(3):699-705.</p>	<p>Clinical Trial</p>	<p>All patients received the following five consecutive treatment periods:                      Phase 1 (Aspirin 100 mg/day for 7 days)                      Phase 2 (Clopidogrel 75 mg/day + aspirin 100 mg/day for 7 days)                      Phase 3 (After a washout period for clopidogrel and aspirin treatment, clopidogrel treatment at 75 mg/day for 7 days)                      Phase 4 (After a washout period for clopidogrel, aspirin treatment at 300 mg/day for 14 days)                      Phase 5 (Aspirin 300 mg/day + clopidogrel 75 mg for 7 days)                      Washout periods for either drug consisted of 7 days between Phases 2 and 3 and 14 days between Phases 3 and 4</p>	<p>There were no bleeding complications noted with any of the treatments.</p>
<p>Julian DG, Chamberlain DA, Pocock SJ, Bernard R, Chamberlain D, Bothwick L, Irving J, Murdoch W, Pohl J, Wood D, Penny J, Millar-Craig M, Robson D, Vallance B, Hine K, Powell-Jackson J, Varma M, Joseph S, Greenwood T, et al. 1996. A comparison of aspirin and anticoagulation following thrombolysis for myocardial infarction (the AFTER study): A multicentre unblinded randomised clinical trial. <i>British Medical Journal</i> 313(7070):1429-1431.</p>	<p>Clinical Trial</p>	<p>Aspirin 150 mg/day                      Anticoagulation therapy (1000 U/hr of I.V. heparin followed by warfarin or other oral anticoagulant to INR 2 to 2.5)</p>	<p>Severe bleeding occurred in 13 (2.5%) patients in the anticoagulation group and 5 (1.0%) in the aspirin group. The incidence of stroke and severe bleeding combined was significantly less common in the aspirin group (odds ratio 0.44; 95% CI: 0.20 to 0.97; p=0.04) than in the anticoagulation group.</p>

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Reference	Type of Article	Aspirin Doses/Treatment Groups	Bleeding Data
<p>Berge E, Abdelnoor M, Nakstad PH, Sandset PM. 2000. Low molecular-weight heparin versus aspirin in patients with acute ischaemic stroke and atrial fibrillation: a double-blind randomised study. HAEST Study Group. Heparin in Acute Embolic Stroke Trial. <i>Lancet</i> 355(9211):1205-1210.</p>	<p>Clinical Trial</p>	<p>Aspirin 160 mg/day Dalteparin 100 IU/kg BID SC</p>	<p>The frequency of symptomatic cerebral hemorrhages (dalteparin: 2.7%; aspirin: 1.8%) or symptomatic and asymptomatic cerebral hemorrhages (dalteparin: 11.6%; aspirin: 14.2%) during the first 14 days of treatment was similar between the two treatment groups; however, the hemorrhages that occurred in the dalteparin group were more severe. Dalteparin was associated with a significantly higher frequency of extracerebral hemorrhages (5.8%) versus aspirin (1.8%).</p>
<p>Coumadin Aspirin Reinfarction Study (CARS) Investigators. 1997. Randomised double-blind trial of fixed low-dose warfarin with aspirin after myocardial infarction. <i>Lancet</i> 350(9075):389-396.</p>	<p>Clinical Trial</p>	<p>Aspirin 160 mg/day Aspirin 80 mg/day + Warfarin (1 or 3 mg)</p>	<p>For spontaneous major hemorrhage (not procedure related), one-year life table estimates (95% CI) were 0.74% (0.43-1.1) in the 160 mg/day aspirin group (n=30) and 1.4% (0.94-1.8) in the 3 mg warfarin/80 mg/day aspirin group (n=52) (p=0.014 log rank on follow-up). The one-year life estimate (95% CI) for spontaneous major hemorrhage in the 1 mg warfarin/80 mg/day aspirin group was 1.0% (0.56-1.0) (n=26), which was similar to that for 160 mg/day aspirin.</p>
<p>CAST (Chinese Acute Stroke Trial) Collaborative Group. 1997. CAST: Randomised placebo-controlled trial of early aspirin use in 20,000 patients with acute ischaemic stroke. <i>Lancet</i> 349(9066):1641-1649.</p>	<p>Clinical Trial</p>	<p>Aspirin 160 mg/day Placebo</p>	<p>Aspirin was associated with a small but significant excess of 2.7 transfused or fatal extracranial bleeds per 1000 patients versus placebo (86 [0.8%] vs. 58 [0.6%]; p=0.02). In the analysis of patients alive at the end of the treatment period, the excess of non-fatal transfused bleeds in aspirin-treated patients was 1.9 per 1000 patients versus placebo (47 [0.5%] vs. 27 [0.3%], p=0.02).</p>

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Reference	Type of Article	Aspirin Doses/Treatment Groups	Bleeding Data
Hurlen M, Abdelnoor M, Smith P, Erikssen J, Arnesen H. 2002. Warfarin, aspirin, or both after myocardial infarction. <i>New England Journal of Medicine</i> 347(13):969-974.	Clinical Trial	Aspirin 160 mg/day Warfarin to INR 2.8 - 4.2 Aspirin 75 mg/day + Warfarin to INR 2.0 - 2.5	There were 69 nonfatal major bleeding episodes in patients receiving treatment with the study medication: 8 receiving aspirin (0.17 % per year), 33 receiving warfarin (0.68% per year), and 28 receiving combined therapy (0.57% per year). The difference was significant ( $p < 0.001$ ), with a rate ratio of 0.25 (95% CI: 0.10 to 0.60) for the comparison of aspirin and warfarin. The incidence of minor bleeding episodes was 0.84%, 2.14% and 2.70% per year, respectively, for the aspirin, warfarin and combined treatment groups.
Ivert T, Intonti M, Stain-Malmgren R, Dumitrescu A, Blomback M. 1998. Effects of aprotinin during cardiopulmonary bypass in patients treated with acetylsalicylic acid. <i>Scandinavian Cardiovascular Journal</i> 32(5):289-295.	Clinical Trial	Aspirin 160 mg/day High-dose aprotinin + Aspirin 160 mg/day Low-dose aprotinin + Aspirin 160 mg/day	The median total blood loss was approximately 2.6 L among subjects treated with aspirin alone and 1.4 L less (52% reduction) among aprotinin-treated subjects.
Second SYMPHONY Investigators. 2001. Randomized trial of aspirin, sibralfiban, or both for secondary prevention after acute coronary syndromes. <i>Circulation</i> 103(13):1727-1733.	Clinical Trial	Aspirin 160 mg/day Aspirin 160 mg/day + Low-dose sibralfiban (3.0, 4.5, or 6.0 mg/day based on weight and serum creatinine) High-dose sibralfiban (3.0, 4.5, or 6.0 mg/day based on weight and serum creatinine)	Major bleeding was significantly more frequent in low-dose sibralfiban + aspirin patients (5.7%) versus aspirin alone (4.0%) but not in high-dose sibralfiban patients (4.6%).

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Reference	Type of Article	Aspirin Doses/Treatment Groups	Bleeding Data
SYMPHONY Investigators. 2000. Comparison of sibralfiban with aspirin for prevention of cardiovascular events after acute coronary syndromes: a randomised trial. <i>Lancet</i> 355(9201):337-345.	Clinical Trial	<p>Aspirin 160 mg/day</p> <p>Low-dose sibralfiban (Sibralfiban doses [3.0, 4.5, or 6.0 mg/day] were based on a model accounting for weight and serum creatinine and designed to achieve at least 25% steady-state inhibition of platelet aggregation)</p> <p>High-dose sibralfiban (Sibralfiban doses [3.0, 4.5, or 6.0 mg/day] were based on a model accounting for weight and serum creatinine and designed to achieve at least 50% steady-state inhibition of platelet aggregation)</p>	<p>Major bleeding was significantly more common with high-dose sibralfiban (171 [5.7%]) than with aspirin (120 [3.9%]) or low-dose sibralfiban (159 [5.2%]). Transfusions were more common in the sibralfiban groups than in the aspirin group. Bleeding data (% incidence) for the aspirin-alone treatment group only:</p> <p>Major and minor bleeding: (13.0%)                      Major bleeding: (3.9%)                      Minor bleeding: (12.6%)                      Insignificant bleeding: (7.2%)                      Any bleeding: (18.5%)                      Bleeding resulting in dose adjustment: (0.9%)                      Study drug stopped due to bleeding: (1.4%)</p>
Cook NR, Hebert PR, Manson JE, Buring JE, Hennekens CH. 2000. Self-selected post-trial aspirin use and subsequent cardiovascular disease and mortality in the Physicians' Health Study. <i>Archives of Internal Medicine</i> 160(7):921-928.	Clinical Trial	<p>0-13 days post-trial aspirin use/year</p> <p>14-120 days post-trial aspirin use/year</p> <p>121-179 days post-trial aspirin use/year</p> <p>≥180 days post-trial aspirin use/year</p>	<p>Self-selected post-trial aspirin use for 180 versus 0-13 days/year yielded the following safety results (presented as Risk Ratios [95% CI]):</p> <p>Total stroke: 1.02 (0.74-1.39), p=0.96                      Hemorrhagic stroke: 1.29 (0.52-3.20), p=0.44</p>
Fiore LD, Ezekowitz MD, Brophy MT, Lu D, Sacco J, Peduzzi P. 2002. Department of Veterans Affairs Cooperative Studies Program Clinical Trial comparing combined warfarin and aspirin with aspirin alone in survivors of acute myocardial infarction: primary results of the CHAMP study. <i>Circulation</i> 105(5):557-563.	Clinical Trial	<p>Aspirin 162 mg/day</p> <p>Aspirin 81 mg/day + warfarin to INR 1.5-2.5</p>	<p>The incidence of major bleeding complications was significantly lower in the aspirin group than in the combination group (0.72 vs. 1.28 events per 100 patient-years, respectively; p&lt;0.001). The incidence of minor bleeding complications was also significantly lower in the aspirin group than in the combination group (1.11 vs. 5.14 events per 100 patient-years, respectively; p&lt;0.001). The incidence of intracranial hemorrhage was identical between the two groups (14 patients in each group). Fatal hemorrhage occurred in 7 patients in the aspirin group and 10 patients in the combination group.</p>

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Reference	Type of Article	Aspirin Doses/Treatment Groups	Bleeding Data
<b>High-Dose Aspirin (&gt;200 mg/day)</b>			
<p>Hart RG, Benavente O, McBride R, Pearce LA. 1999. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. <i>Annals of Internal Medicine</i> 131(7):492-501.</p>	<p>Meta-analysis</p>	<p>Aspirin (25-1300 mg/day) versus placebo                      Warfarin (mean INR 2.0-2.6) versus placebo                      Warfarin (mean INR 2.2-3.1) versus aspirin (75-325 mg/day)</p>	<p><u>Aspirin versus Placebo Trials (N=6)</u>                      Only 7 cases of intracranial bleeding (4 aspirin recipients and 3 placebo recipients; rate for aspirin, 0.2% per year) and 28 major extracranial hemorrhages (13 aspirin recipients and 15 placebo recipients) occurred in the 6 trials. According to data from 4 of the trials, all-cause mortality was not significantly reduced by aspirin (relative risk reduction, 16% [CI, -5% to 33%]).</p> <p><u>Warfarin versus Aspirin Trials (N=5)</u>                      Persons who received warfarin had more than twice as many intracranial hemorrhages as those who received aspirin (17 compared with 7) (relative risk, 2.1 [95% CI: 1.0 to 4.6]). Major extracranial hemorrhage was increased in persons who received warfarin compared with those who received aspirin (relative risk, 2.0 [95% CI: 1.2 to 3.4]; absolute risk increase, 0.2% per year). On the basis of available data from 4 of the trials, all-cause mortality was similar in persons who received adjusted-dose warfarin and those who received aspirin (relative risk reduction, 8% [CI, -21% to 30%]).</p>

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Reference	Type of Article	Aspirin Doses/Treatment Groups	Bleeding Data
Weisman SM, Graham DY. 2002. Evaluation of the benefits and risks of low-dose aspirin in the secondary prevention of cardiovascular and cerebrovascular events. Archives of Internal Medicine 162(19):2197-2202.	Meta-analysis	Aspirin doses investigated in these 6 studies included 50, 75, 300 and 324 mg/day Placebo	<p>Based on the studies included in this meta-analysis, the risk ratio (95% CI) for gastrointestinal tract bleeding was 2.5 (1.4 - 4.7; p=0.001) following aspirin treatment.</p> <p>Overall, gastrointestinal bleeding was a rare finding, with only 58 reports across the 6 studies (41 in the aspirin groups; 17 in the placebo groups). Only about half of the cases of gastrointestinal bleeding were deemed severe enough to require withdrawal. Importantly, there were no reported deaths related to gastrointestinal bleeding, and gastrointestinal bleeding led to almost no permanent morbidity (that was reported by the investigators). Only 1 report, the United Kingdom Transient Ischaemic Attack (UK-TIA) trial, demonstrated a statistically significant increased risk of gastrointestinal bleeding as a result of aspirin intake (1991).</p> <p>Cerebral hemorrhage could not be adequately evaluated in this meta-analysis. Only 2 of the 6 trials reported cases of hemorrhagic stroke (UK-TIA and the Swedish Aspirin Low-Dose Trial [SALT]) and, importantly, in both trials, cerebrovascular ischemic events were the qualifying events for study inclusion. Despite these limitations, and while the numbers are small, the findings in these 2 studies suggest an excess risk of hemorrhagic stroke in those allocated aspirin (18 vs. 6) that is similar to the risk of gastrointestinal bleeding.</p>

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Reference	Type of Article	Aspirin Doses/Treatment Groups	Bleeding Data
Evans A, Perez I, Yu G, Kalra L. 2001. Should stroke subtype influence anticoagulation decisions to prevent recurrence in stroke patients with atrial fibrillation? <i>Stroke</i> 32(12):2828-2832.	Clinical Trial	Aspirin 75 to 300 mg/day Warfarin to a target INR of 2.0 to 3.0	Annualized Event Rate (% and 95% CI) for warfarin versus aspirin; p-value Total Bleeding Events: 12.1 (8.8–15.3) vs. 3.1 (1.4–4.9); p<0.01 Major Bleeding Events (excluding intracranial hemorrhage): 2.5 (1.0–3.9) vs. 0.6 (0–1.3); p<0.05 Minor Bleeding Events: 9.6 (6.7–12.5) vs. 2.5 (0.9–4.2); p<0.01 Intracranial Hemorrhage: 0.7 (0–1.4) vs. 0.3 (0–0.8); p=NS Recurrent stroke + major bleeding events: 7.4 (5.5–9.2) vs. 10.1 (8.6–11.5); p<0.05
Srinivasan AK, Grayson AD, Pullan DM, Fabri BM, Dihmis WC. 2003. Effect of preoperative aspirin use in off-pump coronary artery bypass operations. <i>Annals of Thoracic Surgery</i> 76(1):41-45.	Retrospective Study	Patients who continued taking aspirin therapy within 7 days before OPCAB (aspirin users). Propensity-matched patients who had OPCAB but whose aspirin therapy was stopped a week before operation (nonaspirin users).	There were no significant differences between aspirin and non-aspirin users on post-operative blood loss (845 mL vs. 775 mL), re-exploration for bleeding (3.5% versus 3.5%), and GI bleeding (1.2% versus 1.2%). There were no significant differences in transfusion requirements for red blood cells, platelets, or fresh frozen plasma for aspirin and nonaspirin users.
Schmulling S, Rudolf J, Strotmann-Tack T, Grond M, Schneeweis S, Sobesky J, Thiel A, Heiss W-D. 2003. Acetylsalicylic acid pretreatment, concomitant heparin therapy and the risk of early intracranial hemorrhage following systemic thrombolysis for acute ischemic stroke. <i>Cerebrovascular Diseases</i> 16(3):183-190.	Clinical Trial	Prior to stroke: Pretreated with aspirin 100 to 500 mg/day Not pretreated with aspirin After thrombolysis with rt-PA: Low-dose heparin 10,000 IU/day High-dose heparin >15,000-25,000 IU/day No heparin	There was no relationship of hemorrhagic complications within the first 48 hours to aspirin pretreatment (p=0.15), or heparin application (p=0.38), but there was a relationship to stroke severity (National Institutes of Health Stroke Scale) at baseline (p=0.01).
Mangano DT. 2002. Aspirin and mortality from coronary bypass surgery. <i>New England Journal of Medicine</i> 347(17):1309-1317.	Clinical Trial	Aspirin up to 650 mg/day	The percentages of patients with gastrointestinal bleeding (1.1% versus 2.0%, p=0.01), other bleeding (1.7% versus 3.3%, p < 0.001), or requiring re-operation because of bleeding (1.9% versus 5.2%, p < 0.001) were lower for patients treated with aspirin compared to patients not using aspirin following coronary bypass surgery.

**APPENDIX 2. SUMMARY OF BLEEDING DATA – PUBLICATIONS PROVIDING ADDITIONAL SAFETY INFORMATION**

Reference	Type of Article	Aspirin Doses/Treatment Groups	Bleeding Data
He J, Whelton PK, Vu B, Klag MJ. 1998. Aspirin and risk of hemorrhagic stroke: a meta-analysis of randomized controlled trials. <i>Journal of the American Medical Association</i> 280(22):1930-1935.	Meta-analysis	Mean dosage of aspirin administered across the 16 trials: 273 mg/day	Aspirin treatment was associated with an absolute risk increase in hemorrhagic stroke of 12 events per 10,000 persons (95% CI: 5-20, p<0.001). A total of 108 hemorrhagic stroke cases occurred in 13 of the 16 trials included in the meta-analysis.
Bath PM, Lindenstrom E, Boysen G, De Deyn P, Friis P, Leys D, Marttila R, Olsson J, O'Neill D, Orgogozo J, Ringelstein B, van der Sande J, Turpie AG. 2001. Tinzaparin in acute ischaemic stroke (TAIST): a randomised aspirin-controlled trial. <i>Lancet</i> 358(9283):702-710.	Clinical Trial	Aspirin 300 mg/day Tinzaparin high-dose (175 anti-Xa IU/kg daily) Tinzaparin medium-dose (100 anti-Xa IU/kg daily)	The rate of symptomatic intracranial hemorrhage was significantly higher among patients assigned high-dose tinzaparin than in those assigned aspirin. No significant differences in major or minor extracranial bleeding were observed among the treatment groups.  Bleeding data (% incidence) for the aspirin-alone treatment group only: Symptomatic intracranial hemorrhage: 0.2% Major extracranial bleeding: 0.4% Non-major extracranial bleeding: 4.9%
Chen ZM, Sandercock P, Pan HC, Counsell C, Collins R, Liu LS, Xie JX, Warlow C, Peto R. 2000. Indications for early aspirin use in acute ischemic stroke : A combined analysis of 40 000 randomized patients from the chinese acute stroke trial and the international stroke trial. <i>Stroke</i> 31(6):1240-1249.	Meta-analysis	CAST (Aspirin 160 mg/day. Placebo given to the control group.) IST (Aspirin 300 mg/day; control group not given placebo.) In addition, half of the aspirin-allocated and half of the control patients were allocated SC heparin.	There was an increase of 2 (SD 1) per 1000 in hemorrhagic stroke or hemorrhagic transformation of the original infarct (1.0% versus 0.8%, 2p=0.07, aspirin versus control, respectively). From this meta-analysis aspirin was also associated with an excess noncerebral bleeds (2P=0.00001).
Gullov AL, Koefoed BG, Petersen P, Pedersen TS, Andersen ED, Godtfredsen J, Boysen G. 1998. Fixed minidose warfarin and aspirin alone and in combination vs adjusted-dose warfarin for stroke prevention in atrial fibrillation: Second Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation Study. <i>Archives of Internal Medicine</i> 158(14):1513-1521.	Clinical Trial (AFASAK 2)	Aspirin 300 mg/day Warfarin 1.25 mg/day Warfarin 1.25 mg/day + aspirin 300 mg/day Adjusted dose warfarin (INR 2.0 to 3.0)	The cumulative incidence of bleeding events after 3 years of treatment was 24.7% in patients receiving warfarin alone; 24.4% in patients receiving warfarin + aspirin; 30.0% in patients receiving aspirin; and 41.1% in patients receiving adjusted-dose warfarin. The rate of bleeding was significantly higher in patients receiving adjusted-dose warfarin (p=0.03). At 3 years, overall adverse experiences occurred at approximately the same rate for the aspirin and adjusted-dose warfarin groups.

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Reference	Type of Article	Aspirin Doses/Treatment Groups	Bleeding Data
<p>Gullov AL, Koefoed BG, Petersen P. 1999. Bleeding during warfarin and aspirin therapy in patients with atrial fibrillation: the AFASAK 2 study. Atrial Fibrillation, Aspirin, and Anticoagulation. Archives of Internal Medicine 159(12):1322-1328.</p>	<p>Clinical Trial (AFASAK 2)</p>	<p>Aspirin 300 mg/day                      Warfarin 1.25 mg/day                      Warfarin 1.25 mg/day + aspirin 300 mg/day                      Adjusted dose warfarin (INR 2.0 to 3.0)</p>	<p>In this trial, there were 139 minor hemorrhagic events in 120 subjects. There was no significant difference between the number of gastrointestinal, nose, and skin bleeding events across the treatment groups. Gross hematuria was significantly more frequent in the adjusted-dose warfarin group than in any other treatment groups (p=0.01). More nose bleeds were noted in the adjusted-dose warfarin group and the aspirin group than in the other two treatment groups (p=0.025).</p> <p>With regard to bleeding rates, the rate of major bleeding ranged from 0.3% to 1.4% per year among the four treatment groups (aspirin=1.4%; 95% CI: 0.6-3.4). The very small number of major events and, consequently, the low incidence rates did not allow for statistical comparison, but the events seem equally distributed across the four groups. The rate of intracranial major bleeding ranged from 0% to 0.6% across the groups (aspirin=0.3%). In contrast to major bleeds, minor bleeding was significantly more frequent in subjects receiving adjusted-dose warfarin (11.8%; 95% CI: 8.8-16) than in the warfarin (5.6%, 95% CI: 4.5-7.0), warfarin plus aspirin (7.4%; 95% CI: 5.1-10.7), and aspirin (7.1%; 95% CI: 5.8-8.7) treatment groups.</p>

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Cruz-Fernandez JM, Lopez-Bescos L, Garcia-Dorado D, Lopez Garcia-Aranda V, Cabades A, Martin-Jadraque L, Velasco JA, Castro-Beiras A, Torres F, Marfil F, Navarro E. 2000. Randomized comparative trial of triflusal and aspirin following acute myocardial infarction. <i>European Heart Journal</i> 21(6):457-465.	Clinical Trial	Aspirin 300 mg/day Triflusal 600 mg/day	In general, the incidence of hemorrhagic adverse events considered at least possibly related to study medication (triflusal or aspirin) was similar between the two treatment groups. All hemorrhagic events were more common in the aspirin (3.6%) than in the triflusal (2.4%) group but the difference in incidence was not significant. Similarly, differences in incidence of bleeding associated with the and digestive, skin and renal systems were not significant (0.88% versus 1.49% for GI bleeding, 0.62% versus 0.88% for cutaneous bleeding, and 0.18% versus 0.35% for urinary tract bleeding in the triflusal vs. aspirin groups, respectively). A significant difference in central nervous system bleeding was observed with a lower incidence in the triflusal (0.27%) than aspirin (0.97%) group (p=0.03).
IST Collaborative Group (International Stroke Trial). 1997. The International Stroke Trial (IST): A randomised trial of aspirin, subcutaneous heparin, both, or neither among 19 435 patients with acute ischaemic stroke. <i>Lancet</i> 349(9065):1569-1581.	Clinical Trial	Aspirin 300 mg/day Unfractionated heparin (5000 IU [low-dose] or 12500 IU [medium-dose] SC BID) Aspirin (300 mg/day) + Heparin (5000 IU [low-dose] or 12500 IU [medium-dose] SC BID) Using a factorial study design, approximately one-half of the subjects received aspirin (N=9720) and approximately one-half received no aspirin (N=9715). In addition, approximately one-half received heparin (N=9717), split approximately evenly between the low- and medium-dose heparin, and approximately one-half (N=9718) received no heparin.	Heparin- versus non-heparin-treated subjects had fewer recurrent ischemic strokes within 14 days (2.9% versus 3.8%) (2p=0.005) but this benefit was completely offset by a similar-sized increase in hemorrhagic stroke (1.2% versus 0.4%) (2p<0.00001). A highly significant excess of 9 (SD: 1) transfused or fatal extracranial bleeds per 1000 subjects allocated heparin was also observed (1.3% versus 0.4%) (2p<0.00001). Subjects receiving aspirin versus no aspirin-treatment also had significantly fewer recurrent ischemic strokes within 14 days (2.8% versus 3.9%) (2p<0.001) and this benefit was not offset by any significant excess of hemorrhagic strokes (0.9% versus 0.8%). There was a significant excess of 5 (SD: 1) transfused or fatal extracranial bleeds per 1000 subjects treated with aspirin (1.1% versus 0.6%) (2p=0.0004) versus no aspirin.

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Reference	Type of Article	Aspirin Doses/Treatment Groups	Bleeding Data
Aronow WS, Ahn C, Kronzon I, Gutstein H. 2000. Effect of warfarin versus aspirin on the incidence of new thromboembolic stroke in older persons with chronic atrial fibrillation and abnormal and normal left ventricular ejection fraction. American Journal of Cardiology 85(8):1033-1035.	Observational Study	Aspirin 325 mg/day Warfarin (INR 2.0-3.0, mean ratio 2.4)	Aspirin treatment was terminated because of gastrointestinal bleeding in 6 persons.
Chan K-L, Dumesnil Jean G, Cujec B, Sanfilippo Anthony J, Jue J, Turek Michele A, Robinson Trevor I, Moher D. 2003. A randomized trial of aspirin on the risk of embolic events in patients with infective endocarditis. Journal of the American College of Cardiology 42(5):775-780.	Clinical Trial	Aspirin 325 mg/day Placebo	There was a trend toward a higher incidence of bleeding (major and minor episodes) in patients taking aspirin (28.8%) versus placebo (14.5%; p=0.075), resulting in an odds ratio of 1.92 (95% CI: 0.76-4.86).
CAPRIE Steering Committee (Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events). 1996. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet 348(9038):1329-1339.  Harker LA, Boissel JP, Pilgrim AJ, Gent M. 1999. Comparative safety and tolerability of clopidogrel and aspirin: results from CAPRIE. CAPRIE Steering Committee and Investigators. Clopidogrel versus aspirin in patients at risk of ischaemic events. Drug Safety 21(4):325-335.	Clinical Trial (CAPRIE)	Aspirin 325 mg/day Clopidogrel 75 mg/day	Any bleeding disorder occurred in 9.27% of the clopidogrel-treated patients and 9.28% of patients receiving aspirin (p=NS), and intracranial hemorrhage occurred in 0.35% of the clopidogrel-treated patients and 0.49% of patients receiving aspirin (p=NS). However, gastrointestinal hemorrhages occurred in 1.99% of patients treated with clopidogrel and 2.66% of those treated with aspirin (p<0.05).
Creager MA. 1998. Results of the CAPRIE trial: efficacy and safety of clopidogrel. Vascular medicine 3(3):257-260.	Clinical Trial (CAPRIE)	Aspirin 325 mg/day Clopidogrel 75 mg/day	In addition to the bleeding data presented by the CAPRIE Steering Committee, this publication reported that there were 30% more hospitalizations for gastrointestinal bleeding in the aspirin-treated group than in the clopidogrel-treated group.

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Reference	Type of Article	Aspirin Doses/Treatment Groups	Bleeding Data
Bhatt DL, Hirsch AT, Ringleb PA, Hacke W, Topol EJ. 2000. Reduction in the need for hospitalization for recurrent ischemic events and bleeding with clopidogrel instead of aspirin. American Heart Journal 140(1):67-73.	Clinical Trial (CAPRIE)	Aspirin 325 mg/day Clopidogrel 75 mg/day	<p>There was a statistically significant decrease in re-hospitalizations for any ischemic or bleeding event for clopidogrel compared with aspirin. An examination of the actual number of re-hospitalizations (including subjects with multiple hospitalizations) for ischemic events or bleeding revealed 1502 re-hospitalizations (95 per 1000 patient years) in the clopidogrel group versus 1673 (106 per 1000 patient years) in the aspirin group (p=0.010).</p> <p>There was a 12.6% rate of vascular death, stroke, MI, or hospitalization for an ischemic or bleeding event in the clopidogrel group per year versus a 13.7% event rate in the aspirin group (p=0.011). This translates to a relative risk reduction of 7.9% (95% CI: 1.9-13.7). Thus 91 subjects would need to be treated for 1 year with clopidogrel instead of aspirin to prevent one event.</p>
Bhatt DL, Marso SP, Hirsch AT, Ringleb PA, Hacke W, Topol EJ. 2002. Amplified benefit of Clopidogrel versus Aspirin in patients with diabetes mellitus. American Journal of Cardiology 90(6):625-628.	Clinical Trial (CAPRIE)	Aspirin 325 mg/day Clopidogrel 75 mg/day	<p>The number of re-hospitalizations for diabetics in the CAPRIE study due to any ischemic or bleeding event was significantly lower with clopidogrel (13.3%) than with aspirin (15.6%), representing a relative risk reduction of 14.5% (95% CI, 0.2 to 26.7, p=0.047). The number of re-hospitalizations for diabetics in the CAPRIE study due to any bleeding event alone was also significantly lower with clopidogrel (1.8%) than with aspirin (2.8%), representing a relative risk reduction of 37.0% (95% CI, 3.8 to 58.7, p=0.031).</p>

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Reference	Type of Article	Aspirin Doses/Treatment Groups	Bleeding Data
Johnson WC, Williford WO. 2002. Benefits, morbidity, and mortality associated with long-term administration of oral anticoagulant therapy to patients with peripheral arterial bypass procedures: a prospective randomized study. <i>Journal of Vascular Surgery</i> 35(3):413-421.	Clinical Trial	Aspirin 325 mg/day Aspirin 325 mg/day + Warfarin INR 1.4-2.8	During the 848 patient years of warfarin therapy, there were six hemorrhagic deaths (0.007/treatment year). There were 133 deaths (31.8%) in the warfarin + aspirin group (combined prosthetic and vein bypass) compared with 95 deaths (23.0%) in the aspirin combined group (RR: 1.41; 95% CI: 1.09-1.84) (p=0.01). Four subjects sustained lethal intracranial hemorrhage. Thirty-five subjects in the warfarin + aspirin group and 15 subjects in the aspirin group had major hemorrhagic complications (p=0.02). Transfusions were administered more frequently in the warfarin + aspirin group (24 versus 11 subjects). Medical intervention for a bleeding problem occurred more frequently in subjects treated with warfarin (62 versus 29). Minor events such as epistaxis, bruising, and minor bleeding also occurred more frequently in the subjects treated with warfarin (199 versus 112).
Leon MB, Baim DS, Popma JJ, Gordon PC, Cutlip DE, Ho KK, Giambartolomei A, Diver DJ, Lasorda DM, Williams DO, Pocock SJ, Kuntz RE. 1998. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. <i>New England Journal of Medicine</i> 339(23):1665-1671.	Clinical Trial	Aspirin 325 mg/day Aspirin 325 mg/day + Warfarin (to INR 2.0-2.5) + Heparin i.v. (dosed to an aPTT of 40 to 60 seconds) Aspirin 325 mg/day + Ticlopidine 500 mg/day	Hemorrhagic complications occurred in 10 patients (1.8%) who received aspirin alone, 34 (6.2%) who received aspirin and heparin/warfarin, and 30 (5.5%) who received aspirin and ticlopidine (p<0.001 for the comparison of all three groups).
Matias-Guiu J, Ferro Jose M, Alvarez-Sabin J, Torres F. 2003. Comparison of triflusal and aspirin for prevention of vascular events in patients after cerebral infarction: the TACIP Study: a randomized, double-blind, multicenter trial. <i>Stroke</i> 34(4):840-848.	Clinical Trial	Aspirin 325 mg/day Triflusal 600 mg/day	Patients treated with aspirin compared with triflusal showed a significantly higher overall incidence of hemorrhagic adverse events (25.2% versus 16.7%; odds ratio, 0.76; 95% CI, 0.67 to 0.86; p<0.001) as well as hemorrhagic adverse events related to the study medication (21.8% versus 13.7%; odds ratio, 0.74; 95% CI, 0.65 to 0.85; p<0.001). The incidence of minor bleeding was also significantly higher in the aspirin group (22.1%) than in the triflusal group (15.2%) (p<0.001).

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<p>Mohr JP, Thompson JL, Lazar RM, Levin B, Sacco RL, Furie KL, Kistler JP, Albers GW, Pettigrew LC, Adams HP, Jackson CM, Pullicino P. 2001. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. <i>New England Journal of Medicine</i> 345(20):1444-1451.</p>	<p>Clinical Trial</p>	<p>Aspirin 325 mg/day Warfarin INR 1.4-2.8</p>	<p>The rates of major hemorrhage were low and similar between treatment groups (2.22 per 100 patient-years in the warfarin group and 1.49 per 100 patient-years in the aspirin group).</p>
<p>Sarac TP, Huber TS, Back MR, Ozaki CK, Carlton LM, Flynn TC, Seeger JM. 1998. Warfarin improves the outcome of infrainguinal vein bypass grafting at high risk for failure. <i>Journal of Vascular Surgery</i> 28(3):446-457.</p>	<p>Clinical Trial</p>	<p>Aspirin 325 mg/day Aspirin: 325 mg/day + Warfarin INR 2 to 3</p>	<p>The incidence rates of GI (11% versus 3%), central nervous system (4% versus 3%), and genitourinary (0% versus 9%) hemorrhage were not significantly different between the aspirin and aspirin + warfarin groups, respectively.</p>
<p>SPAF Investigators. 1996. Bleeding during antithrombotic therapy in patients with atrial fibrillation. <i>Archives of Internal Medicine</i> 156(4):409-416.</p>	<p>Retrospective Study</p>	<p>Aspirin 325 mg/day Warfarin (approximate INR=2.0 to 4.5)</p>	<p>The rates of all major bleeding were significantly higher in those assigned to warfarin (2.3% per year; 95% CI, 1.7 to 3.2) compared with the aspirin group (1.1% per year; 95% CI, 0.7 to 1.8) (RR, 2.1; 95% CI, 1.1 to 3.1; p=0.02). Intracranial hemorrhage occurred at 0.9% per year (95% CI: 0.5-1.5) with warfarin and 0.3% per year (95% CI: 0.1-0.8 with aspirin (RR, 2.4; p=0.08). The risks of all major hemorrhage (RR, 2.6; p=0.009) and intracranial hemorrhage (RR, 3.2; p=0.05) were greater in those older than 75 years versus younger patients.</p>

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<b>Reference</b>	<b>Type of Article</b>	<b>Aspirin Doses/Treatment Groups</b>	<b>Bleeding Data</b>
SPAF III Writing Committee (Stroke Prevention in Atrial Fibrillation). 1998. Patients with nonvalvular atrial fibrillation at low risk of stroke during treatment with aspirin: Stroke Prevention in Atrial Fibrillation III Study. Journal of the American Medical Association 279(16):1273-1277.	Clinical Trial	Aspirin 325 mg/day	Bleeding data, presented as number of events, annualized rates in % (95% CI): Intracranial hemorrhage: 2 events, 0.1% (0.03-0.5); one of these events immediately followed fibrinolytic therapy given for acute myocardial infarction All strokes (ischemic and hemorrhagic): 38 events, 2.2% (1.6-3.0) Major non-CNS hemorrhage: 11 events, 0.6% (0.3-1.1); 4 of these 11 events occurred in patients receiving warfarin following withdrawal from aspirin therapy; of the remaining 7 events, 6 were gastrointestinal hemorrhages
Obialo CI, Conner AC, Lebon LF. 2003. Maintaining patency of tunneled hemodialysis catheters - Efficacy of aspirin compared to warfarin. Scandinavian Journal of Urology and Nephrology 37(2):172-176.	Clinical Trial	Aspirin 325 mg/day Warfarin (INR of 2-3) Control (Subjects receiving neither aspirin or warfarin)	All the GI bleeding complications occurred among patients in the aspirin or warfarin groups (p=0.02, chi squared=7.9). Five of the patients had hematemesis from gastric erosions and gastritis while two had hematochezia from bleeding arteriovenous malformations. The incidence of bleeding did not differ significantly between the aspirin and warfarin treatment groups. Patients who had GI bleeding were older than those with no bleeding complications (63 ± 11 versus 56 ± 16 years, p=0.2). However, among aspirin users the bleeding risk associated with age was 1.14 (CI 1.0 - 1.3, p=0.008). Although GI bleeding complications occurred more frequently in patients on aspirin, the relative risk of bleeding in association with aspirin usage was 0.71 (CI 0.11 - 4.4, p=0.7); however, the association between GI bleeding and diabetes showed a non-significant positive association (Cramer's V=0.3, p=0.1). Six out of seven patients (86%) with GI bleeding had diabetes. One of the patients on warfarin had a fall and developed a subdural hematoma that was uneventfully evacuated.

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<p>WASID Study Group (Warfarin-Aspirin Symptomatic Intracranial Disease). 1998. Prognosis of patients with symptomatic vertebral or basilar artery stenosis. <i>Stroke</i> 29(7):1389-1392.</p>	<p>Clinical Trial</p>	<p>Aspirin (dose not specified; 21 of 26 patients were treated with at least 325 mg/day.) Warfarin (dose not specified; warfarin therapy was typically adjusted to maintain prothrombin times in the range of 1.2 to 1.6 times control)</p>	<p>Hemorrhagic complications occurred in 7 patients on warfarin (5 minor, 2 major: 1 fatal intracerebral hemorrhage and 1 fatal gastrointestinal hemorrhage). The rates of both minor and major hemorrhagic complications were 11 per 100 patient-years of follow-up in the warfarin group compared with 0 per 100 patient-years of follow-up in the aspirin group (p&lt;0.01). The rate of major hemorrhagic complications in the warfarin group was 3.2 per 100 patient-years of follow-up.</p>
<p>Gorelick Philip B, Richardson D, Kelly M, Ruland S, Hung E, et al. 2003. Aspirin and ticlopidine for prevention of recurrent stroke in black patients: a randomized trial. <i>Journal of the American Medical Association</i> 289(22):2947-2957.</p>	<p>Clinical Trial</p>	<p>Aspirin 650 mg/day Ticlopidine 500 mg/day</p>	<p>Major gastrointestinal tract hemorrhage was slightly more common in aspirin-treated subjects (0.9% versus 0.4%) but the difference between treatment groups was not significant. Gastrointestinal tract hemorrhage requiring premature discontinuation from the study was also slightly more common among subjects receiving aspirin than ticlopidine (0.6% versus 0.2%) but the difference was not significant.</p>
<p>Lanas A, Bajador E, Serrano P, Arroyo M, Fuentes J, Santolaria S. 1998. Effects of nitrate and prophylactic aspirin on upper gastrointestinal bleeding: A retrospective case-control study. <i>Journal of International Medical Research</i> 26(3):120-128.</p>	<p>Retrospective Case-Control</p>	<p>Cases: N=159 (non-aspirin NSAID use), N=134 (aspirin use ≥500 mg), N=93 (low-dose aspirin use &lt;500 mg/day, 76 of 93 cases used 200 mg/day), N=20 (low-dose aspirin + nitrate use), N=35 (nitrates), N=79 (anti-secretory drugs)  Controls: N=68 (non-aspirin NSAID use), N=11 (aspirin use ≥500 mg), N=84 (low-dose aspirin use, &lt;500 mg/day, 58 of 84 controls used 200 mg/day), N=28 (low-dose aspirin + nitrates), N=85 (nitrates), N=138 (anti-secretory drugs)</p>	<p>Logistic regression analysis identified low-dose aspirin as an independent risk factor for gastrointestinal bleeding (Odds ratio [OR], 2.39; 95% CI, 1.8-3.3; p&lt;0.00001). The combination of low-dose aspirin and nitrates was not associated with an increased risk in bleeding (p=NS).</p>

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<p>Lanas A, Bajador E, Serrano P, Fuentes J, Carreno S, Guardia J, Sanz M, Montoro M, Sainz R. 2000. Nitrovasodilators, low-dose aspirin, other nonsteroidal antiinflammatory drugs, and the risk of upper gastrointestinal bleeding. New England Journal of Medicine 343(12):834-839.</p>	<p>Case Study</p>	<p>Patients (N=1122)                      Controls (N=2231)                      Collected as part of the results:                      Any nonsteroidal anti-inflammatory drug other than low-dose aspirin (N=520 patients; N=229 controls)                      Low-dose (<math>\leq 300</math> mg/day) aspirin alone (N=120 patients; N=206 controls)                      Nitrovasodilators (N=60 patients; N=137 controls)                      Antisecretory medication (N=135 patients; N=206 controls)</p>	<p>In the week before hospital admission, 520 (46.3%) of the patients with bleeding had taken a nonsteroidal anti-inflammatory drug other than low-dose aspirin, 120 (10.7%) had taken low-dose aspirin, 60 (5.3%) a nitrovasodilator, and 135 (12.0%) an antisecretory agent. Adjusting for age, sex, and clinical risk factors, the use of a nonsteroidal anti-inflammatory drug other than low-dose aspirin was independently associated with an increased risk of bleeding from a peptic ulcer (OR, 7.4; 95% CI, 4.5 to 12.0; <math>p &lt; 0.001</math>), as was the use of low-dose aspirin alone (OR, 2.4; 95% CI, 1.8 to 3.3; <math>p &lt; 0.001</math>). The use of a nitrovasodilator was associated with a decreased risk of bleeding (OR, 0.6; 95% CI, 0.4 to 0.9), as was antisecretory therapy (OR, 0.6; 95% CI, 0.4 to 0.8). The use of a nitrovasodilator was independently associated with a decreased risk of bleeding in patients taking any type of nonsteroidal anti-inflammatory drug other than aspirin (OR, 0.3; 95% CI, 0.1 to 0.9), patients taking aspirin at any dose (OR, 3.1; 95% CI, 1.7 to 05.9; <math>p &lt; 0.001</math>), and patients taking low-dose aspirin only (OR, 0.5; 95% CI, 0.2 to 0.9). Antisecretory therapy also decreased the risk of bleeding in these patient populations.</p>