Supplementary Online Content

Zheng SL, Roddick AJ. Association of aspirin use for primary prevention with cardiovascular events and bleeding events: a systematic review and meta-analysis. JAMA. doi:10.1001/jama.2018.20578

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods 1: Search strategy

A systematic review on the efficacy of aspirin for the primary prevention of cardiovascular events was undertaken by the U.S. Preventive Services Task Force was published in 2016. The search included all relevant studies published prior to January 2015.

Therefore the search strategy for this systematic review was conducted to update the previous meta-analysis.

Studies were searched through November 1, 2018.

Search terms were as follows:

Aspirin or Acetylsalicylic acid (t/ab)

AND

Cardiovascular or mortality or myocardial infarction or stroke (t/ab)

AND

Primary prevention (t/ab)

The search was conducted through the Cochrane Central Register of Controlled Trials register, which includes articles indexed on Pubmed and Embase.

eMethods 2: Detailed statistical methods

Estimated trial 10-year cardiovascular risk

In order to investigate the effects of aspirin on cardiovascular and bleeding outcomes in populations across the range of cardiovascular risk, we estimated the cardiovascular risk in individual trials. The primary outcome (cardiovascular mortality, non-fatal MI and non-fatal stroke) was taken as the major cardiovascular event for which risk was calculated. For each trial, the risk of the primary outcome in the group taking no aspirin was calculated, before being divided by the mean follow-up time (in years) to give the annualised event rate. This was then multiplied by ten to give the 10-year estimated event rate. Confidence intervals were estimated by assuming that events were distributed according to a Poisson distribution.

Bayesian Meta-analysis

For the primary meta-analysis, a Bayesian approach was undertaken using the *gemtc* package[1] in R (version 3.4.1)[2] and JAGS (version 4.3.0)[3].

For the frequentist meta-analysis the *meta* package was used[4].

Natural logarithms of reported hazard ratios and corresponding standard errors were extracted from studies where available. The number of events and duration of follow-up (in person-years) were extracted from all other studies, allowing for studies with different lengths of follow-up to be incorporated into the analysis on the hazard ratio scale. This assumes that events occurred at a constant rate during each of these trials.

Fixed- and random-effects models were generated for each outcome using Poisson likelihood and log link using non-informative vague priors[5]. A Markov Chain Monte Carlo (MCMC) approach was used with 5000 adaptation iterations followed by 100,000 iterations of 4 chains. The potential scale reduction factor (PSRF) was used to assess chain convergence, using a cut-off of 1.05[6].

Heterogeneity was assessed using the I^2 statistic. An I^2 of <25% was considered to represent low heterogeneity, 25-50% moderate heterogeneity, and >50% high heterogeneity.

The Deviance Information Criterion was used to select fixed- or random-effects meta-analysis for each outcome, as has been utilized previously[7]. A difference of greater than 3 units was considered important, and the model with the lowest DIC was used for analysis[8]. Where the DIC was similar between models (within 3 units), model selection was achieved based on heterogeneity in the fixed-effect model, with a random-effects model favored if I^2 >25%.

For the Bayesian meta-analysis 95% credible intervals (CrI) were calculated, and 95% CrI that exclude 1 were treated as statistically significant.

Absolute risk difference (ARD)

For each outcome, the absolute risk in the 'no aspirin' population was calculated as the number of events divided by the total number of participants.

The relative risk and 95% confidence intervals (CI) for each outcome were estimated by random-effects frequentist pairwise meta-analysis using the Mantel-Haenzel method. The relative risk and baseline absolute risk were used to calculate the absolute risk difference with corresponding 95% CI. Negative values indicate a reduction in risk with aspirin treatment and positive values indicate an increased risk.

Numbers needed to treat or harm were calculated for all outcomes with a statistically significant reduction or increase in risk.

Cancer outcomes

Incident cancer (defined as new cancer diagnosis) and cancer mortality were additional exploratory endpoints. Data was extracted on cancer outcomes from studies identified in the primary literature search. Additional related publications providing information on cancer outcomes from included studies were searched on PubMed using the trial name, first or senior author, and the term "cancer". Meta-analyses (both using trial level and individual patient data) were identified, with data extracted from them if they could not be identified from trial publications.

eMethods 3: Deviance information criterion and model selection

All patients		DIC			
	Efficacy	**Fixed**	**Random**	I^2 (%) *	**Model**
	Composite outcome	19.38	21.24	0	fixed
	All-cause mortality	14.28	16.27	0	fixed
	Cardiovascular mortality	24.56	26.53	0	fixed
	All myocardial infarction	48.96	38.72	42	random
	Total stroke	30.13	31.30	1	fixed
	Ischemic stroke	25.81	25.72	18	fixed
	Safety				
	Major Bleeding	27.17	28.48	0	fixed
	Intracranial Bleeding	25.40	27.24	0	fixed
	Major GI Bleeding	28.46	29.74	0	fixed
	Cancer				
	Incident Cancer	27.06	27.93	25	random
	Cancer Mortality	29.66	29.25	17	fixed
Low risk	**Efficacy**				
	Composite outcome	8.04	9.81	0	fixed
	All-cause mortality	7.47	8.93	0	fixed
	Cardiovascular mortality	9.15	10.55	0	fixed
	All myocardial infarction	15.68	14.81	32	random
	Total stroke	17.22	16.97	26	random
	Ischemic stroke	14.45	13.75	33	random
	Safety				
	Major Bleeding	11.88	13.46	11	fixed
	Intracranial Bleeding	11.45	13.00	0	fixed
	Major GI Bleeding	13.81	15.15	9	fixed
	Cancer				
	Incident Cancer	11.45	11.03	41	random
	Cancer Mortality	13.30	11.53	42	random
High risk	**Efficacy**				
	Composite outcome	12.71	14.05	0	fixed

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eMethods 3: Deviance information criterion and model selection (Continued)

		DIC			
High risk	**Efficacy**	**Fixed**	**Random**	**I^2 (%)** *	**Model**
	All-cause mortality	8.79	10.02	0	fixed
	Cardiovascular mortality	16.69	18.68	14	fixed
	All myocardial infarction	26.93	26.03	26	random
	Total stroke	18.33	19.38	11	fixed
	Ischemic stroke	16.93	18.25	8	fixed
	Safety				
	Major Bleeding	17.14	17.39	10	fixed
	Intracranial Bleeding	15.05	16.28	0	fixed
	Major GI Bleeding	16.61	16.80	15	fixed
	Cancer				
	Incident Cancer	14.23	15.52	3	fixed
	Cancer Mortality	14.74	16.33	0	fixed
Diabetes	**Efficacy**				
	Composite outcome	12.47	14.06	0	fixed
	All-cause mortality	7.50	8.74	0	fixed
	Cardiovascular mortality	10.15	10.34	51	random
	All myocardial infarction	26.40	27.29	13	fixed
	Total stroke	20.79	21.49	13	fixed
	Ischemic stroke	8.65	6.41	77	random
	Safety				
	Major Bleeding	6.06	7.02	0	fixed
	Intracranial Bleeding	6.03	6.20	1	fixed
	Major GI Bleeding	6.06	6.25	1	fixed
	Cancer				
	Incident Cancer	6.55	6.98	34	random
	Cancer Mortality	8.57	8.90	39	random

*I^2 values obtained from the fixed-effect model.

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eTable 1: Outcome definitions

Trial	Primary	ACM	CVM	MI	All strokes	Ischemic strokes	Major bleeding	Intracranial bleeding	GI bleeding
British Doctors Study[9], 1988	MI, stroke (ischemic, hemorrhagic, unknown), vascular death (including sudden death, pulmonary embolism and hemorrhage)	Any death	Not specified	MI (Not specified)	Ischemic, hemorrhagic and unknown	Diagnosed by clinicians and without the use of CT scanning	ATT meta-analysis (Not defined)	ATT meta-analysis (Not defined)	ATT meta-analysis (Not defined)
Physicians' Health Study[10], 1989	CVM, MI and stroke (ischemic, hemorrhagic, unknown)	Any death	Cardiovascular "mechanism" of death	WHO definition from 1971	Ischemic, hemorrhagic and unknown (defined by ICD codes)	By neurologist's judgement	ATT meta-analysis (Not defined)	ATT meta-analysis (Not defined)	ATT meta-analysis (Not defined)
Hypertension Optimal Treatment[11], 1998	Fatal and non-fatal MI, fatal and non-fatal stroke (ischemic, hemorrhagic, unknown), 'all other cardiovascular deaths'	Any death	Death occurring within 28 days of cardiovascular event with no obvious non-cardiovascular cause	Two of: central chest pain for >15 minutes, transient elevation of enzymes indicating myocardial damage, or typical electrocardiographic changes New-onset Q or QS waves without clinical signs of MI were defined as silent MI	Ischemic, hemorrhagic or unknown	Not included in analysis – study does not specify aetiology	ATT meta-analysis (Not defined)	ATT meta-analysis (Not defined)	ATT meta-analysis (Not defined)
Thrombosis Prevention Trial (TPT)[12], 1998	Coronary death, all myocardial infarction, all stroke	Any death	Not specified	MI (Not Specified)	Ischemic, hemorrhagic or unknown	Ischemic based on imaging or necropsy findings	ATT meta-analysis (Not defined)	ATT meta-analysis (Not defined)	ATT meta-analysis (Not defined)
Primary Prevention Project (PPP)[13], 2001	CVM, MI and stroke (ischemic, hemorrhagic, unknown)	Any death	Deaths within 28 days of cardiovascular event with no other evident cause, sudden death, death from heart failure, cardiovascular deaths as defined by ICD-9	Two of: central chest pain of typical intensity and duration, transient elevation of enzymes indicating myocardial damage, or typical electrocardiographic changes	Ischemic, hemorrhagic or unknown	Ischemic based on appropriate imaging or necropsy findings where available	ATT meta-analysis (Not defined)	ATT meta-analysis (Not defined)	ATT meta-analysis (Not defined)

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eTable 1: Outcome definitions (continued)

Trial	Primary	ACM	CVM	MI	All strokes	Ischemic strokes	Major bleeding	Intracranial bleeding	GI bleeding
Women's Health Study (WHS)[14], 2005	CVM, non-fatal MI, non-fatal stroke (ischemic or hemorrhagic)	Any death	Confirmed cardiovascular cause based on autopsy reports, death certificates, medical records, and information obtained from next of kin or other family members	Symptoms meeting WHO criteria and associated with abnormal levels of cardiac enzymes or electrocardiographic changes	Ischemic or hemorrhagic	Ischemic based on CT or MRI findings	ATT meta-analysis (Not defined)	ATT meta-analysis (Not defined)	ATT meta-analysis (Not defined)
Prevention of Arterial Disease and Diabetes (POPADAD)[15], 2008	Death from coronary heart disease or stroke, non-fatal myocardial infarction, non-fatal stroke	Any death	Death from coronary heart disease or stroke as per study definitions	MI According to WHO criteria	Stroke (WHO definition – presumed to include hemorrhagic and ischemic causes)	Not reported	Not reported	Not reported	Not specified
Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD)[16], 2008	Fatal and nonfatal coronary heart disease, fatal and nonfatal cerebrovascular disease	Any death	Death from ischemic stroke or MI	MI (Not specified)	Stroke (ischemic, hemorrhagic)	Ischemic stroke (Not specified)	Severe GI bleeding and hemorrhagic stroke	Hemorrhagic stroke (Not specified)	Major GI bleeding (Not specified)
Aspirin for Asymptomatic Atherosclerosis (AAA)[17], 2010	Fatal or nonfatal coronary event or stroke (ischemic, hemorrhagic, unknown)	Any death	Coronary or stroke (ischemic, hemorrhagic, unknown) death	MI (Not specified)	Stroke (ischemic, hemorrhagic, unknown)	Ischemic stroke (Not specified)	Major hemorrhage (hemorrhagic stroke, subarachnoid hemorrhage), gastrointestinal or other requiring admission to hospital for intervention to control bleeding	Hemorrhagic stroke or subarachnoic hemorrhage	Gastrointestinal bleeding requiring admission to hospital for intervention to control bleeding
Japanese Primary Prevention Project (JPPP)[18], 2014	CVM, non-fatal MI, non-fatal stroke (ischemic, hemorrhagic)	Any death	Not specified	MI (ESC/ACC Definition)	Ischemic or hemorrhagic (including subarachnoid)	Imaging evidence of cerebral infarction accompanied by an acute regional neurological deficit maintained for 24 hours	Serious extracranial hemorrhage requiring hospitalization or transfusion, and intracranial hemorrhage	Intracranial hemorrhage or subarachnoid hemorrhage	Not included in analysis – Not specified

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eTable 1: Outcome definitions (continued)

Trial	Primary	ACM	CVM	MI	All strokes	Ischemic strokes	Major bleeding	Intracranial bleeding	GI bleeding
A Study of Cardiovascular Events in Diabetes (ASCEND)[19], 2018	Non-fatal MI, non-fatal stroke (ischemic only) or TIA, vascular death	Any death	Vascular death excluding hemorrhagic stroke	MI	**Not included in analysis – only reports ischemic stroke**	Ischemic stroke			
Aspirin to Reduce Risk of Initial Vascular Events (ARRIVE)[20], 2018	Cardiovascular death, non-fatal MI and non-fatal stroke (ischemic, hemorrhagic, unknown)	Any death	Cardiovascular death (not specified)	MI (not specified)	Ischemic, hemorrhagic or unknown	Ischemic stroke (not specified)	Major according to GUSTO criteria	Hemorrhagic stroke	Severe gastrointestinal bleed
Aspirin in Reducing Events in the Elderly (ASPREE)[21], 2018	Coronary heart disease death, non-fatal MI (ESC and ACC definitions), fatal and non-fatal stroke (ischemic, hemorrhagic, uncertain and subarachnoid hemorrhage strokes)	Any death	Death from stroke or coronary heart disease	MI (ESC/ACC definition)	Ischemic, hemorrhagic and uncertain causes, and subarachnoid hemorrhage	Ischemic stroke	Hemorrhagic stroke and non-stroke clinically significant bleeding (requiring transfusion, hospitalisation for >24h, prolonged hospitalisation by >24h with bleeding, fatal bleeding)	Hemorrhagic stroke, subdural or extradural hemorrhage, subarachnoid hemorrhage	Upper or lower gastrointestinal bleed

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eTable 2: Risk of Bias Assessment

Trial	Sequence generation	Allocation concealment	Blinding	Detection bias	Attrition bias	Reporting bias	Overall Risk of Bias
British Doctors' Study[9], 1988	Low "Randomly allocated by computer"	Unclear Not reported	High "Placebo tablets were not used, so that treatment was not blind."	Unclear "All participating doctors were asked to complete a brief questionnaire … about their health and their use of aspirin…"	Low "Data on mortality were thought to be complete and data on morbidity virtually complete."	Low ROB assessors found no concerns on reporting quality.	High
Physicians' Health Study[10], 1989	Low "randomly assigned"	Unclear Not reported	Low "assigned at random to receive aspirin … and to receive aspirin placebo."	Unclear "They were also sent brief questionnaires asking about… the occurrence of any relevant events."	Low "99.7% were still providing information on morbidity, and the vital status of all 22,071 doctors was known."	Low ROB assessors found no concerns on reporting quality.	Low
Hypertension Optimal Treatment[11], 1998	Low "randomly assigned"	Low "randomisation was computer-generated based on communications by fax between investigators and the Study Coordinating Centre"	Low "Patients were randomised in a double-blind way, to a low dose, 75 mg daily, of acetylsalicylic acid or identical-looking placebo tablets."	Unclear "A classification of all reported events was made by the Independent Clinical Event Committee based on all available information… All events were classified without any knowledge of the actual medication or the treatment group to which the patients had been assigned."	Low "A total of 2·6% patients were lost to follow-up."	Low ROB assessors found no concerns on reporting quality.	Low
Thrombosis Prevention Trial (TPT)[12], 1998	Low "Allocation to treatment was done randomly"	Low "computer-generated random numbers balanced between the four treatment groups"	Low "Treatment was double-blind"	Low "reviewed by their general practitioners each year … in addition to which the research nurse annually searched all the notes … for possible end-points"	Low "The number for whom no information on possible non-fatal events was available was 1·1%."	Low ROB assessors found no concerns on reporting quality.	Low

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eTable 2: Risk of Bias Assessment (continued)

Trial	Sequence generation	Allocation concealment	Blinding	Detection bias	Attrition bias	Reporting bias	Overall Risk of Bias
Primary Prevention Project (PPP)[13], 2001	Low "Randomly allocated"	Low "Centrally assigned … with a computer-generated randomisation table … in random permuted blocks"	High "Patients were randomly allocated to receive aspirin … or no aspirin"	Low "Follow-up clinical visits were scheduled yearly and included re-assessment of … outcome events."	Low "At the end of the study 92.3% patients had clinical follow-up."	Low ROB assessors found no concerns on reporting quality.	High
Women's Health Study (WHS)[14], 2005	Low "randomized, double-blind, placebo-controlled trial"	Unclear Not reported	Low "assigned to receive aspirin and … to receive placebo"	Unclear "Every 12 months, … sent … questionnaires on compliance, side effects, the occurrence of relevant clinical end points… Study … end-point ascertainment were continued in a blinded fashion through the scheduled end of the trial… Medical records were obtained … and were reviewed in a blinded fashion by an end-points committee of physicians"	Low "Rates of follow-up with respect to morbidity and mortality were 97.2 percent complete and 99.4 percent complete, respectively"	Low ROB assessors found no concerns on reporting quality.	Low
Prevention of Arterial Disease and Diabetes (POPADAD)[15], 2008	Low "patients were randomly assigned to one of four treatment groups"	Low "allocation sequence used randomised permuted blocks of eight and was computer generated by the trial statisticians"	Low "interventions were daily aspirin 100 mg or placebo tablet"	Low "Follow-up evaluations were done every six months. At these visits we recorded outcome events, adverse events, and interventions"	Low "Overall, 1074 (of 1276) participants had their final follow-up in 2006"	Low ROB assessors found no concerns on reporting quality.	Low

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eTable 2: Risk of Bias Assessment (continued)

Trial	Sequence generation	Allocation concealment	Blinding	Detection bias	Attrition bias	Reporting bias	Overall Risk of Bias
Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD)[16], 2008	Low "Enrolled patients were randomly assigned to the aspirin group or the non aspirin group."	Low "The randomization was performed as non stratified randomization from a random number table. The study center prepared the sealed envelopes with random assignments and distributed them by mail"	High "prospective, randomized, open-label, controlled trial"	Low "Follow-up visits were scheduled every 2 weeks for patients seen in a clinic setting and every 4 weeks for patients seen in a hospital setting."	Low "A total of 193 patients (of 2539) were lost to follow-up, and data for those patients were censored at the day of last follow-up."	Low ROB assessors found no concerns on reporting quality.	High
Aspirin for Asymptomatic Atherosclerosis (AAA)[17], 2010	Low "double blind, randomized controlled trial of once daily low-dose aspirin (100 mg) vs placebo"	Low "Consecutive participant study numbers were assigned to aspirin or placebo with permuted blocks of size 8, which varied randomly. A staff member not involved in the study produced the computer generated randomization list."	Low "double blind, randomized controlled trial of once daily low-dose aspirin (100 mg) vs placebo"	Low "Ascertainment of possible events was sought annually from participant follow-up, a study reply card attached to general practitioner notes, flagging for death at the NHS Central Registry, and linkage to databases of deaths and hospital discharges at NHS National Services Scotland."	Low "Ten participants (0.3%) were censored because they either emigrated or could not be contacted."	Low ROB assessors found no concerns on reporting quality.	Low

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eTable 2: Risk of Bias Assessment (continued)

Trial	Sequence generation	Allocation concealment	Blinding	Detection bias	Attrition bias	Reporting bias	Overall Risk of Bias
Japanese Primary Prevention Project (JPPP)[18], 2014	Low "Pseudorandom numbers were generated using the Mersenne Twister method"	Low "The study statistician generated the random allocation sequence using a central computerized system"	High "randomized, open-label, parallel-group clinical trial"	Low "the following Variables were evaluated in the clinic when patients met with the study physician: disease outcomes, adverse events…"	Low "For analyses of the primary and secondary endpoints, 194 patients (1.3%) were excluded from the randomized population owing to protocol violations or deviations"	Low ROB assessors found no concerns on reporting quality.	High
A Study of Cardiovascular Events in Diabetes (ASCEND)[19], 2018	Low "randomized trial"	Low "Using minimized randomization"	Low "participants to receive 100 mg of aspirin once daily or a matching placebo tablet"	Unclear "we sent follow-up questionnaires … to participants every 6 months until the end of the trial. In these questionnaires, we sought information regarding all serious adverse events (including potential trial outcomes)… nonserious adverse events resulting in discontinuation of the trial regimen, and any symptomatic bleeding episodes" "Confirmation and further information was sought from GPs"	Low "complete follow-up data were available for 15,341 participants (99.1%)"	Low ROB assessors found no concerns on reporting quality.	Low
Aspirin to Reduce Risk of Initial Vascular Events (ARRIVE)[20], 2018	Low "Randomly assigned"	Low "computer-generated randomisation code	Low "Patients, investigators and their staff, the sponsor, and others involved in treating the patients or data collection were	Low "Patients, investigators and their staff, the sponsor, and others involved in treating the patients or data collection were	Low "Over the course of the study …29.6% of patients terminated the study prematurely (29.4% in the aspirin	Low ROB assessors found no concerns on reporting quality.	Low

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		using balanced permuted blocks"	masked to the identity of the treatment."	masked to the identity of the treatment."	group and 29.9% in the placebo group)."		

eTable 2: Risk of Bias Assessment (continued)

Trial	Sequence generation	Allocation concealment	Blinding	Detection bias	Attrition bias	Reporting bias	Overall Risk of Bias
Aspirin in Reducing Events in the Elderly (ASPREE)[21], 2018	Low "randomly assigned"	Low "Randomization was stratified according to trial center and age"	Low "Trial participants, investigators, and general practitioner associate investigators were unaware of the trial-group assignments"	Low "Committees whose members were unaware of the trial-group assignments were responsible for adjudication of all potential clinical end-point events."	Low "1.5% of the participants in the aspirin group and 1.6% of those in the placebo group had been lost to follow-up by the end of the trial"	Low ROB assessors found no concerns on reporting quality.	Low

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eTable 3: Absolute risk differences and numbers needed to treat

Efficacy	All patients ARD	NNT	Low Risk ARD	NNT	High Risk ARD	NNT	Diabetes ARD	NNT
Composite outcome	-0.41 (-0.59 to -0.23)	242	-0.34 (-0.52 to -0.14)	297	-0.63 (-1.04 to -0.18)	160	-0.65 (-1.17 to -0.09)	153
All-cause mortality	-0.13 (-0.32 to 0.07)		-0.01 (-0.27 to 0.27)		-0.43 (-0.84 to 0.02)		-0.24 (-0.91 to 0.49)	
Cardiovascular mortality	-0.07 (-0.17 to 0.04)		-0.07 (-0.16 to 0.03)		-0.04 (-0.32 to 0.27)		-0.05 (-0.94 to 1.27)	
All myocardial infarction	-0.28 (-0.47 to -0.05)	361	-0.27 (-0.49 to 0.00)	366	-0.32 (-0.74 to 0.16)		-0.26 (-0.88 to 0.47)	
All stroke	-0.09 (-0.20 to 0.04)		-0.04 (-0.21 to 0.14)		-0.19 (-0.49 to 0.16)		-0.77 (-1.48 to 0.16)	
Ischemic stroke	-0.19 (-0.30 to -0.06)	540	-0.16 (-0.29 to -0.02)	623	-0.28 (-0.63 to 0.12)		-0.83 (-1.70 to 0.50)	
Incident Cancer	0.03 (-0.37 to 0.46)		0.41 (-0.13 to 1.01)		-0.30 (-0.76 to 0.19)		-0.68 (-2.09 to 0.95)	
Cancer Mortality	0.05 (-0.11 to 0.23)		0.16 (-0.06 to 0.42)		-0.13 (-0.41 to 0.17)		0.16 (-0.56 to 1.02)	

Safety	All patients ARD	NNH	Low Risk ARD	NNH	High Risk ARD	NNH	Diabetes ARD	NNH
Major Bleeding	0.47 (0.34 to 0.62)	210	0.40 (0.25 to 0.57)	249	0.64 (0.35 to 0.97)	152	0.80 (0.29 to 1.39)	121
Intracranial Bleeding	0.11 (0.04 to 0.18)	927	0.13 (0.05 to 0.22)	796	0.07 (-0.04 to 0.21)		0.12 (-0.09 to 0.43)	
Major GI Bleeding	0.30 (0.20 to 0.41)	334	0.27 (0.15 to 0.40)	376	0.39 (0.16 to 0.69)	255	0.41 (0.06 to 0.86)	243

Absolute risk differences (ARDs), Number Needed to Treat (NNT) and Number Needed to Harm (NNH) for included outcomes. Negative ARD values indicate favoring aspirin, positive ARD values indicate favoring no aspirin. NNT and NNH values are reported only for outcomes with a statistically significant ARD.

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eTable 4: Total stroke outcomes

		Aspirin		No Aspirin				
	Studies	**Events**	**Participants**	**Events**	**Participants**	**ARR (95% CI)**	**HR (95% CrI)**	I^2
All participants	12	1116	73,883	1136	72,317	0.10 (-0.03 to 0.22)	0.93 (0.86 to 1.02)	1
Low risk participants	6	752	56,212	788	56,354	0.04 (-0.15 to 0.20)	0.95 (0.79 to 1.16)	6
High risk participants	7	381	17,671	380	15,963	0.22 (-0.07 to 0.49)	0.89 (0.77 to 1.03)	11
Participants with diabetes	7	128	4048	156	3960	0.50 (-0.05 to 0.97)	0.78 (0.61 to 1.00)*	13

*Upper confidence interval 1.004

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eTable 5: Event rates for efficacy and safety outcomes

Outcome	Events per 10,000 participant-years							
	All participants		Low Risk		High Risk		Diabetes	
	Aspirin	No aspirin	Aspirin	No aspirin	Aspirin	No aspirin	Aspirin	No aspirin
Efficacy								
Composite outcome	60.2	65.2	41.3	46.4	109.2	117.9	103.6	114.1
All-cause mortality	69.4	70.0	50.5	50.4	118.5	124.9	134.2	137.6
Cardiovascular mortality	19.1	19.5	10.7	11.9	40.7	40.7	38.3	40.4
All myocardial infarction	28.1	31.2	17.2	21.0	56.5	59.8	59.8	62.6
Total stroke	24.0	25.0	19.9	20.9	41.5	44.9	59.0	74.2
Ischemic stroke	18.4	21.4	14.7	17.1	30.8	36.9	40.3	46.7
Cancer incidence	105.4	105.5	97.7	93.8	121.8	132.4	162.7	166.2
Cancer mortality	31.2	30.1	23.8	21.6	48.8	51.9	61.9	60.9
Safety								
Major Bleeding	23.1	16.4	19.2	13.4	37.7	28.3	54.7	42.4
Intracranial Bleeding	6.7	5.1	6.5	4.6	7.4	6.3	10.0	8.3
Major GI Bleeding	12.9	8.2	10.5	6.7	19.5	12.6	22.6	16.7

Trials were deemed low or high risk if the 10-year cardiovascular risk for the primary cardiovascular outcome was less than 10%, or 10% or more respectively. The Women's Health Study did not report the number of patients in the high cardiovascular risk subgroup; this study was therefore excluded from event rate calculations for participants at high risk of the primary outcome.

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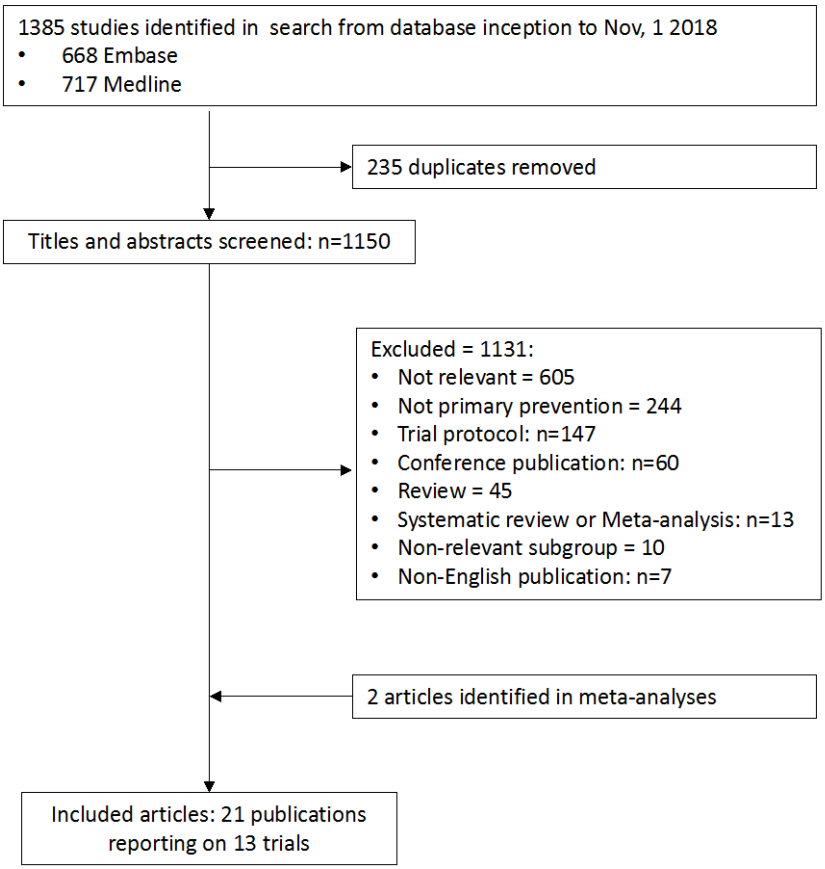
eTable 6: Sensitivity analyses

Outcome	Sensitivity Analysis			
	Total daily aspirin dose ≤100mg 11 studies; N = 134,470	**Double-blind, placebo-controlled studies** 9 studies; N = 135,043	**Studies published since the year 2000** 9 studies; N = 113,140	**Excluding studies enrolling patients with asymptomatic PAD** 11 studies; N = 156,874
Efficacy				
Composite outcome	0.89 (0.83 to 0.95)	0.88 (0.83 to 0.94)	0.91 (0.84 to 0.98)	0.88 (0.83 to 0.93)
All-cause mortality	0.95 (0.87 to 1.03)	0.96 (0.88 to 1.03)	0.94 (0.85 to 1.04)	0.94 (0.88 to 1.01)
Cardiovascular mortality	0.91 (0.80 to 1.05)	0.96 (0.84 to 1.09)	0.88 (0.73 to 1.06)	0.92 (0.82 to 1.04)
All myocardial infarction	0.87 (0.76 to 1.00)*	0.84 (0.70 to 1.03)	0.94 (0.81 to 1.08)	0.80 (0.68 to 0.95)
Total stroke	0.90 (0.82 to 0.98)	0.93 (0.84 to 1.02)	0.89 (0.80 to 0.98)	0.95 (0.87 to 1.03)
Ischemic stroke	0.79 (0.74 to 0.85)	0.85 (0.69 to 1.06)	0.80 (0.74 to 0.86)	0.81 (0.76 to 0.87)
Safety				
Major bleeding	1.43 (1.30 to 1.57)	1.41 (1.28 to 1.55)	1.39 (1.26 to 1.53)	1.42 (1.30 to 1.56)
Intracranial bleeding	1.31 (1.11 to 1.56)	1.33 (1.11 to 1.60)	1.34 (1.13 to 1.60)	1.33 (1.13 to 1.57)
Major GI bleeding	1.55 (1.36 to 1.77)	1.54 (1.35 to 1.76)	1.48 (1.28 to 1.71)	1.57 (1.38 to 1.79)
Exploratory				
Incident cancer	1.01 (0.92 to 1.08)	0.99 (0.89 to 1.06)	1.01 (0.91 to 1.10)	1.02 (0.98 to 1.07)
Cancer mortality	1.04 (0.96 to 1.12)	1.03 (0.95 to 1.12)	1.04 (0.96 to 1.12)	1.05 (0.97 to 1.13)

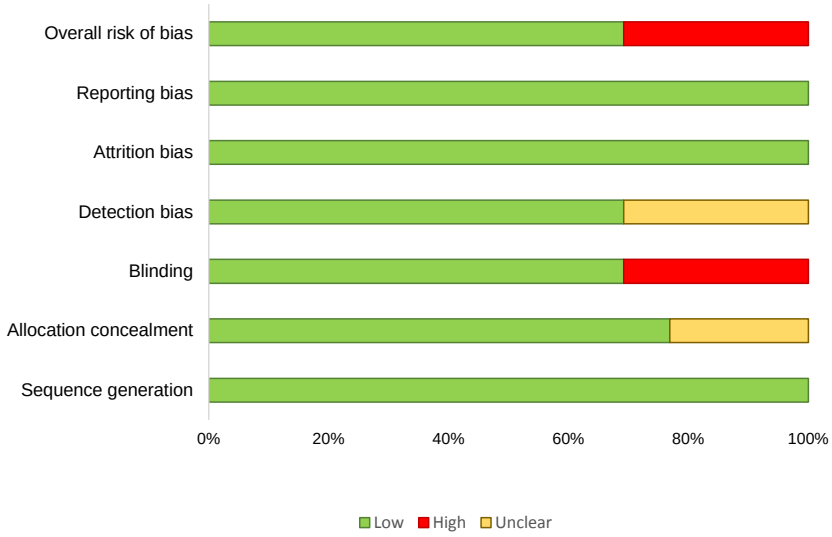
Sensitivity analyses for all efficacy, safety and exploratory outcomes. Data presented as Hazard Ratio (95% CrI). N denotes the number of participants included in each analysis. GI – gastrointestinal; PAD – peripheral arterial disease. *Upper confidence interval 0.9989.

Formatted Table

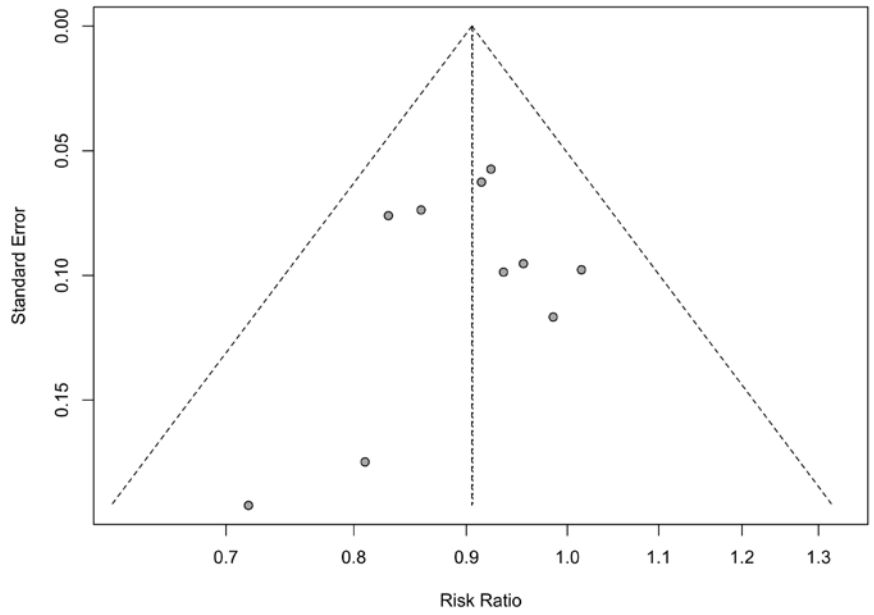
eFigure 1: Study Flow Chart



eFigure 2: Risk of bias summary



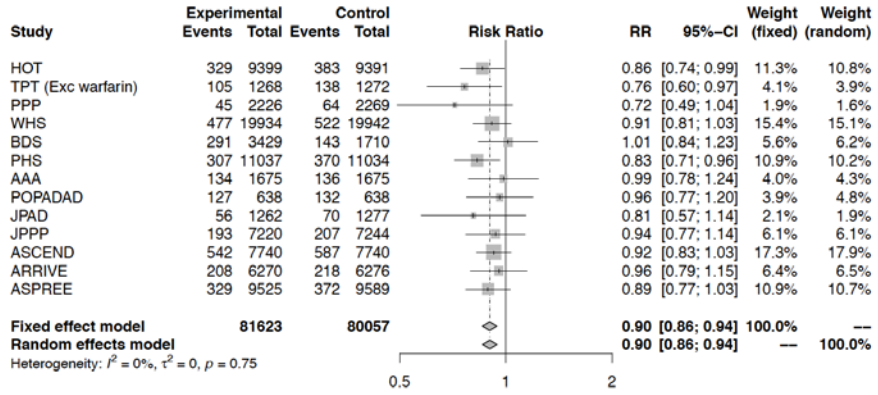
eFigure 3: Funnel plot for primary cardiovascular outcome



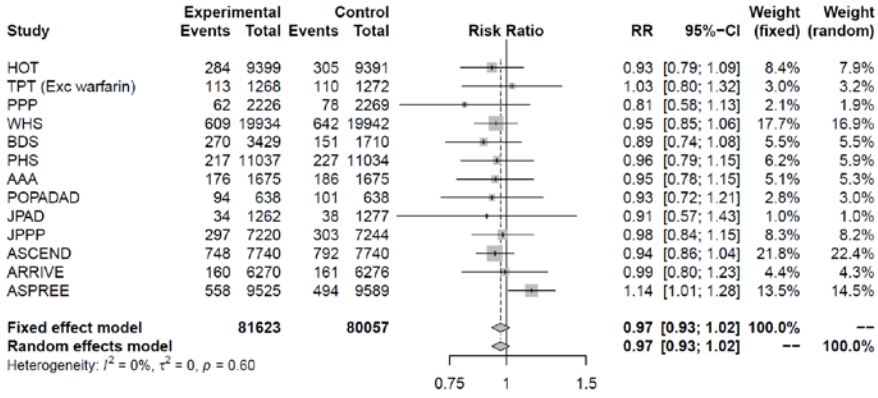
Egger Test: -0.47 (standard error: 0.77); t = -0.59, P = 0.57.

eFigure 4: Frequentist analysis forest plots

Composite outcome

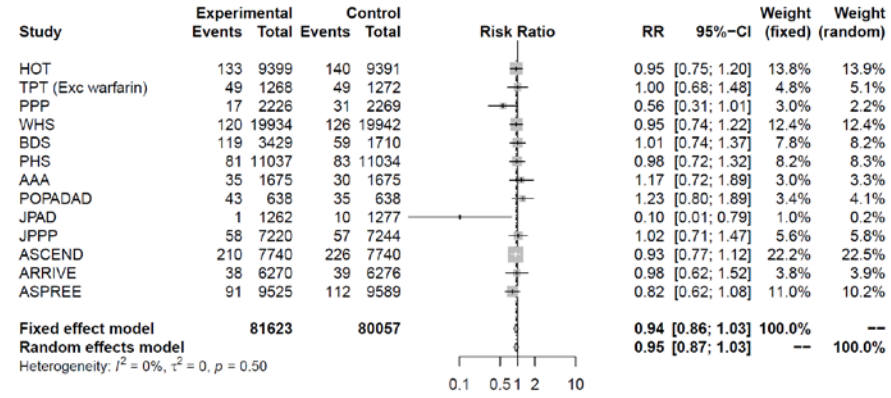


All-cause mortality

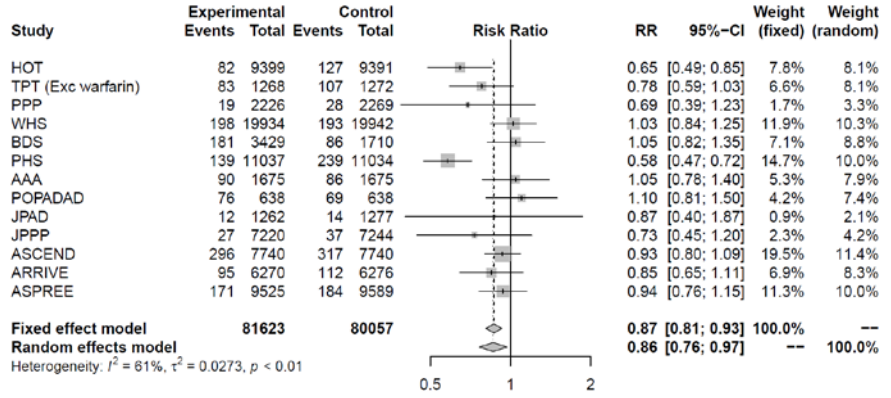


eFigure 4: Frequentist analysis forest plots (Continued)

Cardiovascular mortality

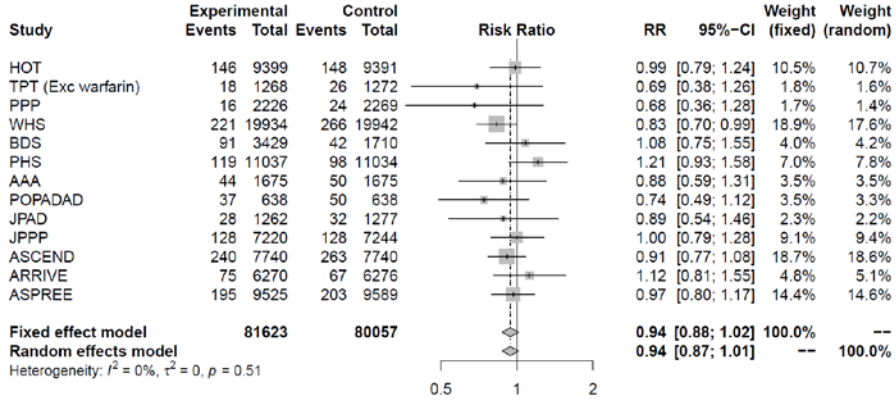


All myocardial infarction

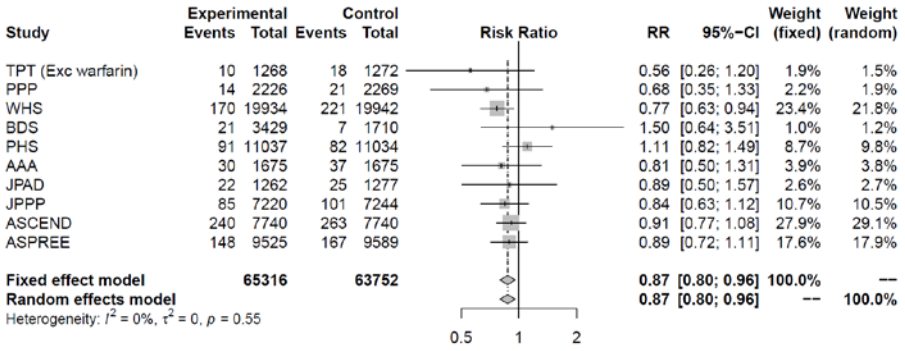


eFigure 4: Frequentist analysis forest plots (Continued)

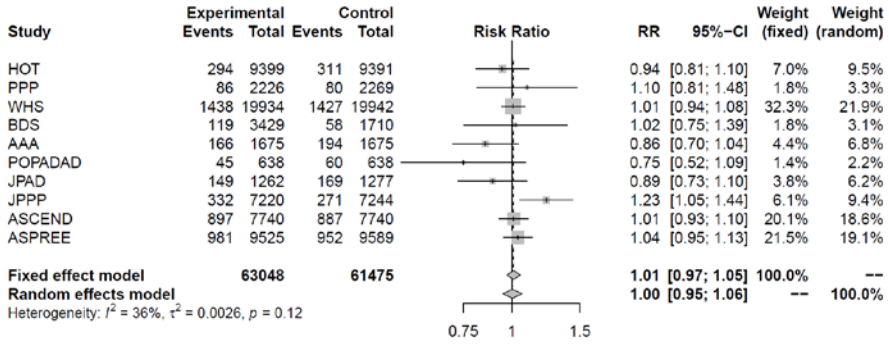
Total stroke



Ischemic stroke

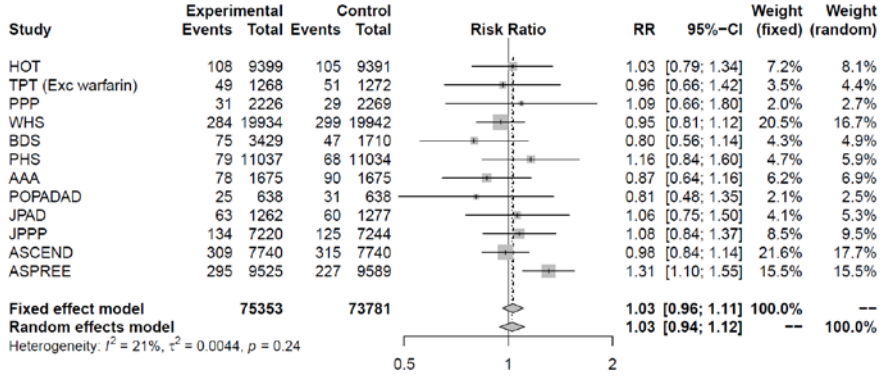


Incident Cancer

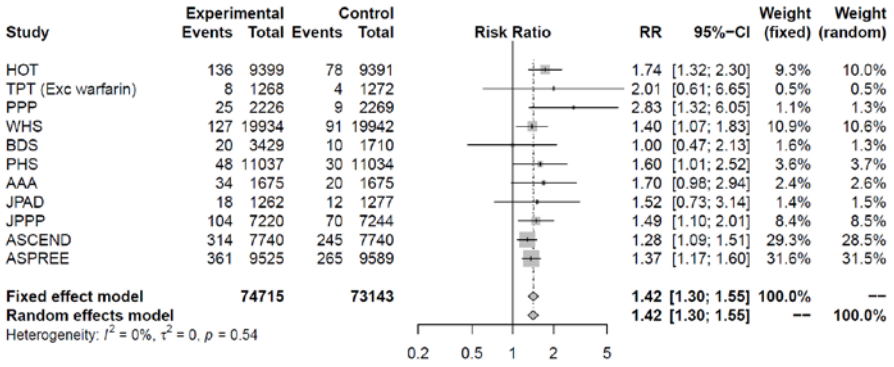


eFigure 4: Frequentist analysis forest plots (Continued)

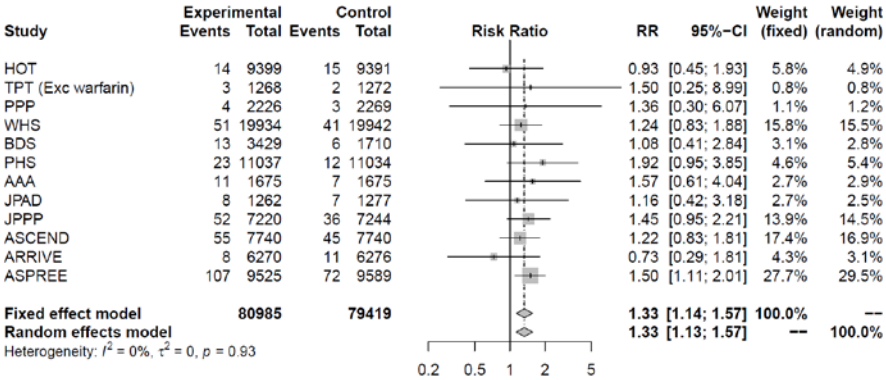
Cancer Mortality



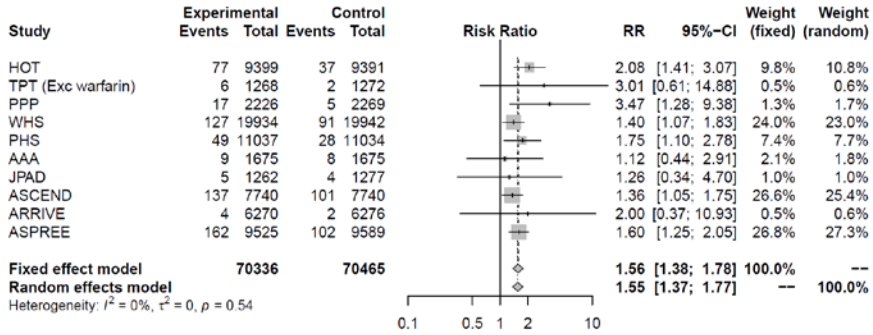
Major bleeding



Intracranial bleeding



eFigure 4: Frequentist analysis forest plots (Continued)
Major gastrointestinal bleeding



Frequentist pairwise meta-analysis forest plots.
Experimental indicates treatment with aspirin, while Control denotes no aspirin. RR – risk ratio; CI – confidence interval.
Study acronyms: AAA – Aspirin for Asymptomatic Atherosclerosis[17]; ARRIVE – Aspirin to Reduce Risk of Initial Vascular Events[20]; ASCEND – A Study of Cardiovascular Events in Diabetes[19]; ASPREE – Aspirin in Reducing Events in the Elderly[21]; BDS – British Doctor's Study[9]; HOT – Hypertension Optimal Treatment[11]; JPAD – Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes[16]; JPPP – Japanese Primary Prevention Project[18]; PHS – Physician's Health Study[10]; POPADAD – Prevention of Progression of Arterial Disease and Diabetes[15]; PPP – Primary Prevention Project[13]; TPT – Thrombosis Prevention Trial[12]; WHS – Women's Health Study[14].

Supplemental references

1. van Valkenhoef G, Kuiper J. Network Meta-Analysis Using Bayesian Methods. R package version 0.8-2. . 2016; https://CRAN.R-project.org/package=gemtc.
2. *R: A language and environment for statistical computing* [computer program]. R Foundation for Statistical Computing, Vienna, Austria; 2008.
3. Plummer M. JAGS: a program for analysis of Bayesian graphical models using Gibbs sampling. *Proceedings of the 3rd International Workshop on Distributed Statistical Computing (DSC 2003).* 2003.
4. Schwarzer G. meta: An R package for meta-analysis. *R News.* 2007;7(3):40-45.
5. Dias S, Sutton AJ, Ades AE, Welton NJ. Evidence synthesis for decision making 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomized controlled trials. *Medical decision making : an international journal of the Society for Medical Decision Making.* 2013;33(5):607-617.
6. Brooks SP, Gelman A. General methods for monitoring convergence of iterative simulations. *Journal of Computational and Graphical Statistics.* 1998;7:434-455.
7. Zheng SL, Roddick AJ, Aghar-Jaffar R, et al. Association between use of sodium-glucose cotransporter 2 inhibitors, glucagon-like peptide 1 agonists, and dipeptidyl peptidase 4 inhibitors with all-cause mortality in patients with type 2 diabetes: A systematic review and meta-analysis. *JAMA.* 2018;319(15):1580-1591.
8. Dias S, Sutton AJ, Welton NJ, Ades AE. Evidence Synthesis for Decision Making 3: Heterogeneity—Subgroups, Meta-Regression, Bias, and Bias-Adjustment. *Medical Decision Making.* 2013;33(5):618-640.
9. Peto R, Gray R, Collins R, et al. Randomised trial of prophylactic daily aspirin in British male doctors. *Br Med J (Clin Res Ed).* 1988;296(6618):313-316.
10. Final report on the aspirin component of the ongoing Physician's Health Study. *N Engl J Med.* 1989;321(3):129-135.

11. Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. *Lancet (London, England).* 1998;351(9118):1755-1762.
12. Thrombosis prevention trial: randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. The Medical Research Council's General Practice Research Framework. *Lancet (London, England).* 1998;351(9098):233-241.
13. de Gaetano G. Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general practice. Collaborative Group of the Primary Prevention Project. *Lancet (London, England).* 2001;357(9250):89-95.
14. Ridker PM, Cook NR, Lee I-M, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med.* 2005;352(13):1293-1304.
15. Belch J, MacCuish A, Campbell I, et al. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. *BMJ.* 2008;337:a1840.
16. Ogawa H, Nakayama M, Morimoto T, et al. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. *JAMA.* Vol 3002008:2134-2141.
17. Fowkes FGR, Price JF, Stewart MCW, et al. Aspirin for prevention of cardiovascular events in a general population screened for a low ankle brachial index: a randomized controlled trial. *JAMA.* 2010;303(9):841-848.
18. Ikeda Y, Shimada K, Teramoto T, et al. Low-dose aspirin for primary prevention of cardiovascular events in Japanese patients 60 years or older with atherosclerotic risk factors: a randomized clinical trial. *JAMA.* 2014;312(23):2510-2520.

19. Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus. *N Engl J Med.* 2018.
20. Gaziano JM, Brotons C, Coppolecchia R, et al. Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial. *Lancet (London, England).* 2018.
21. McNeil JJ, Nelson MR, Woods RL, et al. Effect of Aspirin on All-Cause Mortality in the Healthy Elderly. *New England Journal of Medicine.* 2018.