Aspirin for Primary Prevention of Cardiovascular Events: Meta-Analysis of Randomized Controlled Trials and Subgroup Analysis by Sex and Diabetes Status

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Aspirin for Primary Prevention of Cardiovascular Events: Meta-Analysis of Randomized Controlled Trials and Subgroup Analysis by Sex and Diabetes Status

Manling Xie1,2,3, Zhilei Shan1,2,3, Yan Zhang1,2, Sijing Chen1,2, Wei Yang1,2, Wei Bao1,2, Ying Rong1,2, Xuefeng Yu3, Frank B. Hu4*, Liegang Liu1,2*

1 Department of Nutrition and Food Hygiene, Hubei Key Laboratory of Food Nutrition and Safety, School of Public Health, Tongji Medical College, Huazhong University of Science & Technology, Wuhan, China, 2 Ministry of Education Key Laboratory of Environment and Health, School of Public Health, Tongji Medical College, Huazhong University of Science & Technology, Wuhan, China, 3 Division of Endocrinology, Department of Internal Medicine, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China, 4 Department of Nutrition and Epidemiology, Harvard School of Public Health, Boston, Massachusetts, United States of America

Abstract

Objective: To evaluate the benefits and harms of aspirin for the primary prevention of CVD and determine whether the effects vary by sex and diabetes status.

Methods: We searched Medline, Embase, and Cochrane databases for randomized controlled trials comparing the effects of aspirin with placebo or control in people with no pre-existing CVD. Two investigators independently extracted data and assessed the study quality. Analyses were performed using Stata version 12.

Results: Fourteen trials (107,686 participants) were eligible. Aspirin was associated with reductions in major cardiovascular events (risk ratio, 0.90; 95% confidence interval, 0.85–0.95), myocardial infarction (0.86; 0.75–0.93), ischemic stroke (0.86; 0.75–0.98) and all-cause mortality (0.94; 0.89–0.99). There were also increases in hemorrhagic stroke (1.34; 1.01–1.79) and major bleeding (1.55; 1.35–1.78) with aspirin. The number needed to treat to prevent 1 major cardiovascular event over a mean follow-up of 6.8 years was 284. By comparison, the numbers needed to harm to cause 1 major bleeding is 299. In subgroup analyses, pooled results demonstrated a reduction in myocardial infarction among men (0.71; 0.59–0.85) and ischemic stroke among women (0.77; 0.63–0.93). Aspirin use was associated with a reduction (0.65; 0.51–0.82) in myocardial infarction among diabetic men. In meta-regression analyses, the results suggested that aspirin therapy might be associated with a decrease in stroke among diabetic women and a decrease in MI among diabetic men and risk reductions achieved with low doses (75 mg/day) were as large as those obtained with higher doses (650 mg/day).

Conclusions: The use of low-dose aspirin was beneficial for primary prevention of CVD and the decision regarding an aspirin regimen should be made on an individual patient basis. The effects of aspirin therapy varied by sex and diabetes status. A clear benefit of aspirin in the primary prevention of CVD in people with diabetes needs more trials.

Introduction

The burden of cardiovascular disease (CVD) is substantial. The most recent (2013) statistics on heart disease and stroke from the American Heart Association (AHA) estimate that the annual direct and indirect cost of CVD and stroke in the United States alone are $323 billion [1]. From 2000 to 2010, the total number of inpatient cardiovascular operations and procedures increased 28%, from 5,939,000 to 7,588,000. By 2030, 40.8% of the US population is projected to have some form of CVD, and the annual cost will increase to $1.13 trillion [1]. These strong upward trends underline the importance of primary prevention for those who are already at high risk of CVD.

The use of low-dose aspirin for primary prevention of CVD is recommended by many key guidelines [2,3]. However, a recent published study and a review [4,5] stated that the benefit of aspirin for the primary prevention of cardiovascular events was relatively small for individuals regardless of diabetic status and could easily be offset by the risk of hemorrhage. These studies challenge current recommendations, which are based on outcomes from several meta-analyses [6–10], prompting re-evaluation of the
efficacy of aspirin. An important sex-specific meta-analysis showed that the effects of aspirin varied by sex [6]. However, it was conducted in 2006 and included only six primary prevention trials. In addition, the results were not confirmed in the Antithrombotic Trialists’ Collaboration meta-analysis and a recent publication which did not find significant sex difference in treatment effect [7,11]. Several guidelines [12,13] recommend aspirin for the primary prevention of cardiovascular events in patients with diabetes at risk of CVD, but others [2,14] do not. This conflict reflects the lack of definitive evidence. Existing recommendations are primarily based on extrapolations from indirect evidence, given the absence of statistically significant results in published meta-analyses in diabetics [15–23].

Therefore, we performed a new meta-analysis to re-assess the effects of aspirin for primary prevention of CVD and to investigate whether the effects vary by sex and diabetes status. Compared to the previous sex-specific meta-analyses, we enrolled almost twice that of previously published data. Given the limited power to detect interactions, even in a meta-analysis combining the results from several studies [24], we used multiple statistical methods to examine the diabetes-aspirin interaction and sex-aspirin interaction and their consistent results strengthen our conclusions.

Methods

For this meta-analysis, we used methods and definitions from previous meta-analyses [6] and performed our meta-analysis in line with approach recommended by the PRISMA statement [25]. Full study protocol is provided as Text S1.

Data Sources and Searches

Randomized controlled trials (RCTs) comparing the effect of aspirin with placebo or control in people without pre-existing CVD on outcomes of interest were eligible for inclusion. We identified trials by searching Medline, Embase, and Central (the Cochrane Central Register of Controlled Trials) from inception to December 2012. Reference lists from previously published relevant systematic reviews were also screened for additional studies [6,8,15]. The search strategies are as follows: First we searched terms “aspirin*” [MeSH] and term “primary prevention”. Then the Boolean term “AND” was used to combine these two terms. Highly sensitive filters were used to limit results to randomized controlled trials and human studies. We searched only studies published in English. A similar search strategy was used for Embase and Central.

Study Selection

Two authors independently reviewed search results by title and abstract, then full text to identify eligible trials. Selection criteria included: (1) Prospective, randomized, controlled, open, or blinded trials. (2) Participants without clinical CVD (e.g., established or symptomatic) were randomly assigned to aspirin (any dose) versus placebo or control group for the primary prevention of CVD. (3) Trials carried out on a background of anticoagulation were eligible. (4) Follow-up had to exceed 90 days, because such short follow-up would not permit detection of cardiovascular outcomes related to aspirin treatment for primary prevention.

Outcomes

The outcomes of interest for both aspirin and control groups included major cardiovascular events (MCE, defined as death from cardiovascular causes, nonfatal myocardial infarction, and nonfatal stroke); myocardial infarction (MI, fatal and nonfatal); stroke (fatal and nonfatal; ischemic and hemorrhagic); ischemic stroke; cardiovascular mortality; total mortality (death from any cause); hemorrhagic stroke and major bleeding. Definitions for major bleeding varied across studies. However, participant-level data was unavailable to allow reclassification according to standard criteria [26–29]. Among all bleeding events, the gastrointestinal hemorrhage is one of the most common and serious complications of long-term aspirin use.

Data Extraction and Quality Assessment

Two investigators independently extracted data and evaluated the methodological quality using criteria previously published [29]. An arbitrator settled discrepancies by discussion in accordance with our selection criteria. We collected some basic information on the studies and outcomes of interest listed above. Data were collected from the original articles, previously published meta-analyses, and through contact with study authors.

Data Synthesis and Analysis

Analyses were performed using Stata version 12 (Stata Corp). Heterogeneity was assessed by Cochran’s Q-test and the I² statistic [30]. A P value less than 0.10 indicated significant heterogeneity. For the I² metric, we defined low, moderate, and high I² values as 25%, 50%, and 75%, respectively [31]. We estimated the results with pooled relative risks (RR) and 95% confidence intervals (CI) using a Mantel-Haenszel fixed-effect model when the heterogeneity was negligible or moderate and a DerSimonian and Laird random-effects model when heterogeneity was significant [32]. All analyses were based on the intention-to-treat principle. A 2-tailed P-value 0.05 was considered statistically significant.

To explore potential sources of heterogeneity, we collected sufficient information to conduct particular subgroup analyses to determine the sex-aspirin interaction and diabetes-aspirin interaction. Because there is limited power to detect interactions, even in a meta-analysis combining the results from several studies, and it is not sufficient to conclude that the relative risks from the subgroups significantly different from each other when the two estimates and P values seem very different [24]. Thus, we implemented two methods to determine whether a difference exists in subgroup analysis. First, we estimated the pooled ratio of RRs comparing the aspirin effect in patients with and without diabetes and in patients with different genders across trials. Second, we used the method of Alfman and Bland to compare the pooled RR and its 95% CI across subgroups [24]. In addition, we calculated numbers needed to treat (NNT) and numbers needed to harm (NNH) to examine the risk vs. benefit of aspirin therapy for some endpoints [33]. Values of NNT and NNH provided herein represent the number of persons that need to be treated with aspirin for 6.8 years (the overall mean follow-up time in our study) to avert or incur, respectively, 1 event.

We also performed meta-regression analyses to appraise the impact of gender and the daily dose of aspirin on outcomes [34]. Publication bias was assessed by the funnel plot and the Beggs’s and Egger’s tests. We performed a sensitivity analysis to examine the robustness of the results, systematically removing one study from the analysis and recalculating the results.

Results

Description of Trials

Details of the included studies appear in Table 1. Table S1 outlines the baseline characteristics and the interventions of the
Table 1. Design of trials included in the meta-analysis.

<table>
<thead>
<tr>
<th>Studies</th>
<th>Year of publication</th>
<th>Country</th>
<th>No. of participants</th>
<th>No. of Aspirin group</th>
<th>Patients population</th>
<th>Mean years of follow-up</th>
<th>Aspirin dose</th>
<th>Primary outcome measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDT [35]</td>
<td>1988</td>
<td>UK</td>
<td>5139</td>
<td>3429</td>
<td>Healthy male doctors</td>
<td>5.6</td>
<td>500 mg daily or 300 mg if requested</td>
<td>Cardiovascular mortality, nonfatal MI, stroke</td>
</tr>
<tr>
<td>PHS [36]</td>
<td>1989</td>
<td>USA</td>
<td>22071</td>
<td>11037</td>
<td>Healthy male doctors</td>
<td>5</td>
<td>325 mg every other day</td>
<td>Cardiovascular mortality</td>
</tr>
<tr>
<td>ETDRS [37]</td>
<td>1992</td>
<td>Mixed</td>
<td>3711</td>
<td>1856</td>
<td>Men and women with diabetes</td>
<td>5</td>
<td>650 mg daily</td>
<td>All cause mortality</td>
</tr>
<tr>
<td>ACBS [38]</td>
<td>1995</td>
<td>Unclear</td>
<td>372</td>
<td>188</td>
<td>Individuals with asymptomatic carotid stenosis</td>
<td>2.4</td>
<td>325 mg daily</td>
<td>Clinical event in the composite end point</td>
</tr>
<tr>
<td>TPT [39]</td>
<td>1998</td>
<td>UK</td>
<td>5085</td>
<td>2545</td>
<td>Men at high risk of CVD</td>
<td>6.7*</td>
<td>75 mg daily</td>
<td>All ischemic heart disease (coronary death and fatal and nonfatal MI)</td>
</tr>
<tr>
<td>HOT [40]</td>
<td>1998</td>
<td>Mixed</td>
<td>18790</td>
<td>9399</td>
<td>Men and women at high risk of hypertension</td>
<td>3.8</td>
<td>75 mg daily</td>
<td>Cardiovascular mortality, nonfatal MI, stroke</td>
</tr>
<tr>
<td>PPP [41]</td>
<td>2001</td>
<td>Italy</td>
<td>4495</td>
<td>2226</td>
<td>Men and women with 1 cardiovascular risk factor</td>
<td>3.7</td>
<td>100 mg daily</td>
<td>Cardiovascular mortality, MI, stroke</td>
</tr>
<tr>
<td>ECLAP [42]</td>
<td>2004</td>
<td>Unclear</td>
<td>518</td>
<td>253</td>
<td>Patients with polycythemia vera</td>
<td>3</td>
<td>100 mg daily</td>
<td>Two composite end point</td>
</tr>
<tr>
<td>WHS [43]</td>
<td>2005</td>
<td>USA</td>
<td>39876</td>
<td>19934</td>
<td>Healthy women</td>
<td>10.1</td>
<td>100 mg every other day</td>
<td>Cardiovascular mortality, nonfatal MI, stroke</td>
</tr>
<tr>
<td>CLIPS [44]</td>
<td>2007</td>
<td>European</td>
<td>366</td>
<td>185</td>
<td>Patients with peripheral arterial disease</td>
<td>2</td>
<td>100 mg daily</td>
<td>MCEs</td>
</tr>
<tr>
<td>APLASA [45]</td>
<td>2007</td>
<td>Mixed</td>
<td>98</td>
<td>48</td>
<td>Asymptomatic, persistently antiphospholipid</td>
<td>2.3</td>
<td>81 mg daily</td>
<td>Incident acute thrombosis (arterial or venous) confirmed by appropriate imaging studies</td>
</tr>
<tr>
<td>POPADAD [46]</td>
<td>2008</td>
<td>UK</td>
<td>1276</td>
<td>638</td>
<td>Men and women with diabetes and ABI ≤ 0.96</td>
<td>6.7</td>
<td>100 mg daily</td>
<td>Cardiovascular mortality, nonfatal MI, stroke, critical limb ischemia</td>
</tr>
<tr>
<td>JPAD [47]</td>
<td>2008</td>
<td>Japan</td>
<td>2539</td>
<td>1262</td>
<td>Men and women with diabetes</td>
<td>4.4*</td>
<td>81 or 100 mg daily</td>
<td>All ischemic heart disease, stroke and peripheral artery disease.</td>
</tr>
<tr>
<td>AAA [48]</td>
<td>2010</td>
<td>UK</td>
<td>3350</td>
<td>1675</td>
<td>Men and women in general population with ABI ≤ 0.95</td>
<td>8.2</td>
<td>100 mg daily</td>
<td>Cardiovascular mortality, MI, stroke and revascularization</td>
</tr>
</tbody>
</table>

*Median year follow-up.

PHS = Physicians Health Study. BDT = British Doctor’s Trial. TPT = Thrombosis Prevention Trial. HOT = Hypertension Optimal Treatment trial. PPP = Primary Prevention Project. WHS = Women’s Health Study. POPADAD = Prevention of Progression of Arterial Disease and Diabetes trial. JPAD = Japanese primary Prevention of Atherosclerosis with Aspirin for Diabetes trial. AAA = Aspirin for Asymptomatic Atherosclerosis trial. ETDRS = the Early Treatment Diabetic Retinopathy Study. APLASA = Antiphospholipid Antibody Acetyl-salicylic Acid study. ECLAP = European Collaboration on Low-Dose Aspirin in Polycythemia Vera study. CLIPS = Critical Leg Ischaemia Prevention Study. ACBS = Asymptomatic Cervical Bruit Study. MCEs = major cardiovascular events; MI = myocardial infarction.

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participants. We identified fourteen [35–48] prospective randomized controlled trials comprised 107,686 participants for inclusion from 373 potentially eligible studies (Figure 1). A total of 734,170 person-years of exposure were recorded: 372,757 in the aspirin group and 361,413 in the placebo or control group. Specifically, three trials included apparently healthy health care professionals [35,36,43]. Only one of the 14 studies included a small proportion (<10%) of participants with pre-existing established cardiovascular events [37]. In addition, few studies have populations with high prevalence of CVD risk factors, e.g., hypertension [40], polycythemia vera [42], and peripheral arterial disease [44].

Risk of Bias in Individual Trials
The risk of bias in trials is presented in Table S2. Randomization was stated in all studies, but the allocation concealment was adequately described in only eight studies and unclear in the remainder. Two trials were open-labeled [41,47], and placebo tablets were not used in the control group in one trial [35]. Outcome assessment was not blinded in one trial [35] and unclear in two [42,45]. The description of incomplete outcome data was not adequate in two trials [36,43]. Three studies had a vitamin component [41,43,44], one had a beta carotene component [36], one had an anti-oxidant component [46], and one had a warfarin component [39].

Clinical Outcomes
Efficacy Data: Major Cardiovascular Events. Aspirin use was associated with a 10% reduction in MCEs (No. of events/No. of totals, 2392/54487 vs 2505/52827; RR, 0.90; 95% CI, 0.85 to 0.95; P<0.01; Figure 2, Figure S4-A in File S1). The NNT to avoid 1 MCE over 6.8 years was 284. There was no significant heterogeneity among the studies in this analysis (Q = 14.17, P = 0.01; I² = 15.3%).

Myocardial Infarction. There was also a 14% reduction in the risk of MI with aspirin (1258/54675 vs 1388/53011; RR, 0.86; 95% CI, 0.75 to 0.98; P = 0.02; Figure 2, Figure S4-B in File S1). The NNT to avoid 1 MI over 6.8 years was 315. However, heterogeneity was significant (Q = 28.17, P = 0.01; I² = 53.9%).

Stroke. There was no reduction in the risk of overall stroke (856/54371 vs 855/52961; RR, 0.95; 95% CI, 0.87 to 1.05; P = 0.34; Figure 2, Figure S4-C in File S1) and no significant heterogeneity (Q = 14.33, P = 0.28; I² = 16.3%). When we examined stroke subtypes (ischemic and hemorrhagic) from the available data, we found a 14% reduction (374/42999 vs 427/41350; RR, 0.86; 95% CI, 0.73 to 0.98; P = 0.03; Figure 2, Figure S4-D in File S1) in the risk of ischemic stroke without significant heterogeneity (Q = 9.60, P = 0.30; I² = 16.6%). The NNT to avoid 1 l ischemic stroke over 6.8 years was 614.

All-Cause and Cardiovascular Mortality. Pooled results demonstrated a 6% reduction in the risk of all-cause mortality

![Flow chart of articles selection for this systematic review and meta-analysis.](doi:10.1371/journal.pone.0090286.g001)
(2329/54627 vs 2334/52961; RR, 0.94; 95% CI, 0.89 to 0.99; P = 0.03; Figure 2, Figure S4-E in File S1). The NNT to avoid all-cause mortality over 6.8 years was 697. The heterogeneity was not significant (Q = 5.87, P = 0.92; I² = 0%). However, there was no reduction in cardiovascular morality (993/54627 vs 855/52961; RR, 1.04; 95% CI, 0.86 to 1.25; P = 0.69; Figure 2, Figure S4-F in File S1) and the heterogeneity was significant (Q = 32.68, P < 0.01; I² = 63.3%).

**Safety Data: Hemorrhagic stroke.** Aspirin was associated with a 34% increase in hemorrhagic stroke (113/42999 vs 79/41350; RR, 1.34; 95% CI, 1.01 to 1.79; P = 0.05; Figure 2, Figure S4-G in File S1). The NNH to cause 1 hemorrhagic stroke over 6.8 years was 1394. Heterogeneity was not significant (Q = 3.89, P = 0.87; I² = 0%).

**Major bleeding.** Pooled results demonstrated a 55% increase in the risk of major bleeding (522/54439 vs 329/52722; RR, 1.55; 95% CI, 1.35 to 1.78; P < 0.01; Figure 2, Figure S4-H in File S1). The NNT to cause 1 major bleeding over 6.8 years was 299. In aggregate, heterogeneity was moderate in this analysis (Q = 17.47, P = 0.10; I² = 37.0%).

### Subgroup Analysis

#### The effects of aspirin by gender.
Details of the included studies in the subgroup analyses by sex appear in Table S3.

For the endpoint of MCE, aspirin was associated with a 12% reduction (879/28575 vs 998/28643; RR, 0.88; 95% CI, 0.81 to 0.96; P = 0.01) among women, and a 12% reduction (1368/25426 vs 1394/23688; RR, 0.88; 95% CI, 0.82 to 0.95; P < 0.01) among men, without significant heterogeneity (Table 2).

Pooled results demonstrated a 29% reduction (616/23953 vs 760/22257; RR, 0.71; 95% CI, 0.59 to 0.83; P < 0.01; Q = 12.86, P = 0.03; I² = 61.1%) in the risk of MI among men and a 23% reduction (176/21211 vs 230/21248; RR, 0.77; 95% CI, 0.63 to 0.93; P = 0.01; Q = 0.05, P = 0.82; I² = 0%) in the risk of ischemic stroke among women (Table 2).

For hemorrhagic stroke with aspirin, pooled results demonstrated no significant increase (51/21211 vs 43/21248; RR, 1.19; 95% CI, 0.79 to 1.77; P = 0.41) among women but a 69% increase (50/17960 vs 25/16247; RR, 1.69; 95% CI, 1.05 to 2.72; P = 0.03) among men (Table 2). There was no significant heterogeneity among the studies in this analysis.

Aspirin use was also associated with a significant risk of major bleeding irrespective of sex. Pooled results demonstrated a 55% increase (183/25648 vs 118/25694; RR, 1.55; 95% CI, 1.23 to 1.96; P < 0.01; Q = 3.15, P = 0.21; I² = 36.6%) among women and a 79% increase (195/22922 vs 102/21227; RR, 1.79; 95% CI, 1.41 to 2.27; P < 0.01; Q = 2.27, P = 0.69; I² = 0%) among men (Table 2).

When we used the method of Altman and Bland to compare the pooled RR and its 95% CI of MI (P = 0.02) and stroke (P = 0.01), the results also provide strong support for gender difference in the reduction of MI and stroke.

#### The effects of aspirin by diabetes status.
Details of the included studies in the subgroup analyses by diabetes status appear in Table S4-A and Table S4-B.

The estimate stratified by diabetes status was significant only for the outcome of MCEs. Pooled results demonstrated a 9% reduction (1285/35626 vs 1268/34021; RR, 0.91; 95% CI, 0.84 to 0.98, P = 0.01) among nondiabetic patients but no significant reduction among diabetic patients (Table 2). Given that the small number of the diabetic patients, we stratified the trials by the percentage of diabetic patients (<50% vs ≥50%). For trials with percentage of diabetic patients <50% and ≥50%, the RRs of MI were 0.85 (95% CI 0.72 to 0.99; P = 0.04; Q = 20.57, P = 0.02; I² = 56.2%) and 0.88 (95% CI 0.65 to 1.20; P = 0.42; Q = 6.97, P = 0.07; I² = 57.0%) respectively, and the RRs of major bleeding were 1.67 (95% CI, 1.43 to 1.94; P < 0.01; Q = 5.78, P = 0.37; I² = 0%) and 1.12 (95% CI, 0.82 to 1.54; P = 0.46; Q = 5.89, P = 0.07; I² = 0%).
Table 2. Outcomes of subgroup analyses by sex and diabetes status.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Aspirin Male</th>
<th>Aspirin Female</th>
<th>Control Male</th>
<th>Control Female</th>
<th>Rate ratio (95% CI)</th>
<th>I² (%)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCEs</td>
<td>1368/25426</td>
<td>1394/23688</td>
<td>879/28643</td>
<td>989/28643</td>
<td>0.88 (0.82–0.95)</td>
<td>8.6</td>
<td>0.5</td>
</tr>
<tr>
<td>MI</td>
<td>616/23953</td>
<td>760/22257</td>
<td>316/26473</td>
<td>334/26484</td>
<td>0.71 (0.59–0.85)</td>
<td>61.1</td>
<td>0.02</td>
</tr>
<tr>
<td>Stroke</td>
<td>406/23953</td>
<td>320/22257</td>
<td>319/26217</td>
<td>374/26484</td>
<td>1.13 (0.98–1.31)</td>
<td>0</td>
<td>0.01</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>141/17960</td>
<td>129/16274</td>
<td>176/21211</td>
<td>230/21248</td>
<td>1.02 (0.80–1.30)</td>
<td>23.5</td>
<td>0.08</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>50/17960</td>
<td>25/16274</td>
<td>51/21211</td>
<td>43/21248</td>
<td>1.69 (1.05–2.72)</td>
<td>0</td>
<td>0.27</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>539/24239</td>
<td>480/22534</td>
<td>276/26825</td>
<td>303/26845</td>
<td>0.97 (0.86–1.10)</td>
<td>3.9</td>
<td>0.47</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>1046/23953</td>
<td>981/22257</td>
<td>836/26473</td>
<td>903/26484</td>
<td>0.93 (0.85–1.01)</td>
<td>0</td>
<td>0.56</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>195/22122</td>
<td>102/21227</td>
<td>183/25648</td>
<td>118/25694</td>
<td>1.79 (1.41–2.27)</td>
<td>0</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Diabetes Non-diabetes Diabetes Non-diabetes Diabetes Non-diabetes

| MCEs                      | 615/5663     | 698/5601      | 1285/35626   | 1268/34021     | 0.92 (0.83–1.01)    | 0      | 0.87    |
| MI                        | 406/5840     | 457/5788      | 517/42142    | 631/42250      | 0.85 (0.66–1.10)    | 54.1   | 0.94    |
| Stroke                    | 221/5938     | 236/5859      | 620/47762    | 595/46429      | 0.92 (0.77–1.10)    | 27.2   | 0.56    |
| Cardiovascular mortality  | 313/5027     | 345/5031      | 510/11984    | 162/12031      | 0.91 (0.97–1.05)    | 45.5   | 0.74    |
| All-cause mortality       | 533/5027     | 561/5031      | 447/11984    | 500/12031      | 0.95 (0.85–1.06)    | 0      | 0.53    |

Diabetes rate <50% Diabetes rate >50%

| MCEs                      | 1876/50546   | 1973/48876    | 516/3941     | 568/3951       | 0.90 (0.84–0.95)    | 0.91 (0.82–1.01)    | 5.6    | 46.5   | 0.86 |
| MI                        | 913/50734    | 998/49060     | 345/3941     | 390/3951       | 0.85 (0.72–0.99)    | 0.88 (0.65–1.20)    | 56.2   | 57     | 0.84 |
| Stroke                    | 695/50430    | 688/49010     | 161/3941     | 167/3951       | 0.95 (0.86–1.06)    | 0.97 (0.78–1.19)    | 20.4   | 29.8   | 0.87 |
| Ischemic stroke           | 347/41099    | 400/39435     | 27/1900      | 27/1915        | 0.85 (0.73–0.98)    | 1.01 (0.60–1.71)    | 30.8   | 0      | 0.54 |
| Hemorrhagic stroke        | 106/41099    | 73/39435      | 7/1900       | 6/1915         | 1.35 (1.01–1.82)    | 1.18 (0.40–3.49)    | 0      | 0      | 0.81 |
| Cardiovascular mortality  | 648/50686    | 540/49010     | 285/3941     | 315/3951       | 1.06 (0.85–1.32)    | 0.95 (0.58–1.55)    | 65.9   | 57.8   | 0.69 |
| All-cause mortality       | 1854/50686   | 1825/49010    | 475/3941     | 509/3951       | 0.94 (0.88–1.00)    | 0.93 (0.83–1.05)    | 0      | 0      | 0.87 |
| Major bleeding            | 441/50498    | 257/48771     | 81/3941      | 72/3951        | 1.67 (1.43–1.94)    | 1.12 (0.82–1.54)    | 0      | 49.1   | 0.03 |

*For interaction.
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heterogeneity between trials substantially decreased (921/23704 vs 956/22035; RR, 0.88; 95%CI, 0.81 to 0.96; P<0.01, Q = 11.14, P = 0.43; I² = 1.3%).

Publication Bias

We used a comprehensive literature search strategy to minimize the risk of publication bias. Results of Begg’s and Egger’s tests for asymmetry were not statistically significant (Figure S3).

Discussion

In a comparison of aspirin with placebo or control for the prevention of CVD, we found significant benefits of 10, 14, and 14% risk reduction for the outcomes of MCEs, MI, and ischemic stroke respectively in the overall population. Meanwhile, there were also clear harms of 34% relative increase in hemorrhagic stroke and 55% relative increase in major bleeding events. Our subgroup and meta-regression analyses indicated that the effects of aspirin therapy varied by sex and diabetes status. Aspirin use was associated with a significant reduction in the risk of cardiovascular events in both sexes but different specific types of benefits: a reduction in MI among men and a reduction in ischemic stroke among women. Aspirin had no significant effect on CVD in the overall diabetic population, but was associated with a reduction in MI among men with diabetes.

Although the results indicate a significant increase in bleeding complications, it is not sensible to conclude that the benefit of aspirin is offset by the risk of bleeding. First, we should estimate not only the incidence of benefits and harms, but also take into account the consequences of both harms and benefits on quality of life [49]. Setting aside the potentially fatal MI or stroke, it is clear that a non-fatal stroke or MI is more likely to result in long-term disability than a non-fatal gastrointestinal or other extracranial bleed. Although serious intracranial and extracranial bleed may also cause serious results, our results suggest that the benefit of reducing risk of ischemic stroke outweigh the harm hemorrhagic stroke. In addition, there are several methods to mitigate these adverse effects, for example, clinicians can remind those patients who decide to begin or continue an aspirin regimen for primary prevention of CVD, of the early recognition of the signs and symptoms as well as the risk factors of gastrointestinal bleeding. These risk factors include age, gender, upper gastrointestinal tract pain, gastrointestinal ulcers, NSAID use, uncontrolled hypertension, concomitant use of anticoagulants, and family history of gastrointestinal ulcers and so on [50].
Second, some of the previous published trials were criticized that few subjects exceeded the threshold for aspirin prophylaxis recommended by the American Heart Association [51]. In addition, evidence shows that >60% of aspirin users were above 60 years of age, 4–6% had a recent history of peptic ulcers, and over 13% used other non-steroidal antiinflammatory drugs [52]. It is obvious that the gastrointestinal harms would outweigh the cardiovascular benefits in certain groups whose gastrointestinal risk is high but cardiovascular risk is low. Thus, some of the previous published trials may overestimate the harm effect of the aspirin.

Third, the Antithrombotic Trialists’ Collaborative, an individual-level meta-analysis of RCTs, indicated that the absolute benefits of aspirin were on a small order of magnitude in primary prevention and the effects of aspirin do not significantly depend on smoking history, blood pressure, total cholesterol, body-mass index, history of diabetes, or predicted risk of coronary heart disease [7]. However, the small number and rare events in these particular subgroups are not sufficient for precise estimate, and thus this paper provides insufficient evidence to answer the question of which particular category of individuals derive the most benefit from aspirin therapy. More highly powered analyses for specific populations are expected based on two major ongoing trials: the Aspirin to Reduce Risk of Initial Vascular Events (ARRIVE) Study (http://www.arrive-study.com/EN/study.cfm) and Aspirin in Reducing Events in the Elderly (ASPREE) [53].

The results of our subgroup analysis consistent with prior studies indicate that there is no significant benefit of aspirin therapy among patients with diabetes, but this may be due to inadequate power because the point estimate was similar to that among nondiabetics but with a wider confidence interval. It is well established that diabetes mellitus is associated with an increased risk of CVD [54]. Among diabetes patients, the coagulation system is altered, because plasma levels of procoagulant factors are increased while fibrinolytic capacity is decreased [55].

The mechanisms of the antithrombotic effects of low-doses aspirin involve two aspects: cyclooxygenase (COX)-dependent actions and COX-independent actions [56]. Low-dose aspirin is considered to induce a permanent inactivation of COX-1 which results in the inhibition of platelet aggregation [57,58]. In many people, generation of new platelets and recovery of COX-dependent platelet aggregation can reverse to a certain degree this effect within 24 hours after administration of aspirin [59]. Thus successive and low-dose daily administration of aspirin is essential to maintain inactivation of platelet COX-1. However, patients with type 2 diabetes have been demonstrated to be characterized by a large inter-individual variability in the recovery of COX-1 activity and enhanced platelet turnover rate which represents an important determinant of the extent and duration of platelet inhibition on repeated dosing with low-dose aspirin [60–63]. Thus it is possible that the current use of a once-a-day and low-dose regimen may not be sufficient to induce clinical benefits among diabetic patients [64–67]. More studies are needed to demonstrate whether a higher frequency of aspirin administration and possibly a higher daily dosage can optimize treatment with aspirin in diabetic patients. In addition, considerable efforts are needed to illuminate the relation between decreased responsiveness to aspirin and the COX-independent antithrombotic effects [56].

Platelet dysfunction, increased platelet aggregation and aspirin insensitivity were more common in patients with type 2 diabetes compared to nondiabetic people [68] [62]. In addition, insulin resistance and hyperglycaemia are reported to contribute to these alterations [55]. Among our eligible 14 studies, 6 were published before 2000. The management and treatments of diabetes have been improved over the decades. Thus, the treatments of diabetes are much different between the old studies and recent studies. These differences of the treatments may have impact on the effect of aspirin in diabetes subgroup analysis.

Our meta-regression analyses indicate that aspirin therapy may have different effects between the sexes in diabetic patients. Although there is no evidence that the pharmacodynamics of platelet inhibition by aspirin is any different in women than in men, the overall risk of CVD for people with diabetes is reported to be increased two-to threefold in men, and three-to fivefold in women [23]. More highly powered subgroup analyses for specific populations are awaited based on two major ongoing trials: A Study of Cardiovascular Events in Diabetes (ASCEND, International Standard Randomised Controlled Trial Number ISRCTN60635500, http://www.cts.ac.uk/ascend/) and the Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes (ACCEPT-D, Current Controlled Trials ISRCTN48110081) [69], which enrolled more than 15,000 diabetic patients without prior cardiovascular events to assess the effect of aspirin in the prevention of cardiovascular events. These trials may provide sufficient data to identify patients who derive the most benefit from aspirin therapy.

In sex subgroup analysis, our results are consistent with the previous sex-specific meta-analysis [6], but our findings conflicted with a recent publication which did not find any significant sex different in treatment effect [7,11]. There are several potential explanations for the different effects between sexes.

First, the different epidemiologic characteristics of cardiovascular disease between men and women may contribute to the different benefits. After age 40 years, men have a 49% lifetime risk for a coronary heart disease event, while women have a 32% risk. Men have a higher risk for MI, while the lifetime risk for ischemic stroke is greater in women than men from age 55 to 75 (17–18% in women and 13–14% in men) [2], and the risk of gastrointestinal bleeding is approximately twice as high in men than women [50].

Second, although some evidence indicates that there is no difference in pharmacodynamics of platelet inhibition by aspirin between the sexes and the ‘aspirin resistance’ may not exist [70–72], there is still insufficient evidence to support these conclusions. In fact, few randomized trials have measured ‘aspirin resistance’ directly, whether gender plays an important part in ‘aspirin resistance’ remains a question for future research [73–76].

The range of the dosage varies from 75 to 650 mg/day in eligible trials. Our analysis suggests that risk reductions achieved with low doses (75 mg/day) were similar to those obtained with higher doses (650 mg/day). In fact, it is reported that the successive daily administration of 30 mg of aspirin is sufficient to result in virtually inactivation of COX-1 [77]. However, there is no trial using this dosage. It is reported that apart from the inhibition of platelet aggregation, the impairment of cytoprotection in the gastrointestinal mucosa which is clearly dose-dependent also increases risk of upper gastrointestinal bleeding associated with aspirin therapy [72]. Thus, it is very likely that lower dosage of aspirin would decrease the bleeding complications. There is a
need for additional placebo-controlled trials to demonstrate whether lower dosage of aspirin should be recommended for primary prevention of CVD in the future. However, because of the varied definitions of major bleeding among the studies, the result of our meta-regression does not indicate a clear does-effect relation which conflicts with previous published studies [78,79].

We acknowledge several limitations of our studies. First, we observed moderate heterogeneity among trials for some outcomes of interest. However, we have no access to patient-level data and our author response rate was relatively low, which may have led to limited statistical power. Second, the data were insufficient to report separate outcomes for type 1 and type 2 diabetes and different sexes in diabetic patients. Finally, the data on bleeding in our analyses were not sufficient to estimate whether changes in the dose of aspirin might reduce the risk of hemorrhage and whether further attempts at dosage reduction may compromise therapeutic efficacy.

In conclusion, our results demonstrate a significant net benefit to risk of aspirin for the primary prevention of CVD, and the decision regarding an aspirin regimen should be made on an individual patient basis, after careful evaluation of the trade-off between benefits and harms by the physician and patient. The effects of aspirin therapy vary by sex. Additional evidence is necessary before we make specific recommendations for aspirin use according to diabetes status.

Supporting Information
Figure S1 Meta-regression between the effects or complications of aspirin and daily dose of aspirin. (DOI)

References
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