

B. Statement of Grounds

1. Executive Summary

Cardiovascular disease remains the number one killer of men and women in the United States and imposes a financial burden in the range of hundreds of billions of dollars. Although lifestyle modifications and pharmacologic interventions are prescribed to reduce risk factors such as high cholesterol, hypertension, and diabetes some risk factors (family history, age, gender) are non-modifiable. As a pharmacologic treatment, aspirin has been used extensively and is approved by the FDA for the reduction of heart attack in patients with a previous heart attack, TIA, stroke, angina, PTCA, CABG, or carotid endarterectomy. If taken during a suspected heart attack, aspirin significantly reduces the risk of death by 23% and is professionally labeled for this indication by the FDA.

In 1988, the aspirin component of the Physicians' Health Study (PHS) of 22,071 apparently healthy men randomized to aspirin or placebo was terminated early, based on the unanimous recommendation of the independent and external Data and Safety Monitoring Board, due principally to the emergence of a statistically extreme ($p < 0.00001$) 44% reduction in first myocardial infarction (MI). The Cardio-Renal Drugs Advisory Committee recommended to the U.S. Food and Drug Administration to professionally label aspirin to prevent first MI. The agency did not act on this recommendation because the only other trial, the British Doctors' Trial (BDT) of 5139 men showed no significant benefits. Since that time, three additional randomized trials of aspirin in the primary prevention of MI that included men and women have been published. A computerized search of the English literature from 1988 to the present revealed five published trials: PHS (22,071), BDT (5139), Thrombosis Prevention Trial (5085), Hypertension Optimal Treatment Study (18,790) and the Primary Prevention Project (4495). Among 55,580 randomized participants (11,466 women), there was a statistically significant reduction of 32% in first MI due to aspirin, no significant effects on non-fatal stroke or vascular death but a significant reduction in all important vascular events of 15%. The current evidence provides strong support for the initial finding from the PHS that aspirin reduces risk of a first MI. For apparently healthy individuals for whom the 10-year risk of a first coronary event is 6 to 10% or more according to the US

Preventive Services Task Force and the American Heart Association respectively, the benefits of long-term aspirin use are likely to outweigh any risks.

This Petition requests FDA approval for expanded cardiovascular indications and labeling for the use of an aspirin regimen (75mg-325mg) to reduce the risk of a first myocardial infarction in patients with a CHD risk of 10% or greater over 10 years or in patients for whom there is positive benefit-risk as assessed by their health care providers.

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2. Introduction

Background: The first reported trial of aspirin in the primary prevention of cardiovascular diseases (CVD) was the Physicians' Health Study (PHS)¹, which randomized 22,071 apparently healthy male physicians aged 40-84 years in a 2x2 factorial design to 325 mg of aspirin on alternate days (supplied as Bufferin from Bristol Myers Squibb), 50mg of beta-carotene on alternate days, both active agents or placebo. After 5 years of treatment and follow-up, the trial was terminated early based on the unanimous recommendation of the independent Data and Safety Monitoring Board, due principally to the emergence of a statistically extreme ($p < 0.00001$) 44% reduction in the risk of a first MI². The British Doctors' Trial (BDT)³ randomized 5139 apparently healthy male physicians aged 50-78 to 500 mg of aspirin (regular, soluble or effervescent supplied by Aspirin Foundation) daily or open control for 6 years. There was no significant benefit on the risk of a first MI but this trial had less than 50% power to detect even a 44% or greater reduction. Accordingly, an overview of these two trials⁴ demonstrated a statistically extreme ($p < 0.00002$) 33% reduction in the risk of a first MI. At that time, the Cardio-Renal Drugs Advisory Committee to the US Food and Drug Administration (FDA) voted to approve professional labeling of aspirin to reduce the risk of a first MI. The FDA failed to accept that recommendation, largely because the only two reported trials were interpreted to show divergent results⁵. Ten years later, in 1998, two additional trials of primary prevention were published, namely, the Thrombosis Prevention Trial (TPT)⁶ and the Hypertension Optimal Treatment Study (HOT)⁷. The TPT randomized 5085 men at high risk of CVD, aged 45-69 in a 2x2 factorial design to 75 mg of aspirin (controlled-release from Bayer AG) daily or warfarin mean dose 4.1 mg/day, both active agents or placebo for over 5 years and demonstrated a significant 32% reduction of a first non-fatal MI⁶. The HOT trial randomized 18,790 participants

(9907 men and 8883 women) aged 50-80 with diastolic blood pressure from 100-115 mmHg in a 2x2 factorial design to 75 mg of aspirin (Bamycor, Astra) daily, felodipine 5mg/day with variable escalating doses, both active agents or placebo for 4 years and demonstrated a significant 36% decrease in risk of a first MI as well as a significant 15% reduction in any important vascular event⁷.

Objective: From 1988 to 1998 a computerized search of the English literature identified four published randomized trials of aspirin in the primary prevention of CVD. In previous meta-analysis of these trials, aspirin therapy significantly reduced the risk of a first MI by 32%, as well as any important vascular event (nonfatal MI, nonfatal stroke or vascular death) by 13%.⁸ From 1998 to the present, a subsequent review of the English literature revealed one additional primary prevention trial of aspirin as well as new guidelines on the use of aspirin in the primary prevention of CVD.

The fifth and most recently published primary prevention trial of aspirin is the Primary Prevention Project (PPP).⁹ In this trial, 4495 apparently healthy men (1912) and women (2583) aged 50 to over 80 years with one or more major risk factors for CVD were randomized in a 2x2 factorial design to 100 mg of enteric-coated aspirin daily (supplied by Bayer AG), vitamin E 300 mg/day, both active agents or open control. The trial was terminated early due principally to the emergence of significant reductions among aspirin takers in all cardiovascular events of 23% as well as cardiovascular death of 44% in the context of previous individual trials and their meta-analysis. There were also possible but non-significant reductions in MI of 31% and stroke of 33%.

Recently, the US Preventive Services Task Force (USPSTF)¹⁰ and the American Heart Association (AHA)¹¹ have issued new guidelines for aspirin in the primary prevention of MI in apparently healthy men and women.

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3. Methods

Data Sources: To perform the meta-analysis, published data were used from the PHS², the BDT³, the TPT⁶, the HOT study⁷ and the PPP⁹ (Table 1). The outcomes examined were the same as those used for the meta-analysis of secondary prevention¹², namely, a combined endpoint of any important vascular event, which includes nonfatal MI or nonfatal stroke or vascular death and each of the components separately.

Study Selection: The criteria for inclusion of trials was as follows: (1) aspirin alone was used for the primary prevention of CVD as opposed to combined interventions, (2) comparisons of outcome were made between aspirin and either placebo or open control, (3) data were available on MI, stroke and vascular deaths.

Data Extraction: Stratified analyses was performed by trial to avoid direct comparisons between individuals in trials. We calculated the observed (O) minus the expected (E) number of events, and its variance (V), from standard 2x2 tables of outcome by treatment. These were then summed over trials to give the grand total for $O-E$ events and its V . We then based significance tests on comparisons of $z=(O-E)/\text{square root } V$ with the standard normal distribution; p denotes the two-sided significance level. The typical odds ratio for these trials was calculated by the one step method from $b=(O-E)/V$, either as $\exp(b)$ or, for rare events, as $(2+b)/(2-b)$. For odds ratios between 0.5 and 2 these two methods give almost identical answers¹².

The British Doctors' Trial³ used a two to one randomization ratio so we multiplied the control group in this trial by two when calculating "adjusted" control totals. When comparing the percentages affected in the treatment and in the adjusted control groups, we calculated the standard error of the difference (D) between these percentages as D/z .¹²

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4. Results

Data Synthesis: A total of 2402 CVD endpoints occurred among 55,580 randomized participants of which 11,466 were women. There was no significant evidence of heterogeneity among the trials. Table 2 shows the number of participants that experienced nonfatal MI and nonfatal stroke. For nonfatal MI, there was a statistically significant reduction of 32% associated with aspirin therapy (RR, 0.68, 95% CI, 0.59-0.79). For nonfatal stroke, there was no significant effect, but the confidence intervals included the plausible decrease seen in the trials of secondary prevention¹² as well as a small to moderate increase (RR, 1.06, 95% CI, 0.87-1.29).

With respect to stroke subtypes, Table 3 shows there was a possible non-significant 3% reduction in ischemic stroke but the confidence intervals were wide (RR, 0.97, 95% CI, 0.77-1.22). For hemorrhagic stroke, although based on small numbers of events, there was an apparent 56% increase, which almost reached statistical significance (RR, 1.56, 95% CI, 0.99 to 2.46).

Table 4 shows that the proportion of participants that experienced any important vascular event (combined endpoint of vascular death, nonfatal MI or nonfatal stroke) was generally lower in the treated groups. In the meta-analysis, there was a statistically significant 15% reduction in the risk of any important vascular event associated with aspirin therapy (RR, 0.85; 95% CI, 0.79-0.93). For vascular deaths, there was no significant reduction in risk although the confidence intervals were wide and included the plausible decrease seen in the trials of secondary prevention¹² as well as a small increase (RR, 0.98, 95% CI, 0.85-1.12).

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5. Conclusions

The current totality of evidence provides strong support for the initial findings from the PHS^{1,2} that aspirin significantly reduces the risk of a first MI in apparently healthy individuals. This meta-analysis indicates that aspirin significantly reduces the risk of a first MI by 32% and any important vascular event by 15%. There are still insufficient numbers of strokes or vascular deaths to yield conclusive evidence. The magnitude of reduction of a first MI is similar to that of the secondary prevention trials¹²,

nonetheless, since the absolute risks are so much lower in primary than in secondary prevention, the absolute benefits are similarly lower.

For hemorrhagic stroke, overviews of secondary and primary prevention trials suggest an increased risk of about 1 to 2 per 1000 patients. These comparisons reinforce the observation that in primary and secondary prevention trials, serious adverse effects, principally hemorrhagic stroke, tend to be about the same.

Of the five primary prevention trials of aspirin completed to date, HOT⁷ randomized 8883 women and PPP⁹ 2583 for a total of 11,466. In HOT, subgroup analyses were presented for women and there was a possible 19% but non-significant reduction in risk of a first MI.¹³ In PPP, the authors reported that the magnitude of benefit in women and men were equal to that of the overall reduction in risk of a first MI of 31%. Thus the overall point estimate of the reduction in risk of a first MI of aspirin in women is about 22% but there remain insufficient numbers of strokes and vascular deaths. In this regard, if a daily dose of 50 mg has clinical relevance, the ongoing Women's Health Study¹⁴ should provide importantly relevant information on stroke as well as its subtypes and vascular death. In the meta-analysis of secondary prevention trials, daily doses of 75 mg to over 1500 mg demonstrated a significant 25% ($\pm 3\%$ SE) reduction in important vascular events. In the meta-analysis of the 3 secondary prevention trials of less than 75 mg daily, the corresponding reduction was 13% ($\pm 8\%$ SE).¹²

The absolute benefit of aspirin is greater to the individual patient in secondary prevention and to the health of the general public in primary prevention. Thus the more widespread and appropriate use of aspirin would avoid over 25,000 premature CVD events in secondary prevention but over 150,000 in primary prevention.¹⁵

With respect to aspirin in the primary prevention of CVD, considerations for use include the 10-year risk of the individual, the side effects of the long-term administration of aspirin and the clear reduction in risk of a first MI. The USPSTF recommends aspirin for all men and women whose 10-year risk of a first coronary event is 6% or more.¹⁰ The AHA recommends aspirin for men and women whose 10-year risk of a first coronary event is 10% or more.¹¹ The AHA recommendation is virtually identical to the results of a previous meta-analysis of risks.¹⁶ This 10-year risk of 10% or more is also the level at which the recently published National Cholesterol Education Program Guidelines

recommend initiation of statin treatment.^{17,18} Furthermore, the very different mechanisms of action of aspirin (primarily on thrombosis) and statins (primarily on atherosclerosis) suggested that their benefits were additive¹⁹ and recent data have demonstrated this to be the case.²⁰

For all these reasons this Petition requests FDA approval for expanded cardiovascular indications and labeling for the use of an aspirin regimen (75mg-325mg) to reduce the risk of a first myocardial infarction in patients with a CHD risk of 10% or greater over 10 years or in patients for whom there is positive benefit-risk as assessed by their health care provider.

Table 1. Features of the 5 Randomized Trials of Aspirin in the Primary Prevention of Cardiovascular Disease

<i>Features</i>	Physicians' Health Study (1988)	British Doctors' Trial (1988)	Thrombosis Prevention Trial (1998)	Hypertensive Optimal Treatment Study (1998)	Primary Prevention Project (2001)
No. of subjects randomized	22071	5139	5085	18790	4495
Follow-up (years)	5 (mean)	6 (mean)	25	4 (mean)	3.6 (mean)
Patient population	Apparently healthy male physicians	Apparently healthy male physicians	Men at high risk for cardiovascular disease	Men and women with hypertension and diastolic blood pressure from 100-115 mm Hg	Men and women with one or more major cardiovascular risk factor
Age range (years)	40-84	50-78	45-69	50-80	50-80+
Female sex (%)	0	0	0	47	57.7
Aspirin dose	325 mg every other day	500 mg daily	75 mg daily (controlled release)	75 mg daily	100 mg daily

Table 2. Nonfatal Myocardial Infarction (MIs) and Nonfatal Stroke in the 5 Randomized Trials of Aspirin in the Primary Prevention of Cardiovascular Disease

Trial name	<u>Aspirin</u>			<u>Control</u>		
	Nonfatal MI	Nonfatal Stroke	No. of Subjects Randomized	Nonfatal MI	Nonfatal Stroke	No. of Subjects Randomized
PHS	129	110	11037	213	92	11034
BDT	80	61	3429*	41	27	1710*
TPT	94	33	2545	137	42	2540
HOT†
PPP	15	15	2226	22	18	2269
Total	318	219	19237	413	179	17553

Statistical Analysis

Relative Risk 0.68 1.06
 95% Confidence (0.59-0.79) (0.87-1.29)
 interval

PHS=Physicians' Health Study, BHT=British Doctors' Trial, TPT=Thrombosis Prevention Trial, HOT=Hypertension Optimal Treatment study, PPP=Primary Prevention Project

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

†Data not available

Table 3. Ischemic Versus Hemorrhagic Stroke (Fatal and Nonfatal) in the 5 Randomized Trials of Aspirin in the Primary Prevention of Cardiovascular Disease

Trial name	Aspirin			Control		
	Ischemic Stroke	Hemorrhagic Stroke	No. of Subjects Randomized	Ischemic Stroke	Hemorrhagic Stroke	No. of Subjects Randomized
PHS	91	23	11037	82	12	11034
BDT	21	13	3429*	7	6	1710*
TPT	21	12	2545	33	6	2540
HOT†
PPP	14	2	2226	21	3	2269
Total	147	50	19237	141	27	17553

Statistical Analysis

Relative Risk 0.97 1.56
 95% Confidence interval (0.77-1.22) (0.99-2.46)

PHS=Physicians' Health Study, BDT=British Doctors' Trial, TPT=Thrombosis Prevention Trial, HOT=Hypertension Optimal Treatment study, PPP=Primary Prevention Project

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

†Data not available

Table 4. Any Important Vascular Event and Vascular Death in the 5 Randomized Trials of Aspirin in the Primary Prevention of Cardiovascular Disease

	Aspirin			Control		
	Any important vascular event	Vascular death	Subjects	Any important vascular event	Vascular death	Subjects
PHS	307	81	11037	370	83	11034
BOT	289	148	3429	147	79	1710
TPT	228	101	2545	260	81	2540
HOT	315	133	9399	368	140	9391
PPP	47	17	2226	71	31	2269
Total	1186	480	28636	1216	414	26944
Statistical analysis						
Relative risk	0.85	0.98				
95% Confidence interval	0.79-0.93	0.85-1.12				

PHS-Physicians' Health Study, BOT-British Doctors' Trial, TPT-Thrombosis Prevention Trial, HOT-Hypertension Optimal Treatment study, PPP-Primary Prevention Project

Table 5: The Physicians' Health Study (PHS) Study Report

Title of Study: Final report of the aspirin component of the ongoing Physicians' Health Study
Investigators: Steering Committee of the Physicians' Health Study Research Group
Study center(s): Physicians from all over the USA (coordinating center: Harvard Medical School and Brigham & Women's Hospital, Boston, MA/U.S.A.: Hennekens C)
Publication (reference): New Engl. J. Med. 321: 129-135, 1989 [7]
Studied period (years): 1982-1987
Objectives: Reduction in cardiovascular mortality in apparently healthy physicians
Methodology: Randomized, double-blind, placebo-controlled
Number of subjects (total and for each treatment): n = 22,071 subjects in total: aspirin: n = 11,037 subjects; placebo: n = 11,034 subjects
Diagnosis and criteria for inclusion: No personal history of: MI, stroke, TIA, cancer, current liver or renal disease, peptic ulcer, gout, use of other platelet active drugs, contraindication to aspirin, use of NSAIDs or Vitamin A
Test product, dose: 325 mg/every other day
Duration of treatment: Average follow-up of five years
Reference therapy, dose: Placebo
Criteria for evaluation: Cardiovascular mortality, MI, stroke
SUMMARY – CONCLUSIONS: Efficacy results: 44% reduction in the risk of MI (relative risk: 0.56; 95% CI 0.45 – 0.70; $p < 0.00001$) in the aspirin group. This risk reduction was significant for both fatal and non-fatal MI. The reduction in the risk of MI was apparent only among those who were 50 years of age and older ($p = 0.02$). The benefit was present at all levels of cholesterol, but appeared greatest at low levels ($p = 0.04$). A slightly increased risk of stroke among those taking aspirin was not statistically significant (relative risk: 1.22; 95% CI 0.93 – 1.60; $p = 0.15$); this trend was observed primarily in the subgroup with hemorrhagic stroke (relative risk: 2.14; 95% CI 0.96 – 4.77; $p = 0.06$). No reduction in mortality from all cardiovascular causes was associated with aspirin (relative risk: 0.96; 95% CI 0.60 – 1.54; $p = 0.87$). However, the risk of fatal MI was significantly reduced in the aspirin group: 10 subjects in the aspirin group Vs 28 in the placebo group ($p = 0.004$). To help clarify a risk-to-benefit ratio, a combined endpoint consisting of non-fatal MI, non-fatal stroke and death from a cardiovascular cause was considered. This yielded a statistically significant 18% reduction in important vascular events Among those assigned to aspirin relative risk: 0.82; 95% CI 0.70 – 0.96; $p = 0.01$). Safety results: Significant adverse events and No. of cases: 1 death in the aspirin group from gastrointestinal hemorrhage

	Aspirin	Placebo	
Upper GI ulcer:	1.5% of patients	1.3% of patients	p=0.08 (n.s.)
Esophageal ulcer:	0.1% of patients	0.05% of patients	p=0.23 (n.s.)
Gastric ulcer:	0.2% of patients	0.1% of patients	p=0.11 (n.s.)
Duodenal ulcer:	0.4% of patients	0.2% of patients	p=0.03
Peptic ulcer:	1.4% of patients	1.2% of patients	p=0.11 (n.s.)
Haematemesis:	0.3% of patients	0.3% of patients	p=0.22 (n.s.)
Melaena:	3.3% of patients	2.2% of patients	P<0.00001

Conclusion:
Aspirin significantly reduced the incidence of total MI (fatal and nonfatal)

Table 6: British Doctors' Trial (BDT) Study Report

<p>Title of Study: Randomized trial of prophylactic daily aspirin in British male doctors</p>
<p>Investigators: Peto R, Gray R, Collins R, Wheatley K, Hennekens C, Jamrozik K, Warlow C, Hafner B, Thompson E, Norton S, Gilliland J, Doll R</p>
<p>Study Center(s): Coordinating center: University of Oxford, Oxford, UK</p>
<p>Publication (reference): Brit. Med. J 296: 313-316, 1988 [6]</p>
<p>Studied period (years): 1978 - 1984</p>
<p>Objectives: Prevention of cerebro- and cardiovascular events in healthy male physicians</p>
<p>Methodology: Randomized, open</p>
<p>Number of subjects (total and for each treatment): n = 5,139 persons in total; aspirin: n = 3,429 persons, avoid aspirin (control): n = 1,710 persons</p>
<p>Diagnosis and criteria for inclusion: No history of MI, stroke, or TIA, not currently taking aspirin, no contraindications to aspirin</p>
<p>Test product, dose: Aspirin: 500 mg/day, or if subsequently requested, 300 mg/day enteric-coated tablets</p>
<p>Duration of treatment: 6 years (average)</p>
<p>Reference therapy, dose: Avoid aspirin (control)</p>
<p>Criteria for evaluation: MI, stroke, TIA, mortality from stroke, MI or other cardiovascular conditions, total mortality, migraine</p>
<p>SUMMARY - CONCLUSIONS:</p> <p>Efficacy results: The incidence of TIAs was significantly reduced by aspirin treatment ($p < 0.05$). There was no difference in the incidence of MI or stroke between the aspirin and the control group. Total mortality was non-significantly reduced by 10% in the aspirin group.</p> <p>Migraine and certain types of musculoskeletal pain were reported significantly less often in the aspirin group ($p < 0.001$).</p> <p>No. of patients who withdrew: 1,348 people (~39%) for all reasons in the aspirin group, while ~11% allocated to avoid aspirin started taking it.</p> <p>Safety results: Peptic ulcer was reported significantly more often ($p < 0.05$) in the aspirin group.</p> <p>Conclusion: No firm conclusion can be drawn from the study, this is due to the fact that during the study period 39% of the participants in the aspirin group ceased taking aspirin, whereas 11% of the control group abandoned their regimen and started taking aspirin.</p>

Table 7: The Thrombosis Prevention Trial (TPT) Study Report

<p>Title of Study: Thrombosis prevention trial: Randomized trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk (TPT)</p>
<p>Investigators: Medical Research Council's General Practice Research Framework</p>
<p>Study center(s): 108 practices in the UK belonging to the MRC General Practice Research Framework (coordinating center: MRC Epidemiology and Medical Care Unit, Wolfson Institute of Preventive Medicine, London / UK; Meade TW)</p>
<p>Publication (reference): Lancet 351: 233-241, 1998 [8]</p>
<p>Studied period (years): 1984 – 1989 (non factorial warfarin vs. placebo phase); 1989-1997</p>
<p>Objectives: Primary prevention of ischemic heart disease in men at increased risk</p>
<p>Methodology: Multicenter, randomized, double-blind, placebo-controlled</p>
<p>Number of subjects (total and for each treatment): n=5,085 patients in total; warfarin + aspirin: n=1,277 patients; warfarin plus aspirin placebo: n=1,268 patients; aspirin plus warfarin placebo: n=1,268 patients; aspirin placebo plus warfarin placebo: n=1,272 patients</p>
<p>Diagnosis and criteria for inclusion: High risk of ischemic heart disease (IHD) including smoking history, family history of premature IHD, BMI, hypertension, no history of current or recent peptic ulcer, possible or definite MI or stroke, other incompatible medication, cholesterol levels, plasma fibrinogen concentrations and plasma factor VII coagulant activity</p>
<p>Test product, dose: Aspirin 75 mg/day, warfarin: individual dose; mean dosage: 4.1 mg/day</p>
<p>Duration of treatment: 6.8 years (median participation)</p>
<p>Reference therapy, dose: aspirin placebo: 1 tablet/day, warfarin placebo: 1 tablet/day</p>
<p>Criteria for evaluation: Primary endpoints: all IHD (sum of coronary death and fatal and non-fatal MI), treatment effects on fatal (coronary death and fatal MI) and non-fatal IHD; secondary endpoint: stroke</p>
<p>SUMMARY – CONCLUSIONS: Efficacy results: The main effect of warfarin (warfarin plus aspirin, warfarin vs. aspirin and placebo) was a reduction in all IHD of 21% (95%CI 4- 35, p=0.02), chiefly due to a 39% reduction (95% C 15-57, p=0.003) in fatal events so that warfarin reduced the death rate from all causes by 17% (95% CI 1-30, p=0.04). The main effect of aspirin (aspirin plus warfarin, vs warfarin and placebo) was a reduction in all IDH of 20% (95% C-135, p=0.04), almost entirely due to a 32% reduction (95% CI 12-48. P=0.004) in non-fatal events. Absolute reductions in all IHD due to warfarin or aspirin were 2.6 and 2.3 per 1000 person years, respectively. Warfarin plus aspirin reduced all IDH by 34% (95% CI 11-51, p=0.006) compared with placebo.</p> <p>No. of patients who withdrew: For all causes n=2,969 patients in total (warfarin + aspirin: n=751 patients; warfarin plus aspirin placebo: n=735 patients; aspirin plus warfarin placebo: n=735 patients; aspirin placebo + warfarin placebo n=748 patients)</p> <p>Safety results: Significant adverse events: No. of cases:</p>

	+			
	<u>Warfarin = aspirin</u>	<u>Warfarin</u>	<u>ASA</u>	<u>Placebo</u>
<u>Major bleedings</u>				
Upper gastrointestinal	7	8 (2 fatal)	5*	1 (fatal)
Lower gastrointestinal	0	1	0	1
Indeterminate GI	2 (1 fatal)	0	1	0
<u>Underlying renal-tract cancer</u>	1	0	1	0
<u>Other</u>	2	0	1 (fatal)	2 (1 fatal)

* 1 underlying gastric cancer

Conclusion:

The main effect of ASA was a reduction in all IHD of 20% (95% CI 1-35, p=0.04), almost entirely due to a 32% reduction (95% CI 12-48, p=0.004) in non-fatal events.

Table 8: The Hypertension Optimal Treatment Trial (HOT) Study Report

<p>Title of Study: Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomized trial</p>
<p>Investigators: Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S, Menard J, Rahn KH, Wedel H, Westerling S (HOT Study Group)</p>
<p>Study center(s): Hospital outpatient clinics in 26 countries in Europe, North and South America and Asia (coordinating center: Ostra Hospital, Goteborg, Sweden)</p>
<p>Publication (reference): Lancet 351: 1755-1762, 1998 [9]</p>
<p>Studied period (years): 1992-1997</p>
<p>Objectives: Assessment of association between major cardiovascular events (non fatal MI, non fatal stroke, and cardiovascular death) and target diastolic blood pressure, and the potential benefit of low-dose aspirin in addition to treatment of hypertension to reduce cardiovascular events</p>
<p>Methodology: Multicenter, randomized, double-blind, placebo-controlled</p>
<p>Number of subjects (total and for each treatment): n = 18,790 patients in total: aspirin: n = 9,399 subjects; placebo: n = 9,391 subjects</p>
<p>Diagnosis and criteria for inclusion: Hypertension (diastolic blood pressure between 100 and 115 mmHg), age 50-80 years</p>
<p>Test product, dose: Aspirin 75 mg/day</p>
<p>Duration of treatment: Average follow up: 3.8 years</p>
<p>Reference therapy, dose: Placebo (all patients received antihypertensive therapy)</p>
<p>Criteria for evaluation: Major cardiovascular events (fatal and non fatal MI, fatal and non fatal strokes, cardiovascular death)</p>
<p>SUMMARY – CONCLUSIONS:</p>

Efficacy results – Antihypertensive treatments: All patients received 5 mg/day felodipine. Additional therapy and dose increments in four further steps which could include ACE inhibitors, β blockers or diuretics were prescribed to reach the randomized target diastolic blood pressures of ≤ 90 mmHg, ≤ 85 mmHg, ≤ 80 mmHg. In the three target groups, the diastolic blood pressure was reduced from a mean of 105 mmHg to a mean of 85.2 mmHg, 83.2 mmHg and 81.1 mmHg, respectively. Differences in cardiovascular event rates were small. The trend for the reduction of all myocardial infarction was of borderline significance (28% in ≤ 85 mmHg s. 25% in ≤ 80 mmHg, $p=0.05$).

Aspirin treatments: Aspirin significantly reduced major cardiovascular events by 15% ($p=0.03$) and all myocardial infarction by 36% ($p=0.02$), with no effect on stroke. Cardiovascular mortality and total mortality were non-significantly lower by 5% ($p=0.65$) and 7% ($p=0.36$), respectively as compared to patients receiving placebo.

Safety results:

There were 7 fatal bleeds in the aspirin group and 8 in the placebo group and 129 vs 70 non-fatal bleeds in the two groups, respectively ($p<0.001$).

Conclusion:

Aspirin significantly reduced major cardiovascular events by 15% ($p=0.03$) and all myocardial infarction by 36% ($p=0.002$), with no effect on stroke

Table 9: Primary Prevention Project (PPP) Study Report

<p>Title of Study: Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomized trial in general practice</p>
<p>Investigators: Collaborative group of the Primary Prevention Project (PPP), Italy</p>
<p>Study center(s): 315 general practitioners and 15 hospital hypertension units</p>
<p>Publication (reference): Lancet 2001; 357: 89-95 [10]</p>
<p>Studied period (years): Recruitment 1994-1998</p>
<p>Objectives: To investigate in general practice the efficacy of antiplatelets and antioxidants in primary prevention of cardiovascular events in people with or more major cardiovascular risk factors</p>
<p>Methodology: Randomized, controlled, open 2x2 factorial design</p>
<p>Number of subjects (total and for each treatment): 4,495 participants; 2,226 given aspirin, 2,231 given vitamin E</p>
<p>Diagnosis and criteria for inclusion: People with one or more of the following: hypertension, hypercholesterolemia, diabetes, obesity, family history of premature MI, or individuals who were elderly (≥ 65 year old)</p>
<p>Test product, dose: Aspirin, 100 mg/day</p>
<p>Duration of treatment: Median follow-up: 4 years (Study terminated early at the second planned interim analysis due to new documentation of aspirin's efficacy in primary prevention and the new projected unrealistically long follow up time for the Vitamin E group.)</p>
<p>Reference therapy, dose: Vitamin E 300mg/day</p>
<p>Criteria for evaluation: Cumulative rate of cardiovascular death, nonfatal MI and nonfatal stroke</p>
<p>SUMMARY – CONCLUSIONS:</p> <p>Efficacy results: Aspirin lowered the frequency of all endpoints, being significant for cardiovascular death (1.4 to 0.8%; RR 0.56 [95% CI 0.31-0.99]), and total cardiovascular events (8.2 to 6.3%; RR 0.77 [95% CI 0.62-0.95])</p> <p>Safety results: Severe bleedings were more frequent in the aspirin group (1.1% vs 0.3%, $p < 0.0008$).</p> <p>Conclusion: Low dose aspirin given in addition to treatment of specific risk factors contributes an additional preventive effect, with an acceptable safety profile.</p>