Supplementary Appendix

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

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Effects of aspirin for primary prevention in people with diabetes

Supplementary Appendix

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Supplementary Methods

Recruitment

Potentially eligible participants with diabetes were identified from centrally-held registers (e.g. for retinopathy screening) and General Practice-held disease registers.[1] In many cases these electronic searches allowed the exclusion of those with a coded diagnosis of cardiovascular disease. A total of 423,403 potentially eligible individuals were invited via these different routes of recruitment, of which 29% (121,254 people) returned a screening questionnaire. About two-thirds of people who responded, declined to join the trial and a further 14,451 did not meet the eligibility criteria (including those who indicated a prior history of cardiovascular disease).[2] After review of the questionnaire data, 26,462 participants (6% of those originally invited) were willing and eligible to join ASCEND and entered a 2-month run-in phase on placebo treatment. About 40% of all patients who entered the run-in phase dropped out before randomization and reasons for withdrawal have been reported.[2] Towards the end of the 2-month run-in phase, randomization questionnaires were sent to 22,579 individuals, of whom 15,480 responded that they remained willing and eligible, and were randomized into ASCEND using a minimization algorithm to ensure balance by prognostic variables (age, sex, duration of diabetes, history of treated hypertension, smoking status, ethnic origin, and, if available from centrally measured blood and urine samples, total cholesterol, HbA1c, and urine albumin/creatinine ratio). Overall 3.7% of those invited were randomized. During the pre-randomization Run-in phase, a blood and urine sampling kit was sent with a supplementary information leaflet and consent form, and participants were asked to take this kit to their General Practice for sample collection. This allowed a baseline measure of blood pressure, weight and height to be recorded at the general practice. Blood and urine samples were then mailed to the central laboratory in the containers provided and laboratory methods have been described.[2] Sixty-three percent of randomized participants returned a usable blood and/or urine sample within 4 days of sample collection and provided consent for analyses.

Post-randomization follow-up

Follow-up was conducted largely by mail, supplemented by information from central registries. Randomized participants received a follow-up questionnaire 6-monthly (either paper or via a weblink to a secure online version[3]) asking about the occurrence of specific cardiovascular events (including heart attack, admission to hospital with angina or chest pain, stroke, mini-stroke and revascularization procedures), any bleeding event for which medical advice was sought, cancer diagnoses, and any other serious illnesses and admissions to hospital, adherence with study medication and use of other relevant medications (such as antiplatelet agents or anticoagulants). Questionnaires can be viewed at https://ascend.medsci.ox.ac.uk/about/further-information

Confirmation and further information was sought from GPs about reports of possible cardiovascular events and any reported bleeds. Information on relevant events was reviewed by coordinating centre clinicians, blind to treatment assignment, and events adjudicated according to prespecified criteria (see below). Additional follow-up for death, cancer and hospitalisations was obtained from NHS Digital (formerly the Health and Social Care Information Centre), the NHS Wales Informatics Service in England and Wales, and the Information Services Division of NHS Scotland. Ethics approval has been obtained for additional follow-up after the scheduled treatment period via these central registries to assess the longer-term effects on cancer and on other outcomes.

Post-randomization sampling

During 2012, at mean follow-up of 2.5 years, 1800 participants who had provided a blood and urine sample during the pre-randomization Run-in phase were randomly selected to be sent a blood and urine collection kit and asked to attend their local General Practice. At the time of sampling, blood pressure and weight were also measured and information returned with the samples. 1247 participants returned a sample with consent (1225 provided both blood and urine samples, 6 blood only, 16 urine only and 553 invited participants provided neither) but not all samples were usable

(see Table S6). Samples were received and assayed at the central laboratory in the Clinical Trial Service Unit at the University of Oxford for HbA1c, total and HDL cholesterol, apolipoprotein B and A1 and cystatin C using previously reported methods.[2] Comparisons at each time point between treatment groups are reliable but comparisons between baseline and follow-up could be subject to assay drift/recalibration effects and differences in sample processing (for example follow-up assays were all conducted on frozen samples). Furthermore, the manufacturers' reagents, calibrators and settings (Dade Behring/Siemens Germany) for cystatin c were modified between the analysis of baseline and follow-up samples in order to align to the International Federation of Clinical Chemistry reference materials developed following the standardisation of cystatin C measurement in 2010. Estimated GFR was calculated from blood cystatin C concentration using the CKD-EPI formula.[4] Urine samples were used to measure 11-dehydroxy-thromboxane B2 (UTxB2) and aspirin assignment effectively suppressed UTxB2 to <1500 pg/mg creatinine in line with expectations.[5]

Statistical analysis

When the trial was designed in 2003 we assumed, based on previous randomized trial data in similar populations, a rate for the composite outcome of non-fatal myocardial infarction or non-fatal stroke or cardiovascular death (excluding confirmed intracranial hemorrhage) of 2% per year and estimated that a trial of 10,000 participants with 5 years' follow-up would provide good power to detect reductions of 20-25% in this outcome similar to those seen in the secondary prevention setting. However, during the first few years of the trial, it became apparent that the reported event rate (blinded across both groups) among those recruited was substantially lower than anticipated (at around 0.6% pa), potentially adversely affecting study power. In addition, since transient ischemic attacks (TIAs) are associated with an increased risk of subsequent stroke and patients are routinely started on aspirin after TIAs, their inclusion in the primary outcome is rational and would increase the chances of detecting effects of aspirin on ischemic cerebrovascular events. Furthermore, TIA is associated with lower cognitive function score and increased dementia risk suggesting long term adverse consequences despite initial resolution of symptoms.[6] The Anti-Thrombotic Trialists' Collaboration meta-analysis of the 6 primary prevention trials[7] also suggested that a more modest

risk reduction of 10-15% in serious vascular events* was likely with aspirin assignment, rather than 20-25% as previously anticipated. As a consequence, the Trial Steering Committee decided in 2009 to amend the protocol (see below), but this required agreement from Bayer to provide additional aspirin and placebo tablets and from Solvay to provide additional omega-3 fatty acid and placebo capsules before the final decision could be made. These discussions occurred during 2010 and the Protocol change was approved by the North West Multi-centre Research Ethics Committee in early 2011. The agreed amendment was to expand the primary "serious vascular event" (SVE) outcome to include TIAs, to increase the sample size to at least 15,000 participants, and extend the duration of scheduled follow-up to at least 7 years. Based on an observed event rate of 1.2-1.3% per year (blinded across both groups) 7.5 years follow-up provided 90% power at $p<0.05$ to detect a 15% difference in the risk of SVE in the aspirin group compared to the placebo group.

[*The definition of the ASCEND SVE differs from that used in the Anti-Thrombotic Trialists' Collaboration analyses (ATTC).[7] The ATTC serious vascular event is defined as myocardial infarction, stroke, or death from a vascular cause (including sudden death, pulmonary embolism and hemorrhage). In the ATTC, fatal hemorrhage is included both in the SVE outcome and in the major bleed outcome, whereas in ASCEND it is included only in the major bleed outcome.]

In pre-specified analyses we used the log-rank methods[8,9] to conduct intention-to-treat comparisons of the time to first event of a particular type in patients in the aspirin group and those in the placebo group. If a patient had an MI followed by a stroke, they would be counted in each category (e.g. in Figure 2) but would only be counted once in the composite outcome of SVE. Similarly for a patient who had a major bleed at more than one site. A two-tailed P-value <0.05 was to be considered statistically significant for the primary safety and efficacy outcomes. Allowance was to be made for multiple hypothesis testing in the interpretation of analyses of secondary and exploratory outcomes, without a formal P value adjustment. Reported 95% confidence intervals for these outcomes are not adjusted for multiplicity and inferences drawn from these intervals may not be reproducible.

Subgroup analyses have been confined to those that were pre-specified in the Data Analysis Plan with the exception of additional subgroup analyses according to body mass index and body weight (prompted by a recent publication[10] suggesting interaction of the effects of aspirin by body weight) and by statin use, as requested by an external reviewer.

Primary and secondary outcomes

The primary efficacy assessments involved intention-to-treat comparisons among all randomized participants of assignment to aspirin versus placebo and, separately, of omega-3 fatty acids versus placebo on the first occurrence of any “serious vascular event” (SVE), defined as:

- non-fatal myocardial infarction; or
- non-fatal stroke (excluding confirmed intracranial hemorrhage) or TIA; or
- vascular death excluding confirmed intracranial hemorrhage (defined as International Classification of Diseases 10th revision [ICD-10] I00-52 or I63-99, ie, excluding subarachnoid hemorrhage [I60], intracerebral hemorrhage [I61], and other non-traumatic intracranial hemorrhage [I62]).

Secondary efficacy assessments of aspirin involved intention-to-treat comparisons during the scheduled treatment period among all randomized participants on the first occurrence of:

i. any incident gastrointestinal (GI) tract cancer (i.e. any GI cancer excluding pancreas and hepatobiliary), overall and after exclusion of the first three years of follow-up;

ii. the expanded vascular endpoint of “SVE or revascularization” (including coronary and non-coronary revascularizations).

Primary safety assessment

The primary safety assessments involved intention-to-treat comparisons among all randomized patients of assignment to aspirin versus placebo on the first occurrence of “any major bleed”, defined as:

- any confirmed intracranial hemorrhage (including intracerebral, subarachnoid, subdural or any other intracranial hemorrhage); or
- sight-threatening eye bleeding; or
- any other serious bleeding episode.

Adherence to study treatment

A participant's adherence to study treatment once they are no longer at risk of the primary outcome is irrelevant to the primary comparison, therefore, average adherence among participants while at risk of the primary outcome, weighted for person-years at risk of the primary outcome, was estimated as follows. The estimated times at which each participant's adherence to taking study aspirin/placebo or non-study antiplatelet therapy changed were constructed, based on supply of study treatment packs, reported adherence to study aspirin/placebo, and reported use of other antiplatelet therapy. Intervals during which each participant was adherent were constructed using these estimated times. The average adherence within each treatment arm and time period of interest was calculated as the sum over all participants of the adherent days divided by the sum over all participants of the days at risk. In a parallel manner, the average compliance weighted by time at risk of major bleed was also calculated for predicting the effects of full compliance on major bleed.

Baseline vascular risk score and predicted absolute effects with full adherence

As specified in the Data Analysis Plan,[2] to identify risk factors for serious vascular events, we used Poisson regression to estimate the linear dependence of the log of the event rate on age, sex, smoking, systolic blood pressure, body mass index, duration of diabetes, HbA1c, assignment to aspirin versus placebo and assignment to omega-3 versus placebo. Leave-one-out cross-validation was used to avoid over-fitting (i.e., the risk for each person was estimated using data from everyone except that person). The results of this model, with treatment assignment set to placebo were used

to classify the baseline 5-year risk of serious vascular event (including TIA) without aspirin of all participants (including those allocated aspirin) as <5%, 5-10%, ≥10% (following a similar approach to that used in the ATTC meta-analysis[7]). The predicted absolute incidence rates of SVE and major bleed with taking and not taking aspirin within each of the three baseline levels of vascular risk were estimated by multiplying the absolute event rate in the placebo arm in the baseline risk group by the overall rate ratio for the effect of aspirin adjusted to complete adherence to aspirin, RRc: for an overall observed rate ratio, RR, and an adherence difference, c, between the treatment arms, RRc was estimated by $RR^{(1/c)}$.

Definition of events and adjudication

It is well recognised that detailed adjudication of outcomes in cardiovascular trials does not affect the overall trial results.[11] However, since outcomes in ASCEND were mainly reported by participants, adjudication was undertaken in order to confirm that the outcomes had occurred. Further information was sought for all reported primary and secondary outcomes and also for reported events that might be potential outcomes (e.g. hospitalisation with angina, anemia) and all reported bleeds. For non-cancer outcomes, a standard form was mailed to the participant's General Practitioner asking them to confirm that the event occurred and to send relevant documentation (e.g. hospital discharge summary, out-patient clinic letter, brain imaging report or other relevant information). For cancer events, the Cancer Registry and Hospital Episode Statistics were reviewed initially and further information sought from the participant's GP only where discrepancies occurred.

Returned supporting documents were reviewed by coordinating centre clinicians blind to the participant's treatment assignment. If incomplete information was returned, the coded information collected by all NHS Hospitals in the UK in the Hospital Episode Statistics dataset was also reviewed. Events where insufficient information was available to either confirm the participant reported event or to refute the event (i.e. to be confident that the event did not occur) remain as reported and are considered to be "unrefuted". Such events are counted in the analysis. Events were adjudicated according to standard definitions summarised below.

Myocardial infarction (MI)

An event was considered to be an MI if there was evidence of cardiac necrosis (consistent elevation in cardiac biomarkers or relevant autopsy findings) and there was other evidence of an acute MI (including symptoms of ischemia, recent coronary intervention, death, new ECG changes, evidence of a new myocardial defect on cardiac imaging or an acute coronary occlusion at angiography) and no other diagnosis was likely. Troponin was the preferred cardiac biomarker but creatine kinase (CK) or CK-MB was acceptable. The interpretation of the cardiac biomarker depended on the clinical setting but, except in the context of coronary revascularization, at least one value above the upper reference limit was considered to indicative of MI. If original ECG tracings or cardiac biomarker results were not available, it was acceptable to rely upon a report of the findings, e.g. in a discharge summary. Silent MI is not included.

Stroke

Stroke was defined as an acute symptomatic episode of focal or global neurological dysfunction caused by brain, spinal or retinal vascular injury as a result of hemorrhage or infarction which lasted >24 hours, lead to death or was associated with evidence of an acute infarct or hemorrhage on brain imaging corresponding with the clinical syndrome. Strokes were further subdivided by etiology, including confirmed ischemic, confirmed hemorrhagic or uncertain etiology. Hemorrhagic conversion of an ischemic/embolic infarct was considered to be an ischemic stroke. Confirmed hemorrhagic stroke included focal or global neurological dysfunction caused by subarachnoid or intracerebral hemorrhages in the absence of a secondary cause such as trauma.

Adjudication of strokes in ASCEND was based on information provided by the participant's General Practitioner, including copies of relevant outpatient clinic and discharge letters, therefore information about the level of disability following a stroke may have been limited. Stroke events were considered to be disabling if the participant required assistance from another person to perform their activities of daily living and were considered to be non-disabling if no such assistance was required. The assessment of disability was based on the latest information available at the time of adjudication.

Transient ischemic attack (TIA)

TIA was defined as a transient episode of neurological dysfunction, lasting less than 24 hours, caused by brain, spinal cord, or retinal ischemia, without clear evidence of acute infarction, hemorrhage, trauma or another cause. If there was evidence of brain infarction or hemorrhage on imaging consistent with the clinical findings the event was considered to be a stroke irrespective of the duration of symptoms. Brain imaging was not required to confirm a TIA.

Coronary and non-coronary revascularisation

Coronary revascularization included coronary angioplasty, stenting or coronary artery bypass grafting. Non-coronary revascularization included peripheral angioplasty or stenting, atherectomy, thrombectomy, embolectomy, catheter directed thrombolysis, arterial bypass surgery and aneurysm repair (surgical or endovascular). Arterial embolization (e.g. cranial aneurysm coiling or embolization procedures to treat hemorrhage), amputation procedures and procedures on the venous or pulmonary systems were not included. Attempted procedures which were not completed because of technical difficulties were considered to be a revascularization procedure.

Cancer

Cancer events were considered incident, and included in the analysis, if that participant was not known to have had cancer at that site prior to randomization, or if the cancer was fatal. The main cancer analyses exclude non-fatal non-melanoma skin cancer.

Amputation

Amputation events were considered to be “minor” if they involved the amputation of a digit (finger or toe). All other amputation events were considered to be “major”.

Fatal outcomes

All deaths were adjudicated and this included a review of the death certificate and information about events preceding the death. If, following adjudication, a preceding event was considered to be the underlying cause of the subsequent death, the event was classified as fatal.

Major bleed

Major bleeds included any intracranial bleed, sight-threatening eye bleeds or other bleeding if the participant required hospitalisation or transfusion, or it was fatal or disabling. Intracranial bleeds included spontaneous intracranial bleeds or those associated with injury in the absence of major trauma. Sight-threatening eye bleeds included any clinically significant retinal bleeds presenting with symptoms outside of routine retinopathy screening which required laser photocoagulation, surgery or intra-ocular injections or any intra-ocular bleeding resulting in permanent visual loss. Other bleeding events were coded according to the anatomic site at which the bleeding occurred and were further subdivided by severity using a classification based on the Bleeding Academic Research Consortium (BARC) classification[12] (table below). Bleeding events were considered to be "serious" if the participant required hospitalisation or transfusion, or if the bleed caused death or was disabling. Serious bleeds were those in ASCEND categories H, S, L and F.

ASCEND classification of bleeding by severity

ASCEND bleeding category	Criteria for each category (based on a modified version of the BARC bleeding definition)
M	Minimal bleeding that was not actionable and does not cause the participant to seek unscheduled treatment or investigation (participant did not see a doctor for the bleeding event).
N	Bleeding where participant seeks medical advice, but no action was taken, or where it is not possible to determine if any action was taken.

T	Any overt, actionable sign of hemorrhage (e.g. more bleeding than would be expected for a clinical circumstance) **where the patient <u>was not</u> admitted to hospital for the bleed** and did not meet the criteria for suffixes H, S, L or F, but where the bleeding did meet at least one of the following criteria: - requiring medical or surgical intervention by a healthcare professional, - leading to an increased level of care, - prompting further evaluation or investigation beyond the initial consultation
H	Any overt, actionable sign of hemorrhage (e.g. more bleeding than would be expected for a clinical circumstance) **where the patient <u>was</u> admitted to hospital for the bleed, or where the bleeding led to a prolongation of an existing hospital stay,** but did not meet the criteria for suffixes S, L or F.
S	- Overt bleeding plus hemoglobin drop[1] of 3-5 g/dL - Any transfusion with overt bleeding
L	- Overt bleeding plus hemoglobin drop† >5 g/dL - Bleeding that required surgical intervention for control (excluding minor surgery). [2] - Bleeding that led to the participant being admitted to a high dependency area, or required treatment with vasoactive agents, to manage the bleeding event or sequela.
F	Fatal bleeding[3] (bleeding that definitely or probably led to death).

[1] Provided the hemoglobin drop is related to the bleed.
[2]Within the BARC definition minor surgery includes dental surgery, nasal surgery, skin surgery and hemorrhoid surgery.
[3] Within the BARC definition fatal bleeding is defined as "*bleeding that directly causes death with no other explainable cause.*"

Supplementary Figures

Figure S1: Consort diagram

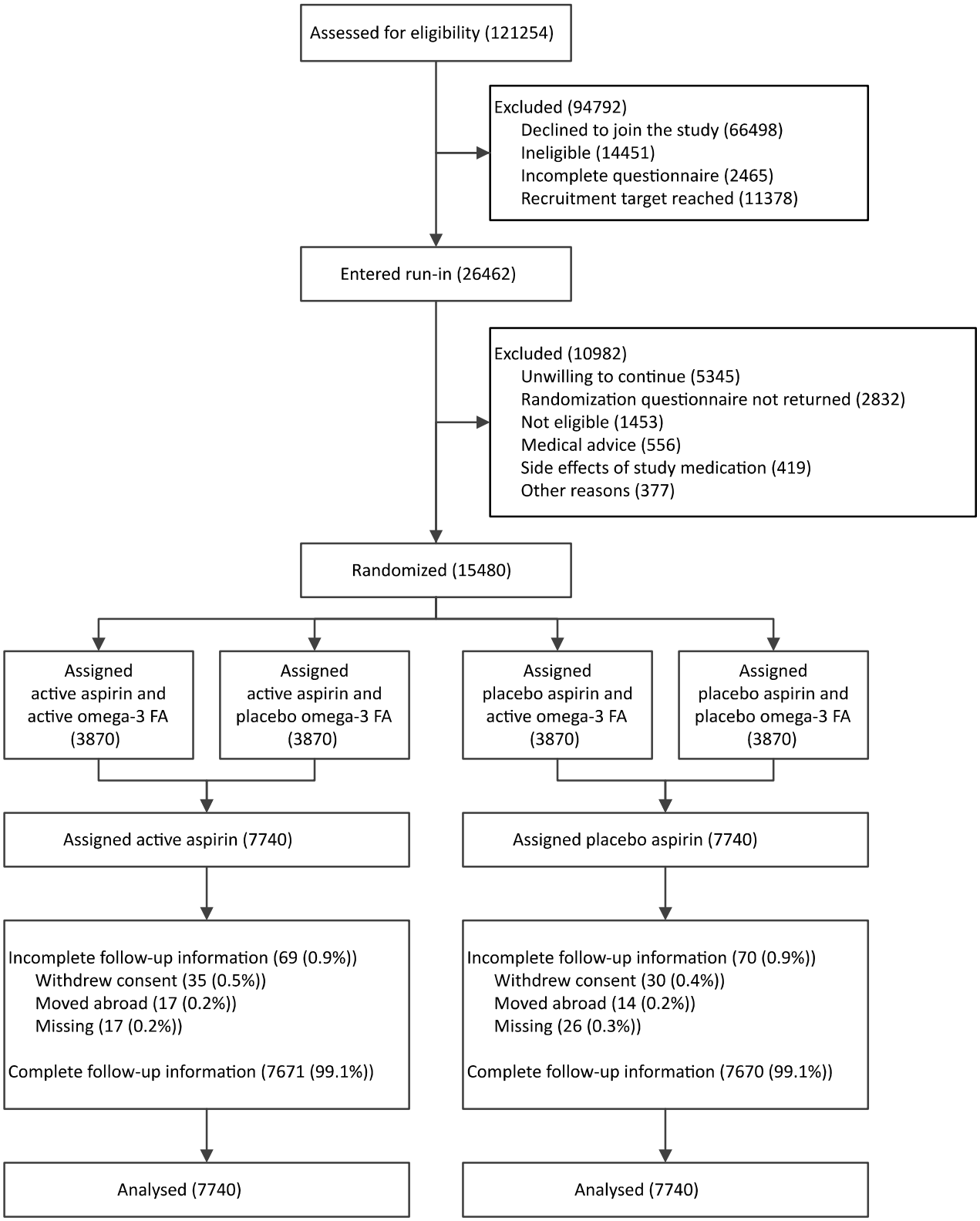
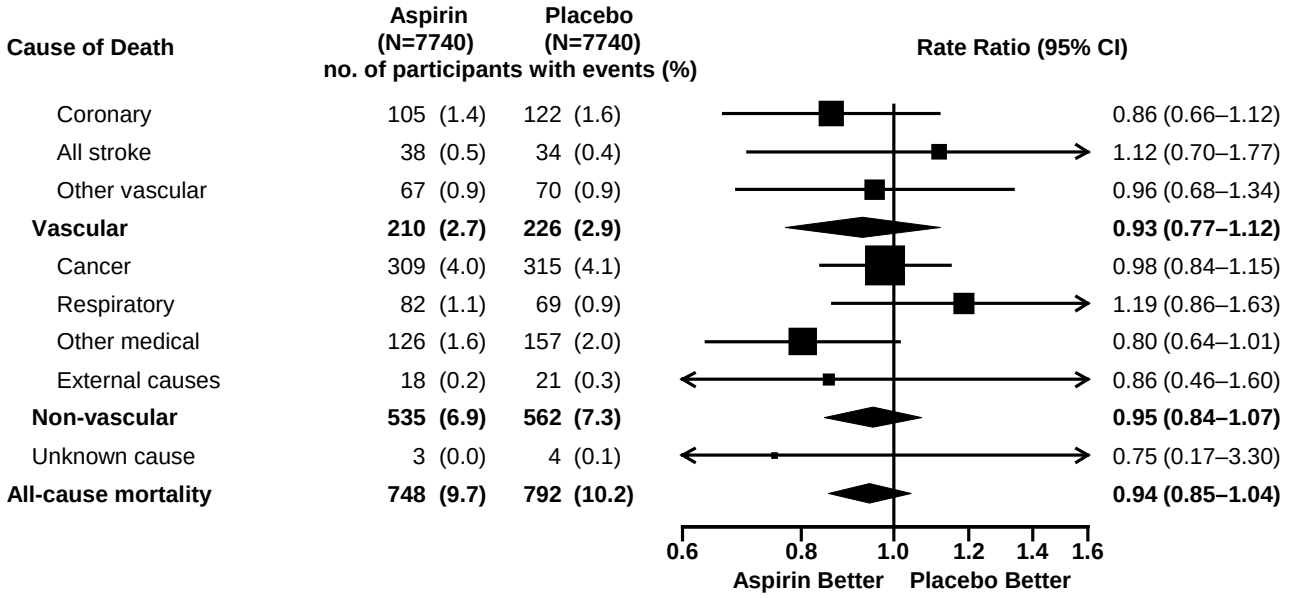


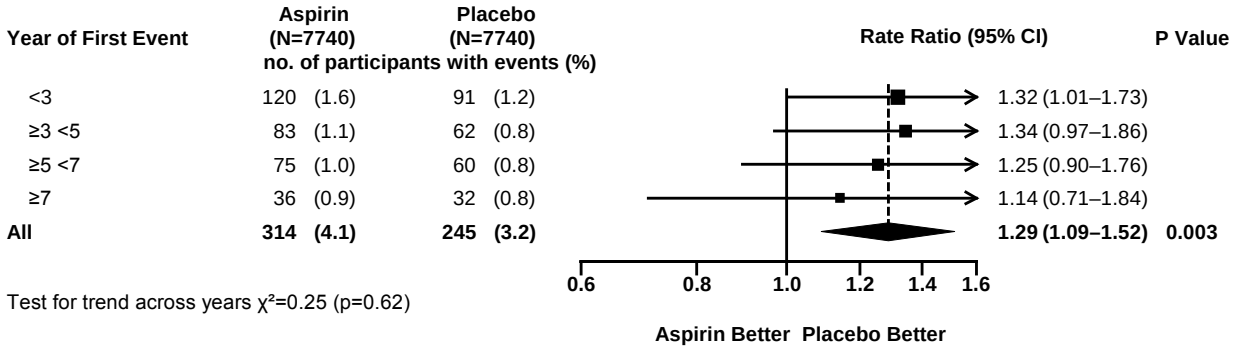
Figure S2: Effects of aspirin assignment on total and cause-specific mortality



95% confidence intervals are unadjusted for multiplicity.

Counts (and percentages) are of the participants with a death of the listed type during follow-up. Rate ratios comparing the outcome among participants assigned to aspirin versus the outcome among those assigned to placebo are plotted. For individual outcomes, rate ratios are plotted as squares, with the size of each square proportional to the amount of statistical information, and horizontal lines represent 95% CIs. For composite outcomes, rate ratios and their corresponding 95% confidence intervals are represented by diamonds. Squares or diamonds to the left of the solid vertical line indicate benefit with aspirin.

Figure S3: Major bleed by years of follow-up

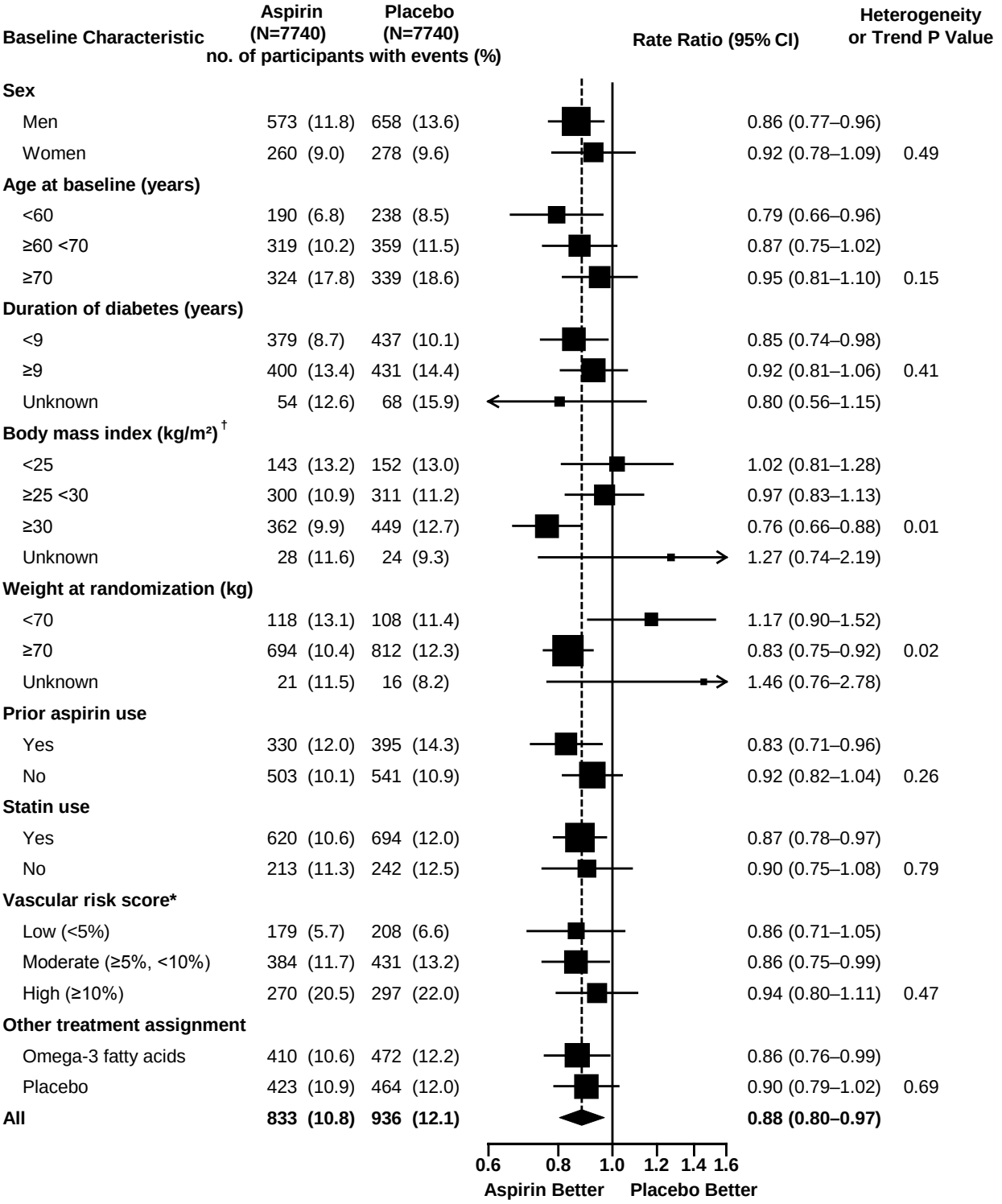


Test for trend across years χ^2=0.25 (p=0.62)

95% confidence intervals are unadjusted for multiplicity.

The rate ratios for the first major bleed among the patients in the aspirin group versus the control group are shown according to the period of follow-up. The numbers at risk decline with each period of follow-up because of censoring, so the percentages are the number of events as a proportion of the number at risk at the start of each period. For each period of follow-up rate ratios are plotted as squares, with the size of each square proportional to the amount of statistical information that was available, the horizontal lines represent 95% confidence intervals.

Figure S4: Effects of aspirin assignment on serious vascular event or revascularization in different types of participant



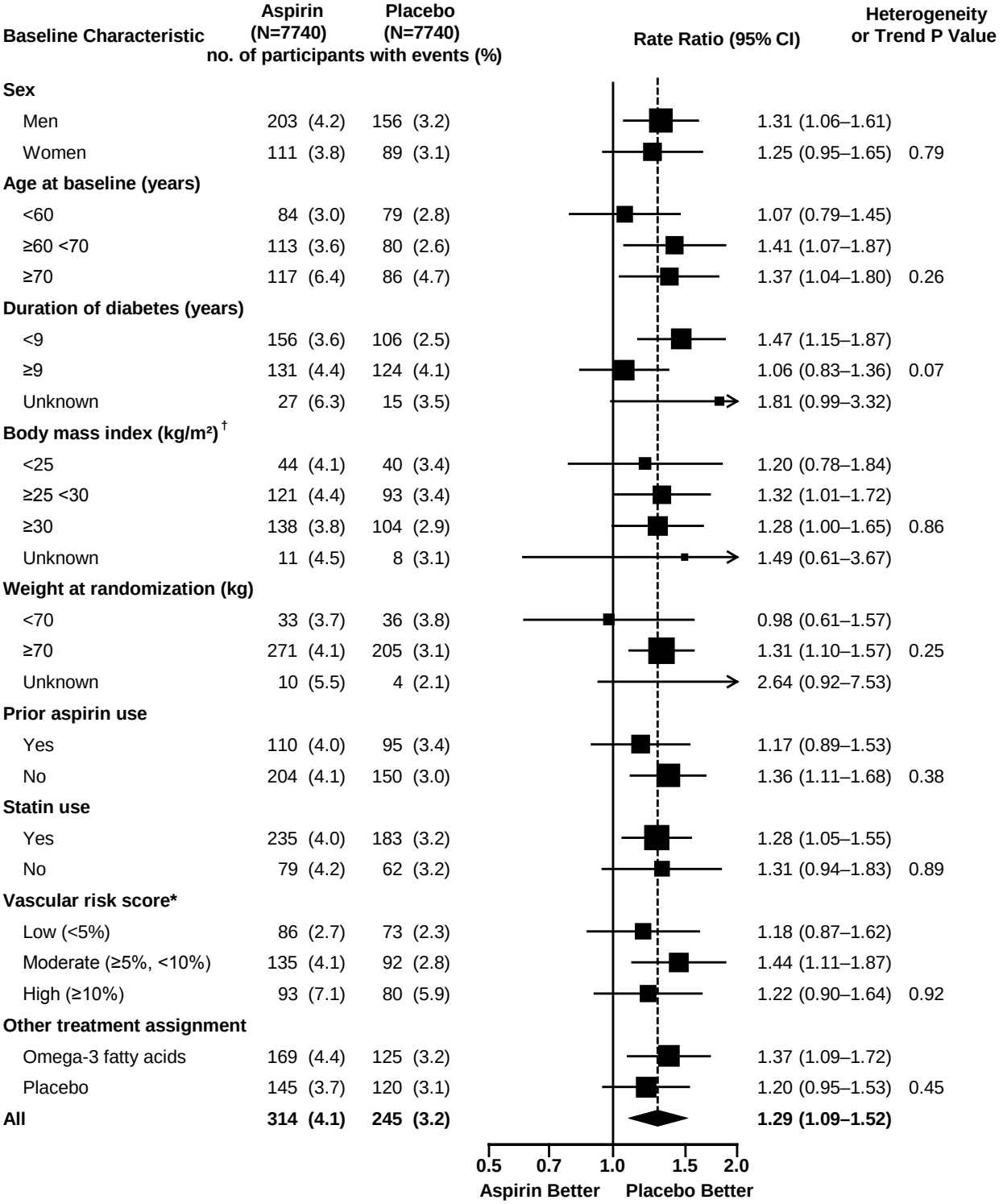
95% confidence intervals are unadjusted for multiplicity.

† Based on self-reported height and weight.

* predicted 5 year risk of SVE (including transient ischemic attack) without aspirin or omega-3 fatty acid

Counts (and percentages) are of the participants with a particular baseline characteristic with a first serious vascular event during follow-up. Rate ratios comparing the outcome among participants assigned to aspirin versus the outcome among those assigned to placebo are plotted. For individual baseline categories, rate ratios are plotted as squares, with the size of each square proportional to the amount of statistical information, and horizontal lines represent 95% confidence intervals. For the overall result, the rate ratio and its corresponding 95% CI is represented by a diamond. Tests of heterogeneity or trend (as appropriate) are shown for each baseline characteristic.

Figure S5: Effects of aspirin assignment on major bleed in different types of participant



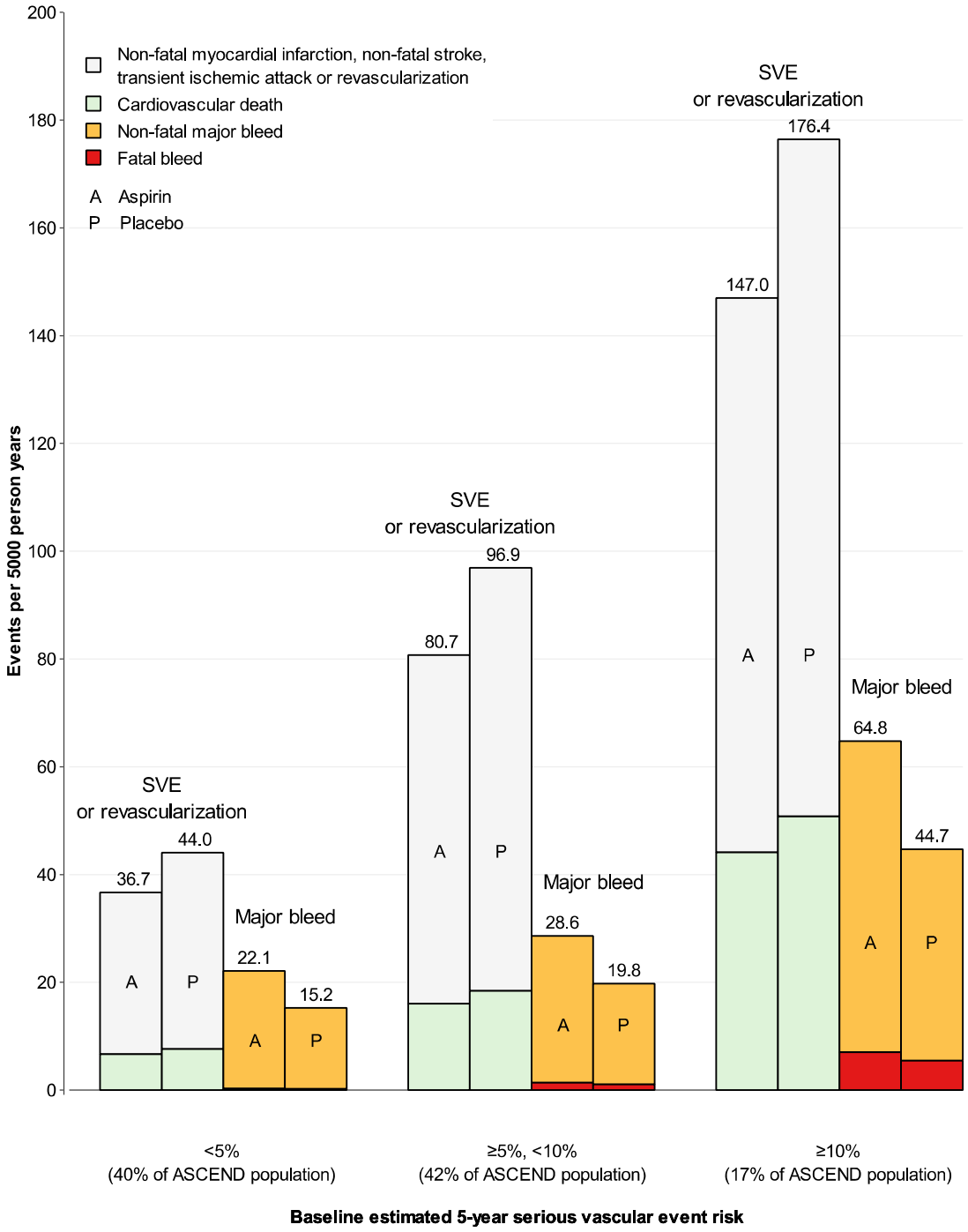
95% confidence intervals are unadjusted for multiplicity.

† Based on self-reported height and weight.

* predicted 5 year risk of SVE (including transient ischemic attack) without aspirin or omega-3 fatty acid

Conventions are as for Figure S4

Figure S6: The predicted absolute effects of taking aspirin on serious vascular event or revascularization and major bleed in categories of participant sub-divided by vascular risk

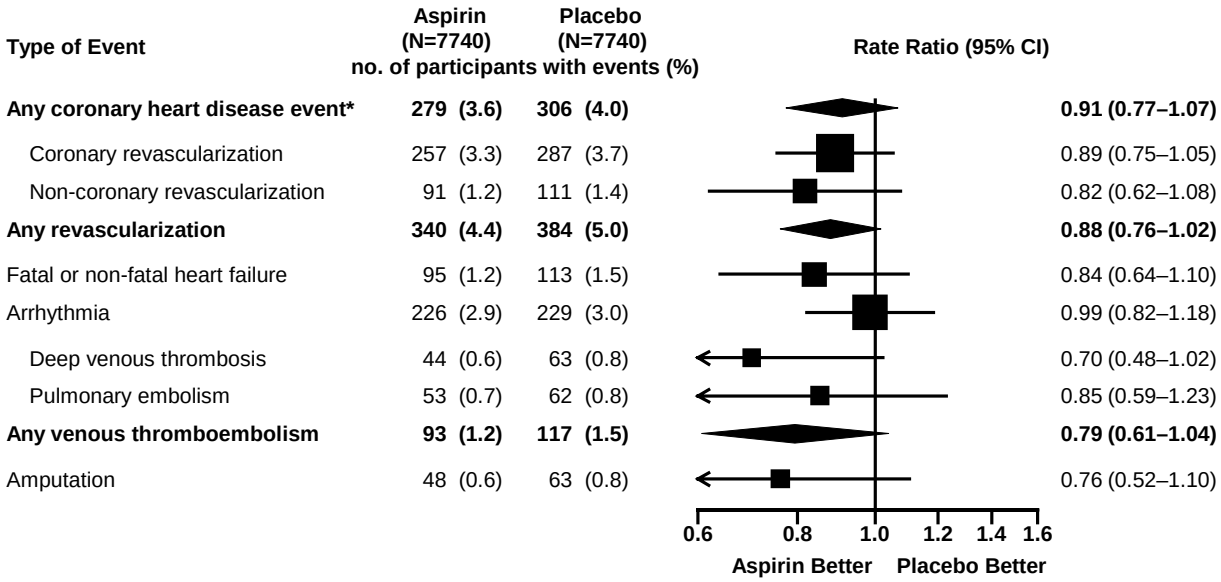


Predicted numbers of events per 5000 person years

Serious vascular events (SVE) avoided	5.9	12.5	24.4
SVE or revascularizations avoided	7.4	16.2	29.4
Major bleeds caused	6.8	8.9	20.1

The predicted absolute incidence rates of SVE or revascularisation and of major bleed with taking versus not taking aspirin within each of the three baseline levels of vascular risk were estimated by multiplying the absolute event rate in the placebo arm in each risk group by the overall rate ratio for the effect of aspirin adjusted to complete adherence to aspirin, RRc. For an overall observed rate ratio, RR, and an adherence difference c, between the treatment arms, RRc was estimated by $RR^{(1/c)}$. For further details of the calculation of vascular risk score see Supplementary Methods. The estimated number of serious vascular events avoided and bleeding events caused by taking aspirin is expressed per 5000 person years.

Figure S7: Effects of aspirin assignment on other vascular outcomes



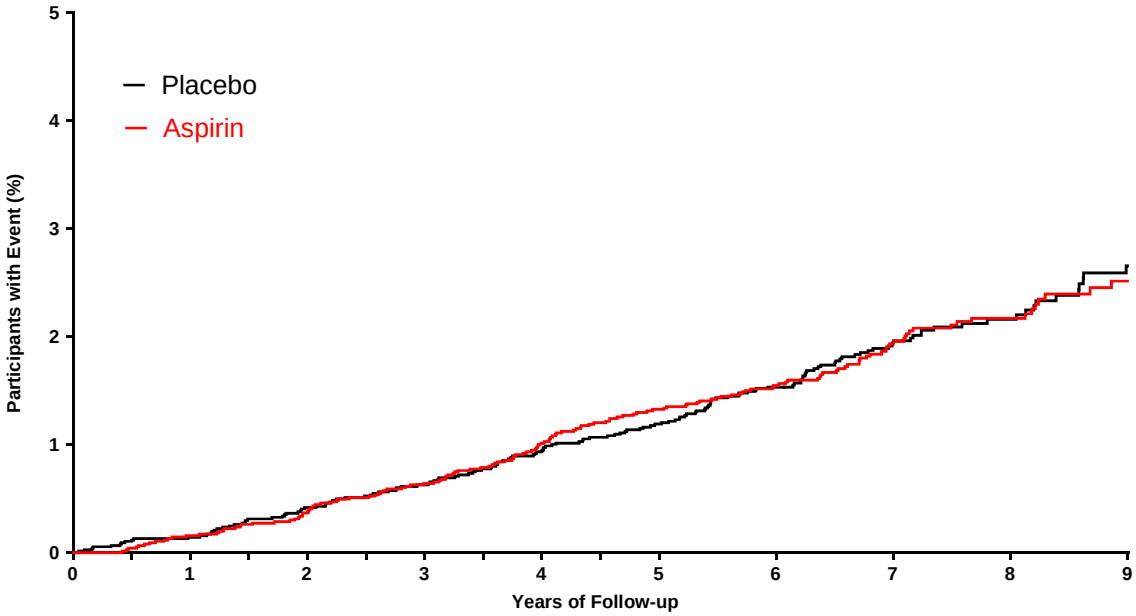
95% confidence intervals are unadjusted for multiplicity.

* Composite of non-fatal myocardial infarction or coronary death

Counts (and percentages) are of the participants with a first event of the listed type during follow-up. A single participant may have had multiple events and, therefore, contribute information to more than one row. Rate ratios comparing the outcome among participants assigned to aspirin versus the outcome among those assigned to placebo are plotted. For individual outcomes, rate ratios are plotted as squares, with the size of each square proportional to the amount of statistical information, and horizontal lines represent 95% confidence intervals. For composite outcomes, rate ratios and their corresponding 95% CIs are represented by diamonds. Squares or diamonds to the left of the solid vertical line indicate benefit with aspirin.

Figure S8: Effect of aspirin assignment on fatal or non-fatal gastrointestinal tract cancer

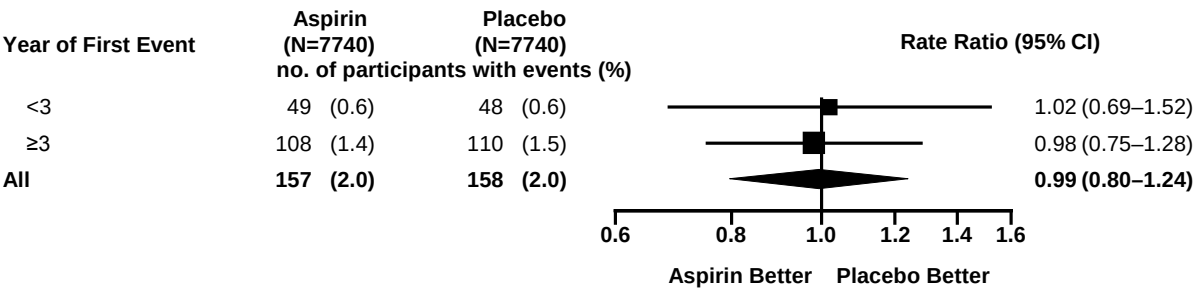
A Time to gastrointestinal tract cancer (excluding non-fatal recurrence of pre-randomization cancer)



No. at Risk										
Placebo	7740	7689	7604	7505	7400	7272	6046	4105	2321	1507
Aspirin	7740	7689	7612	7515	7391	7278	6033	4129	2334	1513
Cumulative benefit per 1000 participants in Aspirin group ± SE		-0±1	0±1	-0±1	-1±2	-1±2	-0±2	0±2	-0±3	1±3

The numbers of patients at risk at the start of each year of follow-up are shown, along with the cumulative number (+/- SE) of participants avoiding events per 1000 in the aspirin group compared with those in the placebo group.

B Gastrointestinal tract cancer by year of follow-up (excluding non-fatal recurrence of pre-randomization cancer)



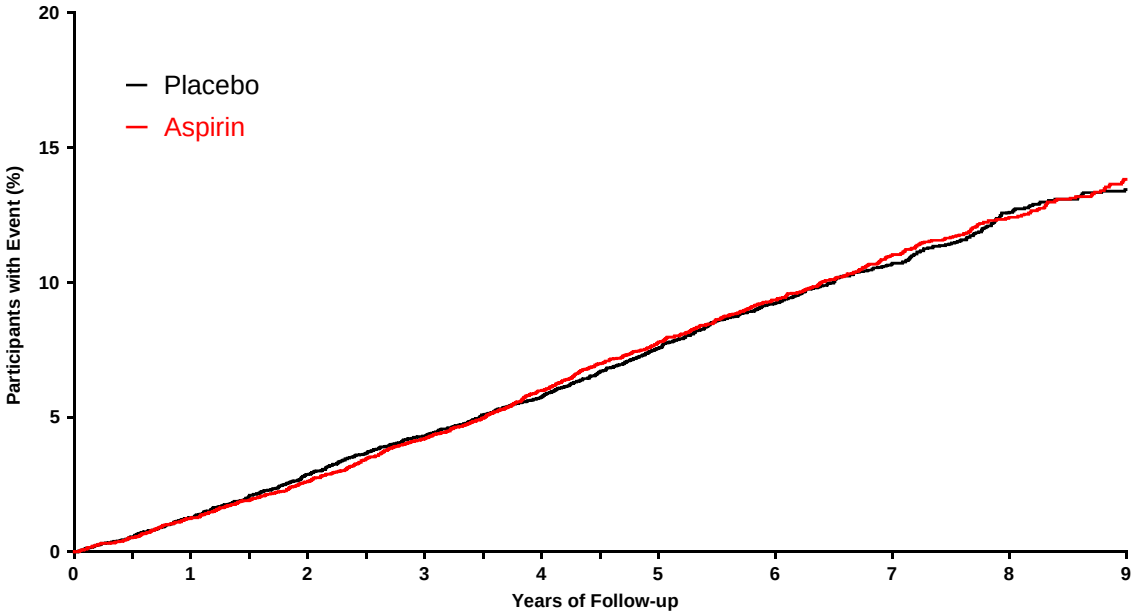
Test for trend across years χ^2=0.02 (p=0.88)

95% confidence intervals are unadjusted for multiplicity.

Panel A shows a Kaplan-Meier plot of the first fatal or non-fatal gastrointestinal tract cancer during follow-up. The numbers of patients at risk at the start of each year of follow-up are shown, along with the mean (±SE) absolute differences in incidence rates between the patients in the aspirin groups and those in the placebo group. Panel B shows the rate ratios for the first fatal or non-fatal gastrointestinal tract cancer among the patients in the aspirin group versus the control group according to the period of follow-up. The numbers at risk decline with each period of follow-up because of censoring, so the percentages are the number of events as a proportion of the number at risk. For each period of follow-up rate ratios are plotted as squares, with the size of each square proportional to the amount of statistical information that was available, the horizontal lines represent 95% confidence intervals.

Figure S9: Effect of aspirin assignment on fatal or non-fatal cancer

A Time to any cancer (excluding non-fatal non-melanoma skin cancer and non-fatal recurrence of pre-randomization cancer)

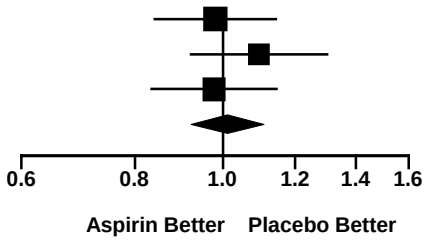


No. at Risk										
Placebo	7740	7618	7460	7304	7150	6943	5721	3872	2173	1407
Aspirin	7740	7619	7477	7312	7120	6931	5700	3880	2196	1410
Cumulative benefit per 1000 participants in Aspirin group ± SE		0±2	2±3	1±3	-2±4	-2±4	-1±5	-3±5	2±6	-4±7

The numbers of patients at risk at the start of each year of follow-up are shown, along with the cumulative number (+/- SE) of participants avoiding events per 1000 in the aspirin group compared with those in the placebo group.

B Any cancer by year of follow-up (excluding non-fatal non-melanoma skin cancer and non-fatal recurrence of pre-randomization cancer)

Year of First Event	Aspirin (N=7740)	Placebo (N=7740)	Rate Ratio (95% CI)	P Value
	no. of participants with events (%)			
<3	324 (4.2)	330 (4.3)	0.98 (0.84–1.14)	
≥3 <5	271 (3.7)	248 (3.4)	1.10 (0.92–1.30)	
≥5	302 (4.4)	309 (4.5)	0.98 (0.83–1.15)	
All	**897 (11.6)**	**887 (11.5)**	**1.01 (0.92–1.11)**	



Test for trend across years χ^2=0.00 (p=0.99)

95% confidence intervals are unadjusted for multiplicity.

Panel A shows a Kaplan-Meier plot of the first fatal or non-fatal cancer during follow-up. The conventions are as for Figure S8.

Supplementary Tables

Table S1: Additional baseline characteristics by treatment assignment

Table S1: Additional baseline characteristics by treatment assignment

Characteristic	Aspirin (N=7740)		Placebo (N=7740)	
Townsend Index[†]				
<-3	2502	(32%)	2602	(34%)
≥-3, <0	3023	(39%)	2999	(39%)
≥0, <2	1037	(13%)	1000	(13%)
≥2, <4	686	(9%)	629	(8%)
≥4, <6	351	(5%)	352	(5%)
≥6	121	(2%)	140	(2%)
Diabetes management				
Diet only	1271	(16%)	1258	(16%)
Any hypoglycaemic (including GLP-1 inhibitors) but not insulin	4510	(58%)	4510	(58%)
Insulin with or without any other hypoglycaemic agent	1959	(25%)	1972	(25%)
Diabetic retinopathy				
Yes	1526	(20%)	1497	(19%)
No	6144	(79%)	6169	(80%)
Diastolic blood pressure (mmHg)[‡]				
<75	2113	(27%)	2110	(27%)
≥75 <85	2325	(30%)	2294	(30%)
≥85	1066	(14%)	1125	(15%)
Unknown	2236	(29%)	2211	(29%)
Mean (SD)	77.0	(9.4)	77.2	(9.5)
Weight at randomization (kg)				
<70	903	(12%)	944	(12%)
≥70	6655	(86%)	6601	(85%)
Unknown	182	(2%)	195	(3%)
Non-study treatment				
Insulin	1959	(25%)	1972	(25%)
Metformin	5055	(65%)	5038	(65%)
Sulphonylurea	2064	(27%)	2081	(27%)
Thiazolidinedione	894	(12%)	897	(12%)
Other hypoglycaemic agent	344	(4%)	349	(5%)
ACE Inhibitor or ARB	4520	(58%)	4535	(59%)
Beta-blocker	1016	(13%)	1013	(13%)
Calcium channel blocker	1926	(25%)	1847	(24%)
Thiazide or related diuretic	1480	(19%)	1477	(19%)
NSAID	670	(9%)	663	(9%)
Proton pump inhibitor	1073	(14%)	1181	(15%)

[†] Measure of socioeconomic status calculated using postcode at randomization. Higher value indicates greater deprivation.
[‡] At time of blood collection, generally before randomization.
ACE: angiotensin-converting-enzyme; ARB: angiotensin II receptor blockers; NSAID: nonsteroidal anti-inflammatory drug.
The difference in proton pump inhibitor use at baseline was P=0.01 unadjusted for multiple comparisons.

Table S2: Baseline biochemical measures by treatment assignment

Measurement	Aspirin (N=7740)		Placebo (N=7740)	
HbA1c (IFCC mmol/mol)				
<48	1661	(21%)	1611	(21%)
≥48 <64	2314	(30%)	2350	(30%)
≥64	926	(12%)	951	(12%)
No usable sample collected	2839	(37%)	2828	(37%)
Mean (SD)	55	(13)	55	(13)
Total cholesterol (mg/dL)				
<155	2293	(30%)	2261	(29%)
≥155 <193	1875	(24%)	1920	(25%)
≥193	735	(9%)	735	(9%)
No usable sample collected	2837	(37%)	2824	(36%)
Mean (SD)	161	(34)	161	(33)
Non-HDL cholesterol (mg/dL)				
<97	1691	(22%)	1699	(22%)
≥97 <135	2213	(29%)	2180	(28%)
≥135	992	(13%)	1025	(13%)
No usable sample collected	2844	(37%)	2836	(37%)
Mean (SD)	112	(33)	112	(32)
HDL cholesterol (mg/dL)				
<39	1116	(14%)	1054	(14%)
≥39 < 58	2708	(35%)	2815	(36%)
≥58	1072	(14%)	1035	(13%)
No usable sample collected	2844	(37%)	2836	(37%)
Mean (SD)	49	(14)	49	(14)
Apolipoprotein B (mg/dL)				
<70	1438	(19%)	1409	(18%)
≥70 <90	1934	(25%)	1968	(25%)
≥90	1512	(20%)	1518	(20%)
No usable sample collected	2856	(37%)	2845	(37%)
Mean (SD)	82.1	(21)	82.2	(20)
Apolipoprotein A1 (mg/dL)				
<140	1894	(24%)	1876	(24%)
≥140 <160	1528	(20%)	1585	(20%)
≥160	1473	(19%)	1443	(19%)
No usable sample collected	2845	(37%)	2836	(37%)
Mean (SD)	149.6	(25)	149.4	(25)
eGFR (ml/min/1.73m^2)$^+$				
≥90	2265	(29%)	2258	(29%)
≥60 <90	1986	(26%)	2030	(26%)
<60	649	(8%)	627	(8%)
No usable sample collected	2840	(37%)	2825	(36%)
Mean (SD)	85.2	(21)	85.2	(21)
Urinary albumin/creatinine ratio (mg/mmol)				
≥3	621	(8%)	627	(8%)
<3	4267	(55%)	4259	(55%)
No usable sample collected	2852	(37%)	2854	(37%)
Median (IQR)	0.56	(0.00-1.33)	0.55	(0.18-1.34)

$^+$ Calculated from blood cystatin C concentration using the CKD-EPI formula (see Supplementary Methods).
To convert the values for cholesterol to millimoles per liter, multiply by 0.02586.
There are no significant differences between the assigned groups.

Table S3: Completeness of follow-up at study end

Final follow-up (FU) status	Aspirin (N=7740)		Placebo (N=7740)	
Complete follow-up information	7671	(99%)	7670	(99%)
Final FU completed by participant or carer	5763	(74%)	5682	(73%)
Final FU completed by GP	999	(13%)	1045	(14%)
Final FU completed by registry	224	(3%)	218	(3%)
Died (FU for morbidity complete)	685	(9%)	725	(9%)
Incomplete follow-up information	69	(1%)	70	(1%)
Consent withdrawn	35	(0.5%)	30	(0.4%)
Moved abroad	17	(0.2%)	14	(0.2%)
Died (FU for morbidity not complete)	9	(0.1%)	13	(0.2%)
No final FU information	8	(0.1%)	13	(0.2%)

Table S4: Use of antiplatelet during follow-up

	Aspirin		Placebo		Difference
Time since randomization or baseline characteristic	N	Study aspirin or non-study antiplatelet	N	Non-study antiplatelet	
Years of follow-up					
<3 years	7740	86%	7740	3%	82%
≥3 <5 years	7404	74%	7342	7%	67%
≥5 <7 years	7096	66%	7001	8%	58%
≥7 years	3967	59%	3892	10%	50%
Sex					
Men	4843	77%	4841	6%	71%
Women	2897	72%	2899	5%	67%
Age at baseline (years)					
<60	2795	75%	2795	5%	70%
≥60 <70	3123	77%	3124	6%	71%
≥70	1822	72%	1821	6%	65%
Duration of diabetes (years)					
<9	4337	75%	4322	5%	70%
≥9	2976	75%	2989	6%	69%
Unknown	427	73%	429	7%	66%
Body mass index (kg/m^2)†					
<25	1080	76%	1169	5%	71%
≥25 <30	2753	76%	2776	6%	70%
≥30	3665	75%	3536	6%	69%
Unknown	242	74%	259	8%	66%
Prior aspirin use					
Yes	2740	80%	2768	8%	72%
No	5000	73%	4972	4%	68%
Prior statin use					
Yes	5854	77%	5799	6%	71%
No	1886	70%	1941	5%	65%
Vascular risk score*					
Low (<5%)	3128	76%	3136	4%	72%
Moderate (≥5%, <10%)	3294	76%	3254	7%	69%
High (≥10%)	1318	72%	1350	6%	65%
Other treatment assignment					
Omega-3 fatty acids	3870	75%	3870	6%	69%
Placebo	3870	76%	3870	6%	70%
Weighted study average among those at risk of SVE	7740	75%	7740	6%	69%

Assumed to be adherent to study aspirin if the participant had previously been adherent, was still receiving study medication and not reported stopping treatment and information received within the previous 7 months.
† Based on self-reported height and weight.
* Predicted 5 year risk of serious vascular event (including transient ischemic attack) without aspirin or omega-3 fatty acids.

Table S5: Reasons for stopping study medication before the end of the study

Reason for discontinuation	Aspirin		Placebo	
Patient wishes	1372	(17.7%)	1424	(18.4%)
Bruising or minor bleeding	115	(1.5%)	72	(0.9%)
Major bleeding	42	(0.5%)	24	(0.3%)
Antiplatelet treatment for clear indication	630	(8.1%)	748	(9.7%)
Antiplatelet treatment without clear indication	257	(3.3%)	241	(3.1%)
Anticoagulant treatment	249	(3.2%)	267	(3.4%)
Upper GI symptoms, diagnosis or procedure	195	(2.5%)	205	(2.6%)
Lower GI symptoms, diagnosis or procedure	74	(1.0%)	50	(0.6%)
Other symptoms, diagnosis or procedure	358	(4.6%)	391	(5.1%)
Administrative reason (e.g. moved abroad)	237	(3.1%)	257	(3.3%)
Other	299	(3.9%)	236	(3.0%)
Stopped for any reason	3828	(49.5%)	3915	(50.6%)

Reasons were ascertained from free text on questionnaires or following a telephone call to the participant or their managing doctor. The predominant reason was recorded with adverse events taking priority over patient wishes or administrative reasons.

Table S6: Proportion of participants reporting use of non-study treatments at randomization and after a mean of 6.7 years of follow-up

Medication	Aspirin		Placebo	
Number of patients				
Randomization	7740		7740	
6.7 years	5671		5576	
Statin				
Randomization	5854	(75.6%)	5799	(74.9%)
6.7 years	4219	(74.4%)	4158	(74.6%)
ACE inhibitor or ARB				
Randomization	4520	(58.4%)	4535	(58.6%)
6.7 years	3615	(63.7%)	3527	(63.3%)
Insulin				
Randomization	1959	(25.3%)	1972	(25.5%)
6.7 years	1555	(27.4%)	1517	(27.2%)
Metformin				
Randomization	5055	(65.3%)	5038	(65.1%)
6.7 years	3937	(69.4%)	3817	(68.5%)
Sulphonylurea				
Randomization	2064	(26.7%)	2081	(26.9%)
6.7 years	1707	(30.1%)	1685	(30.2%)
Thiazolidinedione				
Randomization	894	(11.6%)	897	(11.6%)
6.7 years	316	(5.6%)	286	(5.1%)
Other hypoglycaemic agent				
Randomization	344	(4.4%)	349	(4.5%)
6.7 years	896	(15.8%)	923	(16.6%)
Beta-blocker				
Randomization	1016	(13.1%)	1013	(13.1%)
6.7 years	961	(16.9%)	964	(17.3%)
Calcium channel blocker				
Randomization	1926	(24.9%)	1847	(23.9%)
6.7 years	1726	(30.4%)	1650	(29.6%)
Thiazide or related diuretic				
Randomization	1480	(19.1%)	1477	(19.1%)
6.7 years	937	(16.5%)	869	(15.6%)
Proton pump inhibitor				
Randomization	1073	(13.9%)	1181	(15.3%)
6.7 years	1370	(24.2%)	1392	(25.0%)
NSAID				
Randomization	670	(8.7%)	663	(8.6%)
6.7 years	402	(7.1%)	440	(7.9%)

ACE: angiotensin-converting-enzyme; ARB: angiotensin II receptor blockers; NSAID: nonsteroidal anti-inflammatory drug.
The difference in proton pump inhibitor use at baseline was P=0.01 unadjusted for multiple comparisons.

Table S7: Cardiovascular risk factors in a randomly selected subset of participants at 2.5 years follow-up

	Aspirin		Placebo		
Measurement	Baseline	Follow-up	Baseline	Follow-up	Between group difference (95% CI) at follow-up adjusted for baseline
Total cholesterol (mg/dL)	160 (1.5)	156 (1.6)	159 (1.5)	156 (1.4)	-0.1 (-3.6, 3.4)
HDL cholesterol (mg/dL)	48 (0.6)	48 (0.6)	49 (0.6)	48 (0.6)	0.3 (-0.6, 1.2)
Non-HDL cholesterol (mg/dL)	111 (1.4)	108 (1.5)	110 (1.4)	108 (1.3)	-0.2 (-3.4, 3.1)
Apolipoprotein B (mg/dL)	81 (0.9)	79 (1.0)	81 (0.9)	78 (0.9)	0.6 (-1.5, 2.6)
Apolipoprotein A1 (mg/dL)	148 (1.2)	147 (1.2)	149 (1.1)	147 (1.2)	1.0 (-1.2, 3.2)
eGFR (ml/min/1.73m^2)*	84 (1.0)	76 (1.0)	85 (0.9)	74 (1.0)	1.8 (0.3, 3.4)
HbA1c (IFCC; mmol/mol)	53 (0.5)	56 (0.6)	54 (0.5)	57 (0.6)	-1.2 (-2.4, 0.1)
Systolic blood pressure (mmHg)	137 (0.7)	136 (0.6)	137 (0.6)	138 (0.6)	-2.5 (-4.2, -0.9)
Weight (kg)	90 (0.8)	89 (0.8)	89 (0.7)	88 (0.7)	-0.2 (-1.1, 0.7)
Urinary albumin/creatinine ratio (mg/mmol)	0.5 (0.2-1.2)	0.6 (0.3-1.6)	0.5 (0.0-1.2)	0.7 (0.4-1.5)	0.5 (-1.2, 2.2)

Results shown are mean (SE) except for urinary albumin/creatinine ratio, for which median (IQR) is shown.
Comparisons at each time point between treatment groups are reliable but comparisons between baseline and follow-up could be subject to assay drift/recalibration effects and differences in sample processing (for example follow-up assays were all conducted on frozen samples).
Numbers ranged from 469-590 in the aspirin group and 480-630 in the placebo group.
To convert the values for cholesterol to millimoles per liter, multiply by 0.02586.
* Calculated from cystatin C with different analysis methods used at baseline and follow-up (see Supplementary methods).

Table S8: Effect of aspirin assignment on hemorrhagic stroke, the components of intracranial bleed and on fatal and non-fatal major bleeding

Type of event	Aspirin (N=7740)		Placebo (N=7740)		Rate ratio (95% CI)
Hemorrhagic stroke by disability					
Fatal	11	(0.1%)	9	(0.1%)	
Disabling	4	(0.1%)	4	(0.1%)	
Non-disabling	6	(0.1%)	8	(0.1%)	
Unknown disability	4	(0.1%)	6	(0.1%)	
Any hemorrhagic stroke	**25**	**(0.3%)**	**26**	**(0.3%)**	**0.96 (0.55-1.66)**
Intracranial bleeding by site					
Intracerebral bleed	25	(0.3%)	21	(0.3%)	
Subarachnoid bleed	7	(0.1%)	8	(0.1%)	
Subdural, other or unspecified intracranial bleed	26	(0.3%)	17	(0.2%)	
Any intracranial bleed	**55**	**(0.7%)**	**45**	**(0.6%)**	**1.22 (0.82-1.81)**
Fatal and non-fatal major bleed					
Fatal bleed	19	(0.2%)	16	(0.2%)	1.18 (0.61-2.30)
Non-fatal bleed	298	(3.9%)	233	(3.0%)	1.28 (1.08-1.52)
Any major bleed	**314**	**(4.1%)**	**245**	**(3.2%)**	**1.29 (1.09-1.52)**

95% confidence intervals are unadjusted for multiplicity.

Table S9: Effect of aspirin assignment on reported microvascular complications

Microvascular complication	Aspirin		Placebo	
Retinopathy				
Retinopathy at baseline	1526 / 7670	(20%)	1497 / 7666	(20%)
Retinopathy at FU (whole cohort)	1840 / 5623	(33%)	1789 / 5532	(32%)
Retinopathy at FU (No baseline retinopathy)	1043 / 4498	(23%)	996 / 4449	(22%)
Laser treatment				
Laser at baseline	444 / 7670	(6%)	483 / 7666	(6%)
Laser at FU (whole cohort)	486 / 5623	(9%)	471 / 5532	(9%)
Laser at FU (No baseline laser)	129 / 4498	(3%)	95 / 4449	(2%)
Neuropathy	1207 / 5623	(21%)	1229 / 5532	(22%)

Self-report from participant questionnaires.
FU, Follow-up.

Table S10: Reported Fatal or non-fatal Serious Adverse Events by MedDRA System Organ Class

Interactive tables available at NEJM.org

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