Supplementary Appendix

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

Supplement to: McNeil JJ, Wolfe R, Woods RL, et al. Effect of aspirin on cardiovascular events and bleeding in the healthy elderly. N Engl J Med 2018;379:1509-18. DOI: 10.1056/NEJMoa1805819

The ASPREE (ASPirin in Reducing events in the Elderly) trial

SUPPLEMENTARY APPENDIX

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Pinkstone J, Pinson J, Pither A, Plenderleith J, Pliatsios B, Plunkett M, Pokharel C, Poland D, Polgar V, Polmear D, Pologanathan G, Pope I, Popp L, Portelli A, Potter T, Powell Kendra, Powell Kristine, Powell V, Power R, Powles A, Poynton N, Pranavan S, Prasad R, Praszkier S, Preiss J, Pretorius P, Price C, Price I, Price K, Price M, Priest C, Pring M, Profitt C, Protassow A, Psaradellis IJA, Psycharis J, Pucilowski D, Pun K, Qamar F, Quach S, Radcliff E, Radcliffe B, Radcliffe J, Radford J, Ragg P, Rahel E, Rahim T, Rahman F, Rahmanamlashi N, Rajasooriar S, Rajendra I, Rajini E, Raman A, Ramsay A, Ramsey J, Rana U, Rankin M, Rao UV, Rapley M, Rasaratnam S, Rashid A, Ratnaike L, Rattan J, Ratten K, Rattraywood C, Rayner E, Rea J, Rea PC, Reddy Sanganakal, Reddy Shradhanand, Reed R, Reeves C, Reichl T, Reid J, Reid K, Remyn P, Renfrey S, Renouf E, Renshaw P, Retchford A, Reynolds F, Reza R, Rezk L, Rhee J, Rhodes F, Rice A, Richards J, Richards R, Richardson A, Richardson GT, 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SUPPLEMENTARY MATERIALS

ASPREE END POINT DEFINITIONS & ADJUDICATION CRITERIA

(ASPREE Protocol www.aspree.org)

CARDIOVASCULAR DISEASE

Definitions Definitions and process for adjudication of fatal and non-fatal cardiovascular events

Cardiovascular events included a) Coronary heart disease death, b) non-fatal myocardial infarction (MI), c) fatal and non-fatal stroke, d) non-coronary cardiac or vascular death and e) hospitalization for heart failure.

Source information from hospitals/medical centers, treating physicians, death certificates, medical records, hospital information obtained from the next of kin or other family members where relevant was collected, sent to the ASPREE Data Management Center and presented to adjudicators of the Death, Cardiac or Stroke EACs as appropriate. Adjudicators were blinded to participant identity and treatment arm.

a) Coronary heart disease death was defined as death from MI, sudden cardiac death, rapid cardiac death (death after possible MI), cardiac failure death (with coronary cause) and other coronary death.

- MI - Autopsy or death certificate diagnosis, with definitive or suspected diagnosis of MI within 4 weeks of death.
- Sudden cardiac death - Death occurring within one hour of the onset of new cardiac symptoms (ischemic chest symptoms or sudden collapse) or unwitnessed death after last being seen without new cardiac symptoms, and in each case, without any coronary disease (clinically or at autopsy) that could have been rapidly fatal.
- Rapid cardiac death (death after possible MI) - Death within 1-24 hours of the onset of severe cardiac symptoms unrelated to other known causes. Death in hospital with possible MI (i.e. participants who have had typical ischemic pain and whose ECG and enzyme results fulfil the criteria for definitive MI and in whom there was no good evidence for another diagnosis for the event).
- Cardiac failure death - Death due to heart failure (prior NYHA Class III-IV dyspnea), without any defined non-coronary cause.
- Other coronary death - Any death where the underlying cause was certified as coronary (and where there is no evidence of non-coronary cause of death, clinically or at autopsy).

The Death EAC was responsible for determining if events met this definition. Time-to-event for coronary heart disease death was taken as the date of death recorded on death certification.

b) Non-fatal MI was defined according to the American College of Cardiology & European Society of Cardiology definition [1] and classified as either acute evolving or recent MI, or established MI.

Criteria for acute, evolving or recent MI include either one of the following:

1. Typical rise in troponin or CK-MB as biochemical markers of myocardial necrosis with at least one of the following:
   - ischemic symptoms;
   - development of pathologic Q waves on the ECG;
   - ECG changes indicative of ischemia (ST segment elevation or depression);
   - coronary artery intervention (e.g. coronary angioplasty).
2. Pathologic findings of an acute MI. Criteria for established MI include either one of the following:

- Development of new pathologic Q waves on serial ECGs. The patient may or may not remember previous symptoms. Biochemical markers of myocardial necrosis may have normalized, depending on the length of time that has passed since the infarct developed.
- Pathologic findings of a healed or healing MI.

The Cardiac EAC was responsible for determining if events met this definition. Time-to-event for non-fatal MI was taken as the date of troponin rise for acute, evolving or recent MI, and the date of ECG or pathology report for established MI.

c) Fatal and non-fatal stroke were defined according to the World Health Organization (WHO) definition as rapidly developing clinical signs of focal (or global) disturbance of cerebral function lasting more than 24 hours (unless interrupted by surgery or death) with no apparent cause other than of vascular origin [2]. This definition excluded cases of primary cerebral tumor, cerebral metastasis, subdural hematoma, post seizure palsy, brain trauma, and transient ischemic attack.
Fatal stroke was defined as any death due to the rapid onset of a new neurological deficit attributed to obstruction or rupture in the intra-cranial or extra-cranial cerebral arterial system.
The Stroke EAC was responsible for determining if events met this definition. Time-to-event for stroke was taken as the date of first evidence of disturbance of cerebral function.

Confirmed strokes were further classified as:

- Ischemic stroke (included in cardiovascular end point)
- Ischemic stroke with hemorrhagic transformation (included in cardiovascular end point)
- Stroke type uncertain (included in cardiovascular end point)
- Hemorrhagic stroke (included in major hemorrhage end point)
- Sub-arachnoid hemorrhage stroke (included in major hemorrhage end point)

Ischemic stroke sub-classification - Cerebral infarction could be confirmed by autopsy. The TOAST classification for subtype of acute ischemic stroke was utilized, in which both clinical features and ancillary tests (laboratory, radiology, and ultrasonography) were used to categorize five subtypes [3]

1. large artery atherosclerosis (embolus/thrombosis);
2. cardio embolism (high risk/medium risk);
3. small-vessel occlusion (lacunae);
4. stroke of other determined etiology;
5. stroke of undetermined etiology:
    (a) two or more causes identified;
    (b) negative evaluation;
    (c) incomplete evaluation.

Distinction between ischemic and hemorrhagic stroke could be made only with appropriate imaging as outlined in the table below:

	CT	MRI
Ischemic stroke	An area of low attenuation or a normal appearance in the vascular territory that corresponded to the recent symptoms and signs	A critically relevant area of increased signal on diffusion weighted imaging, a slight hypointensity with or without mass effect on T1-weighted images, a bright area of hyper-intensity with or without mass effect on T2-weighted images, or evidence of recent infarction on diffusion weighted MRI
Hemorrhagic	An area of hyperdensity within	An area of hypointensity or isointensity

stroke	the brain parenchyma with or without extension into the ventricles or subarachnoid space or, for scans performed beyond 1 week, an area of attenuation with ring enhancement after injection of contrast	on T1-weighted images or an area of marked hypointensity on gradient echo and T2-weighted images, or by autopsy demonstrating the origin of the hemorrhage as the cerebral parenchyma

NB: Rarer causes and sites of intracerebral hemorrhage such as underlying arteriovenous malformation and spinal cord hemorrhage were documented.

Hemorrhagic stroke sub-classification – Sub-classification was used for hemorrhagic strokes based on imaging information, as described in the table above. To complement the use of the TOAST classification for thrombo-embolic stroke, the extent of intracerebral hemorrhage was qualtified by assessing hemorrhage site and volume by CT or MRI. Volume was assessed by utilizing the ABC/2 formula with hemorrhage sites as lobar, basal ganglionic or brain stem. [4]

Sub-arachnoid hemorrhages (SAH) – These were reviewed by the Stroke EAC. SAH must have satisfied all the criteria above to be considered as stroke. SAH that did not meet the above criteria were adjudicated as 'Not stroke end point – intracranial bleed present but event did not meet the stroke criteria.' Events with this outcome were sent to the neurologist on the Clinically Significant Bleeding (CSB) EAC who determined whether the event met the CSB criteria.

d) Non-coronary cardiac or vascular death – Health or coronial records of death or sudden death attributable to cardiac-related or vascular-related origins that were not due to coronary or myocardial ischemic were provided to the Death EAC for consideration. If considered appropriate, other EACs such as the Cardiac or Stroke EACs adjudicated the event. Such deaths may have included those attributed to AAA rupture, large vessel atherosclerosis, cardiomyopathy, cardiomegaly, myocarditis, peripheral vascular disease.

The Death EAC was responsible for determining if events met this definition. Time-to-event for non-coronary or vascular death was taken as the date of death recorded on death certification.

e) Hospitalization due to cardiac failure - Hospital discharge diagnosis of cardiac failure triggered an assessment by the Cardiac EAC. Hospitalization for heart failure was defined as an unplanned overnight stay, or longer, in a hospital environment (emergency room, observation unit or inpatient care) or similar facility. Heart failure was defined as a patient having typical symptoms (e.g., dyspnea, fatigue) that occurred at rest or on effort that was characterized by objective evidence of an underlying structural abnormality or cardiac dysfunction that impairs the ability of the ventricle to fill with or eject blood (particularly during exercise). The diagnosis of heart failure may have been further strengthened by a beneficial clinical response to treatment(s) directed towards amelioration of symptoms associated with this condition. Where possible, heart failure diagnosis was confirmed by demonstrated pulmonary congestion or edema on chest imaging. If chest imaging was not available, documented evidence of clinical signs of pulmonary oedema (e.g. rales > 1/3 up the lung fields thought to be of cardiac causes), pulmonary capillary wedge pressure >18 mmHg or B-type natriuretic peptide of >500pg/ml were utilised to confirm the diagnosis of heart failure.

The Cardiac EAC was responsible for determining if events met this definition. Time-to-event for hospitalization for heart failure was taken as the date of hospitalization. Each blinded case was sent to two adjudicators and if there was discordance in the outcome, the case was sent to a third adjudicator for a decision. Any case could be taken to a meeting of the EAC for discussion if an adjudicator needed to seek clarification in interpreting the notes or applying the decision rules.

MAJOR HEMORRHAGE

Definition and processes for adjudication

Major hemorrhage includes

a) hemorrhagic stroke and

b) non-stroke clinically significant bleeding.

a) Hemorrhagic stroke definition and adjudication

Refer to the stroke section c) of Cardiovascular Disease, above.

b) Clinically significant bleeding (CSB) definition and adjudication

Clinically significant bleeding was defined as non-stroke intracranial bleeding and extracranial bleeding at gastrointestinal or other sites that required transfusion, hospitalization for more than 24 hours, prolonged hospitalization by more than 24 hours with bleeding as the principal reason, surgery, or was fatal. [5]

The ASPREE definition of clinically significant bleeding required that bleeding was substantiated by the documentation of one of the following on the medical record:

- Observed bleeding (e.g., bleeding observed on gastroscope / cystoscope etc.)
- Reasonable report of symptoms of bleeding (e.g., melena or hematemesis)
- Medical, nursing or paramedical report
- Imaging evidence such as CT/MRI for intracerebral hemorrhage

Note: Low hemoglobin or drop in hemoglobin without one of the above did not satisfy the criteria of substantiated bleeding.

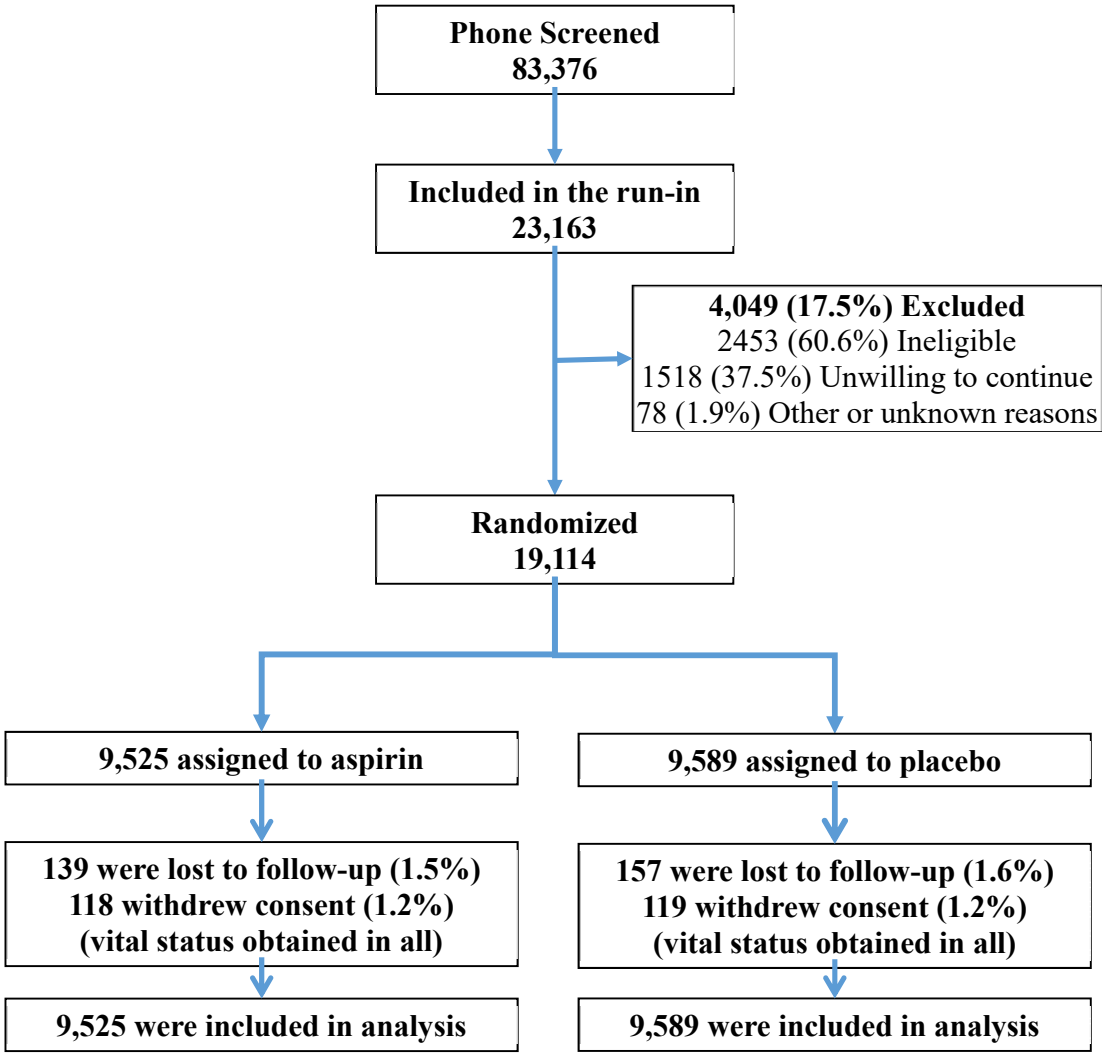
Specific decision rules developed by the CSB EAC included:

- If hospitalization criterion was to be utilized, bleeding must have been the principal reason for hospitalization, prolongation of hospitalization or surgery and must be substantiated.
- Additional adjudication occurred on whether the event was spontaneous (e.g., bleeding esophageal varices or gastric ulcer) or induced (e.g., trauma).
- Elective in-patient surgical procedure (included therapeutic endoscopic procedures) with prolonged stay, repeat surgery, or transfusion: ‘Case does not meet CSB defintion’
- Elective in-patient surgical procedure (included therapeutic endoscopic procedures) readmitted after discharge primarily for bleeding:- ‘Case meets CSB definition’
- Elective out-patient procedure (included therapeutic endoscopic procedures) readmitted, prolonged stay, repeat surgery, or transfusion:- ‘Case meets CSB definition’
- Non-elective inpatient procedure (included therapeutic endoscopic procedures) readmitted, prolonged stay, repeat surgery, or transfusion:- ‘Case meets CSB defintion’
- A positive fecal occult blood test was insufficient to substantiate observed CSB:- ‘Case does not meet CSB definition’

Source information from clinical case notes and hospital medical records related to these events was collected, sent to the ASPREE Data Management Center and presented to adjudicators on the CSB EAC. Adjudicators were blinded to participant identity and treatment arm. Each blinded case was sent to two adjudicators and if there was discordance in the outcome, the case was sent to a third adjudicator for a decision. Any case could be taken to a meeting of the EAC for discussion if an adjudicator needed to seek clarification in interpreting the notes or applying the decision rules.

SUPPLEMENTARY FIGURES

Figure S1: CONSORT diagram for the ASPREE trial.



* The most common exclusions were ineligibility due to cardiovascular disease history, compliance <80% during a 4 week placebo run-in period, 3MS <78, failed Katz Activity of Daily Living, low hemoglobin, high blood pressure or General Practitioner/Primary Care Physician opinion. Note that participants could have more than one ineligibility criterion. All information up to the point of withdrawal was included in the analyses.

Figure S2: Cumulative incidence of the end point that was not prespecified of major adverse cardiovascular events (MACE) in aspirin and placebo study groups.

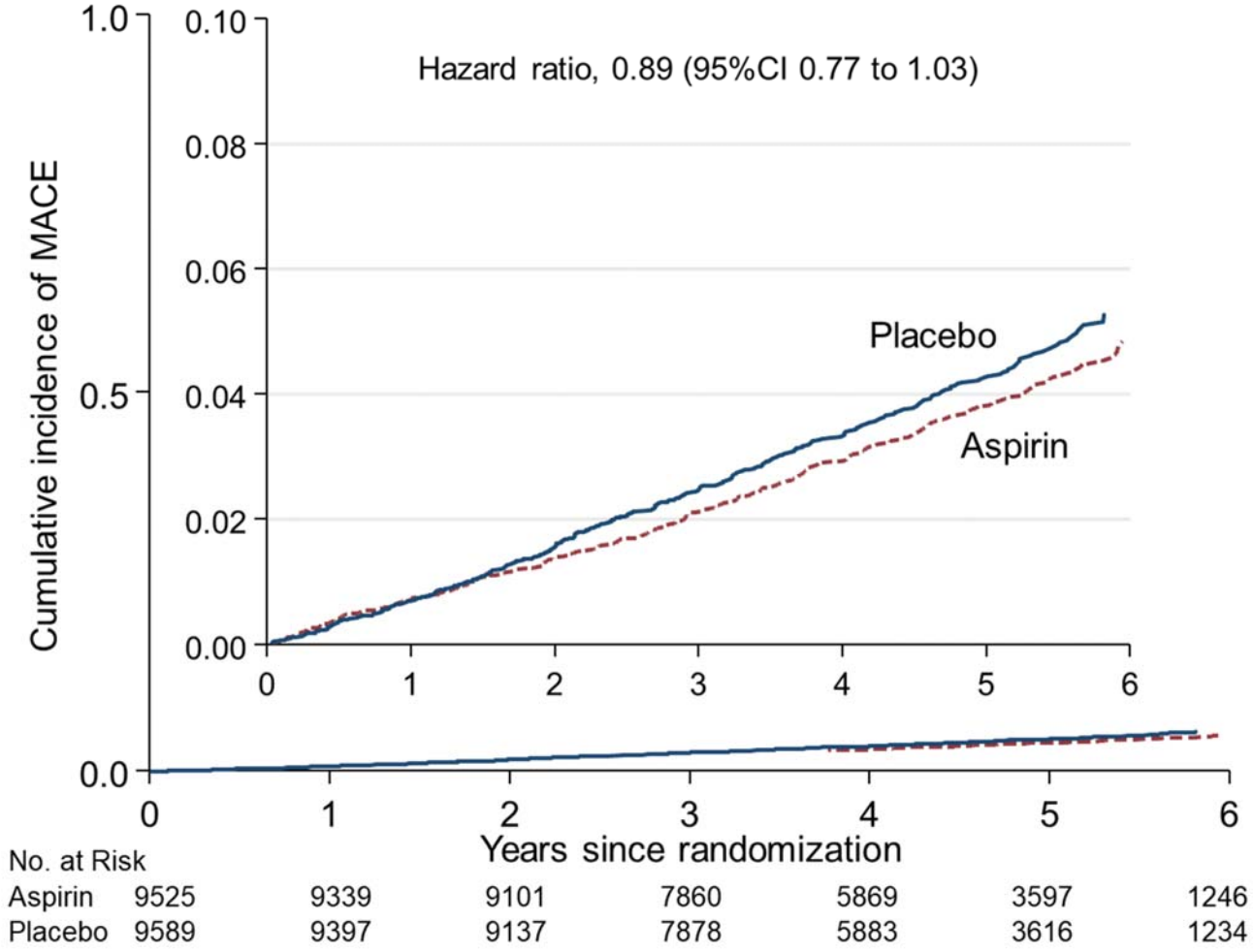


Figure S3: Cumulative incidence of myocardial infarction (MI) in aspirin and placebo study groups.

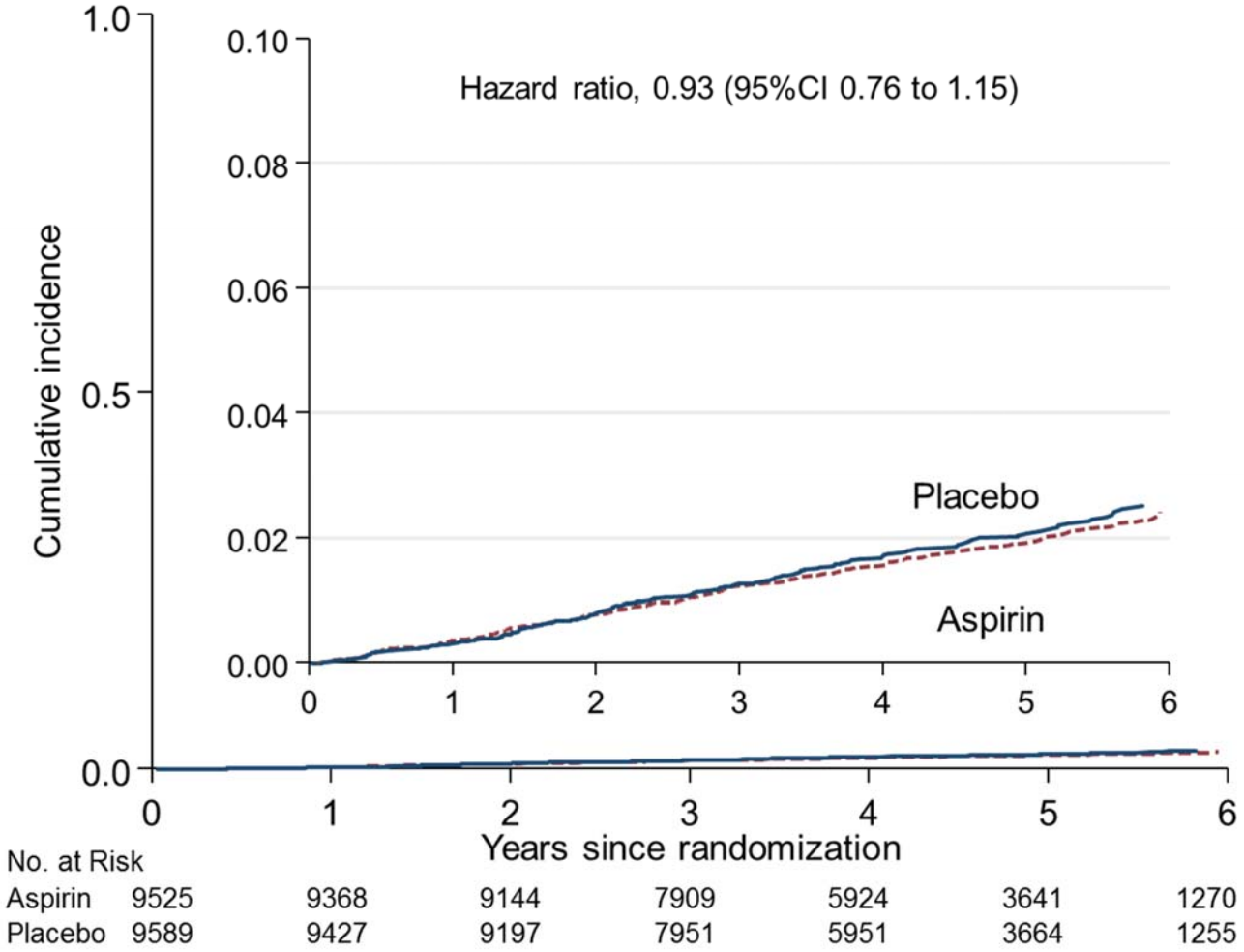


Figure S4: Cumulative incidence of ischemic stroke in aspirin and placebo study groups.

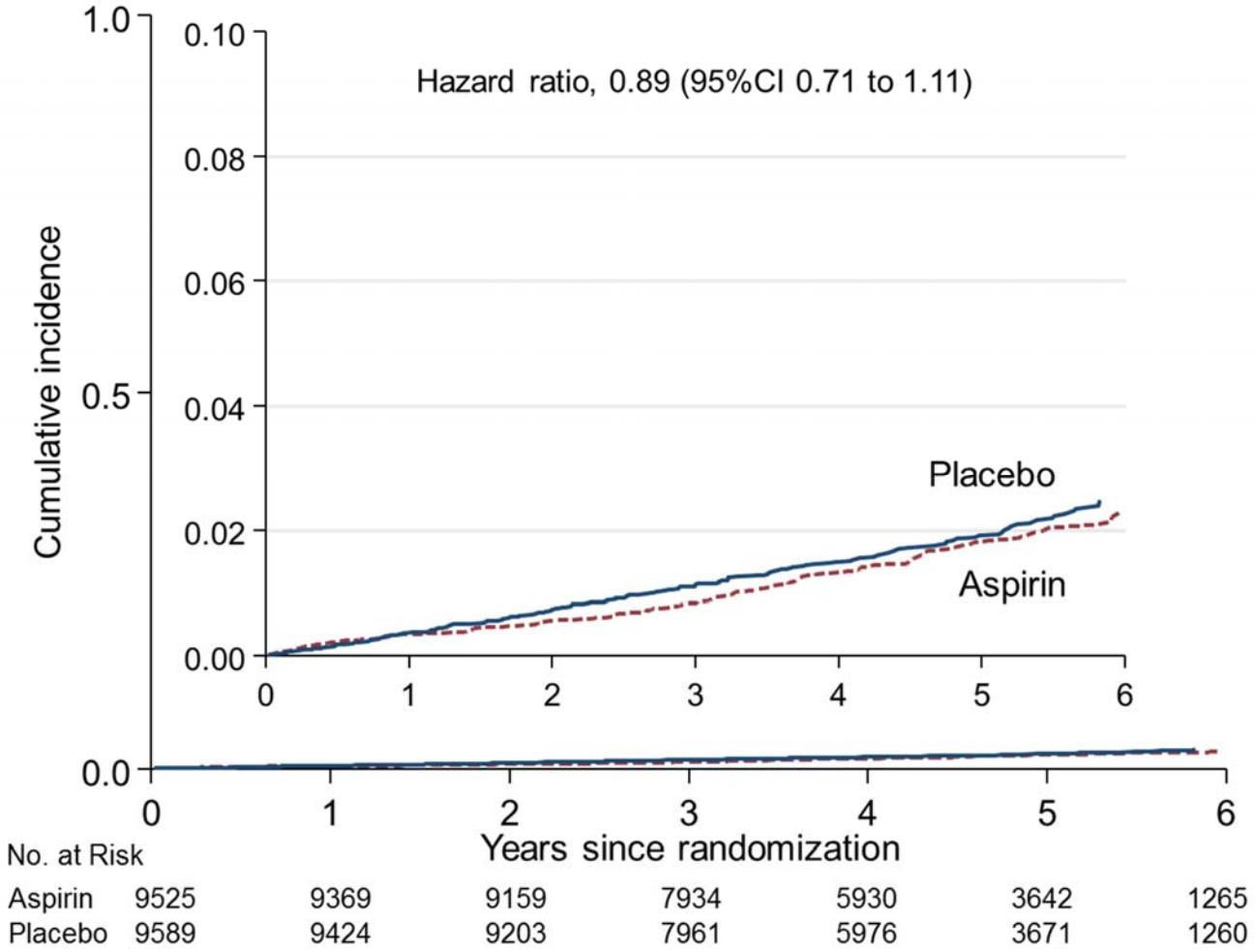
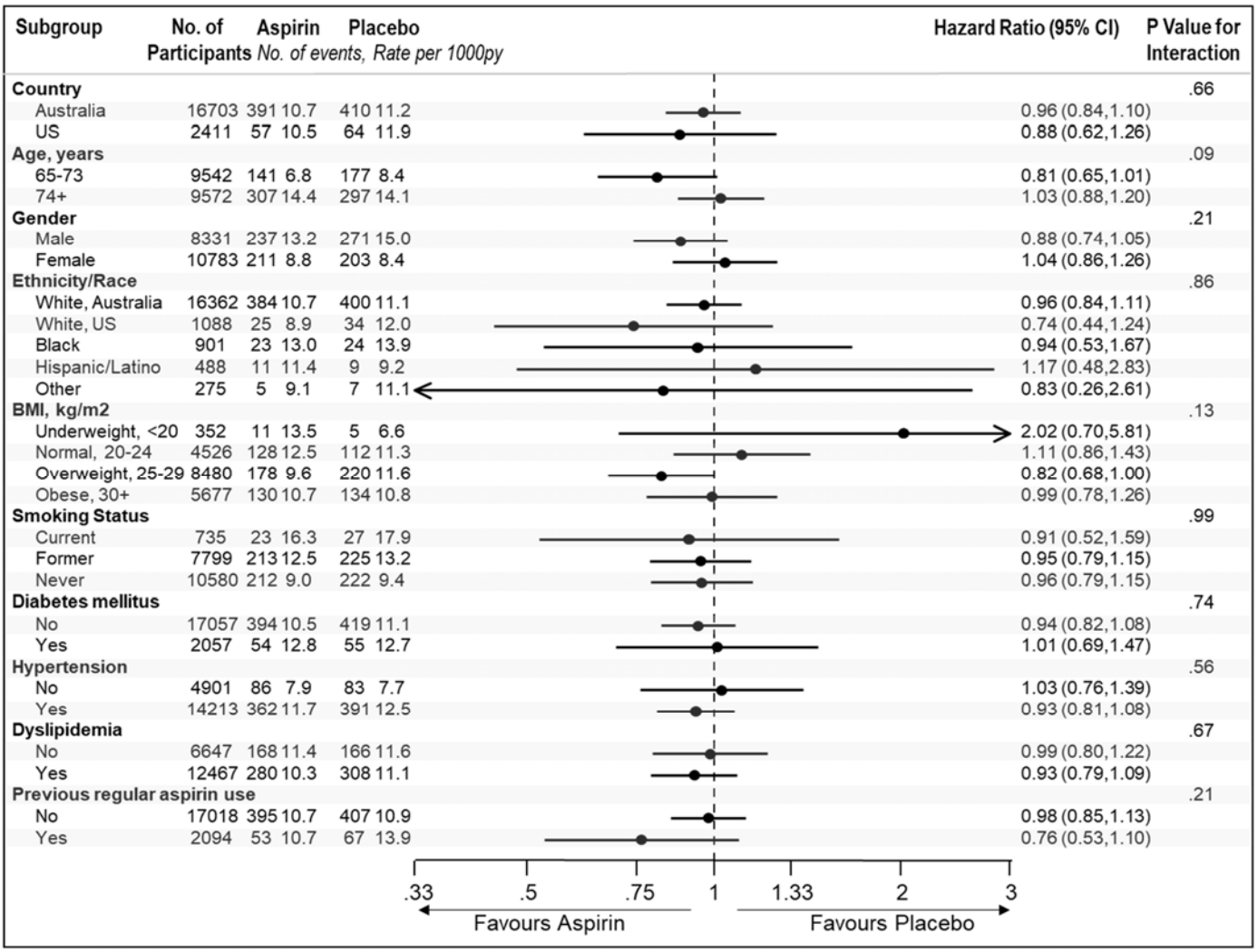
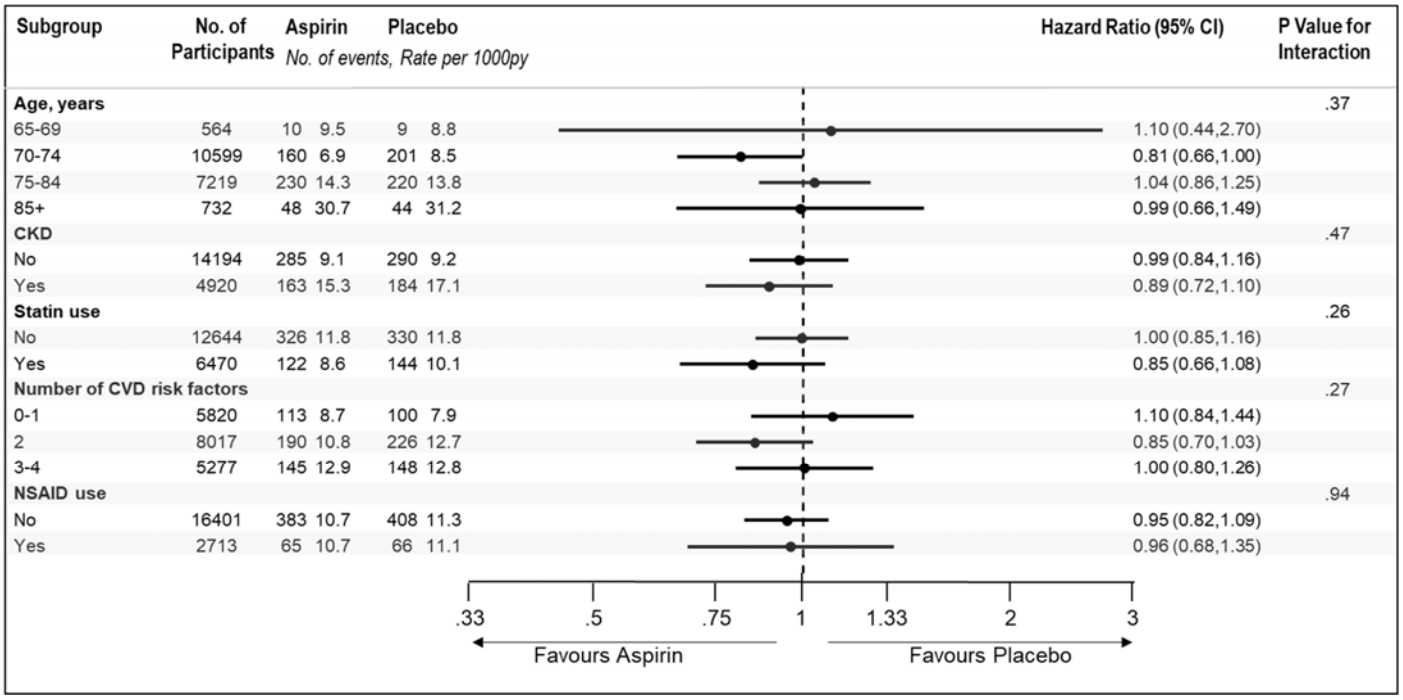


Figure S5: Forest plot of aspirin effect on the cardiovascular disease secondary end point in prespecified subgroups



Ethnicity/Race 'Other' is defined as any category with <200 participants overall, which includes Aboriginal/Torres Strait Islander (12), Native American (6), More than one race (64), Native Hawaiian / Pacific Islander (11) and those who were not Hispanic and who did not state their ethnicity/race (18); Diabetes mellitus is defined from self-report or fasting glucose ≥126mg/dL or on treatment for diabetes; Hypertension is defined as 'on treatment' for high blood pressure, BP, or BP > 140/90 mmHg at study entry; Dyslipidemia defined as those taking cholesterol-lowering medications or serum cholesterol ≥212mg/dL (≥5.5mmol/L; Australia) and ≥240mg/dL (≥6.2mmol/L; U.S.) or low-density lipoprotein, LDL>160 mg/dL (>4.1mmol/L); Previous regular aspirin use was self-reported regular use of aspirin immediately prior to first baseline visit with a one-month washout prior to randomization to study medication.

Figure S6: Forest plot of aspirin effect on the cardiovascular disease secondary end point in subgroups that were not prespecified



CKD (chronic kidney disease) defined as estimated glomerular filtration rate, eGFR, < 60 ml/min/1.73m^2 or urinary albumin to creatinine ratio ≥3mg/mmol; CVD (cardiovascular disease) risk factors include the following four conditions: hypertension, diabetes, dyslipidemia and smoking; Statin use included 483 individuals (247 aspirin and 236 placebo) on non-statin lipid lowering therapies; NSAID = non-steroidal anti-inflammatory drug (other than aspirin) self-reported use at first baseline visit.

Figure S7: Forest plot of aspirin effect on the posthoc end point major adverse cardiovascular events (MACE) in prespecified subgroups

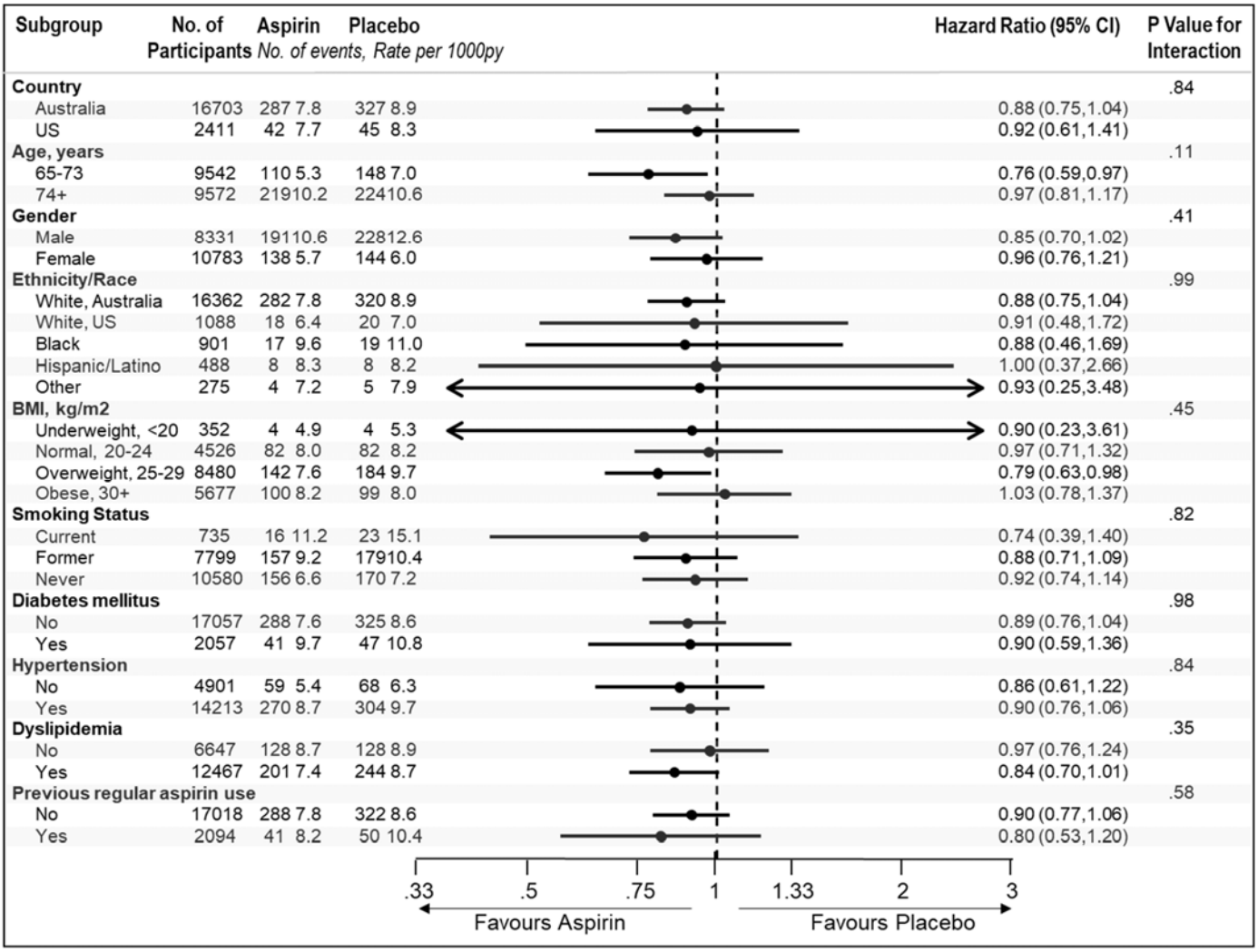


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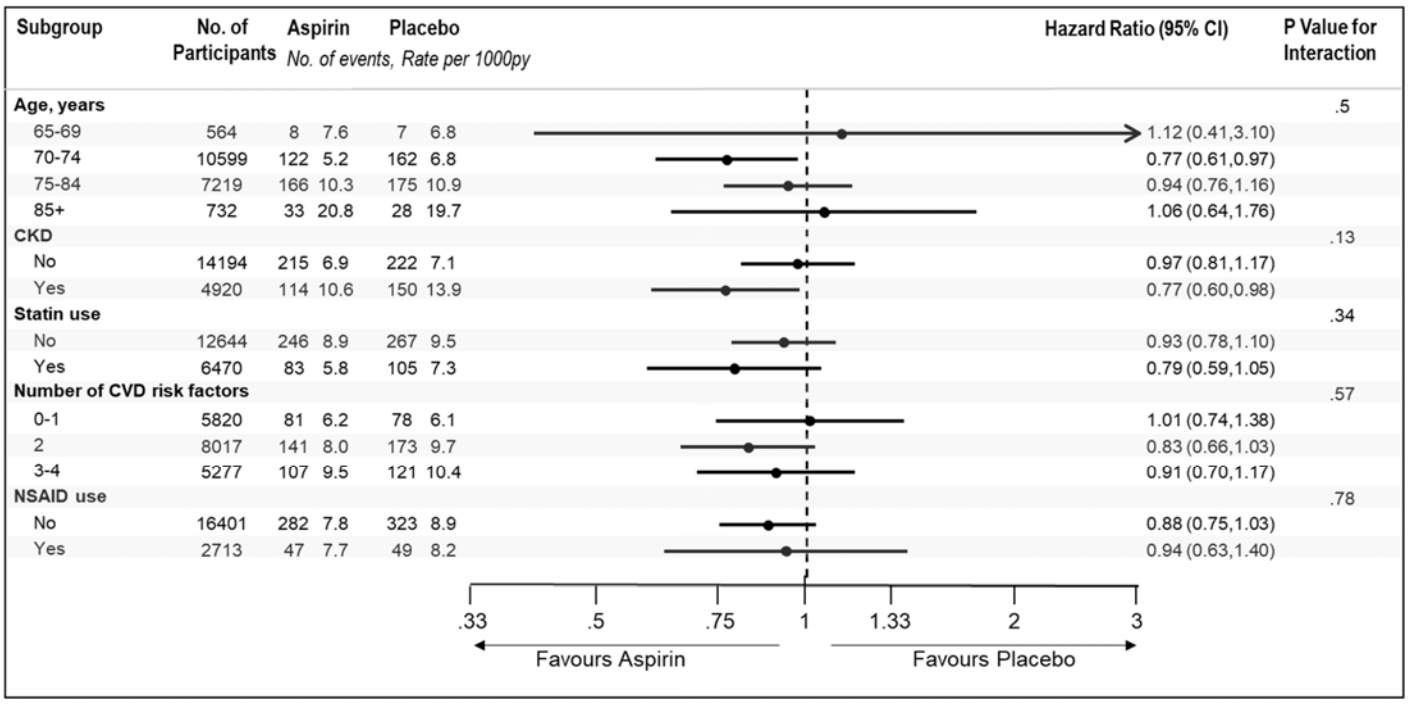
Figure S8: Forest plot of aspirin effect on the posthoc end point major adverse cardiovascular events (MACE) in subgroups that were not prespecified



CKD (chronic kidney disease) defined as estimated glomerular filtration rate, eGFR, < 60 ml/min/1.73m^2 or urinary albumin to creatinine ratio ≥3mg/mmol; CVD (cardiovascular disease) risk factors include the following four conditions: hypertension, diabetes, dyslipidemia and smoking; Statin use included 483 individuals (247 aspirin and 236 placebo) on non-statin lipid lowering therapies; NSAID = non-steroidal anti-inflammatory drug (other than aspirin) self-reported use at first baseline visit.

Figure S9: Cumulative incidence of intracranial bleeding (including hemorrhagic stroke) in aspirin and placebo study groups.

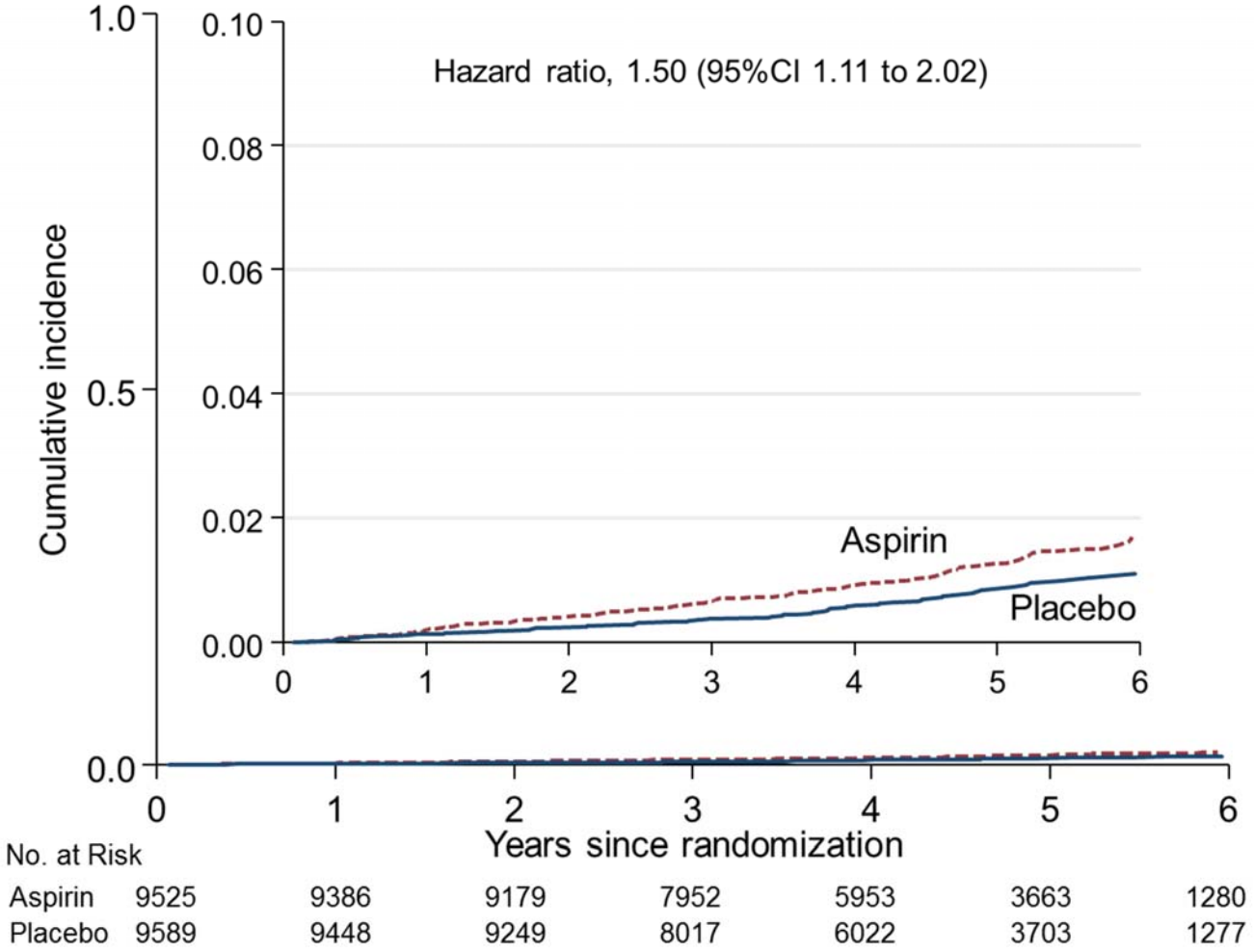
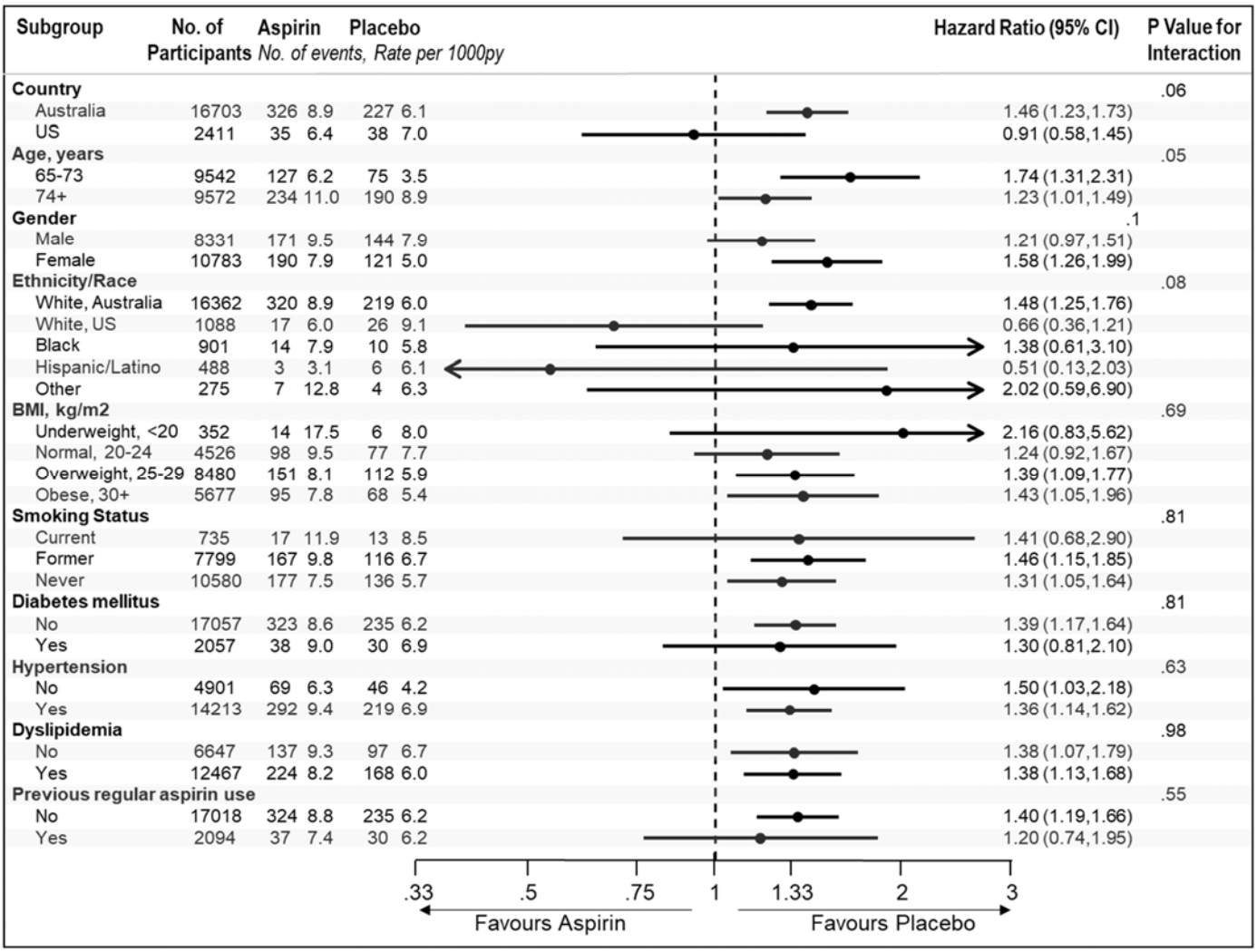
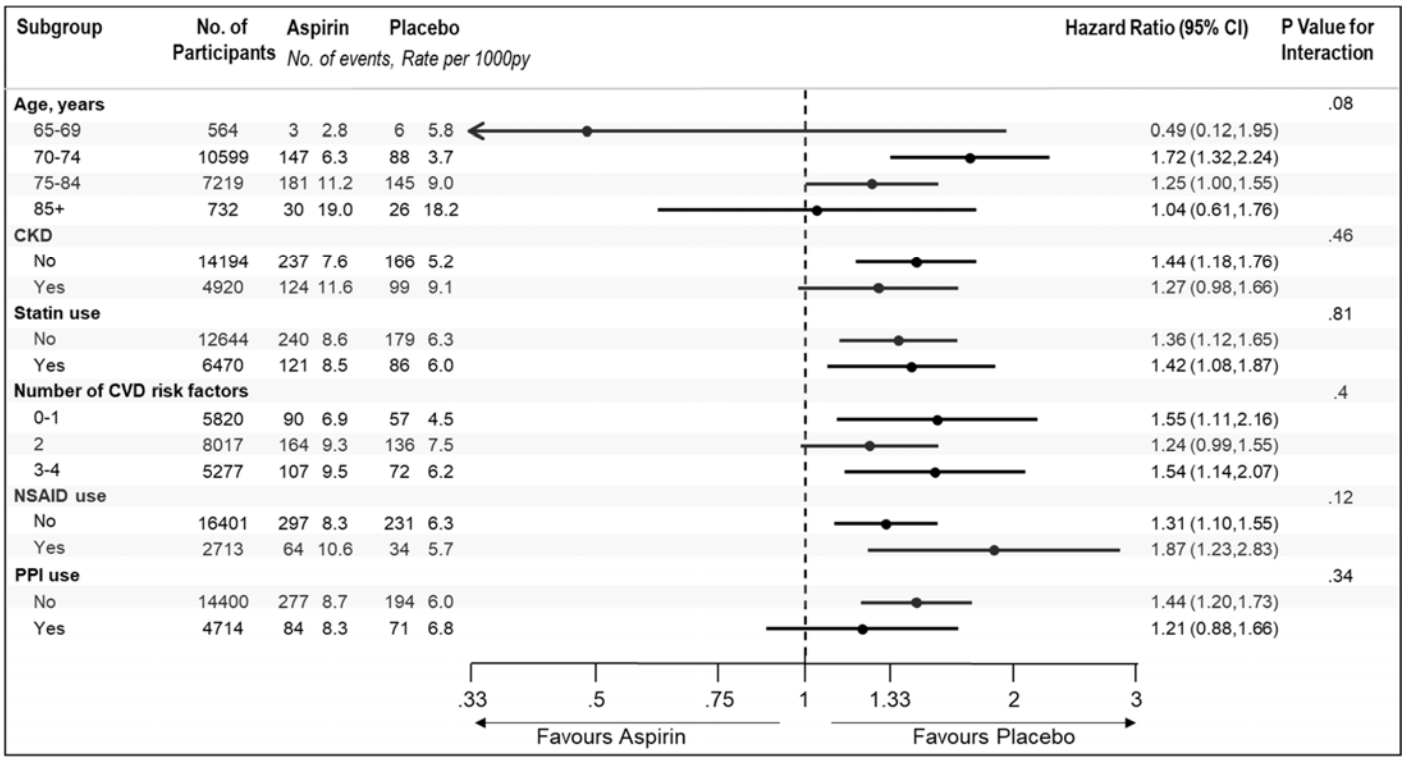


Figure S10: Forest plot of aspirin effect on the major hemorrhage secondary end point in prespecified subgroups



Ethnicity/Race 'Other' is defined as any category with <200 participants overall, which includes Aboriginal/Torres Strait Islander (12), Native American (6), More than one race (64), Native Hawaiian / Pacific Islander (11) and those who were not Hispanic and who did not state their ethnicity/race (18); Diabetes mellitus is defined from self-report or fasting glucose ≥126mg/dL or on treatment for diabetes; Hypertension is defined as 'on treatment' for high blood pressure, BP, or BP > 140/90 mmHg at study entry; Dyslipidemia defined as those taking cholesterol-lowering medications or serum cholesterol ≥212mg/dL (≥5.5mmol/L; Australia) and ≥240mg/dL (≥6.2mmol/L; U.S.) or low-density lipoprotein, LDL>160 mg/dL (>4.1mmol/L); Previous regular aspirin use was self-reported regular use of aspirin immediately prior to first baseline visit with a one-month washout prior to randomization to study medication.

Figure S11: Forest plot of aspirin effect on the major hemorrhage secondary end point in subgroups that were not prespecified



CKD (chronic kidney disease) defined as estimated glomerular filtration rate, eGFR, < 60 ml/min/1.73m^2 or urinary albumin to creatinine ratio ≥3mg/mmol; CVD (cardiovascular disease) risk factors include the following four conditions: hypertension, diabetes, dyslipidemia and smoking; Statin use included 483 individuals (247 aspirin and 236 placebo) on non-statin lipid lowering therapies; NSAID = non-steroidal anti-inflammatory drug (other than aspirin) self-reported use at first baseline visit; PPI = proton pump inhibitor drug self-reported use at first baseline visit.

SUPPLEMENTARY TABLES

Table S1: ASPREE Eligibility Criteria

Inclusion criteria
- able to give informed consent
- able to attend a study visit
- men and women
- aged 70 years and older (no upper age limit) except for U.S. blacks and Hispanics who were aged 65 years and older (no upper age limit)
Exclusion criteria
- a past history of cardiovascular or cerebrovascular event or established CVD, defined as myocardial infarction (MI), heart failure, angina pectoris, stroke, transient ischemic attack, >50% carotid stenosis or previous carotid endarterectomy or stenting, coronary artery angioplasty or stenting, coronary artery bypass grafting, abdominal aortic aneurysm
- a clinical diagnosis of atrial fibrillation
- a clinical diagnosis of dementia or score of <78 out of 100 on Modified Mini-Mental State (3MS) examination [6] administered by trained study staff
- physical disability as defined by severe difficulty or inability to perform independently any of the 6 Katz basic activities of daily living (ADLs) which include bathing, transferring from chair or bed, toileting, dressing, eating, walking across a room [7]
- a condition with a high current or recurrent risk of bleeding, anemia (hemoglobin <12 g/dl males, <11 g/dl females)
- a condition likely to cause death within 5 years (opinion of the General Practitioner or Primary Care Physician)
- current continuous use of other antiplatelet or anticoagulant medication
- current use of aspirin for secondary prevention
- uncontrolled high blood pressure (systolic BP ≥180mmHg and/or diastolic BP ≥105mmHg)
- unwilling to cease regular aspirin being taken for primary prevention
- pill taking compliance of <80% during a 4-week placebo run-in phase
- current participation in another clinical trial

Eligibility: Participants were generally healthy individuals aged 65 years and older (U.S. blacks or Hispanics) or 70 years and older (all other groups). The age differential was permitted to ensure that black and Hispanic populations could be represented in the trial, given evidence of higher burden of disease necessitating aspirin use [8]. Interested potential community-dwelling participants were screened by phone for suitability and eligibility. After obtaining informed consent, study eligibility was determined at 'in person' study visits utilizing the inclusion/exclusion criteria shown above and previously described [8, 9].

Table S2: ASPREE health measures and definitions

Annual health measures
- demographics and lifestyle factors
- blood pressure, heart rate
- weight, waist circumference
- cardiovascular & renal biomarkers (fasting lipids, hemoglobin, blood glucose, creatinine, urine ACR)
- depression screen (CES-D-10) [10]
- LIFE disability questionnaire [11] including the Katz basic Activities of Daily Living [7] (including walking across a room, bathing, dressing, transferring from a bed or chair, using the toilet, and eating; participants selected one of the following options for completing these tasks with 'no difficulty', 'a little difficulty' 'some difficulty', 'a lot of difficulty' or 'unable to perform independently'; and, as a check, answered whether assistance from another person was required to complete)
- quality of life questionnaire (SF-12) including calculations of MCS (Mental Component Score) and PCS (Physical Component Score) [12]
- clinical events
6 month phone calls
- confirmation of living circumstances
- administration of the Katz basic Activities of Daily Living
- questions regarding daily study medication adherence
- clinical and adverse events reports
Biennial health measures
- neurocognitive assessments included Modified Mini-Mental State examination (3MS) [6], Hopkins Verbal Learning Test – Revised (HVLT-R) [13], Controlled Oral Word Association Test (COWAT) [14], Symbol Digit Modalities Test (SDMT) [15]
- physical function tests (3m gait speed [16], handgrip strength [17])
Baseline/final visit health measure
- height
Health definitions
- diabetes mellitus - self report of diabetes mellitus or fasting glucose ≥126mg/dL (≥7mmol/L) or on treatment for diabetes.

- hypertension - on treatment for high BP or BP > 140/90 mmHg at study entry
- dyslipidemia - taking cholesterol-lowering medications or serum cholesterol ≥212mg/dL (≥5.5mmol/L; Australia) and ≥240mg/dL (≥6.2mmol/L; U.S.) or LDL>160 mg/dL (>4.1mmol/L) [9,18] .
- CKD (Chronic kidney disease) - eGFR < 60 ml/min/1.73m^2 or urinary albumin to creatinine ratio ≥3mg/mmol
- Smoking status – current smoker, former smoker or never smoked
- Ethnicity / race – all participants self-identified as Hispanic or not and then selected one category from the following: White/Caucasian, Black/African American, Aboriginal or Torres Strait Islander, Native American, Asian, Native Hawaiian/Other Pacific Islander/Maori, more than one race or other. The category white includes those who did not identify as Hispanic and identified as White/Caucasian.
- Multi-morbidity for the purposes of this report includes the following conditions: hypertension, diabetes, dyslipidemia and CKD
- Frailty - 'Prefrail' included anyone with 1 or 2 criteria and 'Frail' included anyone with 3 or more criteria of the adapted Fried frailty criteria. These included body weight (BMI <20kg/m^2), strength (hand grip in lowest 20% of participants by sex and Fried-defined sex-specific BMI categories), exhaustion (taken from the self-reported CES-D-10 responses, indicating at least one of the following conditions was present for 3 days or more during the last week, (a) "I felt that everything I did was an effort" or (b) "I could not get going") walking speed (3m gait speed in lowest 20% of participants by sex and Fried-defined sex-specific height categories) and physical activity (taken from the self reported Life questionnaire, indicating yes to "In the last 2 weeks, no walking outside the home, or walked outside home but longest amount of time walked without sitting down to rest was less than 10 minutes"). [18]

Further details of these health measures and how they were assessed or recorded can be found in [8, 9] and www.aspree.org (Protocol)

Table S3: All vascular and hemorrhagic events (including multiple events of same type per participant) by aspirin and placebo group

	All participants n=19,114			Aspirin n=9,525			Placebo n=9,589		
		No. of pts, %			No. of pts, %			No. of pts, %	
Deaths with cardiac cause									
Non-coronary cardiac or vascular death		72	0.4%		28	0.3%		44	0.5%
Coronary heart disease death		96	0.5%		44	0.5%		52	0.5%
Myocardial infarction		*28*	*0.1%*		*14*	*0.1%*		*14*	*0.1%*
Other coronary		*25*	*0.1%*		*8*	*0.1%*		*17*	*0.2%*
Rapid cardiac		*4*	*0.0%*		*2*	*0.0%*		*2*	*0.0%*
Sudden cardiac		*19*	*0.1%*		*7*	*0.1%*		*12*	*0.1%*
Cardiac failure		*20*	*0.1%*		*13*	*0.1%*		*7*	*0.1%*
Stroke death		63	0.3%		34	0.4%		29	0.3%
Ischemic stroke		*27*	*0.1%*		*15*	*0.2%*		*12*	*0.1%*
Uncertain type		*2*	*0.0%*		*1*	*0.0%*		*1*	*0.0%*
Deaths with hemorrhagic cause									
Stroke death, continued.									
Subarachnoid hemorrhagic stroke		*8*	*0.0%*		*5*	*0.1%*		*3*	*0.0%*
Hemorrhagic stroke		*26*	*0.1%*		*13*	*0.1%*		*13*	*0.1%*
Major hemorrhagic (non-stroke)		18	0.1%		10	0.1%		8	0.1%
	No. of events	**No. of pts, %**		**No. of events**	**No. of pts, %**		**No. of events**	**No. of pts, %**	
Cardiac events									
Myocardial infarction*	351	324	1.7%	167	156	1.6%	184	168	1.8%
Hospitalization for heart failure	207	171	0.9%	108	88	0.9%	99	83	0.9%
Stroke events									
All stroke	424	398	2.1%	209	195	2.0%	215	203	2.1%
Ischemic stroke†	*331*	*311*	*1.6%*	*156*	*146*	*1.5%*	*175*	*165*	*1.7%*
Uncertain type	*3*	*3*	*0.0%*	*2*	*2*	*0.0%*	*1*	*1*	*0.0%*
Subarachnoid hemorrhagic stroke	*14*	*14*	*0.1%*	*8*	*8*	*0.1%*	*6*	*6*	*0.1%*
Hemorrhagic stroke	*76*	*74*	*0.4%*	*43*	*42*	*0.4%*	*33*	*32*	*0.3%*
Major hemorrhage (non stroke) events	603	540	2.8%	352	315	3.3%	251	225	2.3%

* Includes 1 case of established myocardial infarction, all other cases are acute, recent or evolving. Excludes 24 myocardial infarction events for which death due to any coronary heart disease cause occurred within 30 days.

† Includes 9 ischemic strokes with hemorrhagic transformation in 9 participants, 6 aspirin and 3 placebo. In this table ischemic stroke only includes stroke events adjudicated as ischemic, i.e. it does not include uncertain type. Stroke events of uncertain type after adjudication are listed separately.

Table S4: Breakdown of major hemorrhagic events by subcategory

	All			Aspirin			Placebo		
	No. of events	No. of pts, %		No. of events	No. of pts, %		No. of events	No. of pts, %	
Fatal hemorrhagic events									
Hemorrhagic stroke		26	0.1%		13	0.1%		13	0.1%
Subarachnoid hemorrhagic stroke		8	0.0%		5	0.1%		3	0.0%
Major hemorrhage (non-stroke)		18	0.1%		10	0.1%		8	0.1%
Hemorrhagic events									
Hemorrhagic stroke	76	74	0.4%	43	42	0.4%	33	32	0.3%
Lobar	*43*	*41*		*23*	*22*		*20*	*19*	
Basal ganglionic	*20*	*20*		*14*	*14*		*6*	*6*	
Brain stem	*4*	*4*		*2*	*2*		*2*	*2*	
Other	*9*	*9*		*4*	*4*		*5*	*5*	
Subarachnoid hemorrhagic stroke	14	14	0.1%	8	8	0.1%	6	6	0.1%
Major hemorrhage (non-stroke)	603	540	2.8%	352	315	3.3%	251	225	2.3%
Gastrointestinal (lower)	*136*	*127*		*77*	*73*		*59*	*54*	
Gastrointestinal (upper)	*150*	*137*		*99*	*89*		*51*	*48*	
Excessive/multiple trauma	*18*	*17*		*7*	*7*		*11*	*10*	
*Other**	*201*	*189*		*106*	*101*		*95*	*88*	
Non-stroke intracranial bleeds (without stroke symptoms)									
Intraventricular bleed (nontraumatic)	*2*	*2*		*2*	*2*		*0*	*0*	
Intraventricular bleed (traumatic)	*0*	*0*		*0*	*0*		*0*	*0*	
Subarachnoid hemorrhage (nontraumatic)	*3*	*3*		*2*	*2*		*1*	*1*	
Subarachnoid hemorrhage (traumatic)	*15*	*15*		*9*	*9*		*6*	*6*	
Subdural hemorrhage (nontraumatic)	*17*	*15*		*11*	*10*		*6*	*5*	
Subdural hemorrhage (traumatic)	*49*	*46*		*30*	*29*		*19*	*17*	
Extradural hemorrhage (nontraumatic)	*0*	*0*		*0*	*0*		*0*	*0*	
Extradural hemorrhage (traumatic)	*1*	*1*		*1*	*1*		*0*	*0*	
Parenchymal hematoma (nontraumatic)	*4*	*3*		*4*	*3*		*0*	*0*	
Parenchymal hematoma (traumatic)	*7*	*7*		*4*	*4*		*3*	*3*	

For the total number of events, participants can contribute more than one event of a given type and can contribute multiple types of event. For the number of participants (pts), participants contribute only one of each type of event.

* Other includes: hematuria, surgical site bleeding, bleeding following trauma, epistaxis, etc.

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