

ATTACHMENT 3

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Summary of Aspirin Efficacy Information

SUMMARY OF ASPIRIN EFFICACY INFORMATION

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List of Abbreviations

ACS	acute coronary syndromes
ARR	absolute risk reduction
ATC	Antithrombotic Trialists' Collaboration
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
CURE	Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial
ECG	electrocardiogram
ESPS	European Stroke Prevention Study
FDA	Food and Drug Administration
GP IIb/IIIa	glycoprotein IIb/IIIa receptor
HR	hazard ratio
ISIS-2	Second International Study of Infarct Survival
MI	myocardial infarction
N	number
ns	not specified
NS	not significant
NSAIDs	non-steroidal anti-inflammatory drugs
PAF	primary atrial fibrillation
PCI	percutaneous coronary intervention
PTCA	percutaneous transluminal coronary angioplasty
PVD	peripheral vascular disease
QOD	every other day
RR	relative risk
RRR	relative risk reduction
SALT	Swedish Aspirin Low-dose Trial
SAPAT	Swedish Angina Pectoris Aspirin Trial
SE	standard error
TIA	transient ischemic attack
TIMI	Thrombolysis in Myocardial Infarction

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 and efficacy 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.”

To expedite the approval process for aspirin in the treatment of acute MI, FDA published a Notice of Proposed Rulemaking on June 13, 1996 [61 FR 30002]. Regarding the findings from the Second International Study of Infarct Survival (ISIS-2) study (ISIS-2 Collaborative Group, 1988), that proposal [61 FR 30006] stated in part:

“The Agency has determined that the ISIS-2 study supports the use of aspirin at a dose of 162.5 mg/day, started as soon as possible after an infarction and continued for at least 30 days, to reduce the risk of fatal and non-fatal cardiovascular and cerebrovascular events in subjects with a suspected MI.”

The proposal [61 FR 30006] continues, *“After the 30-day recommended treatment with aspirin for acute MI, physicians should consider further therapy based on the labeling for dosage and administration of aspirin to prevent recurrent MI (reinfarction).”*

In the October 23, 1998 Final Rule [63 FR 56802], FDA codified the acute MI indication and refined its evaluation of the dose needed for secondary prevention as new data and analyses were made available. FDA considered data from the Antiplatelet Trialists' Collaboration (1994), the United Kingdom-TIA study (UK-TIA Study Group, 1988), the Danish Very Low Dose study (Boysen et al., 1988), the Swedish Aspirin Low-dose Trial (SALT Collaborative Group, 1991), European Stroke Prevention Study-2 (ESPS-2) for TIA or stroke prevention (Diener et al., 1996), and the Swedish Angina Pectoris Aspirin Trial (SAPAT) in chronic stable angina (Juul-Moller et al., 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."

Given that the SAPAT study used a dose of 75 mg/day for cardiovascular indications, FDA also recommended that the dose range for secondary prevention of MI be changed from 300-325 mg/day to 75-325 mg/day.

Furthermore, in the 1998 Final Rule, FDA 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."

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® (pravastatin sodium). This product, PRAVIGARD™ 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®. FDA's approval of PRAVIGARD™ 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™ PAC review.

McNeil's Petition proposes to modify the current monograph professional labeling (21CFR 330.11) based on data that has become available since the 1998 Final Rule. 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 ≤ 150 mg/day versus > 150 mg/day follows.

1.2. Efficacy Conclusions Supported

Data from the publications discussed in this aspirin efficacy summary are consistent with the FDA's previous conclusions [63 FR 56806]:

- Doses of aspirin within the range of 50–150 mg daily are equally effective for the prevention of serious vascular events (non-fatal MI, non-fatal stroke, and vascular death).
- The recommended aspirin dose for chronic administration is 50–150 mg daily, which is safe and effective for prevention of recurrent MI, ischemic stroke and TIA and for treatment of unstable angina pectoris or chronic stable angina pectoris. Aspirin is recommended for patients who undergo revascularization procedures, such as coronary artery bypass grafting, 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 EFFICACY SUMMARY FORMAT

A discussion of the general methodology used to identify articles included in this aspirin efficacy summary is presented in Section 3. This includes a description of the initial literature search that was performed, as well as a description of the criteria that were developed to identify and group articles containing relevant efficacy data. Section 3 also includes a brief description of the articles in each publication grouping and the order of presentation.

In Section 4, information on study design and patient populations, including study objectives, key inclusion and exclusion criteria, patient characteristics (age, sex, and if available, relevant medical conditions at study entry), efficacy endpoints, and a brief description of statistical methodology is presented. In Section 5, a summary of subject accountability and extent of exposure to aspirin is presented, including the number of patients exposed to specific doses and duration of exposure.

Efficacy data from each of the publication groupings are presented in Section 6. In publications where the primary focus included comparisons between another antiplatelet medication plus aspirin versus placebo plus aspirin, only data for placebo plus aspirin (i.e., aspirin alone) is presented.

A publication that substantiates the reduced antiplatelet effect of aspirin when co-administered with ibuprofen is presented and discussed in Section 7.

Finally, Section 8 provides a summary of efficacy and a discussion of overall conclusions, and Section 9 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 MYOCARDIAL 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	2791934	(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	2796554	(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 GASTROINTESTINALDISEASES 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	2796554	(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

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 summarized in the same way and used for safety information purposes if they captured data on bleeding events associated with aspirin. Otherwise, these articles were considered not relevant and were not summarized.

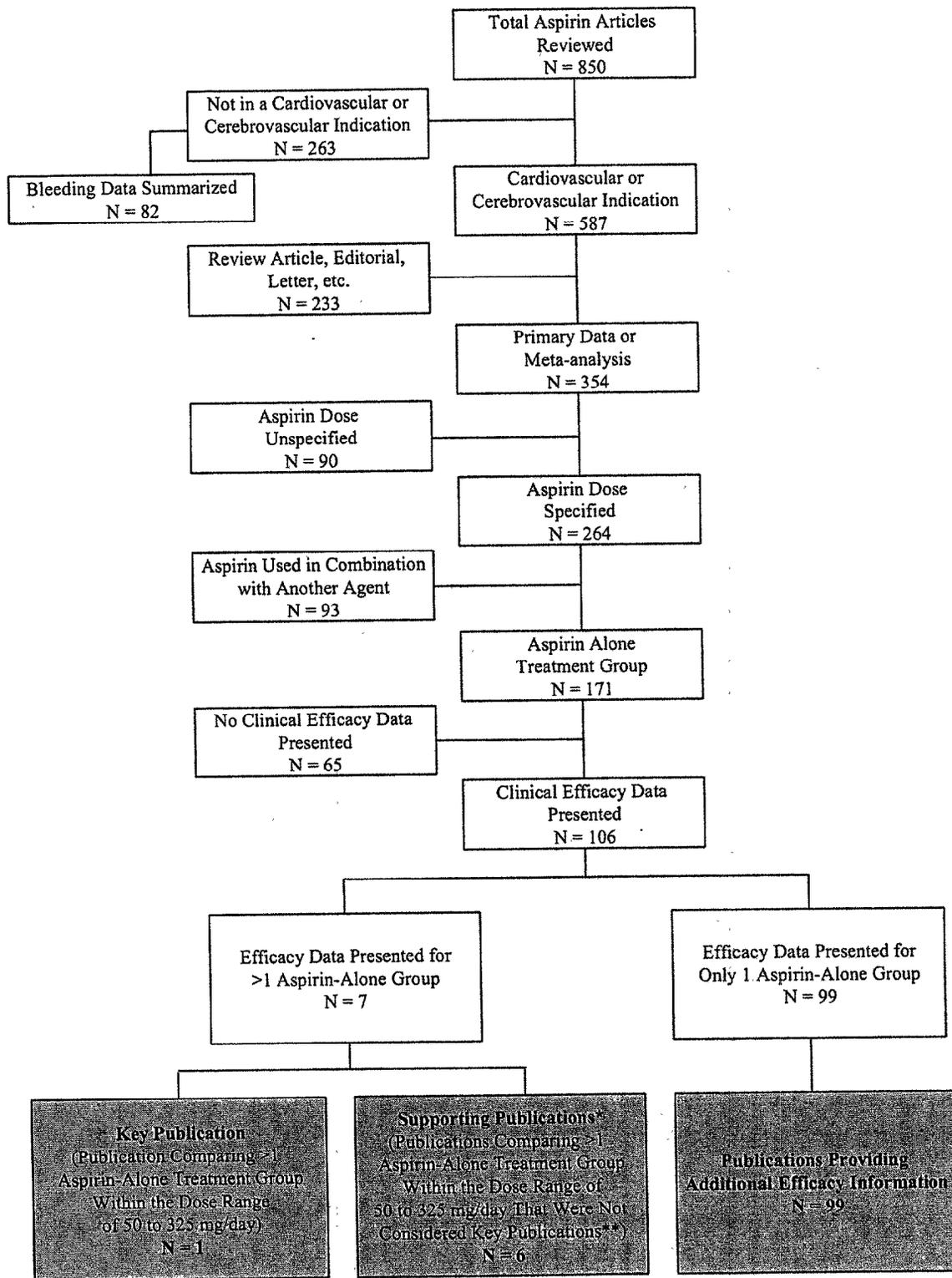
For articles that involved the use of aspirin in a cardiovascular and/or cerebrovascular indication that were considered to be review articles, editorials, letters, and commentaries, etc., the following information was summarized:

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

3.2. Efficacy Summary Methodology

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

Figure 1 Flowchart of Literature Search Methodology – Efficacy Data



* The Supporting Publications grouping also includes publications that did not compare >1 aspirin-alone treatment group within the dose range of 50 to 325 mg/day.

** These publications were not considered Key Publications primarily due to study design issues.

Of the 850 articles reviewed, a total of 587 described 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 efficacy outcome information, resulting in a total of 106 articles. Articles reporting no efficacy data or reporting only efficacy findings based on laboratory assessments are not included in this aspirin efficacy summary (65 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 aspirin efficacy summary, we sought to further identify the aspirin dose(s) within the range of 50–325 mg/day that confer the most favorable efficacy profile for aspirin.

The 106 articles included in this ISE are classified into three major groupings. The first two groupings include articles that reported efficacy 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 1 article summarizing the results of a meta-analysis in which direct comparisons of efficacy 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 Publication). This grouping forms the basis of this ISE and the proposed labeling change in the recommended aspirin dose, from 50 - 325 mg/day to 75 -199 mg/day. The second grouping (i.e., Supporting Publications) is comprised of 6 articles summarizing the results of clinical trials or meta-analyses that either (1) compared efficacy outcome data for at least two aspirin-alone treatment groups that fell within the dose range of 50 - 325 mg/day but, due to study design issues, were not considered Key Publications, or (2) did not compare efficacy outcome data between at least two aspirin-alone treatment groups that fell within the dose range of interest. Finally, the third grouping is comprised of 99 articles summarizing the results of clinical trials, meta-analyses, or other studies in which efficacy outcome data were presented for a single aspirin-alone treatment group, thereby not allowing for direct comparisons between aspirin doses (i.e., Publications Providing Additional Efficacy Information). The inclusion of this third publication grouping in this submission serves to ensure that all aspirin-related efficacy 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.

3.2.1. Key Publication

The Key Publication presenting efficacy data relevant to the proposed labeling change in the recommended aspirin dose, from 50 - 325 mg/day to 75 - 199 mg/day, is the Antithrombotic Trialists' Collaboration (2002), a large meta-analysis in which direct comparisons of efficacy outcome data were made between at least two aspirin-alone treatment groups that fell within the dose range of 50 - 325 mg/day. Results from the ATC form the basis of this ISE. This meta-analysis included a total of 212,000 patients from 287 randomized trials who were at increased risk of occlusive vascular events. Aspirin was the most widely studied antiplatelet drug in this analysis. Comparisons of different aspirin doses comprise some of the most convincing data to date that low daily doses of aspirin (75 - 150 mg/day) are at least as effective as higher daily doses (>200 mg/day) in reducing the incidence of non-fatal MI, non-fatal stroke, and vascular death. Study features of the ATC meta-analysis are presented in Table 1.

Table 1 Table of Studies – Key Publication

Reference	Total Subjects	Patient Population	Treatment Groups (N)	Treatment Duration	Type of Article
Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. British Medical Journal. 2002;324(7329) 71-86.	212,000	Patients at high risk of occlusive vascular events	Antiplatelet vs. control (135,000) Different antiplatelet regimens (77,000) Aspirin dose: (<75 mg to 1500 mg/day) ¹	Not specified ²	Meta-analysis ³

1. Doses of antiplatelet therapies and controls used in individual studies included in the ATC meta-analysis were not specified. Exposure data for each trial included in the ATC meta-analysis can be found at www.bmj.com. Of note, aspirin was the most widely studied antiplatelet drug.
2. Duration of treatment of antiplatelet therapies used in studies included in the ATC meta-analysis was not specified in the article. Exposure data for each trial included in the ATC meta-analysis can be found at www.bmj.com. Of note, trials that included oral antiplatelet regimens were eligible for inclusion in the meta-analysis only if they had assessed >1 day of treatment. Trials of parenteral administration of antiplatelet regimens of any duration were included.
3. Only studies that were believed to have used a randomization method and that contained two randomized groups that differed only with respect to the antiplatelet comparison of interest were included in the ATC meta-analysis. Details regarding study design for each trial included in the ATC meta-analysis can be found at www.bmj.com.

3.2.2. Supporting Publications

The Supporting Publications grouping is comprised of 6 articles that either (1) compared efficacy outcome data for at least two aspirin-alone treatment groups that fell within the dose range of 50 to 325 mg/day but, due to study design issues, were not considered Key Publications, or (2) did not compare efficacy outcome data between at least two aspirin-alone treatment groups that fell within the dose range of interest. Nonetheless, since these publications present efficacy data for more than one aspirin-alone treatment group, they allow for a dose-by-dose comparison of efficacy. Table 2 summarizes the six publications included in this study grouping, as well as the order of presentation throughout the efficacy summary.

Table 2. Table of Studies – Supporting Publications				
Reference	Total Subjects	Patient Population	Treatment Groups (N)	Treatment Duration
Clinical Trials				
Posada IS, Barriaes V. Alternate-day dosing of aspirin in atrial fibrillation. American Heart Journal. 1999;138(1pt.1):137-143.	285	Patients with PAF	Aspirin 125 mg/day (104) Aspirin 125 mg QOD (90) Placebo (91)	Evaluation period was 550 days (mean)
Taylor DW, Barnett HJ, 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 (ACE) Trial Collaborators. Lancet. 1999;353(9171):2179-2184.	2804	Patients undergoing carotid endarterectomy	Aspirin 81 mg/day (698) ¹ Aspirin 325 mg/day (697) ¹ Aspirin 650 mg/day (703) ¹ Aspirin 1300 mg/day (706) ¹	Aspirin initiated prior to surgery and continued for 3 months post-surgery
Peters RJG, Mehta SR, Fox KAA, Zhao F, Lewis BS, Kopecky SL, Diaz R, Commerford PJ, Valentin V, Yusuf S. 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. Circulation. 2003;108(14):1682-1687.	12,562	Patients with ACS without ST-segment elevation	Aspirin ≤100 mg/day + Clopidogrel vs. Aspirin alone (5320) ² Aspirin 101-199 mg/day + Clopidogrel vs. Aspirin alone (3109) ² Aspirin ≥200 mg/day + Clopidogrel vs. Aspirin alone (4110) ² Aspirin dose: 75-325 mg/day; median: 150 mg/day ³ Clopidogrel: 300 mg loading dose followed by 75 mg/day	3 to 12 months (mean: 9 months) ⁴

Table 2. Table of Studies – Supporting Publications				
Reference	Total Subjects	Patient Population	Treatment Groups (N)	Treatment Duration
Topol EJ, Easton D, Harrington RA, Amarenco P, Califf RM, Graffagnino C, Davis S, Diener H-C, Ferguson J, Fitzgerald D, Granett J, Shuaib A, Koudstaal PJ, Theroux P, Van de Werf F, Sigmon K, Pieper K, Vallee M, Willerson JT. 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 coronary or cerebrovascular disease	Lotrafiban + Aspirin (4600) Placebo + Aspirin (4590) Aspirin: 75-325 mg/day ³ Lotrafiban: 30 or 50 mg BID ⁵	Maximum of 2 years
Meta-Analyses				
Algra A, Van Gijn J. Aspirin at any dose above 30 mg offers only modest protection after cerebral ischaemia. <i>Journal of Neurology, Neurosurgery and Psychiatry</i> . 1996;60(2):197-199.	6171 ⁶	Patients who have had a TIA or non-disabling stroke	Aspirin ≤100 mg/day (1661) ⁷ Aspirin 300 mg/day (1620) ⁷ Aspirin ≥900 mg/day (3704) ⁷	ns
Johnson ES, Lanes SF, Wentworth CE, Satterfield MH, Abebe BL, Dicker LW. A meta-regression analysis of the dose-response effect of aspirin on stroke. <i>Archives of Internal Medicine</i> . 1999;159(11):1248-1253.	9629 ⁶	Patients who have had a recent TIA or stroke	Aspirin 50-1500 mg/day (5228) Placebo (4401)	Average follow-up 32 months

Abbreviations: TIA: transient ischemic attack; ACS: acute coronary syndrome; PAF: primary atrial fibrillation; QOD: every other day; CAD: coronary artery disease; BID: twice daily; ns: not specified

1. Patients in all 4 treatment groups also received placebo.
2. Patients in the CURE study were randomized to receive clopidogrel or placebo plus aspirin. In the analysis by Peters et al. included in this table, patients from the CURE study were divided into treatment groups by aspirin dose (≤100, 101-199, and ≥200 mg/day) (total of 6 treatment groups). The number of patients were only given for the combined treatment groups at each aspirin dose (e.g., clopidogrel + aspirin ≤100 mg/day vs. aspirin alone). Number of patients for the aspirin alone treatment groups were not included in the article.
3. The exact dose of aspirin patients received was determined by the Investigator.
4. 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.
5. The dose of lotrafiban was dependent on age and creatinine clearance.
6. Data from the following studies were included in the meta-analyses by both Algra and Van Gijn, 1996 and Johnson et al., 1999: SALT (1991), UK-TIA (1988, 1991), Danish Cooperative Study (1983), AITIA (1977), Canadian Cooperative Study (1978), Reuther and Dorndorf (1978), the Swedish Cooperative Study (1987), and AICLA (1983).
7. Number of patients represents the combined number receiving aspirin or control.

For this publication grouping, efficacy data from publications of four clinical trials are presented first in each section of the ISE followed by data from two small meta-analyses.

The publication of the placebo-controlled study by Posada et al. (1999), which examined the protective effects of low-dose aspirin therapy against cerebrovascular disease when taken daily versus every other day, is presented first. This publication was not considered a 'Key Publication' because, although this study examined the effect of two aspirin dose regimens (every day vs. every other day), the 125 mg dose was used in both regimens. In addition, several study design limitations, including small sample size due to early termination of the study and lower than expected incidence of stroke, confound the results of this study.

The second publication in this grouping is that of a controlled trial by Taylor et al. (1999), which investigated the relationship between lower versus higher daily doses of aspirin and perioperative complication rates in patients undergoing carotid endarterectomy. Although this trial compared aspirin doses of 81, 325, 650, and 1300 mg/day, the primary analysis of this study was the comparison between the two low-dose groups combined (81 and 325 mg/day) versus the two high-dose groups combined (650 and 1300 mg/day). Comparisons between the 81 and 325 mg/day doses and between the 650 and 1300 mg/day doses were performed as secondary analyses, but the data were not presented in the publication.

In the remaining two clinical trial publications, which include a post-hoc analysis of the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial (Peters et al., 2003) and a summary of efficacy data from the Blockade of the Glycoprotein IIb/IIIa Receptor to Avoid Vascular Occlusion (BRAVO) trial (Topol et al., 2003), aspirin combined with another antiplatelet medication (CURE) or a glycoprotein IIb/IIIa antagonist (BRAVO) was the primary comparison of interest. In both trials, control groups included patients who received aspirin alone, allowing the effect of a range of aspirin doses on cardiovascular and cerebrovascular outcomes to be evaluated. However, subjects enrolled in both the CURE and the BRAVO trials were not randomized to different aspirin doses, but rather received aspirin at a dose determined by the Investigator, thereby limiting their usefulness in assessing the efficacy of aspirin.

Finally, efficacy data from publications of two meta-analyses are presented. In the analysis presented by Algra and van Gijn (1996), the effect of different aspirin doses on the composite endpoint of vascular death, stroke, or MI was evaluated using data from patients in 10 randomized studies, most of which were placebo-controlled. Johnson et al. (1999) performed a similar analysis using a similar patient population from 11 randomized, placebo-controlled studies to evaluate the dose-response relationship between aspirin and stroke. It should be noted that significant overlap in trials included in the two meta-analyses exists including data from SALT (1991), UK-TIA (1988, 1991), Danish Cooperative Study (1983), Aspirin in Transient Ischemic Attacks (1977), Canadian Cooperative Study (1978), Reuther and Dorndorf (1978), the Swedish Cooperative Study (1987), and Bousser et al. (1983).

Furthermore, the majority of trials included in these two analyses were also included in the much larger ATC meta-analysis and are, therefore, considered to be "Supporting Publications."

3.2.3. Publications Providing Additional Efficacy Information

The publications providing additional efficacy information include 99 articles summarizing the results of primary data from a clinical trial, meta-analysis, or other study in which efficacy data are presented for a single aspirin-alone treatment group. These articles describe a wide range of studies including clinical trials, meta-analyses, case studies, retrospective studies, population studies, follow-up studies and observational studies. 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 efficacy data from the publications included in this grouping is provided in Section 6.3 and a tabular presentation of the efficacy data is provided in Appendix 2 of this ISE. However, it is important to note that meaningful comparisons of efficacy across the different publications are difficult, primarily due to differences in the methods of deriving and presenting efficacy data across studies (e.g., incidence rates, relative risks, annualized event rates, odds ratios, hazard ratios, etc.), differences in study-specific endpoints (e.g., a variety of individual and composite endpoints), and differences in treatment durations.

The inclusion of this publication grouping in this submission serves to ensure that all aspirin-related efficacy 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 OF RELEVANT PUBLISHED STUDIES AND STUDY POPULATION CHARACTERISTICS

This section provides a brief overview of publications included in this ISE in terms of study design characteristics (patient population, study objectives, inclusion and exclusion criteria, treatment groups) efficacy endpoints, and statistical methodology. All descriptions were derived directly from the methods section of each publication.

4.1. Key Publication

4.1.1. Antithrombotic Trialists' Collaboration, 2002

The Antithrombotic Trialists' Collaboration (2002) meta-analysis was based on data from 212,000 patients in 287 randomized studies. The primary objective of the analysis was to determine the effects of antiplatelet therapy among patients at high annual risk (over 3% a

year) of vascular events based on evidence of pre-existing disease (previous occlusive event or predisposing condition).

Relevant trials were identified by searching electronic databases (MEDLINE™, EMBASE™, DERWENT™, SCISEARCH™, and BIOSIS™) and the trial registers of the Cochrane Stroke and Peripheral Vascular Disease Groups. Trials were also identified by manual searching of journals, abstracts, and meeting proceedings, as well as reference lists of trials and review articles, and by inquiry among colleagues. The goal was to identify all trials, published or otherwise, that were available by September 1997 and that compared an antiplatelet regimen with a control or a different antiplatelet regimen. All studies included in the analysis were believed to have used a randomization method that precluded prior knowledge of the next treatment to be allocated and were "unconfounded" (i.e., contained two randomized groups that differed only with respect to the antiplatelet comparison of interest). Trials involving oral antiplatelet regimens were eligible only if they had assessed more than one day of treatment, but trials of parenteral antiplatelet regimens of any duration were included.

Details about method of randomization, blinding of treatment allocation, duration of treatment, and duration of follow-up (if different) were obtained for all potentially eligible trials. In addition, a tabular summary of the number of patients originally allocated to each treatment group (without any post-randomization exclusions) and the number of patients experiencing particular outcomes during the scheduled follow-up period were obtained.

For trials that had randomized ≥ 200 patients, individual patient data (baseline characteristics, dates of randomization, follow-up, and any vascular events that had occurred) were collected.

Analyses were based on data from 197 studies involving 135,000 patients where antiplatelet therapy was compared to a non-antiplatelet control group, and from 90 studies involving 77,000 patients where comparisons were made between different antiplatelet therapies. Aspirin was the most widely studied antiplatelet drug. The primary measure of outcome was a "serious vascular event" (i.e., non-fatal myocardial infarction, non-fatal stroke, or death from a vascular or unknown cause [most deaths in high risk patients are likely to be due to vascular causes]). Deaths were divided into those with a vascular cause (cardiac, cerebrovascular, venous thromboembolic, hemorrhagic, other vascular, or unknown cause) and those that were considered to be definitely non-vascular in nature. Strokes were subdivided into intracranial hemorrhages (intracerebral, subdural, subarachnoid, and extradural hemorrhages) and strokes of ischemic or unknown etiology.

No demographic data were presented for the patients included in the meta-analysis. Information regarding patient characteristics can be obtained from individual trials included in the analyses and referenced in the ATC publication.

Proportional and absolute effects of antiplatelet treatment were determined. Analyses were stratified by trial to avoid direct comparisons between individuals in different studies. The typical odds ratio for these trials was calculated by the one step method from $b = (O-E)/V$, either as $\exp(b)$ or, for rare events, as $(2 + b)/(2-b)$.

Additional details regarding study design and statistical methods employed in this meta-analysis can be found in the original publication.

4.2. Supporting Publications

In addition to the brief description of study design for this grouping of publications, patient characteristics, including patient population, age, and sex are summarized in Table 3 below. The data presented in Table 3 represent patients exposed to aspirin alone.

Table 3. Summary of Patient Characteristics – Supporting Publications

Reference	N	Patient Population	Age (years)	Sex (%M/%F)
Clinical Trials				
Posada et al., 1999	194	Patients with PAF	66-67	Aspirin 125 mg/day: 55/45 Aspirin 125 mg QOD: 49/51 Placebo: 49/51
Taylor et al., 1999	2804	Patients undergoing carotid endarterectomy	69 (median) ¹	Aspirin 81 mg/day: 68/32 Aspirin 325 mg/day: 71/29 Aspirin 650 mg/day: 71/29 Aspirin 1300 mg/day: 70/30
Peters et al., 2003	6303 ²	Patients with ACS without ST-segment elevation	64.2 ³	Aspirin ≤100 mg/day: 58.8/41.2 ⁴ Aspirin 101-199 mg/day: 61.1/38.9 ⁴ Aspirin ≥200 mg/day: 65.4/34.6 ⁴
Topol et al., 2003	4589	Patients with CAD or cerebrovascular disease	62.2	Placebo + Aspirin: 71.2/28.8
Meta Analyses				
Algra and van Gijn, 1999	3482	Patients who have had a TIA or non-disabling stroke	59-68	ns
Johnson et al., 1999	5228	Patients who have had a recent TIA or stroke (secondary prevention)	63	63.3/36.7%

Abbreviations: TIA: transient ischemic attack; ACS: acute coronary syndrome; PAF: primary atrial fibrillation; CAD: coronary artery disease; ns: not specified

1. Median age was 69 years in all 4 treatment groups.
2. Represents the total number of patients randomized to the placebo (i.e., aspirin-alone) treatment group per 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.
3. Mean age was not specified in the analysis by Peters et al., 2003, and was obtained from the original CURE study.
4. Includes patients randomized to aspirin plus placebo or aspirin plus clopidogrel.

4.2.1. Posada et al., 1999

The study by Posada et al. (1999) was a multicenter, randomized, placebo-controlled study of open-label aspirin in adult patients with primary atrial fibrillation (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.

There were a total of 285 patients enrolled in the study. Not included were patients who had general contraindications for 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.

Endpoints included the following: (1) global and cardiovascular mortality rates across the 3 treatment groups; (2) cerebrovascular accident of any kind, including thrombotic, embolic, or hemorrhagic (severity was classified according to the criteria of the European Stroke Prevention Study; ESPS Group, 1987); (3) other embolic events, including acute episodes of mesenteric ischemia or peripheral embolism; and (4) MIs, the need for coronary surgery, or admissions to the hospital due to episodes of unstable angina. The incidence of stroke, MI, cardiovascular death, and the need for coronary surgery were considered as a composite of major cardiovascular events.

Data from the three treatment groups were compared by actuarial curves. The Wilcoxon test and chi-square distribution log rank test were used for the analysis of significance in the differences observed. The data were analyzed with the intention-to-treat method.

4.2.2. Taylor et al., 1999

The study by Taylor et al. (1999) was a multicenter, 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. The study also evaluated the safety of aspirin at the above doses by assessing bleeding complications.

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 (81, 325, 650, or 1300 mg/day) 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 effect of aspirin dose on perioperative complication rates was measured by the occurrence of strokes, MIs, and death. Neurological assessments were performed on discharge from the hospital and at 30 days and three months after surgery. Cross-sectional brain imaging was performed if cerebrovascular events were suspected, at the discretion of the neurologist and surgeon. All reports of these events were assessed by an adjudication committee masked to treatment group and chaired by the principal study neurologist. Deaths were assessed for underlying cause. Strokes were assessed for territory, type, severity, and duration. Stroke severity was based on the modified Rankin scale (scores: 1, mild; 2, moderate; 3, severe) (de Haan et al., 1995) at the final 3-month follow-up assessment. The planned composite endpoints were as follows: all strokes, MIs, and deaths; all strokes and deaths; and ipsilateral strokes and deaths.

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 χ^2 test. Comparisons between the 81 and 325 mg/day doses and between the 650 and 1300 mg/day doses were performed as secondary analyses. All reported p-values were two-tailed.

4.2.3. Peters et al., 2003

This post-hoc observational analysis of the CURE study presented by Peters et al. (2003) was 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 acute coronary syndromes (ACS).

A total of 12,562 patients from 28 countries were enrolled in the study. 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 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 IIb/IIIa receptor (GP IIb/IIIa) inhibitor fewer than 3 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 three to 12 months (mean: 9 months).

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 10 to 15% had a history of CABG.

The first co-primary endpoint was the combined incidence of cardiovascular death, MI, or stroke. The second co-primary endpoint was the composite of cardiovascular death, MI, stroke or refractory ischemia. The risk of major and minor bleeding was also assessed.

For analysis, patients were divided into three groups based on daily aspirin dose at the time of randomization (≤ 100 , 101–199, or ≥ 200 mg/day). All hazard ratios (HRs) and 95% CIs for primary and secondary outcomes comparing clopidogrel and placebo were derived by use of the Cox proportional hazards model. Efficacy HRs were adjusted for sex, weight, hypertension, components of the Thrombolysis in Myocardial Infarction (TIMI) risk scores (Rao et al., 1988), and rates of angiography, PCI, and CABG.

4.2.4. Topol et al., 2003

The BRAVO study presented by Topol et al. (2003) was a randomized, double-blind, placebo-controlled, study of lotrafiban, an oral GP IIb/IIIa antagonist, in patients with coronary and cerebrovascular disease.

A total of 9190 patients from 23 countries were enrolled in the study. Patients were included if they had 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 and unstable angina), approximately 36% had cerebrovascular disease (TIA and 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 assigned to receive lotrafiban or placebo. The dose of lotrafiban was either 30 or 50 mg twice daily (BID) depending on age and creatinine clearance. 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.

The primary efficacy endpoint was the composite of death, MI, stroke, recurrent ischemia requiring hospitalization, and urgent revascularization. The incidence of serious bleeding, any bleeding, or any transfusion was also assessed.

No statistical methods from the publication of the BRAVO study are included in the ISE since only incidence of efficacy endpoints is discussed.

4.2.5. Algra and van Gijn, 1996

Algra and van Gijn (1996) conducted a meta-analysis of stroke that included data from 10 randomized trials (these trials were among the 18 studies included in the second cycle of the Antiplatelet Trialists Collaboration, 2002). The purpose of the analysis was to evaluate the relative efficacy of low (≤ 100 mg/day), medium (300 mg/day), and high (≥ 900 mg/day) doses of aspirin in patients following a TIA or non-disabling stroke.

Trials in which aspirin-only was compared with control treatment were selected for the analysis. The 10 studies contributed a total of 6171 patients to the analysis and all of the studies were placebo-controlled with the exception of the Toulouse TIA trial. The mean age

of patients across the studies ranged from 59-68 years. Information on sex was not presented in this publication. The percentage of patients with a TIA at baseline ranged from 0-100% across studies.

The primary efficacy measure was the composite outcome of vascular death, stroke, or MI. The relative risk and corresponding relative risk reduction $[(1 - \text{relative risk}) \times 100]$ were used as the effect measure. Data from the different trials were combined by means of the Mantel-Haenszel method. Cumulative meta-analysis by date of publication was performed according to methods referenced in the original publication. Poisson regression was used to test for statistically significant differences in the efficacy of low, medium, and high doses of aspirin.

4.2.6. Johnson et al., 1999

Johnson et al. (1999) conducted a meta-regression analysis of stroke using data from 11 published randomized, placebo-controlled secondary prevention trials. The primary objective of the analysis was to evaluate the dose-response relationship between aspirin and stroke in high risk patients. Regression methods were used to evaluate the stroke risk reduction per milligram of aspirin across a broad range of doses (50–1500 mg/day).

Relevant trials were identified by Medline searches and by consulting reference lists of reviews to identify additional articles. All studies included in the analysis had an aspirin-only treatment arm, reported the occurrence of stroke alone, and were published through April 30, 1996. The 11 studies contributed a total of 9629 patients to the analysis with 5228 randomized to aspirin-only treatment groups (50–1500 mg/day) and 4401 randomized to placebo only. Ten of the studies included only patients who had a history of at least one recent TIA or stroke. In the remaining study 94% of the patients in both the aspirin and placebo treatment arms had had a previous TIA or stroke. Consequently all 11 studies were considered secondary prevention trials.

Data on demographics, inclusion and exclusion criteria, treatment regimen, duration of follow-up, and stroke were abstracted from published data only, and from aspirin-only and placebo-only treatment arms. A total of 63.3% of patients were male and mean age across the studies was 63 years (range: 59-73 years). Detailed information on the number of patients with stroke was also obtained. Stroke was diagnosed in part on the basis of symptoms, with most of the studies requiring symptoms of at least 24 hours duration.

Information was abstracted from the studies to conduct an intention-to-treat meta-regression analysis, the primary analysis in most of the published studies. Accordingly, outcome data represent the number of patients who experienced an outcome of interest among all randomized subjects. Most studies attempted to follow-up all patients for the duration of the

study regardless of whether patients experienced an event of interest or withdrew for another reason. Events that occurred after study withdrawal or medication discontinuation were included in the meta-analysis whenever reported. The average follow-up period was 32 months.

Risk ratios for stroke were estimated by constructing contingency tables based on the number of patients randomized and the number of patients experiencing events. Summary effect estimates adjusted for study with the Mantel-Haenszel estimator and 95% CIs were calculated. Weighted least-squares linear regression was used to evaluate variation between studies, to model the risk ratio as a function of aspirin dose in milligrams, to test for trends, and to graph the predicted dose-response curve. The dependent variable for the regression was the natural log of each study-specific RR for stroke, weighted by the inverse of its variance.

4.3. Publications Providing Additional Efficacy Information

The 99 publications included in this grouping describe a wide range of studies (clinical trials, meta-analyses, case studies, retrospective studies, population studies, follow-up studies and observational studies) in a variety of patient populations. In general, the patient populations 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 children aged between seven months and ≤ 18 years to elderly patients aged ≥ 75 years. 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 Publication

5.1.1. Antithrombotic Trialists' Collaboration, 2002

The publication of the ATC meta-analysis included data from comparisons of several different antiplatelet medications and treatment regimens. Table 4 represents exposure data for the comparisons relevant to this aspirin efficacy summary. These include meta-analyses using data from clinical trials in which different aspirin doses were compared to controls or meta-analyses using data from clinical trials in which more than one aspirin dose was investigated. Data presented in the table were derived directly from figures presented in the ATC publication and include information for patients exposed to aspirin only.

Table 4. Summary of Subject Accountability and Exposure to Aspirin – ATC, 2002

Reference	N ¹	Aspirin Doses ¹	Number of Patients Exposed ¹		Duration of Exposure
ATC, 2002	29,652	<75 mg/day 75-150 mg/day 160-325 mg/day 500-1500 mg/day	1827 ² 3370 ² 13,240 ² 11,215 ²		ns
	6767	≥75 mg/day vs. 75-325 mg/day ³ 500-1500 mg/day vs. 75-325 mg/day ⁵	1795 ⁴ 1608 ⁴	1775 ⁴ 1589 ⁴	ns

Abbreviations: ns: not specified; vs.: versus

1. Exposure data presented are from 2 separate comparisons presented in the ATC. The first included meta-analyses using data from clinical trials in which different aspirin doses were compared to controls (N=29,652). The second included meta-analyses using data from clinical trials in which more than one aspirin dose was investigated (N=6767). Data presented represents patients exposed to aspirin only.
2. Patients may have contributed to more than 1 dose comparison.
3. Includes 2 trials comparing 75-325 vs. <75 mg/day and 1 trial of 500-1500 vs. <75 mg/day.
4. Represents number of patients in each aspirin treatment regimen (e.g., ≥75 mg/day vs. 75-325 mg/day).
5. Includes 1 trial comparing 1400 vs. 350 mg/day and another (excluding patients with acute stroke) comparing 1000 vs. 300 mg/day among patients who were also given dipyridamole.

In the meta-analyses using data from clinical trials in which different aspirin doses were compared to controls, a total of 29,652 patients from 65 trials were exposed to doses of aspirin that ranged from <75 to 500–1500 mg/day, as shown in Table 4. Meta-analyses using data from clinical trials in which more than one aspirin dose was investigated included a total of 6767 patients from 10 clinical trials. These patients were exposed to aspirin doses ≥75 mg/day versus 75–325 mg/day or 500–1500 mg/day versus 75–325 mg/day.

5.2. Supporting Publications

A brief description of subject accountability and exposure to aspirin is presented for each publication and summarized in

Table 5 below. The data presented in the table represent patients exposed to aspirin alone, unless noted otherwise.

Table 5. Summary of Subject Accountability and Exposure to Aspirin – Supporting Publications

Reference	N	Aspirin Doses	Number of Patients Exposed	Duration of Exposure
Clinical Trials				
Posada et al., 1999	194	125 mg/day	104	Mean evaluation period: 510 days
		125 mg QOD	90	Mean evaluation period: 600 days
Taylor et al., 1999	2804	81 mg/day	698	Aspirin treatment was started prior to surgery and continued for 3 months post-surgery
		325 mg/day	697	
		650 mg/day	703	
		1300 mg/day	706	
Peters et al., 2003	6303 ¹	≤100 mg/day	5320 ²	Mean: 9 months ³
		101-199 mg/day	3109 ²	
		≥200 mg/day	4110 ²	
Topol et al., 2003 ⁴	4589	75-162 mg/day	2410	Up to 2 years
		>162 mg/day	2179	
Meta Analyses				
Algra and van Gijn, 1999	3482	≤100 mg/day	826	ns
		300 mg/day	806	
		900 mg/day	345	
		1000 mg/day	101	
		1200 mg/day	815	
		1300 mg/day	306	
		1500 mg/day	283	
Johnson et al., 1999	5228	50 mg/day	1649	Mean follow-up: 32 months
		75 mg/day	676	
		300 mg/day	1210	
		650 mg/day	65	
		990 mg/day	198	
		1000 mg/day	101	
		1200 mg/day	815	
		1300 mg/day	232	
		1500 mg/day	282	

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

1. Represents the total number of patients randomized to the placebo (i.e., aspirin-alone) treatment group per 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.
2. The number of patients exposed by aspirin dose was not presented in the publication by Peters et al, 2003. Patients represented in the aspirin treatment groups include those who were taking aspirin alone and aspirin plus clopidogrel. The exact dose of aspirin patients received was at the discretion of the investigator. Doses in the range of 75-325 mg were recommended in the study protocol.
3. Duration of exposure per 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.
4. Patients in the BRAVO study received placebo plus aspirin or lotrafiban plus aspirin. The exact dose of aspirin patients received was at the discretion of the investigator (75-325 mg/day).

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.

Of note, 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. Peters et al., 2003

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) 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.

5.2.4. 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 Itofiban plus aspirin treatment groups; 25th and 75th percentiles, respectively were 279 and 463 days in the placebo plus aspirin treatment groups).

5.2.5. Algra and van Gijn, 1999

In the meta-analysis presented by Algra and van Gijn (1999) a total of 3482 patients from 10 trials received ≤ 100 mg/day (N=826), 300 mg/day (N=806), or ≥ 900 mg/day (N=1850) of aspirin, as presented in

Table 5. Duration of exposure for each aspirin dose was not specified in the meta-analysis but is available from publications of the individual studies referenced in the article.

5.2.6. Johnson et al., 1999

Among the 5228 patients from 11 trials included in the meta-analysis presented by Johnson et al. (1999), exposure to aspirin alone ranged from a low of 50 mg/day to a high of 1500 mg/day, as outlined in

Table 5. The average follow-up was 32 months.

5.3. Publications Providing Additional Efficacy Information

The publications providing additional efficacy information included a wide range of study sizes and treatment durations. For the individual studies included 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 exposed ranged from 1002 patients in seven trials (Tangelder et al., 1999) to a large meta-analysis of 55,462 patients in 16 trials (He et al., 1998). Aspirin doses utilized in the individual studies or in the studies included in the meta-analyses ranged from 50 to 990 mg/day with a duration of treatment (where specified) ranging from a mean of one day up to 12 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 EFFICACY INFORMATION

6.1. Key Publication

6.1.1. Antithrombotic Trialists' Collaboration, 2002

As noted previously, this aspirin efficacy summary and the efficacy data relevant to the proposed aspirin dose labeling change from 75–325 mg/day to 75–150 mg/day for cardiovascular protection and from 50–325 mg/day to 50–150 mg/day for cerebrovascular protection are primarily based on the findings from the ATC meta-analysis, which included data from 212,000 patients in 287 randomized trials who were at increased risk of occlusive vascular disease. The overall objective of the analysis was to evaluate the effectiveness of

various antiplatelet regimens in preventing serious vascular events (non-fatal MI, non-fatal stroke, and vascular death). Aspirin was the most widely studied antiplatelet drug in the ATC meta-analysis. Because the efficacy of low-dose aspirin in cardiovascular and cerebrovascular indications is the focus of this Petition, only data generated from comparisons of one aspirin regimen versus another aspirin regimen (<75 mg/day vs. ≥75 mg/day and 75–325 mg/day vs. 500–1500 mg/day) or different aspirin doses versus no aspirin (controls) (<75 mg/day, 75–150 mg/day, 160–325 mg/day, and 500–1500 mg/day) are discussed in this aspirin efficacy summary.

Comparison of Aspirin Doses Across Studies

Comparison of the incidence of vascular events across 65 trials (59,395 patients) in which different aspirin doses were compared to controls (no aspirin) revealed that no particular range of aspirin dose ≥75 mg/day was preferable for the prevention of serious vascular events, as shown in Table 6. The proportional reduction (% odds reduction) in vascular events was similar for doses of 75–150 mg/day (32%), 160–325 mg/day (26%), and 500–1500 mg/day (19%), suggesting that there is no difference in the occurrence of vascular events in patients treated with lower versus higher doses of aspirin. At doses <75 mg/day, the incidence of vascular events was higher and the proportional reduction was lower (13%), suggesting that doses of aspirin below 75 mg/day may be less effective in preventing vascular events. It should be noted that data generated for the <75 mg/day aspirin dose were derived from only three studies.

Table 6. Incidence and Proportional Reduction in Vascular Events From Comparisons of Different Aspirin Doses Versus Controls¹ – ATC, 2002

Trial Category	Number of Trials	Number of Vascular Events/Number Exposed (%)		% Odds Reduction (SE)
		Aspirin	Adjusted Control ²	
<75 mg/day	3	316/1827 (17.3)	354/1828 (19.4)	13 (8)
75–150 mg/day	12	366/3370 (10.9)	517/3406 (15.2)	32 (6)
160–325 mg/day	19	1526/13240 (11.5)	1963/13273 (14.8)	26 (3)
500–1500 mg/day	34	1621/11215 (14.5)	1930/11236 (17.2)	19 (3)
Any dose ³	65	3829/29652 (12.9)	4764/29743 (16.0)	23 (2)

Abbreviations: SE: standard error

1. Includes data from high-risk patients except those with acute stroke. Only meta-analyses involving 500 patients or more are represented in the table.
2. Controls include patients who did not receive aspirin.
3. Some trials contributed to more than 1 comparison.

Direct Comparison of More Than One Aspirin Dose Within Studies

A separate meta-analysis was also conducted using data from clinical trials in which more than one aspirin dose was investigated and the results are presented in Table 7. Data from 3570 patients in three trials showed that there was also no significant difference in the incidence of vascular events when doses of aspirin ≥ 75 mg/day (14.2%) were directly compared with doses < 75 mg/day (13.2%). Similar results were observed when 500–1500 mg/day (14.1%) doses were directly compared with 75–325 mg/day doses (14.5%) using data from 3197 patients in seven trials. As expected, the proportional reduction in vascular events was small in both comparisons (3% and –8%, respectively). More importantly, this small proportional reduction in events strongly suggests that the lower doses of aspirin used in these comparisons are as efficacious as higher doses in this patient population.

Table 7. Incidence and Proportional Reduction in Vascular Events From Comparisons of Different Aspirin Regimens¹ – ATC, 2002

Trial Category	Number of Trials	Number of Vascular Events/Number Exposed (%)		% Odds Reduction (SE)
		Regimen 1	Regimen 2	
≥ 75 vs. < 75 mg/day ²	3	254/1795 (14.2)	234/1775 (13.2)	–8 (10)
500-1500 vs. 75–325 mg/day ³	7	227/1608 (14.1)	231/1589 (14.5%)	3 (10)
Subtotal	10	481/3403 (14.1)	465/3364 (13.8)	–3 (7)

Abbreviations: vs.: versus

1. Includes data from high-risk patients except those with acute stroke. Only meta-analyses involving 500 patients or more are represented in the table.
2. Includes 2 trials comparing 75–325 vs. < 75 mg/day and 1 trial of 500–1500 vs. < 75 mg/day.
3. Includes 1 trial comparing 1400 vs. 350 mg/day and another (excluding patients with acute stroke) comparing 1000 vs. 300 mg/day among patients who were also given dipyridamole.

In conclusion, the results of these analyses from the ATC verify that lower doses of aspirin (50–150 mg/day) are as effective as higher doses in preventing serious vascular events among high-risk patients.

6.2. Supporting Publications

A by-publication summary of efficacy results from the four clinical trials and two meta-analyses that provide other relevant efficacy data to support the proposed aspirin labeling change from 75–325 mg/day to 75–150 mg/day for cardiovascular protection and from 50–325 mg/day to 50–150 mg/day for cerebrovascular protection are discussed below.

6.2.1. Posada et al., 1999

The placebo-controlled study presented in the publication by Posada et al. (1999) examined the protective effects of low-dose aspirin therapy (125 mg) when taken daily versus every other day in a high-risk population of patients with PAF. Table 8 summarizes absolute and relative risk reductions for daily and alternate-day aspirin dosing in this study.

Table 8 Absolute and Relative Risk Reductions for Daily and Alternate Day Aspirin Dosing – Posada et al., 1999

Event	Aspirin 125 mg/day (N=104) N (%)	Placebo (N=91) N (%)	%ARR (95% CI)/%RRR	p-value
Cardiovascular deaths	5 (4.8)	6 (6.6)	1.8 (-4.2 to 7.8)/ 27	NS
Strokes	4 (3.8)	3 (3.3)	0.5 (-1.1 to 2.1)/ 13	NS
Major events ¹	8 (7.7)	10 (11.0)	3.3 (-4.7 to 11.3)/ 43	NS
Event	Aspirin 125 mg QOD (N=90) N (%)	Placebo (N=91) N (%)	%ARR (95% CI)/%RRR	p-value
Cardiovascular deaths	1 (1.1)	6 (6.6)	5.5 (0.5 to 10.5)/ 80	0.02
Strokes	1 (1.1)	3 (3.3)	2.2 (-1.8 to 6.2)/ 65	0.05
Major events ¹	2 (2.2)	10 (11.0)	8.8 (1.8 to 15.8)/ 80	0.001
Event	Aspirin 125 mg/day vs. Aspirin 125 mg QOD p-value			
Cardiovascular deaths	0.8 ²			
Strokes	0.4 ²			
Major events ¹	0.8 ²			

Abbreviations: QOD: every other day; ARR: absolute risk reduction; RRR: relative risk reduction; NS: not significant

1. Major cardiovascular events include a composite of stroke, MI, cardiovascular death, and need for coronary surgery.
2. P-value for trend showing survival free from each corresponding event.

A total of 19 deaths occurred during the 550-day (mean) evaluation period. Thirteen (13) of these deaths were considered to be of cardiovascular origin. When data from the treatment groups were compared using actuarial curves, a reduction in the overall mortality rate was observed in the alternate-day dosing group compared to placebo because of a decrease in cardiovascular mortality.

There was an 80% relative reduction in cardiovascular mortality when patients taking aspirin on alternate days (1.1%) were compared to placebo (6.6%) (p=0.02), as shown in Table 8. The trend for survival free from cardiovascular mortality demonstrated no difference between the aspirin daily and alternate-day dosing groups (p=0.8). No difference in the cardiovascular mortality rate was observed between the daily dosing (4.8%) and placebo treatment groups (6.6%).

Four (4) patients taking aspirin daily (3.8%), 1 patient (1.1%) taking aspirin on alternate days, and 3 patients (3.3%) taking placebo suffered a stroke. There was a significant difference in the occurrence of stroke in the alternate-day dosing group compared to placebo ($p=0.05$). The trend for survival free from stroke demonstrated no difference between the aspirin daily and alternate-day dosing groups ($p=0.4$).

When the composite endpoint of occurrence of cardiovascular events (stroke, MI, cardiovascular death, and need for coronary surgery) was compared across the treatment groups, there was an 80% relative reduction among patients taking 125 mg on alternate days (2.2%) compared with those taking placebo (11.0%; $p=0.001$). There was no difference in occurrence of major cardiovascular events between patients taking aspirin daily (7.7%) and placebo (11.0%). The trend for survival free from major cardiovascular events demonstrated no difference between the aspirin daily and alternate-day dosing groups ($p=0.8$).

Based on these analyses, the authors conclude that 125 mg aspirin taken every other day appeared to be effective in preventing major cardiovascular events among high-risk patients with PAF. However, these results should be interpreted carefully for several reasons. First, the authors' conclusions are based on comparisons between aspirin and placebo treatment groups which demonstrate a significant reduction in cardiovascular mortality, stroke, and major cardiovascular events among patients taking aspirin on alternate days. When the more relevant comparisons of alternate versus daily dosing were performed, no statistically significant difference between the treatment groups was observed for any of these endpoints. The study also has limitations due to the relatively small sample size, resulting from early termination of the study, and the low incidence of stroke that occurred over the 2-year treatment period, making it difficult to draw meaningful conclusions from data comparisons. A 12% incidence of stroke was expected; however the observed incidence was only 3.3% among patients receiving placebo after 12 months. Thus, the study population was at intermediate rather than at high risk of stroke.

6.2.2. Taylor et al., 1999

In the study presented by Taylor et al. (1999), the relationship between low (81 and 325 mg/day) versus high (650 and 1300 mg/day) doses of aspirin and perioperative complication rates in 2804 patients undergoing carotid endarterectomy was examined. Treatment with aspirin was started prior to surgery and continued for three months post-surgery. Table 9 summarizes failure rates at 30 days and three months after carotid endarterectomy for the efficacy analysis population and for all patients by dose of aspirin.

Table 9. Failure Rates at 30 Days and Three Months after Carotid Endarterectomy by Aspirin Dose – Taylor et al., 1999

Event	Event Rate		p-value
	Low-dose aspirin (81 and 325 mg/day)	High-dose aspirin (650 and 1300 mg/day)	
Efficacy Analysis			
Number of patients	566	550	
Any stroke, MI, or death:			
30 days	21 (3.7%)	45 (8.2%)	0.002
3 months	24 (4.2%)	55 (10.0%)	0.0002
All Patients			
Number of patients	1395	1409	
Any stroke, MI, or death:			
30 days	75 (5.4%)	99 (7.0%)	0.07
3 months	87 (6.2%)	118 (8.4%)	0.03

Abbreviations: MI: myocardial infarction

The efficacy analysis was performed using data from 566 patients in the low-dose and 550 patients in the high-dose treatment groups (N=1116 patients). Patients taking ≥ 650 mg/day aspirin prior to randomization, and patients randomized within one day of surgery were excluded from this analysis. In the efficacy population, strokes occurred in 18 patients (3.2%) taking low-dose aspirin compared to 38 patients (6.9%) taking high-dose aspirin. Similarly, five patients (0.9%) in the low-dose aspirin group and 18 patients (3.3%) in the high-dose aspirin group had an MI, and nine patients (1.6%) taking low doses of aspirin compared to 12 patients (2.2%) taking high doses of aspirin died.

As shown in Table 9, when the combined rate of stroke, MI, and death were examined in patients included in the efficacy analysis, event rates were found to be lower in the low-dose aspirin group at both the 30-day (low-dose: 21 patients [3.7%]; high-dose: 45 patients [8.2%]; $p=0.002$) and 3-month (low-dose: 24 patients [4.2%]; high-dose: 55 patients [10.0%]; $p=0.0002$) assessments. Similar results were observed for the combined endpoint for all patients at 30 days (low-dose: 75 patients [5.4%]; high-dose: 99 patients [7.0%]; $p=0.07$) and three months (low-dose: 87 patients [6.2%]; high-dose: 118 patients [8.4%]; $p=0.03$) (N=2804).

Secondary analyses were also performed to probe for potential differences between the 81 and 325 mg/day doses and between the 650 and 1300 mg/day doses. Although no data are presented in the publication, the authors make a point of noting that no significant differences were observed in either of these analyses. These results provide additional evidence that low doses of aspirin are as effective as higher aspirin doses in preventing perioperative complications in this patient population.

In conclusion, the risk of stroke, MI, and death within 30 days and three months of carotid endarterectomy is lower for patients taking 81 or 325 mg/day of aspirin than for those taking

650 or 1300 mg/day. Additionally, there were no significant differences observed between the 81 and 325 mg/day aspirin treatment groups (the dose range of interest) in any of the analyses.

6.2.3. Peters et al., 2003

The post-hoc observational analysis of the CURE study data presented in the publication by Peters et al. (2003) evaluated the benefits and risks of adding clopidogrel to a range of aspirin doses (≤ 100 , 101–199, and ≥ 200 mg/day) in the treatment of patients with ACS. For the purposes of this aspirin efficacy summary, only data from the control groups, which included patients who received aspirin alone, were evaluated following an average treatment duration of nine months. Table 10 summarizes the combined incidence of cardiovascular death, MI, and stroke by aspirin dose.

Table 10. Incidence of Cardiovascular Death, MI, and Stroke by Aspirin Dose – Peters et al., 2003

Dose Group or Parameter	Incidence
Aspirin ≤ 100 mg/day	10.5%
Aspirin 101–199 mg/day	9.8%
Aspirin ≥ 200 mg/day	13.6%
	HR (95% CI)
Adjusted HR for 101–199 vs. ≤ 100 mg/day ¹	1.0 (0.82 to 1.23)
Adjusted HR for ≥ 200 vs. ≤ 100 mg/day ¹	1.3 (1.08 to 1.52)

Abbreviations: HR: hazard ratio; vs.: versus

Note: number of patients in the publication by Peters was given by aspirin dose but included patients receiving aspirin plus clopidogrel, as well as aspirin alone

1. Adjusted for sex, weight, hypertension, components of the TIMI risk score, rates of angiography, PCI and CABG

The incidence of cardiovascular death, MI, and stroke among patients taking ≤ 100 mg/day (10.5%), 101–199 mg/day (9.8%), and ≥ 200 mg/day (13.6%) for an average duration of 9 months was similar. As shown in Table 10, the adjusted hazard ratio (95% confidence interval [CI]) was 1.0 (0.82-1.23) when the medium (101–199 mg/day) and lowest (≤ 100 mg/day) aspirin doses were compared, and 1.3 (1.08-1.52) when the highest (≥ 200 mg/day) and lowest (≤ 100 mg/day) doses were compared. Similar results were observed in the incidence of the second co-primary endpoint (the composite of cardiovascular death, non-fatal MI, stroke, and refractory ischemia), which was 18.2% (≤ 100 mg/day), 17.2% (101–199 mg/day), and 20.7% (≥ 200 mg/day) across the three dose groups.

In this large, international trial, the dose of aspirin prescribed was at the discretion of the Investigator and strongly dependent on the center at which the patient was treated. Further, the choice of dose by the center was associated with geographic location. That is, a patient

was more likely to receive ≥ 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 ≤ 100 mg/day, respectively, were most commonly used. Under these circumstances, any argument seeking to establish causality between aspirin dose and efficacy outcome measures must account for the confounding effects of site and geography.

In conclusion, aspirin doses ≤ 199 mg/day appeared to be as effective as doses ≥ 200 mg/day, either alone or in combination with clopidogrel, in reducing the occurrence of cardiovascular death, MI, and stroke in patients with ACS. However, when interpreting these results, it should be noted that patients were not randomly assigned to aspirin groups. Rather, the dose of aspirin was prescribed by individual Investigators and was also strongly dependent on both study center and geographic location.

6.2.4. Topol et al., 2003

The BRAVO study presented in the publication by Topol et al. (2003) evaluated the effect of the platelet GP IIb/IIIa antagonist, lotrafiban, in 9190 patients with coronary artery disease (CAD) or cerebrovascular disease. Similar to the subanalysis of the CURE trial data, this study also included control patients who received aspirin alone at a dose determined by the Investigator. Thus, for the purposes of this aspirin efficacy summary, the effect of low-dose (75-162 mg/day) (N=2410) and higher doses of aspirin (>162 mg/day) (N=2179) were compared. The duration of treatment was ≤ 2 years or a median of 366 days (25th and 75th percentiles were 279 and 463 days, respectively). Of note, the trial was terminated prematurely because of a statistically significant excess of mortality in the lotrafiban group. Table 11 summarizes the incidence of the composite endpoint and individual components of the composite endpoint by dose of aspirin.

Table 11. Incidence of the Composite Endpoint and Individual Components of the Composite Endpoint by Aspirin Dose – Topol et al., 2003

Outcome	Outcomes by Aspirin Dose	
	Low Dose (75-162 mg/day) (N=2410)	High Dose (>162 mg/day) (N=2179)
Primary endpoint ¹	16.4%	18.6%
Death, MI, stroke	6.2%	6.1%
Death	2.8%	1.7%
MI	2.0%	2.1%
Stroke	2.1%	2.8%
Urgent hospitalization	9.5%	10.6%
Urgent revascularization	7.3%	10.0%

Abbreviations: MI: myocardial infarction

1. The primary endpoint was a composite of all-case mortality, MI, stroke, recurrent ischemia requiring hospitalization, and urgent revascularization.

Doses of aspirin >162 mg/day (18.6%) were associated with an increased risk of the primary composite endpoint compared with lower doses of aspirin (16.4%). These results reflect the higher incidence of stroke (low dose: 2.1%; high dose: 2.8%), urgent hospitalization (low dose: 9.5%; high dose: 10.6%), and urgent revascularization (low dose: 7.3%; high dose: 10.0%) among patients taking >162 mg/day of aspirin, as shown in Table 11. Death occurred at a higher incidence in the low-dose (2.8%) compared to the high-dose (1.7%) aspirin group, and no between treatment group differences were observed in the incidence of MI (low dose: 2.0%; high dose: 2.1%).

In conclusion, aspirin doses of 75–162 mg/day appeared to be at least as effective as doses >162 mg/day in reducing the incidence of stroke, recurrent ischemia requiring hospitalization, and urgent revascularization in patients with CAD or cerebrovascular disease, but not total mortality. The fact that patients were not randomly assigned to aspirin treatment groups, but received a dose of aspirin determined by an Investigator, should be considered when interpreting the results of this study.

6.2.5. Algra and van Gijn, 1996

The meta-analysis presented in the publication by Algra and van Gijn (1996), evaluated the efficacy of various doses of aspirin (≤ 100 , 300, and ≥ 900 mg/day) in patients who had suffered a TIA or non-disabling stroke. Table 12 presents the number of vascular events and the corresponding relative risk reduction in the composite outcome of vascular death, stroke, and MI by dose of aspirin.

Table 12. Relative Risk Reduction in Vascular Events (Composite of Death, Stroke, and MI) by Aspirin Dose - Algra and van Gijn, 1996

Aspirin Dose	Number of Vascular Events	RRR (95% CI)
≤ 100 mg/day (N=826)	184	13% (-3 to 27)
300 mg/day (N=806)	174	9% (-9 to 24)
≥ 900 mg/day (N=1850)	352	14% (2 to 24)
Overall effect estimate – all trials	710	13% (4 to 21)

Abbreviations: RRR: relative risk reduction; CI: confidence interval

Results of the analysis showed that all aspirin dose groups had similar efficacy in preventing vascular events. The overall relative risk reductions (95% CI) were 13% (-3 to 27), 9% (-9 to 24), and 14% (2 to 24) for the ≤ 100 , 300, and ≥ 900 mg/day dosing regimens. Following statistical testing, no significant differences in efficacy across any of the three aspirin dose groups was observed. The overall relative risk reduction (95% CI) for the combined data from all 10 trials was 13% (4 to 21).

In conclusion, based on the results of this meta-analysis, doses of aspirin ≤ 100 mg/day are as efficacious as higher doses (up to 1500 mg/day) in the secondary prevention of vascular

events following cerebral ischemia. As noted in Section 3.2.2, clinical trials included in the current meta-analysis overlap significantly with the meta-analyses presented by both the ATC (2002) and Johnson et al. (1999), an important consideration when evaluating primary data.

6.2.6. Johnson et al., 1999

The meta-analysis presented by Johnson et al. (1999) evaluated the dose-response relationship between aspirin (≤ 75 , 300, 650, and >900 mg/day) and stroke in patients who had suffered a recent TIA or stroke.

Results of the analysis of study-specific risk ratios using weighted linear regression revealed no linear dose-response effect of aspirin therapy on stroke risk reduction during the average follow-up period of 32 months. Risk ratio estimates were similar across the doses used in the trials, which ranged from as low as 50 to as high as 1500 mg/day. No evidence of a linear dose-response trend ($p=0.49$), or quadratic dose-response trend ($p=0.85$) was observed. When risk ratios were summarized across all studies, aspirin was found to reduce the risk of stroke by approximately 15% (risk ratio, 95% CI: 0.85, 0.77-0.94).

In conclusion, based on the results of this meta-analysis, aspirin reduces the risk of stroke by 15%, an effect that is uniform across a wide range of doses from 50–1500 mg/day. As noted above, there is considerable overlap in clinical studies included in the current meta-analysis and those performed by both the ATC (2002) and Algra and van Gijn (1996).

6.3. Publications Providing Additional Efficacy Information

A summary of efficacy findings from the studies included in this grouping is presented in Appendix 2. As discussed in Section 3.2.3 above, meaningful comparisons of efficacy across the different studies in this grouping are difficult, primarily due to differences in the methods of deriving and presenting efficacy data across studies (e.g., incidence rates, relative risks, annualized event rates, odds ratios, hazard ratios, etc.), differences in study-specific endpoints, and differences in treatment durations. For example, in the Coumadin Aspirin Reinfarction Study (CARS), treatment with aspirin 160 mg/day was associated with a one-year life table estimate of 8.6% for the composite of first occurrence of nonfatal myocardial reinfarction, nonfatal ischemic stroke, or cardiovascular death (CARS Investigators, 1997).

Treatment with aspirin at a dose of 325 mg/day was associated with a 12.4% incidence of the combined endpoint of nonfatal acute MI, nonfatal stroke, or vascular death in a study by Matias-Guiu et al. (2003). While the two composite events are similar, the differences in the methods of reporting the rates of these events (one-year life table estimate versus incidence) as well as the differences in the duration of treatment/follow-up in the two studies (14 months versus one to three years) do not allow for a direct comparison of the efficacy at different aspirin doses between these two studies.

Similarly, in the CAST study, aspirin at a dose of 160 mg/day was associated with a 5.3% incidence of the combined endpoint of death or nonfatal stroke, and a 3.2% incidence of fatal and nonfatal recurrent strokes (CAST Collaborative Group, 1997). On the other hand, in the Stroke Prevention in Atrial Fibrillation III study (SPAF III), the annualized rate of the primary events of ischemic stroke and non-CNS emboli associated with the use of aspirin 325 mg/day was 2.2%, and for all deaths was 1.8% (SPAF III Writing Committee, 1998). In this case, the differences in the study-specific endpoints evaluated in each of the studies do not permit a direct comparison of the efficacy at different aspirin doses between these two studies.

In addition, in some studies the efficacy results for aspirin were reported relative to a comparator agent rather than placebo or control. For example, in the CARS study mentioned above, the relative risk of a primary event associated with the use of aspirin 160 mg/day of 1.03 was reported relative to the comparator treatment group (warfarin plus aspirin), thereby not allowing for comparisons of efficacy with other studies that reported efficacy results for aspirin relative to placebo or control. Therefore, due to the difficulties encountered in making comparisons between different studies, across-publication efficacy conclusions could not be made from this group of studies.

The inclusion of this publication grouping in this submission serves to ensure that all aspirin-related efficacy 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 Petition.

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.

The proposed labeling change in the recommended aspirin dose, from 50–325 mg/day to 50–150 mg daily, is also supported by published efficacy data demonstrating that doses of aspirin in the range of 50–150 mg/day are equally effective for the prevention of serious cerebrovascular events (non-fatal stroke) and doses of aspirin in the range of 75–150

mg/day are equally effective for the prevention of serious cardiovascular events (non-fatal MI and vascular death). In particular, the Antithrombotic Trialists' Collaboration (ATC) meta-analysis demonstrates that the reduction in the occurrence of serious vascular events across a range of aspirin doses from less than 75 mg/day, 75–150 mg/day, and 500–1500 mg/day in patients at risk of occlusive vascular disease, is similar. Cardiovascular and cerebrovascular disease benefit is no greater at aspirin doses above 150 mg or below 150 mg/day. In addition, the small proportional reduction in events observed in direct comparisons of doses less than 75 mg/day versus greater than or equal to 75 mg/day demonstrates that lower doses of aspirin used in these comparisons are as efficacious as higher doses in this patient population.

Efficacy Conclusions

- Doses of aspirin within the range of 50–150 mg daily are equally effective for the prevention of serious vascular events (non-fatal MI, non-fatal stroke, and vascular death).
- The recommended aspirin dose for chronic administration is 50–150 mg daily, which is safe and effective for prevention of recurrent MI, ischemic stroke and TIA and for treatment of unstable angina pectoris or chronic stable angina pectoris. Aspirin is recommended for patients who undergo revascularization procedures, such as coronary artery bypass grafting, angioplasty, or carotid endarterectomy, if there is a pre-existing condition for which aspirin is already indicated. Therapy should be continued indefinitely.

8. REFERENCES

8.1. Key Publication

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

8.2. Supporting Publications

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APPENDIX 1. TABLE OF STUDIES - PUBLICATIONS PROVIDING ADDITIONAL EFFICACY INFORMATION

Reference	Total Subjects	Patient Population	Treatment Groups (n)	Treatment Duration	Type of Article
Low-Dose Aspirin (≤200 mg/day)					
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	6300	A meta-analysis of 6 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 325 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
Wilterdink JL, Easton JD. 1999. Dipyridamole plus aspirin in cerebrovascular disease. Archives of Neurology 56(9):1087-1092.	11,919	ESPS-2 trial: Patients who had experienced TIA or ischemic stroke within previous 3 months Antiplatelet Trialists' Collaboration Trials: Includes 14 trials across patient populations	ESPS-2 trial treatments (n=6602): Aspirin 50 mg/day Sustained-release dipyridamole 400 mg/day Aspirin 50 mg/day + dipyridamole 400 mg/day Placebo Antiplatelet Trialists' Collaboration trial treatments (n=5317): Aspirin alone (dosages varied from 150-1300 mg/day; median aspirin dose=975 mg/day) Aspirin + dipyridamole tablets (median aspirin dose=225 mg/day)	Treatment duration across the studies not specified in the article	Meta-analysis
Atrial Fibrillation Investigators. 1997. The efficacy of aspirin in patients with atrial fibrillation: analysis of pooled data from 3 randomized trials. Archives of Internal Medicine 157(11):1237-1240.	2574	Pooled individual patient data from 3 randomized trials: the Atrial Fibrillation, Aspirin, Anticoagulation Study (AFASAK), the European Atrial Fibrillation Trial (EAFT), and the Stroke Prevention in Atrial Fibrillation 1 Study (SPAF1)	AFASAK: aspirin 75 mg/day or placebo (n=672) EAFT: aspirin 300 mg/day or placebo (n=782) SPAF1: aspirin 325 mg/day or placebo (n=1120)	Treatment duration not specified in the article	Meta-analysis

APPENDIX 1. TABLE OF STUDIES - PUBLICATIONS PROVIDING ADDITIONAL EFFICACY INFORMATION

Reference	Total Subjects	Patient Population	Treatment Groups (n)	Treatment Duration	Type of Article
Hart RG, Halperin JL, McBride R, Benavente O, Man-Son-Hing M, Kronmal RA. 2000. Aspirin for the primary prevention of stroke and other major vascular events: meta-analysis and hypotheses. Archives of Neurology 57(3):326-332	52,251	Primary prevention in high risk patients	Aspirin 75 mg/day or placebo (n=21,330) Aspirin 325 mg QOD or placebo (n=22,071) Aspirin 500 to 650 mg/day or placebo (n=8850)	Average follow-up period of 4.6 years	Meta-analysis
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.	51,085	Healthy male physicians (PHS, BDT), high risk men - top 20% of risk score distribution (TPT), men/ women with hypertension and diastolic BP 100 to 115 mmHg (HOT)	Aspirin 75 mg/day or placebo (n=18,790) Aspirin 75 mg/day-controlled release or placebo (n=5085) Aspirin 325 mg QOD or placebo (n=22,071) Aspirin 500 mg/day or open-label control (n=5139)	Mean duration of treatment and follow-up of 4 to 6 years	Meta-analysis
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. Heart (British Cardiac Society) 85(3):265-271.	48,540	This meta-analysis included patients enrolled across 4 randomized 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 (TPT, n=1268) (HOT, n=9399) Aspirin 162.5 mg/day (PHS) (n=11,037) Aspirin 500 mg/day (BDT) (n=3429) Placebo (n=23,407)	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. BMJ 322(7282):321-326.	3298	Meta-analysis of 5 randomized trials (AFASAK 1, AFASAK 2, SPAF II, SIFA, PATAF) in patients with AF	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

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Reference	Total Subjects	Patient Population	Treatment Groups (n)	Treatment Duration	Type of Article
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.	40,090	A subset of 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 versus placebo) (n=20,655) IST (Aspirin 300 mg/day versus control) (n=19,435)	CAST (4 weeks) IST (2 weeks)	Meta-analysis
Mangano DT. 2002. Aspirin and mortality from coronary bypass surgery. <i>New England Journal of Medicine</i> 347(17):1309-1317.	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 within 48 hours after revascularization (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
Klootwijk P, Meij S, Melkert R, Lenderink T, Simoons ML. 1998. Reduction of recurrent ischemia with abciximab during continuous ECG-ischemia monitoring in patients with unstable angina refractory to standard treatment (CAPTURE). <i>Circulation</i> 98(14):1358-1364.	332	Patients with refractory unstable angina. This was a sub-study of the CAPTURE study.	Aspirin minimum daily dose of 50 mg/day + Abciximab 0.25 mg/kg bolus followed by a continuous infusion of 10 mg/min (n=169) Aspirin minimum daily dose of 50 mg/day + Placebo (n=163)	Follow-up occurred for 30 days	Clinical Trial
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.	8856	A meta-analysis of 16 randomized trials testing long-term (>3 months) use of anti-thrombotic agents in patients with atrial fibrillation	Aspirin from 50 to 1300 mg/day versus placebo (n=3119) Warfarin (adjusted dose for an INR of 2.0-2.6 for primary prevention trials; adjusted to INR of 2.9 for the one secondary prevention trial) versus placebo (n=2900) Warfarin to INR 2.2 to 3.1 versus Aspirin 75-325 mg/day (n=2837)	Treatment duration >3 months across the trials included in this meta-analysis	Meta-analysis

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Reference	Total Subjects	Patient Population	Treatment Groups (n)	Treatment Duration	Type of Article
Kalra L, Perez I, Smithard DG, Sulch D. 2000. Does prior use of aspirin affect outcome in ischemic stroke? American Journal of Medicine 108(3):205-209.	1457	All patients with a diagnosis of acute hemispheric stroke in a White, largely middle class, suburban population in South East England.	Aspirin median daily dose of 75 mg, range of 75 to 300 mg/day. Aspirin was used regularly before the stroke by 650 (45%) of patients.	Treatment duration not specified in the article.	Population-Based Study
Srinivasan AK, Grayson AD, Pullan DM, Fabri BM, Dihmis WC. 2003. Effect of preoperative aspirin use in off-pump coronary artery bypass operations. Annals of Thoracic Surgery 76(1):41-45.	340	Patients who underwent off-pump coronary artery bypass operation (OPCAB) for the first time between January 1998 and September 2001	Aspirin 75 to 300 mg/day (n=170) Nonaspirin users (n=170)	Treatment duration not specified in the article.	Retrospective Study
Evans A, Perez I, Yu G, Kalra L. 2001. Should stroke subtype influence anticoagulation decisions to prevent recurrence in stroke patients with atrial fibrillation? Stroke 32(12):2828-2832.	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 INR 2.0 to 3.0 (n=214)	Patients were treated and followed for up to 2 years	Clinical Trial
Budaj A, Yusuf S, Mehta SR, Fox KAA, Tognoni G, Zhao F, Chrolavicius S, Hunt D, Keltai M, Franzosi mg. 2002. Benefit of clopidogrel in patients with acute coronary syndromes without ST-segment elevation in various risk groups. Circulation 106(13):1622-1626.	12,562	Patients hospitalized within 24 hours after onset of symptoms (patients with ECG changes or elevation in serum levels of cardiac enzymes) without ST-segment elevation (i.e., the Clopidogrel in Unstable angina to prevent Recurrent Events [CURE] Trial).	Aspirin 75-325 mg/day + Clopidogrel 300 mg loading dose followed by clopidogrel 75 mg/day (n=6259) Aspirin 75-325 mg/day + Placebo (n=6303)	Average duration of treatment=9 months	Clinical Trial
CURE Trial Investigators (Clopidogrel In Unstable Angina To Prevent Recurrent Events). 2001. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. New England Journal of Medicine 345(7):494-502.	12,562	Patients hospitalized within 24 hours after onset of symptoms (patients with ECG changes or elevation in serum levels of cardiac enzymes) without ST-segment elevation (CURE Trial)	Aspirin 75-325 mg/day + Clopidogrel 300 mg loading dose followed by clopidogrel 75 mg/day (n=6259) Aspirin 75-325 mg/day + Placebo (n=6303)	3 to 12 months, with a mean treatment duration of 9 months	Clinical Trial

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Mehta SR, Yusuf S, Peters RJG, Bertrand ME, Lewis BS, Natarajan MK, Malmberg K, Rupprecht H, Zhao F, Chrolavicius S, Copland I, Fox KA. 2001. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. <i>Lancet</i> 358(9281):527-533.	2658	Subjects with symptoms indicative of acute coronary syndrome and non-ST-segment elevation of >1 mm on ECG	Double-blind phase: Clopidogrel 300 mg/day + Aspirin 75-325 mg/day (n=1313) Placebo + Aspirin 75-325 mg/day (n=1345) Open label phase (after PCI): Clopidogrel or ticlopidine (Dose unspecified) Aspirin (Dose unspecified)	Subjects were pretreated with aspirin and study medication for a median of 6 days before PCI during the initial hospital admission, and for a median of 10 days overall. After PCI, most subjects received open-label study medication for approximately 4 weeks, after which study drug was restarted for a mean of 8 months.	Clinical Trial
Morais J. 2002. Insights from CURE: using clopidogrel on top of standard therapy. <i>Cerebrovascular diseases</i> 13(Suppl 1):17-21.	12,562	Patients who presented within past 24 hours of onset of the most recent episode of ischemic chest pain/symptoms with suspected acute coronary syndrome without ST-segment elevation >1 mm	Clopidogrel loading dose of 300 mg followed by 75 mg/day + Aspirin 75-325 mg/day (n=6259) Placebo + Aspirin 75-325 mg/day (n=6303)	Average treatment duration=9 months (range of 3 to 12 months)	Clinical Trial
Yusuf S, Mehta SR, Zhao F, Gersh BJ, Commerford PJ, et al. 2003. Early and late effects of clopidogrel in patients with acute coronary syndromes. <i>Circulation</i> 107(7):966-972.	12,562	Patients hospitalized within 24 hours after onset of symptoms (patients with ECG changes or elevation in serum levels of cardiac enzymes) without ST-segment elevation (CURE Trial).	Clopidogrel loading dose of 300 mg administered immediately followed by 75 mg/day + Aspirin 75-325 mg/day (n=6259) Placebo + Aspirin 75-325 mg/day (n=6303)	Average duration of treatment=9 months	Clinical Trial
Castillo J, Leira R, Moro MA, Lizasoain I, Serena J, Davalos A. 2003. Neuroprotective effects of aspirin in patients with acute cerebral infarction. <i>Neuroscience Letters</i> 339(3):248-250.	238	Subjects with a first episode of hemispheric ischemic stroke of less than 24 hours duration. These subjects formed part of a larger group of 270 subjects included in a prospective study associated with neurological deterioration.	Aspirin 75-500 mg/day at the time of stroke onset (n=63) No aspirin at the time of stroke onset (n=175)	Treatment duration was not relevant in this study	Clinical Trial

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Reference	Total Subjects	Patient Population	Treatment Groups (n)	Treatment Duration	Type of Article
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.	55,462	Patients from 16 clinical trials (identified by a MEDLINE search) who received aspirin or a control treatment.	Aspirin 75-1500 mg/day (Mean dose=273 mg/day)	Mean duration of treatment across the 16 trials=37 months.	Meta-analysis
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.	1316	Patients with a TIA or minor ischemic stroke within the preceding 6 months	Aspirin group (Aspirin 30 mg/day [95% of patients], 75 mg/day [3% of patients], or 100 mg/day [2% of patients]) (n=665) Anticoagulant group (Target INR value of 3.0 to 4.5 achieved with phenprocoumon, acenocoumarol, or warfarin. Phenprocoumon was the preferred anticoagulant.) (n=651)	Mean follow-up=14 months	Clinical Trial
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.	8	Patients with noncardioembolic ischemic stroke and medium to high levels of anticardiolipin antibodies (aCL) or lupus anticoagulant (LAC)	Low-dose aspirin, dose not specified during the treatment period. During the follow-up period from the time of the stroke, aspirin doses ranged from 38-80 mg.	Median follow-up=8.9 years	Case Study
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.	6602	Patients with a TIA or ischemic stroke within the preceding 3 months	Aspirin 50 mg/day (n=1649) Dipyridamole 400 mg/day (n=1654) Aspirin 50 mg/day + Dipyridamole 400 mg/day (n=1650) Placebo (n=1649)	Follow-up period=2 years	Clinical Trial
Diener HC, Darius H, Bertrand-Hardy JM, Humphreys M. 2001. Cardiac safety in the European Stroke Prevention Study 2 (ESPS2). <i>International Journal of Clinical Practice</i> 55(3):162-163.	6602	TIA or stroke within preceding three months (ESPS-2 study) stratified by presence of prior history or ECG indicative of angina pectoris (CHD) or MI at entry into ESPS2 study.	Aspirin 50 mg/day (n=1649) Dipyridamole 400 mg/day (n=1654) Aspirin 50 mg/day + Dipyridamole 400 mg/day (n=1650) Placebo (n=1649)	Follow-up period=2 years	Clinical Trial

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Reference	Total Subjects	Patient Population	Treatment Groups (n)	Treatment Duration	Type of Article
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.	6602	Patients with a TIA or ischemic stroke within the preceding 3 months	Aspirin 50 mg/day (n=1649) Dipyridamole 400 mg/day (n=1654) Aspirin 50 mg/day + Dipyridamole 400 mg/day (n=1650) Placebo (n=1649)	Follow-up period=2 years	Clinical Trial
Ishikawa K, Kanamasa K, Hama J, Ogawa I, Takenaka T, Naito T, Yamamoto T, Nakai S, Oyaizu M, Kimura A, Yamamoto K, Katori R. 1997. Aspirin plus either dipyridamole or ticlopidine is effective in preventing recurrent myocardial infarction. <i>Japanese Circulation Journal</i> 61(1):38-45.	618	Patients with a prior MI	Aspirin 50 mg/day + dipyridamole 150 mg/day (n=113) Aspirin 50 mg/day + ticlopidine 200 mg/day (n=253) Aspirin 50 mg/day or dipyridamole 150 mg/day or ticlopidine 200 mg/day alone (n=252) No antiplatelet treatment (n=465)	Not specified; mean observation period of 12.5 months	Clinical Trial
Sivenius J, Cunha L, Diener HC, Forbes C, Laakso M, Lowenthal A, Smets P, Riekkinen P. 1999. Second European Stroke Prevention Study: antiplatelet therapy is effective regardless of age. ESPS2 Working Group. <i>Acta neurologica Scandinavica</i> 99(1):54-60.	6602	Patients with a recent TIA or stroke enrolled in the ESPS-2 Study	Aspirin 50 mg/day Dipyridamole modified-release 400 mg/day Aspirin 50 mg/day + Dipyridamole 400 mg/day Placebo	Follow-up period was 2 years regardless of medication compliance	Clinical Trial
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.	1506	Subjects with unstable CAD (unstable angina or non-Q-wave MI) (Fragmin During Instability in Coronary Artery Disease Study [FRISC]).	Dalteparin 120 IU/kg body weight (maximum 10,000 IU) BID SC for 6 days; subjects then received 7500 IU/day for the next 35-45 days (n=746) Placebo (n=760) All subjects received an initial 300 mg dose of aspirin and 75 mg/day thereafter. Beta-blockers, as well as calcium antagonists and organic nitrates, were also administered as needed.	Treatment duration: 40-50 days Follow-up: 5-7 months	Clinical Trial

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Knottenbelt C, Brennan PJ, Meade TW. 2002. Antithrombotic treatment and the incidence of angina pectoris. Archives of Internal Medicine 162(8):881-886.	5499	Male subjects who were at increased risk of coronary heart disease	Aspirin 75 mg/day controlled release + Warfarin (Started at 2.5 mg/day and adjusted to INR 1.5) (n=1269) Warfarin + placebo (n=1260) Aspirin 75 mg/day controlled release + placebo (n=1252) Double placebo (n=1259)	Participants were followed up for a median of 6.8 years for major outcomes (MI or coronary death). Median follow-up for systematic inquiry about incident angina was 5 years	Clinical Trial
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.	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 controlled release + placebo warfarin (n=1268) Warfarin mean stable INR of 1.47 [4.1 mg/day] + placebo aspirin (n=1268) Warfarin mean stable INR of 1.47 [4.1 mg/day] + Aspirin 75 mg/day controlled release (n=1277) Placebo warfarin + placebo aspirin (n=1272)	Median of 6.8 years	Clinical Trial
Meade TW, Brennan PJ. 2000. Determination of who may derive most benefit from aspirin in primary prevention: subgroup results from a randomised controlled trial. British Medical Journal 321(7252):13-17.	5499	Men considered to be at increased risk of coronary heart disease (i.e., those in the top 20 or 25% based on a risk score)	Aspirin 75 mg/day in a controlled-release formulation + Warfarin 2.5 mg/day with monthly dose adjustments to an INR of 1.5 Warfarin plus placebo Aspirin plus placebo Double Placebo	Treatment duration not specified in the article.	Clinical Trial

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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.	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 for 3 months + heparin [heparin stopped within 48 hours] (n=139) Aspirin 80 mg/day + heparin [until INR 2.0-3.0] followed by Coumarin for 3 months (n=135)	3 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.	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) Warfarin to INR of 2.0 to 2.5 + Aspirin 80 mg/day (n=44) Following the 12-month treatment period, 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
Oosterga M, Anthonio RL, De Kam PJ, Kingma JH, Crijns HJGM, Van Gilst WH. 1998. Effects of aspirin on angiotensin-converting enzyme inhibition and left ventricular dilation one year after acute myocardial infarction. <i>American Journal of Cardiology</i> 81(10):1178-1181.	298	Male and female patients with a first anterior wall MI who originally entered the Captopril and Thrombolysis Study (CATS)	The Captopril and Thrombolysis Study (CATS) was a comparison between captopril and placebo after completion of streptokinase infusion; however, this paper looked at the effect of low dose aspirin (dose not specified) taken prior to the event on acute (infarct size) and long term (LV dilation) outcomes following a first anterior wall MI. Patients were treated with aspirin (80-100 mg/day) after the event at the discretion of the investigator	Duration of aspirin exposure prior to enrollment not reported. Aspirin taken at discretion of investigator following enrollment lasted for the 28-day study duration	Clinical Trial

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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.	999	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 pulverized carbasalate calcium]; equivalent to 80 mg/day aspirin] (n=336) Oral anticoagulants (Phenprocoumon or acenocoumarol) with a target INR of 3.0-4.0 (n=330) Aspirin 80 mg/day + Oral anticoagulants (target INR of 2.0-2.5) (n=333)	Median follow-up=12 months	Clinical Trial
Akaike M, Azuma H, Kagawa A, Matsumoto K, Hayashi I, Tamura K, Nishiuchi T, Iuchi T, Takamori N, Aihara KI, Yoshida T, Kanagawa Y, Matsumoto T. 2002. Effect of aspirin treatment on serum concentrations of lipoprotein(a) in patients with atherosclerotic diseases. <i>Clinical Chemistry</i> 48(9):1454-1459.	70	Subjects with CAD or cerebral infarction who had high serum lipoprotein(a) [Lp(a)] (≥ 300 mg/L) or low serum Lp(a) (<300 mg/L). All subjects were Japanese	Aspirin 81 mg/day [+ high Lp(a)] (n=37) Aspirin 81 mg/day [+ low Lp(a)] (n=33)	6 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.	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=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.	4495	Subjects with one or more cardiovascular risks	Aspirin 100 mg/day (n=2226) No aspirin (n=2269) (Each with or without Vitamin E)	Mean follow-up was 3.6 years for a total of 16,390 person years	Clinical Trial

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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.	50	Subjects with aneurysmal subarachnoid hemorrhage who had undergone surgery within 4 days after the subarachnoid hemorrhage	Aspirin 100 mg suppositories (n=24) Placebo (n=26)	21 days	Clinical Trial
Lee TK, Chan KW, 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.	466	Patients who had a first non-cardiogenic stable ischemic stroke (including lacunar infarction) or reversible ischemic neurological deficit and were 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) Nicametate citrate 50 mg/day, initiated within 3 to 6 weeks after the onset of stroke (n=244)	Aspirin (Mean follow-up of 612 days) Nicametate citrate (Mean follow-up of 625 days)	Clinical Trial
Garcia Rodriguez LA, Varas C, Patrono C. 2000. Differential effects of aspirin and non-aspirin nonsteroidal antiinflammatory drugs in the primary prevention of myocardial infarction in postmenopausal women. <i>Epidemiology</i> 11(4):382-387.	1,013	Female subjects with first validated case of MI identified from a cohort of women registered in the General Practice Research Database between January 1991 and December 1995 who had no history of MI, other coronary heart disease, stroke, neoplasms, coagulopathies, vasculitis, and alcohol-related diseases	Aspirin: 150 mg/day or >150 mg/day (300 mg/day accounting for close to 90% of this dose category) Nonaspirin NSAID: low-/medium-dose or high-dose categories	Duration of therapy was defined as the period for which "continuous" supply was prescribed.	Case Study
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.	1036	Patients with MI who received anistreplase thrombolysis	Aspirin 150 mg/day (n=519) Anticoagulation therapy (1000 U/hr of I.V. heparin followed by warfarin or other oral anticoagulant; heparin discontinued when INR >2 and maintained between 2-2.5) (n=517)	Aspirin given immediately after anistreplase and then daily for 3 months Heparin given 6 hours after anistreplase; warfarin or other anticoagulant given within 24 hours after anistreplase for 3 months	Clinical Trial

APPENDIX 1. TABLE OF STUDIES - PUBLICATIONS PROVIDING ADDITIONAL EFFICACY INFORMATION

Reference	Total Subjects	Patient Population	Treatment Groups (n)	Treatment Duration	Type of Article
O'Connor FF, Shields DC, Fitzgerald A, Cannon CP, Braunwald E, Fitzgerald DJ. 2001b. Genetic variation in glycoprotein IIb/IIIa (GPIIb/IIIa) as a determinant of the responses to an oral GPIIb/IIIa antagonist in patients with unstable coronary syndromes. Blood 98(12):3256-3260.	1014	Substudy of OPUS-TIMI-16 examining the safety and efficacy of orbofiban in patients with unstable coronary syndromes.	Orbofiban 50/30 mg group (50 mg orbofiban bid for 30 days followed by 30 mg bid + aspirin 150-162 mg daily) (n=353) Orbofiban 50/50 mg group (50 mg orbofiban bid for 30 days followed by 50 mg bid + aspirin 150-162 mg daily) (n=308) Placebo group (placebo + aspirin 150-162 mg daily) (n=353)	Variable (1-15 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.	449	Subjects with acute ischemic stroke and AF	Aspirin 160 mg/day + placebo ampules SC BID (n=225) Dalteparin 100 IU/kg SC BID + placebo tablets (n=224)	14 days (range: 11-17 days) or until earlier discharge	Clinical Trial
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.	21,106	Patients with suspected acute ischemic stroke	Aspirin 160 mg/day (n=10,554) Placebo (n=10,552)	4 weeks	Clinical Trial
Courmadin 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.	8803	Subjects who had had an MI 3-21 days prior to enrollment.	Aspirin 160 mg/day (n=3393) Warfarin 1 mg + Aspirin 80 mg/day (n=2028) Warfarin 3 mg + Aspirin 80 mg/day (n=3382) The dose of warfarin was reduced if a subject's INR was above 3.5	The median follow-up period was 14 months	Clinical Trial

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Reference	Total Subjects	Patient Population	Treatment Groups (n)	Treatment Duration	Type of Article
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.	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)	Mean duration was 1445 days	Clinical Trial
O'Connor CM, Gattis WA, Hellkamp AS, Langer A, Larsen RL, Harrington RA, Berkowitz SD, O'Gara PT, Kopecky SL, Gheorghide M, Daly R, Califf RM, Fuster V. 2001a. Comparison of two aspirin doses on ischemic stroke in post-myocardial infarction patients in the warfarin (Coumadin) Aspirin Reinfarction Study (CARS). <i>American Journal of Cardiology</i> 88(5):541-546.	5421	Subjects who had an MI 3-21 days prior to enrollment.	Aspirin 160 mg/day (n=3393) Warfarin 1 mg + Aspirin 80 mg/day (n=2028)	The median follow-up period was 14 months	Clinical Trial
Scrutinio D, Cimminiello C, Marubini E, Pitzalis MV, Di Biase M, Rizzon P. 2001. Ticlopidine versus aspirin after myocardial infarction (STAMI) trial. <i>Journal of the American College of Cardiology</i> 37(5):1259-1265.	1470	Survivors of acute MI (AMI) treated with thrombolysis	Aspirin 160 mg/day (n=736) Ticlopidine 500 mg/day (n=734)	Follow-up period=6 months	Clinical Trial
Second SYMPHONY Investigators. 2001. Randomized trial of aspirin, sibrifiban, or both for secondary prevention after acute coronary syndromes. <i>Circulation</i> 103(13):1727-1733.	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)	Mean follow-up period of approximately 95 days	Clinical Trial

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Reference	Total Subjects	Patient Population	Treatment Groups (n)	Treatment Duration	Type of Article
SYMPHONY Investigators. 2000. Comparison of sibrifiban with aspirin for prevention of cardiovascular events after acute coronary syndromes: a randomised trial. Lancet 355(9201):337-345.	9233	Patients with MI or angina	Aspirin 160 mg/day (n=3089)	90 days	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.	5059	Long-term follow-up of patients who had an MI within 14 days of original admission and who were not being treated with high-dose ASA or NSAIDs	Aspirin 162 mg/day (n=2537) Aspirin 81 mg/day + Warfarin [INR 1.5-2.5 IU] (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
Ariyo A, Hennekens CH, Stampfer MJ, Ridker PM. 1998. Lipoprotein (a), lipids, aspirin, and risk of myocardial infarction in the Physician's Health Study. Journal of Cardiovascular Risk 5(4):273-278.	592	Follow-up analysis from the Physicians' Health Study (PHS), a randomized, double-blind, placebo-controlled trial of aspirin and beta-carotene for the primary prevention of cardiovascular disease and cancer in 22,071 apparently healthy male physicians.	Aspirin 325 mg QOD (n=255) Placebo (n=337)	Treatment duration was an average of 60 months	Case Study

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Reference	Total Subjects	Patient Population	Treatment Groups (n)	Treatment Duration	Type of Article
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.	18,496	Apparently healthy male physicians	Aspirin 325 mg QOD	Treatment duration up to 12 years	Observational Study
Ma J, Hennekens CH, Ridker PM, Stampfer MJ. 1999. A prospective study of fibrinogen and risk of myocardial infarction in the Physicians' Health Study. Journal of the American College of Cardiology 33(5):1347-1352.	398	Nested within the Physicians' Health Study (PHS), this analysis involved blood samples taken from 199 physicians who subsequently developed myocardial infarction after 5 years of follow-up. Each case was matched with a sample from a subject free of MI	Aspirin 325 mg QOD versus placebo Aspirin assignment in case subjects was 32%; aspirin assignment in control subjects was 46% Subjects were also randomly assigned to take QOD beta-carotene (50 mg) in a 2 X 2 factorial design	Approximately 5 years	Case Control
High-Dose Aspirin (>200 mg/day)					
Bar Dayan Y, Levy Y, Amital H, Shoenfeld Y. 1997. Aspirin for prevention of myocardial infarction. A double-edge sword. Annales de Medecine Interne 148(6):430-433.	15	Patients treated with low-dose aspirin for secondary prevention of ischemic heart disease who had upper GI bleeding and were admitted to the hospital because of unstable angina or MI	Aspirin 100 mg/day (n=1) Aspirin 250 mg/day (n=13) Aspirin 325 mg/day (n=0) Aspirin 500 mg/day (n=1)	Unknown: 4 subjects <1 month: 4 subjects 1 month to 1 year: 1 subject >1 year: 6 subjects	Case Study
Strater R, Kurnik K, Heller C, Schobess R, Luigs P, Nowak-Gottl U. 2001. Aspirin versus low-dose low-molecular-weight heparin: Anti-thrombotic therapy in pediatric ischemic stroke patients: A prospective follow-up study. Stroke 32(11):2554-2558.	135	White children 7 months to 18 years with a first episode of an ischemic stroke	Aspirin 4 mg/kg body weight per day; range, 2 to 5 mg/kg (n=49) Low-dose low-molecular weight (LMWH) heparin (enoxaparin [1 to 1.5 mg/kg body weight per day] or dalteparin [75 to 125 anti-Xa U/kg body wt per day]) (n=86)	Treatment for 6 to 14 months Follow-up for 8 to 48 months	Clinical Trial

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Reference	Total Subjects	Patient Population	Treatment Groups (n)	Treatment Duration	Type of Article
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 AGG. 2001. Tinzaparin in acute ischaemic stroke (TAIST): a randomised aspirin-controlled trial. <i>Lancet</i> 358(9283):702-710.	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
Cesarone MR, Laurora G, DeSanctis MT, Incandela L, Fugazza L, Girardello R, Poli A, Peracino L, Ambrosoli L, Belcaro G. 1999. Effects of triflusal on arteriosclerosis progression assessed with high-resolution arterial ultrasound. <i>Angiology</i> 50(6):455-463.	43	Patients with subclinical atherosclerotic lesions as classified by ultrasound arterial morphology entered the study. Patients with significant cerebrovascular or cardiovascular disorders requiring treatment were excluded.	Aspirin 300 mg QD (n=22) Triflusal 300 mg BID (n=21)	Two-week placebo run-in followed by 12 months of treatment	Clinical Trial
Cruz Fernandez JM, Lopez GAV, Marfil Montoya F, Pabon Osuna P, Navarro Salas E, Garcia-Dorado D, Lopez-Bescos L. 1999. Managing acute myocardial infarction: Clinical implications of the TIM study. <i>European Heart Journal, Supplement 1(F):F12-F18.</i>	2275	Subjects hospitalized within 24 hours of AMI symptom onset were randomized	Aspirin 300 mg/day (n=1140) Triflusal 600 mg/day (n=1135)	The primary and secondary endpoints were measured at 35 days after AMI	Clinical Trial
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.	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)	35 days	Clinical Trial

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Reference	Total Subjects	Patient Population	Treatment Groups (n)	Treatment Duration	Type of Article
Droste DW, Sonne M, Siemens HJ, Kaps M. 1996. Asymptomatic circulating cerebral emboli and cerebral blood flow velocity under aspirin and ticlopidine in patients with cerebrovascular disease. <i>Neurological Research</i> 18(5):449-453.	53	Inpatients admitted to the hospital for cerebral ischemia and outpatients with varying degrees of carotid stenosis	Aspirin 300 mg QD for 2 weeks followed by ticlopidine 250 mg BID for 2 weeks (n=26) Treatment scheme reversed (n=27)	14 days of the first medication followed by 14 days of the second medication	Clinical Trial
Goertler M, Baeumer M, Kross R, Blaser T, Lutze G, Jost S, Wallesch CW. 1999. Rapid decline of cerebral microemboli of arterial origin after intravenous acetylsalicylic acid. <i>Stroke</i> 30(1):66-69.	9	Patients with TIA or minor strokes attributable to the territory of the middle cerebral artery (nondisabling cerebral ischemia of probable arterioembolic origin and had not started on antiplatelet or anticoagulant medications since the onset of symptoms)	Aspirin 500 mg i.v. bolus into the antecubital vein following 1-hour of continuous microembolic signals (MES) monitoring. Aspirin 300 mg/day p.o. was started the day after the i.v. bolus	Not specified	Clinical Trial
Gullov AL, Koefoed BG, Petersen P, Pedersen TS, Andersen ED, Godfredsen 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.	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 to INR 2.0 to 3.0 (n=170)	Approximately 3 years	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. <i>Lancet</i> 349(9065):1569-1581.	19,435	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 (n=9720) No aspirin (n=9715) Unfractionated heparin (5000 IU [low-dose] or 12500 IU [medium-dose] SC BID) (n=9717) No heparin (n=9718)	Treatment was to continue for 14 days or until prior discharge	Clinical Trial

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Reference	Total Subjects	Patient Population	Treatment Groups (n)	Treatment Duration	Type of Article
Mas JL, Arquizan C, Lamy C, Zuber M, Cabanes L, Derumeaux G, Coste J. 2001. Recurrent cerebrovascular events associated with patent foramen ovale, atrial septal aneurysm, or both. <i>New England Journal of Medicine</i> 345(24):1740-1746.	581	Eligible patients (18-55 years) and who had an ischemic stroke (defined as a neurological deficit that lasted more than 24 hours) within the preceding three months for which no definite cause had been identified after a standardized work-up	Aspirin 300 mg/day Patients without atrial septal abnormalities (n=304) Patients with atrial septal abnormalities (n=277)	Mean follow-up of 37.8 months	Follow-up study
Ryglewicz D, Baranska-Gieruszczak M, Czlonkowska A, Lechowicz W, Hier DB. 1997. Stroke recurrence among 30 days survivors of ischemic stroke in a prospective community-based study. <i>Neurological Research</i> 19(4):377-379.	209	A cohort of patients who survived 30 days after 'first-ever-in-lifetime-ischemic-stroke' were followed for 1 year for recurrent stroke	Aspirin 300 mg/day in 134 (64%) of patients	Only 81 (38.7%) of patients continued antiplatelet therapy for the whole year.	Population-Based Study
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. <i>American Journal of Cardiology</i> 85(8):1033-1035.	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)	Follow-up averaged 36 months	Observational Study
Bartorelli AL, Trabattoni D, Montorsi P, Fabbicocchi F, Galli S, Ravagnani P, Grancini L, Cozzi S, Loaldi A. 2002. Aspirin alone antiplatelet regimen after intracoronary placement of the Carbostent: The Antares study. <i>Catheterization and Cardiovascular Interventions</i> 55(2):150-156.	110	Patients undergoing intracoronary Carbostent implantation at a Milan hospital	Aspirin 325 mg/day alone in all patients (aspirin 500 mg i.v. was administered immediately before the procedure if the patient had not been pretreated with aspirin)	Aspirin treatment was continued indefinitely after the procedure	Clinical Trial

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Reference	Total Subjects	Patient Population	Treatment Groups (n)	Treatment Duration	Type of Article
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.	19,099	Subjects with atherosclerotic disease manifested as recent ischemic stroke or MI or symptomatic PAD	Aspirin 325 mg/day (n=9546) Clopidogrel 75 mg/day (n=9553)	1-3 years	Clinical Trial
Bhatt DL, Chew DP, Hirsch AT, Topol EJ. 2001. Clopidogrel reduced recurrent ischaemic events in patients with previous cardiac surgery more than aspirin. <i>Evidence-Based Medicine</i> 6(4):114	1480	Subgroup analysis of the CAPRIE study: Patients with recent ischemic stroke, MI, or peripheral artery disease who also had cardiac surgery	Aspirin 325 mg/day (n=705) Clopidogrel 75 mg/day (n=775)	1 to 3 years	Commentary-Treatment Guideline
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.	3866	In this retrospective subanalysis of the CAPRIE 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)	1-3 years	Retrospective Subanalysis
Cannon CP. 2002. Effectiveness of clopidogrel versus aspirin in preventing acute myocardial infarction in patients with symptomatic atherothrombosis (CAPRIE trial). <i>American Journal of Cardiology</i> 90(7):760-762.	19,185	Patients with symptomatic atherosclerosis manifested as recent ischemic stroke, MI, or peripheral artery disease	Aspirin 325 mg/day (n=9586) Clopidogrel 75 mg/day (n=9599)	1-3 years (mean follow-up of 1.9 years)	Retrospective Analysis
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). <i>Lancet</i> 348(9038):1329-1339.	19,185	Patients with symptomatic atherosclerosis manifested as recent ischemic stroke, MI, or peripheral artery disease (CAPRIE Trial)	Aspirin 325 mg/day (n=9586) Clopidogrel 75 mg/day (n=9599)	1 to 3 years	Clinical Trial

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Reference	Total Subjects	Patient Population	Treatment Groups (n)	Treatment Duration	Type of Article
Chan K-L, Dumesnil JG, Cujec B, Sanfilippo AJ, Jue J, Turek MA, Robinson TI, Moher D. 2003. A randomized trial of aspirin on the risk of embolic events in patients with infective endocarditis. <i>Journal of the American College of Cardiology</i> 42(5):775-780.	115	Patients with infective endocarditis between 16 and 80 years of age	Aspirin 325 mg/day (n=60) Placebo (n=55)	4 weeks	Clinical Trial
Creager MA. 1998. Results of the CAPRIE trial: efficacy and safety of clopidogrel. <i>Vascular medicine</i> 3(3):257-260.	19,185	Patients with symptomatic atherosclerosis manifested as recent ischemic stroke, MI, or peripheral artery disease (CAPRIE Trial)	Aspirin 325 mg/day (n=9586) Clopidogrel 75 mg/day (n=9599)	1-3 years	Clinical Trial
Ferro M, Crivello R, Rizzotti M. 2000. Comparison of subcutaneous calcium heparin and acetylsalicylic acid in the prevention of ischemic events and death after myocardial infarction: a randomized trial in a consecutive series of 90 patients. <i>Heart Disease</i> 2(4):278-281	90	Patients discharged from a coronary care unit after acute myocardial infarction	Aspirin 325 mg/day (n=46) Aspirin 325 mg/day + Calcium heparin 12,500 IU daily (n=44)	Aspirin (6 months) Calcium heparin + aspirin (heparin for 3 months followed by aspirin 325 mg/day for 3 months)	Clinical Trial
Goldstein RE, Andrews M, Hall WJ, Moss AJ. 1996. Marked reduction in long-term cardiac deaths with aspirin after a coronary event. <i>Journal of the American College of Cardiology</i> 28(2):326-330.	936	From the Multicenter Study of Myocardial Ischemia (patients after an acute MI or unstable angina)	Patients taking aspirin regularly (n=751): dosing at baseline: 325 mg/day (n=585) 250 mg/day (n=93) 160 mg/day (n=6) 80 mg/day (n=29) 325 mg QOD (n=11) Other dosing patterns (n=27) Patients not taking aspirin regularly (n=185)	Follow-up occurred for an average of 23 months. A total of 695 of the 751 regular aspirin users continued their regular aspirin use. Of these 695 patients, 676 took 250 mg or 325 mg aspirin QD. Aspirin doses <250 mg were taken by relatively few patients	Retrospective Study

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Hall P, Nakamura S, Maiello L, Itoh A, Blengino S, Martini G, Ferraro M, Colombo A. 1996. A randomized comparison of combined ticlopidine and aspirin therapy versus aspirin therapy alone after successful intravascular ultrasound-guided stent implantation. <i>Circulation</i> 93(2):215-222.	226	Patients after successful intravascular ultrasound-guided stent implantation	Aspirin 325 mg/day (n=103) Ticlopidine 250 mg BID + Aspirin 325 mg/day (n=123)	Aspirin group: indefinitely. Ticlopidine + aspirin group: ticlopidine for 1 month and aspirin for 5 days Follow-up: 2 months	Clinical Trial
Harker LA, Boissel JP, Pilgrim AJ, Gent M. 1999. Comparative safety and tolerability of clopidogrel and aspirin: results from CAPRIE.. <i>Drug Safety</i> 21(4):325-335.	19,185	Patients with symptomatic atherosclerosis manifested as recent ischemic stroke, MI, or symptomatic peripheral artery disease	Aspirin 325 mg/day (n=9586) Clopidogrel 75 mg/day (n=9599)	1 to 3 years	Clinical Trial
Hart RG, Pearce LA, McBride R, Rothbart RM, Asinger RW. 1999b. Factors associated with ischemic stroke during aspirin therapy in atrial fibrillation: analysis of 2012 participants in the SPAF I-III clinical trials. <i>Stroke</i> 30(6):1223-1229.	2012	This study was a pooled analysis of the data from the SPAF I-III trials, which enrolled patients with documented sustained or recurrent atrial fibrillation (AF) without mitral stenosis or prosthetic cardiac valves from 25 clinical sites	Aspirin 325 mg/day (n=1722) Aspirin 325 mg/day + Warfarin (mean daily dose was 2.1 mg) (n=290)	Follow-up: 2 years	Meta-analysis
Homma S, Sacco RL, Di Tullio MR, Sciacca RR, Mohr JP. 2002. Effect of medical treatment in stroke patients with patent foramen ovale: Patent foramen ovale in Cryptogenic Stroke Study. <i>Circulation</i> 105(22):2625-2631.	630	Patients who had experienced ischemic stroke within the previous 30 days	Aspirin 325 mg/day (n=318) Warfarin 2 mg/day (n=312)	Treatment duration up to 2 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.	831	Subjects who underwent peripheral arterial bypass surgery.	Aspirin 325 mg/day (n=413) Aspirin 325 mg/day + Warfarin 5 mg/day with a target INR of 1.4-2.8 (n=418)	Prosthetic bypass (Average follow-up period=36.6 months) Vein bypass (Average follow-up period=39.3 months.)	Clinical Trial

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Leon MB, Baim DS, Popma JJ, Gordon PC, Cutlip DE, Ho KKL, 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.	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	Aspirin 325 mg/day (n=557) Aspirin 325 mg/day + Heparin i.v. to an aPTT of 40 to 60 seconds, substituted with oral warfarin once an INR of 2.0 to 2.5 was reached) (n=550) Aspirin 325 mg/day + Ticlopidine 500 mg/day (n=546)	30 days	Clinical Trial
Matias-Guiu J, Ferro JM, 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.	2107	Patients (40 years 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. Mean follow-up: 30.1 months	Clinical Trial
Mehran R, Aymong ED, Ashby DT, Fischell T, Whitworth H Jr, Siegel R, et al. 2003. Safety of an aspirin-alone regimen after intracoronary stenting with a heparin-coated stent: Final results of the HOPE (HEPACOAT and an antithrombotic regimen of aspirin alone) Study. <i>Circulation</i> 108(9):1078-1083.	200	Patients with evidence of ischemia or lesions in native coronary vessel	Aspirin 325 mg/day	The article states that aspirin was taken through hospital discharge	Clinical Trial
Miller VT, Pearce LA, Feinberg WM, Rothrock JF, Anderson DC, Hart RG. 1996. Differential effect of aspirin versus warfarin on clinical stroke types in patients with atrial fibrillation. <i>Neurology</i> 46(1):238-240.	49	Patients enrolled in the SPAF II study who suffered an ischemic stroke during the trial	Aspirin 325 mg/day (n=545) Warfarin adjusted to maintain INR 2.0 to 4.5 (n=555)	Duration of treatment prior to the development of stroke not specified in the article	Clinical Trial

APPENDIX 1. TABLE OF STUDIES - PUBLICATIONS PROVIDING ADDITIONAL EFFICACY INFORMATION

Reference	Total Subjects	Patient Population	Treatment Groups (n)	Treatment Duration	Type of Article
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.	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 and has scores of 3 or more on the Glasgow Outcome Scale	Aspirin 325 mg/day (n=1103) Warfarin 2 mg/day to INR 1.4 to 2.8(n=1103)	2 years	Clinical Trial
Obialo CI, Conner AC, Lebon LF. 2003. Maintaining patency of tunneled hemodialysis catheters - Efficacy of aspirin compared to warfarin. <i>Scandinavian Journal of Urology and Nephrology</i> 37(2):172-176.	63	Patients with cuffed tunneled hemodialysis catheters awaiting maturation of their arteriovenous fistulae	Aspirin 325 mg/day (n=21) Warfarin (dose-adjusted to INR of 2-3) (n=11) Control (neither aspirin or warfarin) (n=31)	Follow-up period=120 days	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.	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 to INR 2 to 3 + heparin 15 units/kg (n=32)	3 to 5 years	Clinical Trial
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. <i>Journal of the American Medical Association</i> 279(16):1273-1277.	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 at age older than 75 years)	Aspirin 325 mg/day	Patients were treated and followed for a mean of 2 years	Clinical Trial

APPENDIX 1. TABLE OF STUDIES - PUBLICATIONS PROVIDING ADDITIONAL EFFICACY INFORMATION

Reference	Total Subjects	Patient Population	Treatment Groups (n)	Treatment Duration	Type of Article
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.	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 (no specific dose required or specified; 21 of 26 patients were treated with at least 325 mg/day) (n=26) Warfarin (no specific dose required or specified; warfarin therapy was typically adjusted to maintain prothrombin times in the range of 1.2 to 1.6 times control (n=42) It should be noted that none of the investigational centers were using prothrombin time international normalized ratio for measuring levels of anticoagulation during the study period of 1985 to 1991)	Patients were treated and followed for a median of 13.8 months	Retrospective Study
Westrich GH, Haas SB, Mosca P, Peterson M. 2000. Meta-analysis of thromboembolic prophylaxis after total knee arthroplasty. <i>Journal of Bone and Joint Surgery</i> . 82(6):795-800.	6001	Patients after total knee arthroplasty from 23 studies	Aspirin between 325 and 650 mg/day Warfarin 5 or 10 mg on the evening before or night of operation with daily doses on the first or second day after operation with PT time kept at 1.3 to 1.5 of normal Low Molecular Weight Heparin Intermittent pneumatic compression started during or after the operation.	Treatment duration not specified in the article	Meta-analysis
Young B, Moore WS, Robertson JT, Toole JF, Ernst CB, Cohen SN, Broderick JP, Dempsey RJ, Hosking JD. 1996. An analysis of perioperative surgical mortality and morbidity in the Asymptomatic Carotid Atherosclerosis Study. <i>Stroke</i> 27(12):2216-2224.	825	There were 1662 subjects with $\geq 60\%$ carotid stenosis enrolled in the Asymptomatic Carotid Atherosclerosis Study (ACAS). Subjects in the current study included those from ACAS randomized to the surgical arm of the study (underwent carotid endarterectomy)	Aspirin 325 mg/day All subjects in the ACAS also underwent aggressive risk factor reduction	Treatment duration for aspirin was not given in the current study	Clinical Trial

APPENDIX 1. TABLE OF STUDIES - PUBLICATIONS PROVIDING ADDITIONAL EFFICACY INFORMATION

Reference	Total Subjects	Patient Population	Treatment Groups (n)	Treatment Duration	Type of Article
Cesarone MR, Belcaro G, Nicolaides AN, Incandela L, De Sanctis MT, Geroulakos G, Lennox A, Myers KA, Moia M, Ippolito E, Winford M. 2002. Venous thrombosis from air travel: The LONFLIT3 study: Prevention with aspirin vs low-molecular-weight heparin (LMWH) in high-risk subjects: A randomized trial. <i>Angiology</i> 53(1):1-6.	300	Subjects at high risk for DVT	Aspirin 400 mg/day x 3 days starting 12 hours before the beginning of the flight LMWH (enoxaparin) 1,000 IU per 10 kg body weight injected between 2-4 hours before the flight Control (no prophylaxis)	3 days for aspirin group; 1 day for LMWH group	Clinical Trial
Grotemeyer KH, Evers S, Fischer M, Husstedt IW. 2000. Piracetam versus acetylsalicylic acid in secondary stroke prophylaxis. A double-blind, randomized, parallel group, 2 year follow-up study. <i>Journal of the Neurological Sciences</i> 181(1-2):65-72.	563	Patients after stroke as confirmed by computed tomography (CT) or magnetic resonance imaging (MRI)	Aspirin 200 mg TID (n=307) Piracetam 1600 mg TID (n=256)	2 years	Clinical Trial

APPENDIX 1. TABLE OF STUDIES - PUBLICATIONS PROVIDING ADDITIONAL EFFICACY INFORMATION

Reference	Total Subjects	Patient Population	Treatment Groups (n)	Treatment Duration	Type of Article
Tangelder MJD, Lawson JA, Algra A, Eikelboom BC. 1999. Systematic review of randomized controlled trials of aspirin and oral anticoagulants in the prevention of graft occlusion and ischemic events after infrainguinal bypass surgery. <i>Journal of Vascular Surgery</i> 30(4):701-709.	1002	Patients after infrainguinal bypass surgery in 7 published studies	<u>Green (1982):</u> Aspirin 975 mg/day (n=16) Aspirin 975 mg/day + dipyridamole (DP) 225 mg/day (n=16) Placebo (n=17) <u>Goldman (1984):</u> Aspirin 900 mg/day + DP 225 mg/day (n=22) Placebo (n=31) <u>Kohler (1984):</u> Aspirin 975 mg/day + DP 225 mg/day (n=50) Placebo (n=50) <u>Donaldson (1985):</u> Aspirin 990 mg/day + DP 225 mg/day (n=33) Placebo (n=32) <u>McCollum (1991):</u> Aspirin 600 mg/day + DP 300 mg/day (n=286) Placebo (n=263) <u>Kretchmer (1992):</u> Phenprocoumon 2.4-4.8 INR (n=66) No treatment (n=64) <u>Sarac (1998):</u> Warfarin 2-3 INR + Aspirin 325 mg/day (n=32) Aspirin 325 mg/day (n=24)	12 to 120 months	Meta-analysis
Gorelick PB, 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.	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

APPENDIX 2. SUMMARY OF EFFICACY RESULTS - PUBLICATIONS PROVIDING ADDITIONAL EFFICACY INFORMATION

Reference	Type of Article	Total Subjects	Treatment Groups (n)	Efficacy Data
Low-Dose Aspirin (≤ 200 mg/day)				
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	6300	Aspirin doses investigated in these 6 studies included 50, 75, 300 and 325 mg/day. (n=3127) Placebo (n=3173)	All-cause mortality: 0.82 risk ratio (95% CI 0.7-0.99; p=0.03); 18% risk reduction MI: 0.7 risk ratio (95% CI 0.6 - 0.8; p<0.001); 30% risk reduction Stroke: 0.8 risk ratio (95% CI 0.7-1.0; p=0.07); 20% risk reduction MI was reported in 5 of the 6 studies, while stroke was reported in only 2 studies. To include all studies, the authors created the event category 'vascular events' to summarize all reports of MI, stroke, and other vascular events including vascular death. Vascular events: 0.7 risk ratio (95% CI 0.6 - 0.8; p<0.001); 30% risk reduction
Wilterdink JL, Easton JD. 1999. Dipyridamole plus aspirin in cerebrovascular disease. Archives of Neurology 56(9):1087-1092.	Meta-analysis	11,919	ESPS-2 trial treatments (n=6602): Aspirin 50 mg/day Sustained-release dipyridamole 400 mg/day Aspirin 50 mg/day + dipyridamole 400 mg/day Placebo Antiplatelet Trialists' Collaboration trial treatments (n=5317): Aspirin alone (dosages varied from 150-1300 mg/day; median aspirin dose = 975 mg/day) Aspirin + dipyridamole tablets (median aspirin dose = 225 mg/day)	% odds reduction for each outcome event for dipyridamole plus aspirin vs. aspirin alone: 14 trials analyzed by the Antiplatelet Trialists: Nonfatal MI -4%; nonfatal stroke 12%; vascular death -7%, all vascular events -3%; nonvascular death -28%; total deaths -11% 3 trials involving patients with cerebrovascular disease: Nonfatal MI -7%; nonfatal stroke 17%; vascular death -6%, all vascular events 6%; nonvascular death -26%; total deaths -12% ESPS-2 trial plus the 14 trials from the Antiplatelet Trialists Collaboration: Nonfatal MI -4%; nonfatal stroke 23%; vascular death -3%, all vascular events 10%; nonvascular death -14%; total deaths -6% ESPS-2 trial plus the 3 cerebrovascular trials: Nonfatal MI -6%; nonfatal stroke 25%; vascular death -1%, all vascular events 18%; nonvascular death -11%; total deaths -5%

APPENDIX 2. SUMMARY OF EFFICACY RESULTS - PUBLICATIONS PROVIDING ADDITIONAL EFFICACY INFORMATION

Reference	Type of Article	Total Subjects	Treatment Groups (n)	Efficacy Data
<p>Atrial Fibrillation Investigators. 1997. The efficacy of aspirin in patients with atrial fibrillation: analysis of pooled data from 3 randomized trials. Archives of Internal Medicine 157(11):1237-1240.</p>	<p>Meta-analysis</p>	<p>2574</p>	<p>AFASAK: aspirin 75 mg/day or placebo (n=672) EAFT: aspirin 300 mg/day or placebo (n=782) SPAF1: aspirin 325 mg/day or placebo (n=1120)</p>	<p>Aspirin therapy seemed particularly effective in younger patients and in patients with hypertension in SPAF1, but not in the other 2 studies. When all patients were combined, those with a history of hypertension had a statistically significant 36% relative reduction in the risk of stroke associated with aspirin therapy (p=0.009). However, the interaction between a history of hypertension and aspirin therapy (p=0.08) did not reach conventional statistical significance, nor did the interaction of any other variables with aspirin efficacy.</p> <p>The overall relative risk reduction with aspirin therapy was 21% (95% CI: 0% to 38%; p=0.05). Disabling stroke occurrence was decreased by 17% (95% CI: -12% to 38%; p=0.23) and non-disabling stroke occurrence by 27% (95% CI: -7% to 51%; p=0.10). In SPAF1 and EAFT, the frequency of stroke, MI, or vascular death was 13.5% in the control group and 10.8% in the aspirin group (relative risk reduction, 19% [95% CI: 1% to 34%; p=0.04]). The AFASAK study did not consider MI an outcome event.</p> <p>Aspirin therapy was not efficacious in patients without risk factors for stroke (increasing age, history of hypertension, previous stroke or TIA, and diabetes). It did appear to be more effective in patients with clinical risk factors (relative risk reduction, 28% [95% CI: 7% to 44%; p=0.01]), although the interaction between the presence of these factors and aspirin therapy was not significant (p=0.10). A secondary analysis in patients with a previous stroke or TIA, the strongest risk factor, showed a relative risk reduction with aspirin use of 19% (95% CI: -7% to 39%; p=0.13) in these patients. In patients with a history of hypertension or diabetes but with no previous stroke or TIA, the relative risk reduction with aspirin use was 54% (95% CI: 17% to 74%; p=0.009; interaction term, p=0.02). Except for patients younger than 65 years, the absolute risk of stroke with aspirin therapy did not decrease below 3.0% per year for any of the risk strata.</p>

APPENDIX 2. SUMMARY OF EFFICACY RESULTS - PUBLICATIONS PROVIDING ADDITIONAL EFFICACY INFORMATION

Reference	Type of Article	Total Subjects	Treatment Groups (n)	Efficacy Data
<p>Hart RG, Halperin JL, McBride R, Benavente O, Man-Son-Hing M, Kronmal RA. 2000. Aspirin for the primary prevention of stroke and other major vascular events: meta-analysis and hypotheses. Archives of Neurology 57(3):326-332.</p>	<p>Meta-analysis</p>	<p>52,251</p>	<p>Aspirin 75 mg/day or placebo (n=21,330) Aspirin 325 mg QOD or placebo (n=22,071) Aspirin 500 to 650 mg/day or placebo (n=8850)</p>	<p>Aspirin therapy was associated with modest increases in the rate of all stroke (includes ischemic and hemorrhagic) in the BDT, USPHS, and ETDRS, a decrease in the MRC-TPT, and no appreciable effect in the HOT, but was not statistically significant in any individual clinical trial or their pooled results (relative risk [RR], 1.08; 95% CI: 0.95-1.24). This contrasted with a highly significant reduction in MI in these trials, with an overall RR reduction in MI of 26% (RR: 0.74; 95% CI: 0.68-0.82; p<0.001). Pooled analysis of all 5 trials revealed a RR of 0.93 (95% CI: 0.83-1.03) for deaths categorized as vascular and 0.94 (95% CI: 0.87-1.01) for all cause mortality.</p> <p>No net effect of aspirin therapy on stroke was noted in the clinical trials of participants with vascular risk factors (i.e., HOT, MRS-TPT, and ETDRS) (RR=1.02; 95% CI: 0.86-1.21) compared to a small increase in the 2 trials of men without risk factors (i.e., USPHS and BDT) (RR: 1.20; 95% CI: 0.96-1.49). Pooled experience in participants with manifest vascular disease (i.e., high risk) by the ATC yielded a 27% RR reduction in stroke (RR: 0.73; 95% CI: 0.67-0.79) by antiplatelet therapy. This effect was incompatible with the effect of aspirin therapy in the 5 clinical trials of primary prevention (p=0.001). In contrast, the effect of aspirin therapy for prevention of MI is similar for those with vs. without vascular disease (about 25%) and for participants with vs. without vascular risk factors in the 5 primary prevention clinical trials (23% vs. 26% reductions, respectively).</p>
<p>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.</p>	<p>Meta-analysis</p>	<p>51,085</p>	<p>Aspirin 75 mg/day or placebo (n=18,790) Aspirin 75 mg/day-controlled release or placebo (n=5085) Aspirin 325 mg QOD or placebo (n=22,071) Aspirin 500 mg/day or open-label control (n=5139)</p>	<p>Subjects who received aspirin therapy had significant reductions of 32% (95% CI: 21%-41%) for nonfatal MI and 13% (95% CI: 5%-19%) for any important vascular event. No significant difference between treatment groups in the risk of ischemic stroke was observed (RR: 1.01, 95% CI: 0.79-1.30).</p>

APPENDIX 2. SUMMARY OF EFFICACY RESULTS - PUBLICATIONS PROVIDING ADDITIONAL EFFICACY INFORMATION				
Reference	Type of Article	Total Subjects	Treatment Groups (n)	Efficacy Data
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. Heart 85(3):265-271.	Meta-analysis	48,540	Aspirin 75 mg/day (TPT, n=1268) (HOT, n=9399) Aspirin 162.5 mg/day (PHS) (n=11,037) Aspirin 500 mg/day (BDT) (n=3429) Placebo (n=23,407)	Aspirin for primary prevention significantly reduced the annual risk of all CV events by 15% (95% CI, 6 to 22) and MIs by 30% (95% CI, 21 to 38), and non-significantly reduced all deaths by 6% (95% CI, -4 to 15). Aspirin non-significantly increased the annual risk of stroke by 6% (95% CI, -24 to 9).
Taylor FC, Cohen H, Ebrahim S. 2001. Systematic review of long term anticoagulation or antiplatelet treatment in patients with non-rheumatic atrial fibrillation. BMJ 322(7282):321-326.	Meta-analysis	3298	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)	The pooled odds ratios (OR) from the fixed effects model showed non-significant trends in favor of anticoagulation in deaths from stroke (OR 0.74; 95% CI: 0.39 to 1.46) and vascular death (OR, 0.86; 95% CI: 0.63 to 1.17). When a random effects model was used because of heterogeneity across trials, there was also no significant difference in the combined fatal and non-fatal events (OR, 0.79; 95% CI: 0.61 to 1.02). Only AFASAK 1 reported greater benefits from long term anticoagulation than antiplatelet treatment, with a 67% reduction in the risk of non-fatal stroke, results that should be interpreted with caution due to the lower methodological quality of this trial and the lower aspirin dose (75 mg/day) used in this trial compared with the other trials.
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.	Meta-analysis	40,090	CAST (Aspirin 160 mg/day versus placebo) (n=20,655) IST (Aspirin 300 mg/day versus control) (n=19,435)	There was a significant reduction of 7 (SD 1) per 1000 in recurrent ischemic stroke (320 [1.6%] aspirin versus 457 [2.3%] control, 2p<0.000001) and a less clearly significant reduction of 4 (SD 2) per 1000 in death without further stroke (5.0% versus 5.4%, 2p=0.05). There was no apparent effect on further stroke of unknown cause (0.9% versus 0.9%, aspirin versus control, respectively). There was an overall 9 (SD 3) per 1000 risk reduction in the composite of any further stroke or death in-hospital (8.2% vs. 9.1%, 2p=0.001). For the composite outcome of death or dependency, the absolute benefit was slightly greater at 12 (SD 5) per 1000 (45.6% vs. 46.9% for aspirin vs. control, 2p=0.01). The absolute reduction of 7 per 1000 (1.6% vs. 2.3% for aspirin vs. control) in recurrent ischemic stroke corresponds to a proportional reduction of 30%. This did not differ significantly with respect to age, sex, level of consciousness, atrial fibrillation, CT findings, blood pressure, stroke subtype, or concomitant heparin use.

APPENDIX 2. SUMMARY OF EFFICACY RESULTS - PUBLICATIONS PROVIDING ADDITIONAL EFFICACY INFORMATION

Reference	Type of Article	Total Subjects	Treatment Groups (n)	Efficacy Data
Mangano DT. 2002. Aspirin and mortality from coronary bypass surgery. <i>New England Journal of Medicine</i> 347(17):1309-1317.	Clinical Trial	5022	Aspirin up to 650 mg/day within 48 hours after revascularization (n=2999) No aspirin (n=2023)	Patients receiving aspirin within 48 hours after revascularization had a significantly reduced mortality (1.3%) compared to patients not receiving aspirin (4.0%, p<0.001). Aspirin therapy significantly reduced the incidence of MI (2.8% vs. 5.4%, p<0.001), congestive heart failure (5.8% vs. 11.0%, p<0.001), death from cardiac causes (1.1% vs. 3.1%, p<0.001), stroke (1.3% vs. 2.6%, p=0.01), encephalopathy (0.4% vs. 2.4%, p<0.001), and death from cerebral causes (0.2% vs. 0.8%, p=0.02). An analysis of fatal and non-fatal events by aspirin dose (for doses from 75 mg to 325 mg) was performed (data not provided); no dose effect was found.
Klootwijk P, Meij S, Melkert R, Lenderink T, Simoons ML. 1998. Reduction of recurrent ischemia with abciximab during continuous ECG-ischemia monitoring in patients with unstable angina refractory to standard treatment (CAPTURE). <i>Circulation</i> 98(14):1358-1364.	Clinical Trial	332	Aspirin minimum daily dose of 50 mg/day + Abciximab 0.25 mg/kg bolus followed by a continuous infusion of 10 mg/min (n=169) Aspirin minimum daily dose of 50 mg/day + Placebo (n=163)	Patients were monitored from start of treatment through 6 hours after coronary intervention. Recurrent ischemia was detected in 31 (18%) of the 169 abciximab and in 37 (23%) of the 163 placebo patients (p=0.34). Excluding the time period of the PTCA and the stay in the catheterization laboratory, only 9 (5%) of abciximab versus 22 (14%) of placebo patients had ≥2 ST episodes. Similarly, only 5 (3%) of abciximab versus 15 (9%) of placebo patients had ≥3 ST episodes (p=0.02). Symptomatic episodes occurred in 5 (3%) of abciximab and 13 (8%) of placebo patients (p=0.05). In patients with ischemia, abciximab significantly reduced total ischemic burden parameters (as defined by the duration of ischemia per patient, the sum of the area under the curve of the ST vector magnitude during ST episodes, the sum of the area under the ST trend curve of all leads involved, or the sum of the area under the curve of all 12 leads during ST episodes). Thus, patients receiving abciximab had significantly less frequent and fewer severe ischemic episodes.

APPENDIX 2. SUMMARY OF EFFICACY RESULTS - PUBLICATIONS PROVIDING ADDITIONAL EFFICACY INFORMATION

Reference	Type of Article	Total Subjects	Treatment Groups (n)	Efficacy Data
<p>Hart RG, Benavente O, McBride R, Pearce LA. 1999a. 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>8856</p>	<p>Aspirin from 50 to 1300 mg/day versus placebo (n=3119) Warfarin (adjusted dose for an INR of 2.0 - 2.6 for primary prevention trials; adjusted to INR of 2.9 for the one secondary prevention trial) versus placebo (n=2900) Warfarin to INR 2.2 to 3.1 versus Aspirin 75-325 mg/day (n=2837)</p>	<p><u>Aspirin versus Placebo Trials (N=6)</u> Meta-analysis of 6 trials (average follow-up 1.5 years per patient) showed that aspirin reduced the incidence of stroke by 22% (95% CI, 2% to 38%). On the basis of these 6 trials, the absolute risk reduction was 1.5% per year (number needed to treat [NNT], 67) for primary prevention and 2.5% per year (NNT, 40) for secondary prevention. Although all 6 trials showed trends toward reduced stroke that were associated with aspirin, this result was statistically significant in only 1 study. When disabling stroke from the 3 largest trials that reported stroke severity was considered, aspirin use was associated with a relative risk reduction of 13% (95% CI, -19% to 36%). When only ischemic strokes were considered from the 3 largest trials, aspirin resulted in a 23% reduction (95% CI, 0% to 40%). According to data from 4 trials, all-cause mortality was not significantly reduced by aspirin (RRR 16%, 95% CI: -5% to 33%).</p> <p><u>Warfarin versus Aspirin Trials (N=5)</u> The effect of warfarin on stroke compared with that of aspirin varied widely among these 5 trials (mean follow-up 2.2 years per patient). No statistically significant heterogeneity was seen (p=0.09), and meta-analysis showed that adjusted-dose warfarin reduced overall relative risk for all stroke by 36% (95% CI, 14% to 52%) compared with aspirin. When only ischemic strokes were considered, adjusted dose warfarin was associated with a 46% (95% CI, 27% to 60%) relative risk reduction compared with aspirin. This difference in relative risk reduction—all strokes compared with only ischemic strokes—was mostly caused by the higher absolute risk for intracranial hemorrhage during warfarin therapy in 1 study. On the basis of data from 4 studies, all-cause mortality was similar in patients who received adjusted-dose warfarin and those who received aspirin (RRR, 95% CI: 8%, -21% to 30%).</p>

APPENDIX 2. SUMMARY OF EFFICACY RESULTS - PUBLICATIONS PROVIDING ADDITIONAL EFFICACY INFORMATION

Reference	Type of Article	Total Subjects	Treatment Groups (n)	Efficacy Data
Kalra L, Perez I, Smithard DG, Sulch D. 2000. Does prior use of aspirin affect outcome in ischemic stroke? American Journal of Medicine 108(3):205-209.	Population-Based Study	1457	Aspirin median daily dose of 75 mg, range of 75 to 300 mg/day. Aspirin was used regularly before the stroke by 650 (45%) of patients.	Use of aspirin prior to stroke was associated with lower 4-week mortality compared with no aspirin use prior to stroke (14% versus 20%, p<0.01) (relative risk, 95% CI: 0.7, 0.6 to 0.9). Beneficial effects of prior aspirin use on 4-week mortality were seen in patients with atherosclerotic strokes (15% versus 21%, p<0.05) and with cardioembolic strokes (21% versus 34%, p<0.05), but not among patients with strokes due to small vessel occlusion (10% versus 11%, p=0.8). Prior aspirin use was also associated with lower mortality in patients in whom the cause of ischemic stroke could not be determined (15% versus 22%, p<0.01). The difference in mortality between the aspirin and nonaspirin group continued to be significant, even when patients with hemorrhagic and other strokes were included (14% versus 21%). The effect of prior aspirin use on mortality was independent of age, gender, other risk factors, and use of other medication.
Srinivasan AK, Grayson AD, Pullan DM, Fabri BM, Dihmis WC. 2003. Effect of preoperative aspirin use in off-pump coronary artery bypass operations. Annals of Thoracic Surgery 76(1):41-45.	Retro-spective Study	340	Aspirin 75 to 300 mg/day (n=170) Nonaspirin users (n=170)	Among patients who had first time off-pump coronary artery bypass operation, there were no significant differences between aspirin and nonaspirin users in in-hospital mortality rate (1.2% versus 1.8%), stroke (0.6% versus 0), and MI (2.4% versus 1.2%). There was a statistically significant difference in post-operative length of stay, although the median was the same in both groups (7 versus 7 days, p<0.001).

APPENDIX 2. SUMMARY OF EFFICACY RESULTS - PUBLICATIONS PROVIDING ADDITIONAL EFFICACY INFORMATION

Reference	Type of Article	Total Subjects	Treatment Groups (n)	Efficacy Data
<p>Evans A, Perez I, Yu G, Kalra L. 2001. Should stroke subtype influence anticoagulation decisions to prevent recurrence in stroke patients with atrial fibrillation? Stroke 32(12):2828-2832.</p>	<p>Clinical Trial</p>	<p>386</p>	<p>Aspirin 75 to 300 mg/day (n=172) Warfarin to INR 2.0 to 3.0 (n=214)</p>	<p>Annual recurrent stroke rate (% and 95% CI) in ischemic stroke patients for warfarin versus aspirin; p-value:</p> <ul style="list-style-type: none"> • All strokes: 4.9 (2.9–7.0) versus 9.5 (6.3–12.7); P <0.02 • Ischemic Stroke: 4.2 (2.3–6.2) versus 9.2 (6.1–12.4); p<0.01 • Fatal Strokes/Strokes Leading to Major Disability: 0.9 (0.02–1.8) versus 3.9 (1.9–6.0); p<0.01 • Total Deaths: 6.5 (4.1–8.8) versus 8.1 (5.1–11.1); p=NS • Vascular Deaths: 4.0 (2.2–5.9) versus 5.9 (3.4–8.4); p=NS • Cerebral Deaths (stroke): 0.4 (0–1.1) versus 2.0 (0.5–3.4); p=NS • Cardiac Deaths: 2.5 (1.0–3.9) versus 3.1 (1.3–4.9); p=NS <p>Annual recurrent stroke rate (% and 95% CI) in ischemic stroke patients by initial stroke subtype for warfarin versus aspirin; p-value:</p> <ul style="list-style-type: none"> • Cardioembolic: 3.3 (1.2-5.5) versus 10.7 (6.3-15.1); p<0.01 • Undetermined: 5.2 (0.1-10.3) versus 6.4 (0.8-12.2); p=NS • Lacunar: 8.8 (3.1-14.6) versus 8.9 (1.8-16.1); p=NS • Total: 4.9 (2.9-7.0) versus 9.5 (6.3-12.7); p=NS
<p>Budaj A, Yusuf S, Mehta SR, Fox KAA, Tognoni G, Zhao F, Chrolavicius S, Hunt D, Keltai M, Franzosi mg. 2002. Benefit of clopidogrel in patients with acute coronary syndromes without ST-segment elevation in various risk groups. Circulation 106(13):1622-1626.</p>	<p>Clinical Trial (CURE)</p>	<p>12,562</p>	<p>Aspirin 75-325 mg/day + Clopidogrel 300 mg loading dose followed by clopidogrel 75 mg/day (n=6259) Aspirin 75-325 mg/day + Placebo (n=6303)</p>	<p>Among patients with acute coronary syndrome without ST-segment elevation, the primary (cardiovascular death, non-fatal MI, or stroke) and coprimary (composite of the primary outcome or refractory angina) composite endpoints and their components increased proportionally with increasing risk according to the TIMI risk score. The impact of clopidogrel versus placebo on the rate of the primary outcome was as follows:</p> <p>Low-risk group (TIMI score 0 to 2), 4.1% vs. 5.7% (RR, 95% CI: 0.71, 0.52-0.97; p<0.04)</p> <p>Intermediate-risk group (TIMI score 3 to 4), 9.8% versus 11.4% (RR, 95% CI: 0.85, 0.74-0.98; p<0.03)</p> <p>High-risk group (TIMI score 5 to 7), 15.9% versus 20.7% (RR, 0.73; 95% CI, 0.60-0.90; p<0.004).</p> <p>There was no evidence of statistical heterogeneity among the groups.</p>

APPENDIX 2. SUMMARY OF EFFICACY RESULTS - PUBLICATIONS PROVIDING ADDITIONAL EFFICACY INFORMATION

Reference	Type of Article	Total Subjects	Treatment Groups (n)	Efficacy Data
<p>CURE Trial Investigators (Clopidogrel In Unstable Angina To Prevent Recurrent Events). 2001. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. New England Journal of Medicine 345(7):494-502.</p>	<p>Clinical Trial (CURE)</p>	<p>12,562</p>	<p>Aspirin 75-325 mg/day + Clopidogrel 300 mg loading dose followed by clopidogrel 75 mg/day (n=6259) Aspirin 75-325 mg/day + Placebo (n=6303)</p>	<p><u>Outcomes</u> The first primary outcome (death from cardiovascular causes, nonfatal MI, or stroke) occurred in 9.3% of patients in the clopidogrel group and 11.4% of patients in the placebo group (RR, 95% CI: 0.80, 0.72-0.90; p<0.001). The second primary outcome (composite of first primary outcome or refractory ischemia) occurred in 16.5% of patients in the clopidogrel group and 18.8% of patients in the placebo group (RR, 95% CI: 0.86, 0.79-0.94; p<0.001). The rate of each component of these composite outcomes also tended to be lower in the clopidogrel group. The clearest difference was observed in the rates of MI (clopidogrel: 5.2%; placebo: 6.7%; RR, 95% CI: 0.77, 0.67-0.89). Less of a difference was observed for CV death (clopidogrel: 5.1%; placebo: 5.5%; RR, 95% CI: 0.93, 0.79-1.08) and stroke (clopidogrel: 1.2%; placebo: 1.4%; RR, 95% CI: 0.86, 0.63-1.18). With respect to refractory ischemia, the difference was observed primarily in first events that occurred during the initial hospitalization (clopidogrel: 1.4%; placebo: 2.0%; RR, 95% CI: 0.68, 0.52-0.90; p=0.007). Significantly fewer patients in the clopidogrel group than in the placebo group had severe ischemia (2.8% versus 3.8%, respectively; RR, 95% CI: 0.74, 0.61-0.90; p=0.003), or recurrent angina (20.9% versus 22.9%, respectively; RR, 95% CI: 0.91, 0.85-0.98; p=0.01). Radiologic evidence of heart failure was found in fewer patients in the clopidogrel group versus the placebo group (3.7% versus 4.4%, respectively; RR, 95% CI: 0.82, 0.69 -0.98; p=0.03).</p> <p><u>Temporal Trends</u> The rate of the first primary outcome was lower in the clopidogrel group both within the first 30 days after randomization and between 30 days and the end of the study. Further analysis indicated that the benefit of clopidogrel was apparent within a few hours after randomization, with the rate of death from cardiovascular causes, nonfatal MI, stroke, or refractory or severe ischemia significantly lower in the clopidogrel group by 24 hours after randomization (clopidogrel: 1.4%; placebo: 2.1%; RR, 95% CI: 0.66, 0.51-0.86).</p>

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Reference	Type of Article	Total Subjects	Treatment Groups (n)	Efficacy Data
<p>Mehta SR, Yusuf S, Peters RJG, Bertrand ME, Lewis BS, Natarajan MK, Malmberg K, Rupprecht H, Zhao F, Chrolavicius S, Copland I, Fox KA. 2001. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. <i>Lancet</i> 358(9281):527-533.</p>	<p>Clinical Trial (PCI-CURE)</p>	<p>2658</p>	<p>Double-blind phase: Clopidogrel 300 mg/day + Aspirin 75-325 mg/day (n=1313) Placebo + Aspirin 75-325 mg/day (n=1345) Open label phase (after PCI): Clopidogrel or ticlopidine (Dose unspecified) Aspirin (Dose unspecified)</p>	<p><u>Events before PCI</u> Significantly fewer patients on clopidogrel than on placebo had an MI (3.6% versus 5.1%, respectively; p=0.04) or the composite of MI or refractory ischemia (12.1% versus 15.3%, respectively; p=0.008).</p> <p><u>Events from PCI to 30 days</u> The percentage of subjects with the primary endpoint of cardiovascular death, MI, or urgent revascularization within 30 days after PCI was significantly lower in the clopidogrel (4.5%) than in the placebo group (6.4%) (RR, 0.70; 95% CI, 0.50-0.97; p=0.03). All deaths within the first 30 days were cardiovascular deaths and were similar between the two groups (approximately 1.0%). Patients on clopidogrel had significantly fewer MIs (clopidogrel: 2.1%; placebo 3.8%) and Q-wave MIs (clopidogrel: 0.8%; placebo 2.4%) than patients on placebo.</p> <p><u>Events from PCI to end of follow-up</u> From the time of PCI to the end of follow-up (mean 8 months after PCI), significantly fewer subjects had cardiovascular deaths, MIs, or any revascularization with clopidogrel (18.3%) than placebo (21.7%) (p=0.03). The percentage of subjects who experienced cardiovascular deaths was similar between the two groups (2.4% versus 2.3%) but there were significantly fewer MIs among subjects treated with clopidogrel (4.5%) than placebo (6.4%) due to a difference in Q-wave MIs (clopidogrel: 1.5%; placebo 3.5%). When events before and after PCI were considered, there was a highly significant difference in the percentage of subjects who suffered a cardiovascular death or MI between the clopidogrel (8.8%) and placebo (12.6%) groups (p=0.002). During PCI, significantly fewer subjects treated with clopidogrel (20.9%) than placebo (26.6%) received intravenous glycoprotein IIb/IIIa inhibitors during PCI (RR, 0.79; 95% CI, 0.69-0.90) (p=0.001). The need for a second revascularization was also lower in the clopidogrel group than the placebo group (14.2% versus 17.1%, respectively; RR, 0.82; 95% CI, 0.68-1.00) (p=0.049).</p>

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Reference	Type of Article	Total Subjects	Treatment Groups (n)	Efficacy Data
Morais J. 2002. Insights from CURE: using clopidogrel on top of standard therapy. Cerebrovascular diseases 13(Suppl 1):17-21.	Clinical Trial (CURE)	12,562	Clopidogrel loading dose of 300 mg followed by 75 mg/day + Aspirin 75-325 mg/day (n=6259) Placebo + Aspirin 75-325 mg/day (n=6303)	The incidence of the first primary endpoint of cardiovascular death, MI, or stroke was 9.3% in the clopidogrel group and 11.4% in the placebo group, corresponding to a relative risk reduction of 20% in favor of clopidogrel (95% CI, 72 - 90%; p<0.001). Moreover there was a consistent benefit of clopidogrel over placebo for the individual outcomes of cardiovascular death, MI, and stroke. A similar level of benefit was observed for both the second primary endpoint composite of CV death, MI, stroke or refractory ischemia (relative risk reduction 14%; 95% CI, 79 - 94%; p<0.001) and refractory ischemia alone.

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Reference	Type of Article	Total Subjects	Treatment Groups (n)	Efficacy Data
<p>Yusuf S, Mehta SR, Zhao F, Gersh BJ, Commerford PJ, et al. 2003. Early and late effects of clopidogrel in patients with acute coronary syndromes. <i>Circulation</i> 107(7):966-972.</p>	<p>Clinical Trial (CURE)</p>	<p>12,562</p>	<p>Clopidogrel loading dose of 300 mg administered immediately followed by 75 mg/day + Aspirin 75-325 mg/day (n=6259) Placebo + Aspirin 75-325 mg/day (n=6303)</p>	<p>Efficacy of clopidogrel/aspirin relative to placebo/aspirin in the first 24 hours after randomization: Risk ratio (95% CI):</p> <ul style="list-style-type: none"> • CV death/MI/stroke: 0.80 (0.48-1.32) • CV death/MI/stroke/refractory ischemia: 0.76 (0.53-1.09) • CV death/MI/stroke/severe ischemia: 0.66 (0.51-0.86) <p>Efficacy of clopidogrel/aspirin relative to placebo/aspirin between 0 to 7 days after randomization: Risk ratio (95% CI):</p> <ul style="list-style-type: none"> • CV death/MI/stroke: 0.82 (0.65-1.04) • CV death/MI/stroke/refractory ischemia: 0.82 (0.69-0.98) • CV death/MI/stroke/severe ischemia: 0.77 (0.67-0.89) <p>Efficacy of clopidogrel/aspirin relative to placebo/aspirin between 8 to 30 days after randomization: Risk ratio (95% CI):</p> <ul style="list-style-type: none"> • CV death/MI/stroke: 0.76 (0.61-0.94) • CV death/MI/stroke/refractory ischemia: 0.83 (0.71-0.98) • CV death/MI/stroke/severe ischemia: 0.86 (0.73-1.01) <p>Efficacy of clopidogrel/aspirin relative to placebo/aspirin between 0 to 30 days after randomization: Risk ratio (95% CI):</p> <ul style="list-style-type: none"> • CV death/MI/stroke: 0.79 (0.67-0.92) • Refractory ischemia: 0.86 (0.72-1.03) • Severe ischemia: 0.75 (0.63-0.88) • CV death/MI/stroke/refractory ischemia: 0.83 (0.73-0.93) • CV death/MI/stroke/in-hospital severe ischemia: 0.81 (0.73-0.90) <p>Efficacy of clopidogrel/aspirin relative to placebo/aspirin between 31 days to 1 year after randomization: Risk ratio (95% CI):</p> <ul style="list-style-type: none"> • CV death/MI/stroke: 0.82 (0.70-0.95) • Refractory ischemia: 0.98 (0.84-1.15) • Severe ischemia: Not applicable • CV death/MI/stroke/refractory ischemia: 0.90 (0.80-1.01) • CV death/MI/stroke/in-hospital severe ischemia: Not applicable <p>Overall, 9.3% of patients experienced CV death, MI, or strokes in the clopidogrel group compared with 11.4% in the placebo group (risk ratio, 95% CI: 0.80, 0.72-0.90; $p < 0.0001$). These results were consistent both early (≤ 30 days) and late (≥ 30 days).</p>

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Reference	Type of Article	Total Subjects	Treatment Groups (n)	Efficacy Data
<p>Castillo J, Leira R, Moro MA, Lizasoain I, Serena J, Davalos A. 2003. Neuroprotective effects of aspirin in patients with acute cerebral infarction. Neuroscience Letters 339(3):248-250.</p>	<p>Clinical Trial</p>	<p>238</p>	<p>Aspirin 75-500 mg/day at the time of stroke onset (n=63) No aspirin at the time of stroke onset (n=175)</p>	<p>Cerebral spinal fluid glutamate concentrations were higher in subjects not taking aspirin ($8.9 \pm 5.2 \mu\text{M/L}$) than in subjects taking aspirin ($4.9 \pm 3.1 \mu\text{M/L}$) ($p < 0.0001$). No correlation between dose of aspirin and glutamate levels was observed. Early neurological deterioration was eight times more frequent in subjects who did not take aspirin. The frequency of early neurological deterioration was not significantly different between subjects taking >200 mg/day of aspirin (9.7%) and those taking <200 mg/day (5.6%). Aspirin treatment at stroke onset showed a 97% reduction in risk of early neurological deterioration after adjustment for significant factors associated with progressing stroke. Aspirin effect remained unchanged after a further adjustment for glutamate concentrations.</p>

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Reference	Type of Article	Total Subjects	Treatment Groups (n)	Efficacy Data
<p>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.</p>	<p>Meta-analysis</p>	<p>55,462</p>	<p>Aspirin 75-1500 mg/day (Mean dose = 273 mg/day)</p>	<p>Absolute risk reduction (95% CI; p-value) associated with aspirin use and the following clinical outcomes:</p> <ul style="list-style-type: none"> • All-cause mortality: 120/10,000 persons (77-162; p<0.001) • Cardiovascular mortality: 97/10,000 persons (59-135; p<0.001) • Total MI: 137/10,000 persons (107-167; p<0.001) • Fatal MI: 36/10,000 persons (16-55; p<0.001) • Total stroke: 31/10,000 persons (5-57; p=0.02) • Ischemic stroke: 39/10,000 persons (17-61; p<0.001) • Fatal stroke: 4/10,000 persons (8-16; p=0.50) <p>The proportional reduction (relative risk, 95% CI; p-value) in clinical outcomes associated with aspirin treatment was as follows:</p> <ul style="list-style-type: none"> • All-cause mortality: 15% (0.85, 0.80-0.90; p<0.001) • Cardiovascular mortality: 16% (0.84, 0.79-0.90; p<0.001) • Total MI: 32% (0.68; 0.62-0.74; p<0.001) • Fatal MI: 22% (0.78; 0.68-0.90; p<0.001) • Total stroke: 12% (0.88, 0.76-1.02; p=0.08) • Ischemic stroke: 18%, (0.82, 0.73-0.92) • Fatal stroke: (1.07, 0.85-1.35; p=0.60) <p>The number needed to treat to prevent one event was as follows:</p> <ul style="list-style-type: none"> • Total MI: 73 • Fatal MI: 278 • Ischemic stroke: 256 <p>Treatment with aspirin was also associated with an increase of 12 (95% CI: 5-20) hemorrhagic strokes per 10,000 persons or an 84% increase in the risk of this stroke subtype (relative risk, 95% CI: 1.84, 1.24-2.74; p<0.001).</p>

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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	1316	Aspirin group (Aspirin 30 mg/day [95% of patients], 75 mg/day [3% of patients], or 100 mg/day [2% of patients]) (n=665) Anticoagulant group (Target INR value of 3.0 to 4.5 achieved with phenprocoumon, acenocoumarol, or warfarin. Phenprocoumon was the preferred anticoagulant.) (n=651)	An excess of the primary outcome event (composite of death from all vascular causes, nonfatal stroke, nonfatal MI, or nonfatal major bleeding complication) 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) over a mean follow-up period of 14 months. 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). The bleeding incidence increased by a factor of 1.43 (95% CI: 0.96-2.13) for each 0.5 unit increase of the achieved International Normalized Ratio (INR). The HR for death from all causes was 2.4 (95% CI: 1.3-4.4). There was no statistically significant difference in the occurrence of major ischemic events. Death from all vascular causes was reported for 24/651 patients in the anticoagulant group versus 11/665 in the aspirin group (HR, 95% CI: 2.3, 1.1-4.6). There was no significant difference in the occurrence of major ischemic events (nonhemorrhagic death from vascular causes, nonfatal ischemic stroke, or nonfatal MI) between the anticoagulant (27/651) and aspirin group (27/665) (HR, 95% CI: 1.03, 0.6-1.75).
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.	Case Study	8	Low-dose aspirin, dose not specified during the treatment period. During the follow-up period from the time of the stroke, aspirin doses ranged from 38-80 mg.	During a median of 8.9 years of follow-up, 2 of the 8 female patients with ischemic stroke as the first thrombotic manifestation of antiphospholipid syndrome (APS), had a recurrent stroke and 1 patient had deep vein thrombosis. With a total of 58 patient years on aspirin, the recurrent stroke rate was 3.5 per 100 patient-years on aspirin (95% CI, 0.4 to 12.5) which is the same range as found in young adults with non-APS-related ischemic stroke.
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.	Clinical Trial (ESPS-2)	6602	Aspirin 50 mg/day (n=1649) Dipyridamole 400 mg/day (n=1654) Aspirin 50 mg/day + Dipyridamole 400 mg/day (n=1650) Placebo (n=1649)	The number of strokes, strokes or deaths, and deaths that occurred during the 2 year follow-up period for the aspirin alone, dipyridamole alone, combination therapy, and placebo treatment groups was as follows: <ul style="list-style-type: none"> • Total strokes: 206, 211, 157, and 250 • Strokes or deaths: 330, 321, 286, and 378 • Deaths: 182, 188, 185, and 202 The 24-month stroke rate was 12.9% in the aspirin alone group, 13.2 in the dipyridamole alone group, 9.9% in the combination group, and 15.8% in the placebo group. Survival curves showed a clear, progressive divergence of the curves for stroke and stroke and death combined, demonstrating a higher probability of endpoint-free survival with the combination treatment of aspirin and dipyridamole regimen than either medication alone. Stroke risk was reduced by 18.1% (p=0.013) with aspirin alone, by 16.3% (p=0.039)

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				<p>with dipyridamole alone, and by 37.0% (p<0.001) with combination therapy, when compared with placebo. The relative risk reductions for the combined endpoint of stroke or death were 13.2% (p=0.016) with aspirin, 15.4% (p=0.015) with dipyridamole, and 24.4% (p<0.001) with the combination. None of the treatments significantly reduced the risk of death alone or of fatal stroke.</p> <p>The number of events avoided per 1,000 patients treated over 2 years for aspirin alone, dipyridamole alone, and combination therapy when compared to placebo was as follows:</p> <ul style="list-style-type: none"> • Stroke: 29, 26, and 58 • Stroke or death: 30, 35, and 56 • Death: 13, 9, and 10 <p>Factorial analysis also demonstrated a highly significant effect of aspirin (p<0.01) and dipyridamole (p<0.01) for preventing TIA, with a risk reduction of 21.9% and 18.3%, respectively. The risk reduction for the combination was 35.9% compared with placebo (p<0.001). The number of patients who had a TIA during the 2 year follow-up period was 206, 215, 172, and 267 for the aspirin alone, dipyridamole alone, combination therapy, and placebo treatment groups.</p> <p>The occurrence of other secondary endpoints for the aspirin alone, dipyridamole alone, combination therapy, and placebo treatment groups was as follows:</p> <ul style="list-style-type: none"> • MI: 39, 48, 35, and 45 (not significant) • Other vascular events (lung embolism, DVT, obstruction of peripheral arteries, and retinal artery occlusion): 38, 35, 21, 54 (p<0.01) • Ischemic events (stroke and/or MI and/or sudden death: 266, 271, 206, and 307 (p<0.001)

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Diener HC, Darius H, Bertrand-Hardy JM, Humphreys M. 2001. Cardiac safety in the European Stroke Prevention Study 2 (ESPS2). International Journal of Clinical Practice 55(3):162-163.	Clinical Trial (ESPS-2)	6602	Aspirin 50 mg/day (n=1649) Dipyridamole 400 mg/day (n=1654) Aspirin 50 mg/day + Dipyridamole 400 mg/day (n=1650) Placebo (n=1649)	In this post-hoc analysis of ESPS2, patients with coronary heart disease or MI at entry who received dipyridamole (includes dipyridamole only and dipyridamole + aspirin groups) were compared with those who did not receive dipyridamole (includes aspirin only and placebo groups). Similarly, all patients treated with aspirin (includes aspirin only and aspirin + dipyridamole groups) were compared with those not receiving aspirin (includes dipyridamole only and placebo groups). There was a trend toward fewer MIs in patients who were on aspirin than in those who were not on aspirin (74 [2.2%] vs. 93 [2.8%], respectively); however, this difference was not statistically significant. There was no difference in all-cause mortality in patients who received aspirin and those who did not (368 [11.2%] vs. 393 [11.9%], respectively). Mortality was identical in patients with CHD or prior MI irrespective of whether they took dipyridamole (213) or not (208) or aspirin (209) or not (212).
Forbes CD. 1997. European Stroke Prevention Study 2: dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. International Journal of Clinical Practice 51(4):205-208.	Clinical Trial (ESPS-2)	6602	Aspirin 50 mg/day (n=1649) Dipyridamole 400 mg/day (n=1654) Aspirin 50 mg/day + Dipyridamole 400 mg/day (n=1650) Placebo (n=1649)	Low-dose acetylsalicylic acid significantly reduced the relative risk of stroke by 18.1% (p=0.013) and stroke or death by 13.2% (p=0.016) compared to placebo. Dipyridamole alone significantly reduced the relative risk of stroke by 16.3% (p=0.039) and stroke or death by 15.4% (p=0.015) compared to placebo. The combination of aspirin + dipyridamole resulted in a significantly greater risk reduction in terms of stroke (37.0%; p=0.001) and stroke or death (24.4%; p=0.001) compared to placebo. Combination treatment was also superior to either agent alone in reducing the relative risk of stroke (p<0.01 for all comparisons). No treatment (aspirin alone, dipyridamole alone, or aspirin + dipyridamole) significantly reduced the relative risk of death compared to placebo. During two years of follow-up, aspirin alone, dipyridamole alone, and the two agents combined significantly reduced TIA events (16.46% of patients in the placebo group experienced a TIA compared to 12.63% in the aspirin alone group, 13.21% in the dipyridamole alone group, and 10.55% in the aspirin + dipyridamole group).

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Reference	Type of Article	Total Subjects	Treatment Groups (n)	Efficacy Data
<p>Ishikawa K, Kanamasa K, Hama J, Ogawa I, Takenaka T, Naito T, Yamamoto T, Nakai S, Oyaizu M, Kimura A, Yamamoto K, Katori R. K. 1997. Aspirin plus either dipyridamole or ticlopidine is effective in preventing recurrent myocardial infarction. Japanese Circulation Journal 61(1):38-45.</p>	<p>Clinical Trial</p>	<p>618</p>	<p>Aspirin 50 mg/day + dipyridamole 150 mg/day (n=113) Aspirin 50 mg/day + ticlopidine 200 mg/day (n=253) Aspirin 50 mg/day or dipyridamole 150 mg/day or ticlopidine 200 mg/day alone (n=252) No antiplatelet treatment (n=465)</p>	<p>Cardiac event rates (nonfatal recurrent MI, fatal recurrent MI, death by congestive heart failure, and sudden death) in patients treated with aspirin alone, dipyridamole alone, and ticlopidine alone were 5.5%, 7.6%, and 2.8%, respectively. Combined treatment with aspirin plus either dipyridamole or ticlopidine resulted in significantly lower cardiac events (1.9%) than did treatment with aspirin, dipyridamole, or ticlopidine alone (p<0.05; OR, 95% CI: 0.39, 0.15-1.01).</p>
<p>Sivenius J, Cunha L, Diener HC, Forbes C, Laakso M, Lowenthal A, Smets P, Riekkinen P. 1999. Second European Stroke Prevention Study: antiplatelet therapy is effective regardless of age. ESPS2 Working Group. Acta neurologica Scandinavica 99(1):54-60.</p>	<p>Clinical Trial (ESPS-2)</p>	<p>6602</p>	<p>Aspirin 50 mg/day Dipyridamole modified-release 400 mg/day Aspirin 50 mg/day + Dipyridamole 400 mg/day Placebo</p>	<p>When the incidence of stroke, stroke and/or death, and vascular events were analyzed by age group (<65 years, 65-74 years, ≥75 years) the greatest benefit was observed in patients receiving aspirin plus dipyridamole (DP) combination therapy.</p> <p>In patients <65 years, factorial design analysis showed that aspirin had a significant effect on all endpoints, while DP produced a significant reduction in vascular endpoints only. In pairwise comparisons (i.e., aspirin, DP, or combination therapy versus placebo), only the combination therapy with aspirin plus DP produced a significant reduction in stroke, stroke and/or death, or vascular events.</p> <p>In the 65-74 year age group, both aspirin and DP produced a significant reduction in most endpoints. In this age group only combination therapy was also shown to be superior to placebo in pairwise comparisons.</p> <p>Among patients ≥75 years of age, factorial design analysis showed aspirin and DP to be equally effective. The pairwise comparisons in this age group showed that combination therapy was significantly superior to placebo in reducing the incidence of all endpoints. Aspirin alone significantly reduced the incidence of stroke and/or death compared to placebo, while DP alone had no significant effect on any endpoint.</p> <p>Thus, combination therapy is superior to either aspirin or DP alone in all three age groups. Combination therapy also provides a statistically significant reduction in the incidence of each endpoint in each age group compared with placebo.</p>

APPENDIX 2. SUMMARY OF EFFICACY RESULTS - PUBLICATIONS PROVIDING ADDITIONAL EFFICACY INFORMATION

Reference	Type of Article	Total Subjects	Treatment Groups (n)	Efficacy Data
<p>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.</p>	<p>Clinical Trial (FRISC)</p>	<p>1506</p>	<p>Dalteparin 120 IU/kg body weight (maximum 10,000 IU) BID SC for 6 days; subjects then received 7500 IU/day for the next 35-45 days. (n=746) Placebo (n=760) All subjects received an initial 300 mg dose of aspirin and 75 mg/day thereafter. Beta-blockers, as well as calcium antagonists and organic nitrates, were also administered as needed.</p>	<p><u>Acute Phase</u> During the first 6 days, the rate of death and new MI was lower in the dalteparin group (1.8%) than in the placebo group (4.8%) (RR, 95% CI: 0.37, 0.20-0.68; p=0.001). Separately, the rate of MI (dalteparin: 1.4%; placebo: 4.4%) (RR, 95% CI: 0.31, 0.16-0.60; p=0.001), and death (dalteparin: 0.9%; placebo: 1.1%) (RR, 95% CI: 0.88, 0.32-2.48; p=0.8) were lower in the dalteparin group than the placebo group. Rates of urgent revascularization (dalteparin: 0.4%; placebo: 1.2%) (RR, 95% CI: 0.33, 0.10-1.10; p=0.07) and need for i.v. heparin (dalteparin: 3.8%; placebo: 7.7%) (RR, 95% CI: 0.49, 0.32-0.75; p=0.001) were also lower in the dalteparin treatment group which indicated a reduction in refractory angina. When combined as a composite endpoint (death, MI, revascularization, or i.v. heparin), the absolute reduction with dalteparin was 4.9% and the relative reduction was 48% during the acute phase.</p> <p><u>Treatment Phase</u> At 40 days, the rates of death or MI as well as the composite endpoint remained lower in the DP group than in the placebo group (dalteparin: 20.5%; placebo: 25.7%; RR, 95% CI: 0.79, 0.66-0.95; p=0.011). The rate of the individual endpoints MI (dalteparin: 6.7%; placebo: 9.7%) (RR, 95% CI: 0.69, 0.49-0.98; p=0.04), revascularization (dalteparin: 12.1%; placebo: 15.5%) (RR, 95% CI: 0.77, 0.60-0.99; p=0.04), and i.v. heparin (dalteparin: 8.4%; placebo: 13.6%) (RR, 95% CI: 0.61, 0.46-0.82; p=0.001), but not death (dalteparin: 2.6%; placebo: 3.0%) (RR, 95% CI: 0.85, 0.47-1.54; p=0.59), were also significantly lower in the dalteparin treatment group. Subgroup analysis suggested that the effects of dalteparin were confined to nonsmokers (80% of the sample) and to patients with non-Q-wave MI.</p> <p><u>Follow-Up Phase</u> At the follow-up visit 4-5 months after the end of treatment, there were no significant differences in the occurrence of death, new MI, or revascularization (composite or as separate endpoints) between the two groups. The rate of heparin infusion remained lower in the dalteparin group (dalteparin: 11.9%; placebo: 16.7%) (RR, 95% CI: 0.71, 0.55-0.91; p=0.008).</p>

APPENDIX 2. SUMMARY OF EFFICACY RESULTS - PUBLICATIONS PROVIDING ADDITIONAL EFFICACY INFORMATION

Reference	Type of Article	Total Subjects	Treatment Groups (n)	Efficacy Data
Knottenbelt C, Brennan PJ, Meade TW. 2002. Antithrombotic treatment and the incidence of angina pectoris. Archives of Internal Medicine 162(8):881-886.	Clinical Trial	5499	Aspirin 75 mg/day controlled release + Warfarin (Started at 2.5 mg/day and adjusted to INR 1.5) (n=1269) Warfarin + placebo (n=1260) Aspirin 75 mg/day controlled release + placebo (n=1252) Double placebo (n=1259)	Warfarin nonsignificantly reduced the incidence of stable angina by 16% (95% CI: -14 to 38). In contrast, treatment with aspirin resulted in a marginally significant increase in the incidence of stable angina by 39% (95% CI: 0 to 91; p=0.05). The difference between subjects who took warfarin alone versus aspirin alone resulted in 37% (95% CI: -1 to 60) fewer cases among those taking warfarin than taking aspirin (p=0.05). When all cases of angina were considered, i.e., stable and unstable, warfarin nonsignificantly reduced cases by 11% (95% CI: -17-32) while aspirin significantly increased the incidence of angina by 33% (95% CI: -77-0) (p=0.05). Warfarin reduced total coronary heart disease events (the combination of coronary death, nonfatal infarction, and angina) by 18% (95% CI: 4 to 30; p=0.01), resulting from the large decrease in major fatal events, along with warfarin's possible effect on angina and its small (nonsignificant) reduction in major nonfatal events. For aspirin, there was a nonsignificant reduction in total coronary heart disease of approximately 8% (95% CI: -10 to 22), the net result of the reduction due to aspirin in major nonfatal events, the small (nonsignificant) increase in fatal events, and the apparent increase in angina.
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.	Clinical Trial (TPT)	5085	Aspirin 75 mg/day controlled release + placebo warfarin (n=1268) Warfarin mean stable INR of 1.47 [4.1 mg/day] + placebo aspirin (n=1268) Warfarin mean stable INR of 1.47 [4.1 mg/day] + Aspirin 75 mg/day controlled release (n=1277) Placebo warfarin + placebo aspirin (n=1272)	Group effects: number of events (rate/1000 person years) for warfarin + aspirin, warfarin alone, aspirin alone, and placebo: <u>Ischemic Heart Disease (IHD)</u> <ul style="list-style-type: none"> All: 71 (8.7), 83 (10.3), 83 (10.2); 107 (13.3) Fatal: 24 (3.0), 19 (2.4), 36 (4.4), 34 (4.2) Non-fatal: 47 (5.8), 64 (8.0), 47 (5.8), 73 (9.0) <u>Stroke</u> <ul style="list-style-type: none"> All: 29 (3.6), 22 (2.7), 18 (2.2), 26 (3.2) Fatal: 12 (1.5), 5 (0.6), 2 (0.2), 1 (0.1) Thrombotic: 11 (1.4), 15 (1.9), 10 (1.2), 18 (2.2) Hemorrhagic: 7 (0.9), 1 (0.1), 2 (0.2), 0 Sub-arachnoid: 2 (0.2), 3 (0.4), 1 (0.1), 2 (0.2) Unknown: 9 (1.1), 3 (0.4), 5 (0.6), 6 (0.7) <u>Death</u> <ul style="list-style-type: none"> All causes: 103 (12.4), 95 (11.4), 113 (13.6), 110 (13.1)