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Memorandum

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SUBJECT: Citizen's Petition requesting the Commissioner of Food and Drug Administration to amend the Final Rule for Professional Labeling for Aspirin. Docket: 77N-0094

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Background

This Citizen's Petition requests FDA approval for expanded cardiovascular indications and labeling for the use of an aspirin regimen (75 mg-325 mg) to reduced the risk of a first myocardial infarction (MI) in patients with coronary heart disease 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. This Petition is based on the results of five major clinical trials: British Doctor's Trial (BDT)¹, Physician's Health Study (PHS)², Thrombosis Prevention Trial (TPT)³, Hypertension Optimal Treatment Study (HOT)⁴, and Primary Prevention Project (PPP)⁵.

The sponsor argues that the results of these trials, involving over 55,000 subjects, "demonstrate in the aggregate that aspirin significantly reduces the risk of a first non-fatal MI by 32%." Also, "based on an independent review of these trials, the American Heart Association (AHA) and the U.S. Preventive Services Task Force published guidelines within the last year recommending that patients with sufficient risk of a first MI be considered for aspirin therapy."

This submission consists of reprints of manuscripts describing the results of the aforementioned clinical trials, and SAS files with data from the HOT study. Thus, the FDA's reviewers could only perform an independent review of the HOT study; for the remainder studies the reviewers were limited to examine the published results.

What follows are individual reviews for the five major clinical trials.

¹ Peto R, et al. Randomised trial of prophylactic daily aspirin in British male doctors. *British Medical Journal* 1988; 296:313-316.

² Steering Committee of The Physicians' Health Study Research Group. Final report on the aspirin component of the ongoing physicians' health study. *New England Journal of Medicine* 1989; 321:129-135.

³ 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. *The Lancet* 1998; 351:233-241.

⁴ Hansson L, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomized trial. *The Lancet* 1998; 351:1755-1762.

⁵ Collaborative Group of the Primary Prevention Project (PPP). Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomized trial in general practice. *The Lancet* 2001; 357:89-95.

Individual Detailed Study Reviews

A. British Doctor's Trial (BDT)

The BDT, a randomized clinical trial, was conducted in 5139 apparently healthy British male doctors, 50 to 78 years of age, to see whether daily aspirin (500 mg ordinary, soluble or effervescent aspirin, as desired, or, if subsequently requested, 300 mg enteric coated aspirin) would “reduce the incidence of and mortality from stroke, myocardial infarction, or other vascular conditions.” Two thirds of the doctors (n=3429) were randomized to aspirin and one third (n=1710) were randomly allocated to avoid aspirin; placebo tablets were not used. History of aspirin use, peptic ulcer disease, stroke, or definite myocardial infarction excluded subjects from the study. Through the use of a questionnaire, every six months, information was specifically requested about possible myocardial infarctions, strokes, and transient ischemic attacks. “Deaths in Britain were discovered partly by replies from relatives to correspondence, partly from the records of the General Medical Council, and partly by flagging National Health Service records at the Office of Population Censuses and Surveys.” The length of treatment spanned from November 1978 (or, for the 762 doctors who joined later, from November 1979) to November 1984. Statistical analyses of the results were based on an “intent to treat” principle. “The principal analysis of death and of other major outcomes included all events occurring within the scheduled treatment period and none thereafter.” According to the sponsor, “data on mortality were thought to be complete and data on morbidity virtually complete.”

With the exception of systolic blood pressure, which was 1 mmHg higher (p=0.05) in the aspirin group than in the control group, baseline characteristics were comparable between the groups.⁶ While 11% of the subjects allocated to avoid aspirin started taking it, 39% (n=1348) of the subjects on aspirin discontinued medication during the trial, 19.5% during the first year, due mainly to gastrointestinal symptoms; including gastrointestinal bleeding, dyspepsia and constipation (Table A1).⁷

Table A1. Discontinuations in the Aspirin Group

Principal reason for stopping Aspirin	1 st year n (%)	Subsequent 5 years† n (%)
Gastrointestinal bleed	39 (1.1)	30 (1.1)
Dyspepsia	340 (9.9)	200 (7.3)
Constipation	36 (1.0)	47 (1.7)
Bleed/Bruising	38 (1.1)	68 (2.5)
Other medical	41 (1.2)	90 (3.3)
Unknown	176 (5.1)	244 (8.9)
Total	670 (19.5)	678 (24.8)

[Adapted from British Medical Journal 1988; 296:314, Table II. †Four years for the 762 (15%) doctors who joined in November 1979.]

Aspirin administration failed to improve mortality (Table A2). There was not a statistically significant difference (~6%) for the overall vascular death rates between the groups, 4.3% (148/3429) aspirin group vs. 4.6% (79/1710) control group. Similarly, for non-vascular death rates, albeit 15% lower in the aspirin group (3.5%; 122/3429) than in the control group (4.2%; 72/1710), the difference was not statistically significant.

No significance differences in the rates of fatal or definite non-fatal myocardial infarctions were detected between the aspirin and control groups, 47.3 vs. 49.6 deaths/10,000 man/years and 42.5 vs. 43.3 first events/10,000 man/years, respectively.

⁶ British Medical Journal 1988; 296:314, Table I.

⁷ British Medical Journal 1988; 296:314, Table II.

Aspirin had disparate effects on cerebrovascular events in that it reduced the occurrence of transient ischemic attacks, 15.9 vs. 27.5 first events/10,000 man/years, $p < 0.05$ however increased the incidence of non-fatal confirmed stroke, 32.4 vs. 28.5 first events/10,000 man/years.

The effect of aspirin treatment on stroke, myocardial infarction, or cardiovascular death had 95% confidence intervals ranging between a 16% benefit and a 26% adverse effect.

Table A2. Cause Specific Death Rates by Allocated Treatment

Cause of Death	Deaths/10000 man years†	
	Aspirin N=3429 Subject years=18820	Controls N=1710 Subject years=9470
Definite MI or stroke:	63.2	62.3
MI	47.3	49.6
Hemorrhagic stroke	5.3	4.2
Occlusive stroke	4.3	3.2
Stroke unknown etiology	6.4	5.3
Other vascular	15.4	21.2
Non-vascular	64.8	76.0
Total	143.5	159.5

[Adapted from British Medical Journal 1988; 296:315, Table III. †Estimated as number of deaths divided by 1.882 or 0.947.]

Aspirin not only lacked a salutatory effect on stroke, myocardial infarction, or cardiovascular death but worsened gastrointestinal morbidity (Table A3), for instance peptic ulcer disease (non-fatal) was reported significantly more often by subjects taking aspirin (46.8 vs. 29.6 first event/10,000 man/years, in the aspirin group and in the control group, respectively, $p < 0.05$). The sponsor stated that “more cases of gastric bleed (non-fatal) were reported in the aspirin group than in the control group.” Numerically the incidence of non-fatal bleeds, not cerebral, was higher for subjects taking aspirin than for the controls, 10.6 vs. 7.4 first event/10,000 man/years.⁸

Table A3. Rates of Certain Non-Fatal Vascular and Non-Vascular Events by Allocated Treatment

Non-fatal adverse events	First events/10000 man years†	
	Aspirin N=3429 Subject years=18820	Controls N=1710 Subject years=9470
Non-fatal MI:		
Confirmed MI	42.5	43.3
Possible MI	11.7	4.2
Non-fatal stroke:		
Confirmed	32.4	28.5
(Disabling+other)	(19.1*+13.3)	(7.4+21.2)
Probably hemorrhagic	1.6	2.1
Probably occlusive	6.9	4.2
Unknown etiology	23.9	22.2
Possible	3.2	3.2
Transient ischemic attack:		
Confirmed	15.9*	27.5
Possible	5.3*	14.8
Bleed (not cerebral)	10.6	7.4
Peptic ulcer	46.8*	29.6

[Adapted from British Medical Journal 1988; 296:315, Table IV. †Estimated (without use of life table methods) as number of subjects ever affected divided by 1.882 or 0.947. * $p < 0.05$.]

⁸ The original publication lacks detailed analyses of adverse events.

In summary, the results from this clinical trial support the notion that aspirin therapy is neither beneficial for the primary prevention of cardiovascular morbid events nor mortality. The data also suggest that aspirin may be associated with a higher risk of peptic ulcer disease.

B. Physician's Health Study (PHS)

The Physician's Health Study was a randomized, double-blind, placebo-controlled trial testing two primary prevention hypotheses: (1) whether 325 mg of aspirin (as Bufferin supplied by Bristol-Myers Products) taken every other day reduces mortality from cardiovascular disease, and (2) whether 50 mg of beta carotene (as Lurotin, supplied by BASF) taken on alternate days decreases the incidence of cancer.

The study's population consisted of male physicians 40 to 84 years of age residing in the United States at the initiation of the study in 1982. Letters of invitation, informed-consent forms, and baseline-questionnaires were sent to 261,248 potential candidates. The exclusion criteria included personal history of MI, stroke or transient ischemic attack, cancer (except non-melanoma skin cancer), current liver or renal disease, peptic ulcer, or gout, contraindications to aspirin, other platelet-active drugs, or non-steroidal anti-inflammatory agents; or current use of vitamin A supplement.

Reported diagnoses were confirmed, based on WHO criteria, after examination of all available information by a committee of physicians, the End Points Committee, that included two internists, one cardiologist, and one neurologist, all blinded to treatment assignment.⁹ Records were available for review for 95.6%, 95.2% and 94.8% of the reported MI, strokes and deaths, respectively.

For the endpoints of MI and stroke, only the first event within each category was counted, and for the combined endpoint of nonfatal MI, nonfatal stroke, and death from a cardiovascular cause, only a subject's first cardiovascular event was counted.¹⁰

A total of 33,223 willing physicians were eligible and were enrolled in a run-in phase (18 weeks), to exclude before randomization those subjects unwilling or unable to comply with the study regimen. Following the run-in phase a total 22,071 physicians were then randomized according to a two-by-two factorial design to one of four treatment groups: active aspirin and active beta carotene; active aspirin and beta carotene placebo; aspirin placebo and active beta carotene; or aspirin placebo and beta carotene placebo; 11037 physicians were randomized to active aspirin and 11034 to receive aspirin placebo.

Every six months for the first year and annually thereafter, the participants were sent brief questionnaires inquiring about their compliance with treatment and the occurrence of any relevant events.

"At a special meeting on December 18, 1987, the external Data Monitoring Board of the Physicians' Health Study took the unusual step of recommending the early termination of the randomized aspirin component of the trial, primarily because a statistically extreme beneficial effect on non-fatal and fatal myocardial infarction had been found." Secondly, the inability of the trial to detect any effect of aspirin on cardiovascular mortality until the year 2000 or later due to the exceptionally low death rate and the fact that over 85% of the participants experiencing nonfatal vascular events were subsequently prescribe aspirin, which made any finding concerning cardiovascular mortality difficult to interpret.

According to the investigators, "by January 25, 1988, the participants have been followed for an average of 60.2 months (range 45.8 to 77.0); 99.7 percent were still providing information on morbidity, and the vital status of all 22071 doctors was known."

⁹ Preliminary report: findings from the aspirin component of the ongoing Physicians' Health Study. *New England Journal of Medicine* 1988; 318:262-264.

¹⁰ For the 15 subjects who had both a nonfatal MI and a nonfatal stroke, both events were counted as events. For the 23 who had a nonfatal MI or stroke, followed by death from a cardiovascular cause, the nonfatal event was included in the analysis of MI or stroke, and the fatal event was included in cardiovascular deaths.

The reported intake of aspirin or other platelet-active drugs was 85.7% in the aspirin group and 14.2% in the placebo group.

Data on demographic characteristics at study entry for the randomized subjects were not reported by the investigators, however they claimed that “as expected with a sample of 22071 participants randomly assigned to treatment groups, there were no differences in the baseline characteristics-age, cigarette smoking, incidence of diabetes mellitus, parental history of myocardial infarction, cholesterol level, systolic blood pressure, diastolic blood pressure, alcohol use, amount of vigorous exercise, and body-mass index.”

This clinical trial was conducted to test two primary-prevention hypotheses: whether aspirin in low doses reduces mortality from cardiovascular disease and whether beta carotene decreases the incidence of cancer. Only the results regarding aspirin effects on cardiovascular morbid and mortal events are discussed in this review. Table B1 provides information on total cardiovascular mortality. There were 81 cardiovascular deaths in the aspirin group versus 83 among those subjects receiving placebo (relative risk 0.96, 95% CI 0.60-1.54, p=0.87). Fewer deaths due to acute myocardial infarction occurred in the aspirin group than in the placebo group, 10 versus 28, respectively, p=0.004. However, for sudden death, albeit not statistically significant, there was an apparent increase in risk (22 in the aspirin group versus 12 in the placebo group, p=0.09). As was the case for cardiovascular mortality, there was no reduction in the risk of deaths from non-cardiovascular causes, 124 in the aspirin group versus 133 in the placebo group (relative risk 0.93, 95% CI 0.72-1.20, p=0.59). Thus, treatment with aspirin failed to have a beneficial influence on cardiovascular or all-cause mortality.

Table B1. Deaths by Treatment Group.

Cause of Death	Aspirin Group	Placebo Group	Relative Risk	95% CI	p-Value
Total CV	81	83	0.96	0.60-1.54	0.87
Acute MI	10	28	0.31	0.14-0.68	0.004
Other IHD	24	25	0.97	0.60-1.55	0.89
Sudden	22	12	1.96	0.91-4.22	0.09
Stroke	10	7	1.44	0.54-3.88	0.47
Other CV	15	11	1.38	0.62-3.05	0.43
Total Non-CV	124	133	1.33	0.72-1.20	0.59
Total§	217	227	2.27	0.80-1.14	0.64

[Adapted from New Engl J Med 1989; 321:132, Table 3. §Additional events that could not be confirmed because records were not available included 23 deaths (12 aspirin and 11 placebo).]

Table B2 summarizes the results of aspirin on cardiovascular events specifically MI and stroke. A total of 139 myocardial infarction events were reported in the aspirin group versus 239 among those subjects receiving placebo, relative risk 0.56, 95% CI 0.45-0.70, p<0.00001. This aspirin effect represents a 44% risk reduction. Conversely, aspirin had an adverse effect on stroke, there were 119 events in the aspirin group and 98 in the placebo group, however this increase in risk was not statistically significant (relative risk 1.22, 95% CI 0.93-1.60, p=0.15).

Table B2. Confirmed† Cardiovascular Events by Treatment Group.

End Point	Aspirin Group	Placebo Group	Relative Risk	95% CI	p-Value
MI					
Fatal	10	26	0.34	0.15-0.75	0.007
Nonfatal	129	213	0.59	0.47-0.74	<0.00001
Total	139	239	0.56	0.45-0.70	<0.00001
Person-years	54,560.0	54,355.7			
Stroke					
Fatal	9	6	1.51	0.54-4.28	0.43
Nonfatal	110	92	1.20	0.91-1.59	0.20
Total	119	98	1.22	0.93-1.60	0.15
Person-years	54650.3	54,635.8			

[†Additional events that could not be confirmed because records were not available included 17 MIs (10 in the aspirin group and 7 in the placebo group) and 11 strokes (3 in the aspirin group and 8 placebo). Adapted from New Engl J Med 1989; 321:131, Table 1.]

Table B3 summarizes the results of further analyzing strokes by subdividing them on ischemic versus hemorrhagic. There were twice as many hemorrhagic strokes in the aspirin group as compared with the placebo group, 23 versus 12 events (relative risk 2.14, 95% CI 0.96-4.77, p=0.06).

Table B3. Subcategories of Stroke by Treatment Group.

Type of Stroke	Aspirin Group	Placebo Group	Relative Risk	95% CI	p-Value
Ischemic	91	82	1.11	0.82-1.50	0.50
Hemorrhagic	23	12	2.14	0.96-4.77	0.06
Unknown cause	5	4	ND	ND	ND
Total	119	98	1.22	0.93-1.60	0.15

[Adapted from New Engl J Med 1989; 321:131, Table 2. ND=not done.]

For the combined endpoint of nonfatal MI, nonfatal stroke, and death from a cardiovascular cause, there were 307 events in the aspirin group versus 370 events in the placebo group (relative risk 0.82, 95% CI 0.70-0.96, p=0.01). This analysis indicates an 18% risk reduction in nonfatal MI, nonfatal stroke, and death from a cardiovascular cause among the subjects receiving aspirin. When the potential effects of risk factors on the combined endpoint were analyzed by the investigators through logistic regression, “the relative risks for each cardiovascular end point were unchanged.”

The investigators also examined “the possible effects of aspirin in subgroups of physicians with various cardiovascular risk factors”, for instance age, cigarette smoking, incidence of diabetes mellitus, parental history of myocardial infarction, cholesterol level, systolic blood pressure, diastolic blood pressure, alcohol use, amount of vigorous exercise, and body-mass index.¹¹ According to the investigators “The effects of aspirin on the risk of myocardial infarction were modified by two coronary risk factors - age and blood cholesterol level. The reduction in the risk of myocardial infarction associated with the use of aspirin was apparent only in those 50 years of age or older (P=0.02). No consistent effect of age on the relation between aspirin and either stroke or cardiovascular mortality was observed. For cholesterol, the beneficial effects of aspirin on myocardial infarction were apparent at all levels but appeared greatest at low levels (P=0.04). For cigarette smoking, the reduction in the risk of myocardial infarction associated with the use of aspirin was similar among those who had never smoked, past smokers, and current smokers. For stroke, cigarette smoking did not modify the effect of aspirin, but for cardiovascular mortality, it appeared to do so (P=0.05). However, neither the observed reduction in risk among nonsmokers (P=0.18) nor the apparently increased risk among current smokers (P=0.20) was significant. Finally, blood-pressure levels had no consistent effect on the association between aspirin and myocardial infarction, stroke, or mortality from cardiovascular causes.”

The number and incidence of adverse events are summarized in Table B4. More subjects in the aspirin group as compared with those in the placebo group had upper gastrointestinal ulcers, 169 versus 138, respectively (relative risk 1.22, 95% CI 0.98-1.22, p=0.08). Of note, 2979 (27.0%) subjects receiving aspirin and 2248 (20.4%) of those taking placebo reported “bleeding problems” including easy bruising, hematemesis, melena, nonspecific gastrointestinal bleeding, epistaxis, or other bleeding (relative risk 1.32, 95% CI 1.25-1.40, p<0.00001). Because of bleeding 48 subjects in the aspirin group and 28 in the placebo group required blood transfusion (relative risk 1.71, 95% CI 1.09-2.69, p=0.02). One death from gastrointestinal hemorrhage was reported in the aspirin group.

¹¹ New Engl J Med 1989; 321:133, Table 4.

Table B4. Adverse Events by Treatment Group.

Adverse Event	Aspirin Group n (%)	Placebo Group n (%)	p-Value
Gastrointestinal Symptoms*	3843 (34.8)	3779 (34.2)	0.48
Upper GI Ulcers	169 (1.5)	138 (1.3)	0.08
Bleeding Problems	2979 (27.0)	2248 (20.4)	<0.0001

[Adapted from New Engl J Med 1989; 321:133, Table 4. *Except ulcer.]

In summary, this clinical trial in a population of healthy US physicians for the primary prevention of mortality from cardiovascular disease demonstrated that 325 mg of aspirin every other day had no salutatory effect on cardiovascular mortality, the pre-specified primary endpoint. Secondary analysis of the data on fatal and nonfatal myocardial infarctions indicated a salutatory effect of aspirin while no beneficial effect on stroke. Aspirin consumption was associated with more cases of nonfatal and fatal strokes.

Aspirin treated-subjects had a higher incidence of upper gastrointestinal ulcers, and a statistically significant higher rate of bleeding problems which was associated with a greater need for blood transfusions.

C. Thrombosis Prevention Trial (TPT)

The TPT was a randomized clinical trial aimed to evaluate “low-intensity” oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischemic heart disease (IHD) in men at increased risk.¹² The trial was carried out in the United Kingdom by 108 group practices in the Medical Research Council’s General Practice Research Framework in men 45 to 69 years of age. Of the 10557 men considered to be at high risk and eligible to participate in the trial a total of 5499 subjects were enrolled. 5085 men joined in four factorial treatment groups: active warfarin and active aspirin (WA, n=1277), active warfarin and placebo aspirin (W, n=1268), placebo warfarin and active aspirin (A, n=1268), and placebo warfarin and placebo aspirin (P, n=1272). According to the investigators’ report the treatment was double-blind, “at least initially.”¹³

Warfarin doses ranged from a starting dose of 2.5 mg/day to upward or downward adjustment of 0.5 to 1.0 mg/day monthly depending on the INR. Aspirin was given as a 75 mg/daily of a controlled release formulation. Of note, trial treatment, but not follow-up, was discontinued after end-points and other major events.

The pre-specified primary endpoint was all IHD defined as “the sum of fatal and non-fatal events (i.e., coronary death and fatal and non-fatal MI).” Secondary endpoints included stroke, “with results for thrombotic and hemorrhagic events to be distinguished as far as possible, depending on whether appropriate imaging or necropsy findings were available.”

Information concerning bleeding episodes was obtained and classified as major, intermediate and minor episodes. “A data monitoring and ethics committee reviewed the results on adverse effects, mainly bleeding, after each period of 4000 person-years and, for the principal results on cardiovascular events, after each period of 8000 person-years.”

Table C1 provides demographic characteristics of the four treatment groups in the factorial stage. Overall, demographic characteristics were well-balanced among the groups.

Table C1. Demographic Characteristics at Trial Entry.

Variable	Aspirin Group N=1268	Placebo Group N=1272
Age (mean±SD, years)	57.7 (6.7)	57.3 (6.6)
Smokers	41.0%	41.6%
Family History	15.3%	16.2%
SBP (mean±SD, mmHg)	139 (18)	139 (18)
BMI (mean±SD, weight/height ²)	27.3 (3.4)	27.5 (3.8)
Cholesterol (mean±SD, mmol/L)	6.4 (1.0)	6.4 (1.0)
Fibrinogen (mean±SD, g/L)	3.06 (0.59)	3.02 (0.57)
Factor VII (mean±SD, % of std)	114 (32)	117 (32)

[Adapted from Lancet 1998; 351:236, Table I.]

The mean INR for warfarin treated subjects was 1.47, representing a difference of 0.47 from those subjects on placebo.

The treatment code was broken in 470 cases including suspected MI or stroke, before emergency surgery or dental treatment, and in some cases of hematuria and in most of the major bleeding episodes. The investigators reported

¹² The Medical Research Council’s General Practice Research Framework. Thrombosis prevention trial: randomized trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease. The Lancet 1998; 351:233-41.

¹³ According to the investigators, “prolonged bleeding after venipuncture and others reports of bleeding (e.g., easy bruising) led some practice staff and men in the trial to assume they were on one of the active treatments and they were probably correct rather more often than by chance.”

that treatment compliance with W and A treatments was high, only ~2% of the tablets were missed according to tablet counts at follow-up visits.

Approximately 50% of the subjects withdrew from the trial, 14%, 29% and 42% at 1 year, 3 years, and 5 years, respectively. The total rates of discontinuation were similar among the groups; WA 58.8%, W 57.9%, A 57.4%, and P 58.8%.

A total of 187 (3.4%) subjects moved away from their follow up site, occurrence or otherwise of non-fatal endpoints was obtained for 129 of these men, five had had an MI and one a stroke. Thus, in 58 (1.1%) men no information on non-fatal events was available.

Table C2 summarizes the number of events and incidence rates per 1000 person years. Of note, the number and incidence, i.e., rates per 1000 person years of all IHD in the A and P groups were not statistically different, 83 versus 107 and 10.2 versus 13.3, respectively. Furthermore, the number and rate of IHD fatal events in the A group was similar to that in the P group, 36 and 4.4 versus 34 and 3.4, respectively. As compared to placebo aspirin treatment did not affect all-cause mortality, 113 deaths in the aspirin group versus 110 in the placebo group. The number of subjects who developed ECG evidence of silent MI did not differ among the groups.

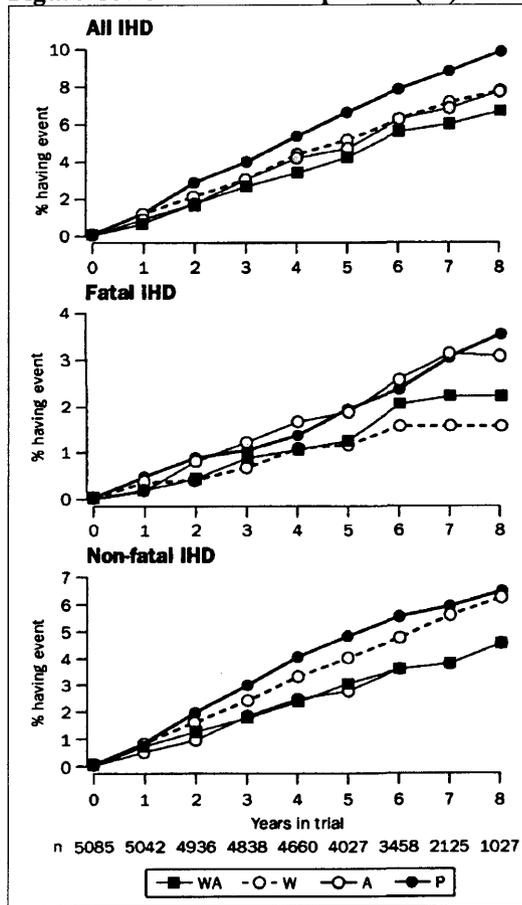
Table C2. Separate Group Effects: Number of Events (rates/1000 person years)

Person years	Numbers of Events (Rates/1000 years)	
	Aspirin N=1268	Placebo N=1272
IHD		
All	83 (10.2)	107 (13.3)
Fatal	36 (4.4)	34 (4.2)
Non-fatal	47 (5.8)	73 (9.0)
Stroke		
All	18 (2.2)	26 (3.2)
Thrombotic	10 (1.2)	18 (2.2)
Hemorrhagic	2 (0.2)	0 (0.0)
Sub-arachnoid	1 (0.1)	2 (0.2)
Unknown	5 (0.6)	6 (0.7)
Fatal	2 (0.2)	1 (0.1)
Death		
IHD or stroke (1 st events)	38	35
IHD (after non-fatal IHD or stroke)	3	8
Stroke (after non-fatal IHD or Stroke)	4	1
Other Cardiovascular	4	5
Cancer	49	51
Other deaths	15	10
All causes	113 (13.6)	110 (13.1)

[Adapted from The Lancet 1998; 351:239, Table 4.]

The cumulative proportions of subjects experiencing IHD events for the four groups are depicted in Figure C3.

Figure C3. Cumulative Proportion (%) of Men with IHD in Separate treatment Groups.



[Sponsor's analysis, The Lancet 1998; 351:238, Figure 3. n=number in trial for specified duration of follow-up.]

The number of episodes of major, intermediate and minor non-cerebral bleeding for the four groups is summarized in Table C4. The A group as compared with the P group had higher number of major (8 vs. 4), intermediate (48 vs. 33) and minor (484 vs. 398, $p < 0.001$) non-cerebral bleeding episodes.

Table C4. Number of Men Having Major, Intermediate, or minor Bleeding Episodes.

Adverse events	Aspirin N=1268 n	Placebo N=1272 n
Major		
Gastrointestinal	6	2 (1)
Underlying renal-tract cancer	1	0
Other	1 (1)	2 (1)
Total	8	4 (2)
Intermediate		
Gastrointestinal	16	8
Genitourinary	16	7
Respiratory	1	0
Nasal/throat	4	4
Ocular	6	5
Skin/locomotor	4	9

Miscellaneous	1	0
Total	48	33
Minor		
Rectal Bleeding	127†	96
Nose bleed	210‡	162
Pink/red urine	52	57
Bruising	237§	166
Any minor bleed	484§	398

[Adapted from The Lancet 1998; 351:239, Table 5. Fatal events in parenthesis. †p<0.05; ‡p<0.01; §p<0.001.]

In summary, treatment with aspirin as compared with placebo failed to show a statistically significant benefit on fatal or non fatal IHD events. The risk of bleeding, independent of site or severity, was higher for those subjects treated with aspirin than those receiving placebo. The investigators' conclusion was that "[their] results give limited, if any, encouragement for the general use of aspirin in primary prevention regardless of risk."

D. Hypertension Optimal Treatment Study (HOT)

The HOT study had a multinational, prospective, randomized, and open design with blinded endpoint evaluation.¹⁴ And it was designed primarily to investigate the relationship between three different target diastolic blood pressures, i.e., ≤ 90 mmHg, ≤ 85 mmHg, and ≤ 80 mmHg during antihypertensive treatment, on cardiovascular morbidity and mortality, and secondarily to determine whether the addition of a low dose of acetylsalicylic acid (ASA, 75 mg daily) to antihypertensive treatment compared to placebo reduces the incidence of pooled major cardiovascular events.¹⁵ Major cardiovascular events were defined as all (fatal and non-fatal) myocardial infarctions, all (fatal and non-fatal) strokes, and all other cardiovascular deaths. Silent myocardial infarctions were documented by taking an electrocardiogram (ECG) at randomization and at the final visit.

The Executive and Steering Committees governed the scientific aspects of the study. An Independent Clinical Event Committee evaluated blindly all events and throughout the study an Independent Safety Committee had full access to all events unblindly. An Independent Data Audit Committee visited randomly selected centers to audit the trial in accordance with the rules of the American Food and Drug Administration.

In this review only the data pertinent to the effects of ASA, compared with placebo, on cardiovascular morbidity and mortality will be analyzed and discussed.

It was estimated that by enrolling 18,000 subjects and followed them for 2.5 years would result in 1,100 clinical events, i.e., non-fatal stroke, non-fatal myocardial infarction or cardiovascular death. It was estimated that that number of events would be needed to show a statistically significant difference in cardiovascular morbidity and mortality between the three target groups. Of note, "the study power calculations were based on the STOP Hypertension study¹⁶ in which the average cardiovascular risk increased, both below and above a diastolic blood pressure of 80 mmHg, by 3% per mmHg, with narrow confidence limits."

Patients, men and women, between 50 and 80 years of age with essential hypertension, diastolic blood pressure between 100 mmHg and 115 mmHg, were eligible for the study. The exclusion criteria included, among others, secondary hypertension, malignant hypertension, diastolic blood pressure >115 mmHg, decompensated congestive heart failure, and history of stroke or myocardial infarction within 12 months prior to randomization. All patients were given felodipine 5 mg daily as the basic antihypertensive therapy. If necessary, additional treatment with β -blockers¹⁷, ACE inhibitors¹⁸ and hydrochlorothiazide were prescribed. Aspirin (Bamycor, Astra), 75 mg daily, or a matching placebo was given under double blind conditions. The investigators planned to terminate the study when 1100 clinical events have occurred, which was estimated to be towards the end of 1995.

"Blood pressure was measured three times with the patient seated after they had had 5 min rest at each prerandomization visit, at randomization, 3 months, and 6 months after randomization and thereafter twice a year; a final visit was made within 1 month of August 31, 1997.

The first patient was enrolled in October 1992, randomization ended in April 1994, and the last day of follow-up was August 31, 1997. A total of 19196 patients were randomized into the study by 1921 investigators from 26 countries in Europe, North and South America, and Asia. According to the investigators "because of the suspicion of incorrect inclusion or data handling at one centre, 403 patients were excluded early in the trial." Thus, data are available for

¹⁴ Hansson L, et al. Prospective Randomized, Open Blinded End-point (PROBE) Study: a novel design for intervention trials. *Blood Pressure* 1992; 1:113-9.

¹⁵ The Hypertension Optimal Treatment Study (The HOT Study). *Blood Pressure* 1993; 2:62-68.

¹⁶ Dahlof B, et al. Morbidity and mortality in the Swedish trial in old patients with hypertension (STOP-Hypertension). *Lancet* 1991; 338:1281-85.

¹⁷ Metoprolol, atenolol, or propranolol.

¹⁸ Ramipril, enalapril or captopril.

18793 patients. In this regard, please note that there is a discrepancy of 3 patients between the numbers of patients published by the investigators in Blood Pressure 1994; 3:322-327 versus Lancet 1998; 351:1755-1762.

Table D1 summarizes the number of patients randomized by country. Of note, European countries, including Israel, enrolled 82.3% of the subjects while the USA randomized only 13.8% of the total population.

Table D1. Number of Randomized Patients by Country/Area.

Country/Area	Number of Randomized Patients
Argentina	47
Austria	628
Belgium	755
Canada	838
Denmark	503
East Asia	205
Finland	373
France	1574
Germany	4674
Great Britain	131
Greece	335
Hungary	194
Israel	411
Italy	2702
Mexico	49
Norway	432
Spain	806
Sweden	492
Switzerland	797
The Netherlands	604
USA	2646
Total	19196

[Sponsor's analysis, Blood Pressure 1994; 3:322-327, Table III, page 324.]

An early publication reported the overall patient demographics for the HOT study.¹⁹ Of the randomized patients, 9055 (47%) were women and 10141 (53%) were men with an average age of 61.5±7.5 years. A total of 1606 (8.4%) suffered from diabetes mellitus, 7.0% from angina pectoris and 3.4% from chronic obstructive pulmonary disease. 306 patients (1.6%) had a history of a previous myocardial infarction and 228 (1.2%) had a previous stroke. Fifty-two percent (n=11005) of the patients were receiving antihypertensive treatment at randomization, 42% were treated with calcium antagonists, 38% ACE inhibitors, 33% diuretics, 28% β-blockers, and 11% other therapies. Treatment for concomitant disorders included lipid lowering drugs 7.3%, non-steroidal anti-inflammatory drugs 6.3%, other analgesics 3.3%, digitalis 2.1%, steroids 1.3%, and anti-arrhythmic agents 1.0%. Patients' demographic characteristics at randomization for the ASA and placebo groups (Table D2) were indistinguishable from each other and in keeping with the demographics of the overall patient population.

¹⁹ Blood Pressure 1994; 3:322-327.

Table D2. Characteristics of ASA- and Placebo-Treated Patients

Events	ASA N=9399	Placebo N=9391
Male/Female (%)	53/47	53/47
Age (Mean±SD, years)	61.5 (7.5)	61.5 (7.5)
Diastolic Blood Pressure (Mean±SD, mmHg)	105 (3.4)	105 (3.4)
Systolic Blood Pressure (Mean±SD, mmHg)	170 (14)	170 (14)
Previous Antihypertensive Rx (%)	52.6	52.6
Diabetes Mellitus (%)	8.0	8.0
Previous MI (%)	1.5	1.5
Other Previous CHD (%)	5.9	6.0
Previous Stroke (%)	1.2	1.2
Smokers (%)	15.9	15.9
Body Mass Index (Mean±SD)*	28.4 (4.6)	28.4 (4.7)

[FDA's analysis, Dr. Chenxiang Le, HFD-710. *Data are from 9394 and 9384 patients in the ASA and placebo groups, respectively.]

In addition to the 403 (2.1%) patients excluded by the investigators early in the trial, 491 (2.5%) patients were lost to follow up, 245 randomized to ASA and 246 were lost from the placebo group. The average follow-up time was 3.8 years (range 3.3-4.9 years) and the total number of patient's years was 71051.

The primary efficacy endpoint, cardiovascular events, was defined as all (fatal and non-fatal) myocardial infarctions, all (fatal and non-fatal) strokes, and all other cardiovascular deaths. There were 388 cardiovascular events in the ASA group versus 425 events in the Placebo group, relative risk 0.91, 95% CI 0.79-1.04, p=0.17. It should be noted that the investigators, in the published results of the HOT study in Lancet 1998; 351:1755-1762, claimed that "Acetylsalicylic acid reduced major cardiovascular events by 15% (p=0.03) and all myocardial infarction by 36% (p=0.002) with no effect on stroke." The aforementioned results on "major cardiovascular events" and "all MI" represent a *post-hoc* analysis of the primary efficacy endpoint and all MI, in that the investigators did not include silent MI²⁰ in their analysis (Table D3). Their explanation, to not include silent MI, was "to make the results comparable with those of other intervention studies and since 14% of the ECGs could not be obtained; silent myocardial infarctions were analyzed separately."

Thus, it should be concluded that aspirin treatment in comparison to placebo failed to have a salutatory effect on major cardiovascular events, all MI, all stroke, cardiovascular mortality and total mortality.

Table D3. Primary efficacy Endpoint and Cardiovascular Events by treatment Group

	ASA N=9399 n	Placebo N=9391 n	p-Value	RR (95% CI)
Primary Efficacy Endpoint:				
CV events	388	425	0.17	0.91 (0.79-1.04)
Secondary Efficacy Analyses:				
All MI	157	184	0.13	0.85 (0.69-1.05)
All Stroke	146	148	0.88	0.98 (0.78-1.24)
CV Mortality	133	140	0.65	0.95 (0.75-1.20)
Total Mortality	284	305	0.36	0.93 (0.79-1.09)
Post-Hoc Analyses				
CV events (- silent MI)	315	368	0.03	0.85 (0.73-0.99)
All MI (- silent cases)	82	127	0.002	0.64 (0.49-0.85)

²⁰ A finding of new Q or QS waves, without clinical signs of myocardial infarction, was defined as a silent myocardial infarction.

[Sponsor's analysis, The Lancet Vol 351, page 1760, Table 6, 1998. CV=cardiovascular events. Results were confirmed by Dr. Chenxiong Le, HFD-710]

The primary efficacy endpoint was also analyzed by gender, race, age, and region (Table D4). The results of this retrospective subgroup analysis of the primary endpoint shows a statistically significant beneficial effect of aspirin only on Black patients (relative risk 0.41, 95% CI 0.19-0.88, p=0.022) and in North America (relative risk 0.65, 95% CI 0.48-0.87, p=0.004).

Table D4. Subgroup Analysis of Primary Efficacy Endpoint by Treatment Group.

Subgroup		Treatment group	Number of events (total patients)	Events/1000 patients years	P-value	Relative risk (95% CI)
Gender	Female	ASA	139 (4437)	8.3	0.22	0.87 (0.69-1.09)
		Placebo	160 (4446)	9.6		
	Male	ASA	249 (4962)	13.6	0.42	0.93 (0.78-1.11)
		Placebo	265 (4945)	14.6		
Race	Black	ASA	9 (316)	8.3	0.022	0.41 (0.19-0.88)
		Placebo	23 (337)	20.6		
	Caucasian	ASA	367 (8806)	11.1	0.43	0.94 (0.82-1.09)
		Placebo	384 (8732)	11.8		
	Oriental	ASA	10 (130)	20.7	0.39	1.51 (0.59-3.82)
		Placebo	8 (152)	13.8		
	Other	ASA	2 (147)	3.7	0.055	0.23 (0.05-1.03)
		Placebo	10 (169)	16.5		
Age	< 65 years old	ASA	199 (6425)	8.2	0.15	0.87 (0.72-1.05)
		Placebo	226 (6376)	9.5		
	≥ 65 years old	ASA	189 (2974)	17.4	0.70	0.96 (0.79-1.17)
		Placebo	199 (3015)	18.1		
Region	Asia	ASA	5 (93)	14.0	1.0	1.0 (0.30-3.27)
		Placebo	6 (112)	14.0		
	Europe	ASA	312 (7597)	10.9	0.84	1.02 (0.87-1.19)
		Placebo	299 (7408)	10.7		
	North America	ASA	70 (1689)	11.8	0.004	0.65 (0.48-0.87)
		Placebo	116 (1844)	18.3		
	South America	ASA	1 (20)	14.4	0.32	0.33 (0.04-2.93)
		Placebo	2 (27)	44.3		

[FDA's analysis, Dr. Chenxiong Le, HFD-710.]

Tables D5 and D6 describes the results of subgroup analysis of all and nonfatal MIs, respectively, by gender and treatment group.

Table D5. Subgroup Analysis of All MIs by Gender and Treatment Group.

Subgroup		Treatment group	Number of events (total patients)	Events/1000 patients years	P-value	Relative risk (95% CI)
Gender	Female	ASA	59 (4437)	3.5	0.78	0.95 (0.67-1.36)
		Placebo	62 (4446)	3.7		
	Male	ASA	98 (4962)	5.3	0.09	0.80 (0.61-1.04)
		Placebo	122 (4945)	6.7		

[FDA's analysis, Dr. Chenxiong Le, HFD-710.]

Table D6. Subgroup Analysis of Nonfatal MIs by Gender and Treatment Group.

Subgroup		Treatment group	Number of events (total patients)	Events/1000 patients years	P-value	Relative risk (95% CI)
Gender	Female	ASA	51 (4437)	3.03	0.50	0.88 (0.60-1.28)
		Placebo	58 (4446)	3.45		
	Male	ASA	92 (4962)	4.98	0.14	0.81 (0.62-1.07)
		Placebo	112 (4945)	6.12		

[FDA's analysis, Dr. Chenxiong Le, HFD-710.]

Albeit the number of fatal bleeds was similar between the aspirin and placebo groups there was an excess (approximately two-fold higher) of major and minor bleeding events, mainly gastrointestinal and nasal, reported in aspirin-treated patients as compared to those receiving placebo (Table D7).

Table D7. Incidence of Bleeding-related Adverse Events by Treatment Group.

Events	ASA N=9399 n	Placebo N=9391 n
Fatal Bleeds		
Total	7	8
Gastrointestinal	5	3
Cerebral	2	3
Other	0	2
Non-Fatal Major Bleeds		
Total	129	70
Gastrointestinal	72	34
Cerebral	12	12
Nasal	22	12
Other	23	12
Minor Bleeds		
Total	156	87
Gastrointestinal	30	18
Nasal	66	24
Purpura	45	25
Other	15	20

[Sponsor's analysis, The Lancet Vol 351, page 1760, Table 7, 1998.]

Table D8 summarizes bleeding events by sex and treatment group.

Table D8: Bleeding events by sex and treatment group (HOT study)

Gender		ASA (n = 9399)	Placebo (n = 9391)	P-value
Female	Fatal bleeds			<0.0001
	Total	2	4	
	Gastrointestinal	1	1	
	Cerebral	1	2	
	Other	0	1	
	Non-fatal major bleeds			
	Total	51	22	
	Gastrointestinal	26	6	
	Cerebral	5	6	
	Nasal	10	4	
Other	10	6		

	Minor bleeds			
	Total	82	37	
	Gastrointestinal	12	2	
	Nasal	34	10	
	Purpura	30	17	
	Other	6	8	
Male	Fatal bleeds			=0.008
	Total	5	4	
	Gastrointestinal	4	2	
	Cerebral	1	1	
	Other	0	1	
	Non-fatal major bleeds			
	Total	78	48	
	Gastrointestinal	46	26	
	Cerebral	7	6	
	Nasal	12	8	
	Other	13	8	
	Minor bleeds			
Total	74	50		
Gastrointestinal	18	16		
Nasal	32	14		
Purpura	15	8		
Other	9	12		

[FDA's analysis, Dr. Chenxiang Le, HFD-710. Note: Events occurred in the same patients were counted as different events.]

In summary, , it should be concluded that aspirin treatment in comparison to placebo failed to have a salutatory effect on all MI, all stroke, cardiovascular mortality or total mortality. Treatment that was associated with a higher overall rate of major and minor bleeds, mainly gastrointestinal and nasal in location.

E. Primary Prevention Project (PPP)

The PPP trial had a controlled, randomized, open-label design and was performed in Italy.²¹ The main objective of the study was “to test whether chronic treatment with aspirin and vitamin E reduced the frequency of major fatal and non-fatal cardiovascular events, with no clinically relevant safety implications.” The study enrolled male and female subjects, ≥ 50 years of age, with at least one of the major recognized cardiovascular risk factors, i.e., old age ≥ 65 years, hypertension (SBP ≥ 160 mmHg or DBP ≥ 95 mmHg), hypercholesterolemia, diabetes mellitus, obesity, and family history of myocardial infarction before 55 years of age in at least one parent or sibling.

Subjects were randomized to receive, in addition to background treatments, aspirin (100 mg enteric-coated a day) or no aspirin, and vitamin E (300 mg α -tocopherol a day), or no vitamin E, following a 2x2 factorial design. Every four months visits were carried out to renew drug supplies and to check tolerance and compliance. Yearly follow-up clinic visits were scheduled for re-assessment of cardiovascular risk factors and recording of outcome events.

The primary composite efficacy endpoint was the cumulative rate of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke.²² Predefined analyses also included cardiovascular deaths, total deaths, total cardiovascular events (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, angina pectoris, transient ischemic attacks, peripheral artery disease, and revascularization procedures).

Safety monitoring: all the adverse “events judged by the physicians to be clinically severe and unexpected, not necessarily drug-related, had to be documented on a standard form and promptly reported to the scientific and organizing committee.”

The study was initiated, managed, and analyzed with no external sponsorship, under the coordination of the scientific and organizing committee and the supervision of an external safety and efficacy monitoring committee (ESEMC).

According to the sponsor’s calculations, 7500 participants followed up for 5 years were needed to verify the hypothesis of a 25% reduction in the frequency rate of the cumulative endpoint with $\alpha=0.05$ and $1-\beta=90\%$.

The sponsor conducted statistical analyses using an intent-to-treat principle.

Of note, at the second planned interim analysis in July 1998, the ESEMC recommended to end the trial based on: “(1) ethical considerations for the aspirin group²³ and (2) feasibility arguments for the vitamin E group.”²⁴ Randomization stopped and the end of follow-up was set for December 31, 1998.

The study randomized 4495 male ($n=2583$, 58%) and female ($n=1912$, 42%) patients with a mean age of 64.4 years, between 1994 and 1998; 4258 (94.7%) subjects were enrolled by general practitioners and 237 (5.3%) by 15 hospital-based hypertension units throughout Italy (Table E1). Overall baseline characteristics were well balanced across the groups. Sixty-six percent of the patients were on antihypertensive drugs, while 12% and 16% were receiving lipid lowering and anti-diabetic drugs, respectively.

²¹ Collaborative Group of the Primary Prevention Project (PPP). Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomized trial in general practice. *The Lancet* 2001; 357:89-95.

²² “Validation of the clinical events included in the main combined endpoint was assured by an ad hoc committee of expert clinicians masked to the treatment assignment.”

²³ Newly available evidence on the benefit of aspirin in primary prevention in people at cardiovascular risk documented in two main studies: Thrombosis Prevention Trial (TPT) and Hypertension Optimal Treatment Study (HOT).

²⁴ “The lower than expected overall rate of events in the absence of any hint of difference between the two randomized populations would have implied an unrealistically long follow-up (further complicated by the absence of any specific financial support).”

Table E1. Baseline Characteristics by Treatment Group

Variable	Aspirin N=2226 n (%)	No Aspirin N=2269 n (%)
Age (mean±SD; years)	64.5 (7.7)	64.3 (7.6)
Sex		
♂	1277 (57)	1306 (58)
♀	949 (43)	963 (42)
Risk factors for inclusion		
Old age	1110 (50)	1136 (50)
Hypertension	1527 (69)	1538 (68)
Hypercholesterolemia	921 (41)	821 (36)
Obesity	492 (22)	544 (24)
Diabetes	377 (17)	365 (16)
Family history of premature MI	241 (11)	225 (10)
Smoker		
Ex-smoker	533 (24)	547 (24)
Current smoker	328 (15)	339 (15)
Other Characteristics (mean±SD)		
SBP mmHg	145.3 (16.5)	145.0 (15.8)
DBP mmHg	85.2 (8.7)	85.6 (8.3)
Serum total cholesterol mmol/L	6.2 (1.2)	6.1 (1.2)
Body mass index (kg/m ²)	27.5 (4.5)	27.7 (4.8)

[Adapted from The Lancet 2001; 357:91, Table 1.]

At study completion 92.3% of the patients had clinical follow-up, and vital status information was attained for 99.3% of the randomized patients. Mean follow-up was 3.6 (SD ±1.0) years (median 4.0 years). By the end of the study 19.3% of patients randomized to aspirin and 13.6% of those randomized to vitamin E discontinued treatment. 7.9% and 1.1% of the patients discontinued the study drug because of adverse events in the aspirin and vitamin E groups, respectively.

Table E2 summarizes the results for the combined primary endpoint and predefined secondary analyses including cardiovascular deaths, total deaths, total cardiovascular events (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, angina pectoris, transient ischemic attacks, peripheral artery disease, and revascularization procedures).

The effect of aspirin on the primary composite efficacy endpoint, the cumulative rate of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke, was not statistically significant ($p=?$). There were 45 (2.0%) events in the aspirin group versus 64 (2.8%) events in the no aspirin group (relative risk ratio 0.71, 95% confidence intervals 0.48-1.04). Aspirin administration resulted only in a statistically significant reduction in cardiovascular deaths ($p=0.049$, relative risk ratio 0.56, 95% CI 0.31-0.99). However, all deaths (62 aspirin versus 78 no aspirin, RR 0.81, 95% CI 0.58-1.13) and non-cardiovascular deaths (45 aspirin versus 47 no aspirin, RR 0.98, 95% CI 0.65-1.46) were not affected by aspirin therapy. The total incidence of cardiovascular events such as non-fatal myocardial infarction, non-fatal stroke, angina pectoris, transient ischemic attack, peripheral artery disease, and revascularization procedure was significantly affected by aspirin ($p=0.014$, relative risk reduction 23%).

Table E2. Efficacy Profile of Aspirin

	Aspirin N=2226 n (%)	No Aspirin N=2269 n (%)	Relative Risk (95% CI)
Primary combined endpoint	45 (2.0)	64 (2.8)	0.71 (0.48-1.04)
All deaths	62 (2.8)	78 (3.4)	0.81 (0.58-1.13)
Cardiovascular	17 (0.8)	31 (1.4)	0.56 (0.31-0.99)
Non-cardiovascular	45 (2.0)	47 (2.0)	0.98 (0.65-1.46)
All MI	19 (0.8)	28 (1.2)	0.69 (0.38-1.23)
Non-fatal MI	15 (0.7)	22 (1.0)	0.69 (0.36-1.33)
All stroke	16 (0.7)	24 (1.1)	0.67 (0.36-1.27)
Non-fatal stroke	15 (0.7)	18 (0.8)	0.84 (0.42-1.67)
Angina pectoris	54 (2.4)	67 (3.0)	0.82 (0.58-1.17)
Transient ischemic attacks	28 (1.3)	40 (1.8)	0.71 (0.44-1.15)
Peripheral artery disease	17 (0.8)	29 (1.3)	0.60 (0.33-1.08)
Revascularization procedure	20 (0.9)	29 (1.3)	0.70 (0.40-1.24)

[Adapted from The Lancet 2001; 357:92, Table 2.]

The number of adverse events, severe and unexpected not necessarily drug-related, reported in each group is summarized in Table E3. Aspirin-treated patients had a greater number of bleeding events than those not receiving aspirin ($p=0.0008$, 1.1% versus 0.3%).

Table E3. Safety Profile of Aspirin and Vitamin E Treatment

Adverse Event	Aspirin N=2226 n	No Aspirin N=2269 n
Bleeding		
Gastrointestinal	17	5
Intracranial (not parenchymal)	2	0
Ocular	1	1
Epsitaxis	2	0
Other	2	0
Gastrointestinal disease (except bleeding)	8	3
Cancer	86	80
Other events	36	21
Total	154	110

[Adapted from The Lancet 2001; 357:93, Table 3.]

In summary, the results from this clinical trial do support the notion that aspirin therapy is beneficial for the primary prevention of cardiovascular mortality. The data furthermore suggest that aspirin may be associated with a higher risk of bleeding, primarily gastrointestinal.

Summary and Comments

Table S1 provides a summary for the 5 clinical trials, the PHS, BDT, TPT, HOT and PPP study. The population consisted of 55580 participants, 44837 (80.7%) males and 10743 (19.3%) females. Only, the HOT and PPP studies randomized females subjects. The PHS and HOT studies enrolled the largest number of subjects 22071 and 18790, respectively. The patient population was heterogeneous among the trials ranging from apparently healthy physicians to subjects at high risk of CVD. The age ranged from 40-84 years. The mean follow-up ranged from 2.5 to 3.8 years. Aspirin was administered daily or every other day, and the dose ranged from 75 mg Q.D. to 500 mg Q.D, including 325 mg QOD.

Table S1. Studies' Summary.

Features	Study				
	PHS	BDT	TPT	HOT	PPP
# of Subjects	22071	5139	5085	18790	4495
Follow-Up (years)*	2.5	?	?	3.8	3.6
Patient Population	Apparently healthy ♂ MD	Apparently healthy ♂ MD	♂ at high risk of CVD	♂ & ♀ with HTN and DBP from 100-115 mmHg	♂ & ♀ with one or more CV risk factor
Age Range (years)	40-84	50-78	45-69	50-80	50-80+
♀Sex (n/%)	0	0	0	8883/47.3	1912/42.5
ASA Dose	325 mg QOD	500 mg QD	75 mg QD	75 mg QD	100 mg QD

[*=mean. ?=not available.]

The results from the analyses of the primary efficacy endpoint for each of the clinical trials are summarized in Table S2. The primary efficacy endpoint for these clinical trials was either cardiovascular mortality alone or a combined endpoint of cardiovascular mortality and morbidity. Of note, in the five clinical trials aspirin therapy, when compared to control or placebo groups, failed to show a statistically significant beneficial effect on the pre-specified primary efficacy endpoints (Table S2). According to the sponsor "for vascular deaths, there was no significant reduction in risk..." (RR 0.98, 95% CI 0.85-1.12, p=?).

Table S2. Primary Efficacy Endpoint.

	Study				
	PHS	BDT	TPT	HOT	PPP
Primary Efficacy Endpoint	CV Mortality.	CV Mortality.	Fatal and nonfatal IHD events.	All (fatal and nonfatal) MI & stroke, & CV mortality.	CV mortality, nonfatal MI & nonfatal stroke.
p-value	0.87	NS	NS	0.17*	NS
RR	0.96	NA	NA	0.91*	0.71
95% CI	0.60-1.54	NA	NA	0.79-1.04*	0.48-1.04

[NS=not significant, actual p-value is missing. NA=not available. *FDA's analysis performed by Dr Chenxiong Le, HFD-710.]

Table S3 summarizes the results of the retrospective analysis of nonfatal and fatal myocardial infarction by study. Because the reviewers were uncertain as to the absolute number of nonfatal and fatal MI events for the DBT study they were excluded from the analysis for the total number of events. In the aspirin group a total of 334 (1.40%) nonfatal MI events were reported versus 478 (1.99%) in the placebo/control group, RR 0.70, 95% CI 0.61-0.80, p<0.0001. Conversely, aspirin therapy did not have a beneficial effect on the incidence of fatal MI, 64 (0.27%) events for aspirin versus 80 (0.33%) events for control/placebo, RR 0.80, 95% CI 0.58-1.11, p=0.18. It should be noticed that out of the five clinical studies only in the PHS aspirin had a beneficial effect on fatal and non-fatal MI.

Table S3. Nonfatal and Fatal Myocardial Infarction in the PHS, BDT, TPT, HOT, and PPP Clinical Trials.

Study	Aspirin		Placebo/Control	
	Nonfatal MI n/N	Fatal MI n/N	Nonfatal MI n/N	Fatal MI n/N
PHS ^a	129/11037	10/11037	213†/11034	26†/11034
BDT ^b	42.5§	47.3‡	43.3§	49.6‡
TPT ^c	47/1268	36/1268	73/1272	34/1272
HOT ^d	143/9399	14/9399	170/9391	14/9391
PPP ^e	15/2226	4/2226	22/2269	6/2269
Total*	334/23930	64/23930	478/23966	80/23966
%*	1.40	0.27	1.99	0.33
p-value**	<0.0001	0.18		
RR***	0.70	0.80		
95% CI***	0.61-0.80	0.58-1.11		

[†p<0.05 vs. aspirin. §=first events/10,000 man/years. ‡=deaths/10,000 man/years. ^aN Engl J Med 1989; 321: Table 1. ^bBritish Medical Journal 1988; 296: Table III and IV. ^cLancet 1998; 351: Table 3. ^dHOT Study database, FDA's analysis performed by Dr. Chenxiang Le, HFD-710. ^eLancet 2001; 357: Table 2. *Study BDT is excluded; **p-values are from Cochran-Mantel-Haenszel statistics stratified by study; ***The relative risk and 95% CI are from Mantel-Haenszel method FDA's analysis performed by Dr. Chenxiang Le, HFD-710.]

Table S4 describes the results of subgroup analyses for all and nonfatal MIs in female subjects from the HOT study.²⁵ In female subjects aspirin therapy did not influence the occurrence all or nonfatal MIs.

Table S4. Subgroup Analysis of All and Nonfatal Myocardial Infarction in Female subjects (HOT Study).

Variable	Treatment group	Number of events (total patients)	Events/1000 patients years	P-value	Relative risk (95% CI)
All MIs	Aspirin	59 (4437)	3.5	0.78	0.95 (0.67-1.36)
	Placebo	62 (4446)	3.7		
Nonfatal MIs	Aspirin	51 (4437)	3.03	0.50	0.88 (0.60-1.28)
	Placebo	58 (4446)	3.45		

[FDA's analysis, Dr. Chenxiang Le, HFD-710.]

Table S5 summarizes the results of the retrospective analysis of nonfatal and fatal stroke by study. Because the reviewers were uncertain as to the absolute number of nonfatal and fatal stroke events in the BDT study the overall results in Table S5 did not include those data. In the aspirin group a total of 261 (1.09%) nonfatal stroke events were reported versus 264 (1.09%) in the placebo/control group, RR 1.0, 95% CI 0.84-1.18, p= 0.97. Similarly, the total incidence of fatal stroke was not affected by aspirin therapy, 38 events for aspirin versus 34 events for control/placebo, RR 1.12, 95% CI 0.70-1.78, p=0.63.

²⁵ The reviewers had no access to datasets from the other trial, the PPP study, that enrolled females.

Table S5. Nonfatal and Fatal Stroke in the PHS, BDT, TPT, HOT, and PPP Clinical Trials.

Study	Aspirin		Placebo/Control	
	Nonfatal Stroke n/N	Fatal Stroke n/N	Nonfatal Stroke n/N	Fatal Stroke n/N
PHS ^a	110/11037	9/11037	92/11034	6/11034
BDT ^b	32.4§	16‡	28.5§	12.7‡
TPT ^c	16/1268	2/1268	25/1272	1/1272
HOT ^d	120/9399	26/9399	127/9391	21/9391
PPP ^e	15/2226	1/2226	18/2269	6/2269
Total*	261/23930	38/23930	262/23966	34/23966
%*	1.09	0.16	1.09	0.14
p-value**	0.97	0.63		
RR***	1.0	1.12		
95% CI***	0.84-1.18	0.70-1.78		

[§=first events/10,000 man/years. ‡=deaths/10,000 man/years. ^aN Engl J Med 1989; 321: Table 1. ^bBritish Medical Journal 1988; 296: Table III and IV. ^cLancet 1998; 351: Table 3. ^dHOT Study database, FDA's analysis, Dr. Chenxiong Le, HFD-710. ^eLancet 2001; 357: Table 2. *Study BDT is excluded; **p-values are from Cochran-Mantel-Haenszel statistics stratified by study; ***The relative risk and 95% CI are from Mantel-Haenszel method FDA's analysis performed by Dr. Chenxiong Le, HFD-710.]

The requested amendment to the Professional Labeling for Aspirin by the Citizen's Petition, is seeking "...FDA approval for expanded cardiovascular indications and labeling for the use of an aspirin regimen (75 mg-325 mg) to reduced the risk of a first myocardial infarction (MI) in patients with coronary heart disease 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." The following issues, in particular, of the Citizen's Petition merit commentary:

- "labeling for the use of an aspirin regimen of 75 mg to 325 mg..."

The dosing of aspirin effective in reducing cardiovascular morbidity and mortality can not unequivocally be established from the available data.

- "...to reduce the risk of a first myocardial infarction (MI) in patients with coronary heart disease 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."

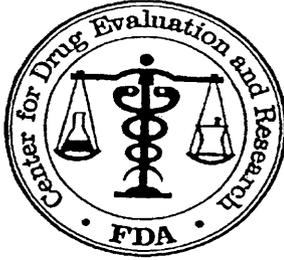
Even though the results of the meta-analysis indicate that aspirin administration reduces the incidence of MI, out of the five clinical studies only in the PHS aspirin had a beneficial effect on fatal and non-fatal MI. More importantly, in the five clinical trials aspirin therapy, when compared to control or placebo groups, failed to show a statistically significant beneficial effect on the pre-specified primary efficacy endpoints that is cardiovascular mortality or cardiovascular morbidity and mortality. In none of the studies non-fatal myocardial infarction was a pre-specified primary endpoint. Thus, the aforementioned facts significantly curtailed and questioned the interpretation of the results from the meta-analysis for aspirin.

The data at hand do not support the contention that aspirin is indicated "to reduce the risk of a first myocardial infarction (MI) in patients with coronary heart disease risk of 10% or greater over 10 years"...In this regard, the population enrolled among the clinical trials was heterogeneous, and whether or not aspirin treatment is effective in reducing the rate of fatal or nonfatal MI in female subjects can not be concluded from the data. It is not clear how a health provider could *a priori* determine that "there is positive benefit-risk" for aspirin use in a particular patient.

With respect to aspirin in the primary prevention of cardiovascular events, primarily nonfatal MI, any consideration for approval should be balanced against the risk from the long-term administration of aspirin such as gastrointestinal adverse events and bleeding.²⁶ By and large, a risk benefit analysis for any drug hitherto can not be quantified with any degree of accuracy. In the case of the long term use of aspirin a beneficial effect of aspirin for the primary prevention of cardiovascular morbidity and mortality could not unambiguously be ascertained. Thus, lack of efficacy

²⁶ The reader is referred to the detailed review for each individual study.

in the face of associated morbidity, i.e., bleeding, prevents the recommendation for the use of aspirin for the primary prevention of cardiovascular morbidity and mortality.



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION

Medical Division: **Division of Cardio-Renal Drug Products (HFD-110)**
Biometrics Division: **Division of Biometrics I (HFD-710)**

NDA NUMBER: Citizen's Petition
SERIAL NUMBER: NA
DATE RECEIVED BY CENTER: April 1, 2003
DRUG NAME: Aspirin
INDICATION: Reduce the Risk of First Myocardial Infarction (MI)
SPONSOR: Bayer
DOCUMENTS REVIEWED: SAS Data Sets of HOT Study and Literature Related to Aspirin and Cardiovascular Risks
STATISTICAL REVIEWER: Chenxiong (Charles) Le, Ph.D. (HFD-710)
STATISTICAL TEAM LEADER: James Hung, Ph.D. (HFD-710)
BIOMETRICS DIVISION DIRECTOR: George Chi, Ph.D. (HFD-710)
CLINICAL REVIEWER: Juan Carlos Pelayo, M.D. (HFD-110)
PROJECT MANAGER: Meg Pease-Fye (HFD-110)

KEY WORDS: Aspirin, MI, Cardiovascular Death, Meta-analysis, Relative risk, Cox proportional-hazards model, Time to event.

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1 Executive Summary of Statistical Findings

1.1 Conclusions and Recommendations

The Sponsor requested amendment to the Professional Labeling of aspirin in this citizen's petition. They are seeking '...FDA approval for expanded cardiovascular indications and labeling for the use of an aspirin regimen (75 mg – 325 mg) to reduce the risk of a first myocardial infarction (MI) in patients with coronary heart disease 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'. Five studies were cited to support the petition: British Doctor's Trial (BDT)¹, Physician's Health Study (PHS)², Thrombosis Prevention Trial (TPT)³, Hypertension Optimal Treatment Study (HOT)⁴, and Primary Prevention Project (PPP)⁵.

The PHS did not achieve statistical significance on the primary endpoint. It gave a very small nominal p-value for nonfatal MI, which was one of the secondary endpoints. This result at best suggested that aspirin might have a potential benefit of reducing the risk of nonfatal MI. However, in the PHS some of the study patients had a prior MI and aspirin is already known to reduce the risk of recurrent MI in such patients.

The HOT study failed on the primary endpoint that should have been considered, that is, including silent MIs. Only when silent MIs were excluded, HOT achieved borderline significance on the primary endpoint and nonfatal MI. When silent MIs were included, the HOT study failed to confirm that potential benefit of aspirin. No other study was able to confirm that either, and no study excluded the patients with a prior MI in the study population.

For reasons and the observations given in Section 2.3.2.2, the results of the post-hoc meta-analysis combining five studies or the Sponsor's meta-analysis of four studies were very difficult to interpret. At best the results suggested the potential benefit of aspirin in reducing 1st nonfatal MI. A randomized clinical trial would be needed to confirm the benefit.

1.2 Overview of Clinical Program and Studies Reviewed

The Sponsor cited 5 large studies (BDT, PHS, TPT, HOT, PPP) to support their petition. The Division was able to obtain the SAS datasets from the HOT study⁴. Data were not available for the other 4 studies. This reviewer was able to independently review the results of the HOT study. The reviews of the other 4 studies were based on the published literature^{1,2,3,5}.

The BDT study¹ was a six year randomized trial which was conducted among 5139 apparently healthy male doctors (3429 in aspirin and 1710 in placebo) to see whether 500 mg aspirin daily would reduce the incidence of mortality, stroke, MI, or other vascular conditions. The PHS study² was a randomized, double-blinded, placebo-controlled clinical trial of aspirin in the prevention of cardiovascular disease and of beta-carotene in the

prevention of cancer in 22071 apparently healthy male physicians (11037 in aspirin and 11034 in placebo). One of the two primary prevention hypotheses was whether the low-dose aspirin (325 mg taken every other day) would reduce the cardiovascular mortality. The mean follow-up time was 2.5 years. The TPT study³ was a randomized clinical trial in 5085 men at high risk of ischemic heart disease (IHD). It was aimed to evaluate low intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of IHD. The patients were randomized in four treatment groups: active warfarin and active aspirin (WA, n=1277), active warfarin and placebo aspirin (W, n=1268), placebo warfarin and active aspirin (A, n=1268), and placebo warfarin and placebo aspirin (P, n=1272). Aspirin was given as a 75 mg daily of a controlled release formulation. The primary endpoint was all IHD defined as the composite of coronary death and fatal and nonfatal MI. The main effect of aspirin was compared between WA and A vs. W and P groups. In the HOT study⁴, 18790 patients with hypertension and diastolic blood pressure between 100 mm Hg and 115 mm Hg were randomly assigned to aspirin 75 mg/day (n=9399) and placebo (n=9391) group. One of the main aims was to find out whether the addition of low doses of aspirin to antihypertensive treatment reduces the rate of major cardiovascular events, where the major cardiovascular events were defined as all (fatal or nonfatal) MI, all (fatal and nonfatal) stroke and all other cardiovascular deaths. The average follow-up time was 3.8 years. The PPP study⁵ was a randomized clinical trial designed to test whether chronic treatment with aspirin and vitamin E reduced the frequency of major fatal and nonfatal cardiovascular events on male or female patients with at least one of the major recognized cardiovascular risk factors. A total of 4495 patients were randomized into aspirin (n=2226) and not aspirin (n=2269) group, with a mean follow-up of 3.6 years. The main combined efficacy endpoint was the cumulative rate of cardiovascular death, nonfatal MI and nonfatal stroke.

1.3 Principal Findings

The PHS study did not achieve statistical significance on the primary endpoint. It appeared to achieve a statistically significant result for reducing the incidence of nonfatal MI, with a nominal p-value < 0.0001. None of the other 4 studies achieved statistical significance for reducing the risk of MI. Although the HOT study reported statistical significance for reducing the incidence of MI⁴, the results were based on the MIs that excluded silent MIs. According to the definitions of the pre-specified endpoints, silent MIs should be included. When silent MIs were included, statistical significance was not achieved for reducing the risk of MI (nominal p-value = 0.13).

The Sponsor's meta-analysis of BDT, PHS, TPT and PPP gives the relative risk of 0.68, 95% CI 0.59 – 0.79 for aspirin on nonfatal MI. However, the results are very difficult to interpret for the following reasons. The relative risks were different among the individual studies, ranging from 0.61 to 0.97. The PHS had the smallest relative risk of 0.61, with a nominal p-value < 0.0001. The slightly smaller HOT study had a relative risk of 0.84, with a nominal p-value = 0.12, which was quite different from the results of PHS. In addition, the patient populations were quite different among the 5 studies, ranging from apparently healthy physicians to patients at high risk of cardiovascular disease and aspirin doses vary across the studies as well (75 mg daily to 500 mg daily).

Only the HOT and TPT studies enrolled female subjects (n=8883 from HOT and n=1912 from TPT). Based on the HOT study, aspirin did not appear to have an effect in reducing the risk of MI in female subjects.

2 Statistical Review and Evaluation of Evidence

2.1 Introduction and Background

This Citizen's Petition requests that FDA approve the use of an aspirin regimen (75 mg-325 mg) for reducing the risk of first myocardial infarction (MI) in patients with coronary heart disease risk. The petition is based on the results of five major clinical trials: British Doctor's Trial (BDT)¹, Physician's Health Study (PHS)², Thrombosis Prevention Trial (TPT)³, Hypertension Optimal Treatment Study (HOT)⁴, and Primary Prevention Project (PPP)⁵.

2.2 Data Analyzed and Sources

The Sponsor did not conduct any of the five clinical trials. The Agency obtained the SAS data sets of the HOT study. This reviewer independently confirmed the results of the HOT study and conducted additional analyses based on the SAS data sets. Since the data were not available for other studies, the statistical review of the other 4 studies was based on the published literature^{1,2,3,5}.

2.3 Statistical Evaluation of Evidence on Efficacy and Safety

2.3.1 The HOT Study

2.3.1.1 Study Design

The HOT study was a large, multinational, prospective, randomized, open with blinded endpoint evaluation trial in patients with hypertension. A total of 19,193 patients from 26 countries with a diastolic blood pressure between 100 mm Hg and 115 mm Hg were randomly assigned in a 1:1:1 ratio to one of the three diastolic blood pressure target group: ≤ 90 mm Hg, 85 mm Hg or 80 mm Hg. Within each group, patients were randomized to a low dose (75 mg daily) of Aspirin or identical-looking placebo tablets in a 1:1 ratio. Patients were stratified on the basis of the following baseline variables: age, sex, previous antihypertensive therapy, smoking, previous MI, previous other coronary heart disease (CHD), previous stroke, and diabetes mellitus. The average follow-up time was 3.8 years, ranging from 3.3 to 4.9 years. The first patient was enrolled in October 1992 and the last day of follow-up was August 31, 1997.

The principle aims of the study were: to assess the association between major cardiovascular events (non-fatal MI, non-fatal stroke, and cardiovascular death) and the target blood pressure groups, to assess the association between major cardiovascular events and the diastolic blood pressure achieved during treatment, and to find out whether the addition of

low doses of aspirin to antihypertensive treatment reduces the rate of major cardiovascular events.

This review is focused on the analyses comparing aspirin with placebo. Because of the suspicion of incorrect inclusion or data handling at one center, 403 patients in that center were excluded early from the trial. As a result, 18,790 patients were randomly assigned to the 75mg/day aspirin (n=9399) group or the placebo group (n=9391).

2.3.1.2 Statistical Methods

A Cox proportional-hazards model was used to calculate relative risks in the analysis of the differences between aspirin and placebo. All tests were two-sided.

The power calculations were based on the STOP Hypertension study in which the average cardiovascular risk increased, both below and above a diastolic blood pressure of 80 mm Hg, by 3% per mm Hg, with narrow confidence limits. On the basis of these calculations, 40,000 patient years were expected to yield the 1100 cardiovascular events needed.

2.3.1.3 Patient Disposition and Demographics

As mentioned before, 403 patients were excluded from the trial because of the suspicion of incorrect inclusion or data handling at one center. In addition, a total of 491 (2.6%) patients (245 in the aspirin group and 246 in the placebo group) were lost to follow-up.

Patient characteristics at randomization are summarized in Table 1. They were almost identical between the two treatment groups.

Table 1. Patient characteristics at randomization (HOT Study)

	Treatment group	
	Aspirin (n=9399)	Placebo (n=9391)
Age (years)	61.5 (7.5)	61.5 (7.5)
Body-mass index (kg/m2)*	28.4 (4.6)	28.4 (4.7)
Diastolic blood pressure (mm Hg)	105 (3.4)	105 (3.4)
Systolic blood pressure (mm Hg)	170 (14)	170 (14)
Men / women (%)	53 /47	53/47
Previous treatment (%)	52.6	52.6
Smokers (%)	15.9	15.9
Previous MI (%)	1.5	1.5
Other previous CHD (%)	5.9	6.0
Previous stroke (%)	1.2	1.2
Diabetes mellitus (%)	8.0	8.0

Data are mean (SD) or % of group. MI = myocardial infarction; CHD = coronary heart disease.

*Data are from 9394 and 9384 patients in the aspirin and placebo groups, respectively.

2.3.1.4 Efficacy Results

For the comparison between the aspirin group and the placebo group, the pre-specified primary endpoint was major cardiovascular event, which was defined as all (fatal and non-fatal) MI, all (fatal and non-fatal) stroke and all other cardiovascular deaths. Silent MI was obtained by comparing the ECGs at baseline and the final visit. A finding of new Q and QS waves, without clinical signs of MI, was defined as a silent MI. An ECG was recorded in 96% of the patients at randomization and in 89% of the patients at the final visit.

Table 2 summarizes the efficacy results comparing the aspirin group with the placebo group. Aspirin seemed to reduce the incidence of major cardiovascular events by 9% over placebo (RR = 0.91, nominal p-value=0.17), but it was not statistically significant. Statistical significance was also not achieved for other endpoints except for major CV events and all MI when silent MIs were excluded.

The paper by Hansson etc⁴ seemed to indicate that the primary endpoint did not include silent MIs for the stated reason being 'to make the results comparable with those of other intervention studies and since 14% of the ECGs could not be obtained, silent MIs were analyzed separately'. It was reported in the paper that statistical significance was achieved for the primary endpoint and all MI. However, there was no election of excluding silent MI in the original definition of the primary endpoint. Therefore, silent MIs should be included in the primary endpoint. Statistical significance was not achieved for the primary endpoint and all MI when silent MI was included.

Table 2. Efficacy Results (HOT Study)

	Aspirin N=9399	Placebo N=9391	P- Value	RR (95% CI)
Major CV events (Silent MI included)	388	425	0.17	0.91 (0.79-1.04)
Major CV events (Silent MI excluded)	315	368	0.03	0.85 (0.73-0.99)
All MI (Silent MI included)	157	184	0.13	0.85 (0.69-1.05)
All MI (Silent MI excluded)	82	127	0.002	0.64 (0.49-0.85)
All Stroke	146	148	0.88	0.98 (0.78-1.24)
CV Mortality	133	140	0.65	0.95 (0.75-1.20)
Total Mortality	284	305	0.36	0.93 (0.79-1.09)

Source: Table 6 of Hansson etc⁴. Independently confirmed by this reviewer.

There were about 1.5% patients having a prior MI in the HOT study. Table 3 presents the results of the major cardiovascular events and all MI if the patients with a prior MI were excluded. The results were very similar to the results in Table 2.

Table 3. Efficacy Results (HOT Study) Excluding Patients with Prior MI

	Aspirin N=9399	Placebo N=9391	P- Value	RR (95% CI)
Major CV events (Silent MI included)	369	404	0.18	0.91 (0.79-1.05)
Major CV events (Silent MI excluded)	297	348	0.04	0.85 (0.73-0.99)
All MI (Silent MI included)	150	178	0.11	0.84 (0.68-1.04)
All MI (Silent MI excluded)	76	122	0.001	0.62 (0.47-0.83)

Source: Reviewer's analysis.

It is worth noting that the study might not have enough power to detect statistical significance based on the original power calculation. The original power calculation showed that 1100 cardiovascular events would be needed. This would require 40,000 patient years, which could be obtained by following 18,000 patients for 2.5 years. But the paper reported that the number of events was lower than expected despite a treatment follow-up period of 3.8 years. In addition, the paper reported that the Clinical Event Committee rejected 24% of all investigator-reported events since they did not meet the classification criteria. As a result, only 813 major CV events were used for the primary endpoint analysis.

2.3.1.5 Subgroup Analyses

Table 4 summarizes the subgroup analysis results for the primary endpoint. The risk reductions were in favor of aspirin in most cases. The results appeared to be inconsistent between North America and Europe. The nominal p-value was 0.004 for North America with a much smaller sample size, while the p-value was 0.84 for Europe with a much larger sample size. In addition, the relative risk was greater than 1 for Europe.

Table 4. Subgroup Analysis of Major CV Event, Silent MIs included (HOT Study)

Subgroup		Treatment group	Number of events (total patients)	Events/1000 patients years	P-value	Relative risk (95% CI)
Gender	Female	ASA	139 (4437)	8.3	0.22	0.87 (0.69-1.09)
		Placebo	160 (4446)	9.6		
	Male	ASA	249 (4962)	13.6	0.42	0.93 (0.78-1.11)
		Placebo	265 (4945)	14.6		
Race	Black	ASA	9 (316)	8.3	0.022	0.41 (0.19-0.88)
		Placebo	23 (337)	20.6		
	Caucasian	ASA	367 (8806)	11.1	0.43	0.94 (0.82-1.09)
		Placebo	384 (8732)	11.8		
	Oriental	ASA	10 (130)	20.7	0.39	1.51 (0.59-3.82)
		Placebo	8 (152)	13.8		
	Other	ASA	2 (147)	3.7	0.055	0.23 (0.05-1.03)
		Placebo	10 (169)	16.5		
Age	< 65 years old	ASA	199 (6425)	8.2	0.15	0.87 (0.72-1.05)
		Placebo	226 (6376)	9.5		
	≥ 65 years old	ASA	189 (2974)	17.4	0.70	0.96 (0.79-1.17)
		Placebo	199 (3015)	18.1		
Region	Asia	ASA	5 (93)	14.0	1.0	1.0 (0.30-3.27)
		Placebo	6 (112)	14.0		

	Europe	ASA	312 (7597)	10.9	0.84	1.02 (0.87-1.19)
		Placebo	299 (7408)	10.7		
	North America	ASA	70 (1689)	11.8	0.004	0.65 (0.48-0.87)
		Placebo	116 (1844)	18.3		
	South America	ASA	1 (20)	14.4	0.32	0.33 (0.04-2.93)
		Placebo	4 (27)	44.3		

Source: Reviewer's analysis.

2.3.1.6 Safety Assessment

Bleeding events are summarized in Table 5. Although fatal bleeds were almost even between the two groups (7 in aspirin group and 8 in placebo group), there appeared to be significantly more non-fatal major and minor bleeds in the aspirin group.

Table 5. Incidence of Bleeding-related Adverse Events by Treatment Group

Events	ASA N=9399 n	Placebo N=9391 n
Fatal Bleeds		
Total	7	8
Gastrointestinal	5	3
Cerebral	2	3
Other	0	2
Non-Fatal Major Bleeds		
Total	129	70
Gastrointestinal	72	34
Cerebral	12	12
Nasal	22	12
Other	23	12
Minor Bleeds		
Total	156	87
Gastrointestinal	30	18
Nasal	66	24
Purpura	45	25
Other	15	20

Source: Table 6 of Hansson et al.⁴

2.3.1.7 Reviewer's Conclusion

Based on the original definition of the efficacy endpoints, the silent MIs should be included in the primary endpoint efficacy analysis.

Including silent MIs, the HOT study suggested that aspirin might reduce major CV events (the composite of fatal and non-fatal MI, fatal and non-fatal stroke and other CV deaths) by 9% with p-value = 0.17 or might reduce MI events by 15% with p-value = 0.13. Neither achieved statistical significance.

2.3.2 Meta-analysis of the HOT, PHS, PPP, TPT and BDT Studies

Another focus of this review is on the meta-analysis of these studies presented in the Sponsor's submitted petition's document. For detailed review of each study, please read the medical review⁶ by Dr. Juan Carlos Pelayo, MD, HFD-110.

2.3.2.1 Sponsor's Meta-analysis

The Sponsor submitted the results of the meta-analysis of the data from the 4 studies (excluding HOT) in seeking the indication of reducing the risk of a 1st MI for aspirin.

Tables 6 and 7 present the results for nonfatal MI, nonfatal stroke, any important vascular event (combined endpoint of vascular death, nonfatal MI or nonfatal stroke) and vascular death. Based on the data in the tables, the results were confirmed independently by this reviewer. The Sponsor claimed that aspirin significantly reduces the risk of a 1st nonfatal MI by 32%.

Similar analyses were conducted by this reviewer including the data from the HOT study. This reviewer used the data a little different from Table 9 because of competing risk issue. See the reviewer's evaluation section for details.

Table 6. Nonfatal MI and Nonfatal Stroke in the 5 Studies

Study	Aspirin			Control		
	Nonfatal MI	Nonfatal Stroke	Total N	Nonfatal MI	Nonfatal Stroke	Total N
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
RR	0.68	1.06				
95% CI	(0.59-0.79)	(0.87-1.29)				

Source: Table 2 of the Sponsor's application.

Table 7. Any Important Vascular Event and Vascular Death in the 5 Studies

Study	Aspirin			Control		
	Any Important Vascular Event	Vascular Death	Total N	Any Important Vascular Event	Vascular Death	Total N
PHS	307	81	11037	370	83	11034
BDT	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
RR	0.85	0.98				
95% CI	0.79-0.93	0.85-1.12				

Source: Table 4 of the Sponsor's application.

2.3.2.2 Reviewer's Evaluation

Table 8 presents some characteristics of the five clinical trials. The PHS and HOT were the largest two studies accounting for 74% of the 55,580 subjects in total. Only HOT and TPT enrolled female subjects (N = 10,743). Among the five studies, the patient populations were very different, ranging from apparently healthy physicians to patients at high risk of CV disease. The aspirin doses were quite different as well (from 75 mg to 500 mg daily, including 325 mg every other day). The primary endpoints were also different.

The primary endpoints did not achieve statistical significance in PHS, BDT, HOT and PPP. For TPT, there were 4 treatment groups in the study (active warfarin and active aspirin (WA), active warfarin and placebo aspirin (W), placebo warfarin and active aspirin (A), placebo warfarin and placebo aspirin (P)). It was reported that the main effect of aspirin (WA and A combined vs. W and P combined) was a reduction of 20% in all IHD (P = 0.04, 95% CI 1% - 35%) almost entirely due to a 32% reduction (P = 0.004, 95% CI 12% - 48%) in nonfatal events. However, the results comparing A with P were not reported in the literature.

Table 8. Some characteristics of the 5 Studies

Features	Study				
	PHS	BDT	TPT	HOT	PPP
Total N	22071	5139	5085	18790	4495
Mean Follow-Up (years)*	2.5	?	?	3.8	3.6
Patient Population	Apparently healthy male MD	Apparently healthy male MD	Male at high risk of CVD	Male and female with HTN and DBP from 100-115 mmHg	Male and female with one or more CV risk factor
Age Range (years)	40-84	50-78	45-69	50-80	50-80+
Female (n/%)	0	0	0	8883/47.3	1912/42.5
Aspirin Dose	325 mg QOD	500 mg QD	75 mg QD	75 mg QD	100 mg QD
Primary Efficacy Endpoint	CV Mortality.	CV Mortality.	Fatal and nonfatal IHD events.	All (fatal and nonfatal) MI & stroke, & CV mortality.	CV mortality, nonfatal MI & nonfatal stroke.
p-value	0.87	NS	NS	0.17*	NS
RR	0.96	NA	NA	0.91*	0.71
95% CI	0.60-1.54	NA	NA	0.79-1.04*	0.48-1.04

Source: Dr. Pelayo's medical review ⁶, Tables S1 and S2. NA: Not Available. NS: Not Statistical Significant

Tables 9, 10 and 11 give the results of each study for all MI, nonfatal and fatal MI. For all MI, the relative risks seemed to be heterogeneous among the five studies (ranging from 0.58

to 0.96, with $P = 0.03$ based on Breslow-Day test of homogeneity of odds ratios). The PHS had the smallest relative risk of 0.58, with a nominal p -value < 0.0001 . However, the slightly smaller HOT study yielded a $RR = 0.85$ with nominal p -value $= 0.14$, which was quite different from the results of PHS.

Based on the reasons and the observations given above, the results from such a post-hoc meta-analysis combining the five or four studies are very difficult to interpret.

The analysis combining the five studies yielded the overall relative risks of 0.77, 0.73 for all and nonfatal MI, respectively, with both nominal p -values < 0.0001 . It is well known that the nominal p -value is very difficult to interpret from a post-hoc meta-analysis. The overall relative risk of fatal MI was 0.91, with nominal p -value $= 0.40$. Excluding PHS (combining the other four studies), the relative risks were 0.85, 0.80, 1.01 for all, nonfatal and fatal MI, respectively. These results seemed to suggest that aspirin may have a potential benefit in reducing the risk of 1st nonfatal MI. A randomized clinical trial is needed to confirm the benefit.

Table 9. All MI in the 5 Studies

Study	Aspirin n/N (%)	Placebo n/N	Relative Risk	P-value	95% CI
BDT	169/3429 (4.93)	88/1710 (5.15)	0.96	0.74	(0.75, 1.23)
HOT*	157/9399 (1.67)	184/9391 (1.96)	0.85	0.14	(0.69, 1.05)
PHS	139/11037 (1.26)	239/11034 (2.17)	0.58	<0.0001	(0.47, 0.72)
PPP	19/2226 (0.85)	28/2269 (1.23)	0.69	0.21	(0.39, 1.23)
TPT*	154/2545 (6.05)	190/2540 (7.48)	0.81	0.04	(0.66, 0.99)
Total**	638/28636 (2.23)	729/26944 (2.71)	0.77	<0.0001	(0.69, 0.85)
Total (-PHS)**	499/17599 (2.84)	490/15910 (3.08)	0.85	0.011	(0.75, 0.96)

*Silent MIs included. **The relative risk, post-hoc nominal p -value and 95% CI are computed using Mantel-Haenszel method.

Table 10. Nonfatal MI in the 5 Studies

Study	Aspirin n/N (%)	Placebo n/N	Relative Risk	P-value	95% CI
BDT	80/3429 (2.33)	41/1710 (2.40)	0.97	0.89	(0.67, 1.41)
HOT*	143/9399 (1.52)	170/9391 (1.81)	0.84	0.12	(0.67, 1.05)
PHS	129/11037 (1.17)	213/11034 (1.93)	0.61	<0.0001	(0.49, 0.75)
PPP	15/2226 (0.67)	22/2269 (0.97)	0.70	0.27	(0.36, 1.34)
TPT*	94/2545 (3.69)	137/2540 (5.39)	0.68	0.004	(0.53, 0.89)
Total**	461/28636 (1.61)	583/26944 (2.16)	0.73	<0.0001	(0.64, 0.82)
Total (-PHS)**	332/17599 (1.89)	370/15910 (2.33)	0.80	0.0024	(0.69, 0.92)

*Silent MIs included. **The relative risk, post-hoc nominal p -value and 95% CI are computed using Mantel-Haenszel method.

Table 11. Fatal MI in the 5 Studies

Study	Aspirin n/N (%)	Placebo n/N	Relative Risk	P-value	95% CI
BDT	89/3429 (2.60)	47/1710 (2.75)	0.94	0.75	(0.67, 1.34)
HOT*	14/9399 (0.15)	14/9391 (0.15)	1.00	1.00	(0.48, 2.10)
PHS	10/11037 (0.09)	26/11034 (0.24)	0.38	0.008	(0.19, 0.80)
PPP*	4/2226 (0.18)	6/2269 (0.26)	0.68	0.55	(0.19, 2.40)
TPT	60/2545 (2.36)	53/2540 (2.09)	1.13	0.51	(0.78, 1.63)
Total**	177/28636 (0.62)	146/26944 (0.54)	0.91	0.40	(0.73, 1.14)
Total (-PHS)**	167/17599 (0.95)	120/15910 (0.75)	1.01	0.93	(0.80, 1.28)

*Silent MIs included. **The relative risk, post-hoc nominal p-value and 95% CI are computed using Mantel-Haenszel method.

Tables 12, 13 and 14 summarize the results for all, nonfatal and fatal strokes. The relative risks were around 1 among the studies, there was no suggestion of potential benefit with aspirin in reducing the risk of stroke. In fact, it is disturbing that the incidence rates of fatal stroke were higher for aspirin in 4 out of the 5 studies, including the two largest studies (PHS and HOT). The overall relative risk was 1.05 when all studies were combined (95% CI 0.91-1.21).

Table 12. All Stroke in the 5 Studies

Study	Aspirin n/N (%)	Placebo n/N	Relative Risk	P-value	95% CI
BDT	91/3429 (2.65)	39/1710 (2.28)	1.16	0.42	(0.80, 1.69)
HOT	146/9399 (1.55)	148/9391 (1.58)	0.99	0.90	(0.79, 1.24)
PHS	119/11037 (1.08)	98/11034 (0.89)	1.21	0.15	(0.93, 1.58)
PPP	16/2226 (0.72)	24/2269 (1.06)	0.68	0.23	(0.36, 1.28)
TPT	47/2545 (1.85)	48/2540 (1.89)	0.98	0.91	(0.66, 1.46)
Total*	419/28636 (1.46)	357/26944 (1.32)	1.05	0.50	(0.91, 1.21)

*The relative risk, post-hoc nominal p-value and 95% CI are computed using Mantel-Haenszel method.

Table 13. Nonfatal Stroke in the 5 Studies

Study	Aspirin n/N (%)	Placebo n/N	Relative Risk	P-value	95% CI
BDT	61/3429 (1.78)	27/1710 (1.58)	1.13	0.60	(0.72, 1.77)
HOT	120/9399 (1.28)	127/9391 (1.35)	0.94	0.65	(0.74, 1.21)
PHS	110/11037 (1.00)	92/11034 (0.83)	1.20	0.20	(0.91, 1.57)
PPP	15/2226 (0.67)	18/2269 (0.79)	0.85	0.64	(0.43, 1.68)
TPT	33/2545 (1.30)	42/2540 (1.65)	0.78	0.29	(0.50, 1.23)
Total *	339/28636 (1.18)	306/26944 (1.14)	1.01	0.88	(0.87, 1.18)

*The relative risk, post-hoc nominal p-value and 95% CI are computed using Mantel-Haenszel method.

Table 14. Fatal Stroke in the 5 Studies

Study	Aspirin n/N (%)	Placebo n/N	Relative Risk	P-value	95% CI
BDT	30/3429 (0.87)	12/1710 (0.70)	1.25	0.52	(0.64, 2.43)
HOT	26/9399 (0.28)	21/9391 (0.22)	1.24	0.47	(0.70, 2.20)
PHS	9/11037 (0.08)	6/11034 (0.05)	1.50	0.44	(0.53, 4.21)
PPP	1/2226 (0.04)	6/2269 (0.26)	0.17	0.06	(0.02, 1.41)
TPT	14/2545 (0.55)	6/2540 (0.24)	2.33	0.07	(0.90, 6.05)
Total*	80/28636 (0.28)	51/26944 (0.19)	1.27	0.18	(0.89, 1.81)

*The relative risk, post-hoc nominal p-value and 95% CI are computed using Mantel-Haenszel method.

There was suspicion that the effect of aspirin in females may be different. Table 16 presents the analysis results of nonfatal MI and all MI for female subjects in the HOT study. The results of fatal MI were not reported since the number of events was too small. It can be seen that aspirin did not appear to have any effect on the female patients in reducing the risk of MI.

Table 15. Subgroup Analysis of All and Nonfatal MI in Female subjects (HOT)

Variable	Treatment group	Number of events (N)	Events/1000 patients years	P-value	Relative risk (95% CI)
All MIs	Aspirin	59 (4437)	3.5	0.78	0.95 (0.67-1.36)
	Placebo	62 (4446)	3.7		
Nonfatal MIs	Aspirin	51 (4437)	3.03	0.50	0.88 (0.60-1.28)
	Placebo	58 (4446)	3.45		

Source: Reviewer's analysis

For any important vascular event (combined endpoint of vascular death, nonfatal MI or nonfatal stroke) and vascular death, the results (Table 17) from this reviewer were very similar to the Sponsor's results (Table 7).

Table 16. Any Important Vascular Event and Vascular Death in the 5 Studies

Study	Aspirin			Control		
	Any Important Vascular Event	Vascular Death	Total N	Any Important Vascular Event	Vascular Death	Total N
PHS	307	81	11037	370	83	11034
BDT	289	148	3429	147	79	1710
TPT	211	101	2545	250	81	2540
HOT	315	133	9399	368	140	9391
PPP	45	17	2226	64	31	2269
Total	1167	480	28636	1199	414	26944
RR	0.86	0.98				
95% CI	0.79-0.93	0.86-1.11				

Source: Reviewer's analysis.

2.3.2.3 Reviewer's Conclusion

Having failed statistical significance on the primary endpoint, the PHS gave a very small p-value for nonfatal MI – one of the secondary endpoints. This result at best suggested that aspirin might have a potential benefit in reducing the risk of nonfatal MI in patients with cardiovascular risk. However, the PHS showed that some of the study patients had a prior MI and aspirin is already known to reduce the risk of recurrent MI in such patients.

The HOT also failed on the primary endpoint that should have been considered, that is, including silent MI. Only excluding silent MI could make the study achieve borderline significance on the primary endpoint and nonfatal MI. That is, if silent MI was included, the HOT study failed to confirm the potential benefit. No other study was able to confirm that either, and no study excluded the patients with a prior MI in the study populations.

For reasons and the observations given in Section 2.3.2.2, the results of the post-hoc meta-analyses combining all five studies or the Sponsor's meta-analysis of four studies are very difficult to interpret. They at best suggest that potential benefit with aspirin in reducing 1st nonfatal MI. A randomized clinical trial would be needed to confirm the benefit.

3 Reference

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