Supplementary Online Content

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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* package¹ in R (version 3.4.1)² and JAGS (version 4.3.0)³.

For the frequentist meta-analysis the meta package was used⁴.

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 priors⁵. 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 1.05⁶.

Heterogeneity was assessed using the l^2 statistic. An l^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 previously⁷. A difference of greater than 3 units was considered important, and the model with the lowest DIC was used for analysis⁸. 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". Metaanalyses (both using trial level and individual patient data) were identified, with data extracted from them if they could not be identified from trial publications.

All patien			DIC		
	Efficacy	Fixed	Random	<i>₽</i> (%) *	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	14.00	40.40		<i>.</i> .
	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

eMethods 3: Deviance information criterion and model selection

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		Γ	DIC		
High risk	Efficacy	Fixed	Random	f² (%) *	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	0.00	7.00	0	<i>c</i> 1
	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

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

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* P values obtained from the fixed-effect model.

eTable 1: Outcome definitions

Trial	Primary	ACM	CVM	МІ	All strokes	Ischemic strokes	Major bleeding	Intracranial bleeding	GI bleeding	Formatted Table
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)	lschemic, 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)	lschemic, 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)	

Trial	Primary	ACM	CVM	МІ	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 electrocardiographi c 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 extracrania hemorrhage requiri hospitalization or transfusion, and intracranial hemorrhage		Not included in analysis – Not specified

eTable 1: Outcome definitions (continued)

Trial	Primary	ACM	СУМ	МІ	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)	lschemic, 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

Trial	Sequence generation	Allocation concealment	Blinding	Detection bias	Attrition bias	Reporting bias	Overall Risk of Bias
	Low	Unclear	High	Unclear	Low	Low	High
British Doctors' Study ⁹ , 1988	"Randomly allocated by computer"	Not reported	"Placebo tablets were not used, so that treatment was not blind."	"All participating doctors were asked to complete a brief questionnaire about their health and their use of aspirin"	"Data on mortality were thought to be complete and data on morbidity virtually complete."	ROB assessors found no concerns on reporting quality.	
	Low	Unclear	Low	Unclear	Low	Low	Low
Physicians' Health Study ¹⁰ , 1989	"randomly assigned"	Not reported	"assigned at random to receive aspirin and to receive aspirin placebo."	"They were also sent brief questionnaires asking about the occurrence of any relevant events."	"99.7% were still providing information on morbidity, and the vital status of all 22,071 doctors was known."	ROB assessors found no concerns on reporting quality.	
	Low	Low	Low	Unclear	Low	Low	Low
Hypertension Optimal Treatment ¹¹ , 1998	"randomly assigned"	"randomisation was computer- generated based on communications by fax between investigators and the Study Coordinating Centre"	"Patients were randomised in a double-blind way, to a low dose, 75 mg daily, of acetylsalicylic acid or identical- looking placebo tablets."	"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."	"A total of 2.6% patients were lost to follow-up."	ROB assessors found no concerns on reporting quality.	
	Low	Low	Low	Low	Low	Low	Low
Thrombosis Prevention Trial (TPT) ¹² , 1998	"Allocation to treatment was done randomly"	"computer- generated random numbers balanced between the four treatment groups"	"Treatment was double-blind"	"reviewed by their general practitioners each year in addition to which the research nurse annually searched all the notes for possible end- points"	"The number for whom no information on possible non-fatal events was available was 1.1%."	ROB assessors found no concerns on reporting quality.	

eTable 2: Risk of Bias Assessment

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

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Trial	Sequence generation	Allocation concealment	Blinding	Detection bias	Attrition bias	Reporting bias	Overall Risk of Bias
	Low	Low	High	Low	Low	Low	High
Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) ¹⁶ , 2008	"Enrolled patients were randomly assigned to the aspirin group or the non aspirin group."	"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"	"prospective, randomized, open- label, controlled trial"	"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."	"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."	ROB assessors found no concerns on reporting quality.	
	Low	mail" Low	Low	Low	Low	Low	Low
Aspirin for Asymptomatic Atherosclerosis (AAA) ¹⁷ , 2010	randomized par controlled trial of once daily low-dose aspirin (100 mg) vs wei placebo" asp with	"Consecutive participant study numbers were assigned to aspirin or placebo with permuted	"double blind, randomized controlled trial of once daily low-dose aspirin (100 mg) vs placebo"	"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	"Ten participants (0.3%) were censored because they either emigrated or could not be contacted."	ROB assessors found no concerns on reporting quality.	
		blocks of size 8, which varied randomly. A staff member not involved in the study produced the computer generated randomization list."		hospital discharges at NHS National Services Scotland."			

Trial	Sequence generation	Allocation concealment	Blinding	Detection bias	Attrition bias	Reporting bias	Overall Risk of
	Low	Low	High	Low	Low	Low	High
Japanese Primary Prevention Project JPPP) ¹⁸ , 2014	"Pseudorandom numbers were generated using the Mersenne Twister method"	"The study statistician generated the random allocation sequence using a central computerized system"	"randomized, open-label, parallel-group clinical trial"	"the following Variables were evaluated in the clinic when patients met with the study physician: disease outcomes, adverse events"	"For analyses of the primary and secondary endpoints, 194 patients (1.3%) were excluded from the randomized population owing to protocol violations or deviations"	ROB assessors found no concerns on reporting quality.	
	Low	Low	Low	Unclear	Low	Low	Low
A Study of ardiovascular Events in Diabetes ASCEND) ¹⁹ , 018	"randomized trial"	"Using minimized randomization"	"participants to receive 100 mg of aspirin once daily or a matching placebo tablet"	"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"	"complete follow-up data were available for 15,341 participants (99.1%)"	ROB assessors found no concerns on reporting quality.	
Aspirin to	Low	Low	Low	Low	Low	Low	Low
educe Risk of nitial Vascular vents ARRIVE) ²⁰ , 018	"Randomly assigned"	"computer- generated randomisation code	"Patients, investigators and their staff, the sponsor, and others involved in treating the patients or data collection were	"Patients, investigators and their staff, the sponsor, and others involved in treating the patients or data collection were	"Over the course of the study29.6% of patients terminated the study prematurely (29.4% in the aspirin	ROB assessors found no concerns on reporting quality.	

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

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

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eTable 3:	Absolute risk differences and numbers needed to treat

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) 0.27) -0.43 (-0.84 to 0.02) -0.24 (-0.91 to 0.49) Cardiovascular mortality -0.07 (-0.17 to 0.04) 0.027) -0.43 (-0.32 to 0.27) -0.05 (-0.94 to 1.27) All myocardial infarction -0.28 (-0.47 to -0.05) 361 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) 0.14) -0.19 (-0.49 to 0.16) -0.77 (-1.48 to 0.16) -0.77 (-1.48 to 0.16) -0.77 (-1.48 to 0.16) -0.77 (-1.48 to 0.16) -0.16 (-0.29 to - -0.30 (-0.76 to 0.19) -0.68 (-2.09 to 0.95) -0.16 (-0.05 to 0.19) -0.30 (-0.76 to 0.19) -0.68 (-2.09 to 0.95) -0.16 (-0.05 to 0.19) -0.16 (-0.56 to 1.02) -0.31 (-0.14 to 0.17) 0.16 (-0.56 to 1.02) -0.44 (-0.21 to 0.16) -0.30 (-0.76 to 0.19) -0.68 (-2.09 to 0.95) -0.13 (-0.41 to 0.17) 0.16 (-0.56 to 1.02) -0.13 (-0.41 to 0.17) 0.16 (-0.56 to 1.02) -0.44 (-0.21 to 0.40) -0.30 (-0.76 to 0.19) -0.58 (-0.29 to 0.35) -0.44 (-0.21 to 0.40) </th <th></th> <th>All patients</th> <th></th> <th>Low Risk</th> <th></th> <th>High Risk</th> <th></th> <th>Diabetes</th> <th></th> <th></th>		All patients		Low Risk		High Risk		Diabetes		
Composite outcome -0.41 (-0.59 to -0.23) 242 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) 0.27) -0.43 (-0.84 to 0.02) -0.24 (-0.91 to 0.49) Cardiovascular mortality -0.07 (-0.17 to 0.04) 0.03) -0.04 (-0.32 to 0.27) -0.26 (-0.94 to 1.27) All myocardial infarction -0.28 (-0.47 to -0.05) 361 0.00 366 -0.32 (-0.74 to 0.16) -0.26 (-0.88 to 0.47) -0.04 (-0.21 to -0.09 (-0.20 to 0.04) 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 0.02 623 -0.28 (-0.63 to 0.12) -0.83 (-1.70 to 0.50) Incident Cancer 0.03 (-0.37 to 0.46) 1.01) -0.30 (-0.76 to 0.19) -0.68 (-2.09 to 0.95) -0.16 (-0.56 to 1.02) Cancer Mortality 0.05 (-0.11 to 0.23) 0.42 -0.13 (-0.41 to 0.17) 0.16 (-0.56 to 1.02) All patients Low Risk High Risk Diabetes Safety ARD NNH ARD NNH ARD <t< th=""><th>Efficacy</th><th>ARD</th><th>NNT</th><th>ARD</th><th>NNT</th><th>ARD</th><th>NNT</th><th>ARD</th><th>NNT</th><th>_</th></t<>	Efficacy	ARD	NNT	ARD	NNT	ARD	NNT	ARD	NNT	_
Composite outcome -0.41 (-0.59 to -0.23) 242 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) 0.27) -0.43 (-0.84 to 0.02) -0.24 (-0.91 to 0.49) Cardiovascular mortality -0.07 (-0.17 to 0.04) 0.03) -0.04 (-0.32 to 0.27) -0.26 (-0.94 to 1.27) All myocardial infarction -0.28 (-0.47 to -0.05) 361 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) 0.14) -0.19 (-0.49 to 0.16) -0.77 (-1.48 to 0.16) -0.77 (-1.48 to 0.16) Ischemic stroke -0.19 (-0.30 to -0.06) 540 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) 1.01) -0.30 (-0.76 to 0.19) -0.68 (-2.09 to 0.95) -0.16 (-0.56 to 1.02) Cancer Mortality 0.05 (-0.11 to 0.23) 0.42 -0.13 (-0.41 to 0.17) 0.16 (-0.56 to 1.02) 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										-
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) 0.03) -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 0.00) 366 -0.32 (-0.74 to 0.16) -0.26 (-0.88 to 0.47) All stroke -0.09 (-0.20 to 0.04) 0.14) -0.19 (-0.49 to 0.16) -0.77 (-1.48 to 0.16) -0.77 (-1.48 to 0.16) All stroke -0.09 (-0.20 to 0.04) 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 0.021 -0.30 (-0.76 to 0.19) -0.68 (-2.09 to 0.50) Incident Cancer 0.03 (-0.37 to 0.46) 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) 0.42) -0.13 (-0.41 to 0.17) 0.16 (-0.56 to 1.02) All patients Low Risk High Risk Diabetes NNH Ard D NNH ARD NNH 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)										
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Cardiovascular mortality -0.07 (-0.17 to 0.04) -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 0.00) 366 -0.32 (-0.74 to 0.16) -0.26 (-0.88 to 0.47) All stroke -0.09 (-0.20 to 0.04) 0.14) -0.19 (-0.49 to 0.16) -0.77 (-1.48 to 0.16) Ischemic stroke -0.19 (-0.30 to -0.06) 540 0.029 to - -0.30 (-0.76 to 0.19) -0.83 (-1.70 to 0.50) Incident Cancer 0.03 (-0.37 to 0.46) 1.01) -0.30 (-0.76 to 0.19) -0.66 (-0.56 to 1.02) Cancer Mortality 0.05 (-0.11 to 0.23) 0.42) -0.13 (-0.41 to 0.17) 0.16 (-0.56 to 1.02) 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 Major 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)		0.40 (0.00 to 0.07)				$0.42(0.04 \pm 0.02)$		$0.04 (0.04 \pm 0.40)$		
Cardiovascular mortality -0.07 (-0.17 to 0.04) 0.03) -0.27 (-0.49 to -0.27 (-0.49 to -0.27 (-0.49 to -0.27 (-0.49 to -0.27 (-0.49 to -0.26 (-0.88 to 0.47) -0.05 (-0.94 to 1.27) All myocardial infarction -0.28 (-0.47 to -0.05) 361 0.000 366 -0.32 (-0.74 to 0.16) -0.26 (-0.88 to 0.47) All stroke -0.09 (-0.20 to 0.04) 0.14) -0.19 (-0.49 to 0.16) -0.77 (-1.48 to 0.16) Ischemic stroke -0.19 (-0.30 to -0.06) 540 0.02) 623 -0.28 (-0.63 to 0.12) -0.83 (-1.70 to 0.50) Incident Cancer 0.03 (-0.37 to 0.46) 1.01) -0.30 (-0.76 to 0.19) -0.68 (-2.09 to 0.95) Onte (-0.06 to Cancer Mortality 0.05 (-0.11 to 0.23) 0.42) -0.13 (-0.41 to 0.17) 0.16 (-0.56 to 1.02) 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 Major 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) 121	All-cause mortality	-0.13(-0.32 to $0.07)$				-0.43 (-0.84 to 0.02)		-0.24 (-0.91 to 0.49)		
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Ischemic stroke -0.19 (-0.30 to -0.06) 540 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) 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) 0.42) -0.13 (-0.41 to 0.17) 0.16 (-0.56 to 1.02) All patients Low Risk High Risk Diabetes Safety ARD NNH ARD NNH 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)	All stroke	-0.09 (-0.20 to 0.04)				-0.19 (-0.49 to 0.16)		-0.77 (-1.48 to 0.16)		
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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) All patients Safety Low Risk ARD High Risk ARD Diabetes 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)	Incident Cancer	0.03 (-0.37 to 0.46)				-0.30 (-0.76 to 0.19)		-0.68 (-2.09 to 0.95)		
Cancer Mortality 0.05 (-0.11 to 0.23) 0.42) -0.13 (-0.41 to 0.17) 0.16 (-0.56 to 1.02) All patients Safety Low Risk ARD NNH High Risk ARD Diabetes NNH Diabetes 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)		0.00 (0.07 10 0.40)		,		0.30 (0.70 10 0.13)		0.00 (2.00 10 0.00)		
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Safety ARD NNH ARD NNH ARD NNH ARD NNH ARD NNH 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)	•	· · · · ·						х		-
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)		All patients		Low Risk		High Risk		Diabetes		
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)	Safety	ARD	NNH	ARD	NNH	ARD	NNH	ARD	NNH	
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)										-
\mathbf{c}	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.

eTable 4: Total stroke outcomes

			Aspirin	Nc	o Aspirin		<u>الم</u>	Fc
	Studies	Events	Participants	Events	Participants	ARR (95% CI)	HR (95% Crl)	P
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

eTable 5: Event rates for efficacy and safety outcomes

Events per 10,000 participant-years

Outcome	All pa	rticipants	Lo	w Risk	Hig	h Risk	Diabetes		
Calcollo	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	

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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.

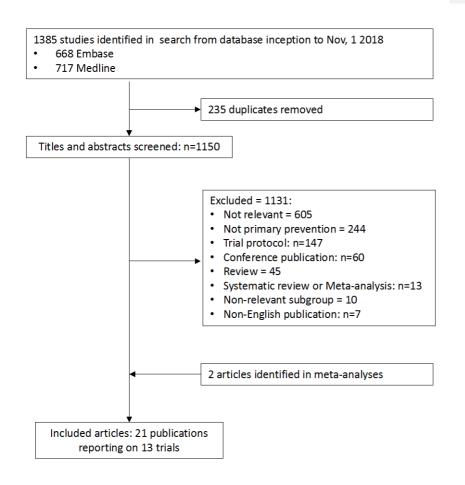
eTable 6: Sensitivity analyses

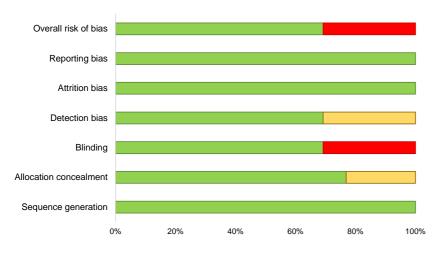
	Sensitivity Analysis												
Outcome	Total daily aspirin dose ≤100mg	Double-blind, placebo- controlled studies	Studies published since the year 2000	Excluding studies enrolling patients with asymptomatic PAD									
	11 studies; N = 134,470	9 studies; N = 135,043	9 studies; N = 113,140	11 studies; 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	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% Crl). N denotes the number of participants included in each analysis. GI – gastrointestinal; PAD – peripheral arterial disease. *Upper confidence interval 0.9989.

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eFigure 1: Study Flow Chart

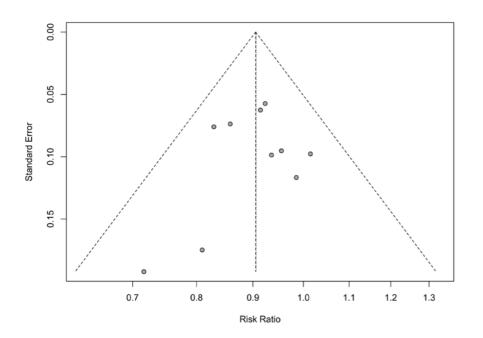




eFigure 2: Risk of bias summary



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

Study	Experi Events		C Events	Control Total	Risk	Ratio	RR	95%-CI	Weight (fixed)	Weight (random)	
HOT	329	9399	383	9391			0.86	[0.74; 0.99]	11.3%	10.8%	
TPT (Exc warfarin)	105	1268	138	1272	*			[0.60; 0.97]	4.1%	3.9%	
PPP	45	2226	64	2269		+		[0.49; 1.04]	1.9%	1.6%	
WHS	477	19934	522	19942		+	0.91	0.81; 1.03	15.4%	15.1%	
BDS	291	3429	143	1710	-	<u>k</u>		[0.84; 1.23]	5.6%	6.2%	
PHS	307	11037	370	11034				[0.71: 0.96]	10.9%	10.2%	
AAA	134	1675	136	1675				[0.78; 1.24]	4.0%	4.3%	
POPADAD	127	638	132	638		<u> </u>	0.96	[0.77: 1.20]	3.9%	4.8%	
JPAD	56	1262	70	1277		<u> </u>	0.81	[0.57; 1.14]	2.1%	1.9%	
JPPP	193	7220	207	7244		<u> </u>	0.94	[0.77: 1.14]	6.1%	6.1%	
ASCEND	542	7740	587	7740		+	0.92	0.83: 1.03	17.3%	17.9%	
ABBIVE	208	6270	218	6276		<u> </u>	0.96	[0.79: 1.15]	6.4%	6.5%	
ASPREE	329	9525	372	9589		+		[0.77; 1.03]	10.9%	10.7%	
Fixed effect model		81623		80057	\$		0.90	[0.86; 0.94]	100.0%		
Random effects model					\$		0.90	[0.86; 0.94]		100.0%	
Heterogeneity: $I^2 = 0\%$, τ^2	= 0, p = 0	.75					7	• • •			
				0	.5	1	2				

All-cause mortality

	Experi	mental	0	ontrol				Weight	Weight
Study	Events	Total	Events	Total	Risk Ratio	RR	95%-CI		(random)
HOT	284	9399	305	9391		0.93	[0.79; 1.09]	8.4%	7.9%
TPT (Exc warfarin)	113	1268	110	1272		1.03	[0.80; 1.32]	3.0%	3.2%
PPP	62	2226	78	2269		0.81	[0.58; 1.13]	2.1%	1.9%
WHS	609	19934	642	19942		0.95	[0.85; 1.06]	17.7%	16.9%
BDS	270	3429	151	1710			[0.74; 1.08]	5.5%	5.5%
PHS	217	11037	227	11034	x	0.96	[0.79; 1.15]	6.2%	5.9%
AAA	176	1675	186	1675		0.95	[0.78; 1.15]	5.1%	5.3%
POPADAD	94	638	101	638		0.93	[0.72; 1.21]	2.8%	3.0%
JPAD	34	1262	38	1277		0.91	[0.57; 1.43]	1.0%	1.0%
JPPP	297	7220	303	7244		0.98	[0.84; 1.15]	8.3%	8.2%
ASCEND	748	7740	792	7740		0.94	[0.86; 1.04]	21.8%	22.4%
ARRIVE	160	6270	161	6276		0.99	[0.80; 1.23]	4.4%	4.3%
ASPREE	558	9525	494	9589		1.14	[1.01; 1.28]	13.5%	14.5%
Fixed effect model		81623		80057		0.97	[0.93; 1.02]	100.0%	
Random effects model					\$	0.97	[0.93; 1.02]		100.0%
Heterogeneity: $I^2 = 0\%$, τ^2	= 0, p = 0	.60							
					0.75 1 1.5				

eFigure 4: Frequentist analysis forest plots (Continued)

Cardiovascular mortality

	Experin	nental	0	ontrol				Weight	Weight
Study	Events	Total	Events	Total	Risk Ratio	RR	95%-CI	(fixed)	(random)
нот	133	9399	140	9391	4	0.95	[0.75; 1.20]	13.8%	13.9%
TPT (Exc warfarin)	49	1268	49	1272			[0.68; 1.48]	4.8%	5.1%
PPP	17	2226	31	2269			[0.31; 1.01]	3.0%	2.2%
WHS	120	19934	126	19942			[0.74; 1.22]	12.4%	12.4%
BDS	119	3429	59	1710	÷		[0.74; 1.37]	7.8%	8.2%
PHS	81	11037	83	11034	+	0.98	[0.72; 1.32]	8.2%	8.3%
AAA	35	1675	30	1675	÷	1.17	[0.72; 1.89]	3.0%	3.3%
POPADAD	43	638	35	638		1.23	[0.80; 1.89]	3.4%	4.1%
JPAD	1	1262	10	1277	l	0.10	[0.01; 0.79]	1.0%	0.2%
JPPP	58	7220	57	7244	+	1.02	[0.71; 1.47]	5.6%	5.8%
ASCEND	210	7740	226	7740	<u>.</u>	0.93	[0.77; 1.12]	22.2%	22.5%
ARRIVE	38	6270	39	6276	+	0.98	[0.62; 1.52]	3.8%	3.9%
ASPREE	91	9525	112	9589	국	0.82	[0.62; 1.08]	11.0%	10.2%
Fixed effect model		81623		80057		0.94	[0.86; 1.03]	100.0%	
Random effects model							[0.87; 1.03]		100.0%
Heterogeneity: $I^2 = 0\%$, τ^2	= 0, p = 0	.50							
					0.1 0.51 2 10				

All myocardial infarction

Study	Experi Events		C Events	ontrol Total	Risk Ratio	RR	95%-CI	Weight (fixed)	Weight (random)
HOT	82	9399	127	9391	— — ——————————————————————————————————	0.65	[0.49; 0.85]	7.8%	8.1%
TPT (Exc warfarin)	83	1268	107	1272		0.78	[0.59; 1.03]	6.6%	8.1%
PPP	19	2226	28	2269		0.69	[0.39; 1.23]	1.7%	3.3%
WHS	198	19934	193	19942	÷	1.03	[0.84; 1.25]	11.9%	10.3%
BDS	181	3429	86	1710	- <u>-</u>	1.05	[0.82; 1.35]	7.1%	8.8%
PHS	139	11037	239	11034	i	0.58	[0.47; 0.72]	14.7%	10.0%
AAA	90	1675	86	1675		1.05	[0.78; 1.40]	5.3%	7.9%
POPADAD	76	638	69	638	÷ =	1.10	[0.81; 1.50]	4.2%	7.4%
JPAD	12	1262	14	1277		0.87	[0.40; 1.87]	0.9%	2.1%
JPPP	27	7220	37	7244		0.73	[0.45; 1.20]	2.3%	4.2%
ASCEND	296	7740	317	7740		0.93	[0.80; 1.09]	19.5%	11.4%
ARRIVE	95	6270	112	6276		0.85	[0.65; 1.11]	6.9%	8.3%
ASPREE	171	9525	184	9589		0.94	[0.76; 1.15]	11.3%	10.0%
Fixed effect model		81623		80057	\$	0.87	[0.81; 0.93]	100.0%	
Random effects model Heterogeneity: $I^2 = 61\%$, t			01		0.5 1 2		[0.76; 0.97]		100.0%

eFigure 4: Frequentist analysis forest plots (Continued)

Total stroke

Study	Experii Events		C Events	ontrol Total		Risk	Ratio		RR	95	%-CI	Weight (fixed)	Weight (random)
HOT	146	9399	148	9391		\rightarrow	-		0.99	[0.79;	1.24]	10.5%	10.7%
TPT (Exc warfarin)	18	1268	26	1272		• •			0.69	[0.38;	1.26]	1.8%	1.6%
PPP	16	2226	24	2269		• •			0.68	[0.36;	1.28]	1.7%	1.4%
WHS	221	19934	266	19942					0.83	[0.70;	0.99	18.9%	17.6%
BDS	91	3429	42	1710			*		1.08	[0.75;	1.55	4.0%	4.2%
PHS	119	11037	98	11034		÷	- 10		1.21	[0.93;	1.58]	7.0%	7.8%
AAA	44	1675	50	1675	_				0.88	[0.59;	1.31]	3.5%	3.5%
POPADAD	37	638	50	638		*	_		0.74	[0.49;	1.12]	3.5%	3.3%
JPAD	28	1262	32	1277					0.89	[0.54;	1.46]	2.3%	2.2%
JPPP	128	7220	128	7244			-		1.00	[0.79;	1.28]	9.1%	9.4%
ASCEND	240	7740	263	7740			_		0.91	[0.77;	1.08]	18.7%	18.6%
ARRIVE	75	6270	67	6276		\rightarrow			1.12	[0.81;	1.55	4.8%	5.1%
ASPREE	195	9525	203	9589		-	-		0.97	[0.80;	1.17]	14.4%	14.6%
Fixed effect model		81623		80057		4			0.94	[0.88;	1.02]	100.0%	
Random effects model									0.94	[0.87;	1.01]		100.0%
Heterogeneity: $I^2 = 0\%$, τ^2	= 0, p = 0	.51								-	-		
					0.5		1	2					

Ischemic stroke

	Experi	mental	0	ontrol				Weight	Weight
Study	Events	Total	Events	Total	Risk Ratio	RR	95%-CI	(fixed)	(random)
TPT (Exc warfarin)	10	1268	18	1272		0.56	[0.26; 1.20]	1.9%	1.5%
PPP	14	2226	21	2269		0.68	[0.35; 1.33]	2.2%	1.9%
WHS	170	19934	221	19942		0.77	[0.63; 0.94]	23.4%	21.8%
BDS	21	3429	7	1710		1.50	[0.64; 3.51]	1.0%	1.2%
PHS	91	11037	82	11034	+ =	1.11	[0.82; 1.49]	8.7%	9.8%
AAA	30	1675	37	1675		0.81	[0.50; 1.31]	3.9%	3.8%
JPAD	22	1262	25	1277		0.89	[0.50; 1.57]	2.6%	2.7%
JPPP	85	7220	101	7244		0.84	[0.63; 1.12]	10.7%	10.5%
ASCEND	240	7740	263	7740		0.91	[0.77; 1.08]	27.9%	29.1%
ASPREE	148	9525	167	9589		0.89	[0.72; 1.11]	17.6%	17.9%
Fixed effect model		65316		63752	÷	0.87	[0.80; 0.96]	100.0%	
Random effects model Heterogeneity: $l^2 = 0\%$, τ^2		55				0.87	[0.80; 0.96]		100.0%
neterogeneity. 7 = 076, 1	- 0, <i>p</i> - 0				0.5 1 2				

Incident Cancer

	Experi	mental	C	ontrol				Weight	Weight
Study	Events	Total	Events	Total	Risk Rati	o RR	95%-CI	(fixed)	(random)
HOT	294	9399	311	9391		0.94	[0.81; 1.10]	7.0%	9.5%
PPP	86	2226	80	2269		1.10	[0.81; 1.48]	1.8%	3.3%
WHS	1438	19934	1427	19942		1.01	[0.94; 1.08]	32.3%	21.9%
BDS	119	3429	58	1710		1.02	[0.75; 1.39]	1.8%	3.1%
AAA	166	1675	194	1675		0.86	[0.70; 1.04]	4.4%	6.8%
POPADAD	45	638	60	638		0.75	[0.52; 1.09]	1.4%	2.2%
JPAD	149	1262	169	1277		0.89	[0.73; 1.10]	3.8%	6.2%
JPPP	332	7220	271	7244	i—	···· 1.23	[1.05; 1.44]	6.1%	9.4%
ASCEND	897	7740	887	7740	÷	1.01	[0.93; 1.10]	20.1%	18.6%
ASPREE	981	9525	952	9589	-	1.04	[0.95; 1.13]	21.5%	19.1%
Fixed effect model		63048		61475	\$		[0.97; 1.05]	100.0%	
Random effects mode Heterogeneity: 1 ² = 36%,		6. p = 0.	12		Ŷ	1.00	[0.95; 1.06]		100.0%
					0.75 1	1.5			

eFigure 4: Frequentist analysis forest plots (Continued)

Cancer Mortality

Study	Experii Events		C Events	Control Total	Risk Ratio	RR	95%-CI	Weight (fixed)	Weight (random)
HOT	108	9399	105	9391	<u>+</u>	1.03	[0.79; 1.34]	7.2%	8.1%
TPT (Exc warfarin)	49	1268	51	1272		0.96	[0.66; 1.42]	3.5%	4.4%
PPP	31	2226	29	2269		1.09	[0.66; 1.80]	2.0%	2.7%
WHS	284	19934	299	19942		0.95	[0.81; 1.12]	20.5%	16.7%
BDS	75	3429	47	1710		0.80	[0.56; 1.14]	4.3%	4.9%
PHS	79	11037	68	11034		1.16	[0.84; 1.60]	4.7%	5.9%
AAA	78	1675	90	1675	i	0.87	[0.64; 1.16]	6.2%	6.9%
POPADAD	25	638	31	638		0.81	[0.48; 1.35]	2.1%	2.5%
JPAD	63	1262	60	1277		1.06	[0.75; 1.50]	4.1%	5.3%
JPPP	134	7220	125	7244		1.08	[0.84; 1.37]	8.5%	9.5%
ASCEND	309	7740	315	7740	- <u></u>	0.98	[0.84; 1.14]	21.6%	17.7%
ASPREE	295	9525	227	9589		1.31	[1.10; 1.55]	15.5%	15.5%
Fixed effect model		75353		73781	-	1.03	[0.96; 1.11]	100.0%	
Random effects model					-	1.03	[0.94; 1.12]		100.0%
Heterogeneity: I ² = 21%, τ	² = 0.0044	p = 0.	24		r i		• • •		
				(0.5 1	2			

Major bleeding

	Experi	mental		Control							Weight	Weight
Study	Events	Total	Events	Total		Risk	Ratio		RR	95%-CI	(fixed)	(random)
HOT	136	9399	78	9391			<u>i = </u>		1.74	[1.32; 2.30]	9.3%	10.0%
TPT (Exc warfarin)	8	1268	4	1272			↓ ÷ • −		- 2.01	[0.61; 6.65]	0.5%	0.5%
PPP	25	2226	9	2269			+		2.83	[1.32; 6.05]	1.1%	1.3%
WHS	127	19934	91	19942					1.40	[1.07; 1.83]	10.9%	10.6%
BDS	20	3429	10	1710			<u> </u>		1.00	[0.47; 2.13]	1.6%	1.3%
PHS	48	11037	30	11034					1.60	[1.01; 2.52]	3.6%	3.7%
AAA	34	1675	20	1675			<u></u> →•		1.70	[0.98; 2.94]	2.4%	2.6%
JPAD	18	1262	12	1277		_	.		1.52	[0.73; 3.14]	1.4%	1.5%
JPPP	104	7220	70	7244			- in		1.49	[1.10; 2.01]	8.4%	8.5%
ASCEND	314	7740	245	7740					1.28	[1.09; 1.51]	29.3%	28.5%
ASPREE	361	9525	265	9589			1		1.37	[1.17; 1.60]	31.6%	31.5%
Fixed effect model		74715		73143			\$		1.42	[1.30; 1.55]	100.0%	
Random effects model							۵		1.42	[1.30; 1.55]		100.0%
Heterogeneity: I ² = 0%, τ ²	= 0, p = 0	.54			Г <u> </u>			-1				
					0.2	0.5	12	5				

Intracranial bleeding

	Experi	nental	c	ontrol					Weight	Weight
Study	Events	Total	Events	Total	Risk	Ratio	RI	R 95%-CI	(fixed)	(random)
нот	14	9399	15	9391			0.9	3 [0.45; 1.93]	5.8%	4.9%
TPT (Exc warfarin)	3	1268	2	1272		1.		0 [0.25; 8.99]		0.8%
PPP	4	2226	3	2269				6 [0.30; 6.07]	1.1%	1.2%
WHS	51	19934	41	19942		- 10		4 [0.83; 1.88]	15.8%	15.5%
BDS	13	3429	6	1710		+	1.0	8 [0.41; 2.84]	3.1%	2.8%
PHS	23	11037	12	11034		++++	- 1.9	2 [0.95; 3.85]	4.6%	5.4%
AAA	11	1675	7	1675	_		- 1.5	7 [0.61; 4.04]	2.7%	2.9%
JPAD	8	1262	7	1277			1.1	6 [0.42; 3.18]	2.7%	2.5%
JPPP	52	7220	36	7244		<u>in</u>	1.4	5 [0.95; 2.21]	13.9%	14.5%
ASCEND	55	7740	45	7740		- <u>-</u>	1.2	2 [0.83; 1.81]	17.4%	16.9%
ARRIVE	8	6270	11	6276		++-	0.7	3 [0.29; 1.81]	4.3%	3.1%
ASPREE	107	9525	72	9589			1.5	0 [1.11; 2.01]	27.7%	29.5%
Fixed effect model		8 09 85		79419				3 [1.14; 1.57]		
Random effects mode							1.3	3 [1.13; 1.57]		100.0%
Heterogeneity: / ² = 0%, t	r = 0, p = 0	.93			1 1		-			
					0.2 0.5	1 2	5			

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

Study	Experin Events		C Events	Control Total	Ris	k Ratio		RR	95%-CI	Weight (fixed)	Weight (random)
HOT	77	9399	37	9391		<u>}</u> ≡−	2	08	[1.41; 3.07]	9.8%	10.8%
TPT (Exc warfarin)	6	1268	2	1272	-	+			[0.61; 14.88]	0.5%	0.6%
PPP	17	2226	5	2269		+-+-	— 3.	47	[1.28: 9.38]	1.3%	1.7%
WHS	127	19934	91	19942		1 1	1.	40	[1.07: 1.83]	24.0%	23.0%
PHS	49	11037	28	11034		<u></u>	1.	75	[1.10; 2.78]	7.4%	7.7%
AAA	9	1675	8	1675		++	1.	12	[0.44: 2.91]	2.1%	1.8%
JPAD	5	1262	4	1277			1.	26	[0.34: 4.70]	1.0%	1.0%
ASCEND	137	7740	101	7740		l ai -	1.	36	[1.05: 1.75]	26.6%	25.4%
ARRIVE	4	6270	2	6276		17.	2	00	[0.37; 10.93]	0.5%	0.6%
ASPREE	162	9525	102	9589		÷			[1.25; 2.05]	26.8%	27.3%
Fixed effect model		70336		70465		\ \ \	1.	56	[1.38; 1.78]	100.0%	
Random effects model Heterogeneity: $l^2 = 0\%$, τ^2		54			г гг г	\ \ \			[1.37; 1.77]		100.0%
fictorogeneity: r = 0.0, r	0, p 0				0.1 0.5	1 2	10				

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 Atherosclerosis¹⁷; ARRIVE – Aspirin to Reduce Risk of Initial Vascular Events²⁰; ASCEND – A Study of Cardiovascular Events in Diabetes¹⁹; ASPREE – Aspirin in Reducing Events in the Elderly²¹; BDS – British Doctor's Study⁹; HOT – Hypertension Optimal Treatment¹¹; JPAD – Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes¹⁶; JPPP – Japanese Primary Prevention Project¹⁸; PHS – Physician's Health Study¹⁰; POPADAD – Prevention of Progression of Arterial Disease and Diabetes¹⁵; PPP – Primary Prevention Project¹³; TPT – Thrombosis Prevention Trial¹²; WHS – Women's Health Study¹⁴.

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