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Aspirin for primary prevention of cardiovascular outcomes in diabetes mellitus: An updated systematic review and meta-analysis

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Abstract

Background: The safety and efficacy of aspirin for the primary prevention of cardiovascular disease in patients with diabetes mellitus remains controversial.

Design: A meta-analysis to investigate the effects of aspirin for the prevention of cardiovascular disease in diabetes mellitus.

Methods: Ten randomized controlled trials were selected using MEDLINE, EMBASE and CENTRAL databases until 27 September 2018. Risk ratios (RRs) with 95% confidence intervals (CIs) and risk differences (RDs) reported as incident events per 1000 person-years were calculated.

Results: In 33,679 patients, aspirin did not significantly reduce the risk of major adverse cardiovascular outcomes (RR 0.93, 95% CI 0.87–1.00, $P = 0.06$; RD −0.68 incident cases per 1000 person-years (95% CI −1.54, 0.17)), cardiovascular mortality (RR 0.95, 95% CI 0.83–1.09, $P = 0.49$; RD 0.11 incident cases per 1000 person-years (95% CI −0.80, 1.02)), myocardial infarction

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Author contribution

SUK contributed to the conception or design of the work. MUK, FA, MSK, ANL and ST contributed to the acquisition, analysis, or interpretation of data for the work. SUK and ZUAA drafted the manuscript. FM, RK and EK critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work ensuring integrity and accuracy.

Declaration of conflicting interests

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(RR 0.91, 95% CI 0.75–1.11, $P = 0.36$; RD −0.66 incident cases per 1000 person-years (95% CI −2.07, 0.75)), or stroke (RR 0.91,95% C, 0.76–1.10, $P = 0.33$; RD −0.55 incident cases per 1000 person-years (95% CI −1.57, 0.47)). There was a significantly higher risk of total bleeding associated with aspirin (RR 1.29, 95% CI 1.07–1.55, $P = 0.01$; RD 1.49 incident cases per 1000 person-years (95% CI 0.36, 2.61)).

Conclusion: The use of aspirin for primary prevention of cardiovascular disease in patients with diabetes mellitus increases the risk of total bleeding without reducing the risk of major adverse cardiovascular outcomes.

Keywords

Cardiovascular disease; diabetes mellitus; primary prevention; aspirin

Background

Aspirin is widely used in patients with established cardiovascular disease (CYD) to prevent major adverse cardiovascular events (MACEs).[1,2] Diabetes mellitus (DM) is associated with a higher risk of CVD.[3,4] While the use of aspirin therapy in DM has increased over time, the role of aspirin for the primary prevention of CVD in DM remains controversial.[4–6] The American College of Cardiology/American Heart Association and American Diabetes Association guidelines advocate the use of low dose aspirin in diabetes patients tailored to the individual risk of CVD and bleeding;[6] whereas the 2016 European Society of Cardiology (ESC) guidelines give the use of aspirin for primary prevention in DM a class III recommendation (evidence or general agreement that given treatment is not effective and might be harmful in some cases; therefore its use is not recommended).[5]

While the current guidelines are largely based on the previous randomized controlled trials (RCTs), a recently published, large ASCEND trial has shed further light on this topic and has the potential to impact clinical practice.[3]

Aim

We performed a meta-analysis to update the evidence base regarding the efficacy and safety of aspirin for the primary prevention of CVD in patients with DM.

Methods

This trial-level meta-analysis was carried out according to the Cochrane Collaboration guidelines and PRISMA statement. We searched RCTs in MEDLINE, EMBASE and the CENTRAL databases until 27 September 2018 using broad search terms (‘aspirin’, ‘salicylic arid’, ‘salicylates’, ‘diabetes mellitus’, ‘primary prevention’, ‘myocardial infarction’, ‘stroke’, ‘transient ischemic attack’, ‘revascularization’, ‘bleeding’ and ‘mortality’). Two authors (MUK and ST) screened studies based on prespecified inclusion criteria: (a) RCTs reporting data on 500 or more diabetes patients (to provide more reliable estimates)[7] receiving aspirin for the primary prevention of CVD for one year or more; and (b) reporting primary or secondary cardiovascular and bleeding outcomes of interest.

Two independent authors (MUK and ST) extracted data on the baseline variables of participants, treatment groups, events, crude estimates, sample size and followup duration of trials on a standard data collection form. Appendices of trials were reviewed for additional information. When provided, data extraction was done on an intention to treat principle. If a trial reported data on different lengths of follow-up, we defaulted to abstracting data on the longer follow-up duration. Authors (MSK and ST) assessed the quality of each trial on the Cochrane risk of bias scale (Table 1).

The data were adjudicated by SUK and any disagreements related to data or quality assessment of the trials were resolved by mutual consensus or referring to the original article. Estimates from each trial were selected most closely to approximate the target primary endpoint of MACE, which consisted of non-fatal myocardial infarction (MI), non-fatal stroke and cardiovascular death. The secondary endpoints were MI, stroke, cardiovascular death, angina, revascularization, transient ischemic attack, all-cause mortality, cancer, cancer-related death, total bleeding, gastrointestinal bleeding and intracranial hemorrhage (ICH).

Comprehensive neta-analysis software version 3.0 (Biostat, Englewood, NJ, USA) was used for performing meta-analysis. Risk ratios (RRs) with 95% confidence intervals (CIs) were used as summary statistics, which were derived from an analysis with adjusted models by person-years (a measure integrating study duration) to compensate for potential differences in study follow-up duration. Risk differences (RDs) were reported as incident events per 1000 person-years. Outcomes were pooled using the DerSimonian and Laird random effects model. Heterogeneity was assessed using Cochrane Q statistics and I^2 with values of 75% or greater consistent with a high degree of heterogeneity. Publication bias was assessed using Egger's regression test. All analyses were conducted at the 5% significance level.

Results

The initial electronic search yielded 2286 citations; 973 citations were removed as duplicates and 915 studies were excluded at title and abstract level screening. Furthermore, 388 full text articles were removed based on a priori selection criteria (Figure 1).

Finally, 10 RCTs (33,679 patients) were included in the analysis. Four trials[3,8–10] were conducted exclusively in diabetes patients and six trials[11–16] provided subgroup analysis data for diabetes patients. Most trials used an aspirin dose of 100 mg/day and the average drug compliance across the trials was 74.5%. The weighted mean follow-up duration was 6.17 ± 2.41 years. Table 1 describes the baseline characteristics of included RCTs and participants, while Table 2 demonstrates the effect of aspirin on all outcomes of interest.

The use of aspirin was not associated with a reduction in the risk of MACEs (RR 0.93, 95% CI 0.87–1.00, $P = 0.06$; RD −0.68 incident cases per 1000 person-years (95% CI −1.54, 0.17)), cardiovascular mortality (RR 0.95, 95% CI 0.83–1.09, $P = 0.49$; RD 0.11 incident cases per 1000 person-years (95% CI −0.80, 1.02)), MI (RR 0.91, 95% CI 0.75–1.11, $P = 0.36$; RD −0.66 incident cases per 1000 person-years (95% CI −2.07, 0.75)), or stroke (RR

0.91, 95% CI 0.76–1.10, $P = 0.33$; RD −0.55 incident cases per 1000 person-years (95% CI −1.57, 0.47)) (Figure 2).

Conversely, there was a significantly higher risk of total bleeding associated with use of aspirin compared with control (RR 1.29, 95% CI 1.07–1.55, $P = 0.01$; RD 1.49 incident cases per 1000 person-years (95% CI 0.36, 2.61)) (Figure 3).

Aspirin had no significant effect on the risk of other cardiocvascular outcomes, mortality, gastrointestinal bleeding, ICH or the incidence of cancer (Table 2). Eggers' regression test did not show a publication bias (P value (two-tailed) = 0.23).

Conclusion

This up-to-date meta-analysis suggests that over a mean follow-up duration of 6 years, the use of aspirin in 33,679 diabetes patients was not associated with a significant reduction in MACEs. Conversely, there was a significantly higher risk of bleeding associated with the use of aspirin. These findings are novel and demand serious clinical consideration regarding the role of aspirin for the primary prevention of cardiovascular outcomes in diabetes patients.

The Anti-Thrombotic Trialists' Collaboration reported that aspirin reduces the risk of cardiovascular outcomes by approximately 25% in patients with vascular disease and diabetes;[17] whereas earlier RCTs of diabetes showed no cardiovascular benefit with use of aspirin.[8–10] The recent ASCEND trial (15,480 patients) showed that the modest cardiovascular benefit achieved by aspirin was largely offset by bleeding events.[3] In absolute terms, approximately 91 patients would need to be treated to prevent one serious cardiovascular event and approximately 112 would need to be treated to cause a major bleed over a mean follow-up of 7.4 years. Comparatively, our cumulative analysis suggests a number needed to harm of approximately 109 cases, while 192 cases would need to be treated to prevent one MACE. These findings indicate that the risk of using aspirin clearly outweighs any potential benefit. Furthermore, like the ASCEND trial, the proposed benefit of cancer prevention with the use of aspirin was also not observed in this analysis.[3]

We compared our results with previous meta-analyses. Butalia et al. (seven RCTs, 11,618 patients) showed that aspirin prevented 109 MACEs per 10,000 patients at the cost of 19 major bleeding events (the RR for the later was not statistically significant).[18] Kunutsor et al. (10 RCTs, 16,690 patients) showed similar results with a 10% reduction in RR of MACEs ($P = 0.03$) with aspirin, but without significantly increasing the rates of bleeding (RR 2.23, 95% CI 0.79–6.34).[19] However, this study included some trials with extremely small sample sizes (i.e. 68 patients), which poses the risk of small study effects.[7] Kokoska et al. (six RCTs, 10,117 patients) were inconclusive regarding the safety and efficacy of aspirin in diabetes.[20] Compared to these meta-analyses,[18–20] the current study should be considered more valid due to robust inclusion criteria which allowed us to generate reliable estimates. Furthermore, this meta-analysis is updated with new evidence on this topic, which enabled us to assess relevant clinical outcomes in the largest pool of trials and participants at an extended follow-up duration.

However, this study does have certain shortcomings. Due to lack of access to individual patient data, heterogeneities related to certain variables, i.e. baseline cardiovascular risk, hemoglobin A1c level, duration of diabetes, BMI or weight could not be adjusted for. Despite this, it appears that each of the trials recruited patients with overall low cardiovascular risk, based on several different cardiovascular risk assessment criteria. The trials included were published from 1989 to 2018 and represent obvious variations in terms of the use of cardiovascular risk-modifying therapies, such as statins or antihypertensive agents, which can ultimately impact cardiovascular outcomes. Finally, it is possible that certain outcomes of interest were not adequately powered for across all the trials.

In summary, our current analysis suggests that aspirin should not be used for the primary prevention of cardiovascular outcomes in diabetes patients in view of the lack of cardiovascular benefits and a higher risk of bleeding. These findings are in line with ESC guidelines and demand an assessment and review of the American professional guidelines.

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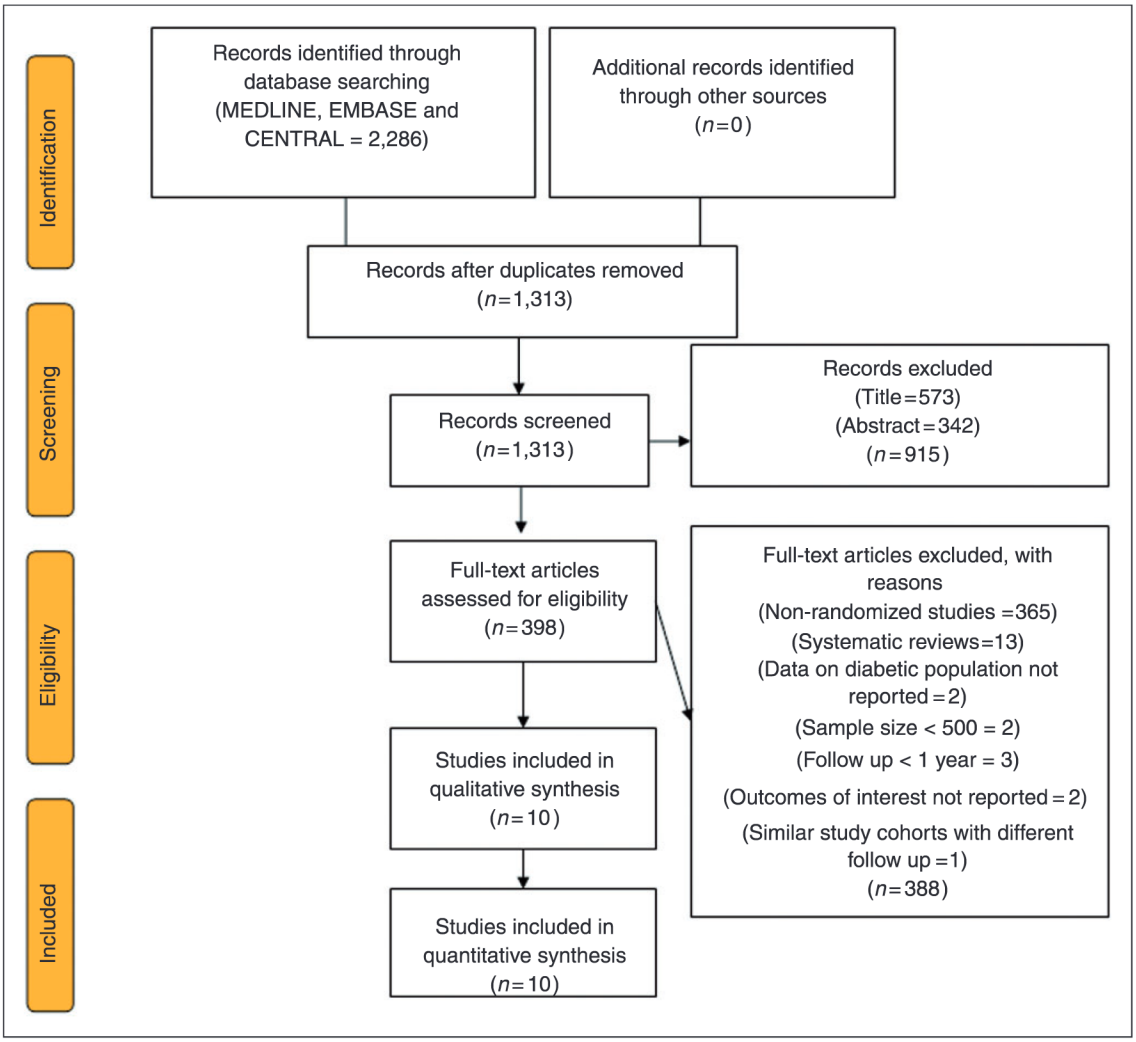

Figure 1.
PRISMA flow chart showing study selection process.

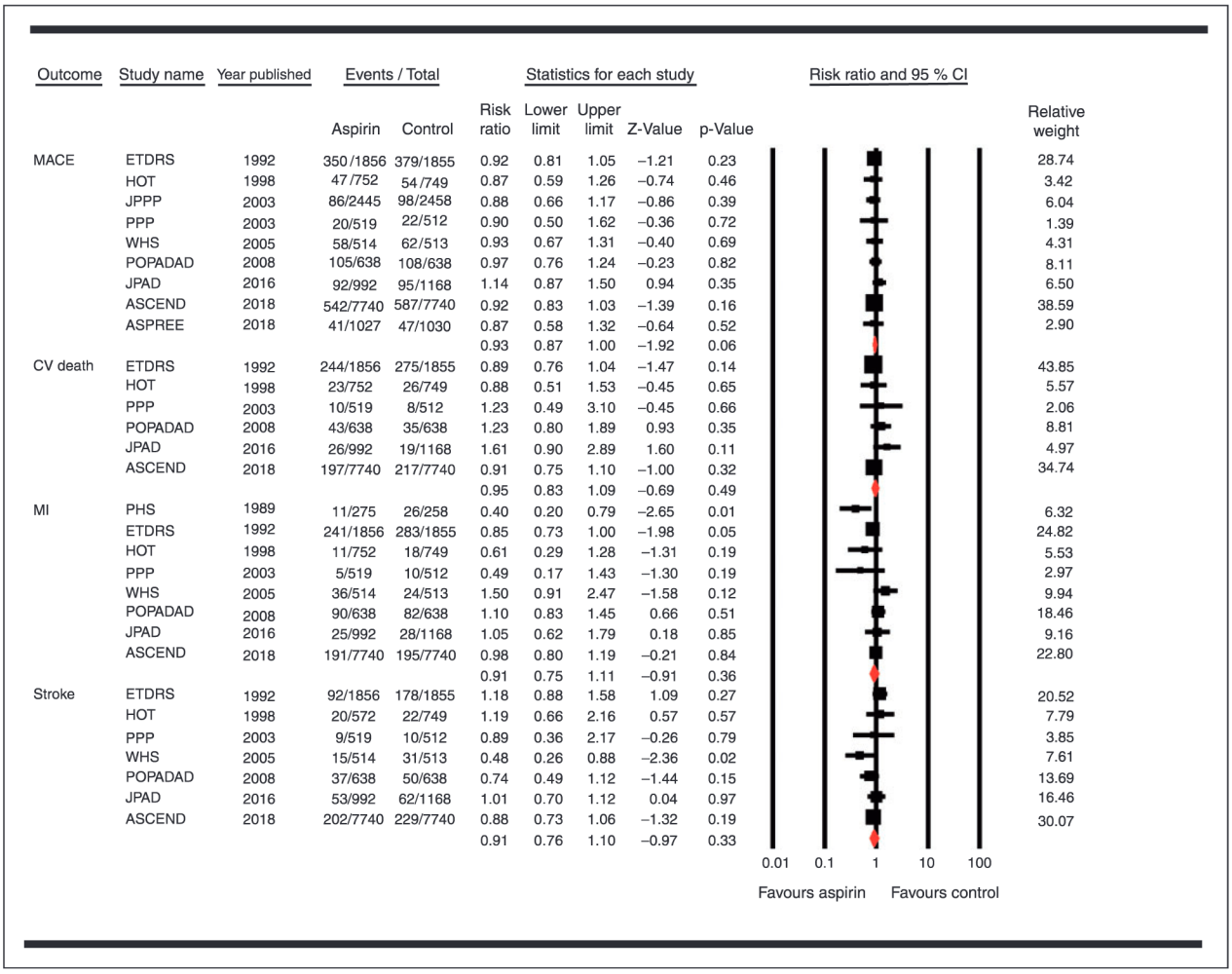

Figure 2.

Forest plot comparing aspirin versus control for major adverse cardiovascular events (MACEs), cardiovascular mortality, myocardial infarction (MI) and stroke.

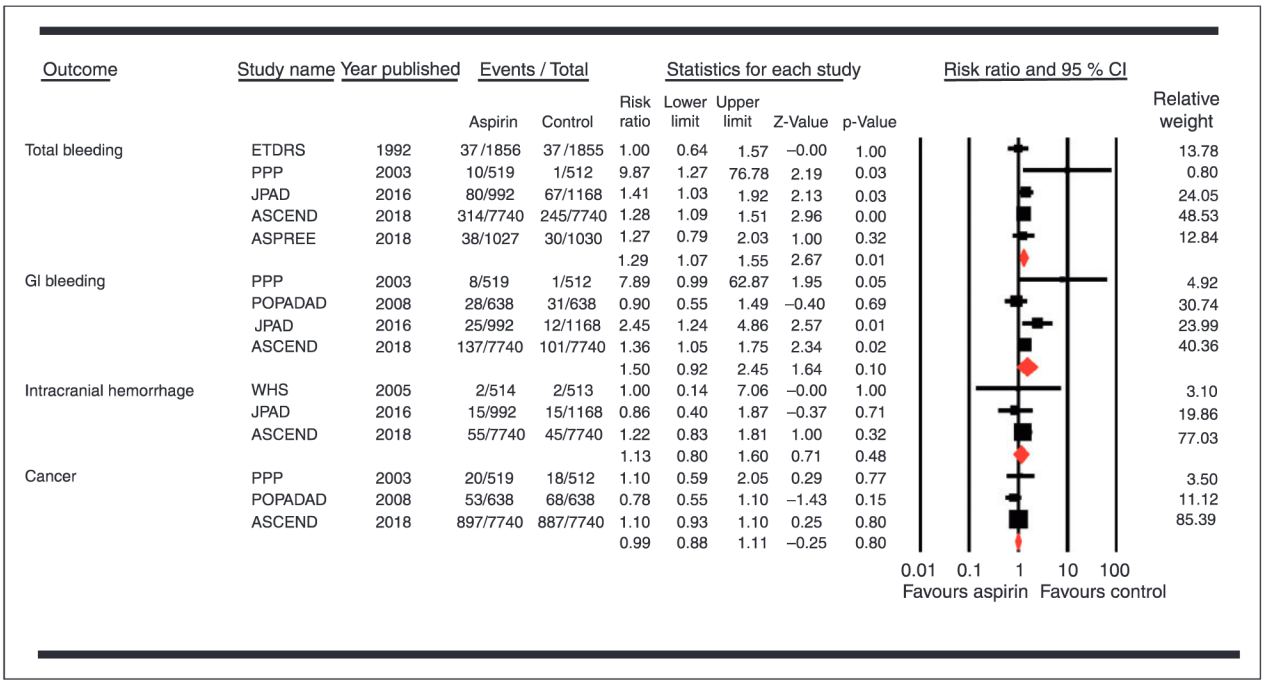

Figure 3.
Forest plot comparing aspirin versus control for safety outcomes.

Table 1.

Baseline characteristics of the selected studies and participants.

Study/year	Location	Population	Diabetes patients (*n*)	Age groups	Men (%)	Aspirin dose	Medication compliance (%)	Follow-up (years)	CRoB[b]
PHS 1989[11]	USA	Healthy men	533	40–84	100	325 mg every other day	–	5.0	*****
ETDRS 1992[8]	USA	Diabetes patients	3711	18–70	56.5	650 mg daily	91.8	5.0	*****
HOT 1998[1,2]	Europe, America, Asia	Patients with hypertension	1501	50–80	53.0	75 mg daily	–	3.8	*****
PPP 2003[1,3]	Italy	>50 Years with known cardiovascular risk factors	1031	64.3[a]	48.2	100 mg daily	71.8	3.7	*****
WHS 2005[1,4]	USA	Healthy women	1027	≥45	0.0	100 mg on alternate days	–	10.1	******
POPADAD 2008[9]	UK	Participants >40 years with diabetes	1276	≥40	44.1	100 mg daily	50.0	6.7	******
JPAD 2017[10]	Japan	Diabetes patients	2160	65[a]	55.0	81 or 100 mg daily	90.0	10.3	******
JPPP 2014[1,5]	Japan	Patients >60 years with multiple risk factors	4903	60–85	42.3	100 mg daily	76.0	5.0	*****
ASCEND 2018[3]	UK	Participants >40 years with diabetes	15480	>40	62.5	100 mg daily	70.0	7.4	******
ASPREE 2018[1,6]	Australia, USA	Healthy elderly >65 years	2057	≥65	43.6	100 mg daily	72.9	4.7	******

[a]Average age.

[b]CRoB consists of seven domains: randomization (selection bias); allocation concealment (selection bias); blinding of patients and personnel (performance bias); blinding of outcome assessment (detection bias); incomplete data reporting (attrition bias); selective reporting (reporting bias) and other biases. Each domain carries one star and five or more stars qualify for a good quality study.

ASPREE: Aspirin in Reducing Events in the Elderly Trial; ASCEND: A Study of Cardiovascular Events in Diabetes Trial; BMD: British Male Doctors study; CRoB: Cochrane Risk of Bias Scale; ETDRS: Early Treatment Diabetic Retinopathy Study; HOT: Hypertension Optimal Treatment trial; JPAD: Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; JPPP: Japanese Primary Prevention Project; PHS: Physicians' Health Study; POPADAD: Prevention Of Progression of Arterial Disease And Diabetes; PPP: Primary Prevention Project; WHS: Women's Health Study.

Table 2.

Effect of aspirin on clinical endpoints.

Outcome	No. of studies	Patients (*n*)	Patients with events/total no. (%)		Rate ratio (95% CI)	*P* value (I^2)	Risk difference/ 1000 patient-years (95% CI)
			ASPIRIN	CONTROL			
MACE	9	33,146	1341/16,483 (8.13%)	1452/16,663 (8.71%)	0.93 (0.87, 1.00)	0.06 (0%)	−0.68 (−1.54, 0.17)
Cardiovascular death	6	25,159	543/12,497 (4.34%)	580/12,662 (4.58%)	0.95 (0.83, 1.09)	0.49 (13%)	0.11 (−0.80, 1.02)
Myocardial infarction	8	26,719	610/13,286 (4.59%)	666/13,433 (4.95%)	0.91 (0.75, 1.11)	0.36 (53%)	−0.66 (−2.07, 0.75)
Stroke	7	27,033	443/13,345 (3.31%)	513/13,688 (3.74%)	0.91 (0.76, 1.10)	0.33 (33%)	−0.55 (−1.57, 0.47)
Angina	3	4467	115/2149 (5.35%)	134/2318 (5.78%)	0.90 (0.71, 1.14)	0.38 (0%)	−0.46 (−1.87, 0.95)
Revascularization	3	17,787	383/8897 (4.30%)	436/8890 (4.90%)	0.88 (0.77, 1.00)	0.06 (0%)	−0.82 (−1.70, 0.06)
Transient ischemic attack	4	19,947	197/9889 (1.99%)	237/10,058 (2.35%)	0.84 (0.69, 1.01)	0.06 (0%)	−0.36 (−0.84, 0.12)
All-cause mortality	7	27,216	1367/13,524 (10.10%)	1409/13,692 (10.29%)	0.0.99 (0.90, 1.09)	89 (23%)	0.27 (−0.98, 1.52)
Cancer-related death	3	17,617	366/8805 (4.15%)	360/8812 (4.08%)	1.07 (0.78, 1.46)	0.67 (48%)	0.95 (−1.89, 3.79)
Total bleeding	5	24,439	479/12,134 (3.94%)	380/12,305 (3.08%)	1.29 (1.07, 1.55)	0.01 (24%)	1.49 (0.36, 2.61)
Gastrointestinal bleeding	4	19,947	198/9889 (2.00%)	145/10,058 (1.44%)	1.50 (0.92, 2.45)	0.10 (63%)	1.08 (0.09, 2.07)
Intracranial hemorrhage	3	18,667	68/9246 (0.73%)	62/9421 (0.65%)	1.13 (0.80, 1.60)	0.48 (0%)	0.11 (−0.18, 0.41)
Cancer	3	17,787	970/8897 (10.90%)	973/8890 (10.94%)	0.0.99 (0.88, 1.11)	80 (8%)	−0.06 (−1.42, 1.30)