

SUPPLEMENTARY DATA

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Table S1. Criteria used for adjudication of clinically significant bleeding events in the ASPREE trial. A bleeding event had to fulfil criteria in both categories A and B to be adjudicated as a confirmed event.

A.	Criteria for substantiated bleeding	Example
	Observed bleeding	Bleeding observed in ED or hospital
	Reasonable report of bleeding symptoms	Description of rectal bleeding
	Medical, nursing or paramedical report	Medical doctor's confirmatory notes
	Imaging evidence	CT showing subdural bleed
B.	Criteria for clinically significant bleeding	Notes
	Hospitalisation for bleeding	Hospitalisation >24 hours
	Blood transfusion required due to bleeding	
	Bleeding requiring surgery for haemostasis	
	Fatal bleeding	

Where adjudication needed further guidance, the following decision rules were used:

1. If hospitalisation criterion is to be utilised, bleeding must be the principal reason for hospitalisation, prolongation of hospitalisation or surgery.
2. A positive faecal occult blood test, anaemia, or haemoglobin drop alone without overt bleeding is insufficient to substantiate bleeding.
3. Additional adjudication will occur on whether intracranial bleeding was spontaneous (non-traumatic) or induced (traumatic).
4. Elective inpatient surgical procedure (includes therapeutic endoscopic procedures) with prolonged stay, repeat surgery, or transfusion do NOT meet criteria
5. Elective inpatient surgical (includes therapeutic endoscopic procedures) readmitted after discharge primarily for bleeding: Does meet criteria
6. Elective outpatient procedure (includes therapeutic endoscopic procedures) admitted primarily for bleeding: Does meet criteria
7. Non-elective inpatient procedure (includes therapeutic endoscopic procedures) readmitted, prolonged stay, repeat surgery, or transfused: Does meet criteria

Table S2. Participant characteristics in aspirin and placebo arms.

	Placebo (n=9589)	Aspirin (n=9525)
Female sex	5410 (56%)	5373 (56%)
Age ≥ 74 years	4766 (50%)	4806 (50%)
Ethnicity- Caucasian		
Ethnicity-African American	450 (5%)	451 (5%)
Smoking		
<i>Never</i>	5316 (55%)	5264 (55%)
<i>Former</i>	3890 (41%)	3909 (41%)
<i>Current</i>	383 (4%)	352 (4%)
Alcohol- current consumption	7333 (76.5)	7309 (76.7)
Waist circumference (median, cm,SD)	97.2 (12.8)	97.1 (13)
Obesity	2857 (30%)	2820 (30%)
Hypertension	7148 (75%)	7065 (74%)
Diabetes	1030 (11%)	1027 (11%)
Chronic kidney disease	2464 (26%)	2456 (26%)
Previous regular aspirin use	1041 (11%)	1053 (11%)
Regular PPI use	2374 (25%)	2340 (25%)
Regular NSAID use	1342 (14%)	1371 (14%)

Table S3. Predicted 5 year risk of upper gastrointestinal bleeding for a 70 and 80 year old person on placebo or aspirin and additional risk factors

Additional risk factors	70 year old		80 year old	
	Placebo	Aspirin	Placebo	Aspirin
None	0.22% (0.14 – 0.33%)	0.40% (0.26 – 0.59%)	0.52% (0.36 – 0.75%)	0.97% (0.68 – 1.35%)
Smoking	0.52% (0.23 – 1.05%)	0.95% (0.43 – 1.87%)	1.24% (0.54 – 2.49%)	2.28% (1.04 – 4.37%)
CKD	0.32% (0.19 – 0.52%)	0.60% (0.37 – 0.92%)	0.78% (0.51 – 1.15%)	1.44% (1.01 – 2.00%)
NSAID use	0.37% (0.21 – 0.63%)	0.69% (0.38 – 1.17%)	0.90% (0.53 – 1.46%)	1.67% (0.96 – 2.71%)
Smoking & NSAID	0.89% (0.38 – 1.82%)	1.64% (0.71 – 3.27%)	2.13% (0.90 – 4.28%)	3.91% (1.69 – 7.61%)
Smoking & CKD	0.77% (0.30 – 1.68%)	1.42% (0.59 – 2.95%)	1.83% (0.74 – 3.85%)	3.37% (1.44 – 6.67%)
Smoking, CKD & NSAID	1.32% (0.52 – 2.85%)	2.43% (0.98 – 5.05%)	3.15% (1.26 – 6.50%)	5.76% (2.38 – 11.32%)

Table S4. Predicted 5 year risk of lower gastrointestinal bleeding for a 70 and 80 year old person with aspirin and additional risk factors

Additional risk factors	70 year old		80 year old	
	Placebo	Aspirin	Placebo	Aspirin
None	0.16% (0.09-0.28%)	0.22% (0.13-0.37%)	0.37% (0.20-0.64%)	0.50% (0.28-0.83%)
Smoking	0.25% (0.14-0.42%)	0.34% (0.18-0.58%)	0.56% (0.30-0.97%)	0.76% (0.41-1.30%)
CKD	0.23% (0.11-0.45%)	0.31% (0.15 – 0.61%)	0.52% (0.26-0.97%)	0.70% (0.35-1.29%)
Hypertension	0.32% (0.21-0.49%)	0.44% (0.29 – 0.65%)	0.73% (0.47-1.09%)	0.99% (0.70-1.36%)
Smoking & Hypertension	0.49% (0.31-0.74%)	0.66% (0.42 – 1.01%)	1.10% (0.72-1.62%)	1.49% (1.00-2.13%)
Smoking &CKD	0.35% (0.17-0.66%)	0.47% (0.22-0.92%)	0.79% (0.40-1.41%)	1.06% (0.54-1.92%)
Smoking, Hypertension & CKD	0.69% (0.42-1.09%)	0.93% (0.54– 1.51%)	1.55% (1.07-2.17%)	2.09% (1.45-2.91%)

Table S5. Absolute risk of overall gastrointestinal bleeding over 1 year for people on placebo or aspirin, according to age and risk factors.

Additional risk factors	70 year old		80 year old	
	Placebo	Aspirin	Placebo	Aspirin
Nil	0.05% (0.03-0.08%)	0.08% (0.05-0.13%)	0.12% (0.07-0.19%)	0.19% (0.12-0.3%)
Smoking	0.11% (0.05-0.21%)	0.17% (0.08-0.34%)	0.25% (0.12-0.5%)	0.41% (0.19-0.8%)
CKD#	0.07% (0.04-0.12%)	0.12% (0.07-0.2%)	0.17% (0.1-0.28%)	0.27% (0.16-0.44%)
Hypertension	0.07% (0.05-0.12%)	0.12% (0.07-0.19%)	0.18% (0.11-0.26%)	0.28% (0.19-0.42%)
At risk WC*	0.07% (0.04-0.1%)	0.11% (0.07-0.17%)	0.16% (0.1-0.25%)	0.25% (0.15-0.4%)
Smoking & at risk WC	0.14% (0.07-0.28%)	0.23% (0.11-0.45%)	0.34% (0.15-0.67%)	0.54% (0.24-1.07%)
Smoking & CKD	0.15% (0.07-0.32%)	0.25% (0.11-0.51%)	0.36% (0.16-0.74%)	0.58% (0.26-1.18%)
CKD, hypertension, at risk WC	0.14% (0.09-0.22%)	0.23% (0.14-0.36%)	0.33% (0.22-0.5%)	0.54% (0.35-0.8%)
Smoking, CKD & at risk WC	0.20 % (0.09-0.42%)	0.33% (0.14-0.68%)	0.48% (0.21-0.99%)	0.77% (0.33-1.59%)
Smoking, hypertension and at risk WC	0.21% (0.11-0.39%)	0.34% (0.17-0.62%)	0.50 % (0.25-0.91%)	0.80% (0.4-1.45%)
Smoking, CKD, at risk WC and hypertension	0.30% (0.15-0.58%)	0.49% (0.23-0.93%)	0.71% (0.35-1.33%)	1.14% (0.55-2.12%)

*WC= waist circumference; # CKD=chronic kidney disease

Figure S1. Consort flow diagram.

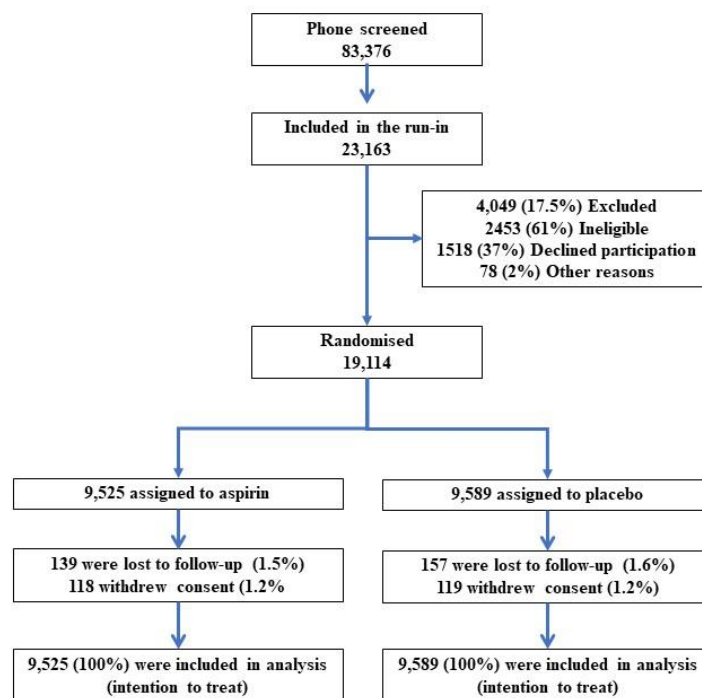
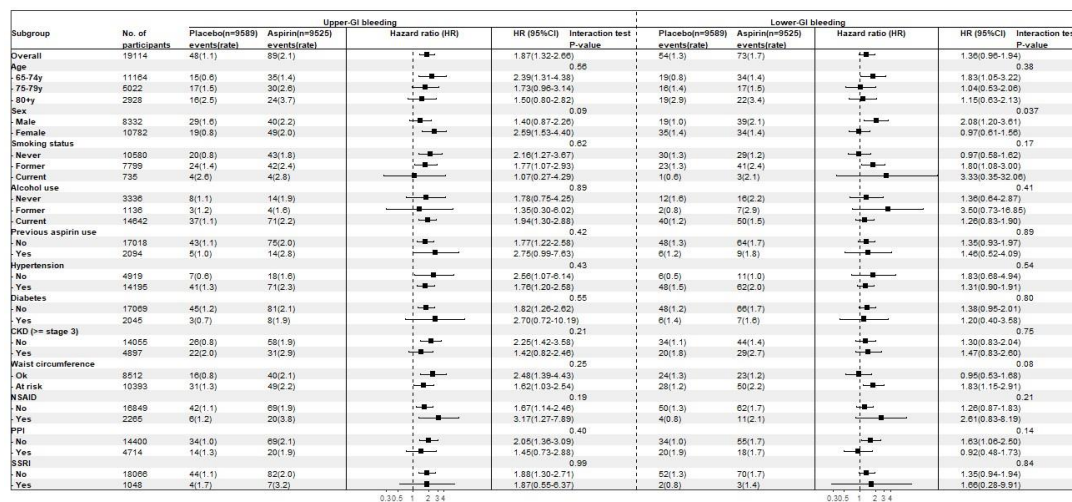
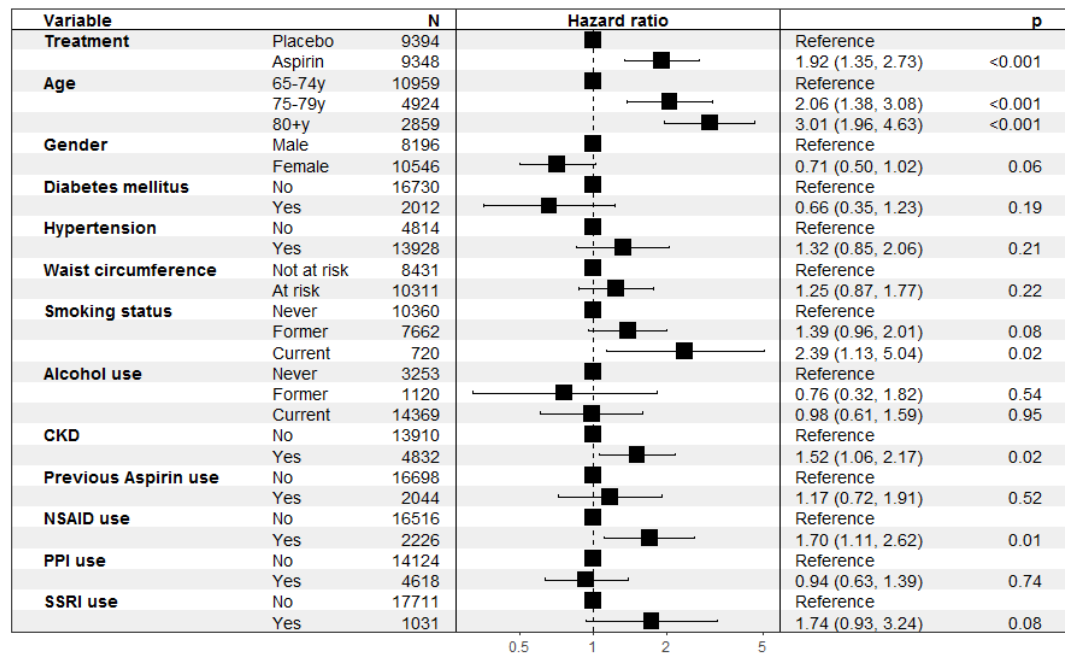


Figure S2. Incidence of upper and lower gastrointestinal bleeding according to subgroup and treatment arm.



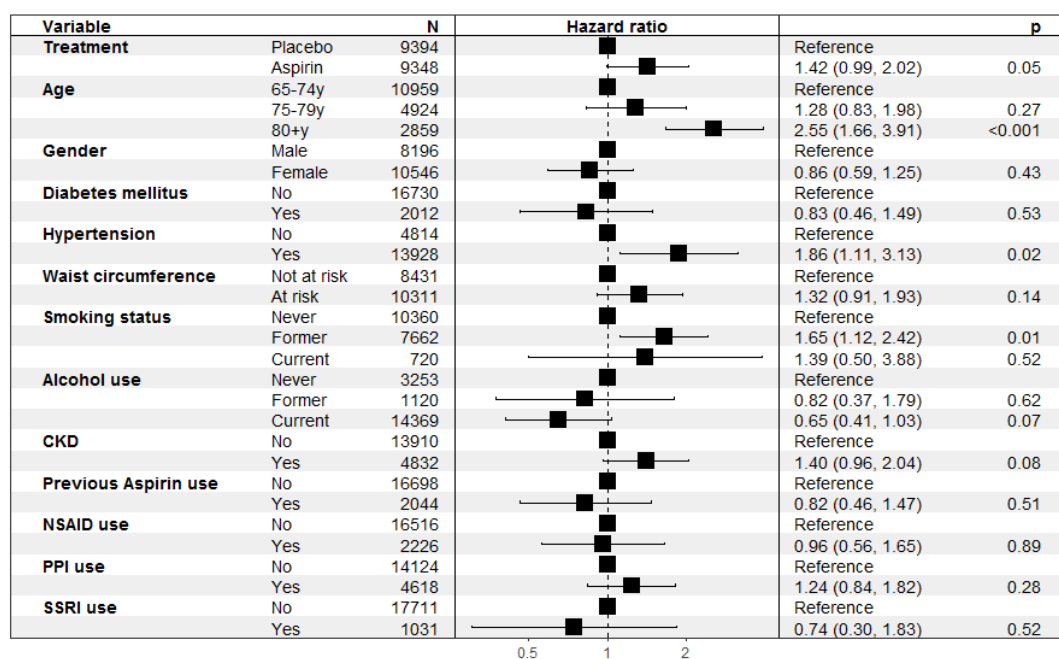
Footnote: Diabetes = self-report of diabetes mellitus or fasting glucose ≥ 126 mg/dL (≥ 7 mmol/L) or on treatment for diabetes. Hypertension = Systolic blood pressure ≥ 140 mmHg or Diastolic blood pressure ≥ 90 mmHg or on treatment for high blood pressure. CKD= Chronic kidney disease = eGFR < 60 ml/min/1.73m² or albumin to creatinine ratio ≥ 3 mg/mmol.

Figure S3. Multivariable model of risk factors for upper gastrointestinal bleeding (HR and 95% CI).



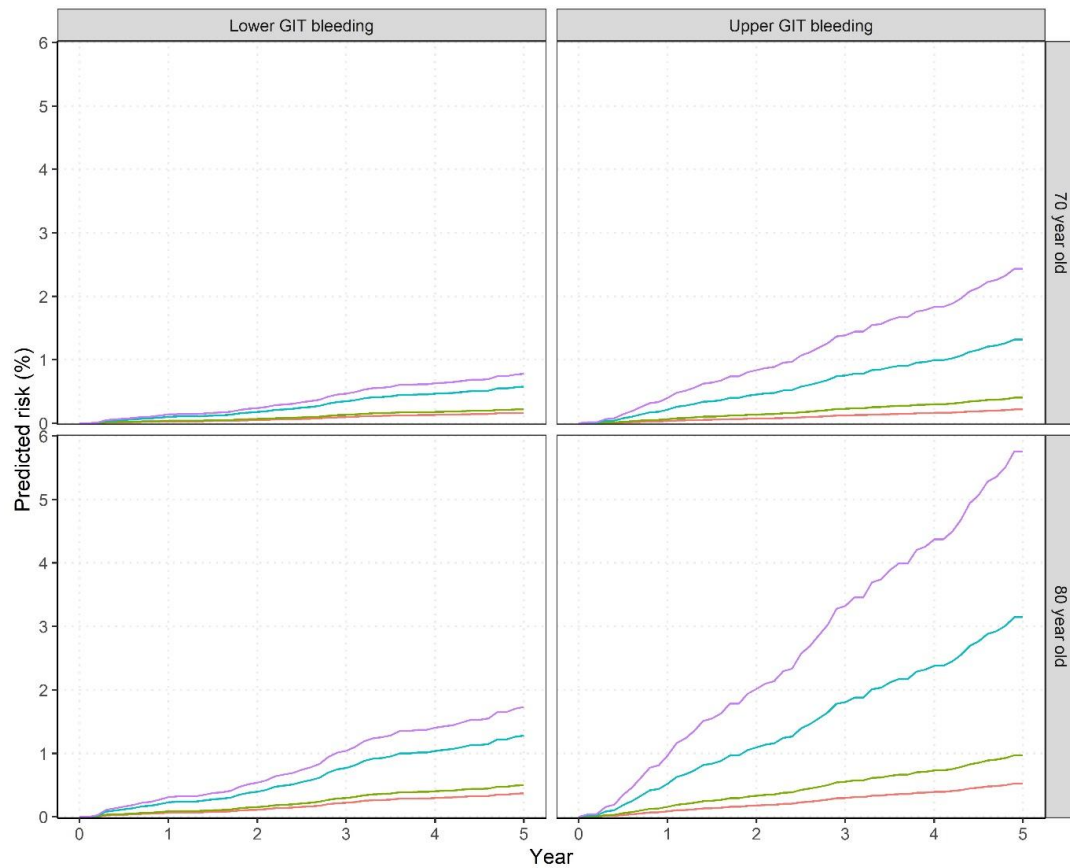
Footnote: Diabetes = self-report of diabetes mellitus or fasting glucose ≥ 126 mg/dL (≥ 7 mmol/L) or on treatment for diabetes. Hypertension = Systolic blood pressure ≥ 140 mmHg or Diastolic blood pressure ≥ 90 mmHg or on treatment for high blood pressure. CKD= Chronic kidney disease = eGFR < 60 ml/min/1.73m² or albumin to creatinine ratio ≥ 3 mg/mmol.

Figure S4. Multivariable model of risk factors for lower gastrointestinal bleeding (HR and 95% CI).



Footnote: Diabetes = self-report of diabetes mellitus or fasting glucose ≥ 126 mg/dL (≥ 7 mmol/L) or on treatment for diabetes. Hypertension = Systolic blood pressure ≥ 140 mmHg or Diastolic blood pressure ≥ 90 mmHg or on treatment for high blood pressure. CKD= Chronic kidney disease = eGFR < 60 ml/min/1.73m² or albumin to creatinine ratio ≥ 3 mg/mmol.

Figure S5. Predicted absolute 5 year bleeding risk for upper and lower gastrointestinal (GIT) bleeding according to age and risk factors.



Footnote: Red line= no risk factors, on placebo, Green line= no risk factors but on aspirin, Blue line= all risk factors and on placebo, Purple line= aspirin and all risk factors; modelled risk factors were smoking, CKD and NSAID use for upper gastrointestinal bleeding, and smoking, hypertension and CKD for lower gastrointestinal bleeding.

