

October 3, 2005

0048 5 OCT -5 AIO :37

Division of Dockets Management  
Food and Drug Administration  
5630 Fishers Lane  
Room 1061 (HFA-305)  
Rockville, Maryland 20852

**Re: Docket 77N-0094**

**Aspirin Primary Prevention Professional Labeling (CP16) – Summary of Information Supporting Petition**

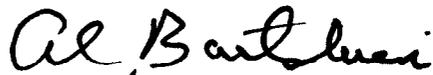
Dear Dr. Stockbridge:

Reference is made to Bayer HealthCare, Consumer Care Division's (Bayer) Citizen Petition submitted on 2/11/03 for the use of aspirin in the primary prevention of myocardial infarction (MI) in those at moderate or greater risk of a cardiovascular event. Based on my keen interest in the ongoing discussion of the use of aspirin for the primary prevention of cardiovascular events, my colleagues and I wish to submit a recent analysis using the data from the six primary prevention trials

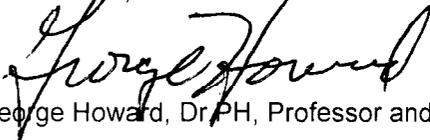
Attached is a brief summary overview analysis of these trials. We have learned from this meta analysis that aspirin appears to be a significant player in the reduction in the incidence of CHD events and non fatal myocardial infarction. The evidence is rather striking from these six trials. The attached report is just a short form of a full length manuscript that we are currently writing and will submit once it is completed. However, sufficient information is given in this summary to indicate we have considered all the key elements of a meta analysis and we look forward to presenting a more detailed publication.

Thank you for your consideration.

Sincerely,



Al Bartolucci, Ph.D. Professor



George Howard, Dr. PH, Professor and Chair

Department of Biostatistics  
Ryals Building, Room 327P  
School of Public Health  
University of Alabama at Birmingham  
1665 University Boulevard  
Birmingham, Alabama 35294-0022

Tel: 205-934-4905

Fax: 205-975-2540

327 Ryals Public Health Building  
1665 University Boulevard  
205 934.4905  
Fax 205 975 2540

The University of  
Alabama at Birmingham  
Mailing Address  
RPHB 327  
1530 3RD AVE S  
BIRMINGHAM AL 35294-0022

77N-0094

SUP 57

**Meta Analysis of Data From The Six  
Primary Prevention Trials of Cardiovascular Events  
Using Aspirin**

**Al Bartolucci, Ph.D.  
George Howard, DrPH**

## INTRODUCTION

Aspirin is an antiplatelet agent that inhibits platelet thromboxane A<sub>2</sub> production and has been shown to be effective for the primary and secondary prevention of atherothrombotic disease.<sup>1,2,3</sup>

With the recent completion of the Women's Health Study<sup>4</sup> (WHS) there are six trials (Physicians' Health Study<sup>5</sup>(PHS), British Doctors Trial<sup>6</sup> (BDT), Hypertension Optimal Treatment Trial<sup>7</sup> (HOT), Primary Prevention Project<sup>8</sup> (PPP), Thrombosis Prevention Trial<sup>9</sup> (TPT), WHS<sup>4</sup>) that have addressed the question of the benefits of aspirin in the primary prevention of cardiovascular events. Meta analyses<sup>2,3</sup> of the first five trials demonstrate a positive outcome for total coronary heart disease (CHD) events and nonfatal myocardial infarctions (MI) but not for cardiovascular (CV) death, total stroke or all cause mortality. The aim of the present analysis was to add data from WHS<sup>4</sup> in order to better understand the meta analytical contribution of all six trials.

## METHODS

### Data

The US Preventive Services Task Force (USPSTF)<sup>3</sup> has recently provided a thorough collection of the data from the first five primary prevention trials (PHS, BDT, HOT, PPP, TPT,) and serves as the key source of data. The methods for data collection have been described.<sup>3</sup> Additionally, the data from the primary publication of the cardiovascular results of the WHS were included.<sup>4</sup>

## Outcomes

- 1) CHD events –nonfatal and fatal MI as well as death due to coronary heart disease.
- 2) Cardiovascular death – death related to coronary heart disease or stroke
- 3) Fatal CHD –death as a result of coronary heart disease
- 4) Nonfatal MI – confirmed MI that did not result in death
- 5) Stroke – ischemic or hemorrhagic stroke that may or may not have resulted in death
- 6) All cause mortality – death related to any cause

## Data analysis

The data provided from the USPSTF analysis<sup>3</sup> for each individual trial and data from the WHS publication<sup>4</sup> were pooled for analysis. This is the traditional overview analysis of the major endpoints of the study not making use at this time of any covariate adjustment. We have not currently performed analyses for bleeding events. For each endpoint described above, a meta-analysis was performed for the comparison of aspirin to placebo/control. A summary odds ratio with 95 % confidence intervals was calculated. The odds ratio is most appropriate for this retrospective look at the data since we are considering achievement versus non achievement of the endpoint of interest. Calculation of the overall effect combining the six studies was done using the Mantel -Haenszel (MH) chi square statistic on one degree of freedom. This test does not assume that patients or subjects on one study can be directly compared to patients on another study. It does not assume that any treatment effects are similar in different studies. It does not assume homogeneity, but does take into account heterogeneity. We used both a fixed effect and a random effect model (Meta Analysis, Biostat, Engelwood, NJ). The results as summarized in the next section were the same for both fixed and random models. Heterogeneity was calculated

using the Chi square test with  $n-1$  degrees of freedom, where  $n$  represented the number of studies contributing to the meta-analysis.

Forest plots were used to assess heterogeneity in a graphical presentation. The purpose being that if significant heterogeneity (defined as a  $p$ -value  $< 0.01$ ) is noted then the Forest Plot allows one to assess this by considering the direction of the results. That is to say that some studies may display results going in different directions i.e. treatment superior to control in some studies contributing to the meta analysis or control superior to treatment in others or if the direction is the same for most or all of the studies then there may be differing degrees of the magnitude of this similar direction across the studies. We also used a weighting factor in our results which depends in part on the size of the study which in turn affects the inverse variance formula which the MH procedure uses for calculation of heterogeneity. The random effects model also helps to account further for the heterogeneity across the studies or between study variation as well as within study variation or patient selection. However, given our summary data the within study variation is not easily assessed.

## **RESULTS**

Among the trials in the analysis, there were 47293 patients treated with aspirin and 45632 with placebo/control. The characteristics of these clinical trials are provided in Table 1.

**Table 1**

Variable	BDT	PHS	TPT	HOT	PPP	WHS
Year	1988	1989	1998	1998	2001	2005
Duration of therapy, †	5.8 y	5 y	6.8 y	3.8 y	3.6 y	10.1 y
Patients (women), n	5139 (0)	22 071 (0)	2540 (0)	18 790 (8883)	4495 (2583)	(39876)
ASA therapy dose (N)	500 mg/d 300 mg/d if later requested (3429)	325 mg qod  (11 037)	75 mg/d (cont. rel.) (1268)	75 mg/d  (9399)	100 mg/d  (2226)	100 mg qod  (19934)
Control (N)	No placebo (1710)	Placebo (11 034)	Placebo (1272)	Placebo (9391)	No placebo (2231)	Placebo (19942)
Additional therapies	None	β-Carotene (50% of patients)	Warfarin‡	Felodipine with or without ACE inhibitor or β-blocker	Vitamin E	Vitamin E
Subjects	Healthy males	Healthy males	Men at high risk for CHD	Men and women with DBP 100-115 mm Hg	Men and women with >1 risk factors for CHD	Healthy females
Age	<60 y (46.9%); 60-69y (39.3%); 70-79 y (13.9%)	Mean, 53 y (range, 40-84 y)	Mean, 57.5 y (range, 45-69 y)	Mean, 61.5 y (range, 50-80 y)	<60 y (29%); 60-69 y (45%); 70-79 y (24%)	45-64y (60.2%); 55-64y (29.5%); ≥65y (10.3%)

BDT: British Doctors' Trial; HOT: Hypertension Optimal Treatment Trial; PHS: Physicians' Health Study; PPP: Primary Prevention Project; TPT: Thrombosis Prevention Trial; WHS: Women's Health Study † Values given are means except for the TPT value, which is the median ‡ Data from patients who received warfarin are not included in this table.

### Meta-analyses: Aspirin versus Placebo/Control

Meta-analyses of all six predefined outcomes and the combined effect of aspirin on these outcomes are shown in table 2 and graphically in Figures 1-6.

**Table 2**

<b>Endpoint</b>	<b>OR</b>	<b>p-value for OR</b>	<b>p-value for test of Heterogeneity</b>
Stroke	0.945	0.336	0.116
CHD	0.780	0.001	0.003
CHD Mortality	0.893	0.293	0.603
Non Fatal CHD	0.755	0.001	0.004
All Cause Mortality	0.935	0.071	0.893
CV events	0.852	0.001	0.250

Note that all odds ratios are less than one. The odds ratio is defined as the ratio of odds of the event (stroke, CHD, CHD mortality, etc.) versus not having the event in aspirin versus placebo. The odds is obviously less in aspirin than in placebo. It is significantly less ( $p < 0.01$ ) for CHD, non fatal CHD and CV events, which is a composite of CV death, MI or Stroke. We also note that there is significant heterogeneity ( $p < 0.01$ ) for several of the endpoints seen in Table 2. This reflects the fact that the studies contributing to that endpoint i.e.: CHD and non fatal CHD had treatment effects that varied sufficiently across studies. In other words, some studies (not shown in Table 2) had confidence intervals on the odds ratio that contained 1.0 indicating no significant difference of aspirin versus placebo and other studies did not contain the value 1.0 indicating a significant difference between aspirin and placebo. This will be detailed in a full manuscript of the results. The point being that the overall difference between aspirin and placebo as reflected in this meta analysis is not affected by significant heterogeneity since we obtained similar results using the random effects model which accounts for the randomness of the effects across the studies. Also note in Figures 1 to 6 the summary diamond at the bottom of each Forest plot is to the left of the vertical line

labeled "1.0" indicating graphically the advantage of aspirin over placebo. The Forest plot is a graphical representation of the odds ratios indicated by the circles and their 95% confidence intervals given by the horizontal lines through the circles. The horizontal vertices on the summary diamonds represent the 95% confidence interval for the summary odds ratio for the six studies.

## **DISCUSSION**

Patients without any apparent history of cardiovascular disease were enrolled in the six large primary prevention trials and our systematic analysis of the outcomes from these trials suggests that aspirin reduces the incidence of CHD events, nonfatal myocardial infarction and cardiovascular events defined as a composite of CV deaths, MI and stroke. However, aspirin had no significant effect on stroke, fatal CHD or all-cause mortality. The issue as to whether there is an overall benefit to aspirin therapy in patients at low to moderate CV risk has been discussed elsewhere and is beyond the scope of this brief communication.<sup>10</sup> It is evident that aspirin is beneficial for patients who have had previous diagnosis of CVD and is probably beneficial to all patients at high risk for developing CHD based on an appropriate assessment of known risk factors.

We conclude based, on the results of our meta analysis, that aspirin appears to significantly reduce risk for total CHD events, nonfatal myocardial infarctions and a composite of MIs, strokes and CV deaths.

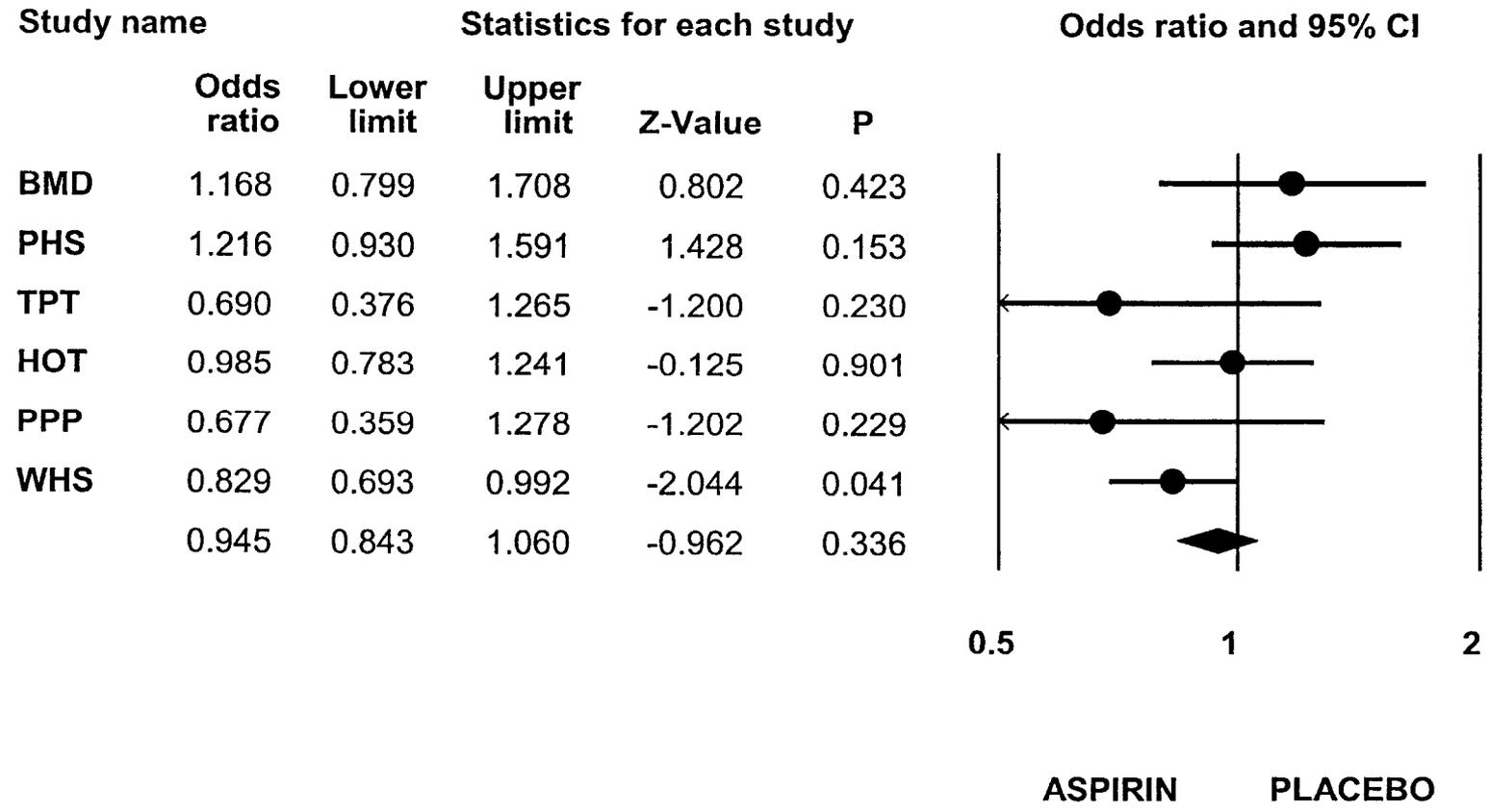
There are two things to note with this analysis. First of all the PHS and WHS studies are larger than the other studies. Thus, the meta analysis accommodates for this difference by assigning them greater weight than the other studies because of their larger sample size. This makes sense as one does not want smaller studies with less information to be weighted the same as larger studies with more information. The weighting factor in our case is sample size. However, weighting can also take into account other information in studies such as length of follow up, the detail of patient characteristics, information on entry and eligibility criteria etc. This kind of information may vary across studies so if available will be scored or weighted differently in each study. We also note that we have significant heterogeneity ( $p < 0.01$ ) for some of the endpoints seen in Table 2 and as we stated above in the Results section the overall difference between aspirin and placebo as reflected in this meta analysis is not affected by significant heterogeneity since we obtained similar results using the random effects model which accounts for the randomness of the effects across the studies.

## REFERENCES

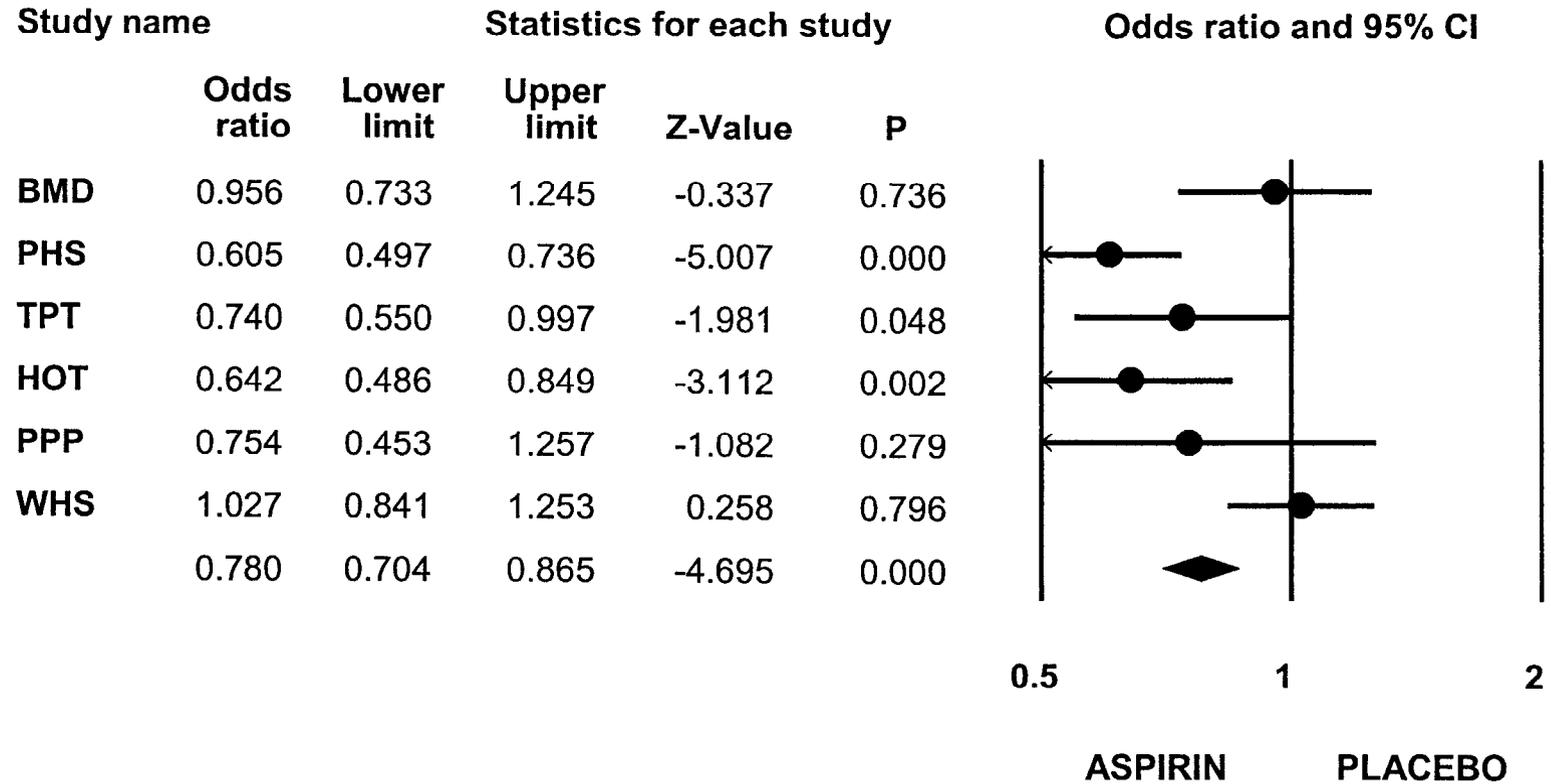
1. Antithrombotic Trialists' Collaboration. *BMJ* 2002;324:71-86.
2. Eidelman RS, Hebert PR, Weisman SM, Hennekens CH. An Update on Aspirin in the Primary Prevention of Cardiovascular Disease. *Arch Intern Med* 2003;163:2006-2010.
3. Hayden et al. Aspirin for the Primary Prevention of Cardiovascular Disease Events: A summary of the evidence. *Ann Intern Med.* 2002;136(2):161-172.
4. Ridker PM, Cook NR, Lee IM, Gordon D, Gaziano JM, Manson JE, Hennekens CH, Buring JE. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med* 2005;352:1293-1304.
5. Final report on the aspirin component of the ongoing Physicians' Health Study. Steering Committee of the Physicians' Health Study Research Group. *N Engl J Med.* 1989;321:129-135.
6. Peto R, Gray R, Collins R, et al. Randomised trial of prophylactic daily aspirin in British male doctors. *Br Med J (Clin Res Ed).* 1988;296(6618):313-316.
7. Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet.* 1998;351(9118):1755-1762.
8. Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general practice. Collaborative Group of the Primary Prevention Project. *Lancet.* 2001;357:89-95.
9. Thrombosis prevention trial: randomised trial of low intensity oral anticoagulation with warfarin and low dose aspirin in the primary prevention of ischemic heart disease in men at increased risk. The Medical Research Council's General Practice Research Framework. *Lancet.* 1998;351:233-241.
10. US Preventive Services Task Force. Aspirin for the Primary Prevention of Cardiovascular Events: Recommendation and Rationale. *Ann Intern Med.* 2002;136:157-160.

# Figure 1

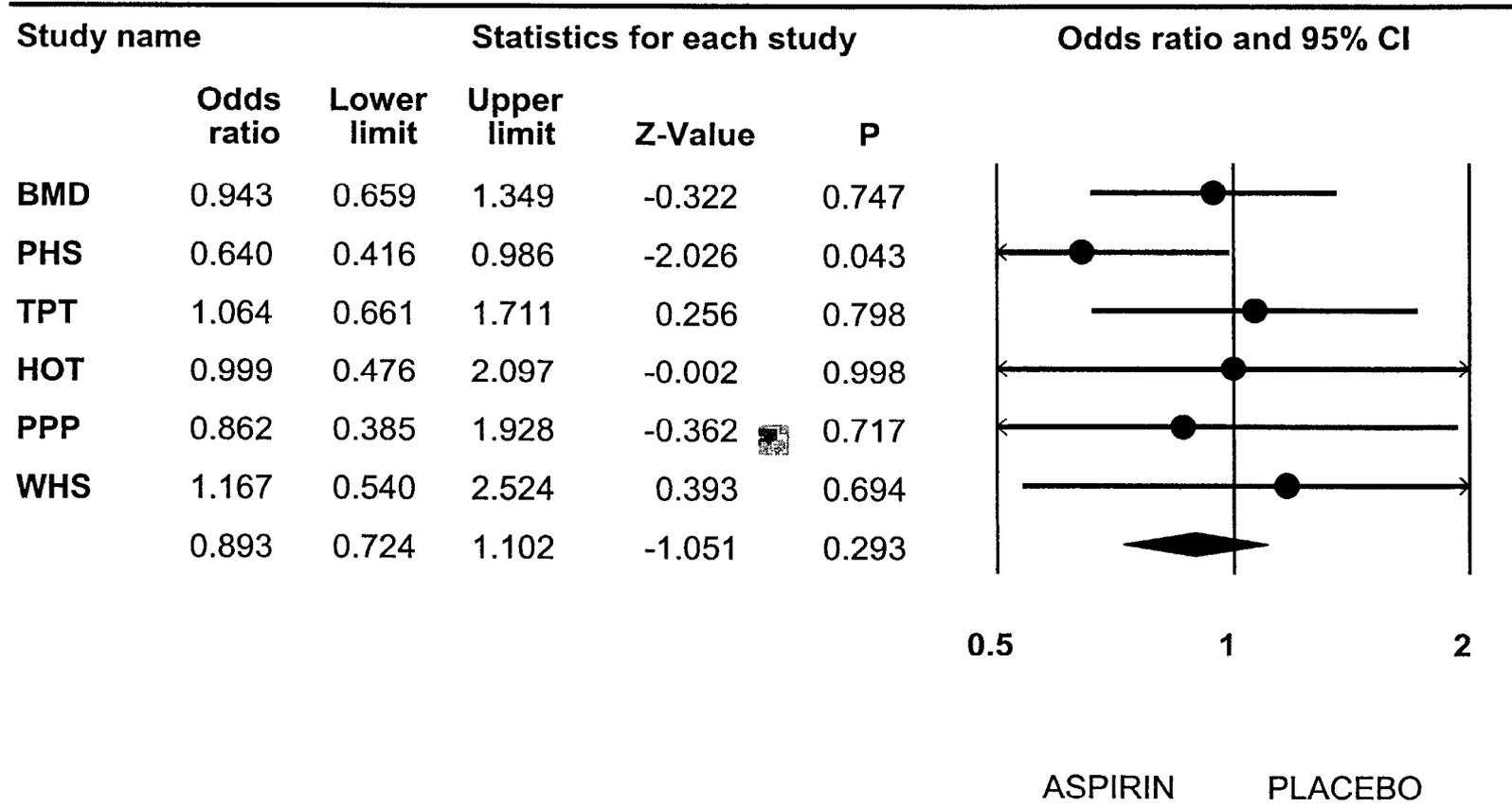
## Meta Analysis of Six Primary Prevention Trials (STROKE)



**Figure 2**  
**Meta Analysis of Six Primary Prevention Trials (Total CHD)**

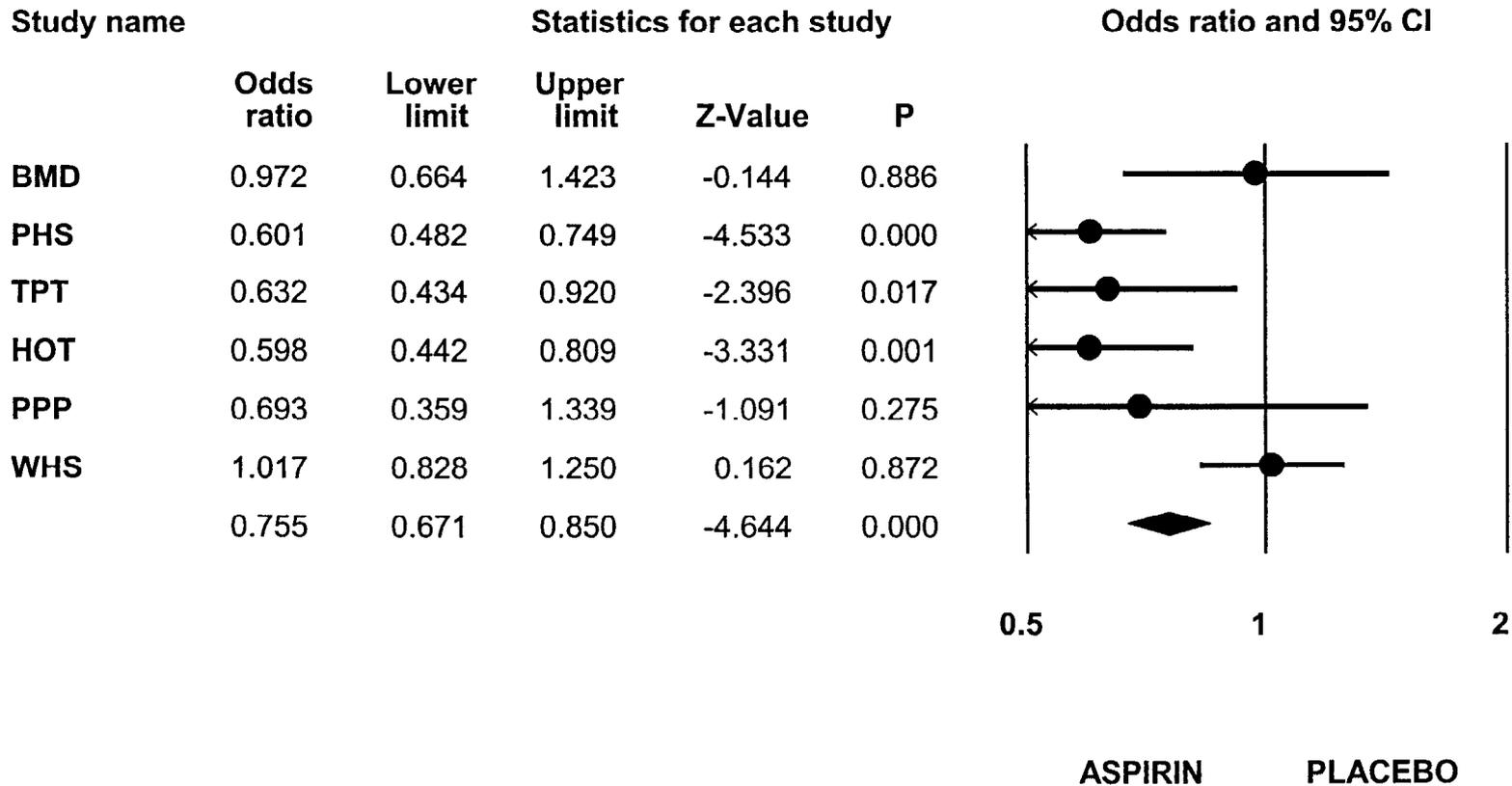


**Figure 3**  
**Meta Analysis of Six Primary Prevention Trials**  
**(CHD Mortality)**



## Figure 4

### Meta Analysis of Six Primary Prevention Trials (Non Fatal CHD Events)



## Figure 5

### Meta Analysis of Six Primary Prevention Trials (All Cause Mortality)

Study name

Statistics for each study

Odds ratio and 95% CI

	Odds ratio	Lower limit	Upper limit	Z-Value	P
<b>BMD</b>	0.882	0.717	1.087	-1.177	0.239
<b>PHS</b>	0.955	0.791	1.152	-0.482	0.630
<b>TPT</b>	1.033	0.785	1.360	0.235	0.814
<b>HOT</b>	0.928	0.788	1.094	-0.889	0.374
<b>PPP</b>	0.805	0.574	1.129	-1.257	0.209
<b>WHS</b>	0.947	0.846	1.060	-0.941	0.347
	0.935	0.870	1.006	-1.806	0.071

