REVIEW

Aspirin for the Primary Prevention of Cardiovascular Events in Women and Men

A Sex-Specific Meta-analysis of Randomized Controlled Trials

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Context Aspirin therapy reduces the risk of cardiovascular disease in adults who are at increased risk. However, it is unclear if women derive the same benefit as men.

Objective To determine if the benefits and risks of aspirin treatment in the primary prevention of cardiovascular disease vary by sex.

Data Sources and Study Selection MEDLINE and the Cochrane Central Register of Controlled Trials databases (1966 to March 2005), bibliographies of retrieved trials, and reports presented at major scientific meetings. Eligible studies were prospective, randomized controlled trials of aspirin therapy in participants without cardiovascular disease that reported data on myocardial infarction (MI), stroke, and cardiovascular mortality. Six trials with a total of 95 456 individuals were identified; 3 trials included only men, 1 included only women, and 2 included both sexes.

Data Extraction Studies were reviewed to determine the number of patients randomized, mean duration of follow-up, and end points (a composite of cardiovascular events [nonfatal MI, nonfatal stroke, and cardiovascular mortality], each of these individual components separately, and major bleeding).

Data Synthesis Among 51 342 women, there were 1285 major cardiovascular events: 625 strokes, 469 MIs, and 364 cardiovascular deaths. Aspirin therapy was associated with a significant 12% reduction in cardiovascular events (odds ratio [OR], 0.88; 95% confidence interval [CI], 0.79-0.99; $P=.03$) and a 17% reduction in stroke (OR, 0.83; 95% CI, 0.70-0.97; $P=.02$), which was a reflection of reduced rates of ischemic stroke (OR, 0.76; 95% CI, 0.63-0.93; $P=.008$). There was no significant effect on MI or cardiovascular mortality. Among 44 114 men, there were 2047 major cardiovascular events: 597 strokes, 1023 MIs, and 776 cardiovascular deaths. Aspirin therapy was associated with a significant 14% reduction in cardiovascular events (OR, 0.86; 95% CI, 0.78-0.94; $P=.01$) and a 32% reduction in MI (OR, 0.68; 95% CI, 0.54-0.86; $P=.001$). There was no significant effect on stroke or cardiovascular mortality. Aspirin treatment increased the risk of bleeding in women (OR, 1.68; 95% CI, 1.13-2.52; $P=.01$) and in men (OR, 1.72; 95% CI, 1.35-2.20; $P<.001$).

Conclusions For women and men, aspirin therapy reduced the risk of a composite of cardiovascular events due to its effect on reducing the risk of ischemic stroke in women and MI in men. Aspirin significantly increased the risk of bleeding to a similar degree among women and men.

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ALTHOUGH THE BENEFITS OF aspirin therapy for reducing the risk of myocardial infarction (MI), stroke, and vascular death among men and women with preexisting cardiovascular disease are well established,[1-3] the role of aspirin in primary prevention is less clear. An overview of 5 randomized trials investigating aspirin therapy for the primary prevention of vascular disease found a significant beneficial effect of aspirin therapy on the prevention of a first MI, but no significant effects on the risk of stroke or vascular death.[4]

Although women were included in only 2 of these studies and accounted for only 20% of the population studied, the US Preventive Services Task Force[5] and the American Heart Association[6] deemed aspirin therapy effective in decreasing the incidence of coronary heart disease in adults of both sexes who are at increased risk. Subsequently, guidelines from the American Heart Association on the primary prevention of cardiovascular disease in women recommended use of low-dose aspirin therapy in women whose 10-year risk of a first coronary event exceeds 20% and consideration

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of use in women whose 10-year risk is 10% to 20%.[7]

In actuality, because of the paucity of data, the effect of aspirin in the primary prevention of cardiovascular disease in women remains uncertain. As a result, the European Society of Cardiology has recommended low-dose aspirin for men at particularly high risk for coronary heart disease, but not for all persons at high risk.[8] The recent Women's Health Study, the first primary prevention trial of aspirin therapy specific to women,[9] demonstrated that aspirin decreased the risk of stroke without affecting the risk of MI or vascular death—an effect different from that found in studies that enrolled exclusively or predominantly men. Thus, a differential beneficial effect of aspirin therapy may exist between men and women.

To better understand the impact of sex on the response to aspirin, we performed a sex-specific meta-analysis of aspirin therapy for the primary prevention of cardiovascular events.

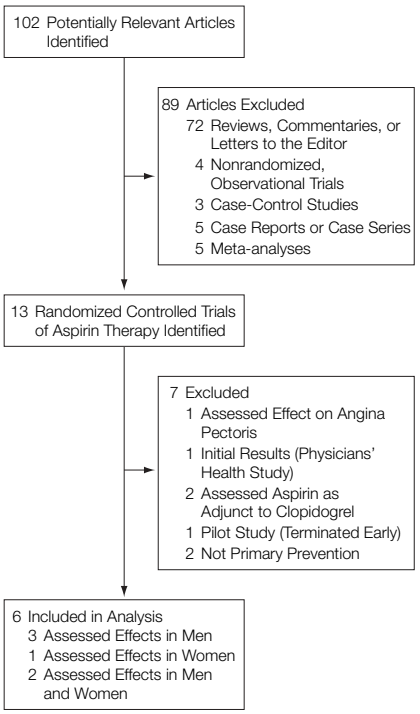
METHODS

The primary aim of this meta-analysis was to determine the effect of aspirin in the primary prevention of cardiovascular disease in women and men independently. A comprehensive MEDLINE database search using Ovid software (Ovid Technologies Inc, New York, NY) was performed to find human studies published in the English language between 1966 and March 2005 using the search terms *aspirin, primary prevention, myocardial infarction, stroke,* and *randomized controlled trials*, as well as combinations of these terms. The bibliographies of retrieved articles were searched for other relevant studies and major scientific meetings were monitored for the results of trials still under way at the time of the MEDLINE search. Data concerning study design, baseline patient characteristics, treatment, follow-up, and results were extracted from these reports. Additional data, when necessary, were derived from personal communication with trial investigators.

Study Selection

Trials that met the following criteria were included: (1) prospective, randomized, controlled, open, or blinded trials; (2) assignment of participants to aspirin treatment or a control group for the primary prevention of cardiovascular disease; and (3) data on cardiovascular death, MI, and stroke. Quality was assessed using criteria that were previously published[10,11] (adequate blinding of randomization, completeness of follow-up, and objectivity of outcome assessments). A total of 102 potentially eligible studies were identified and 89 were excluded because they were not randomized controlled trials (eg, review articles, editorials, letters to the editor, case reports, case-control studies, and meta-analyses). Of the randomized trials, 7 trials did not report end points of interest (eg, improvement in angina pectoris), used aspirin as an adjunct to clopidogrel, were not primary prevention, or included duplicate results and were excluded (FIGURE 1).

Figure 1. Flow Diagram of the Trial Selection Process



Clinical End Points

The clinical end point definitions were similar among the trials. Outcomes examined in the current overview were a composite end point of any major cardiovascular event (cardiovascular mortality, nonfatal MI, or nonfatal stroke), each of the individual components of the composite end point separately, all-cause mortality, and major bleeding. We also examined stroke subtypes (ischemic vs hemorrhagic) from data available in 5 studies. The Hypertension Optimal Treatment trial[12] did not record the type of stroke.

Statistical Analysis

All statistical analyses were performed using the Comprehensive MetaAnalysis program (Biostat, Englewood, NJ). Data were analyzed according to the intention-to-treat principle. The Cochrane Q statistic was calculated to assess heterogeneity among the trials. The Q statistic failed to indicate statistical heterogeneity for any end point. However, because the lack of heterogeneity does not necessarily imply homogeneity, a summary odds ratio (OR) was calculated using a random-effects model from the ORs and the 95% confidence intervals (CIs) for each end point in each study using Mantel-Haenszel methods. The statistical rationale for combining the data have been previously described.[13] The basic principle is that patients allocated to an intervention in a specific trial are only compared with those allocated to the control treatment in the same trial, avoiding direct comparisons of patients across different trials with different designs and lengths of follow-up. These methods provide for combination of information from multiple 2×2 tables, generating a summary OR and its 95% CI. The data were also analyzed using a random-effects model to generate relative risks and 95% CIs. These results did not qualitatively differ from the primary analysis. A P value of less than .05 was judged as statistically significant. To assess publication bias, we generated a funnel plot of the logarithm of effect size and compared it with the SE for each trial.

RESULTS

Search Results

We identified 6 randomized controlled trials[9,12,14-17] for inclusion. Three trials included only men,[14-16] 1 trial included only women,[9] and 2 trials included both sexes.[12,17] In total, 95 456 individuals were enrolled in the 6 trials, of which 51 342 were women.

Details of the included studies appear in TABLE 1. The weighted mean duration of follow-up was 6.4 years. Baseline characteristics of the individuals are presented in TABLE 2. All 6 studies included individuals without documented cardiovascular disease. Specifically, 3 trials[9,14,15] included apparently healthy health care professionals and 3 trials[12,16,17] included individuals with risk factors for cardiovascular disease.

Study Quality

Randomized treatment allocation sequences were generated in all 6 studies. Treatment in 4 of the studies[9,14,16,17] was randomly assigned according to a 2 × 2 factorial design. The Physicians' Health Study,[14] the Women's Health Study,[9] and the Primary Prevention Project[17] each had a vitamin E component, whereas the Thrombosis Prevention Trial[16] had a warfarin component. The Hypertension Optimal Treatment trial[12] assigned participants to a target blood pressure level and to an aspirin or placebo group in a 3 × 2 factorial design. Four studies[9,12,14,16] were placebo-controlled and double-blinded. The British Doctor's Trial[15] and the Primary Prevention Project[17] compared an aspirin group with an open-label control group. All studies randomized equal numbers of individuals to aspirin therapy and to placebo, except the British Doctor's Trial,[15] which used a 2:1 allocation ratio. Three of the trials[12,15,16] were partially or completely funded by pharmaceutical companies. An end points committee in 4 studies,[9,12,14,17] a physician in 1 study,[15] and a research nurse in 1 study[16] adjudicated outcomes in a blinded fashion. Dosage of aspirin ranged from 100 mg every other day to 500 mg daily. Follow-up ranged from 3.6 years to 10.1 years and was more than 95% complete in all trials. There was no evidence of publication bias.

Major Cardiovascular Events

A total of 1285 major cardiovascular events occurred among 51 342 women (FIGURE 2). Each trial reported a decreased risk of cardiovascular events among participants assigned to aspirin. Pooled results confirmed a statistically significant 12% reduction in the odds of cardiovascular events with aspirin therapy among women (OR, 0.88; 95% CI, 0.79-0.99; P=.03).

A total of 2047 major cardiovascular events occurred among 44 114 men. Aspirin therapy was associated with a statistically significant 14% reduction in the odds of cardiovascular events among men (OR, 0.86; 95% CI, 0.78-0.94; P=.01).

Table 1. Design of Trials Included in the Meta-analysis

Source	No. of Individuals	Description of Trial Participants	Female, %	Aspirin Dosage	Mean Follow-up, y
Physicians Health Study,[14] 1989	22 071	Apparently healthy male physicians	0	325 mg every other day	5
British Doctor's Trial,[15] 1988	5139	Apparently healthy male physicians	0	500 mg/d	6
Thrombosis Prevention Trial,[16] 1998	5085	Men at high risk for ischemic heart disease	0	75 mg/d	6.4
Hypertension Optimal Treatment trial,[12] 1998	18 790	Men and women with hypertension	47	75 mg/d	4
Primary Prevention Project,[17] 2001	4495	Men and women with ≥1 major cardiovascular risk factor	58	100 mg/d	3.6
Women's Health Study,[9] 2005	39 876	Apparently healthy female health care professionals	100	100 mg every other day	10.1

Table 2. Characteristics of Men and Women Included in Trials of Aspirin for the Primary Prevention of Cardiovascular Disease*

	Men Only			Hypertension Optimal Treatment		Primary Prevention Project		
	Physicians' Health Study (N = 22 071)	British Doctor's Trial (N = 5139)	Thrombosis Prevention Trial (N = 5085)	Men (n = 9907)	Women (n = 8883)	Men (n = 1912)	Women (n = 2583)	Women's Health Study (N = 39 876)
Age, mean (SD), y	NA	NA	57.3 (6.6)	60.8 (7.1)	62.3 (7.8)	64.0 (7.7)	64.7 (7.4)	54.6 (7.0)
BMI, mean (SD)	NA	NA	27.5 (3.8)	28.5 (NA)	28.4 (NA)	27.5 (3.8)	27.7 (5.2)	26.0 (5.1)
Smoker	2428 (11)	668 (13)	2100 (41)	2100 (21)	888 (10)	391 (21)	276 (11)	5224 (13)
Hypertension	1986 (9)	514 (10)	1322 (26)	9907 (100)	8883 (100)	1285 (67)	1780 (69)	10 328 (26)
SBP, mean (SD), mm Hg	NA	135.1 (0.41)†	139 (18)	NA	NA	144.3 (16.1)	145.7 (16.2)	NA
Cholesterol	NA	NA	325 (6)	585 (6)	551 (6)	599 (31)	1143 (44)	11 763 (29)
Diabetes	441 (2)	103 (2)	NA	773 (8)	728 (8)	355 (19)	387 (15)	1037 (3)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); NA, data not available; SBP, systolic blood pressure.
*Values are expressed as number (percentage) unless otherwise indicated.
†The value in parentheses is a SE.

Myocardial Infarction

Among 51 342 women, there were 469 MIs (Figure 2). The rate of MI was similar both among women receiving aspirin and women receiving control treatment/placebo (OR, 1.01; 95% CI, 0.84-1.21; *P*=.95).

Among 44 144 men, there were 1023 MIs. Aspirin therapy was associated with a statistically significant 32% reduction in the odds of MI among men (OR, 0.68; 95% CI, 0.54-0.86; *P*=.001).

Stroke

A total of 625 strokes occurred among the women (FIGURE 3). Aspirin therapy was associated with a significant 17% reduction in the odds of stroke (OR, 0.83; 95% CI, 0.70-0.97; *P*=.02). With respect to stroke subtypes in women, aspirin was associated with a significant 24% reduction in ischemic stroke (OR, 0.76; 95% CI, 0.63-0.93; *P*=.008) with no apparent effect on hemorrhagic stroke (OR, 1.07; 95% CI, 0.42-2.69; *P*=.89).

A total of 597 strokes occurred among the men. There was a nonsignificant increase in odds of stroke associated with aspirin (OR, 1.13; 95% CI, 0.96-1.33; *P*=.14). With respect to stroke subtypes (Figure 3) in men, aspirin had no significant effect on ischemic stroke (OR, 1.00; 95% CI, 0.72-1.41; *P*=.98) but was associated with a significant 69% increase in the odds of hemorrhagic stroke (OR, 1.69; 95% CI, 1.04-2.73; *P*=.03).

Cardiovascular and All-Cause Mortality

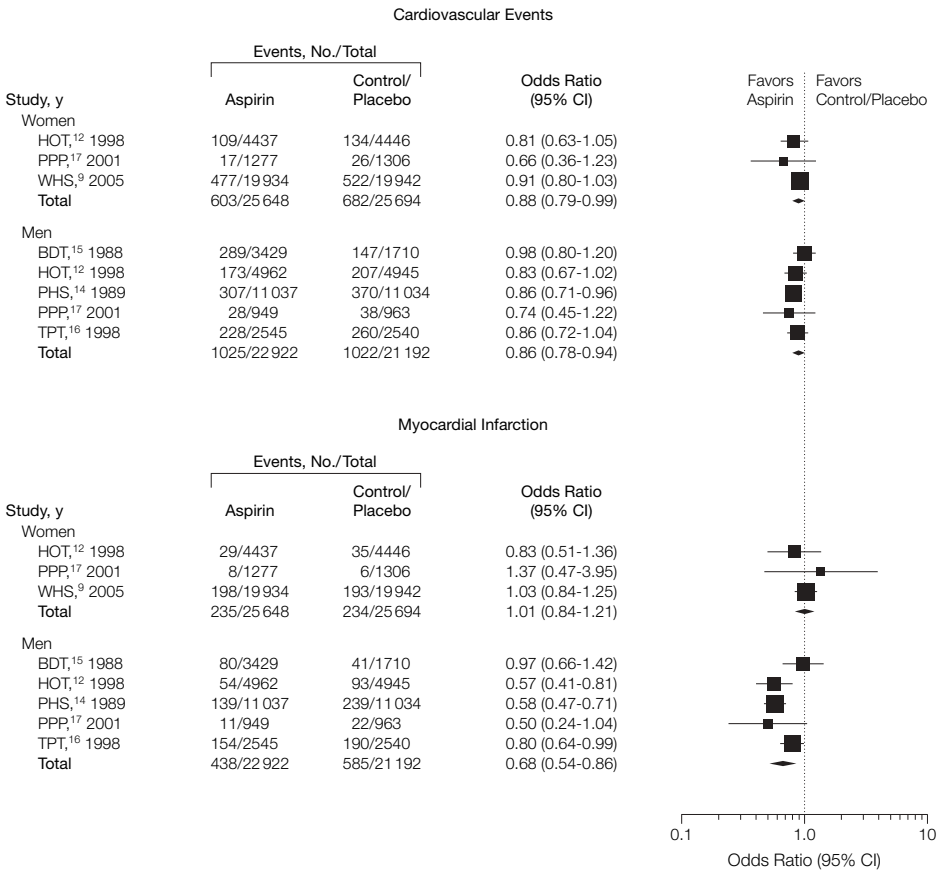
A total of 364 deaths from cardiovascular causes occurred among women while there were 776 cardiovascular deaths among men (FIGURE 4). No aspirin effect was noted among women (OR, 0.90; 95% CI, 0.64-1.28; *P*=.56) or men (OR, 0.99; 95% CI, 0.86-1.14; *P*=.87).

Death from any cause occurred in 1515 women and 1752 men. Again, no aspirin effect was noted among women (OR, 0.94; 95% CI, 0.74-1.19; *P*=.62) or men (OR, 0.93; 95% CI, 0.85-1.03; *P*=.15).

Major Bleeding

A total of 301 major bleeding events occurred among the women (FIGURE 5). Each trial reported an increased risk of

Figure 2. Effect of Aspirin Treatment on the Primary Prevention of Major Cardiovascular Events and Myocardial Infarction



Sizes of data markers are proportional to the amount of data contributed by each trial. Test for heterogeneity for cardiovascular events: women, *P*=.47; men, *P*=.25; and myocardial infarction: women, *P*=.62; men, *P*=.05. BDT indicates British Doctor's Trial; CI, confidence interval; HOT, Hypertension Optimal Treatment trial; PHS, Physicians' Health Study; PPP, Primary Prevention Project; TPT, Thrombosis Prevention Trial; WHS, Women's Health Study.

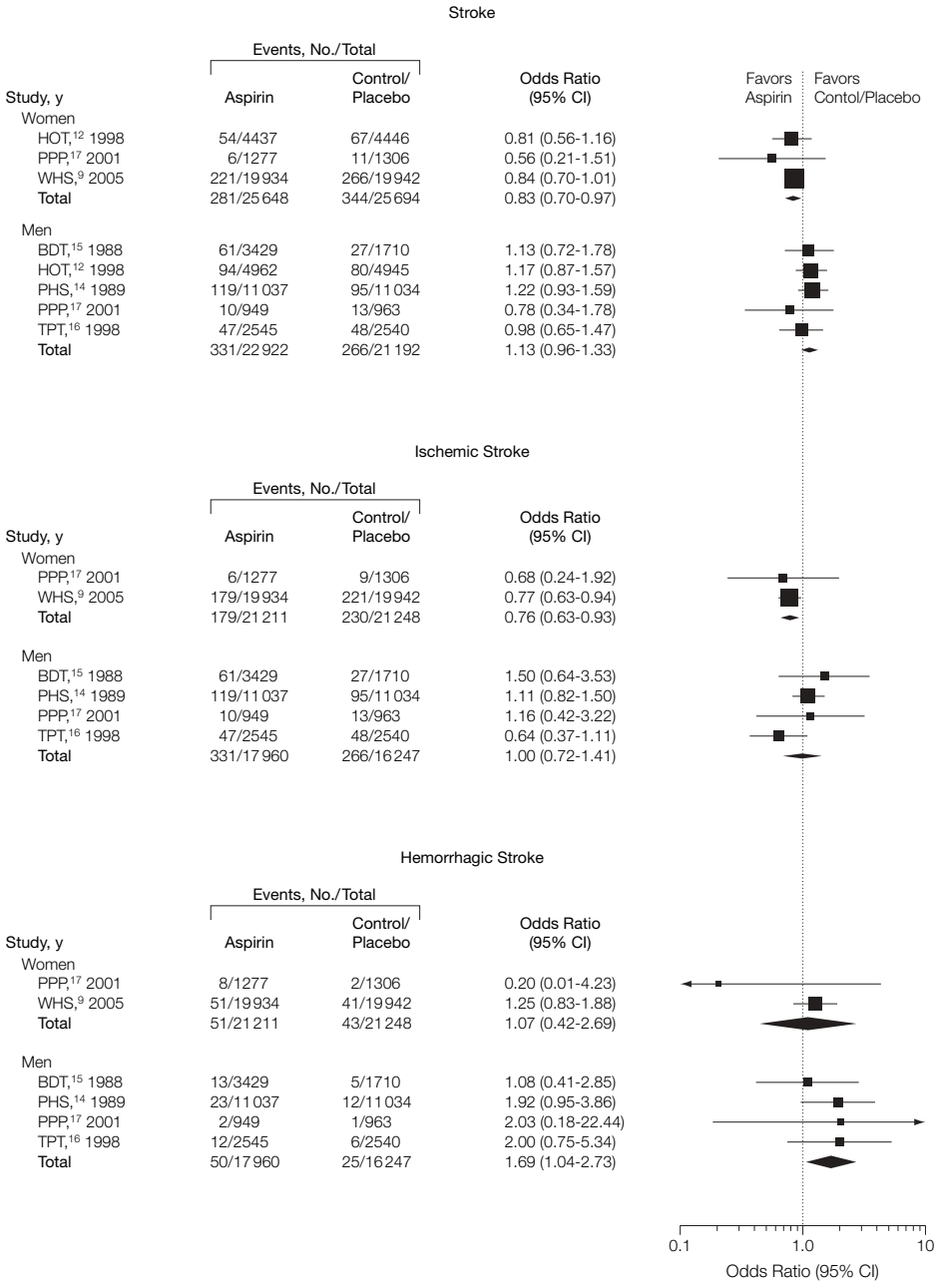
major bleeding associated with aspirin treatment. Pooled results confirm a statistically significant increase in the odds of major bleeding events with aspirin (OR, 1.68; 95% CI, 1.13-2.52; $P=.01$).

A total of 288 major bleeding events occurred among the men. Aspirin therapy was associated with a statistically significant increased odds of major bleeding events among men (OR, 1.72; 95% CI, 1.35-2.20; $P<.001$). The predominant site of bleeding was the gastrointestinal tract.

COMMENT

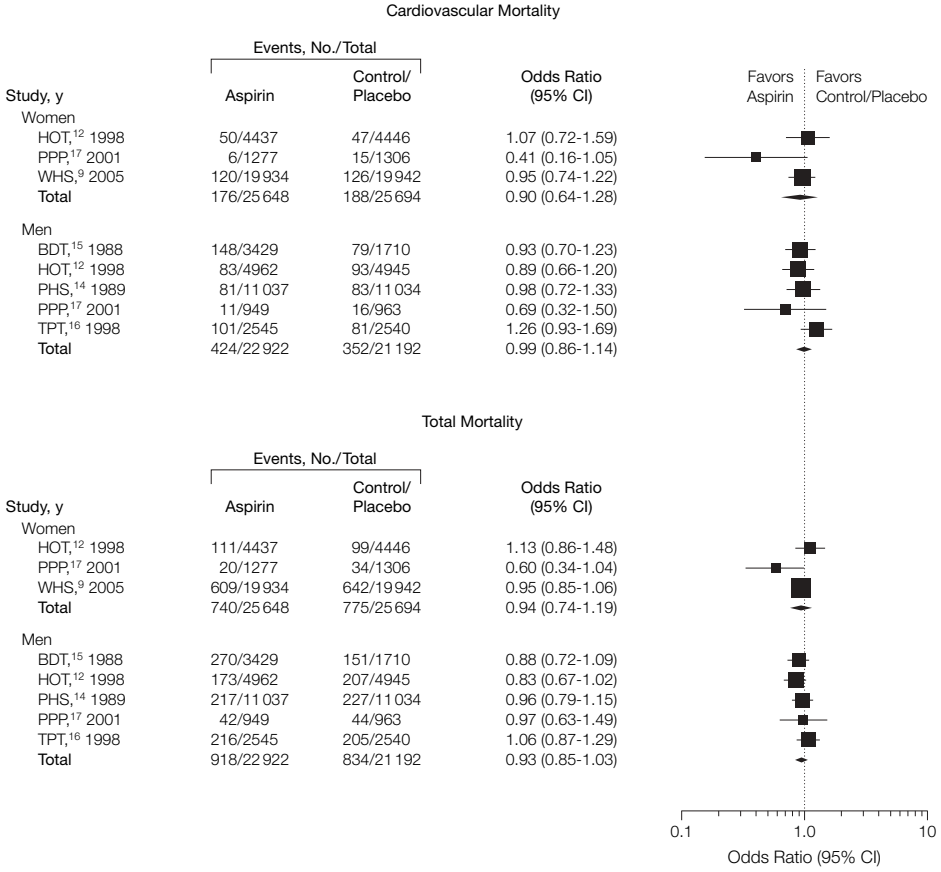
This sex-specific meta-analysis demonstrates that aspirin therapy is

Figure 3. Effect of Aspirin Treatment on the Primary Prevention of Stroke, Ischemic Stroke, and Hemorrhagic Stroke



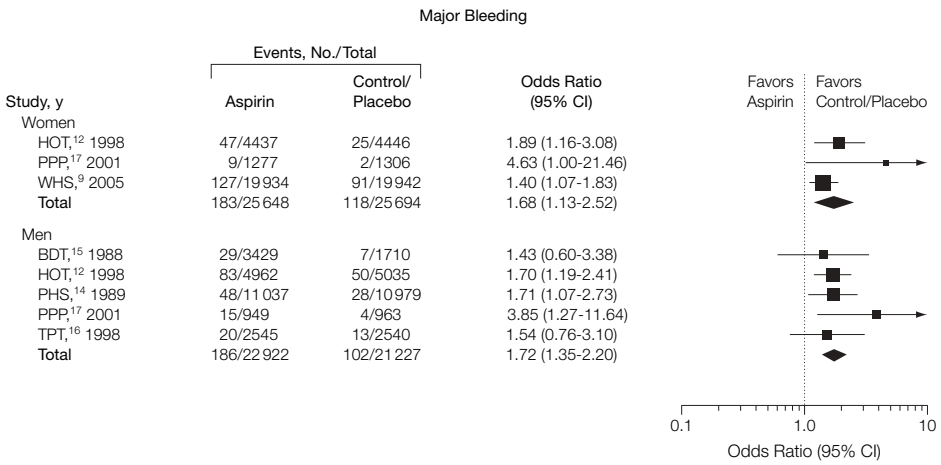
Sizes of data markers are proportional to the amount of data contributed by each trial. Test for heterogeneity for stroke: women, $P=.72$; men, $P=.80$; ischemic stroke: women, $P=.82$; men, $P=.81$; and hemorrhagic stroke: women, $P=.25$; men, $P=.78$. See legend of Figure 2 for expansions of study names. CI indicates confidence interval.

Figure 4. Effect of Aspirin Treatment on the Primary Prevention of Cardiovascular Mortality and Total Mortality



Sizes of data markers are proportional to the amount of data contributed by each trial. Test for heterogeneity for cardiovascular mortality: women, $P=.18$; men, $P=.41$; and total mortality: women, $P=.12$; men, $P=.53$. See legend of Figure 2 for expansions of study names. CI indicates confidence interval.

Figure 5. Effect of Aspirin Treatment on Major Bleeding



Sizes of data markers are proportional to the amount of data contributed by each trial. Test for heterogeneity: women, $P=.21$; men, $P=.68$. See legend of Figure 2 for expansions of study names. CI indicates confidence interval.

associated with a significant reduction in the risk of cardiovascular events in both sexes. However, the specific types of benefit differ in important ways between women and men. For primary prevention of cardiovascular disease in women, aspirin therapy significantly reduced the risk of the composite of cardiovascular events primarily by its effect on reducing the risk of ischemic stroke. Among women, aspirin had no significant effect on the risk of MI. In contrast, for the primary prevention of cardiovascular disease in men, aspirin therapy significantly reduced the risk of the composite of cardiovascular events predominantly by reducing the risk of MI. Among men, aspirin demonstrated a nonsignificant increase in the risk of stroke that was related to the significant increase in the risk of hemorrhagic stroke.

Benefit of Aspirin Therapy

Based on the absolute risk reduction of 0.30% and 0.37% in women and men, respectively, the number needed to treat to prevent 1 cardiovascular event over the mean follow-up of 6.4 years was 333 women and 270 men. In other words, aspirin therapy for an average of 6.4 years results in an average absolute benefit of approximately 3 cardiovascular events prevented per 1000 women and 4 cardiovascular events prevented per 1000 men. Of note, the population studied had a low risk of fatal or nonfatal vascular events. It has been shown that the cardioprotective benefit of aspirin is related to the cardiovascular risk in the population studied.[3] As a result, the absolute risk reduction for these events was small. In addition, the risk of stroke was significantly reduced in women receiving aspirin therapy, corresponding to an average absolute benefit of approximately 2 stroke events per 1000 women treated. By contrast, the risk of MI was significantly reduced in men (and not in women) receiving aspirin therapy, corresponding to an average absolute benefit of approximately 8 MI events prevented per 1000 men treated for 6.4 years.

Harm of Aspirin Therapy

Aspirin treatment resulted in an approximately 70% increase in the risk of major bleeding events among women and men. Based on the absolute risk increase of 0.25% and 0.33% in women and men, respectively, the number needed to harm over 6.4 years of aspirin treatment by causing 1 major bleeding event was 400 women and 303 men. In other words, aspirin therapy for an average of 6.4 years results in an average absolute increase of approximately 2.5 major bleeding events caused per 1000 women and 3 major bleeding events caused per 1000 men.

Mechanism of Aspirin

The mechanisms underlying the effectiveness of aspirin have been studied extensively.[3,18] Experimentally, a single oral 100-mg dose of aspirin is sufficient to completely block the synthesis of thromboxane A_2,[19,20] the predominant pathway by which aspirin inhibits platelet aggregation.[18] When taken daily, the effect of repeated doses is cumulative.[21] At higher doses, the synthesis of prostacyclin is also inhibited,[3] which could paradoxically lead to thrombosis and vasoconstriction. Currently, there is an increasing focus on the role of inflammation in cardiovascular risk. Aspirin has been demonstrated to reduce C-reactive protein.[22] In the Physicians' Health Study, aspirin was most effective in reducing cardiovascular risk in men with the most elevated levels of C-reactive protein.[23] However, the dose of aspirin required to achieve the maximal antiinflammatory effect remains unknown.

Sex Effect

Several possibilities may explain the differences in cardioprotection observed between the sexes. First, evidence exists that there is a difference in aspirin metabolism.[24] Several studies have suggested a reduced pharmacological effect of aspirin among women compared with men.[25,26] Second, event rates of stroke and MI differ. Women have a greater proportion of strokes compared with MIs, whereas men have a greater proportion of MIs compared with strokes. Based on the number of events recorded in our analysis, it would be easiest to find a statistically meaningful difference in the risk of stroke among women and in the risk of MI among men. Third, aspirin resistance tends to be more common among women than men.[27]

Based on laboratory and clinical data,[3,18] current guidelines recommend 75 mg/d to 162 mg/d of aspirin for primary prevention.[5-8] Only the British Doctor's Trial used a dose (500 mg/d) that exceeded this current recommendation. This higher dose is just as effective at inhibiting thromboxane and is more potent at inhibiting prostacyclin, a mechanism with the potential to increase thrombotic events.[18] When the British Doctor's Trial was censored from our analysis of men, the proportional reduction of cardiovascular events increased from 14% to 17% and the proportional reduction in the risk of MI increased from 32% to 36%. The recent Women's Health Study[9] used a lower dose (100 mg every other day) than currently recommended. However, 100 mg every other day has been found to be as effective as 81 mg/d at inhibiting thromboxane and prostacyclin levels.[28]

Limitations

The present study has several potential limitations. First, as in most meta-analyses, these results should be interpreted with caution because aspirin dose, duration of treatment, and lengths of follow-up were not uniform. However, these differences did not result in any statistical difference in the effect size between the trials. Second, despite examination of the totality of the evidence by pooling results from all available randomized trials, the numbers of individual outcome events were infrequent because of the low-risk nature of the populations studied. Consequently, this analysis has limited statistical power to reliably detect differences in the individual end points with aspirin therapy. Third, we were unable to

determine what effect aspirin has on particular subgroups. Only analysis of data from the participants of all available trials would allow the examination of aspirin benefit in particular subgroups. Finally, meta-analysis remains retrospective research that is subject to the methodological deficiencies of the included studies. We minimized the likelihood of bias by developing a detailed protocol before initiating the study, by performing a meticulous search for published and unpublished studies, and by using explicit methods for study selection, data extraction, and data analysis.

CONCLUSION

This meta-analysis of more than 50 000 women and 40 000 men enrolled in 6 randomized trials indicates that low-dose aspirin therapy is associated with a significant reduction in cardiovascular events in both women and men. Our results are particularly noteworthy for the beneficial effect of aspirin on the risk of stroke for women and on the risk of MI for men. Although the present meta-analysis indicates that aspirin may have different effects between the sexes, the relatively small number of MIs among women and strokes among men suggest that further studies are needed before we can conclude that men and women differ in their cardiovascular response to aspirin. Nevertheless, the favorable effect of aspirin on the combined risk of cardiovascular events for women and men is apparent from these randomized studies. Aspirin use is also associated with a significant risk of major bleeding irrespective of sex. Both the beneficial and harmful effects of aspirin should be considered by the physician and patient before initiating aspirin for the primary prevention of cardiovascular disease in both sexes.

Author Contributions: Dr Brown had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Berger, Brown.
Acquisition of data: Berger, Roncaglioni, Avanzini, Pangrazzi, Tognoni, Brown.
Analysis and interpretation of data: Berger, Brown.
Drafting of the manuscript: Berger, Brown.
Critical revision of the manuscript for important intellectual content: Roncaglioni, Avanzini, Pangrazzi, Tognoni, Brown.
Statistical expertise: Berger, Brown.
Financial Disclosures: None reported.

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