CLINICAL RESEARCH STUDY

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Aspirin for Primary Atherosclerotic Cardiovascular Disease Prevention as Baseline Risk Increases: A Meta-Regression Analysis

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ABSTRACT

BACKGROUND: Aspirin has long had a role in the primary prevention of atherosclerotic cardiovascular disease (ASCVD); however, recent randomized controlled trials (RCTs) have challenged this practice. Despite this, aspirin is still commonly recommended for high-risk primary prevention. We tested the hypothesis that aspirin is more efficacious for the primary prevention of ASCVD as the baseline risk increases.

METHODS: RCTs that compared aspirin with control for primary prevention and evaluated ASCVD (composite of myocardial infarction and ischemic stroke) and major bleeding were included. Rate ratios (RR) and 95% confidence intervals (CI) were calculated. A regression analysis was performed using the ASCVD event rate in the control arm of each RCT as the moderator.

RESULTS: Twelve RCTs were identified with 963,829 patient-years of follow-up. Aspirin was associated with a reduction in ASCVD (4.7 vs 5.3 events per 1000 patient-years; RR 0.86; 95% CI, 0.79-0.92). There was increased major bleeding among aspirin users (2.5 vs 1.8 events per 1000 patient-years; RR 1.41; 95% CI, 1.29-1.54). Regression analysis found no relationship between the log RR of ASCVD or major bleeding and rate of ASCVD in the control arm of each RCT.

CONCLUSION: Aspirin is associated with a reduction in ASCVD when used for primary prevention; however, it is unlikely to be clinically significant given the increase in bleeding. More importantly, aspirin's treatment effect does not increase as ASCVD risk increases, as many hypothesize. There is no suggestion from these data that use of aspirin for higher-risk primary prevention patients is beneficial.

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KEYWORDS: Aspirin; Atherosclerotic cardiovascular disease; Ischemic stroke; Major bleeding; Myocardial infarction; Primary prevention

INTRODUCTION

While the role of aspirin in preventing recurrent atherosclerotic cardiovascular disease (ASCVD) events in patients with known ASCVD is well established,[1] aspirin's role in primary ASCVD prevention remains controversial. Older randomized controlled trials (RCTs) had mixed results but generally supported the use of aspirin for primary prevention, but several recent large-scale RCTs have cast doubt on this long-held practice and raised safety concerns.[2-5] ASPREE[3] and ARRIVE,[5] both primary prevention RCTs, found no reduction in ASCVD events despite finding an

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increased risk of major bleeding with randomization to aspirin. Due to the findings of these newer RCTs, the 2019 American College of Cardiology/American Heart Association primary ASCVD prevention guidelines were updated to state that aspirin should not be given to individuals over the age of 70 years or any aged individual with an increased bleeding risk. However, the new guidelines state that aspirin might be considered for primary ASCVD prevention in select adults aged 40-70 years who are at an increased risk of ASCVD events and are not at an increased risk of bleeding (Level IIb recommendation).[6]

Due to the uncertainty surrounding aspirin use in high-risk primary prevention patients, we tested the hypothesis that aspirin is more effective for reducing ASCVD events as the baseline rate of ASCVD increases in individual RCTs. We first performed a systematic review and meta-analysis to analyze ASCVD and major bleeding outcomes in the available RCTs comparing aspirin with control (either placebo or no aspirin) and then performed a meta-regression analysis using the ASCVD event rate (events per 1000 patient-years) in the control arm of each RCT as the marker of ASCVD risk in each individual trial. We also analyzed major bleeding episodes to test the hypothesis that those at high risk of ASCVD events will also be at the highest risk of bleeding when aspirin is used for primary prevention.

CLINICAL SIGNIFICANCE

- Aspirin use resulted in a reduction of atherosclerotic cardiovascular disease events when used for primary prevention; however, this benefit was counterbalanced by an increased risk of major bleeding.
- As the risk of atherosclerotic cardiovascular disease events increases in the available randomized controlled trials, the treatment effect of aspirin for primary prevention is unchanged.

METHODS

The Preferred Reporting Items for Systemic Reviews and Meta-Analysis (PRISMA) document was used as a guide and followed.[7,8] A database search identified all prospective RCTs that tested aspirin for the primary prevention of ASCVD and evaluated at least one of the primary endpoints of this analysis, which included a composite outcome comprised of nonfatal and fatal myocardial infarction and nonfatal and fatal ischemic stroke. Major bleeding was also included and was self-defined by the individual RCT. When an RCT did not specify major bleeding, bleeding events that required hospitalization and blood transfusion were analyzed as major bleeding. When that information was not available, gastrointestinal bleeding and hemorrhagic stroke were included. Relevant English language articles were identified by searching the Medline and Cochrane databases with the terms "aspirin," "cardiovascular disease," and "primary prevention." Also, previously published meta-analyses were used as a source for potential studies to include. The references of all included RCTs were also searched. RCTs that compared aspirin with placebo or control were eligible for inclusion (both open-label and placebo-controlled RCTs).

Two authors (MN and JC) searched all article titles and abstracts. Included articles were evaluated by both authors to assess if the study met inclusion criteria for the meta-analysis. Data were independently recorded in a standardized manner for each RCT. Supplemental appendices were also searched if data were incomplete. Any inconsistencies were reassessed by all parties until the data were determined to be accurate. RCTs of any duration with adult (>18 years) participants testing aspirin (any dose) every day or every other day with no known preexisting coronary or cerbrovascular disease were considered for inclusion. The baseline characteristics table was analyzed in each study to ensure that no participants had been previously diagnosed with ASCVD. Regardless of the prespecified outcome of the original RCT, if the study reported an outcome of interest, it was included in our analysis. We excluded any trials that were not randomized and trials that did not report on any of our prespecified outcomes of interest. We did not exclude open-label trials or 2 × 2 factorial design trials testing aspirin and another intervention. All included studies were graded for bias using the Cochrane Handbook for Systematic Review of Interventions by two authors (MN and JC). Bias was rated on criteria including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting.[9]

The primary analysis was conducted with the Mantel-Haenszel method. Summary rate ratios (RR) with 95% confidence intervals (CI) were calculated using a random effects model. Total patient-years were estimated using trial duration and number of patients in each arm of the included studies. Heterogeneity across all studies was performed using Q statistics and I^2. The 95% CIs were estimated using a binominal distribution. A random effects meta-regression was performed using the rate of ASCVD events in the control arm of each RCT as the moderator to determine if this continuous variable contributed to the heterogeneity in the ASCVD outcome. The ASCVD event rate in the control arm of each trial was calculated by converting the number of control arm events into events per 1000 patient-years. Meta-regression linear graphs were created by plotting our moderator variable (ASCVD event rate per 1000 patient-years in the control arm of each RCT) on the x-axis and the treatment effect size of aspirin on the y-axis (the log of the RR of aspirin's treatment effect on ASCVD events and major bleeding from each RCT). When interpreting the log of the RR on the y-axis, a value of zero corresponds to an RR of one, a negative value corresponds to an RR <1, and a

positive value corresponds to an RR >1. Each circle on the figure represents an included RCT, and the size of the circle is proportional to the weight of each study in the regression model. The darker line in the center represents the regression line, and the outer lighter-colored lines represent the 95% CI. The following statistical tests were utilized in the meta-regression: Tau^2, which estimates the true variance among RCTs, I^2, which represents the ratio of heterogeneity to total observed variation in the RCTs, and R^2 index, which is the proportion of between-study variance explained by the moderator (in this analysis, ASCVD event rate in the control arm of each RCT was the moderator). Also, regression coefficients were calculated and describe how aspirin's treatment effect on ASCVD and major bleeding will change with a unit change in the moderator variable. In addition, a post hoc regression was performed in a similar manner using risk difference as the effect estimate. This was performed because risk ratio is a relative measure and therefore can be insensitive to differences in baseline ASCVD risk. However, the risk difference (or attributable risk) is an absolute measure and is more sensitive to baseline ASCVD risk. The meta-regression and primary analysis were performed using Comprehensive Meta-Analysis Version 3 (2013; Biostat, Englewood, NJ). The forest plots were created with Review Manager (RevMan [Computer program], Version 5.3; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

An exploratory analysis was also performed investigating the year of study publication and aspirin's treatment effect for primary ASCVD prevention. A subgroup analysis was performed between those studies published prior to 2010 (older) and those studies published during or after 2010 (newer). Summary RRs with 95% CI were calculated for both newer and older trials. Each group was assessed for heterogeneity, and the test for subgroup differences was performed using chi-squared and I^2 to assess for heterogeneity of treatment effect between older and newer RCTs. An additional subgroup analysis was performed between those studies using higher doses of aspirin (>100 mg per day) and lower doses of aspirin (≤100 mg per day) analyzing bleeding risk. The test for subgroup differences was also applied.

RESULTS

We identified 12 RCTs[2,3,5,10-18] that compared aspirin with nonaspirin (either placebo or control) for primary ASCVD prevention (n = 145,435), which included a total of 963,829 patient-years of follow-up (Figure 1 and Table 1). The risk of bias in the included RCTs was judged to be low to moderate, as 23/72 (32%) of the domains were graded as high or questionable bias (Figure 2). Included studies were published from 1988-2018 and the dose of aspirin ranged from 75-500 mg (Table 1). Among trials that reported mean age, the weighted mean age of participants was 62.7 years. The mean follow-up duration was 6.8 years (weighted mean 6.1 years). The rate of ASCVD events in the control arms

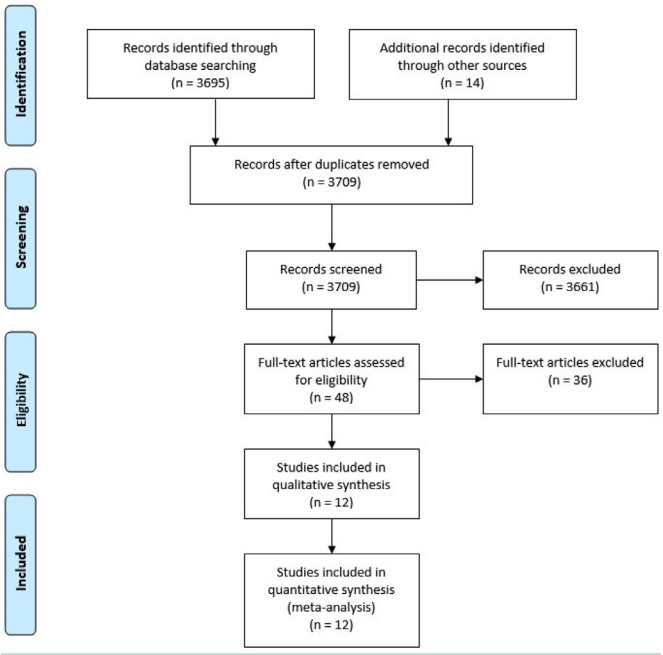

Figure 1 This figure is the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram and represents the number of studies screened, assessed, and included in the meta-analysis.

ranged from 2.1 to 27.8 events per 1000 patient-years, with a median of 7.4 events per 1000 patient-years (Table 2). Aspirin was associated with a statistically significant reduction in ASCVD events compared with no aspirin (4.7 vs 5.3 events per 1000 patient-years; RR 0.86; 95% CI, 0.79-0.92; Figure 3) using the random effects model. There was heterogeneity found among trials analyzing ASCVD events (chi-squared = 16.60, $P = .12$, $I^2 = 34\%$). The meta-regression analysis found no relationship between the log RR of aspirin's treatment effect on ASCVD events and incidence of ASCVD events per 1000 patient-years in the control arm of each trial ($Tau^2 = 0.005$, $I^2 = 33\%$, $R^2 = 0.00$, regression coefficient = −0.008 [95% CI, −0.02-0.007]; Figure 4). When performing the meta-regression using risk difference as the measure of effect estimate, there was no statistically significant relationship between the risk difference of aspirin's treatment effect on ASCVD events and incidence of ASCVD events per 1000 patient-years in the control arm of each trial, although the data trended toward an increased benefit ($Tau^2 = 0.00$, $I^2 = 41.92\%$, $R^2 = 0.59$, regression coefficient = −0.0008 [95% CI, −0.0016-0.00]).

For major bleeding, the event rate in the control arm of RCTs ranged from 0.6 to 8.0 per 1000 patient-years, with a median of 1.6 events per 1000 patient-years (Table 2). Aspirin use resulted in a statistically significant increase in major bleeding events compared with control (2.5 vs 1.8 events per 1000 patient-years; RR 1.41; 95% CI, 1.29-1.54). There was no evidence of heterogeneity among the RCTs when analyzing major bleeding (chi-squared = 9.54, $P = .57$, $I^2 = 0\%$) (Figure 5). The meta-regression analysis

Table 1 Baseline Characteristics of the Included Randomized Controlled Trials*

Study	Year	Follow-Up (Years)	Number of Participants (Mean Age) and Population	Dose of Aspirin	Trial Design	Primary Outcome
BMD[10]	1988	5.9	5139 (mean age not reported), British male physicians	300 mg or 500 mg daily	Open-label	Incidence of vascular events (myocardial infarctions and cerebrovascular events) and mortality
PHS[11]	1989	5.0	22071 (mean age not reported), male physicians	325 mg every other day	Placebo-controlled, 2 × 2 factorial design also testing beta-carotene	Cardiovascular mortality
TPT[17]	1998	6.8	2540 (58 years), men with high risk of ischemic heart disease	75 mg daily	Placebo-controlled, 2 × 2 factorial design also testing warfarin	All ischemic heart disease (coronary death, fatal MI, nonfatal MI)
PPP[18]	2001	3.6	4495 (64 years), men and women with one or more cardiovascular risk factors	100 mg daily	Open-label, 2 × 2 factorial design also testing vitamin E	Cumulative rate of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke
WHS[12]	2005	10.1	39876 (55 years), healthy women	100 mg every other day	Placebo-controlled, 2 × 2 factorial design also testing vitamin E	Composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes
POPADAD[13]	2008	6.7	1276 (60 years), men and women with diabetes and asymptomatic ABI 0.99 or less	100 mg daily	Placebo-controlled, 2 × 2 factorial design also testing antioxidant	Composite of death from coronary heart disease or stroke, nonfatal myocardial infarction or stroke, or amputation above the ankle for critical limb ischemia
JPAD[14]	2008	4.4	2539 (65 years). men and women with type II diabetes	81 or 100 mg daily	Open-label	Atherosclerotic events (fatal and nonfatal ischemic heart disease, fatal and nonfatal stroke and PAD)
AAA[15]	2010	8.2	3350 (62 years), men and women with ABI <0.95	100 mg daily	Placebo-controlled	Composite of initial fatal or nonfatal coronary event or stroke or revascularization
JPPP[16]	2014	5.0	14464 (71 years), men and women with one or more cardiovascular risk factors	100 mg daily	Open-label	Composite of death from cardiovascular events, nonfatal stroke, and nonfatal myocardial infarction
ARRIVE[5]	2018	5	12546 (64 years), men with 2 or more cardiovascular risk factors and women with 3+ risk factors	100 mg daily	Placebo-controlled	Composite outcome of time to first occurrence of cardiovascular death, myocardial infarction, unstable angina, stroke, or TIA

Table 1 (*Continued*)

Study	Year	Follow-Up (Years)	Number of Participants (Mean Age) and Population	Dose of Aspirin	Trial Design	Primary Outcome
ASCEND[2]	2018	7.4	15480 (63 years), men and women with diabetes	100 mg daily	Placebo-controlled	First serious vascular event, first major bleeding event
ASPREE[3]	2018	4.7	19114 (74 years), healthy elderly males and females	100 mg daily	Placebo-controlled	Composite of death, dementia, and persistent physical disability (disability-free survival)

ABI = ankle brachial index; CVD = cardiovascular disease; MI = myocardial infarction; PAD = peripheral arterial disease; TIA = transient ischemic attack.
*Includes trial design, follow-up, number of participants, mean age, dose of aspirin, frequency of aspirin, and primary outcome.

found no statistically significant relationship between the log RR of aspirin's treatment effect on major bleeding and the rate of ASCVD events in the control arm of RCTs (Tau^2 = 0.00, I^2 = 0.0%, R^2 = 0.00, regression coefficient = 0.005 [95% CI, −0.025-0.016]; Figure 6).

The results of the exploratory analysis revealed in older trials (n = 7, published before 2010) that aspirin use resulted in a statistically significant reduction in ASCVD events (RR 0.80; 95% CI, 0.74-0.87). There was nonstatistically significant heterogeneity observed in this subgroup (chi-squared = 12.14, P = .06, I^2 = 51%). Among newer trials (n = 5, published in 2010 or later), aspirin use also resulted in a reduction in ASCVD events (RR 0.91; 95% CI, 0.84-0.98), and there was no heterogeneity (chi-squared = 2.71, P = .61, I^2 = 0%). When performing the test for subgroup differences there was significant heterogeneity of aspirin's treatment effect between older and newer published trials (chi-squared = 4.77, P = .03, I^2 = 79.1%), meaning aspirin had a greater treatment effect in older trials compared with newer trials. A subgroup analysis was performed comparing higher doses of aspirin (>100 mg per day) with lower doses of aspirin (≤100 mg per day). There was no heterogeneity of treatment effect between higher vs lower aspirin doses and major bleeding events (chi-squared = 0.02, P = .89, I^2 = 0%).

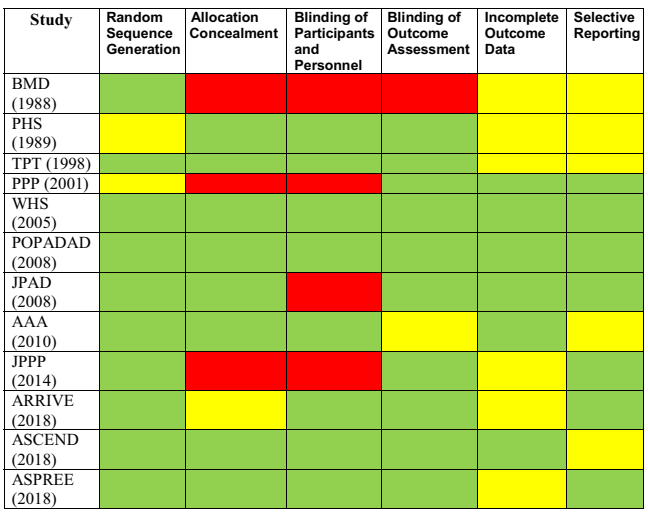

Figure 2 Each included trial was assessed for bias in the domains of random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. Green indicates no risk of bias; red indicates high risk of bias; yellow indicates unclear risk of bias.

DISCUSSION

The two main findings of our study were: 1) spirin resulted in a statistically significant reduction in ASCVD events when used for primary prevention (4.7 vs 5.3 events per 1000 patient-years), but is unlikely to be clinically significant given the increased rate of major bleeding observed with aspirin use (2.5 vs 1.8 per 1000 patient-years; RR 1.41; 95% CI, 1.29-1.54) and 2) meta-regression based on ASCVD event rates in the control arms of primary prevention trials did not find an association of aspirin's treatment effect on the RR of ASCVD events or major bleeding. When performing the regression on the risk difference, these results trended toward an increased benefit for aspirin in higher-risk patients, but this finding did not meet statistical significance. These findings provide evidence against the notion that patients with the highest cardiovascular risk will garner a net benefit from primary prevention aspirin use. As far as we know, this is the first study to perform a meta-regression to assess aspirin's treatment effect in relationship to baseline cardiovascular risk of the clinical trial populations under review. The strength of this technique is that it allows an assessment of aspirin's treatment effect that is based on, not the inclusion criteria of a trial, but the actual event rates of included patients. This assessment of risk represents both known and unknown factors in the baseline population. This was useful, as only three RCTs included baseline ASCVD risk assessments for trial participants.[2,5,12]

The median ASCVD event rate of participants in the control arm populations of this meta-analysis was 7.4

Table 2 ASCVD Events and Major Bleeding Events Per 1000 Patient-Years in Each Trial in the Aspirin Arm and Control Arm

Study Name (Year)	ASCVD Events per 1000 Patient-Years in the Aspirin Arm	ASCVD Events per 1000 Patient-Years in the Control Arm	Major Bleeding per 1000 Patient-Years in the Aspirin Arm	Major Bleeding per 1000 Patient-Years in the Control Arm
BMD (1988)[10]	9.5	9.4	1.7	1.6
PHS (1989)[11]	4.2	5.8	1.3	0.7
TPT (1998)[17]	10.8	14.5	1.3	0.7
PPP (2001)[18]	4.1	6	3.1	1.8
WHS (2005)[12]	1.8	2.1	0.9	0.7
POPADAD (2008)[13]	18.5	27.8	11.2	8
JPAD (2008)[14]	6.2	7	1.8	1.3
AAA (2010)[15]	8.7	9	2.5	1.5
JPPP (2014)[16]	3.1	4.1	2.8	1.6
ARRIVE (2018)[5]	5.2	5.4	0.9	0.6
ASCEND (2018)[2]	9.2	10	5.5	4.3
ASPREE (2018)[3]	7.1	7.8	8.1	5.9

ASCVD = atherosclerotic cardiovascular disease.

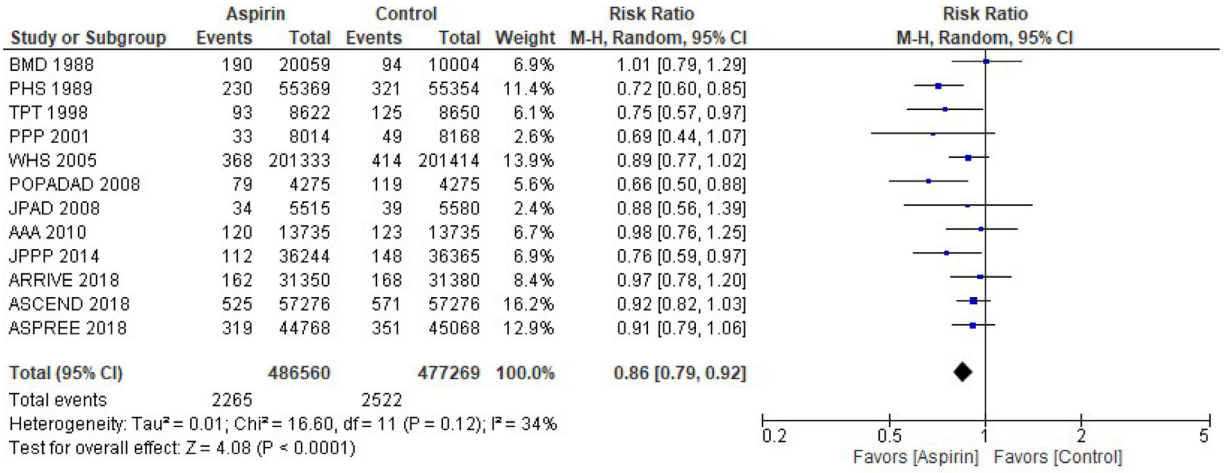

Figure 3 This figure displays the forest plot that shows the rate ratio and 95% confidence interval for aspirin's treatment effect on atherosclerotic cardiovascular disease events among participants randomized to aspirin vs control. For each included study, events and patient-years from each arm are reported.

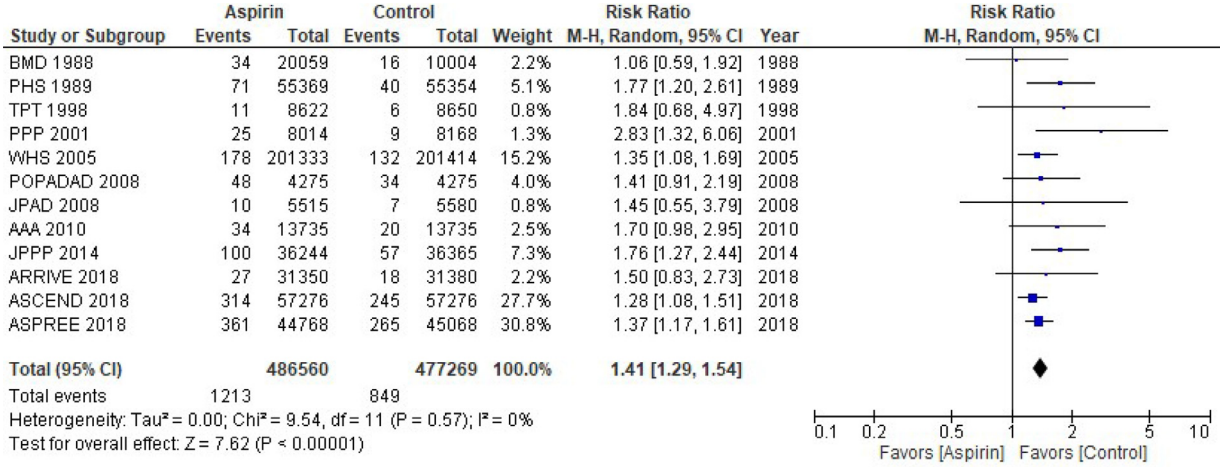

Figure 4 This figure displays the forest plot that shows the rate ratio and 95% confidence interval for aspirin's treatment effect on major bleeding among participants randomized to aspirin vs control. For each included study, events and patient-years from each arm are reported.

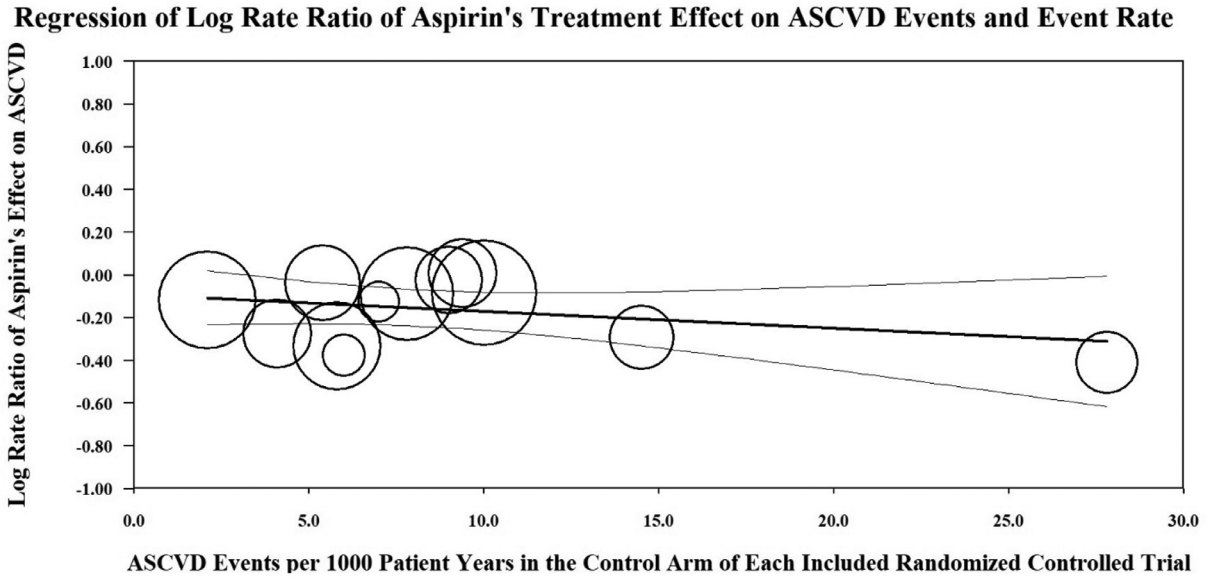

Figure 5 This figure represents the random effects meta-regression. The log rate ratio of aspirin's treatment effect on atherosclerotic cardiovascular disease (ASCVD) events from each trial is plotted on the y-axis. The rate of ASCVD events in the control arm of included randomized trials (moderator variable) is plotted on the x-axis. Each circle on the graph represents an included randomized trial, and the size of the circle is proportional to the weight each study had in the regression model. The darker line in the center is the regression line, and the lighter colored, outer lines represent the 95% confidence interval.

per 1000 patient-years, and the mean ASCVD event rate was 5.3 events per 1000 patient-years. Aspirin use resulted in only 0.6 fewer events per 1000 patient-years. To put this in perspective, the HOPE-3 trial was a primary prevention trial comparing rosuvastatin to placebo in intermediate-risk patients (1% annual risk of cardiovascular disease). Overall, there were 8.6 events per 1000 patient-years in the placebo arm, and rosuvastatin was found to reduce this by 2 ASCVD events (6.6 events per 1000 pateint-years in the rosuvastatin

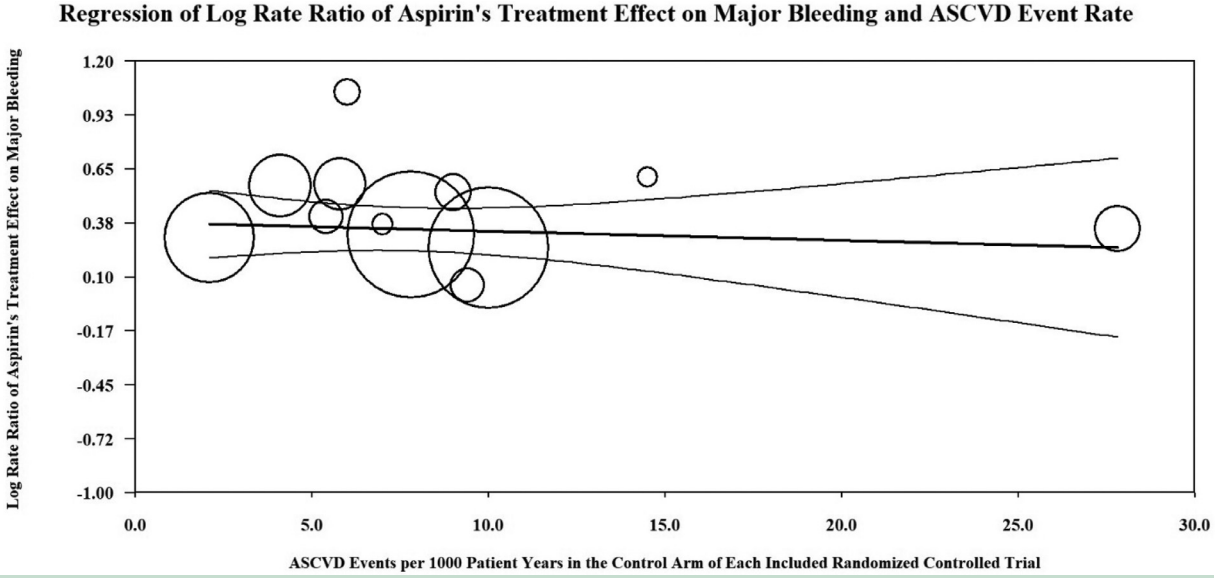

Figure 6 This figure represents the random effects meta-regression. The log rate ratio of aspirin's treatment effect on major bleeding from each trial is plotted on the y-axis. The rate of atherosclerotic cardiovascular disease events in the control arm of included randomized trials (moderator variable) is plotted on the x-axis. Each circle on the graph represents an included randomized trial, and the size of the circle is proportional to the weight each study had in the regression model. The darker line in the center is the regression line, and the lighter colored, outer lines represent the 95% confidence interval.

arm).[19] Furthermore, in the SPRINT trial, which compared intensive vs standard hypertension treatment in patients with and without prior cardiovascular disease, the rate of ASCVD events was 21.1 per 1000 patient-years in the standard arm and 17.7 events per 1000 patient-years in the intensive group, with a reduction of 3.4 ASCVD events per 1000 patient-years. In this study population, about 20% of patients had a diagnosis of prior cardiovascular disease at baseline.[20]

Recently published RCTs have cast doubt on aspirin's role in primary prevention. In patients with diabetes, the ASCEND trial found a 1.1% absolute risk reduction in ASCVD events with aspirin after 7.4 years of follow-up. However, this benefit was counterbalanced by a 0.9% increase in major bleeding (4.1% in the aspirin arm vs 3.2 % in the placebo arm).[2] In elderly patients, the ASPREE trial showed no benefit for aspirin despite increasing the risk of major bleeding and all-cause mortality after 4.7 years of follow-up. The increased mortality was attributed primarily to cancer-related deaths.[3,4] In adults with moderate to high cardiovascular risk (mean 10-year ASCVD risk of 10%-20%), the ARRIVE trial found no ASCVD benefit for those randomized to aspirin compared with placebo, though the observed ASCVD event rate throughout all trial participants was lower than expected.[5]

The results of our meta-analysis are consistent with two recently published meta-analyses. Zheng and Roddick's[21] analysis included 13 RCTs with 164,225 participants, with 1,050,511 years of patient follow-up. They found a reduction in ASCVD events among participants randomized to aspirin (hazard ratio 0.89; 95% CI, 0.84-0.94). This reduction was small, with an absolute risk reduction of 0.41% and a calculated number needed to treat of 241. There was also an increased risk of major bleeding as defined by the individual studies, with a hazard ratio of 1.43 (95% CI, 1.30-1.56) and an absolute risk increase of 0.47%, with a number needed to harm of 210.[21] This study included 13 RCTs, while our analysis included 12. We excluded the HOT trial[22] from our analysis as more than 8.0% of participants in the trial had previously diagnosed ASCVD. Another recent meta-analysis found similar results. Shah et al[23] analyzed 14 RCTs and found a reduction in ASCVD events (RR 0.84; 95% CI, 0.75-0.94). The risk of major bleeding was also increased with aspirin (RR 1.49; 95% CI, 1.32-1.69). An additional subgroup analysis was performed based on year of the published study. When analyzing only older trials (published prior to 2005), aspirin reduced ASCVD events. However, when analyzing only newer trials (published since 2005), aspirin had no effect on the rate of ASCVD events compared with placebo. Both older and newer trials found increased rates of major bleeding among participants randomized to aspirin.[23] In addition to including the HOT trial,[22] this meta-analysis also included the Early Treatment Diabetic Retinopathy Study (ETDRS). ETDRS was excluded from our analysis, as >10% of participants had known ASCVD prior to the start of the study.[24]

Several limitations of the current analysis are worth discussing. This meta-analysis included older RCTs from the 1980s. Cardiovascular disease prevention strategies were different then than now. It has been suggested that fewer participants were taking statin medications for lipid lowering and more participants used tobacco during that time period.[25] This could make the analysis less applicable to current practice and preventative strategies. Statin use across all trials was investigated, however, only 5 of 12 included studies (42%) reported statin use, and no study published prior to the year 2000 reported its use. Furthermore, there was variability in the dose and frequency of aspirin used (Table 1). Not all trials tested low-dose aspirin, which is commonly recommended for primary prevention. In the United States, aspirin 81 mg once per day is commonly used for primary prevention, and no included RCT tested this specific dose of aspirin. Also, major bleeding was defined by the individual RCT and was not standardized across all trials. In addition, a subgroup analysis was attempted with higher-risk groups within each trial; however, this was unable to be performed, as only 2 RCTs provided high-risk subgroup data.[5,12] It is also important to know that meta-regressions and subgroup analyses are observational in nature and are subject to study-level confounders. Our data could also be subject to a bias known as regression to the mean, where a falsely high control group risk will give rise to a falsely high treatment effect estimate and vice versa. This analysis did not control for regression to the mean.

In conclusion, these data suggest that aspirin has limited efficacy for the primary prevention of ASCVD. More importantly, in patients at high risk of their first myocardial infarction or stroke, the treatment effect of aspirin for ASCVD prevention is not greater compared with those at lower risk. While there was a statistically significant reduction in ASCVD events among individuals randomized to aspirin, this is unlikely to be clinically significant when bleeding risk is taken into consideration. Furthermore, this reduction in ASCVD events is less than other treatment modalities aimed at primary prevention, including statins for those at intermediate risk and intensive blood pressure control among hypertensive patients. Despite the thought that aspirin for primary prevention may still be useful for those at high risk for ASCVD, insufficient randomized data currently exist to recommend aspirin in this group.

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