

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

Reference	Type of Article	Total Subjects	Treatment Groups (n)	Efficacy Data
<p>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.</p>	<p>Clinical Trial</p>	<p>5499</p>	<p>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</p>	<p><u>Coronary heart disease:</u>                      As expected, event rates for coronary heart disease within both the aspirin treated and untreated groups rose with increasing levels of the three risk factors (age, cholesterol concentration, and blood pressure). In subjects with systolic blood pressure &gt;145 mmHg, treatment with aspirin was found to be neither beneficial nor harmful (relative risk = 0.94). In contrast, subjects with pressures &lt;130 mmHg had a 45% risk reduction (relative risk = 0.55) and the interaction term was significant (p=0.0015). Interaction with aspirin by age was barely significant (p=0.055) and there was no suggestion of an interaction by cholesterol concentration.</p> <p><u>Stroke:</u>                      There was also a significant interaction between the effect of aspirin (alone) with systolic blood pressure and the rate of stroke. The relative risk of stroke was 0.41 at &lt;130 mmHg compared with 1.42 at &gt;145 mmHg (p=0.006). The possible reduction in benefit with increasing cholesterol concentration was of marginal significance (p=0.036). No interaction by age was observed.</p> <p><u>Major cardiovascular events (coronary heart disease and stroke):</u>                      When data for coronary heart disease and stroke were combined, the increasing benefit of aspirin with lower pressure was highly significant (p=0.0004). Analysis of the data following omission of all hemorrhagic strokes also showed a significant interaction between the effects of aspirin and blood pressure with relative risks of 0.59, 0.68, and 1.08 in the &lt;130 mmHg, 130-145 mmHg, and &gt;145 mmHg groups, respectively.</p>

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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 Anti-thrombotics in the Prevention of Reocclusion In Coronary Thrombolysis (APRICOT)-2 Trial. <i>Circulation</i> 106(6):659-665.	Clinical Trial (APRICOT-2)	274	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)	Reocclusion was observed in 15% of patients receiving aspirin + coumarin compared to 28% receiving aspirin alone (RR=0.55; 95% CI: 0.33 to 0.90, p<0.02). This difference was mainly caused by a reduction in the incidence of TIMI grade 0 to 1 flow (aspirin + coumarin: 9%; aspirin alone: 20%) (RR, 95% CI: 0.46, 0.24 to 0.89; p<0.02). Event-free survival (i.e., a clinical course without death, reinfarction, or revascularization) was significantly higher in patients receiving aspirin + coumarin (86%) compared to patients receiving aspirin alone (66%) (p<0.01). Patients receiving the combined antithrombotic regimen had both a significantly lower reinfarction rate (2% versus 8%; p<0.05) and rate of revascularization (13% versus 31%; p<0.01) than patients taking aspirin alone.
Huynh T, Theroux P, Bogaty P, Nasmith J, Solymoss S. 2001. Aspirin, warfarin, or the combination for secondary prevention of coronary events in patients with acute coronary syndromes and prior coronary artery bypass surgery. <i>Circulation</i> 103(25):3069-3074.	Clinical Trial	135	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	No statistically significant differences existed between groups in the incidence of the primary endpoint (composite of any-cause death, myocardial infarction, or unstable angina requiring a new hospitalization) (warfarin alone [14.1%]; aspirin alone [11.5%]; warfarin + aspirin [11.4%]). Secondary endpoints (death, MI, unstable angina requiring hospitalization, reperfusion procedure, or repeat CABG) occurred less frequently in the aspirin alone than in the other two treatment groups. Data for the secondary endpoints included: (death [0.7%/0.0%/1.6%] for warfarin/aspirin/warfarin + aspirin; MI [3.0%/0.8%/2.9%]; unstable angina [12.6%/11.5%/10.6%]; PCI [4.4%/0.8%/3.3%]; repeat CABG [1.5%/1.5%/1.6%]). None of these differences were statistically significant. Treatment effects in all subgroups analyzed (age, gender, diabetes, and angina class $\geq 3$ ; Canadian Cardiovascular Society) showed no trends for a benefit with warfarin alone or in combination with aspirin over aspirin alone.

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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. American Journal of Cardiology 81(10):1178-1181.	Clinical Trial	298	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	<p>Baseline characteristics: Infarct size determined: No aspirin: cumulative alpha-hydroxy butyrate dehydrogenase (aHBDH) <math>1312 \pm 74</math> IU/L and LV ejection fraction <math>55\% \pm 1</math> [N=148]; Aspirin: cumulative aHBDH <math>1274 \pm 95</math> IU/L and LV ejection fraction <math>55\% \pm 1</math> [N=73]. Results were not statistically significant.</p> <p>LV volume indexes obtained: No aspirin: cumulative aHBDH <math>1238 \pm 97</math> IU/L and LV ejection fraction <math>55\% \pm 1</math> [N=99]; Aspirin: cumulative aHBDH <math>1313 \pm 119</math> IU/L and LV ejection fraction <math>53\% \pm 2</math> [N=55]. Results were not statistically significant.</p> <p>One year after AMI, patients who did not take aspirin at randomization had a significant increase in the LV end-diastolic volume index (LVEDVI) of <math>8.4 \pm 1.9</math> ml/m<sup>2</sup> compared with a mean change of <math>2.1 \pm 2.1</math> ml/m<sup>2</sup> in patients who took aspirin (p=0.03). The mean change in LV end-systolic volume index (LVESVI) was <math>3.4 \pm 1.6</math> ml/m<sup>2</sup> in patients who took aspirin and <math>5.5 \pm 1.4</math> ml/m<sup>2</sup> in patients who did not take aspirin (p=NS) at randomization. Cumulative aHBDH and change in LVESVI and LVEDVI were also classified by aspirin, captopril and placebo treatment; none of these results were clinically significant. In patients who took aspirin at randomization, 2 patients (2.1%) died 1 year after AMI compared with 21 patients (10.3%) who did not take aspirin at randomization (p=0.01).</p>

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<p>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. Lancet 360(9327):109-113.</p>	<p>Clinical Trial (ASPECT-2)</p>	<p>999</p>	<p>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)</p>	<p><i>Primary endpoint:</i>  <u>Death, MI or stroke:</u> aspirin 31 patients (9%) vs. coumadin 17 patients (5%) (hazard ratio = 0.55 [95% CI: 0.30-1.00]) vs. coumadin + aspirin 16 patients (5%) (0.50 [0.27-0.92]).  <i>Secondary endpoints:</i>  <u>Vascular death, MI or stroke:</u> 28 patients/8% (aspirin group), 17 patients/5% (hazard ratio 0.61 [95% CI: 0.33-1.12]; coumadin group) and 15 patients/5% [hazard ratio 0.52 (0.28-0.98)](aspirin + coumadin group).  <u>Death from all causes:</u> 15 patients/4% (aspirin group), 4 patients/1% (hazard ratio 0.28 [0.09-0.82]; coumadin group) and 9 patients/3% (hazard ratio 0.60 [0.26-1.36]; aspirin + coumadin group).  <u>Vascular death:</u> 12 patients/4% (aspirin group), 4 patients/1% (hazard ratio 0.34 [0.11-1.06]; coumadin group) and 8 patients/2% (hazard ratio 0.66 [0.27-1.62]; aspirin + coumadin group).  <u>MI:</u> 14 patients/4% (aspirin group), 13 patients/4% (hazard ratio 0.94 [0.44-2.00]; coumadin group) and 10 patients/3% (hazard ratio 0.70 [0.31-1.58]; aspirin + coumadin group).  <u>Unstable angina:</u> 24 patients/7% (aspirin group), 16 patients/5% (hazard ratio 0.66 [0.35-1.26]; coumadin group) and 16 patients/5% (hazard ratio 0.66 [0.35-1.24]; aspirin + coumadin group).  <u>Revascularization (PTCA/CABG):</u> 39 patients/12% (aspirin group), 34 patients/10% (hazard ratio 0.90 [0.58-1.39]; coumadin group) and 32 patients/10% (hazard ratio 0.83 [0.53-1.29]; aspirin + coumadin group).  <u>All stroke:</u> 5 patients/1% (aspirin group), 0 patients (coumadin group) and 1 patient/0.3% (hazard ratio 0.20 [0.02-1.70]; aspirin + coumadin group).  <u>Ischemic stroke:</u> 5 patients/1% (aspirin group), 0 patients (coumadin group) and 0 patients (coumadin + aspirin group).</p>

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<p>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.</p>	<p>Clinical Trial</p>	<p>70</p>	<p>Aspirin 81 mg/day [+ high lipoprotein(a) {Lp(a)}] (n=37) Aspirin 81 mg/day [+ low Lp(a)] (n=33)</p>	<p>Aspirin significantly decreased serum Lp(a) in subjects with high Lp(a) to <math>88.3\% \pm 2.7\%</math> of the baseline values after 1 month (<math>p &lt; 0.01</math>). Serum Lp(a) concentrations remained low in these subjects at 3 months (<math>85.0\% \pm 3.4\%</math> of baseline values) and 6 months (<math>81.7\% \pm 2.6\%</math> of baseline values) after the start of treatment. In contrast, no significant changes in serum Lp(a) concentrations in subjects with low Lp(a) were observed during the 6-month treatment period.</p> <p>Other variables including serum total cholesterol, HDL-cholesterol, and fasting blood sugar did not change in subjects with either high or low Lp(a) during 6 months of treatment with aspirin.</p> <p>Among the high molecular weight (HMW) isoform groups, the decrease in serum Lp(a) at 6 months after the start of aspirin treatment was significantly greater in the high Lp(a) group (<math>24.6\% \pm 4.5\%</math>) than in the low Lp(a) group (<math>3.2\% \pm 3.0\%</math>) (<math>p &lt; 0.01</math>). Similar results were seen among the low molecular weight (LMW) isoform groups (<math>p &lt; 0.01</math>).</p> <p>Significant correlations between the baseline Lp(a) concentrations and the decrease in Lp(a) after 6 months of aspirin treatment were observed in the high Lp(a) subjects with both the HMW (<math>r = 0.818</math>) (<math>p &lt; 0.01</math>) and LMW (<math>r = 0.511</math>) (<math>p &lt; 0.01</math>) isoforms, but no correlation was seen in the low Lp(a) group.</p>
<p>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.</p>	<p>Clinical Trial (JAMIS)</p>	<p>723</p>	<p>Aspirin 81 mg/day (n=250) Trapidil 300 mg/day (n=243) No antiplatelet therapy (n=230)</p>	<p>Analyses of the primary endpoints showed that the occurrence of reinfarction was reduced in the aspirin group compared with the control group (<math>p = 0.0045</math>) and the occurrence of cardiovascular events was reduced in the trapidil group compared with the control group (<math>p = 0.0039</math>). Reinfarction occurred in 5 patients in the aspirin group, 9 in the trapidil group, and 17 in the control group. The relative risk of reinfarction in the aspirin group was 0.271 (95% CI: 0.101 to 0.722), and that for the trapidil group compared with the control group was 0.501 (95% CI: 0.228 to 1.101). Cardiovascular events (cardiovascular death [including sudden death], reinfarction, uncontrolled unstable angina requiring admission to the hospital, and non-fatal ischemic stroke) occurred in 36 patients in the aspirin group, 22 in the trapidil group, and 42 in the control group. The relative risk of developing cardiovascular events in the aspirin group compared with the control group was 0.789 (95% CI: 0.525 to 1.185) and that for the trapidil group compared with the control group was 0.496 (95% CI: 0.306 to 0.804). Cardiovascular death occurred in 6 patients in the aspirin group, 4 in the trapidil group, and 5 in the control group (RR for aspirin 1.104 [0.342 to 3.569], RR for trapidil 0.757 [0.206 to 2.785]).</p>

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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. Lancet 357(9250):89-95.	Clinical Trial (PPP)	4495	Aspirin 100 mg/day (n=2226) No aspirin (n=2269) (Each with or without Vitamin E)	<p>There was a consistent reduction in the aspirin group for all endpoints. The reduction for cardiovascular deaths (aspirin: 0.8%; no aspirin: 1.4%) (RR, 95% CI: 0.56, 0.31-0.99; p=0.049) and any cardiovascular events (aspirin: 6.3%; no aspirin: 8.2%) (RR, 95% CI: 0.77, 0.62-0.95; p=0.014) was significant. Cardiovascular events included cardiovascular deaths, nonfatal MI, nonfatal stroke, angina pectoris, TIA, PAD, and revascularization procedures.</p> <p>The reduction in occurrence of clinical endpoints was as follows (incidence (%) aspirin vs. no aspirin; relative risk, 95% CI)</p> <p>Combined endpoint (cardiovascular death, non-fatal MI, and non-fatal stroke): 2.0% vs. 2.8%; 0.71, 0.48-1.04</p> <p>MI: 0.8% vs. 1.2%; 0.69, 0.38-1.23; nonfatal MI: 0.7% vs. 1.0%; 0.69, 0.36-1.33</p> <p>Stroke: 0.7% vs. 1.1%; 0.67, 0.36-1.27; nonfatal stroke: 0.7% vs. 0.8%; 0.84, 0.42-1.67</p> <p>Angina pectoris: 2.4% vs. 3.0%; 0.82, 0.58-1.17</p> <p>TIA: 1.3% vs. 1.8%; 0.71, 0.44-1.15</p> <p>Peripheral-artery disease: 0.8% vs. 1.3%; 0.60, 0.33-1.08</p> <p>Revascularization procedure: 0.9% vs. 1.3%; 0.70, 0.40-1.24</p>

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<p>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.</p>	<p>Clinical Trial</p>	<p>50</p>	<p>Aspirin 100 mg suppositories (n=24) Placebo (n=26)</p>	<p>Twenty-five subjects had an episode of clinical deterioration (aspirin: 10 subjects; placebo: 15 subjects) (RR 0.72, 95% CI: 0.41-1.29). In 10 subjects, the deterioration took place immediately postoperatively. Among the 15 subjects with a delayed episode of deterioration in the postoperative period, 4 subjects in the aspirin and 4 subjects in the placebo treatment groups were classified as having definite delayed cerebral ischemia.</p> <p>Of the 25 subjects without clinical deterioration, 6 subjects in the aspirin and 2 subjects in the placebo treatment groups showed a new hypodense lesion on CT. The RR of any hypodensity on CT for subjects treated with aspirin compared with placebo was 0.88 (95% CI: 0.57-1.38).</p> <p>At the 4-month follow-up, 3 subjects had died, but the deaths were not related to the use of aspirin. The distribution of Rankin grades was slightly more favorable in the subjects who had received aspirin but not to a significant degree (p=0.22). On all domains of the Sickness Impact Profile (SIP) and most domains of the SF-36, the mean scores of subjects who received aspirin were better than those of subjects who received placebo, but the differences were not significant with the exception of the domain "sleep and rest" of the SIP (p=0.01). The mean perceived reduction in quality of life at 4 months after subarachnoid hemorrhage compared with before was not significantly different in the aspirin group (11%) compared with the placebo group (16%) (p=0.6).</p>
<p>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.</p>	<p>Clinical Trial</p>	<p>466</p>	<p>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)</p>	<p>Incidence (%) of events related to efficacy: Aspirin vs. nicametate</p> <p><u>Cerebral Reinfarction:</u></p> <ul style="list-style-type: none"> <li>• Non-fatal cerebral reinfarction: 5.9% vs. 11.5%</li> <li>• Fatal cerebral reinfarction: 0.5% vs. 0.4%</li> <li>• All cerebral reinfarctions: 6.4% vs. 11.9%</li> </ul> <p><u>MI</u></p> <ul style="list-style-type: none"> <li>• Non-fatal myocardial infarction: 0.0% vs. 1.2%</li> <li>• Fatal myocardial infarction: 2.3% vs. 0.8%</li> </ul> <p>The 3-year reinfarction-free rates were 88.2% and 80.1% (p=0.057)</p>

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<p>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.</p>	<p>Case Study</p>	<p>1,013</p>	<p>Aspirin: ≤150 mg/day or &gt;150 mg/day (300 mg/day accounting for close to 90% of this dose category) Nonaspirin NSAID: low-/medium-dose or high-dose categories</p>	<p>The overall incidence of MI was 1.6 per 1000 person-years in the study cohort. Smoking (RR, 95% CI: 3.64, 3.04-4.35) and diabetes (RR, 95% CI: 2.45, 1.84-3.26) were the two major risk factors. Hormone replacement therapy was associated with a 28% reduction in the risk of MI.</p> <p>The relative risk of MI associated with current use of aspirin was 0.80 (95% CI: 0.41-1.53). Prophylactic aspirin use (defined as more than one month of treatment in current users) was associated with a RR of 0.56 (95% CI: 0.26-1.21). The greatest reductions in RR were among nonfatal cases of MI (RR, 95% CI: 0.28, 0.08-0.91) (versus fatal cases [RR, 95% CI: 1.36, 0.52-3.57]). In current aspirin users who had been treated with aspirin ≤30 days, the RR of MI was 4.22 (95% CI: 0.99-17.9). The RR of MI in those treated with aspirin ≤30 days was similar for nonfatal (RR, 95% CI: 3.60, 0.77-16.8) and fatal (RR, 95% CI: 3.71, 0.35-38.9) cases of MI. The beneficial effect was observed among women using doses ≤150 mg of aspirin (83% of women used 75 mg) with a RR of 0.30 (95% CI: 0.09-1.00).</p> <p>Current use of any nonaspirin NSAID was not associated with protection from MI (RR, 95% CI: 1.45, 1.18-1.79). This was true when data were stratified by treatment duration, daily dose, or when fatal and nonfatal cases of MI were examined separately. Examination of the use of individual NSAIDs longer than two months (RR, 95% CI: 1.33, 0.91-1.95), as well as long-term use (&gt;1 year) (RR, 95% CI: 1.25, 0.90-1.72) also showed no protective effect.</p>

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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.	Clinical Trial (AFTER)	1036	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)	After 30 days, cardiac death or reinfarction occurred in 11.0% (57/517) of patients treated with anticoagulation and 11.2% (58/519) of patients treated with aspirin (odds ratio 1.02; 95% CI: 0.69 to 1.50; p=0.92). Corresponding findings at 3 months were 13.2% (68/517) and 12.1% (63/519) (odds ratio 0.91; 95% CI: 0.63 to 1.32; p=0.67). At 30 days, death from all causes occurred in 7.2% of patients treated with anticoagulation and 8.1% of patients treated with aspirin (odds ratio 1.14, 95% CI: 0.72-1.81). Corresponding findings at 3 months were 8.1% and 8.9% in the anticoagulation and aspirin-treated groups, respectively (odds ratio, 1.10, 95% CI: 0.71-1.70). In both groups (anticoagulation and aspirin) at both time points (30 days and 3 months), the majority of deaths were cardiac-related. By 3 months, stroke had occurred in 7 patients in the anticoagulation group and in 4 patients in the aspirin group (p=NS).
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. <i>Blood</i> 98(12):3256-3260.	Clinical Trial	1014	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)	Treatment with orbofiban did not affect the primary endpoint (composite of death, MI, recurrent ischemia, or stroke) or the rate of MI irrespective of the genotype. The relative risk (RR) of a primary endpoint event on orbofiban compared with placebo among PIA2 carriers was 1.37 (95% CI: 0.75 to 2.51) and among noncarriers was 0.73 (95% CI: 0.51 to 1.06). Although among PIA2 carriers on orbofiban there was a trend toward a higher RR (2.46) of MI (95% CI: 0.70 to 8.67) compared to placebo, this did not achieve statistical significance.

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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.	Clinical Trial (HAEST)	449	Aspirin 160 mg/day + placebo ampules SC BID (n=225) Dalteparin 100 IU/kg SC BID + placebo tablets daily (n=224)	There was no significant difference between the dalteparin (19 subjects, 8.5%) and aspirin (17 subjects, 7.5%) treatment groups in the frequency of recurrent ischemic stroke during the first 14 days (odds ratio [OR], 95% CI: 1.13, 0.57-2.24). With regard to secondary endpoints, dalteparin (10.7%) was associated with a higher frequency of progression of symptoms within the first 48 hours compared to aspirin (7.6%), and more deaths after 14 days (dalteparin: 9.4%; aspirin 7.1%); however, the differences were not statistically significant. At 14 days, 0.4% (1 patient) of dalteparin-treated patients and 1.3% (3 patients) of aspirin-treated patients had acute MI, but this difference was not statistically significant. There were no significant differences in functional outcome or death at 14 days as measured by the SSS, Barthel Index, modified Rankin Scale, and International Stroke Trial scale. The percentage of patients dependent or dead was 63.0% in the dalteparin group and 64.0% in the aspirin group (difference not significant). At 3 months, there was still no difference in outcome. The percentage dead or dependent was 66.1% in patients allocated to dalteparin and 64.8% in patients allocated to aspirin (difference not significant).

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<p>CAST (Chinese Acute Stroke Trial) Collaborative Group. 1997. CAST: randomised placebo-controlled trial of early aspirin use in 20,000 patients with acute ischaemic stroke. Lancet 349(9066):1641-1649.</p>	<p>Clinical Trial (CAST)</p>	<p>21,106</p>	<p>Aspirin 160 mg/day (n=10,554) Placebo (n=10,552)</p>	<p>There were 343 (3.3%) in-hospital deaths within 4 weeks among patients allocated to aspirin treatment compared with 398 (3.9%) in the placebo group. The proportional reduction in the odds of death in the aspirin group (14%) was statistically significant (p=0.04) and corresponds to an absolute difference of 5.4 fewer deaths per 1000 patients allocated aspirin for about 4 weeks.</p> <p>For the endpoint of fatal and non-fatal recurrent strokes, there were 335 (3.2%) among aspirin-treated patients and 351 (3.4%) in the placebo group. This difference, though not significant, combined a significant reduction of 4.7 recurrent ischemic strokes per 1000 (p=0.01) with a non-significant excess of 2.1 hemorrhagic strokes per 1000.</p> <p>For the combined endpoint of death or non-fatal stroke, there were 545 (5.3%) events in the aspirin group and 614 (5.9%) in the placebo group (p=0.03). This 12% proportional reduction corresponds to 6.8 fewer cases per 1000 patients allocated to aspirin treatment.</p> <p>For the primary outcome of dead or dependent at discharge, there was a nonsignificant trend favoring those allocated to aspirin treatment compared to placebo (3153 [30.5%] vs. 3266 [31.6%]; p=0.08), corresponding to a reduction of 11.4 events per 1000 patients. A total of 377 (3.6%) patients allocated to aspirin vs. 436 (4.2%) allocated to placebo were dead at discharge (p=0.03). This corresponds to 5.8 fewer deaths per 1000 patients allocated to aspirin treatment. At discharge, 2776 (28.0%) patients allocated to aspirin were dependent compared to 2830 (28.7%) receiving placebo (p&gt;0.1). Among patients who were independent at discharge, 3840 (53.8% of those independent) aspirin-allocated patients achieved full recovery compared to 3716 (52.9%) placebo-treated patients. In addition, among patients who were independent at discharge, 3299 (33.3%) aspirin-treated patients had not fully recovered compared to 3307 (33.6%) placebo-treated patients (difference not statistically significant).</p>

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Reference	Type of Article	Total Subjects	Treatment Groups (n)	Efficacy Data
<p>Coumadin Aspirin Reinfarction Study (CARS) Investigators. 1997. Randomised double-blind trial of fixed low-dose warfarin with aspirin after myocardial infarction. Lancet 350(9075):389-396.</p>	<p>Clinical Trial (CARS)</p>	<p>8803</p>	<p>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 on 2 consecutive assessments</p>	<p>One-year life table estimates for the primary event (first occurrence of nonfatal myocardial reinfarction, nonfatal ischemic stroke, or cardiovascular death) were 8.6% (95% CI: 7.6-9.6), 8.4% (95% CI: 7.4-9.4), and 8.8% (95% CI: 7.6-10) for the 160 mg/day aspirin, 3 mg warfarin/80 mg aspirin, and 1 mg warfarin/80 mg/day aspirin treatment groups, respectively.</p> <p>In the 160 mg/day aspirin group compared with the 3 mg warfarin/80 mg/day aspirin group, the relative risk (95% CI) of a primary event was 0.95 (0.81-1.12) (p=0.57). When the 160 mg/day aspirin group was compared to the 1 mg warfarin/80 mg aspirin/day group, the relative risk (95% CI) of a primary event was 1.03 (0.87-1.22) (p=0.74). When the two warfarin/aspirin combination therapies were compared, the relative risk (95% CI) of a primary event was 0.93 (0.78-1.11) (p=0.41).</p> <p>One-year life table estimates for ischemic stroke were 0.58% in patients assigned to 160 mg/day aspirin, compared to 1.1% in patients in the 1 mg warfarin/80 mg/day aspirin group (p=0.05) and 0.8% in patients in the 3 mg warfarin/80 mg aspirin/day group (p=0.16).</p> <p>One-year life table estimates for non-fatal MI were 6.5% in patients assigned to 160 mg/day aspirin compared to 6.6% in patients assigned to 1 mg warfarin/80 mg/day aspirin (p=0.64) and 6.2% in patients assigned to 3 mg warfarin/80 mg/day aspirin (p=0.31).</p> <p>For deaths due to all causes, the one-year life table estimates were 2.3% for patients assigned to 160 mg/day aspirin compared to 2.3% of patients assigned to 1 mg warfarin/80 mg/day aspirin (p=0.11) and 2.9% in patients assigned to 3 mg warfarin/80 mg/day aspirin (p=0.28). For cardiovascular death, one-year life table estimates were 2.1% in patients assigned to 160 mg/day aspirin compared to 2.0% of patients assigned to 1 mg warfarin/80 mg/day aspirin (p=0.26) and 2.5% in patients assigned to 3 mg warfarin/80 mg/day aspirin (p=0.50).</p> <p>One-year life table estimates for primary or secondary events (secondary events included all-cause mortality, silent MI, unstable angina requiring hospital admission, TIA, and systemic embolisation), were similar for all three treatment groups (24% in patients assigned to 160 mg/day aspirin and patients assigned to 1 mg warfarin/80 mg/day aspirin (p=0.67) and 25% in patients assigned to 3 mg warfarin/80 mg/day aspirin (p=0.99). The one-year life table estimates for primary, secondary, or tertiary events (tertiary events defined as coronary bypass surgery and coronary-artery angioplasty) among the three treatment groups were 30% in patients assigned to 160 mg/day aspirin compared to 29% in patients assigned to 1 mg warfarin/80 mg/day aspirin (p=0.25) and 30% in patients assigned to 3 mg warfarin/80 mg/day aspirin (p=0.78).</p>

APPENDIX 2. SUMMARY OF EFFICACY RESULTS - PUBLICATIONS PROVIDING ADDITIONAL EFFICACY INFORMATION				
Reference	Type of Article	Total Subjects	Treatment Groups (n)	Efficacy Data
Hurlen M, Abdelnoor M, Smith P, Erikssen J, Arnesen H. 2002. Warfarin, aspirin, or both after myocardial infarction. <i>New England Journal of Medicine</i> 347(13):969-974.	Clinical Trial	3630	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)	Aspirin/ Warfarin /Aspirin + Warfarin efficacy data: Combination of deaths/reinfarctions/thromboembolic stroke (20.0%/16.7%/15.0% first events, $p \leq 0.03$ favoring Warfarin regimens) Reinfarctions (N's = 117/90/69); rate ratio for aspirin + warfarin vs. aspirin: 0.56 (0.41 to 0.78, $p < 0.001$ ); rate ratio for warfarin vs. aspirin: 0.74 (0.55 to 0.98, $p = 0.03$ ) Thromboembolic strokes (N's = 32/17/17); rate ratio for aspirin + warfarin vs. aspirin: 0.52 (0.28 to 0.98, $p = 0.03$ ); rate ratio for warfarin vs. aspirin: 0.52 (0.28 to 0.97, $p = 0.03$ ) Deaths (N's = 92/96/95) CABG (N's = 224/204/188) PCI (N's = 230/212/242) Events per 100 patient years (N's = 5.16/4.21/3.67) Two or more events (N's = 54/33/29) Events in conjunction with CABG or PCI (N's = 16/11/9)
O'Connor CM, Gattis WA, Hellkamp AS, Langer A, Larsen RL, Harrington RA, Berkowitz SD, O'Gara PT, Kopecky SL, Gheorghiuade 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.	Clinical Trial	5421	Aspirin 160 mg/day (n=3393) Warfarin 1 mg + Aspirin 80 mg/day (n=2028)	A difference in the cumulative risk of time to first ischemic stroke was observed between the two treatment groups. A 2-fold increase in the risk of stroke in the aspirin 80 mg/day + warfarin 1 mg arm vs. the aspirin 160 mg arm was observed. The rate of stroke in the aspirin 80 mg + warfarin 1 mg arm was 1.1% at 1 year vs. 0.6% in the aspirin 160 mg arm ( $p = 0.0534$ ). At 2 years, it was 1.5% vs. 0.9%, respectively, ( $p = NS$ ). The superiority of aspirin 160 mg appeared greatest in the high-risk groups. Statistical trends favoring a greater effect of the higher aspirin dose were observed among patients with Q-wave MI, male patients, and patients aged >70 years. However, due to small N's in these groups, the ability to detect significant differences in these clinical subgroups was limited. A multivariate Cox proportional-hazards model indicated that advanced age, previous stroke or TIA, and aspirin dose were the variables found to be significant predictors of ischemic stroke.

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Reference	Type of Article	Total Subjects	Treatment Groups (n)	Efficacy Data
<p>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.</p>	<p>Clinical Trial (STAMI)</p>	<p>1470</p>	<p>Aspirin 160 mg/day (n=736) Ticlopidine 500 mg/day (n=734)</p>	<p>The primary endpoint (first occurrence of any of the following: fatal and nonfatal MI, fatal and nonfatal stroke, angina, vascular death, or death due to any other cause) occurred in 118 patients: 59 in the ticlopidine group and 59 in the aspirin group. This difference was not statistically significant (p=0.966). There were a total of 5 (0.7%) patients with cardiovascular death in the aspirin group compared to 6 (0.8%) in the ticlopidine group. There was 1 (0.1%) nonvascular death in the ticlopidine group. A total of 18 (2.4%) patients had nonfatal MIs in the aspirin group compared to 8 (1.1%) in the ticlopidine group. A total of 3 (0.4%) patients in the aspirin group had nonfatal stroke compared to 4 (0.5%) in the ticlopidine group. Documented angina occurred in 33 patients (4.5%) in the aspirin group compared to 40 patients (5.4%) in the ticlopidine group.</p> <p>The crude cumulative evidence curves for nonfatal MI started to diverge at Day 20 and maintained this difference throughout the follow-up, showing more effective protection with ticlopidine (p=0.049). The curves for fatal events were similar over time (p=0.558), and the curves for angina and fatal stroke were not significantly different between the aspirin and ticlopidine groups (p=0.342).</p>
<p>Second SYMPHONY Investigators. 2001. Randomized trial of aspirin, sibrafiban, or both for secondary prevention after acute coronary syndromes. <i>Circulation</i> 103(13):1727-1733.</p>	<p>Clinical Trial</p>	<p>6637</p>	<p>Aspirin 160 mg/day (n=2231) Aspirin 160 mg/day + Low-dose sibrafiban (3.0, 4.5, or 6.0 mg/day based on weight and serum creatinine) (n=2232) High-dose sibrafiban (3.0, 4.5, or 6.0 mg/day based on weight and serum creatinine) (n=2174)</p>	<p>The primary endpoint of death, MI, or severe recurrent ischemia did not differ significantly between aspirin (9.3%) and low-dose sibrafiban + aspirin (9.2%), or high-dose sibrafiban (10.5%) patients. Secondary endpoints (death, MI, severe recurrent ischemia, rehospitalization, reversible coronary ischemia, any revascularization, and composite of death or MI) did not differ significantly between aspirin and low-dose sibrafiban + aspirin patients.</p> <p>Death or MI (6.1% of aspirin patients compared to 6.8% of low-dose sibrafiban + aspirin patients and 8.6% of high-dose sibrafiban + aspirin patients) occurred more often with high-dose sibrafiban, as did mortality alone (1.3% of aspirin patients compared to 1.7% of low-dose sibrafiban + aspirin patients and 2.4% of high-dose sibrafiban + aspirin patients) and MI (5.3% of aspirin patients and low-dose sibrafiban + aspirin patients and 6.9% of high-dose sibrafiban + aspirin patients). In patients who stopped study drug use because of trial termination, the rates of death, MI, severe recurrent ischemia, and their composites did not differ significantly among the three groups at &lt;1 month after study termination.</p>

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Reference	Type of Article	Total Subjects	Treatment Groups (n)	Efficacy Data
<p>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.</p>	<p>Clinical Trial</p>	<p>9233</p>	<p>Aspirin 160 mg/day (n=3089)                      Low-dose sibrifiban (n=3105)                      High dose sibrifiban (n=3039)                      (Sibrifiban doses [3.0, 4.5, or 6.0 mg/day] were based on a model accounting for weight and serum creatinine and designed to achieve at least 25% steady-state inhibition of platelet aggregation [low dose] or at least 50% inhibition [high dose])</p>	<p>The 90-day rate of the primary endpoint (composite of death, non-fatal infarction or reinfarction, and severe recurrent ischemia) did not differ significantly between the groups assigned to aspirin (302 [9.8%]), low-dose sibrifiban (310 [10.1%]; odds ratio 1.03 [95% CI 0.87-1.21]), and high-dose sibrifiban (303 [10.1%]; 1.03 [0.87-1.21]). The Kaplan-Meier estimates for the time to the primary composite endpoint were similar among the three treatment groups. The groups did not differ significantly in the rates of the component events or secondary efficacy endpoints (death, MI, severe recurrent ischemia, rehospitalization, reversible coronary ischemia, any revascularization, and composite of death or MI).</p> <p><u>Aspirin\low-dose sibrifiban\high-dose sibrifiban:</u>                      Death or re-infarction: 7.0%\7.4%\7.9%                      Death: 1.8%\2.0%\2.0%                      Myocardial (re)infarction: 5.6%\5.8%\6.5%                      Severe recurrent ischemia: 3.2%\2.8%\2.5%                      Readmission (any cause): 24.3%\26.6%\25.4%                      Reversible coronary ischemia: 3.9%\4.7%\4.1%                      Any revascularization: 23.3%\23.2%\22.2%</p>
<p>Fiore LD, Ezekowitz MD, Brophy MT, Lu D, Sacco J, Peduzzi P. 2002. Department of Veterans Affairs Cooperative Studies Program Clinical Trial comparing combined warfarin and aspirin with aspirin alone in survivors of acute myocardial infarction: primary results of the CHAMP study. Circulation 105(5):557-563.</p>	<p>Clinical Trial (CHAMP)</p>	<p>5059</p>	<p>Aspirin 162 mg/day (n=2537)                      Aspirin 81 mg/day + Warfarin [INR 1.5-2.5 IU] (n=2522)</p>	<p>A total of 438 patients (17.3%) assigned to the aspirin group and 444 patients (17.6%) assigned to the combination group died (log-rank p=0.76). The most common causes of death in both treatment groups were sudden (&lt;1 hour) and definite AMI. Recurrent myocardial infarction occurred in 333 patients (13.1%) taking aspirin and 336 patients (13.3%) taking combination therapy (log-rank p=0.78). Stroke occurred in 89 patients (3.5%) taking aspirin and 79 patients (3.1%) taking combination therapy (log-rank p=0.52). The cumulative 5-year Kaplan-Meier curves were virtually identical for these outcomes as well as for the composite outcome of cardiovascular events.</p>

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

Reference	Type of Article	Total Subjects	Treatment Groups (n)	Efficacy Data
Ariyo A, Hennekens CH, Stampfer MJ, Ridker PM. 1998. Lipoprotein (a), lipids, aspirin, and risk of myocardial infarction in the Physician's Health Study. <i>Journal of Cardiovascular Risk</i> 5(4):273-278.	Case Study	592	Aspirin 325 mg QOD (n=255) Placebo (n=337)	For those subjects with total cholesterol levels $\geq 200$ mg/dl, the age-adjusted, smoking-adjusted relative risk of a first MI associated with lipoprotein (a) levels above the 25th, 50th, 75th, 90th, and 95th percentiles of the control distribution were 0.9, 1.1, 1.6, 1.4, and 1.2 (all NS; p for trend 0.6). The results were similar and not significant for cholesterol levels $< 200$ mg/dl or $\geq 240$ mg/dl. The results were likewise similar and not significant for those subjects assigned to aspirin versus placebo. Relative risks across the 5 centiles for subjects assigned to aspirin ranged from 0.83 to 1.08 and for subjects assigned to placebo from 1.03 to 1.31. There was no significant interaction between aspirin and lipoprotein (a) level for any of these groups.
Cook NR, Hebert PR, Manson JE, Buring JE, Hennekens CH. 2000. Self-selected post-trial aspirin use and subsequent cardiovascular disease and mortality in the Physicians' Health Study. <i>Archives of Internal Medicine</i> 160(7):921-928.	Observational Study	18,496	Aspirin 325 mg QOD	Self-selected post-trial aspirin use for at least 180 days/year versus 0-13 days/year yielded the following efficacy results (presented as Risk Ratios [95% CI]) : MI: 0.72 (0.55-0.95), p=0.02 Ischemic stroke: 0.92 (0.64-1.33), p=0.73 CVD-related death: 0.65 (0.47-0.89), p=0.03 Death due to acute MI: 0.86 (0.41-1.79), p=0.67 Cerebrovascular death: 0.51 (0.25-1.05), p=0.10 Total death: 0.64 (0.54-0.77), p $\leq$ 0.001
Ma J, Hennekens CH, Ridker PM, Stampfer MJ. 1999. A prospective study of fibrinogen and risk of myocardial infarction in the Physicians' Health Study. <i>Journal of the American College of Cardiology</i> 33(5):1347-1352.	Case Control	398	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	Cases had significantly higher baseline fibrinogen levels (geometric mean: 262 mg/dl) than control subjects (245 mg/dl, p=0.02). Those with abnormally high fibrinogen levels ( $\geq 343$ mg/dl, the 90th percentile distribution of control subjects) had a two-fold increase in MI risk (age- and smoking-adjusted relative risk [RR] 2.09, 95% CI: 1.15 to 3.78) compared with those with fibrinogen below 343 mg/dl. Adding aspirin assignment (using placebo as the reference group) into the model did not change the results for fibrinogen (RR=2.09, 95% CI: 1.15 to 3.78); men assigned to aspirin had a 45% reduction in risk (RR=0.55, 95% CI: 0.36 to 0.84), consistent with findings from the PHS study as a whole. There was no evidence of interaction between fibrinogen level and aspirin treatment (p=0.46).

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Reference	Type of Article	Total Subjects	Treatment Groups (n)	Efficacy Data
<b>High-Dose Aspirin (&gt;200 mg/day)</b>				
Bar Dayan Y, Levy Y, Amital H, Shoenfeld Y. 1997. Aspirin for prevention of myocardial infarction. A double-edge sword. <i>Annales de Medecine Interne</i> 148(6):430-433.	Case Study	15	Aspirin 100 mg/day (n=1) Aspirin 250 mg/day (n=13) Aspirin 325 mg/day (n=0) Aspirin 500 mg/day (n=1)	Nine patients presented with acute MI and 6 patients presented with unstable angina.
Strater R, Kurnik K, Heller C, Schobess R, Luigs P, Nowak-Gottl U. 2001. Aspirin versus low-dose low-molecular-weight heparin: Antithrombotic therapy in pediatric ischemic stroke patients: A prospective follow-up study. <i>Stroke</i> 32(11):2554-2558.	Clinical Trial	135	Aspirin 4 mg/kg body weight per day, range, 2 to 5 mg/kg (n=49) Low-dose low-molecular weight 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)	Aspirin: 4/49 (8.2%) had recurrent strokes (3 vascular stroke and 1 infection). Low-molecular weight heparin: 9/86 (10.5%) had recurrent strokes (6 spontaneous, 1 cardiac, 2 vascular). The difference between treatment groups was not clinically significant (p=0.76 Fisher's exact test). Death occurred in 3 of 13 subjects (23%) with recurrent stroke as a result of stroke-associated complications (n=2) and underlying cardiac disorder (n=1). Two of these 3 children had been treated in the low-molecular weight heparin group, and the third had received 3 mg/kg body weight aspirin per day.
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.	Clinical Trial (TAIST)	1486	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)	The proportions independent (i.e., modified Rankin score of 0-2) at 6 months were similar between treatment groups (tinzaparin high dose: 41.5%, tinzaparin medium dose: 42.4%, and aspirin: 42.5%). There were no differential treatment effects between tinzaparin and aspirin on any of the secondary measures of functional outcome, including the Rankin scale and Barthel index at 3 months, and the Barthel index at 6 months. During the in-hospital treatment period, no patient assigned high-dose tinzaparin developed a symptomatic deep-vein thrombosis compared with 9 patients assigned aspirin (1.8%). A total of 14.6%, 14.2%, and 14.9% patients had died at 6 months in the high-dose tinzaparin, medium-dose tinzaparin, and aspirin groups, respectively. Analysis of a Kaplan-Meier survival plot did not reveal any difference among the treatment groups (log-rank test p>0.1).

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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.	Clinical Trial	43	Aspirin 300 mg QD (n=22) Triflusal 300 mg BID (n=21)	ANOVA and Chi-square analyses were conducted on the data, revealing no significant difference between the two groups in the ultrasonic biopsy (UB) score at one year (0.1 average progression in the UB score in the triflusal group versus -1.2 average progression in the aspirin group, [p=0.3]). This indicated a stabilization of the atherosclerotic lesions in both treatment groups without significant progression. When all arterial sites under evaluation are considered, 86% of sites in the triflusal group and 85% of sites in the aspirin group remained unchanged.
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> .	Clinical Trial (TIM)	2275	Aspirin 300 mg/day (n=1140) Triflusal 600 mg/day (n=1135)	Preliminary results of the TIM study: subjects in the triflusal group had an 11.8% lower risk of the primary endpoint (combined incidence of death, nonfatal re-infarction or nonfatal cerebrovascular event) than subjects in the aspirin group but the difference was not significant. However, the incidence of nonfatal cerebrovascular events was significantly reduced by 63%, from 1.3% with aspirin to 0.5% with triflusal (p=0.03). The difference was mainly due to a reduction of nonfatal cerebral hemorrhages from six subjects in the aspirin group to none in those receiving triflusal. There were no significant differences between the treatment groups in the other secondary endpoints (death, nonfatal re-infarction, or the need for urgent revascularization).
Cruz-Fernandez JM, Lopez-Bescos L, Garcia-Dorado D, Lopez Garcia-Aranda V, Cabades A, Martin-Jadraque L, Velasco JA, Castro-Beiras A, Torres F, Marfil F, Navarro E. 2000. Randomized comparative trial of triflusal and aspirin following acute myocardial infarction. <i>European Heart Journal</i> 21(6):457-465.	Clinical Trial (TIM)	2275	Aspirin 300 mg/day (n=1140) Triflusal 600 mg/day (n=1135)	The null hypothesis of no difference between treatments in the primary combined endpoint (composite of death, non-fatal myocardial reinfarction, or non-fatal cerebrovascular events) was accepted with 80% power after recruiting 2124 validated patients giving an adjusted odds ratio estimate [95% CI] for treatment failure of 0.882 [0.634–1.227]. Non-fatal cerebrovascular events were significantly less frequent with triflusal (OR [95% CI]: 0.364 [0.146–0.908]; p=0.030). There was no significant difference between treatments for death (OR [95% CI]: 0.816 [0.564–1.179]; p=0.278), non-fatal reinfarction (OR [95% CI]: 1.577 [0.873–2.848]; p=0.131) or revascularization (OR [95% CI]: 0.864 [0.644–1.161]; p=0.334). <u>Aspirin\Triflusal:</u> Death: 7.62%\6.31% Non-fatal AMI: 1.77%\2.76% Revascularization: 9.83%\8.62%

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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.	Clinical Trial	53	Aspirin 300 mg/day for 2 weeks followed by ticlopidine 250 mg BID for 2 weeks (n=26) Treatment scheme reversed (n=27)	The mean number of embolic signals per hour and vessel (both MCAs) was 15.7 under aspirin and 11.7 under ticlopidine (difference not significant). There were no significant differences between the two groups in the mean number of embolic signals per hour of 12 dB, 16 dB, or 12 and 16 dB regardless of the MCA (left or right) measured. The correlation between the number of emboli under the two medications was high. There were more embolic signals in high grade carotid stenosis.
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.	Clinical Trial	9	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	During a cumulative monitoring time of 40.5 hours, a total of 521 microembolic signals (MES) ipsilateral to the symptomatic stenoses were detected. No signals were observed in contralateral MCAs. For the 1-hour preinjection period, MES appearance indicated a constant incidence of MES over time. In 7 patients, the frequency of MES decreased after the application of aspirin. Two patients who had presented with 6 and 18 MES/h before medication showed no signal (0 MES/h) during continuous 2.5-hour postinjection monitoring. In 5 patients with initial MES rates 13 to 66/h, the incidence started to decrease approximately 30 minutes after i.v. aspirin. In one patient, MES frequency did not respond to aspirin. In the one patient who was receiving aspirin 100 mg/day since former cardiac bypass surgery, only a minor and transient effect could be demonstrated. In patients who responded to aspirin, the mean MES rate continuously decreased after aspirin and was significantly lower than before the 500-mg i.v. bolus (p-value not given).  Within 1 month before aspirin treatment, there were a total of 22 cerebrovascular events among 9 patients (range: 1-5 events per patient). Within 3 months after aspirin treatment, no patient experienced a cerebrovascular event.

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

Reference	Type of Article	Total Subjects	Treatment Groups (n)	Efficacy Data
<p>Gullov AL, Koefoed BG, Petersen P, Pedersen TS, Andersen ED, Godtfredsen J, Boysen G. 1998. Fixed minidose warfarin and aspirin alone and in combination vs adjusted-dose warfarin for stroke prevention in atrial fibrillation: Second Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation Study. Archives of Internal Medicine 158(14):1513-1521.</p>	<p>Clinical Trial</p>	<p>677</p>	<p>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)</p>	<p>The cumulative primary event (stroke or systemic thromboembolic event) rate after 1 year was 5.8% in patients receiving minidose warfarin; 7.2% with warfarin + aspirin; 3.6% with aspirin alone; and 2.8% with adjusted-dose warfarin. The results were not statistically significant (p=0.67). After 3 years, no significant differences were observed between the groups. NOTE: At 3 years, the aspirin-only group had an identical odds ratio to that of adjusted-dose warfarin (1.0), whereas minidose warfarin had an odds ratio of 1.5 and warfarin/aspirin had an odds ratio of 1.6.</p> <p>There were a total of 12, 8, 13, and 14 secondary adverse events (AMI, TIA, and death not due to other endpoints) in the minidose warfarin, warfarin plus aspirin, aspirin-only, and adjusted-dose warfarin groups, respectively, during treatment.</p> <p>There were 4 and 6 deaths in the minidose warfarin and warfarin plus aspirin groups, respectively, during treatment and 10 deaths each in the aspirin-only and adjusted-dose warfarin groups, respectively, during treatment.</p>

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

Reference	Type of Article	Total Subjects	Treatment Groups (n)	Efficacy Data
<p>IST Collaborative Group (International Stroke Trial). 1997. The International Stroke Trial (IST): A randomised trial of aspirin, subcutaneous heparin, both, or neither among 19 435 patients with acute ischaemic stroke. Lancet 349(9065):1569-1581.</p>	<p>Clinical Trial (IST)</p>	<p>19,435</p>	<p>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)</p>	<p>There were slightly fewer deaths within 14 days among subjects treated with aspirin versus no aspirin (9.0% versus 9.4%), corresponding to an absolute reduction of 4 events per 1000 subjects. Subjects receiving aspirin also had significantly fewer recurrent ischemic strokes within 14 days (2.8% versus 3.9%) (2p&lt;0.001) and this benefit was not offset by any significant excess of hemorrhagic strokes (0.9% versus 0.8%). There was a significant reduction in the likelihood of death or any nonfatal recurrent stroke (11.3% versus 12.4%) (2p=0.02), corresponding to 11 (SD: 5) fewer per 1000 treated.</p> <p>In patients without atrial fibrillation, 2.7% treated with aspirin vs. 3.8% not treated with aspirin experienced a recurrent ischemic stroke within 14 days (2p&lt;0.001). A total of 9.6% of patients in this population treated with aspirin died or had a non-fatal stroke within 14 days compared to 11.0% of patients not treated with aspirin (2p&lt;0.01).</p> <p>In those with atrial fibrillation, 3.3% of patients treated with aspirin had a recurrent ischemic stroke within 14 days compared to 4.5% not treated with aspirin. A total of 19.8% of patients with atrial fibrillation treated with aspirin died or had a non-fatal stroke within 14 days compared to 19.9% of those not treated with aspirin.</p> <p>At 6 months, there were fewer deaths among subjects treated with aspirin (21.5% versus not treated with aspirin (22.5%), but the absolute decrease of 10 (SD: 6) per 1000 was not significant. There was little difference in the percentage of subjects alive but dependent, and the unadjusted 13 (SD: 7) reduction per 1000 in death or dependency was not significant (2p=0.06). After adjustment for predicted prognosis, the reduction was similar but the effect was significant (14 [SD: 6] fewer dead or dependent per 1000 2p=0.03)</p>
<p>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. New England Journal of Medicine 345(24):1740-1746.</p>	<p>Follow-up study</p>	<p>581</p>	<p>Aspirin 300 mg/day                      Patients without atrial septal abnormalities (n=304)                      Patients with atrial septal abnormalities (n=277)</p>	<p>Of the 24 patients with a recurrent stroke, only 7 had a decrease in functional status, according to the Rankin score; 6 of the 7 had no septal abnormalities (p=0.07). None of the patients with an atrial septal defect had a recurrent cerebrovascular event.</p> <p>In Cox analyses, the presence of both atrial septal abnormalities (patent foramen ovale and atrial septal aneurysm) was a significant predictor of an increased risk of recurrent stroke (hazard ratio, 4.17, 95% CI: 1.47-11.84, p=0.007) and recurrent stroke or TIA (hazard ratio, 3.91, 95% CI: 1.59-9.59, p=0.003) whereas the presence of a patent foramen ovale alone or an atrial septal aneurysm alone was not.</p>

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Reference	Type of Article	Total Subjects	Treatment Groups (n)	Efficacy Data
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.	Population-Based Study	209	Aspirin 300 mg/day in 134 (64%) of patients	A total of 24 (11.4%) patients had a recurrent stroke. Untreated hypertension prior to the initial stroke was an independent predictor of recurrence (RR, 1.7; 95% CI, 1.2 to 4.1; p<0.05). Among patients with stroke recurrence, only 3 (12%) were treated with aspirin. In the group of patients without recurrent stroke, 42% were treated with aspirin. Aspirin therapy influenced survival. Cumulative risk of death among patients treated with aspirin was 8% at 6 months and 12% at 1 year compared to a 19% 6-month mortality and 45% 1-year mortality in untreated patients (p<0.05).
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.	Observational Study	350	Aspirin 325 mg/day (n=209) Warfarin (INR 2.0-3.0, mean ratio 2.4) (n=141)	Compared with aspirin, warfarin was associated with a 40% and 31% significant reduction in thromboembolic stroke in older persons with chronic AF who had a prior stroke and those with no prior stroke, respectively. In addition, warfarin was associated with a 45% and 36% significant reduction in thromboembolic stroke in persons with abnormal and normal left ventricular (LV) ejection fraction, respectively. Abnormal LV ejection fraction was also a significant independent risk factor for new thromboembolic stroke, with a risk ratio of 3.0. Incidence of new thromboembolic stroke in older persons with chronic atrial fibrillation: <u>Warfarin\Aspirin:</u> Prior stroke: 42%\82% No prior stroke: 25%\56% Abnormal LV ejection fraction: 47%\92% Normal LV ejection fraction: 20%\56%
Bartorelli AL, Trabattoni D, Montorsi P, Fabbicchi 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.	Clinical Trial	110	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)	In-hospital outcome: No stent thrombosis and Q-wave MI were observed. Non-Q-wave MI was diagnosed in two (1.8%) patients. Events within 30 days: No stent thrombosis, Q-wave MI, coronary bypass surgery, or repeat coronary intervention were observed. Chest pain recurred in one patient; repeat angiography showed a patent stent.

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Reference	Type of Article	Total Subjects	Treatment Groups (n)	Efficacy Data
Bhatt DL, Hirsch AT, Ringleb PA, Hacke W, Topol EJ. 2000. Reduction in the need for hospitalization for recurrent ischemic events and bleeding with clopidogrel instead of aspirin. <i>American Heart Journal</i> 140(1):67-73.	Clinical Trial	19,099	Aspirin 325 mg/day (n=9546) Clopidogrel 75 mg/day (n=9553)	There was a statistically significant decrease in re-hospitalizations for any ischemic or bleeding event for clopidogrel compared with aspirin (p=0.015). The decrease was consistent across the different components of re-hospitalization, namely angina, TIA, limb ischemia, and bleeding. An examination of the actual number of re-hospitalizations (including subjects with multiple hospitalizations) for ischemic events or bleeding revealed 1502 re-hospitalizations (95 per 1000 subject years) in the clopidogrel group versus 1673 (106 per 1000 patient years) in the aspirin group (p=0.010). Irrespective of which composite endpoint was examined, there was a reduction in event rates seen with clopidogrel use. There was a 12.6% rate of vascular death, stroke, MI, or hospitalization for an ischemic or bleeding event in the clopidogrel group per year versus a 13.7% event rate in the aspirin group (p=0.011). This translates to an RRR of 7.9% (95% CI: 1.9%-13.7%). Thus 91 subjects would need to be treated for 1 year with clopidogrel instead of aspirin to prevent one event. Adjusting for baseline prognostic variables, clopidogrel therapy was an independent predictor for reduction of vascular death, stroke, MI, or re-hospitalization for ischemic events or bleeding (p=0.009).
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.	Commentary/ Treatment Guideline	1480	Aspirin 325 mg/day (n=705) Clopidogrel 75 mg/day (n=775)	Clopidogrel was associated with decreased annual rates of the primary end point (composite of vascular mortality, MI, and ischemic stroke) (p=0.004), vascular death, MI, and all cause hospitalization. The groups did not differ for annual rates of all cause mortality (3.4% for aspirin versus 2.6% for clopidogrel, p=0.2), or stroke (3.5% versus 2.6%, p=0.2).
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.	Retro- spective Subanalysis	3866	Aspirin 325 mg/day (n=1952) Clopidogrel 75 mg/day (n=1914)	In diabetic patients, the composite event (vascular death, all-cause stroke, MI, or re-hospitalization for ischemia or bleeding) rate per year was 15.6% in the patients randomized to clopidogrel and 17.7% in the patients who received aspirin, with an absolute risk reduction of 2.1% (p=0.042). In non-diabetic patients the corresponding event rates per year were 11.8% and 12.7%, respectively (p=0.096). The percentage of re-hospitalizations for any ischemic event was not significantly lower with clopidogrel (11.6%) than with aspirin (13.3%), representing a relative risk reduction of 12.9% (95% CI, -3.0 to 26.4, p=0.105).

APPENDIX 2. SUMMARY OF EFFICACY RESULTS - PUBLICATIONS PROVIDING ADDITIONAL EFFICACY INFORMATION				
Reference	Type of Article	Total Subjects	Treatment Groups (n)	Efficacy Data
Cannon CP. 2002. Effectiveness of clopidogrel versus aspirin in preventing acute myocardial infarction in patients with symptomatic atherothrombosis (CAPRIE trial). American Journal of Cardiology 90(7):760-762.	Retro-spective Analysis (CAPRIE)	19,185	Aspirin 325 mg/day (n=9586) Clopidogrel 75 mg/day (n=9599)	A new AMI developed in 617 patients. Kaplan-Meier event rates showed that 5.04% of patients treated with aspirin and 4.2% of patients treated with clopidogrel developed AMI, a 19.2% relative risk reduction with clopidogrel (p=0.008). Significant multivariate predictors of AMI were age ≥65 years, a history of diabetes, prior AMI, peripheral arterial disease, prior angina, or prior ischemic stroke, and baseline creatinine >1.3 mg/dL. The risk of AMI was lower in all risk categories in patients treated with clopidogrel than in those treated with aspirin. The benefit of clopidogrel was also consistent across all subgroups (age, gender, diabetes, hypercholesterolemia, prior MI, and prior cardiac surgery) with only borderline evidence of interaction by a history of hypercholesterolemia (p=0.048), with a greater benefit of clopidogrel in patients with a history of hypercholesterolemia.
CAPRIE Steering Committee (Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events). 1996. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet 348(9038):1329-1339.	Clinical Trial (CAPRIE)	19,185	Aspirin 325 mg/day (n=9586) Clopidogrel 75 mg/day (n=9599)	The event rates per year for clopidogrel versus aspirin for each of the outcome events are provided below along with the relative risk reduction associated with clopidogrel (95% CI): Ischemic stroke, MI, or vascular death (primary cluster): 5.32% vs. 5.83%; 8.7% (0.3 to 16.5); p=0.043 Ischemic stroke, MI, amputation, or vascular death: 5.56% vs. 6.01%; 7.6% (-0.8 to 15.3); p=0.076 Vascular death: 1.90% vs. 2.06%; 7.6% (-6.9 to 20.1); p=0.29 Any stroke, MI, or death from any cause: 6.43% vs. 6.90%; 7.0% (-0.9 to 14.2); p=0.081 Death from any cause: 3.05% vs. 3.11%; 2.2% (-9.9 to 12.9); p=0.71 The event rates per year for clopidogrel versus aspirin for the primary cluster of ischemic stroke, MI, or vascular death are provided below along with the relative risk reduction associated with clopidogrel (95% CI) for subgroups of patients who presented first with each of the following conditions: Stroke: 7.15% vs. 7.71%; 7.3% (-5.7 to 18.7); p=0.26 MI: 5.03% vs. 4.84%; -3.7% (-22.1 to 12.0); p=0.66 PAD: 3.71% vs. 4.86%; 23.8% (8.9 to 36.2); p=0.0028

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Reference	Type of Article	Total Subjects	Treatment Groups (n)	Efficacy Data
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.	Clinical Trial	115	Aspirin 325 mg/day (n=60) Placebo (n=55)	In patients with infective endocarditis, clinical embolic events occurred in 28.3% of patients on aspirin and 20.0% of patients on placebo, with an odds ratio of 1.62 (95% CI, 0.68 to 3.86; p=0.287). Heart failure occurred in 39.7% of aspirin-treated patients and 30.9% of placebo-treated patients. In-hospital death occurred in 6.7% of aspirin-treated patients and 10.9% of placebo-treated patients.
Creager MA. 1998. Results of the CAPRIE trial: efficacy and safety of clopidogrel. <i>Vascular medicine</i> 3(3):257-260.	Clinical Trial (CAPRIE)	19,185	Aspirin 325 mg/day (n=9586) Clopidogrel 75 mg/day (n=9599)	Intention-to-treat analysis found that during 17,636 patient years at risk, 939 events occurred in the clopidogrel group at an average rate of 5.32% per year. In the 17,519 patient years at risk among aspirin-treated patients, 1021 events occurred at an average of 5.83% per year. Therefore, the absolute risk reduction achieved with clopidogrel compared with aspirin was 0.51% per year. Using a Cox proportional-hazard model, the relative risk reduction achieved by clopidogrel compared with aspirin was 8.7% (95% CI 0.3–16.5; p=0.043). An on-treatment analysis of the data (including patients receiving only the study drug or data taken from patients within 28 days of discontinuation of the study drug) revealed a relative risk reduction of 9.4% in favor of clopidogrel. Analysis of the data for the secondary outcomes provided similar relative risk reductions of 7–8% in favor of clopidogrel for the cluster of ischemic stroke, myocardial infarction, amputation, or vascular death (p=0.076), for vascular death (p=0.29); and for any stroke, myocardial infarction, or death from any cause (p=0.81). The relative risk reduction for death from any cause was 2.2% (p=0.71). A subsequent analysis of patients in this trial showed a relative risk reduction by clopidogrel of 19.2% in fatal and nonfatal MI (p<0.008).

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Reference	Type of Article	Total Subjects	Treatment Groups (n)	Efficacy Data
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.	Clinical Trial	90	Aspirin 325 mg/day (n=46) Aspirin 325 mg/day + Calcium heparin 12,500 IU daily (n=44)	Ischemic events totaled 36 in the heparin + aspirin group versus 73 in the aspirin alone group (p=0.002). The following is a list of the incidence of various ischemic events for the calcium heparin group vs. the aspirin-alone group: Angina: 18% vs. 22%; p=NS Re-infarction: 0 vs. 2%; p=NS Stroke: 0 vs. 2%; p=NS Cardiac death: 7% vs. 6%; p=NS Indication for PTCA: 11% vs. 13%; p=NS Indication for CABG: 4% vs. 24%; p=0.021 Positive stress test: 16% vs. 35%; p=0.070 Angiography: 25% vs. 54%; p=0.009
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.	Retro-spective Study	936	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)	During follow-up, cardiac death occurred in 22 patients, all-cause mortality in 31 and cardiac death or nonfatal MI in 70. Each of these outcomes was significantly less frequent among regular aspirin users. Cardiac death rate was markedly reduced: 1.6% for aspirin users and 5.4% for nonusers (p=0.005). These differences were not explained by imbalances in predictors of postinfarction risk (e.g., age, prior MI, diabetes mellitus, cigarette smoking) or therapy other than aspirin (e.g., beta-blockers or coronary angioplasty). The Cox hazard ratio was 0.37 (p=0.023). The differences persisted at least 2 years after enrollment. The following outcome events were also lower in regular aspirin users vs. non-users: all-cause mortality (2.5% vs. 6.5%; p=0.011), cardiac death or nonfatal infarction (6.5% vs. 11.4%; p=0.029), nonfatal infarction (5.3% vs. 7.0%; p=NS), and unstable angina (13.9% vs. 11.4%; p=NS). The difference in mortality rate was particularly prominent after thrombolysis: 0.9% for aspirin users and 8.8% for nonusers (p=0.004).

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<b>Reference</b>	<b>Type of Article</b>	<b>Total Subjects</b>	<b>Treatment Groups (n)</b>	<b>Efficacy Data</b>
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.	Clinical Trial	226	Aspirin 325 mg/day (n=103) Ticlopidine 250 mg BID + Aspirin 325 mg/day (n=123)	At 1 month, the rate of stent thrombosis was 2.9% in the aspirin only group and 0.8% in the ticlopidine/aspirin group (p=0.2). Cumulative major clinical events after successful stenting occurred in 3.9% of patients in the aspirin group and 0.8% of patients in the ticlopidine/aspirin group (p=0.1). The frequencies of other clinical outcome events at 1 month for aspirin vs. ticlopidine/aspirin were as follows: MI: 3.9% vs. 0.8%, p=0.1; death: 2.9% vs. 0, p=0.1; repeat PTCA: 1.9% vs. 0.8%, p=0.4; vascular complications: 1.0% vs. 0, p=0.5.
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.	Clinical Trial (CAPRIE)	19,185	Aspirin 325 mg/day (n=9586) Clopidogrel 75 mg/day (n=9599)	Compared with aspirin, clopidogrel reduced the combined risk of ischemic stroke, MI, or vascular death by 8.7% (p=0.043).

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Reference	Type of Article	Total Subjects	Treatment Groups (n)	Efficacy Data
<p>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. Stroke 30(6):1223-1229.</p>	<p>Meta-analysis</p>	<p>2012</p>	<p>Aspirin 325 mg/day (n=1722) Aspirin 325 mg/day + Warfarin (mean daily dose was 2.1 mg) (n=290)</p>	<p>During a total observation period of 3977 patient-years, 130 ischemic and 10 hemorrhagic strokes occurred. Of the ischemic strokes, 55% were classified as probably cardioembolic, 18% as probably noncardioembolic, and the remainder as of uncertain cause. A total of 62% of ischemic strokes were disabling or fatal. The annualized rate of ischemic stroke was 3.3% per year (95% CI, 2.8 - 3.9). The stroke rate was higher in those with prior stroke or TIA (N=159; stroke rate = 13.0% per year; RR, 2.9) versus other participants (N=1853; stroke rate = 2.7% per year; p&lt;0.001).</p> <p>In addition to a prior history of stroke, several other factors were independently and significantly associated with increased stroke risk among all patients in the SPAF studies, including: age &gt;75 years (RR, 1.8 per decade; p&lt;0.001), female sex (RR, 1.6; p=0.01), history of hypertension (RR, 2.0; p&lt;0.001), and systolic BP &gt;160 mmHg (RR, 2.3; p&lt;0.001). Alcohol consumption ≥14 drinks per week was associated with reduced stroke risk (adjusted RR, 0.4; p=0.04). Significant independent associates of disabling/fatal ischemic strokes were similar.</p> <p>A risk stratification scheme was generated based on the findings for patients without prior stroke or TIA (primary prevention). High-risk patients (7.1% stroke rate per year, 22% of the cohort) included women &gt;75 years of age, age &gt;75 years and a history of hypertension, or patients with a systolic BP &gt;160 mmHg. Moderate-risk patients (2.6% stroke rate per year, 37% of the cohort) included diabetics and patients ≤75 years with a history of hypertension. Low-risk patients (0.9% stroke rate per year, 41% of the cohort) had none of the risk high or moderate risk factors.</p>
<p>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. Circulation 105(22):2625-2631.</p>	<p>Clinical Trial</p>	<p>630</p>	<p>Aspirin 325 mg/day (n=318) Warfarin 2 mg/day (n=312)</p>	<p>The analysis focused on the difference in time to primary end points (incidence of recurrent ischemic stroke or death from any cause) between patients with patent foramen ovale (PFO) and without. The results indicated no statistical difference between these 2 groups. There was also no significant difference in time to primary end point between patients on aspirin versus patients on warfarin in patients with PFO (p=0.49; hazard ratio 1.29; 95% CI 0.63 to 2.64; 2-year event rates 13.2% vs. 16.5%, respectively) and those without PFO (p=0.40; hazard ratio 0.80; 95% CI 0.49 to 1.33; 2-year event rates 17.4% vs. 13.4%, respectively).</p>

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<p>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.</p>	<p>Clinical Trial</p>	<p>831</p>	<p>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)</p>	<p>In the prosthetic bypass patency group among the 161 subjects with 8 mm bypasses, there was no significant difference in the lack of patency between the warfarin + aspirin (17%) and aspirin group (24.1%) (p=0.32). However, among the 212 subjects with 6 mm bypasses, there was a significant difference in the lack of patency in the warfarin + aspirin (28.6%) versus the aspirin group (42.1%) (p=0.022). In the vein bypass group, the percentage of subjects in whom patency was lost was similar in the warfarin + aspirin (57 subjects, 24.7%) and aspirin group (57 subjects, 25.1%) (risk ratio, 95% CI: 1.04, 0.72-1.51; p=NS).</p> <p>There were 31.8% deaths in the warfarin + aspirin group compared to 23.0% deaths in the aspirin group (risk ratio, 95% CI: 1.41, 1.09-1.84; p=0.01). The aspirin combined (prosthetic and vein) treatment group had a significantly higher survival rate as compared with the warfarin + aspirin group (p=0.01), which remained significant in the vein group (p=0.037) but not in the prosthetic group (p=0.087).</p>
<p>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.</p>	<p>Clinical Trial</p>	<p>1653</p>	<p>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)</p>	<p>The incidence (%) of primary and secondary events in the first 30 days after stenting is presented below for aspirin, aspirin + warfarin, and aspirin + ticlopidine, respectively, along with a p-value for the comparison of all 3 groups with the chi-square test.</p> <p>Stent thrombosis (the primary endpoint): 3.6%, 2.7%, 0.5%; p=0.001 Death: 0.2%, 0, 0; p-value not applicable Angiographically evident thrombosis: 2.9%, 2.7%, 0.5%; p=0.005 Revascularization of target lesion: 3.4%, 2.5%, 0.5%; p=0.002 Recurrent MI: 2.7%, 2.0%, 0.5%; p=0.01 Cerebrovascular accident: 0.4%, 0.2%, 0; p=0.78</p> <p>The relative risk (95% CI; p-value) of primary and secondary events in the aspirin + ticlopidine group compared to the aspirin alone group and the aspirin + warfarin group, respectively, are listed below:</p> <p>Stent thrombosis: 0.15 (0.05 to 0.43; p&lt;0.001), 0.20 (0.07 to 0.61; p=0.01) Angiographically evident thrombosis: 0.19 (0.06 to 0.57; p=0.001), 0.20 (0.07 to 0.61; p=0.01) Revascularization of target lesion: 0.16 (0.06 to 0.46; p=0.001), 0.22 (0.07 to 0.66; p=0.02) Recurrent MI: 0.20 (0.07 to 0.62; p=0.014), 0.27 (0.08 to 0.90; p=0.11)</p>

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

Reference	Type of Article	Total Subjects	Treatment Groups (n)	Efficacy Data
<p>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.</p>	<p>Clinical Trial (TACIP)</p>	<p>2107</p>	<p>Aspirin 325 mg/day (n=1052) Triflusal 600 mg/day (n=1055)</p>	<p>The following is a list of the incidences of various outcome events for the triflusal vs. aspirin groups as well as the p-value and hazard ratio (95% CI):                      Primary endpoint (combined end point of nonfatal ischemic stroke, nonfatal acute myocardial infarction, or vascular death): 13.1% vs. 12.4%, p=0.647, 1.09 (0.85 to 1.38)                      Overall mortality: 6.4% vs. 5.4%, p=0.357, 1.22 (0.86 to 1.73)                      Vascular death: 3.5% vs. 2.9%, p=0.538, 1.22 (0.75 to 1.96)                      Nonvascular death: 2.9% vs. 2.5%, p=0.592, 1.22 (0.73 to 2.06)                      Nonfatal ischemic stroke: 9.4% vs. 8.8%, p=0.705, 1.09 (0.82 to 1.44)                      Any ischemic stroke: 9.7% vs. 9.6%, p=1.000, 1.03 (0.78 to 1.36)                      Nonfatal AMI: 1.3% vs. 1.4%, p=0.854, 0.95 (0.46 to 1.98)                      Any acute MI: 1.9% vs. 1.4%, p=0.496, 1.36 (0.70 to 2.66)                      Nonfatal systemic thromboembolism: 0.6% vs. 0.8%, p=0.606, 0.76 (0.26 to 2.19)                      Any systemic thromboembolism: 0.8% vs. 0.8%, p=1.000, 1.01 (0.38 to 2.71)</p>
<p>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.</p>	<p>Clinical Trial</p>	<p>200</p>	<p>Aspirin 325 mg/day</p>	<p>During the in-hospital period, non-Q-wave MI occurred in 1.5% of patients. There were no stent thromboses, cardiac deaths, Q-wave MIs, CABGs, or target lesion revascularizations. A composite of any of the above events occurred in 1.5% of patients.                      At the 30-day follow-up, stent thrombosis (the primary endpoint) occurred in 1.0% of patients, Q-wave MI in 1.0%, non-Q-wave MI in 1.5%, and target lesion revascularization in 1.0%. There were no cardiac deaths or CABGs. A composite of any of the above events occurred in 2.5% of patients.</p>

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Reference	Type of Article	Total Subjects	Treatment Groups (n)	Efficacy Data
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.	Clinical Trial	49	Aspirin 325 mg/day (n=545) Warfarin adjusted to maintain INR 2.0 to 4.5 (n=555)	A total of 63 ischemic strokes occurred in 63 patients. Fourteen of these patients were not taking study medication at the time of the event; 10 were assigned to warfarin and 4 to aspirin. Ischemic strokes in patients who had stopped study medication for more than 7 days before the event were not included in the analysis.  The remaining 49 strokes were analyzed; of these, 46 were nonhemorrhagic. Strokes were categorized as follows: cardioembolic, n=18; non-cardioembolic, n=18; uncertain etiology, n=13.  In aspirin-treated patients, strokes were classified as follows: cardioembolic, n=15; non-cardioembolic, n=7; uncertain etiology, n=11.  In warfarin-treated patients, strokes were classified as follows: cardioembolic, n=3; non-cardioembolic, n=11; uncertain etiology, n=2. The stroke rates were significantly lower in the warfarin group (number of events = 16, n=555; rate per year = 1.3%) as compared to the aspirin group (number of events = 33, n=545; rate per year = 2.6%) (p=0.002).
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.	Clinical Trial	2206	Aspirin 325 mg/day (n=1103) Warfarin 2 mg/day to INR 1.4 to 2.8 (n=1103)	Both warfarin and aspirin were equally efficacious for the prevention of recurrent ischemic stroke and death. The primary endpoint of death or recurrent ischemic stroke was reached by 196 of 1103 patients assigned to warfarin (17.8%) and 176 of 1103 assigned to aspirin (16.0%, p=0.25); hazard ratio comparing warfarin with aspirin, 1.13; 95% CI, 0.92 to 1.38).
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.	Clinical Trial	63	Aspirin 325 mg/day (n=21) Warfarin (dose-adjusted to INR of 2-3) (n=11) Control (neither aspirin or warfarin) (n=31)	Primary catheter patency duration was significantly longer among the warfarin and aspirin groups than the control group (aspirin versus control, p<0.0001; warfarin versus control, p<0.0001). There was no significant difference between the aspirin and warfarin groups. The Kaplan-Meier survival plot showed that at 120 days catheter survival was 91%, 73% and 29% among the aspirin, warfarin and control patient groups, respectively (aspirin versus control, p<0.0001; warfarin versus control, p<0.0001; aspirin versus warfarin, p=NS).

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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.	Clinical Trial	56	Aspirin 325 mg/day (n=24) Aspirin 325 mg/day + Warfarin to INR 2 to 3 + heparin 15 units/kg (n=32)	The immediate postoperative primary graft patency rates (97.3% versus 85.2%, p=0.07) and limb salvage rates (100% versus 88.9%, p=0.04) were higher in the warfarin group as compared with aspirin alone group. The cumulative 3-year primary, primary assisted, and secondary patency rates were significantly greater in the warfarin + aspirin group versus the aspirin group (74% versus 51%, p=0.04; 77% versus 56%, p=0.05; 81% versus 56%, p=0.01, respectively). Cumulative limb salvage rates were higher in the warfarin + aspirin group (81% versus 31%, p=0.02). Perioperative mortality (<30 days) was 3% (1 patient) in the warfarin group and zero in the aspirin group (p=NS). MI occurred in 1 patient (3%) in the warfarin group and 2 patients (7%) in the aspirin group (p=NS).
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.	Clinical Trial (SPAF III)	892	Aspirin 325 mg/day	Results, presented as annualized rates in % (95% CI), are as follows: Ischemic stroke: 2.0% (1.5-2.8) Primary events (ischemic stroke + non-CNS emboli): 2.2% (1.6-3.0) Disabling ischemic strokes: 0.8% (0.5-1.3) All strokes (ischemic and hemorrhagic): 2.2% (1.6-3.0) All disabling strokes: 0.9% (0.5-1.4) TIAs: 1.3% (0.9-2.0) All deaths: 1.8% (1.3-2.6) Vascular deaths: 1.0% (0.7-1.6) Stroke, MI or vascular death: 3.5% (2.8-4.5) Develop high-risk features: 6.5% (5.4-7.9) Primary events while low risk: 2.3% (1.7-3.1)

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WASID Study Group (Warfarin-Aspirin Symptomatic Intracranial Disease). 1998. Prognosis of patients with symptomatic vertebral or basilar artery stenosis. Stroke 29(7):1389-1392.	Retro-spective Study	68	<p>Aspirin (no specific dose required or specified; 21 of 26 patients were treated with at least 325 mg/day) (n=26)</p> <p>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)</p> <p>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)</p>	<p>Patients treated with aspirin had a significantly higher rate of ischemic stroke in any vascular territory compared with patients treated with warfarin (stroke rates per 100 patient-years of follow-up were 21.5 on aspirin versus 6.3 on warfarin; p=0.02). There were no significant differences, however, between the 2 groups in the rates of ischemic stroke, MI, and sudden death combined (27.4/100 patient-years on aspirin versus 15.7/100 patient-years on warfarin; p=0.18) or in the rates of MI and sudden death combined (5.9/100 patient-years on aspirin versus 9.4/100 patient-years on warfarin; p=0.49).</p> <p>Of 26 patients treated with aspirin for a median follow-up of 19.7 months, 6 (23%) had a stroke in the same territory as the stenotic intracranial artery (2 of 13 patients [15%] with unilateral vertebral artery stenosis, 3 of 9 patients [33%] with stenosis involving the basilar artery, and 1 of 4 [25%] with PCA or PICA stenosis). The rate of stroke in the same territory as the stenotic artery in patients on aspirin (per 100 patient-years) was 11.7 (9.6 in patients with 50% to 79% stenosis versus 15.1 in patients with 80% to 99% stenosis).</p> <p>Of 42 patients treated with warfarin for a median follow-up of 11 months, 4 (10%) had a stroke in the same territory as the stenotic intracranial artery (2 of 19 [11%] with stenosis involving the basilar artery, 2 of 5 [40%] with bivertebral stenoses, 0 of 13 [0%] with unilateral vertebral artery stenosis, and 0 of 5 [0%] with PCA or PICA stenosis). The rate of stroke in the same territory as the stenotic artery in patients on warfarin (per 100 patient-years) was 6.3 (3.7 in patients with 50% to 79% stenosis versus 8.2% in patients with 80% to 99% stenosis).</p>

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Reference	Type of Article	Total Subjects	Treatment Groups (n)	Efficacy Data
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.	Meta-analysis	6001	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.	The incidence of deep venous thrombosis (DVT) was 53% (1701/3214) in the aspirin group, 45% (541/1203) in the warfarin group, 29% (311/1075) in the low molecular weight heparin (LMWH) group, and 17% (86/509) in the pneumatic compression device groups. Intermittent pneumatic compression devices and LMWH were significantly better than warfarin ( $p < 0.0001$ ) or aspirin ( $p < 0.0001$ ) in preventing DVT. The incidence of asymptomatic pulmonary embolism (PE) was 11.7% (222/1901) in the aspirin group, 8.2% (101/1229) in the warfarin group and 6.3% (24/378) in the pneumatic compression group. No studies with LMWH used routine lung scans. Pneumatic compression was significantly better than aspirin ( $p = 0.0002$ ) and warfarin ( $p = 0.0003$ ) in preventing asymptomatic PE. The incidence of symptomatic PE was 1.3% (23/1800) in the aspirin group, 0.4% (2/559) in the warfarin group, 0.5% (2/416) in the LMWH group and 0% (0/177) in the pneumatic compression group. No statistically significant difference was noted between the above prophylactic regimes due to the very small incidence of symptomatic PE.
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.	Clinical Trial (ACAS)	825	Aspirin 325 mg/day All subjects in the Asymptomatic Carotid Atherosclerosis Study (ACAS) also underwent aggressive risk factor reduction	Of the 721 subjects who underwent carotid endarterectomy (CEA), the perioperative events that were directly related to the procedure included 10 nonfatal strokes, 6 TIAs, 3 MIs, and 1 death (20 events, 19 subjects) for a total event rate of 2.6%. The perioperative stroke and death rate directly attributable to CEA was 1.5%. Of the 415 subjects who underwent arteriography after randomization but before CEA, 1.2% suffered a cerebral infarction, and one death was associated with carotid arteriography. Thus a nearly equal risk of stroke was associated with both CEA and carotid arteriography.

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Cesarone MR, Belcaro G, Nicolaidis 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.	Clinical Trial (LONFLIT3)	300	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)	Control group: 4 patients (4.82%) had deep venous thrombosis (DVT) (equivalent to 3.6% of limbs). There were two superficial thromboses. In total, 4.82% limbs had a thrombotic event. Aspirin group: 3 patients (3.6%) had DVT (equivalent to 1.8% of limbs). There were two superficial thromboses. In total, 3.6% of limbs had a thrombotic event. LMWH group: 0 patients had DVT. There was one superficial thrombosis. In total, 0.61% of limbs had a thrombotic event (p<0.002 in comparison with the other two groups).
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.	Clinical Trial	563	Aspirin 200 mg TID (n=307) Piracetam 1600 mg TID (n=256)	No significant difference was observed for the primary endpoint (rate of new stroke, new TIA, and vascular death) between the piracetam vs. aspirin groups in the ITT analysis (15.2% vs. 11.7%, OR for aspirin, 0.74, 95% CI, 0.45 to 1.20, p=0.2623). The analysis of stroke only showed an incidence of 10.2% in the piracetam group and 7.5% in the aspirin group (OR for aspirin, 0.72, 95% CI, 0.40 to 1.30, p=0.2947). TIA only was observed in 5.1% of patients in the piracetam group and 4.2% in the aspirin group. After excluding those patients who did not respond to antiplatelet medication in vitro, however, piracetam and aspirin were equivalent in secondary stroke prophylaxis (stroke, TIA, or vascular death: 10.1% in the piracetam group versus 9.7% in the aspirin group; stroke only: 5.5% in the piracetam group versus 5.0% in the aspirin group; TIA only: 4.6% in the piracetam group versus 4.7% in the aspirin group).

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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.	Meta-analysis	1002	<p><u>Green</u> (1982):                      Aspirin 975 mg/day (n=16)                      Aspirin 975 mg/day + dipyridamole (DP) 225 mg/day (n=16)                      Placebo (n=17)</p> <p><u>Goldman</u> (1984):                      Aspirin 900 mg/day + DP 225 mg/day (n=22)                      Placebo (n=31)</p> <p><u>Kohler</u> (1984):                      Aspirin 975 mg/day + DP 225 mg/day (n=50)                      Placebo (n=50)</p> <p><u>Donaldson</u> (1985):                      Aspirin 990 mg/day + DP 225 mg/day (n=33)                      Placebo (n=32)</p> <p><u>McCollum</u> (1991):                      Aspirin 600 mg/day + DP 300 mg/day (n=286)                      Placebo (n=263)</p> <p><u>Kretchmer</u> (1992):                      Phenprocoumon 2.4-4.8 INR (n=66)                      No treatment (n=64)</p> <p><u>Sarac</u> (1998):                      Warfarin 2-3 INR + Aspirin 325 mg/day (n=32)                      Aspirin 325 mg/day (n=24)</p>	<p>In 423 patients treated with antiplatelet drugs, 120 (28.4%) bypasses occluded compared with 144 (36.6%) occlusions in 393 randomized control subjects. The relative risk (RR) of occlusion was 0.78 (95%CI 0.64 to 0.95), meaning a proportional risk reduction of 22% and a significant absolute risk reduction of 8.2%. The RR for stroke, reported in three trials, was 0.80 (95% CI 0.41 to 1.57) and for MI was 0.64 (95% CI 0.37 to 1.10). The RR for vascular mortality was 0.71 (95% CI 0.47 to 1.09), with an absolute risk reduction of 3.1%. The RR for overall mortality was 0.92 (95% CI 0.64 to 1.32), with an absolute risk reduction of 0.9%. The RR of the composite outcome (stroke, MI, and vascular mortality) was 0.88 (95% CI 0.64 to 1.2), with an absolute risk reduction of 2%. In one trial that compared aspirin plus warfarin to aspirin alone, the RR of graft occlusion was 0.38 (95% CI 0.15 to 0.95) and the RR for amputation was 0.42 (95% CI 0.16 to 1.08).</p>

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<p>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.</p>	<p>Clinical Trial</p>	<p>1809</p>	<p>Aspirin 650 mg/day (n=907) Ticlopidine 500 mg/day (n=902)</p>	<p>There were 133 subjects (14.7%) treated with ticlopidine and 112 subjects (12.3%) treated with aspirin who suffered recurrent stroke, MI, or vascular death (hazard ratio [HR], 1.22; 95% CI, 0.94 to 1.57). Kaplan-Meier curves for time to these primary outcome measures did not differ significantly between the two treatment groups (p=0.12). Kaplan-Meier curves for time to recurrent fatal or nonfatal stroke did approach a statistically significant reduction favoring aspirin over ticlopidine (p=0.08). Primary and secondary outcome events (%) are listed below for ticlopidine vs. aspirin along with a HR (95% CI) and p-value:                      Recurrent stroke (fatal): 0.4% vs. 0.2%, NA, p=0.45                      Recurrent stroke (nonfatal): 11.3% vs. 9.3%, 1.25 (0.94 to 1.67), p=0.15                      MI (fatal): 0.1% vs. 0, NA, p=0.50                      MI (nonfatal): 0.9% vs. 0.9%, 1.02 (0.38 to 2.71), p=0.99                      Vascular death (major): 0.8% vs. 0.4%, NA, p=0.36                      Vascular death (other): 1.2% vs. 1.5%, 0.80 (0.36 to 1.76), p=0.56                      Any recurrent stroke: 11.9% vs. 9.5%, 1.28 (0.96 to 1.72), p=0.10                      Death (all causes): 5.0% vs. 4.4%, 1.15 (0.74 to 1.77), p=0.56                      Vascular death: 2.5% vs. 2.1%, 1.23 (0.66 to 2.29), p=0.52                      Recurrent stroke or death (all causes): 15.3% vs. 12.9%, 1.22 (0.95 to 1.57), p=0.14                      Recurrent stroke, MI, or death (all causes): 16.1% vs. 13.8%, 1.21 (0.95 to 1.55), p=0.17</p>
<p>QD = once daily; QOD = every other day; BDT = British Doctors' Trial; PHS = Physicians' Health Study; TPT = Thrombosis Prevention Trial; PPP = Primary Prevention Project; ETDRS = Early Treatment of Diabetic Retinopathy Study; HOT = Hypertension Optimal Treatment Study; MI = myocardial infarction; AMI = acute myocardial infarction; IHD = ischemic heart disease; CHD = coronary heart disease; CV = cardiovascular; TIA = transient ischemic attack; SAH = subarachnoid hemorrhage; DVT = deep venous thrombosis; DP = Dipyridamole; LMWH = low molecular weight heparin; INR = International Normalized Ratio; LV = left ventricular; RR = Relative Risk; RRR = Relative Risk Reduction; HR = Hazards Ratio; OR = Odds Ratio; CI = Confidence Interval; CATS = Captopril and Thrombolysis Study; CAPRIE = Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events Trial.</p>				