Meta-Analysis of Multiple Primary Prevention Trials of Cardiovascular Events Using *Aspirin*

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Several meta-analyses have focused on determination of the effectiveness of aspirin (acetylsalicylic acid) in primary prevention of cardiovascular (CV) events. Despite these data, the role of aspirin in primary prevention continues to be investigated. Nine randomized trials have evaluated the benefits of aspirin for the primary prevention of CV events: the British Doctors' Trial (BMD), the Physicians' Health Study (PHS), the Thrombosis Prevention Trial (TPT), the Hypertension Optimal Treatment (HOT) study, the Primary Prevention Project (PPP), the Women's Health Study (WHS), the Aspirin for Asymptomatic Atherosclerosis Trial (AAAT), the Prevention of Progression of Arterial Disease and Diabetes (POPADAD) trial, and the Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) trial. The combined sample consists of about 90,000 subjects divided approximately evenly between those taking aspirin and subjects not taking aspirin or taking placebo. A meta-analysis of these 9 trials assessed 6 CV end points: total coronary heart disease, nonfatal myocardial infarction (MI), total CV events, stroke, CV mortality, and all-cause mortality. No covariate adjustment was performed, and appropriate tests for treatment effect, heterogeneity, and study size bias were applied. The meta-analysis suggested superiority of aspirin for total CV events and nonfatal MI, ($p < 0.05$ for each), with nonsignificant results for decreased risk for stroke, CV mortality, and all-cause mortality. There was no evidence of a statistical bias ($p > 0.05$). In conclusion, aspirin decreased the risk for CV events and nonfatal MI in this large sample. Thus, primary prevention with aspirin decreased the risk for total CV events and nonfatal MI, but there were no significant differences in the incidences of stroke, CV mortality, all-cause mortality and total coronary heart disease. **(Am J Cardiol 2011;107:1796–1801)**

The aim of the present analysis was to examine the more recent trials that have been published since Bartolucci and Howard[1] and add data from those studies to enlarge the sample and thus the power and precision. By adding these studies, it may be increasingly possible to detect moderate, but potentially meaningful, differences that individual trials cannot detect. Added studies to our meta-analysis of the 6 primary prevention studies include the Aspirin for Asymptomatic Atherosclerosis Trial (AAAT),[2] the Prevention of Progression of Arterial Disease and Diabetes (POPADAD)[3] trial, and the Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD)[4] trial.

Methods

In this report, we present a meta-analysis of 9 primary prevention trials with aspirin, including the AAAT, POPADAD, and JPAD trials, added to the 6 trials included in the previous meta-analyses (the Antithrombotic Trialists' Collaboration [ATTC][5] and Bartolucci and Howard[1]). Features of the studies included in the 9 trial meta-analysis are listed in Table 1.

The United States Preventive Services Task Force[6] described the data collection and analysis from the first 5 primary prevention trials—the British Doctors' Trial (BMD), the Physicians' Health Study (PHS), the Thrombosis Prevention Trial (TPT), the Hypertension Optimal Treatment (HOT) study, the Primary Prevention Project (PPP)—and the addition of the new data from the Women's Health Study (WHS) was described by Bartolucci and Howard.[1] The new sources of data are from the AAAT, POPADAD, and JPAD trials.

Because aspirin may have a differential effect on different aspects of cardiovascular (CV) disease, outcomes were classified as follows: (1) total coronary heart disease (CHD) as nonfatal and fatal myocardial infarction (MI) and death due to CHD; (2) nonfatal MI as confirmed MI that did not result in death; (3) total CV events as a composite of CV death, MI, or stroke; (4) stroke as ischemic or hemorrhagic stroke that may or may not have resulted in death; (5) CV mortality as death related to CHD or stroke; and (6) all-cause mortality as death related to any cause. Where applicable (data available), we performed a meta-analysis and summary overview for each of these end points for the 9 study data sets. All 9 studies were screened for these outcomes.

Data from the United States Preventive Services Task Force for each patient trial and data from the WHS, AAAT, JPAD, and POPADAD were combined for analysis. For

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Table 1
Features of the trials included in the 9 study meta-analyses

Trial	6-Study* Meta-Analysis	AAAT	POPADAD	JPAD
Year	1998/2005	1998	2002	2002
Duration (years)	3.6–10.1	10	8	7
Men/women	33,171/51,342	954/2,336	563/713	1,387/1,152
Aspirin dose (mg/dl)	75–300; 100–325	100	100	81–100
Control	Placebo	Placebo	Placebo/antioxidant	Nonaspirin
Subjects	Healthy men/women, DBP 100–115 mm Hg	Men/women, low brachial index	Type 1 and 2 diabetes	Type 2 diabetes
Age (years)	45–80	≥50	Mean 60	Mean 64.5

* Details of the 6 individual primary prevention trials (WHS, BMD, PHS, HOT, PPP, and TPT) are given in Bartolucci and Howard.[1]
DBP = diastolic blood pressure.

Table 2
Statistical significance of cardiovascular end points in the primary prevention trials

Study	Total CHD	Nonfatal MI	CV Events	Stroke	CV Mortality	All-Cause Mortality
WHS				X		
BMD						
PHS	X	X	X		X	
HOT	X	X	X			
PPP						
TPT		X		X		
AAAT						
JPAD					X	X*
POPADAD						

* Coronary and cerebrovascular death only.
X = statistically significant advantage of aspirin versus placebo ($p < 0.05$).

Table 3
Meta-analysis of predefined end points for the 9 study meta-analysis

End Point	Odds Ratio	95% Confidence Interval	p Value	p Value for Heterogeneity
Total CHD	0.854	0.688–1.061	0.154	0.001
Nonfatal MI	0.813	0.667–0.992	0.042	0.004
Total CV events	0.865	0.804–0.930	0.001	0.387
Stroke	0.919	0.828–1.021	0.116	0.232
Cardiovascular mortality	0.956	0.799–1.143	0.619	0.233
All-cause mortality	0.945	0.881–1.014	0.115	0.867

each previously described end point, a meta-analysis was performed for the comparison of aspirin with placebo or control. A summary odds ratio with 95% confidence interval was calculated. The odds ratio is the appropriate effect size statistic for our 5 risk ratio outcomes noted in the previous paragraph. The odds ratio is the ratio of the odds of an event occurring in 1 group to the odds of it occurring in another group. The term is also used to refer to sample-based estimates of this ratio. Obviously, an odds ratio of 1 would indicate even odds or no difference between the 2 groups of aspirin and control with respect to the odds of an event such as MI. Calculation of the overall effect combining the 9 studies used the Mantel-Haenszel chi-square statistic with 1 degree of freedom. This test does not assume that patients in 1 study can be directly compared with those in another study, and it does not assume that any treatment effects are similar in different studies. It does not assume homogeneity but does take into account heterogeneity. Heterogeneity was calculated using the chi-square test with $n - 1$ degrees of freedom, where n represents the number of studies contributing to the meta-analysis. Forest plots were used to assess if there was significant heterogeneity (defined as $p < 0.01$) and allowed assessment by considering the direction of the results. A weighting factor was also used that depended in part on the size of the study, which in turn affected the inverse variance formula that the Mantel-Haenszel procedure uses to calculate heterogeneity. The random-effects model also helps further account for the heterogeneity across the studies, between-study variation, and within-study variation or patient selection. However, given the summary data, within-study variation is not easily assessed. The standard procedure for the assessment of small study effects (i.e., a trend for relatively smaller studies to show larger treatment effects) has been the use of funnel plots using Egger's test.[7,8] There has been considerable discussion regarding the properties of this test.[9–12] The technique of Macaskill et al[11] was used to adjust for this shortcoming (also see Harbord et al[13]).

Results

Among the 9 trials in the analysis, 50,868 subjects were treated with aspirin and 49,170 received placebo or control. Table 2 lists each study and indicates if statistical significance of aspirin versus placebo was reached when using the odds ratio for any of the end points or groups of end points. The combined effects of aspirin on these end points are listed in Table 3. In subjects treated with aspirin, there was significantly decreased risk for nonfatal MI ($p = 0.042$) and total CV events ($p = 0.001$). There was significant heterogeneity ($p \leq 0.01$) for several of the end points listed in Table 3 (e.g., for total CHD events and nonfatal MI). The data for nonfatal MI and total CV events are shown in Figures 1 and 2, respectively.

Figures 1 to 6 present different outcomes in the studies included in the current meta-analysis. They show that most studies have odds ratios <1, with an overall advantage of aspirin over placebo. We had the ability to reexamine our results with respect to previous risk for CHD in studies that

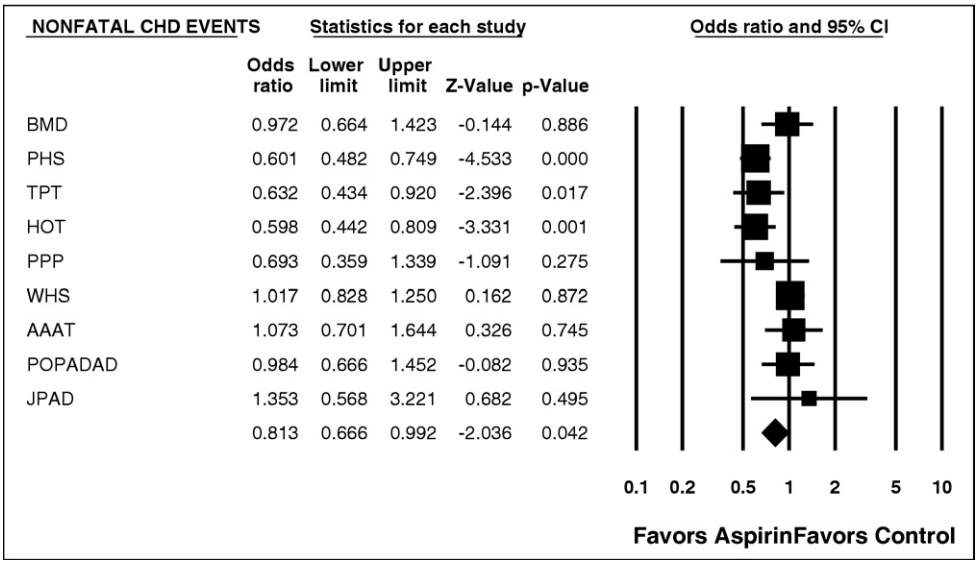

Figure 1. Forest plot of nonfatal CHD events. CI = confidence interval.

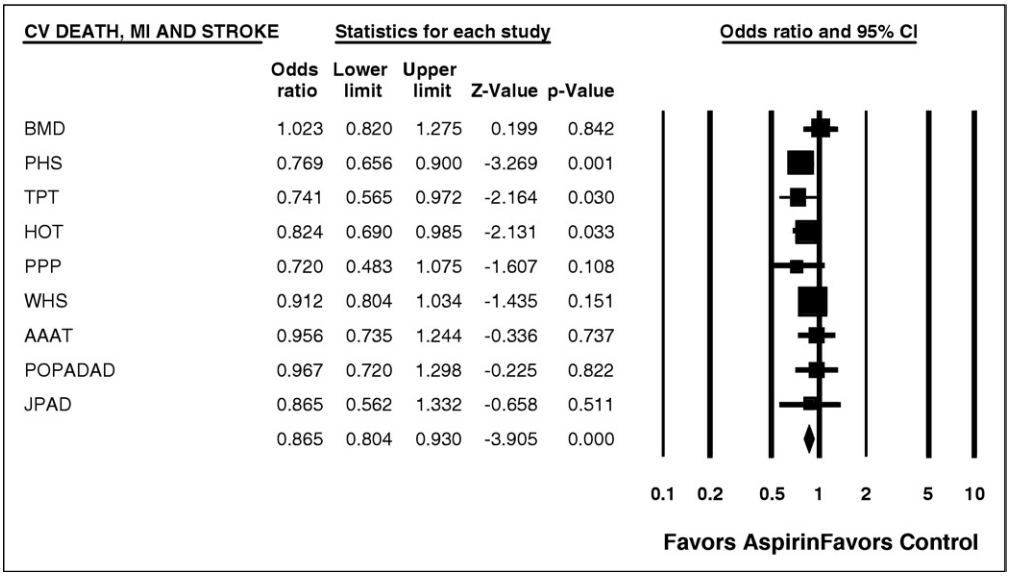

Figure 2. Forest plot of CV deaths, MI, and stroke. CI = confidence interval.

included TPT, PPP, AAAT, POPADAD, and JPAD, and we found no change in our results. The remainder of the studies showed no previous risk for CHD. The results were consistent with those listed in Table 3, all in favor of aspirin.

Discussion

It is evident that aspirin is beneficial for patients who have previously been diagnosed with CHD and is probably beneficial to all patients at high risk for developing CHD, on the basis of an appropriate assessment of known risk factors. However, the 3 most recent studies on the use of aspirin in primary prevention for the most part were statistically inconclusive.[2–4] Although all these studies were underpowered, there was a need to reassess the use of aspirin in this setting. We present a meta-analysis of all trials published to date assessing the effect of aspirin in primary CV prevention. We included the 2 trials conducted in patients with diabetes mellitus and no symptoms of CV disease (POPADAD and JPAD). Although patients with diabetes might represent a population different from those with high CV risk on the basis of the presence of classic risk factors alone, the studies clearly represent the primary prevention setting.

Systematic analysis of the outcomes from the 9 trials confirmed that aspirin decreases the incidence of nonfatal MI and CV events. However, aspirin had no statistically significant effect on CHD, stroke, CV mortality, and all-cause mortality, but was highly significant for overall CV events.

In the ATTC analysis,[5] antiplatelet therapy decreased the combined outcome of any serious vascular event by about 25%, nonfatal MI by about 33%, nonfatal stroke by 25%, and vascular mortality by about 16%. Our results are for the most part consistent with the ATTC's results. The ATTC

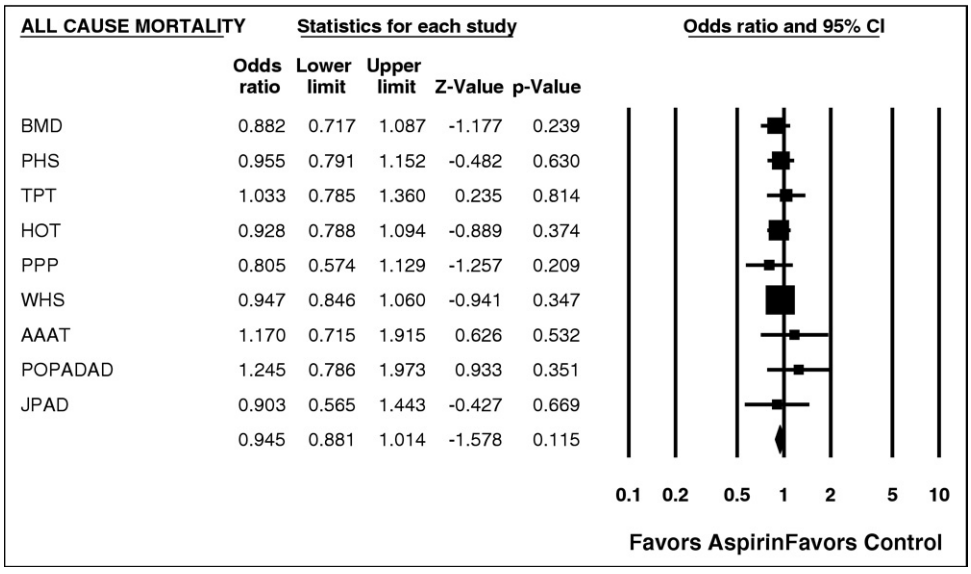

Figure 3. Forest plot of all-cause mortality. CI = confidence interval.

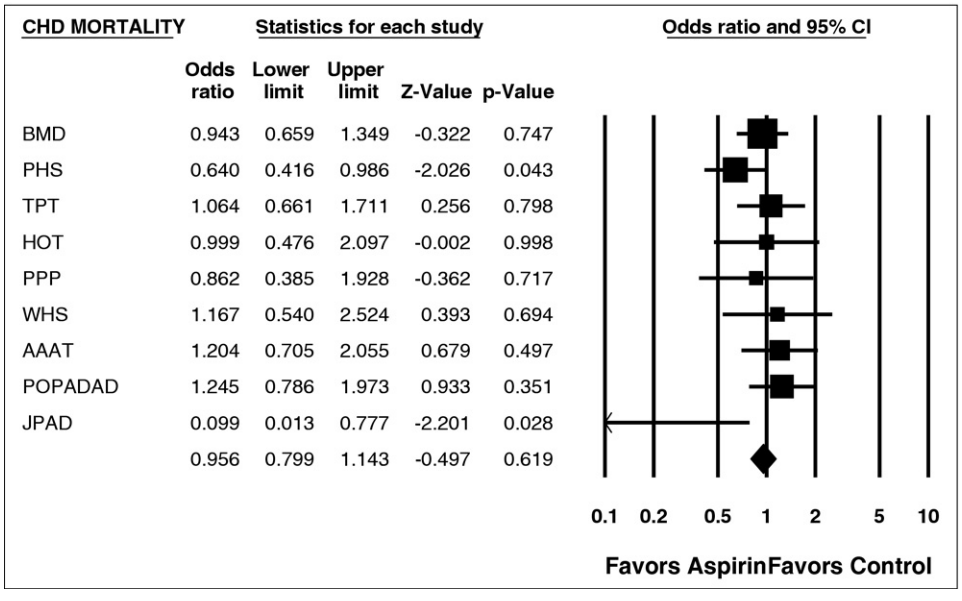

Figure 4. Forest plot of CHD mortality. CI = confidence interval.

caution that in primary prevention aspirin is of uncertain net value, because the reduction in occlusive events needs to be weighed against any increase in major bleeds. Bleeds or major bleeds were not our focus here, and we agree with the ATTC that gastrointestinal bleeds, strokes, and heart attacks may not be equivalent, as we examine these end points separately. See Table 4 for a summary of gastrointestinal bleeds across studies.

In our study, there was heterogeneity across studies for several outcomes. Possible sources of this heterogeneity include patient selection and randomization, baseline disease severity, management of intercurrent outcomes (such as bleeding, gastritis, and hypertension), and treatment strategies. However, the overall difference between aspirin and placebo, as shown in this meta-analysis, is not affected by significant heterogeneity, because similar results were obtained with the random-effects model, which accounts for the randomness of the effects across studies.

The HOT and WHS are relatively larger than the other studies, accounting for approximately 59% of the sample. Thus, the meta-analysis accommodates for this difference by assigning them greater weight (sample size) than the other studies. In addition, these 2 studies, when weighted accordingly in the assessment of study size bias, did not contribute significantly to any bias, as presented in Table 3. 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. This information may vary across studies and, if available, will be scored or weighted differently in each study.

A limitation of our study is that it is a meta-analysis of the results of published studies. Thus, we did not have the

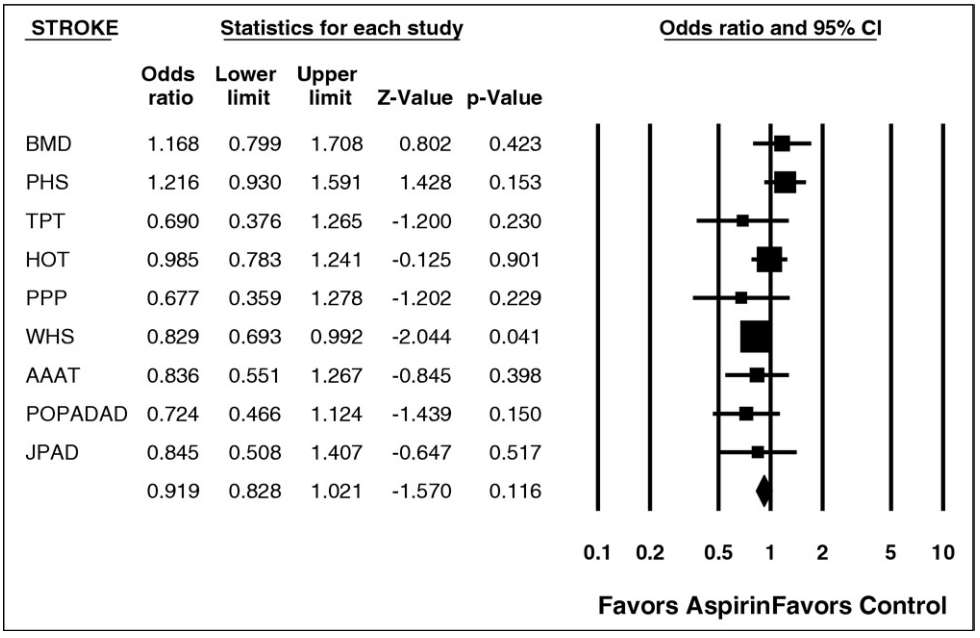

Figure 5. Forest plot of stroke events. CI = confidence interval.

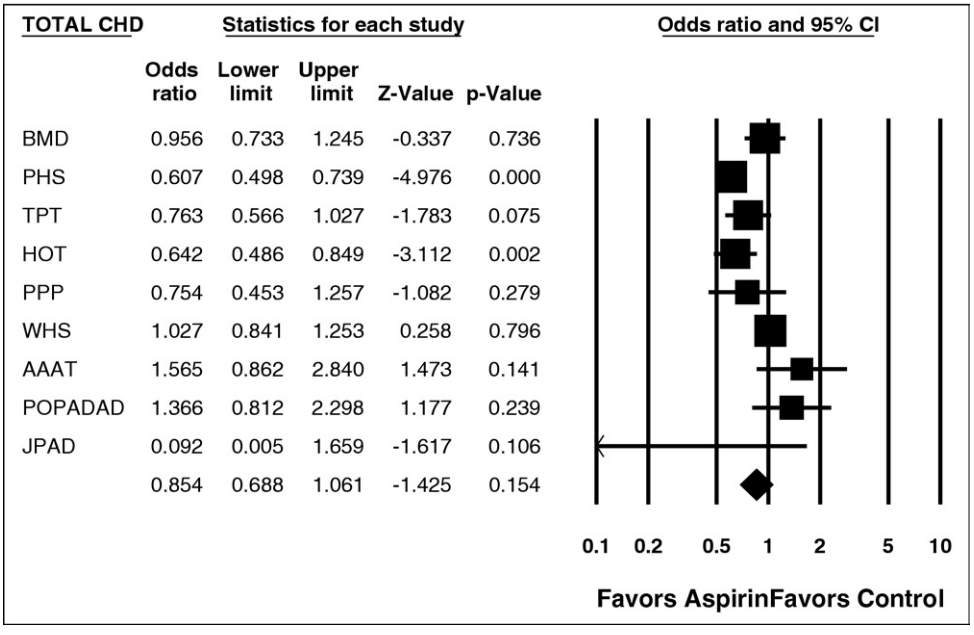

Figure 6. Forest plot of total CHD. CI = confidence interval.

Table 4
Gastrointestinal bleeding for the 9 study meta-analysis

Study	Aspirin	Control
WHS	4.5%	3.8%
BMD	0.3%	0.4%
PHS	4.0%	3.8%
HOT	0.8%	0.4%
PPP	0.8%	0.2%
TPT	1.4%	0.9%
AAAT	0.5%	0.5%
JPAD	0.8%	0.3%
POPADAD	4.4%	4.9%

ability to do thorough cross-study checks that can be done using the raw data. Furthermore, the overall size of our sample and the differing cohorts within each study lend convincing evidence to the advantage of aspirin over placebo or no aspirin for decreasing the risk for CV events in a range of patients. However, the benefits of primary prevention with aspirin must be considered in relation to the potential risks on a patient-by-patient basis.

1. Bartolucci AA, Howard G. Meta-analysis of data from the six primary prevention trials of cardiovascular events using aspirin. *Am J Cardiol* 2006;98:746–750.

2. Fowkes FGR, Price JF, Stewart MC, Butcher I, Leng GC, Pell AC, Sandercock PA, Fox KA, Lowe GD, Murray GD, for the Aspirin for Asymptomatic Atherosclerosis Trialists. Aspirin for prevention of cardiovascular events in a population screened for a low ankle brachial index. *JAMA* 2010;303:841–848.
3. Belch J, MacCuish A, Campbell I, Cobbe S, Taylor R, Prescott RL, Bancroft J, MacEwan S, Shepard J, Macfarlane P, Morris A, Jung R, Kelly C, Connacher A, Peden N, Jamieson A, Matthews D, Leese G, McKnight J, O'Brien I, Semple C, Petrie J, Gordon D, Pringle S, MacWalter R; Prevention of Progression of Arterial Disease and Diabetes Study Group; Diabetes Registry Group; Royal College of Physicians Edinburgh. The Prevention of Progression of Arterial Disease and Diabetes (POPADAD) trial: factorial randomized placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. *BMJ* 2008;337:a1840.
4. Ogawa H, Nakayama M, Morimoto T, Uemura S, Kanauchi M, Doi N, Jinnouchi H, Sugiyama S, Saito Y, for the Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) Trial Investigators. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. *JAMA* 2008;300:2134–2141.
5. Antithrombotic Trialists' Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomized clinical trials. *Lancet* 2009;373:1849–1860.
6. United States Preventive Services Task Force. Aspirin for the primary prevention of cardiovascular events: recommendation and rationale. *Ann Intern Med* 2002;136:157–160.
7. Egger M, Smith D, Schneider M, Minder C. Bias in meta-analysis detected by a simple graphical test. *BMJ* 1997;315:629–634.
8. Egger M, Juni P, Bartlett C, Sterne J. How important are comprehensive literature searches and the assessment of trial quality in systematic reviews? Empirical study. *Health Technol Assess* 2003;7:1–4.
9. Irwig L, Macaskill P, Berry G, Glasziou P. Bias in meta-analysis detected by a simple graphical test. Graphical test is itself biased. *BMJ* 1998;316:470.
10. Sterne J, Egger M, Smith D. Investigating and dealing with publication and other biases in meta-analysis. *BMJ* 2001;323:101–105.
11. Macaskill P, Walter S, Irwig L. A comparison of methods to detect publication bias in meta-analysis. *Stat Med* 2001;20:641–654.
12. Schwarzer G, Antes G, Shumacher M. Inflation of type I error rate in two statistical tests for the detection of publication bias in metaanalysis with binary outcomes. *Stat Med* 2002;21:2465–2477.
13. Harbord R, Egger M, Sterne J. A modified test for small study effects in meta-analysis of controlled trials with binary endpoints. *Stat Med* 2006;25:3443–3457.