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Supplementary appendix

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Age-specific risks, severity, time-course and outcome of bleeding on long-term antiplatelet treatment after vascular events: population-based cohort study

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Web appendix

Age-specific risks, severity, time-course and outcome of bleeding on long-term antiplatelet treatment after vascular events: population-based study

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Web appendix 1. Summary of PPI trials in the prevention of antiplatelet-associated upper-GI complications.

Study	Year	Country	Antiplatelet treatment	Primary/secondary	Patient characteristics	Mean age
vs. Placebo						
Lai[e1]	2002	Hong Kong	low-dose Aspirin	Secondary	High-risk/endoscopic proved history of peptic ulcer	70
AstraZeneca [e2]	NR	Japan	low-dose Aspirin	NR	High-risk/history of peptic ulcer	NR
Scheiman [e3]	2011	20 countries	low-dose Aspirin	Both	High-risk/history of peptic ulcer or age >65yrs or age >60yrs with GI symptoms and erosions or aspirin naïve patients	67
Hsu [e4]	2011	Taiwan	Clopidogrel	Secondary	High-risk/history of peptic ulcer but normal endoscopic exam at entry/cannot take long-term aspirin	72
Yeomans [e5]	2008	10 countries	low-dose Aspirin	Secondary	Non-high risk/older than 60yrs/no baseline peptic ulcer on endoscopy	69
Bhatt [e6]	2010	15 countries	A+C	Secondary	Non-high risk	68
vs. other gastric protection						
Ng [e7]	2010	Hong Kong	low-dose Aspirin	Secondary	High-risk/history of peptic ulcers or erosions with or without bleeding	69
Sugano [e8]	2011	Japan	low-dose Aspirin	Secondary	High-risk/endoscopic proved history of peptic ulcer	69
Sanuki [e9]	2012	Japan	low-dose Aspirin	Secondary	High-risk/endoscopic proved history of peptic ulcer	73
Chan [e10]	2001	Hong Kong	low-dose Aspirin	Secondary	High-risk/endoscopic proved acute peptic ulcer	69
Ng [e11]	2012	Hong Kong	A+C+others	Secondary	Non-high risk	63

Study	Treatment	Control	Primary endpoint	Follow-up	Incidence/treatment	Incidence/control	Hazard Ratio (95%CI)†
vs. Placebo							
Lai[e1]	Lansoprazole	Placebo	Clinical/ulcer complications	1 year	1.6	14.8	10.6(1.3-86.1)*
AstraZeneca [e2]	Esomeprazole	Placebo	Peptic ulcer	1 year	1.7	18.8	0.09 (0.02-0.41)
Scheiman [e3]	Esomeprazole 20mg/40mg	Placebo	Endoscopic/gastric or duodenal ulcer	26 weeks	1.1/1.5	7.4	0.14 (0.07-0.30)/0.19 (0.10-0.37)
HSU [e4]	Esomeprazole	Placebo	Endoscopic/gastric or duodenal ulcer	6 months	1.2	11	NR
Yeomans [e5]	Esomeprazole	Placebo	Endoscopic/gastric or duodenal ulcer	26 weeks	1.8	6.2	NR
Bhatt [e6]	Omeprazole	Placebo	Clinical/composite of upper-GI events	180 days	1.1	2.9	0.34 (0.18-0.63)
vs. other gastric protection							
Ng [e7]	Pantoprazole	Famotidine	Clinical/ulcer complications	48 weeks	0	20	NR
Sugano [e8]	Lansoprazole	Gefarnate	Endoscopic/gastric or duodenal ulcer	7.5m/5.7m (median)	3.7	31.7	0.10 (0.04-0.23)
Sanuki [e9]	Rabeprazole 10mg/20mg	Gefarnate	Endoscopic/gastric or duodenal ulcer	12 weeks	5.5	26.7	0.19 (0.08-0.39)
Chan [e10]	Omeprazole	HP eradication+placebo	Clinical or Endoscopic /GI bleed or Hb drop of 2g/dl	6 months	0.9	1.9	NR
Ng [e11]	Esoprazole	Famotidine	Clinical/upper-GI bleed, perforation or obstruction	19.2 /17.6 weeks	0.6	6.1	0.10 (0.01-0.50)

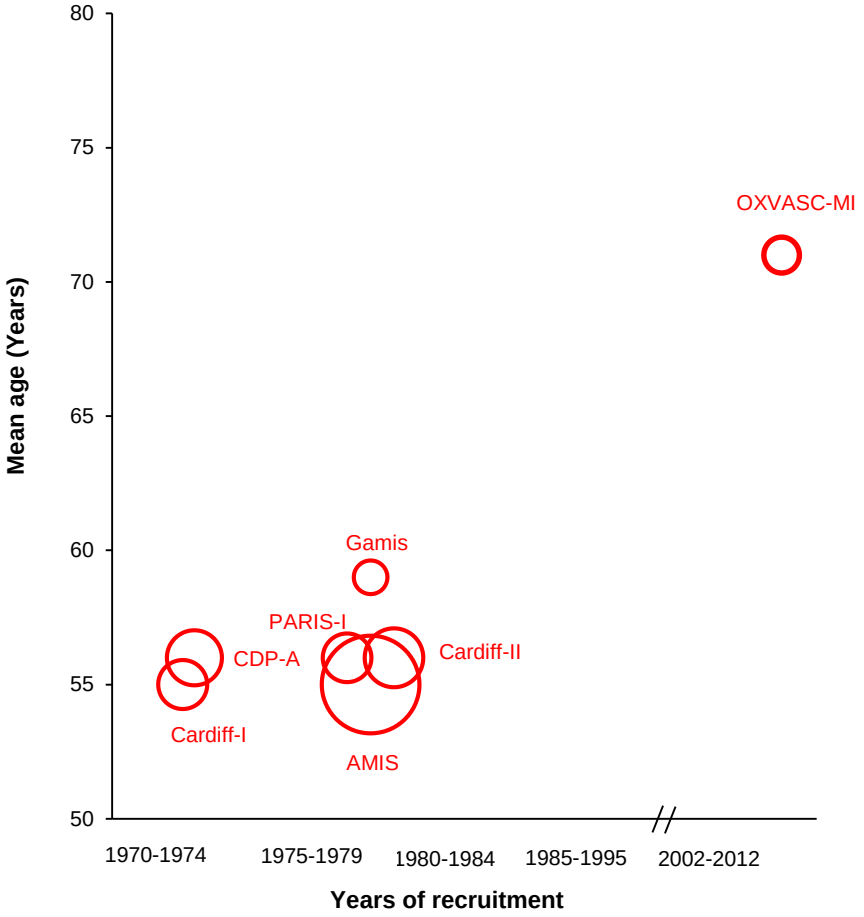
PPI=proton pump inhibitor, A=aspirin, C=Clopidogrel, GI=gastrointestinal, Hb=haemoglobin, NR=not reported, HP=H.pylori. *reported HR for control vs. treatment. †pooled relative risk=0.26 from a systematic review (reference 6 in the main paper).

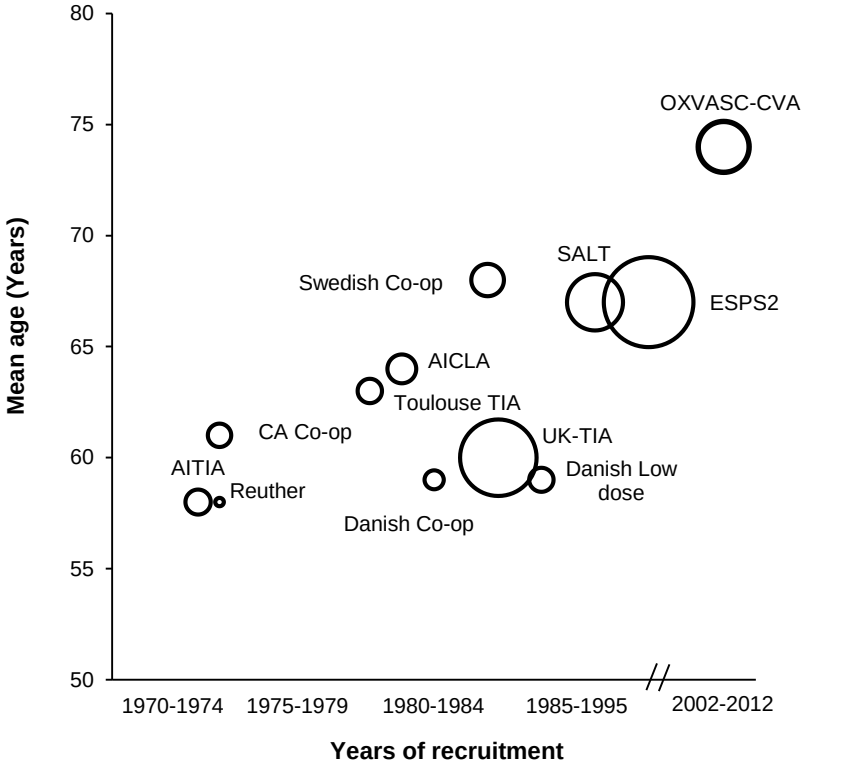
Web appendix 2a. Comparison of the age and follow-up lengths of patients in aspirin trials (aspirin vs. placebo) for secondary prevention vs. OXVASC.

Studies	Publication year	Number of participants	Follow-up (median)	Mean age	Age range	≥75 years%
Post-MI						
Secondary prevention trials						
Cardiff-I[e26]	1974	1239	2 years	55	NR	NR but ≥65 years: 168 (13.6)
Cardiff-II[e27]	1979	1725	1 years	56	NR	27 (1.6)
PARIS-I[e28]	1980	1216	41 months	56	NR	NR but ≥55 years: 694 (57.1)
AMIS[e29]	1980	4524	38 months	55	30-69	0
CDP-A[e30]	1976	1529	22 months	56	30-64	0
Gamis[e31]	1980	626	2 years	59	45-70	0
OXVASC-MI cohort		1094	3.6 years	71	29-101	494 (45.2)
Post-TIA/stroke						
Secondary prevention trials						
AITIA[e12,e25]	1975	319	1 years	58	NR	22 (6.9)
UK-TIA[e13]	1988	2435	4 years	60	≥40	NR
Reuther[e32]	1976	60	2 years	58	NR	NR
CA Co-op[e33]	1978	283	3 years	61	NR	NR
Toulouse TIA[e34]	1982	303	3 years	63	NR	NR
AICLA[e24]	1981	402	3 years	64	NR	64 (15.9)
Danish Co-op[e35]	1980	203	25 months	59	34-75	0
Swedish Co-op[e16]	1987	505	2 years	68	27-93	NR but >65: 243 (48.1)
Danish low dose[e36]	1986	301	23 months	59	NR	NR
SALT[e15]	1991	1363	32 months	67	50-79	NR
ESPS-2[e17]	1996	3298	2 years	67	≥18	895 (27.1)
OXVASC-TIA/stroke cohort		2072	3.7 years	73	21-99	1088 (52.5)

NR= not reported. MI=myocardial infarction.

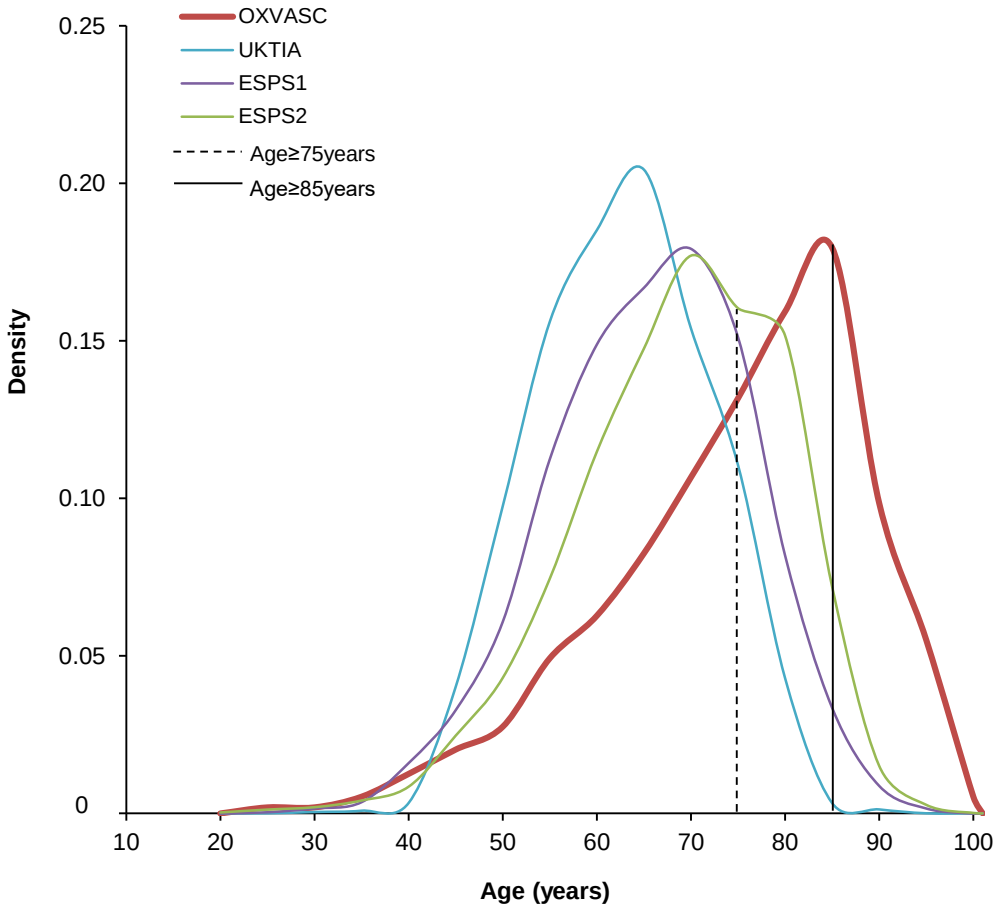
Web appendix 2b. Age of patients in aspirin trials (aspirin vs. placebo) for secondary prevention vs. OXVASC. (Trials plotted by year of recruitment and the size of the circle represents the size of the study; MI=myocardial infarction; CVA=cerebrovascular disease)





Web appendix 2c. Age distribution of patients with TIA or ischaemic stroke in OXVASC and in aspirin trials of secondary prevention.

UK TIA, ESPS1 and ESPS 2 are aspirin trials of secondary prevention. OXVASC included patients with a first-in-study-period myocardial infarction, transient ischaemic attack or ischaemic stroke from 2002 to 2012.



Web appendix 3. Baseline characteristics of patients with myocardial infarction,TIA and ischaemic stroke in OXVASC who were initially treated with antiplatelet medication for secondary prevention stratified by age. Categorial variables are given as n (%). χ^2 test and t test were used to compare categorical and continuous variables between groups.

		Age group		
	All (n=3166)	<75 (n=1584)	≥75 (n=1582)	p
Mean (SD) Age (years)	72.2 (13.4)	61.4 (10.0)	83.0 (5.4)	<0.0001
Mean (SD) Weight (kg)	74.7 (16.1)	79.5 (17.2)	69.8 (13.3)	<0.0001
Female	1449 (45.8)	554 (35.0)	895 (56.6)	<0.0001
Acute event				<0.0001
Ischaemic stroke	1177 (37.2)	511 (32.3)	666 (42.1)	
Transiet ischaemic attack	895 (28.3)	473 (29.9)	422 (26.7)	
Non-ST elevation myocardial infarction	703 (22.2)	333 (21.0)	370 (23.4)	
ST-elevation myocardial infarction	391 (12.3)	267 (16.9)	124 (7.8)	
Prior events				
Stroke	277 (8.8)	85 (5.4)	192 (12.2)	<0.0001
Transient ischaemic attack	226 (7.1)	74 (4.7)	152 (9.6)	<0.0001
Myocardial infarction	369 (11.7)	148 (9.3)	221 (14.0)	<0.0001
Peripheral vascular disease	250 (7.9)	104 (6.6)	146 (9.2)	0.0054
Any previous vascular disease*	902 (28.5)	335 (21.1)	567 (35.8)	<0.0001
Hypertension	1732 (54.8)	754 (47.6)	978 (61.9)	<0.0001
Diabetes	473 (15.0)	251 (15.9)	222 (14.1)	0.16
Hyperlipidaemia	933 (29.5)	486 (30.7)	447 (28.3)	0.14
Current smoking†	576 (18.3)	456 (28.9)	120 (7.7)	<0.0001
Alcohol use >14units/week‡	452 (15.2)	328 (21.8)	124 (8.5)	<0.0001
Anaemia	663 (20.9)	254 (16.0)	409 (25.9)	<0.0001
History of cancer	383 (12.1)	129 (8.2)	254 (16.1)	<0.0001
Chronic liver disease	47 (1.5)	30 (1.9)	17 (1.1)	0.06
Renal failure	45 (1.4)	20 (1.3)	25 (1.6)	0.45
History of peptic ulcer	262 (8.3)	98 (6.2)	164 (10.4)	<0.0001
Atrial fibrillation	380 (12.0)	79 (5.0)	301 (19.1)	<0.0001
Chronic heart failure	308 (9.7)	71 (4.5)	237 (15.0)	<0.0001
Premorbid antiplatelet use	1279 (40.4)	462 (29.2)	817 (51.7)	<0.0001
Premorbid PPI or H2-antagonist	773 (24.4)	323 (20.4)	450 (28.4)	<0.0001
Aspirin-based antiplatelet treatment post-event	3027 (95.7%)	1529 (96.6)	1498 (94.8)	0.0137
Dual antiplatelet post-event††	1256 (39.7)	733 (46.3)	523 (33.1)	<0.0001

*History of vascular disease= history of stroke, TIA, myocardial infarction or peripheral vascular disease. †data missing in 6 patients aged <75years and 15 in patients aged ≥75years; ‡ data missing in 80 patients aged <75years and 122 in patients aged ≥75years. ††Dual antiplatelet treatment =aspirin+clopidogrel and only a small proportion of patients remained on dual antiplatelet treatment in the long-term. Aaemia=baseline haemoglobin <13g/l in men and <12g/l in women. Renal failure=glomerular filtration rate of <30ml/minute estimated using the Cockroft and Gault formula. TIA=Transient ischaemi attack. PPI=Proton Pump Inhibitors. H2-antagonist=Histamine 2 antagonist.

Web appendix 4. Baseline charateristics of patients on premorbid gastric protection vs. those not on gastric protection.

(Gastric protection=proton pump inhibitor or histamine 2 antagonist)

	On gastric protection (n=773)	Not on gastric protection (n=2393)	p	Adjusted p†
Age (mean/SD)	75.4/11.5	71.2/13.9	<0.0001	
Female	381 (49.3)	1068 (44.6)	0.02	0.68
History of vascular disease*	261 (33.8)	641 (26.8)	0.0002	0.03
History of hypertension	470 (60.8)	1262 (52.8)	0.0001	0.009
History of diabetes	138 (17.9)	335 (14.0)	0.009	0.008
History of hyperlipidaemia	267 (34.5)	666 (27.9)	0.0004	0.0002
History of atrial fibrilation	106 (13.7)	275 (11.5)	0.10	0.75
History of cancer	107 (13.8)	276 (11.6)	0.09	0.63
History of chronic liver disease	13 (1.7)	34 (1.4)	0.61	0.42
History of renal failure	14 (1.8)	31 (1.3)	0.30	0.35
History of peptic ulcer	124 (16.1)	138 (5.8)	<0.0001	<0.0001
Anaemia	193 (25.0)	470 (19.6)	0.002	0.03
Current smoking††	112 (14.5)	464 (19.5)	0.002	0.55
Alcohol>14 units/week‡	94 (12.7)	358 (16.1)	0.03	0.48
Premorbid antiplatelet use	378 (48.9)	901 (37.7)	<0.0001	0.001
Dual antiplatelet post-event	305 (39.5)	951 (39.8)	0.87	0.28

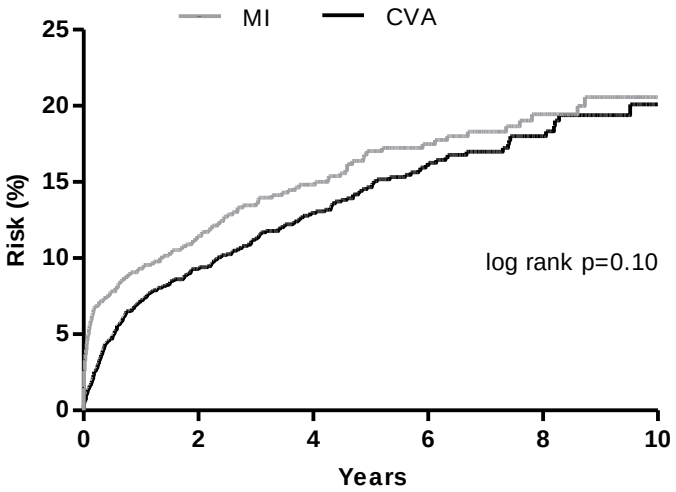
Data are presented in number (%) unless otherwise stated. †Adjusted for age; *History of vascular disease= history of stroke, transient ischaemic attack, myocardial infarction or peripheral vascular disease. ††Data missing in 21 patients. ‡Data missing in 202 patients. Aaemia=baseline haemoglobin<13g/l in men and<12g/l in women. Renal failure=glomerular filtration rate of <30ml/minute estimated using the Cockroft and Gault formula.

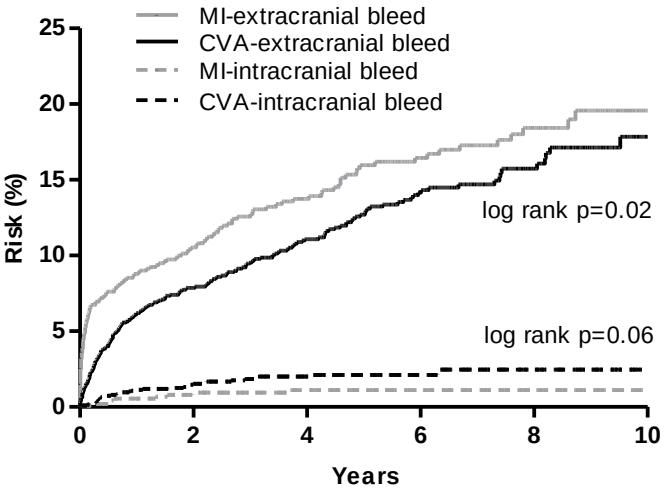
Web appendix 5. Sites of bleeding events requiring medical attention stratified by severity (CURE criteria).

Bleeding site	Severity of bleeding				Total
	Significant non-major	Major non-life threatening	Life threatening	Fatal	
Intracranial (n,%)	0 (0)	0 (0)	21 (26.3)	24 (54.5)	45 (11.1)
Intracerebral (n,%)	0 (0)	0 (0)	11 (13.8)	17 (38.6)	28 (6.9)
Subdural (n,%)	0 (0)	0 (0)	6 (7.5)	4 (9.1)	10 (2.5)
Subarachnoid (n,%)	0 (0)	0 (0)	4 (5.0)	3 (6.8)	7 (1.7)
Gastrointestinal (n,%)	105 (48.2)	47 (74.6)	47 (58.8)	19 (43.2)	218 (53.8)
Upper-gastrointestinal (n,%)	65 (29.8)	38 (60.3)	42 (52.5)	17 (38.6)	162 (40.0)
Lower-gastrointestinal (n,%)	40 (18.3)	9 (14.3)	5 (6.3)	2 (4.5)	56 (13.8)
Epistaxis (n,%)	42 (19.3)	1 (1.6)	1 (1.3)	0 (0)	44 (10.9)
Genitourinary (n,%)	44 (20.2)	7 (11.1)	2 (2.5)	0 (0)	53 (13.1)
Other (n,%)	27 (12.4)	8 (12.7)	9 (11.3)	1 (2.3)	45 (11.1)
Total (n, %total bleed)	218 (53.8)	63 (15.5)	80 (19.8)	44 (10.9)	405

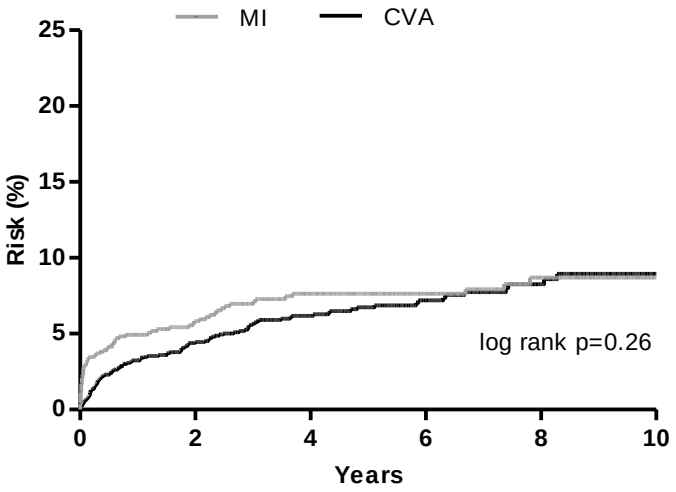
Web appendix 6. Long-term risks of bleeding events requiring medical attention stratified by severity, site of bleeding and index event type.
(MI: myocardial infarction, CVA: cerebrovascular disease)

A. Any bleed

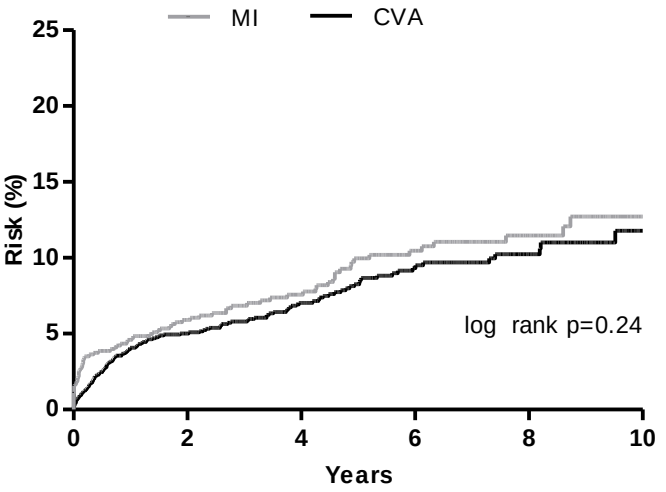




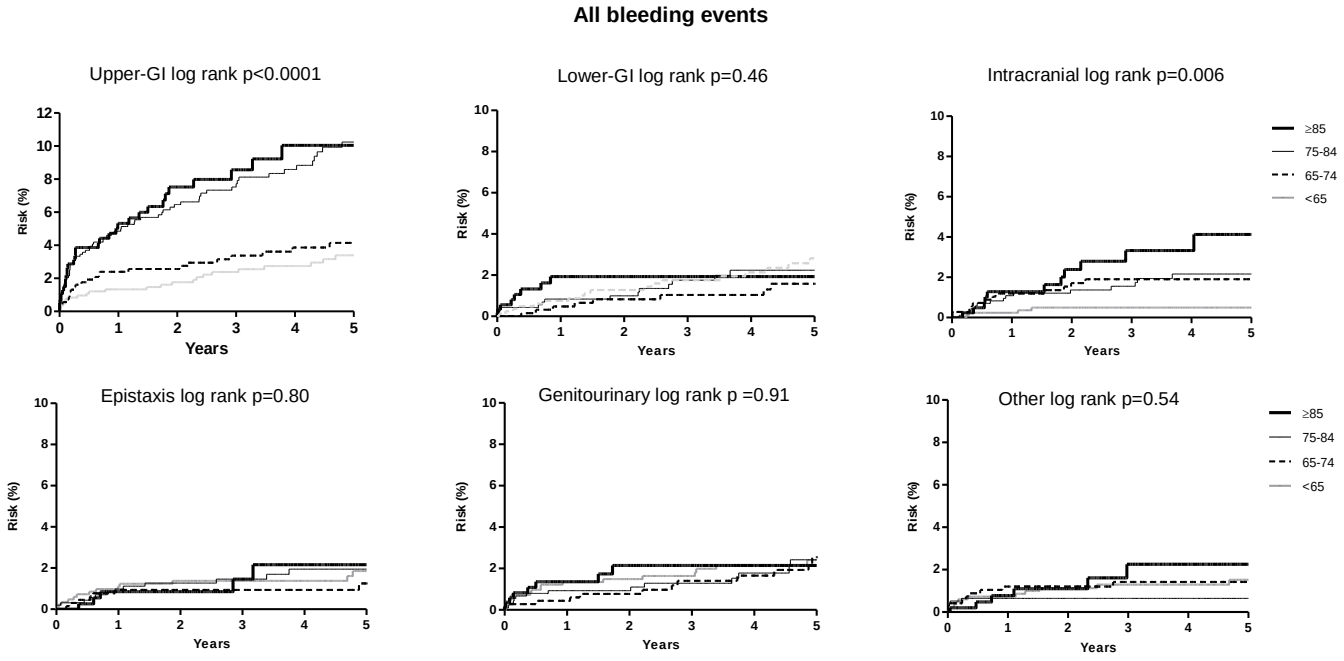
B. Any major bleed

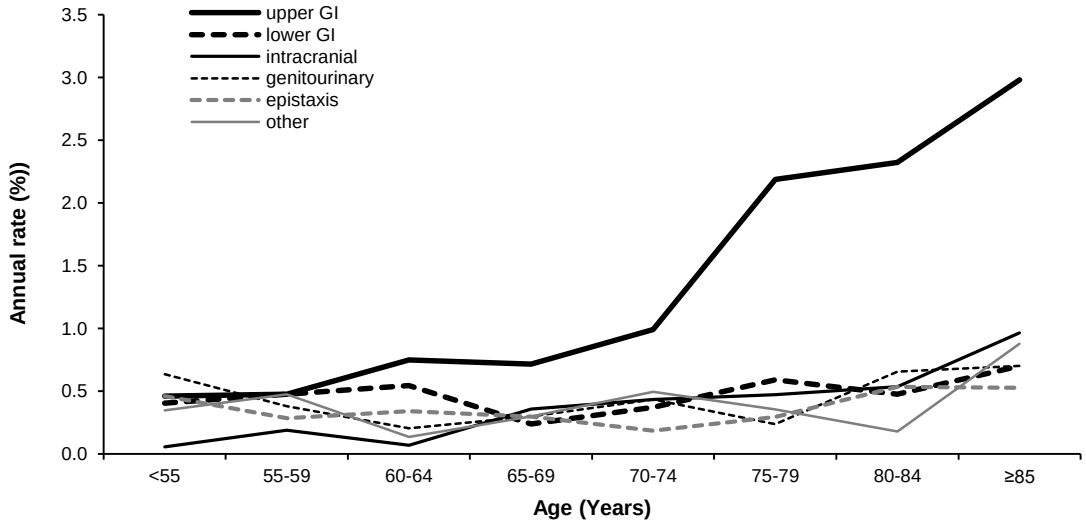


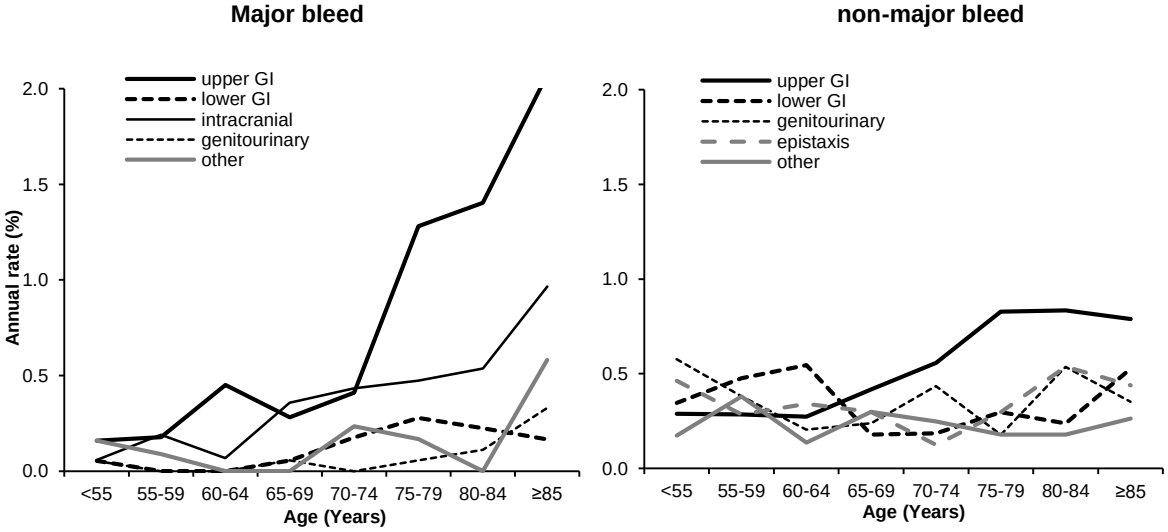
C. Any significant non-major bleed



Web appendix 7. Age-specific risks of bleeding events requiring medical attention stratified by sites and severity of bleeding. (GI=gastrointestinal)







Web appendix 8. Risks of major bleeding vs. recurrent ischaemic vascular events in aspirin-controlled trials for secondary prevention of stroke.

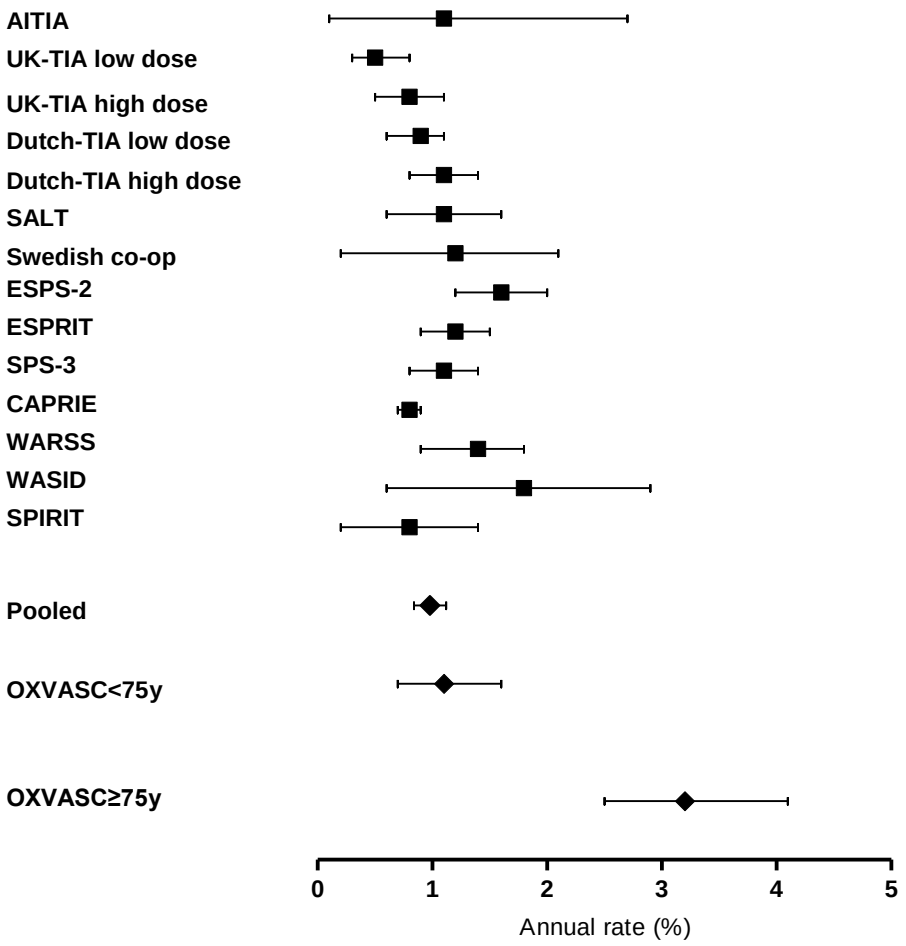
Names	Patient group	Aspirin (mg/day)	Aspirin group (N)	Mean age	Mean follow-up	Patient-years	Major bleed†	Recurrent ischaemic vascular events		Bleed / ischaemic
							N (risk %yr)	Definication of recurrent ischaemic vascular events	N (risk %yr)	Ratio (excess risk of ischaemic/bleed %)
Aspirin vs. placebo										
AITIA (medical arm)[e12]	TIA	1300	88	58	2 years	176	2 (1.1)	Ischaemic stroke and MI	12 (6.8)	0.2:1 (400%)
UK-TIA (low dose)[e13]	TIA and minor stroke	300	806	60	4 years	3224	17 (0.5)	Stroke/MI/vascular death	178 (5.5)	0.1:1 (900%)
UK-TIA (high dose)[e13]	TIA and minor stroke	1200	815	60	4 years	3260	26 (0.8)	Stroke/MI/vascular death	176 (5.4)	0.1:1 (900%)
Dutch TIA (low dose)[e14]	TIA and minor stroke	30	1555	63†	2.6 years	4665	40 (0.9)	Stroke/MI/vascular death	228 (4.9)	0.2:1 (400%)
Dutch TIA (high dose)[e14]	TIA and minor stroke	283	1576	63‡	2.6 years	4728	53 (1.1)	Stroke/MI/vascular death	240 (5.1)	0.2:1 (400%)
SALT[e15]	TIA, minor stroke and retinal artery occlusion	75	676	67	32 months	1803	20 (1.1)	Ischaemic stroke and MI/SCD	136 (7.5)	0.2:1 (400%)
Swedish co-op[e16]	Ischaemic stroke	1500	253	68	2 years	506	6 (1.2)	Ischaemic stroke and MI	50 (9.9)	0.1:1 (900%)
ESPS-2[e17]	TIA and ischaemic stroke	50	1649	67	2 years	3298	53 (1.6)	Ischaemic stroke/MI/sudden death	266 (8.1)	0.2:1 (400%)
Aspirin vs. other antiplatelet agents currently in secondary prevention of stroke										
ESPIRIT[e18]	TIA and minor stroke	30-325	1376	63	3.5 years	4495	53 (1.2)	Non-fatal ischaemic stroke, non-fatal MI or non-haemorrhagic vascular death	174 (3.9)	0.3:1 (233%)
SPS-3[e19]	Recent lacunar infarct	325	1503	63	3.4 years	5110	56 (1.1)	Ischaemic stroke and MI	162 (3.2)	0.3:1 (233%)
CAPRIE[e20]	Ischaemic stroke, MI or PVD	325	9546	63	1.9 years	18233	149 (0.8)	Ischaemic srtoke and MI	922 (5.1)	0.2:1 (400%)
Aspirin vs. Warfain										
WARSS[e21]	Ischaemic stroke	325	1103	63	2 years	2206	30 (1.4)	Ischaemic stroke	123 (5.6)	0.2:1 (400%)
WASID[e22]	TIA and stroke patients with 50-99%intracranial stenosis	1300	280	63	1.8 years	504	9 (1.8)	Ischaemic stroke and MI	64 (12.7)	0.1:1 (900%)
SPIRIT[e23]	TIA and minor stroke	30	665	63	14 months	776	6 (0.8)	Non-fatal ischaemic stroke or non-fatal MI or non-haemorrhagic vascular death	27 (3.5)	0.2:1 (400%)

† not reported, 54.5% >65 years; ‡ not reported, 52.6% >65yrs; TIA=Transient ischaemic attack, MI=myocardial infarction, SCD=sudden cardiac death, PVD=Peripheral vascular disease.

†Defination of major bleed in the trials

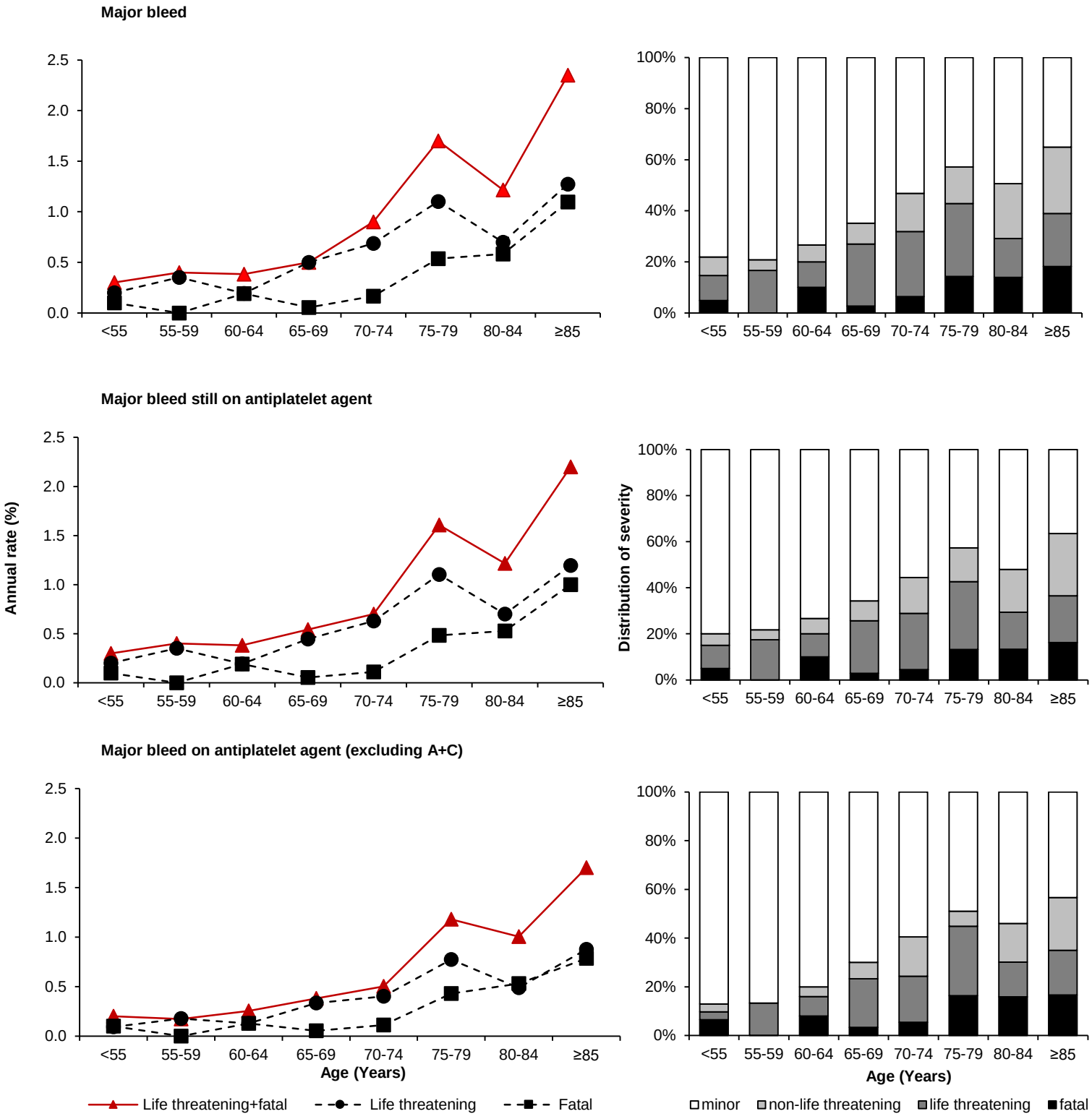
Trial names	Definition of major bleeding
AITIA (medical arm)	Collected from direct description of adverse events
UK TIA (low dose)	Intracranial haemorrhage; GI bleed that was fatal or was admitted to hospital
UK TIA (high dose)	Intracranial haemorrhage; GI bleed that was fatal or was admitted to hospital
Dutch TIA (low dose)	Fatal or if a hospital visit and treatment were necessary. Epistaxis, easy bruising and melena were regarded as minor if no treatment was required
Dutch TIA (high dose)	Fatal or if a hospital visit and treatment were necessary. Epistaxis, easy bruising and melena were regarded as minor if no treatment was required
SALT	Severe bleeding or causing discontinuation of study drug (gastrointestinal/intracranial/other)
Swedish co-op	Intracerebral haemorrhage and other severe haemorrhage
ESPS-2	Moderate (requiring specific treatment but no transfusion)/severe bleeding (requiring blood transfusion) of any site
ESPIRIT	All intracranial bleeding, any fatal bleeding or any bleeding requiring hospital admission
SPS-3	All intracranial bleeding, and extracranial haemorrhage that is serious or life-threatening requiring transfusion or surgery or resulting in permeant functional sequelae or death
CAPRIE	Any severe bleeding
WARSS	Intracranial, intraspinal, intracerebral, subarachnoid, subdural or epidural haemorrhage or any other bleeding event requiring transfusion
WASID	Intracranial haemorrhage or systemic haemorrhage requiring hospitalization, blood transfusion or surgery
SPIRIT	Intracranial bleeding, fatal bleeding and any bleeding requiring hospitalization irrespective of interventions

Web appendix 9. Annual rates of major bleeding in aspirin-controlled trials for secondary prevention of stroke vs. OXVASC (cerebrovascular cohort).



Web appendix 10. Annual rates of life-threatening and fatal bleeding stratified by age (left panels) and the distributions of bleeding of different severity by age (right panels). (A: aspirin, C: clopidogrel)

Annual rate derived as N/100 patient-years



Web appendix 11. Types of the antiplatelet agents patients were taking immediately prior to the bleeding events that required medical attention stratified by age.

	<75 years (n=179)	≥75 years (n=226)	Total
No antiplatelet	6 (3.4)	9 (4.0)	15 (3.7)
Aspirin	114 (63.7)	140 (61.9)	254 (62.7)
Clopidogrel	9 (5.0)	15 (6.6)	24 (5.9)
Dipyridamole	1 (0.6)	0 (0)	1 (0.2)
A+C	28 (15.6)	22 (9.7)	50 (12.3)
A+D	12 (6.7)	13 (5.8)	25 (6.2)
A+heparin	2 (1.1)	11 (4.9)	13 (3.2)
A+C+heparin	5 (2.8)	15 (6.6)	20 (4.9)
A+rt-PA	2 (1.1)	1 (0.4)	3 (0.7)

*A=Aspirin, C=Clopidogrel, D=Dipyridamole, rt-PA= Recombinant tissue plasminogen activator.

Web appendix 12. Risks of major bleeding in patients aged ≥75 years vs. patients aged <75 years stratified by site of bleeding.

	<75 years		≥75 years			
	Risk (per 1000 patient-years)	Cumulated 10-year risk (%)	Risk (per 1000 patient-years)	Cumulated 10-year risk (%)	**HR (95%CI)**	**p**
Major GI bleed	3.60	2.37	17.56	11.46	4.00 (2.62-6.12)	<0.0001
Major upper-GI	2.98	1.93	15.26	9.16	4.13 (2.60-6.57)	<0.0001
Major lower-GI	0.62	0.45	2.30	2.53	3.34 (1.15-9.76)	0.03
Intracranial bleed	2.08	1.28	5.64	3.13	2.21 (1.21-4.05)	0.01
Intracerebral	0.99	0.65	4.18	2.29	3.38 (1.48-7.70)	0.004
Subarachnoid	0.50	0.29	0.63	0.37	1.03 (0.23-4.63)	0.97
Subdural	0.62	0.36	1.05	0.53	1.33 (0.39-4.62)	0.65
Major other	1.37	0.77	3.76	2.21	2.10 (0.99-4.45)	0.06

*GI=gastrointestinal

Web appendix 13. Risks of major bleeding in patients aged ≥75 years vs. patients aged <75 years stratified by type of the index event.

	Ischaemic stroke/TIA cohort		Myocardial infarction cohort	
	HR (95%CI)	p	HR (95%CI)	p
Major bleeds	3.09 (2.06-4.62)	<0.0001	3.27 (1.99-5.37)	<0.0001
Upper-GI	5.43 (2.73-10.81)	<0.0001	3.48 (1.83-6.61)	0.0001
Intracranial bleed	2.06 (1.04-4.07)	0.04	2.20 (0.59-8.23)	0.24
Other	2.06 (0.94-4.52)	0.07	3.44 (1.27-9.32)	0.02

*GI=gastrointestinal

Web appendix 14. Reasons for new or worsening of disability attributable to the bleeding events.

Number (bleed severity: life threatening/non-life threatening major bleed)

	Intracranial bleed (n=11)	**Extracranial bleed** (n=50)
Followed by ischaemic stroke	0	4 (1/3)
Blindness	0	2 (1/1)
Cognitive decline	0	2 (0/2)
Reduced mobility	3 (3/0)	37 (17/20)
General decline	1 (1/0)	3 (0/3)
Symptomatic anaemia (e.g. short of breath)	0	6 (4/2)
New or worsening congestive cardiac failure/pulmonary oedema	0	15 (7/8)
Severe infection or acute renal failure	0	5 (3/2)
Worsening of other co-morbidities	2 (2/0)	8 (3/5)
Subsequent cancer diagnosis and under palliative care	0	4 (3/1)
Intracranial bleed associated neurological deficit	8 (8/0)	1 (0/1)

*CCF=congestive cardiac failure, ARF=acute renal failure

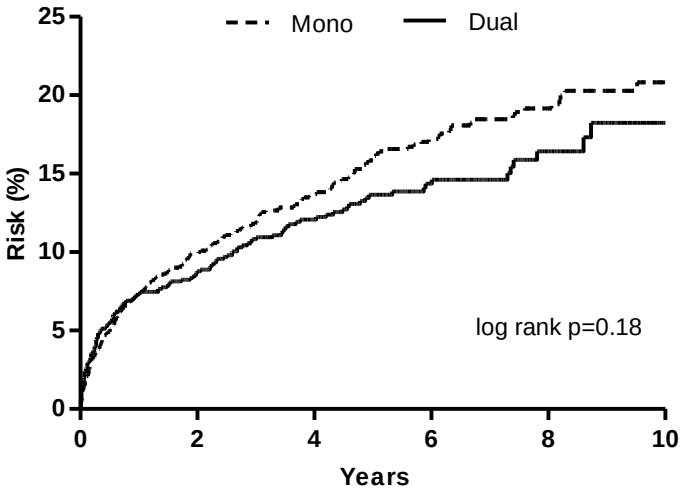
Web appendix 15. Reasons for death attributable to the bleeding events.

	Intracranial bleed (n=24)	**Extracranial bleed** (n=20)
Followed by ischaemic stroke	0	1
Reduced mobility	5	5
New or worsening chronic cardiac failure/pulmonary oedema	0	1
Severe infection or acute renal failure	2	3
Worsening of other co-morbidities	3	1
Subsequent cancer diagnosis and under palliative care	0	2
Herniation-massive intracranial bleed with midline shift and oedema	19	0
Bleeding associated hypovolemic/cardiac shock	0	12

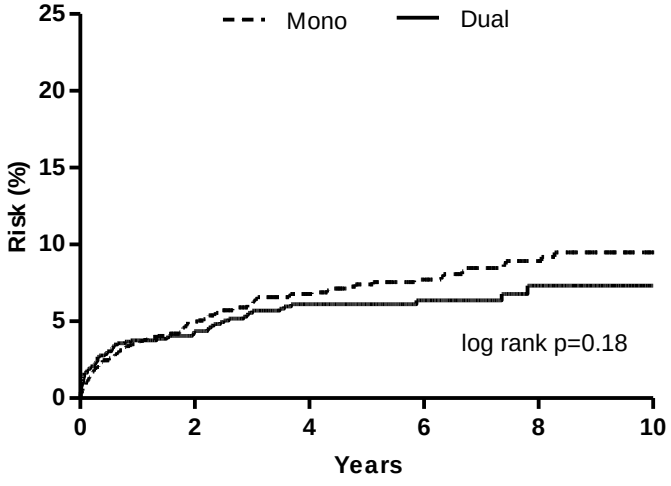
Web appendix 16. Long-term risks of bleeding requiring medical attention stratified by the number of the initial antiplatelet treatment.

(Mono: monotherapy, including also aspirin plus dipyridamole; Dual: dual therapy with aspirin and clopidogrel)

A. Any bleed

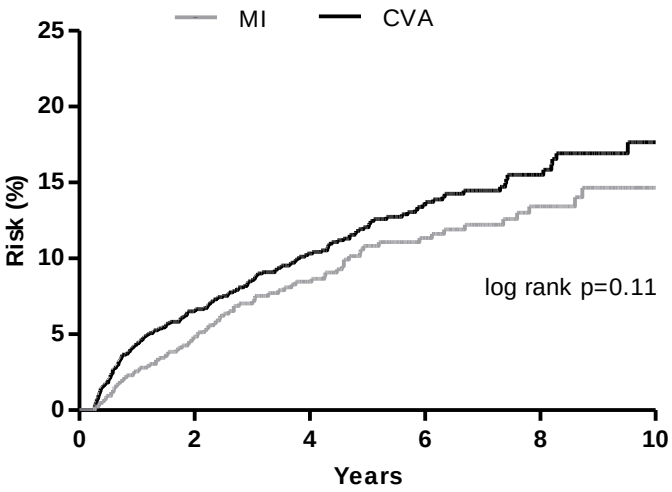


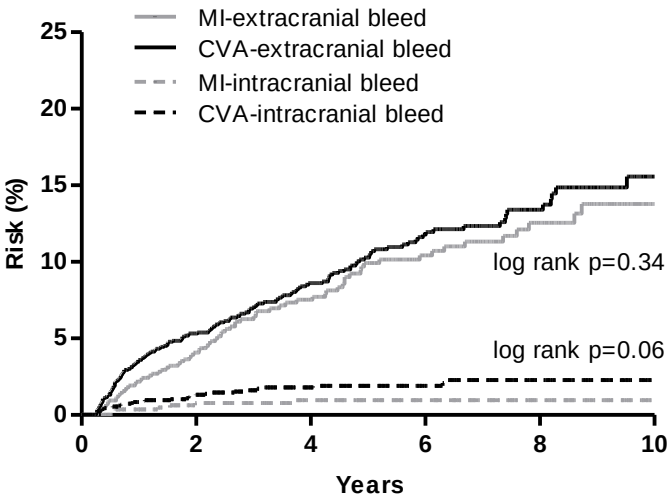
B. Major bleed



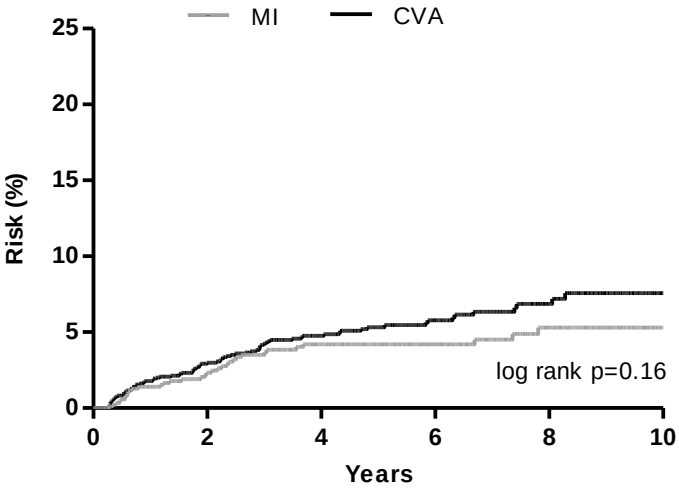
Web appendix 17. Sensitivy analyses of the long-term risks of bleeding events requiring medical attention stratified by severity, site of bleeding and the index event type excluding the first 90 days.
(MI: myocardial infarction, CVA: cerebrovascular disease)

A. Any bleed

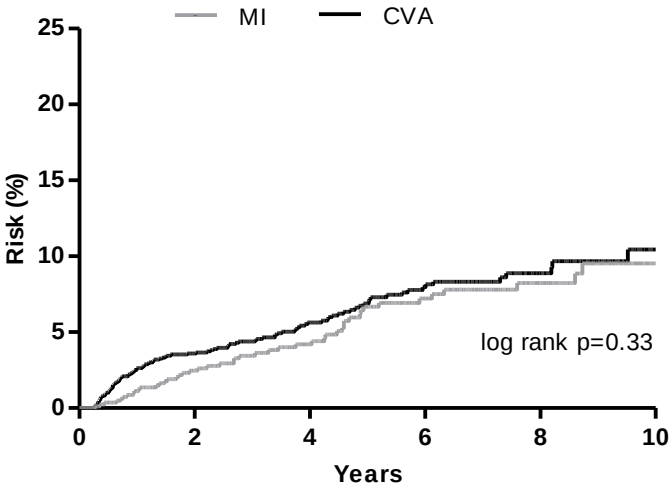




B. Any major bleed

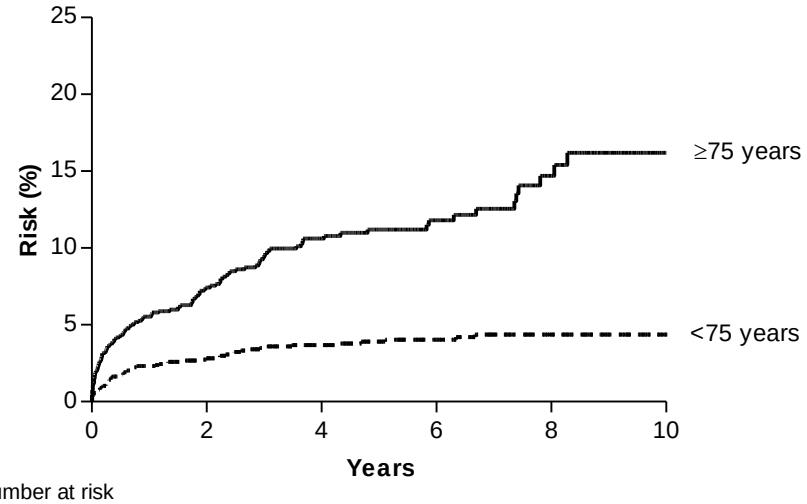


C. Any significant non-major bleed



Web appendix 18. Time-course of risks of major bleeding events in patients ≥75 years versus patients <75 years.

HR=hazard ratio, CI=confidence interval;



Number at risk

<75 years	1584	1243	930	638	371	118
≥75 years	1582	844	504	274	125	31

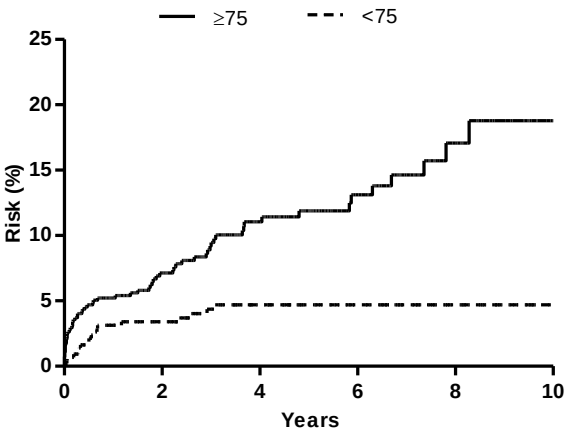
	Year 1	**Year 1-4**	**Year 4-10**
	Event/patient years	Event/patient years	Event/patient years
<75 years	35/1,465	17/3,488	5/3,097
≥75 years	74/1,186	43/2,285	13/1,313
HR (95%CI)	2.45 (1.64-3.67)	3.80 (2.17-6.68)	6.11 (2.17-17.18)

Web appendix 19. Age-specific time-course of major bleeding stratified by premorbid antiplatelet drug use at baseline (A) and in patients who had been stable on antiplatelet treatment for one year (B).

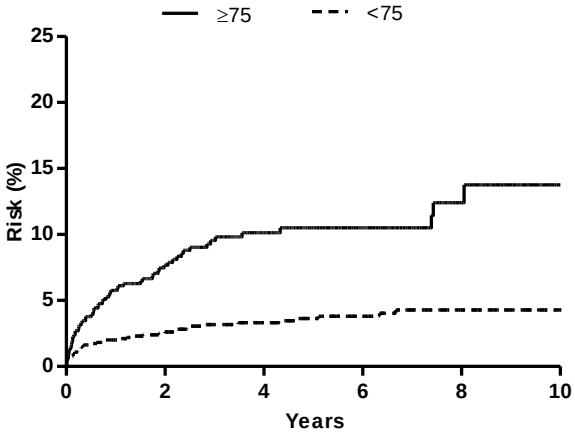
Panel A shows the age-specific time-couse of major bleeding in patients on premorbid antiplatelet drug (A1) and in those not on premorbid antiplatelet drug (A2). Panel B shows the age-specific time-course of major bleeding in patients who had been on antiplatelet treatment for one year after acute TIA, ischaemic stroke or myocardial infarction (i.e. excluding patients who had major bleeding events or had died before one year). Age is classified as the age of the patient at one year.

A. All patients at baseline

A1. On premorbid antiplatelet drug

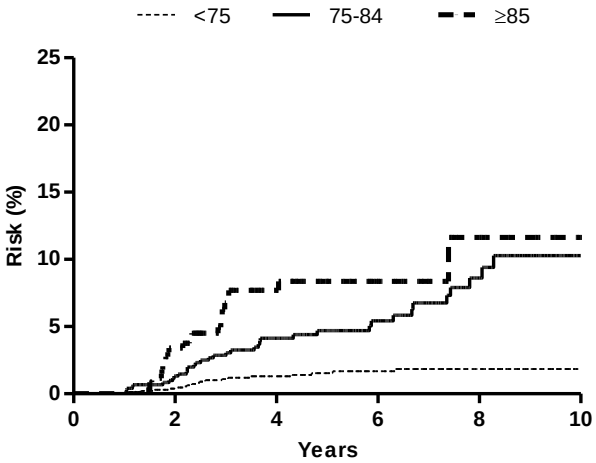


A2. Not on premorbid antiplatelet drug

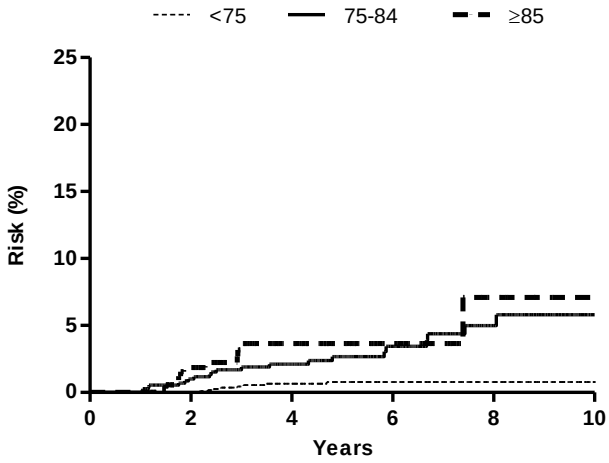


B. Excluding patients who had had a major bleed on antiplatelet treatment during the first year of follow-up

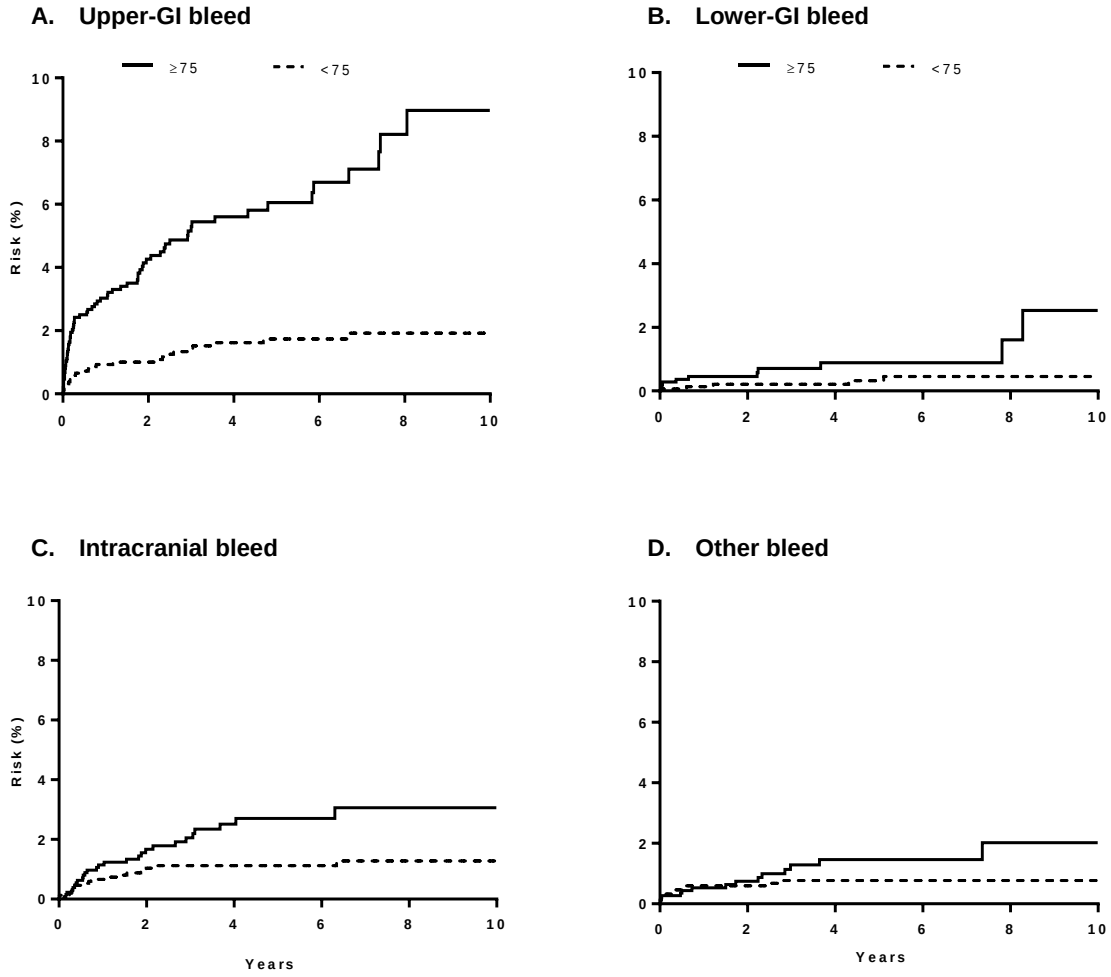
B1. Major bleed



B2. Major upper GI bleed



Web appendix 20. Time-course of major bleeding in patients aged ≥ 75 years vs. patients aged <75 years stratified by site of bleeding. (GI=gastrointestinal)



Web appendix 21. Cumulative 5-year risk of major bleeds and major upper-GI bleeds in OXVASC stratified by the REACH bleeding risk score and by age.

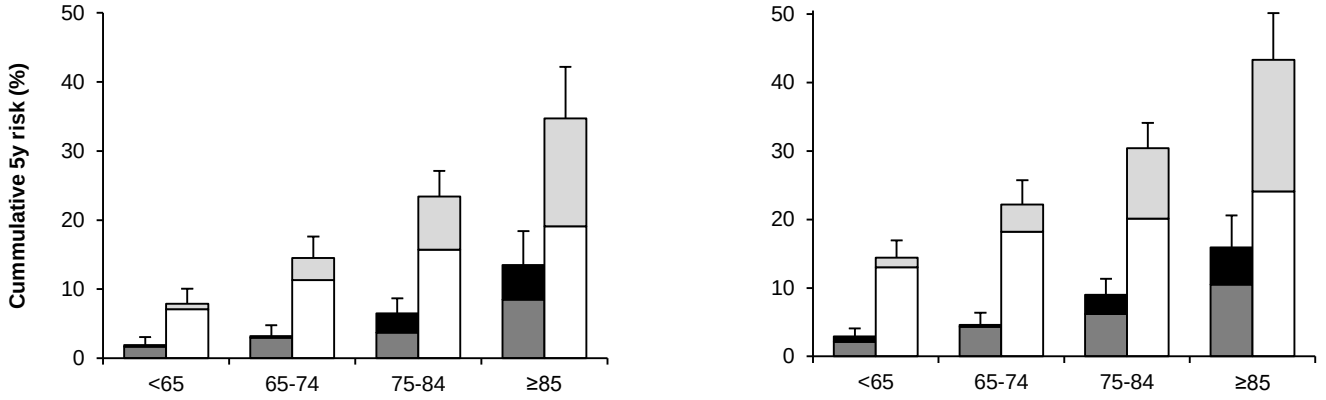
REACH score	N	Major bleeds	Major upper-GI bleeds
		Event (%)	Event (%)
<75 years			
0-6	823	18 (2.6)	6 (0.9)
7-8	482	19 (4.5)	9 (2.3)
≥9	279	17 (7.1)	8 (3.4)
≥75 years			
0-6	0	-	-
7-8	269	18 (9.0)	11 (5.7)
9-10	678	49 (10.1)	27 (5.7)
>10	638	53 (14.0)	29 (7.1)

Web appendix 22. Observed 5-year risks of major bleeding versus recurrent ischaemic events stratified by age and by the REACH bleeding risk score.
(Patients with history of atrial fibrillation on antiplatelet treatment excluded; data presented with 95%CI)

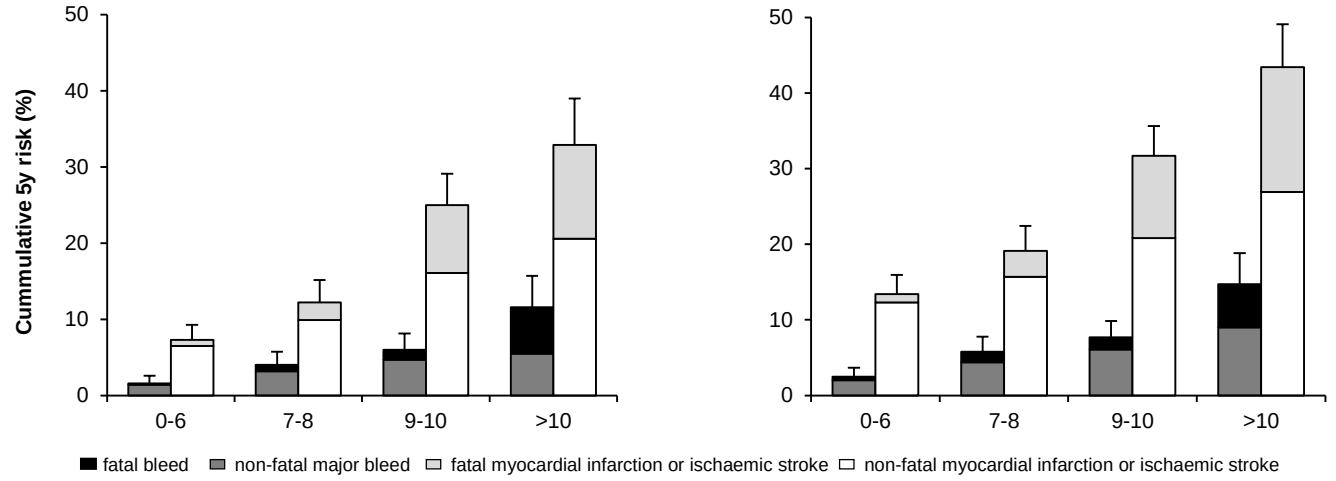
Excluding recurrent ischaemic or bleeding events within 90 days post index events

All events included

Age

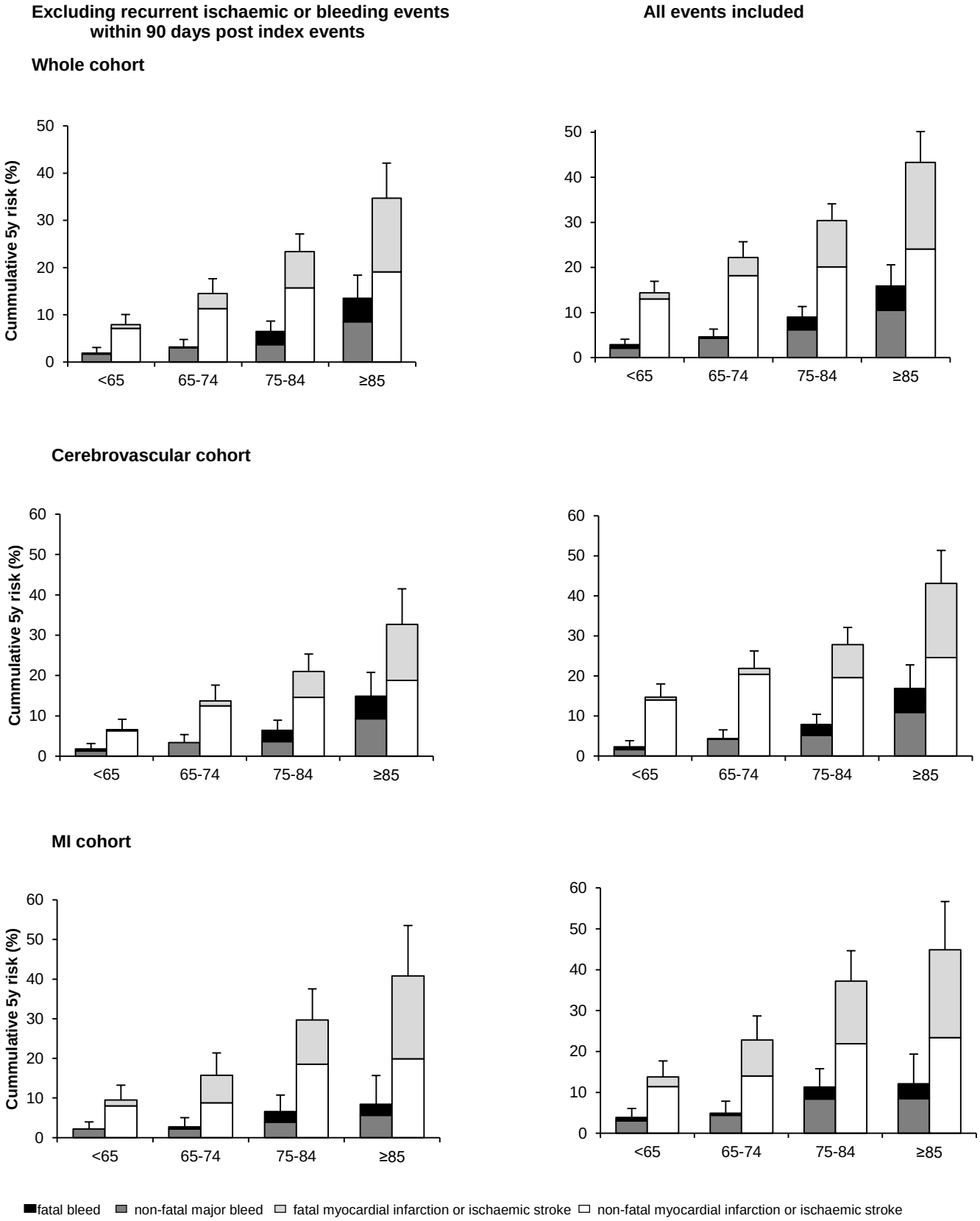


REACH score



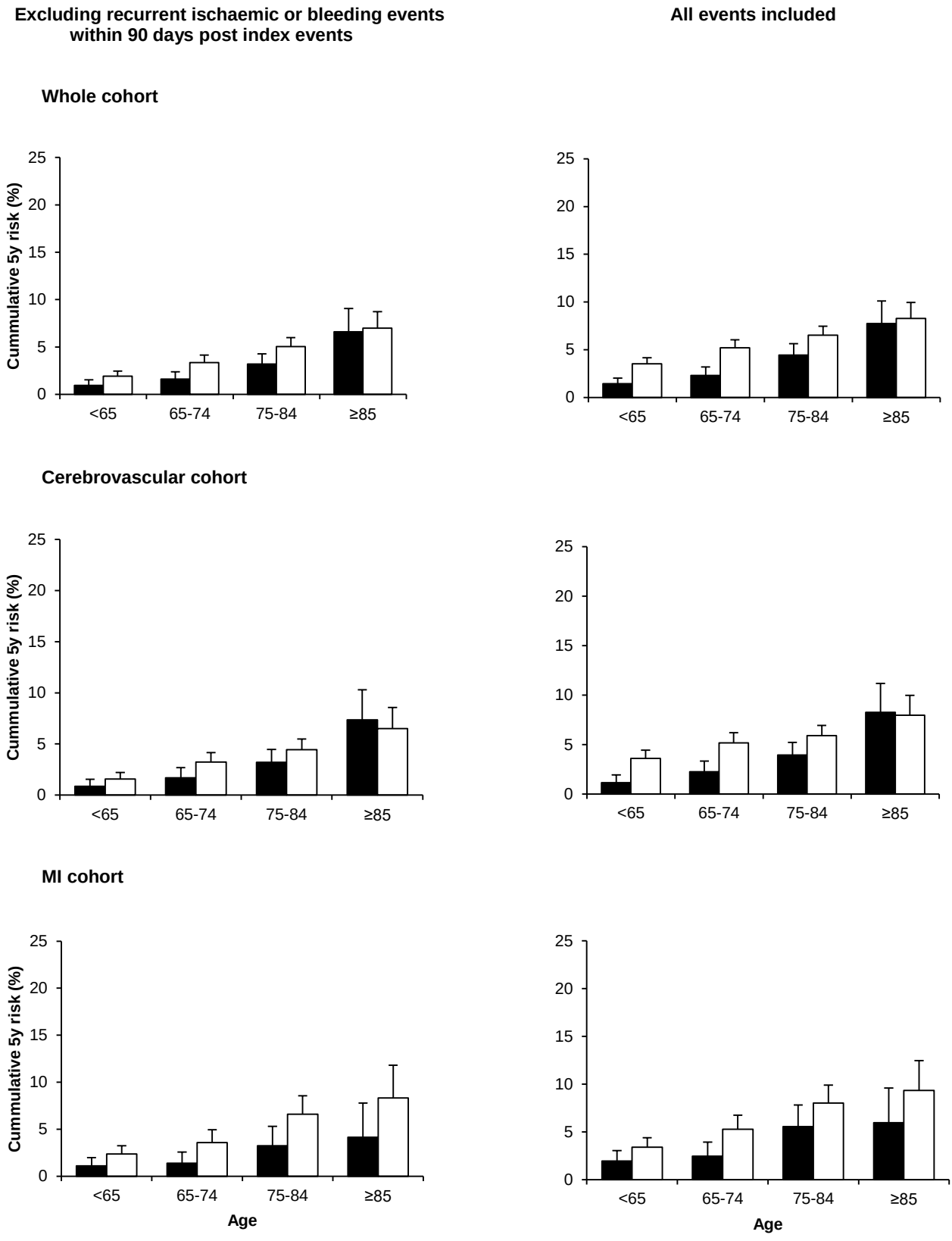
Web appendix 23. Observed age-specific 5-year risks of major bleeding vs. ischaemic events in OXVASC stratified by the type of the index event.

(Patients with history of atrial fibrillation on antiplatelet treatment excluded;MI=myocardial infarction;data presented with 95%CI)

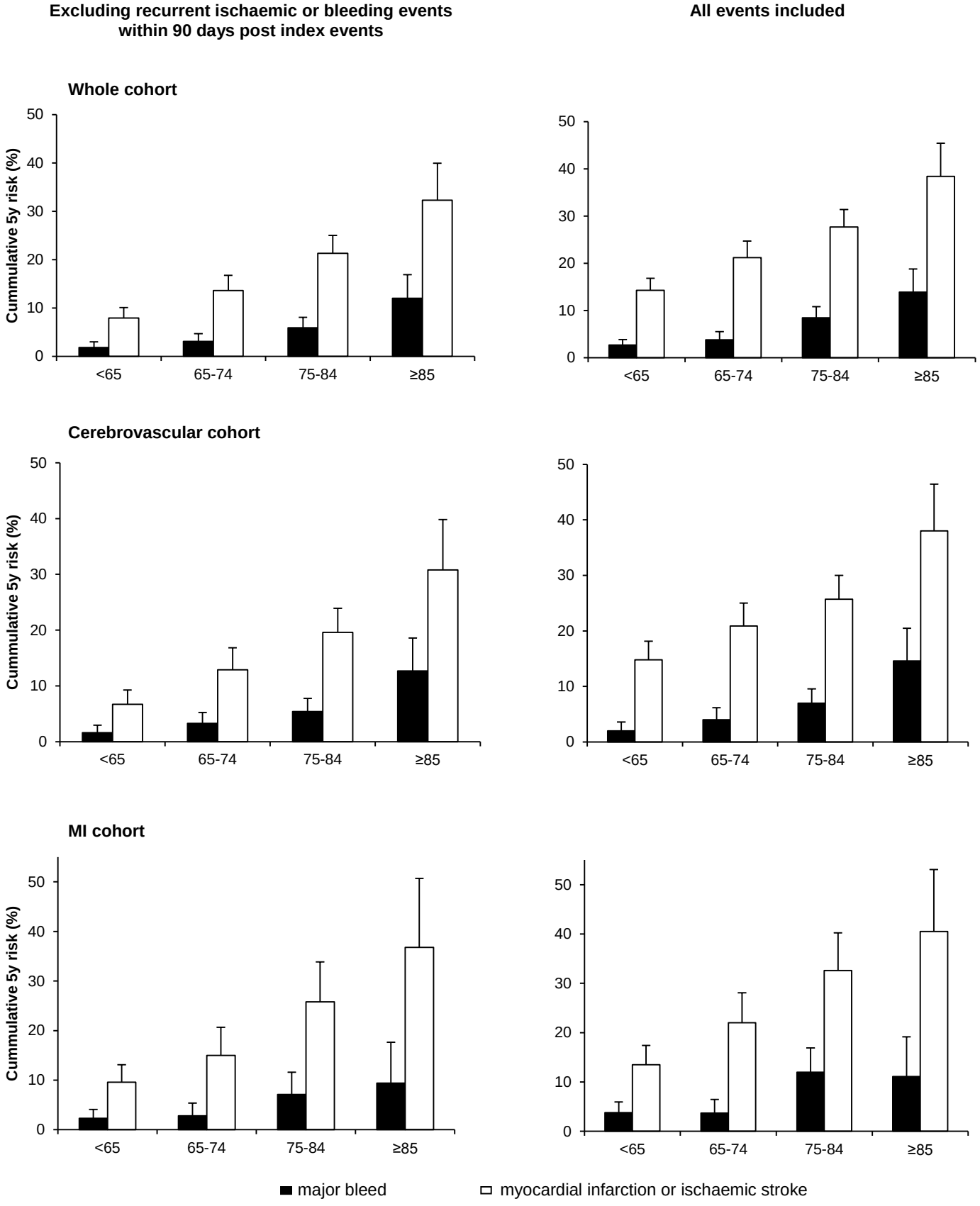


Web appendix 24. Estimated 5-year risk of major bleeding attributable to antiplatelet treatment vs. ischaemic events prevented by antiplatelet treatment stratified by age.

(Patients with history of atrial fibrillation on antiplatelet treatment excluded;MI=myocardial infarction;data presented with 95%CI)

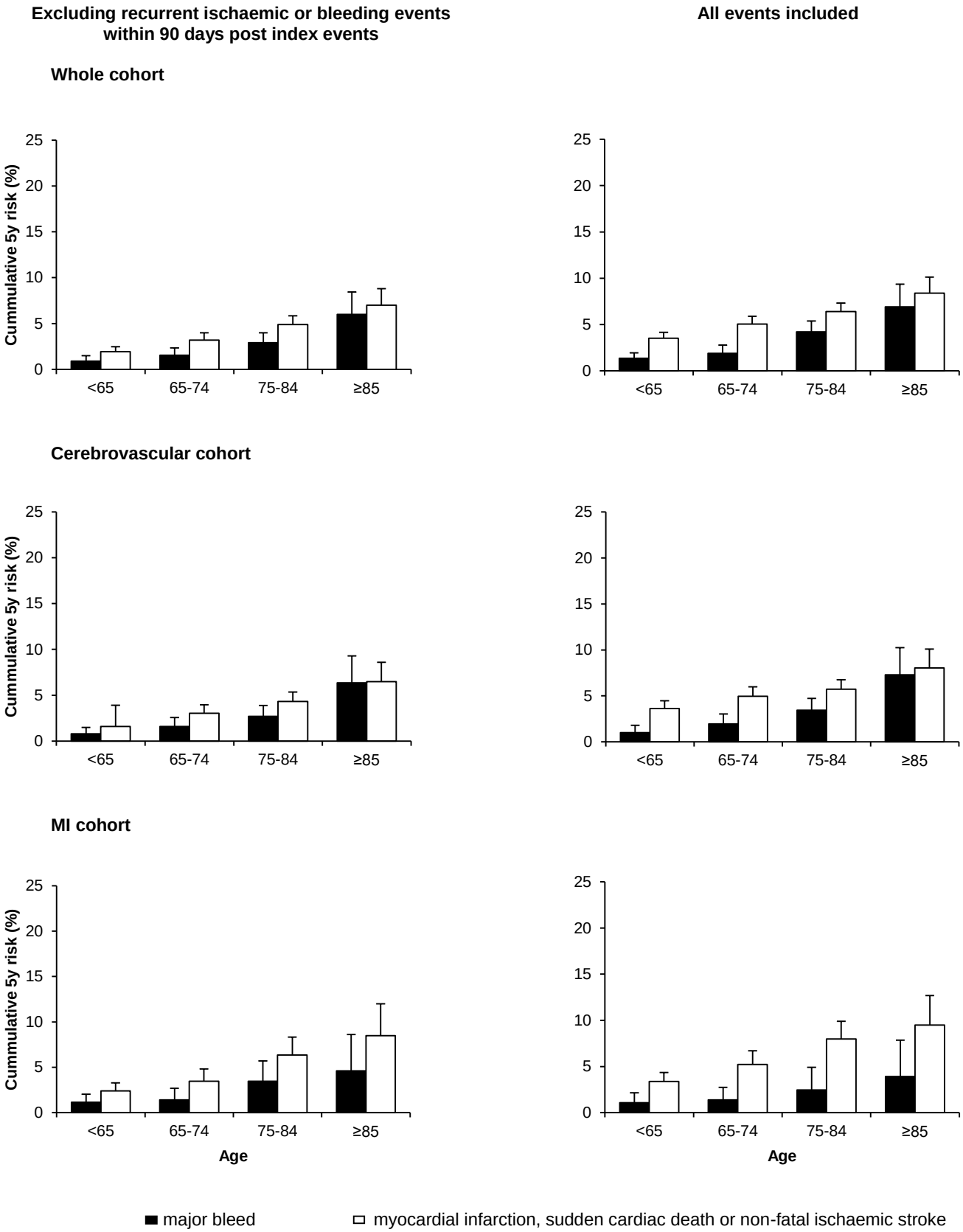


Web appendix 25. Sensitivity analyses censoring at a composite outcome of major bleeding events or recurrent ischaemic events for the observed age-specific 5-year risks of major bleeding vs. ischaemic events. (Patients with history of atrial fibrillation on antiplatelet treatment excluded;MI=myocardial infarction;data presented with 95%CI)



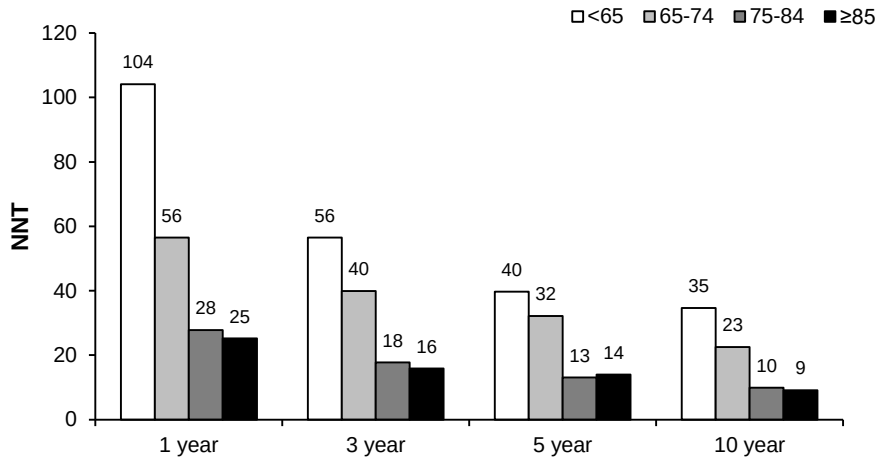
Web appendix 26. Sensitivity analyses censoring at a composite outcome of bleeding events or recurrent ischaemic events for the estimated age-specific 5-year risk of major bleeding attributable to antiplatelet treatment vs. ischaemic events prevented by antiplatelet treatment.

(Patients with history of atrial fibrillation on antiplatelet treatment excluded;MI=myocardial infarction; data presented with 95%CI)

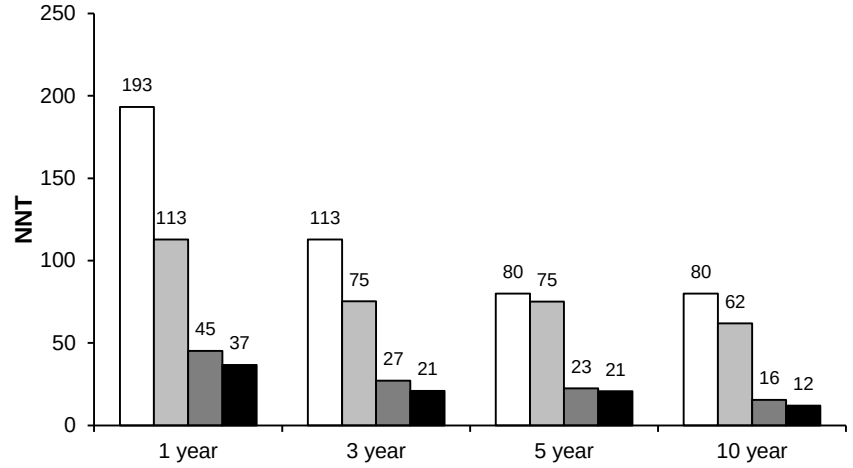


Web appendix 27. Estimated age-specific numbers-needed-to-treat (NNT) to prevent one upper-GI bleed based on different lengths of follow-up in patients on antiplatelet treatment for secondary prevention of vascular events. (Based on the cumulative risks from the Kaplan-Meier curve, using the reported relative risk reduction of 0.26 from a recent systematic review and assuming the efficacy of PPI was similar at different ages and remained consistent with time)

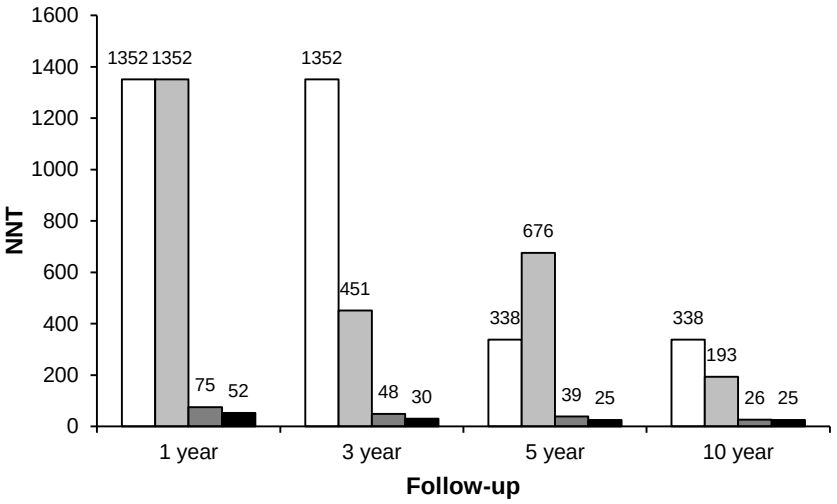
A. Any bleed



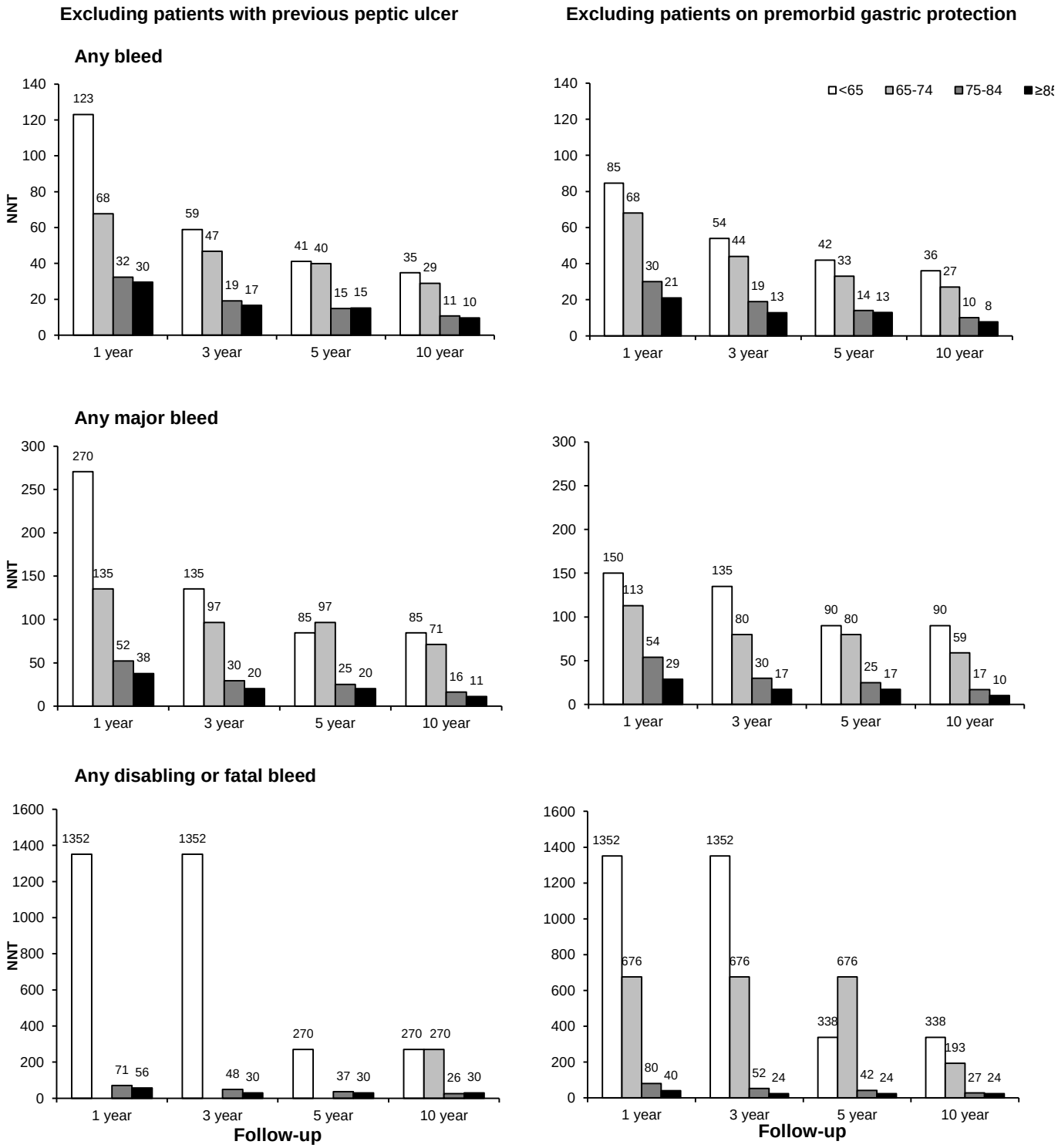
B. Any major bleed



C. Any disabling or fatal bleed



Web appendix 28. Sensitivity analyses of the estimated age-specific numbers-needed-to-treat (NNT) to prevent one upper-GI bleed based on different lengths of follow-up in patients on antiplatelet treatment for secondary prevention of vascular events excluding patients with previous peptic ulcer or excluding patients on premorbid gastric protection agents. (Based on the cumulative risks from the Kaplan-Meier curve, using the reported relative risk reduction of 0.26 from a recent systematic review and assuming the efficacy of PPI was similar at different ages and remained consistent with time)



Web appendix 29. References for PPI trials in the prevention of antiplatelet-associated upper-GI complications.

e1. Lai KC, Lam SK, Chu KM, et al. Lansoprazole for the prevention of recurrences of ulcer complications from long-term low-dose aspirin use. New Engl J Med 2002; 346: 2033-8.

e2. Fujita T, Kutsumi H, Sanuki T, Hayakumo T, Azuma T. Adherence to the preventive strategies for nonsteroidal anti-inflammatory drug- or low-dose aspirin-induced gastrointestinal injuries. J Gastroenterol 2013; 48: 559-73.

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e4. Hsu PI, Lai KH, Liu CP. Esomeprazole with clopidogrel reduces peptic ulcer recurrence, compared with clopidogrel alone, in patients with atherosclerosis. Gastroenterology 2011; 140: 791-8.

e5. Yeomans N, Lanas A, Labenz J, et al. Efficacy of esomeprazole (20 mg once daily) for reducing the risk of gastroduodenal ulcers associated with continuous use of low-dose aspirin. Am J Gastroenterol 2008; 103: 2465-73.

e6. Bhatt DL, Cryer BL, Contant CF, et al. Clopidogrel with or without omeprazole in coronary artery disease. New Engl J Med 2010; 363: 1909-17.

e7. Ng FH, Wong SY, Lam KF, et al. Famotidine is inferior to pantoprazole in preventing recurrence of aspirin-related peptic ulcers or erosions. Gastroenterology 2010; 138: 82-8.

e8. Sugano K, Matsumoto Y, Itabashi T, et al. Lansoprazole for secondary prevention of gastric or duodenal ulcers associated with long-term low-dose aspirin therapy: results of a prospective, multicenter, double-blind, randomized, double-dummy, active-controlled trial. J Gastroenterol 2011; 46: 724-35.

e9. Sanuki T, Fujita T, Kutsumi H, et al. Rabeprazole reduces the recurrence risk of peptic ulcers associated with low-dose aspirin in patients with cardiovascular or cerebrovascular disease: a prospective randomized active-controlled trial. J Gastroenterol 2012; 47: 1186-97.

e10. Chan FK, Chung SC, Suen BY, et al. Preventing recurrent upper gastrointestinal bleeding in patients with Helicobacter pylori infection who are taking low-dose aspirin or naproxen. New Engl J Med 2001; 344: 967-73.

e11. Ng FH, Tunggal P, Chu WM, et al. Esomeprazole compared with famotidine in the prevention of upper gastrointestinal bleeding in patients with acute coronary syndrome or myocardial infarction. Am J Gastroenterol 2012; 107: 389-96.

Web appendix 30. References for aspirin-controlled secondary prevention trials.

e12. Fields WS, Lemak NA, Frankowski RF, Hardy RJ. Controlled Trial of Aspirin in Cerebral Ischemia. Stroke 1977;8:301-16.

e13. Farrell B, Godwin J, Richards S, Warlow C. The United-Kingdom Transient Ischemic Attack (Uk-Tia) Aspirin Trial - Final Results. J Neurol Neurosur Ps 1991;54:1044-54.

e14. Vangijn J, Algra A, Kappelle J, Koudstaal PJ, Vanlatum LJ, Grp DTTS. A Comparison of 2 Doses of Aspirin (30 Mg Vs 283 Mg a Day) in Patients after a Transient Ischemic Attack or Minor Ischemic Stroke. New Engl J Med 1991;325:1261-6.

e15. Norrving B, Elwin CE, Peterson B, et al. Swedish Aspirin Low-Dose Trial (Salt) of 75 Mg Aspirin as Secondary Prophylaxis after Cerebrovascular Ischemic Events. Lancet 1991;338:1345-9.

e16. Britton M, Helmers C, Samuelsson K. High-Dose Acetylsalicylic-Acid after Cerebral Infarction. Stroke 1987;18:325-34.

e17. Diener HC, Cunha L, Forbes C, Sivenius J, Smets P, Lowenthal A. European stroke prevention study .2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. J Neurol Sci 1996;143:1-13.

e18. Group ES, Halkes PH, van Gijn J, Kappelle LJ, Koudstaal PJ, Algra A. Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial. Lancet 2006;367:1665-73.

e19. Benavente OR, Hart RG, McClure LA, et al. Effects of Clopidogrel Added to Aspirin in Patients with Recent Lacunar Stroke. New Engl J Med 2012;367:817-25.

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Web appendix Methods - OXVASC methodology

Study population

The Oxford Vascular Study (OXVASC) is a prospective, population-based cohort study of all incident acute vascular events in all territories (transient ischaemic attack, stroke, acute coronary and peripheral vascular events).

The study population consisted of all 92,728 individuals, irrespective of age, registered with 100 general practitioners (GPs) in nine general practices in Oxfordshire, UK. In the UK, general practices provide primary health care for registered individuals and hold a lifelong record of all medical consultations (from the National Health Service [NHS] and private health care), and details of treatments, blood pressure, and investigations. In Oxfordshire, an estimated 97% of the true residential population is registered with a general practice, with most non-registered individuals being young adults. All participating practices held accurate age-sex patient registers, and allowed regular searches of their computerised diagnostic coding systems. The practices had all collaborated on a previous population-based study, for which they were originally selected to be representative of the urban and rural mix and the deprivation range of Oxfordshire as a whole.[1] Based on the index of multiple deprivation (IMD), the population was less deprived than the rest of England, but had a broad range of deprivation.

The OXVASC population is 94% white people, 3% Asian, 2% Chinese, and 1% Afro-Caribbean.[2] The proportion of whites is similar to that of the UK as a whole (88% white) and to many other western countries ((Australia - 90%; France - 91%; Germany - 93.9%).

Case ascertainment

After a 3-month pilot study, the study started on April 1, 2002, and is ongoing. Ascertainment combined prospective daily searches for acute events (hot pursuit) and retrospective searches of hospital-care and primary-care administrative and diagnostic coding data (cold pursuit).

Hot pursuit was based on:

1) A daily (weekdays only), urgent open-access “TIA clinic” to which participating general practitioners (GPs) and the local accident and emergency department (A&E) send all individuals with suspected TIA or stroke whom they would not normally admit to hospital, with alternative on-call review provision at weekends. Patients too frail to attend are assessed at their residence by a study nurse or doctor.
2) Daily searches and case note review of admissions to the Emergency Assessment Unit, Medical Short Stay Unit, Coronary Care Unit and Cardiothoracic Critical Care Unit, Cardiology, Cardiothoracic, and Vascular Surgery wards, Acute Stroke Unit, Neurology ward and all other general wards when indicated.
3) Daily searches of the local A&E and eye hospital attendance registers.
4) Daily identification via the Bereavement Office of patients dead on arrival at hospital or who died soon after.
5) Daily searches of lists of all patients from the study population in whom a troponin-I level had been requested.
6) Daily assessment of all patients undergoing diagnostic coronary, carotid and peripheral angiography, angioplasty, stenting or vascular surgical procedures in any territory to identify both total burden of vascular invention and any potential missed prior acute events.

Cold pursuit procedures were:

1) Frequent visits to the study practices and monthly searches of practice diagnostic codes.
2) Monthly practice-specific list of all patients admitted to all acute and community NHS hospitals.
3) Monthly listings of all referrals for brain or carotid imaging studies performed in local hospitals.
4) Monthly reviews of all death certificates and coroners reports to review out-of-hospital deaths.
5) Practice-specific listings of all ICD-10 death codes from the local Department of Public Health.

Patients found on GP practice searches who have an event whilst temporarily out of Oxfordshire are included, but visitors who were not registered with one of the study practices are excluded. A study clinician assessed patients as soon as possible after the event in the hospital or at home. Informed consent was sought, if possible, or assent was obtained from a relative.

Data is collected using event-specific forms, for TIA and stroke, acute coronary syndrome or acute peripheral vascular events. Standardised clinical history and cardiovascular examination are recorded. Information recorded from the patient, their hospital records and their general practice records includes details of the clinical event,

medication, past medical history, all investigations relevant to their admission (including blood results, electrocardiography, brain imaging and vascular imaging-duplex ultrasonography, CT-angiography, MR-angiography or DSA) and all interventions occurring subsequent to the event.

If a patient died before assessment, we obtained an eyewitness account of the clinical event and reviewed any relevant records. If death occurred outside the hospital or before investigation, the autopsy result was reviewed. Clinical details are sought from primary care physicians or other clinicians on all deaths of possible vascular aetiology.

All surviving patients are followed-up face-to-face at 1, 6, 12, 60 and 120 months after the initial event by a research nurse or physician and all recurrent vascular events were recorded together with the relevant clinical details and investigations. If face-to-face follow up is not possible, telephone follow-up is performed or enabled via the general practitioner. All recurrent vascular events that presented to medical attention would also be identified acutely by ongoing daily case ascertainment within OXVASC. If a recurrent vascular event was suspected at a follow-up visit or referred by the GPs to clinic or admitted, the patient was re-assessed and investigated by a study physician.

Definition of diagnosis

Although new definitions for stroke and TIA have been suggested recently,[2,3] in order to enable comparison with previous studies, the classic definitions of TIA and stroke are used throughout.[4] A stroke is defined as rapidly developing clinical symptoms and/or signs of focal, and at time global (applied to patients in deep coma and to those with subarachnoid haemorrhage), loss of brain function, with symptoms lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin.[4] A TIA is an acute loss of focal brain or monocular function with symptoms lasting less than 24 hours and which is thought to be caused by inadequate cerebral or ocular blood supply as a result of arterial thrombosis, low flow or embolism associated with arterial, cardiac or haematological disease.[4] All diagnoses were reviewed by a senior neurologist (PMR). With the high rate (97%) of imaging or autopsy in OXVASC, strokes of unknown type were coded as ischaemic.

Acute coronary events are defined using published criteria[5] based on available history, electrocardiography (ECG) findings, cardiac biomarkers (mainly troponin I), and autopsy or death certificate. Non-ST elevation (NSTEMI) and ST-elevation myocardial infarction (STEMI) are defined using standard criteria.[6] Sudden cardiac deaths are coded according to recent recommendations for epidemiological studies,[5] and required a definite history of preceding symptoms consistent with acute coronary ischaemia, or post-mortem evidence of either significant coronary atherosclerosis or acute thrombosis, or a documented myocardial infarction during the previous 28 days.[5] Sudden deaths were coded as probable cardiac deaths in the absence of the above characteristics if the person had a past history of ischaemic heart disease.

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Web appendix Methods – Additional details of statistical analyses

Risk factors included in the analyses to determine predictors of major bleeding and major upper-GI bleeding

Age, sex, body weight, history of vascular disease, known hypertension, diabetes, hyperlipidaemia, smoking, alcohol use, baseline anaemia, history of cancer, chronic liver disease, renal failure, atrial fibrillation, chronic heart failure, history of peptic ulcer, premorbid antiplatelet use, premorbid use of gastric protection and dual antiplatelet therapy post event.

Calculation age-specific antiplatelet treatment attributable risks and benefit

To compare the long-term risk of major bleeding likely to be attributable to antiplatelet treatment with the estimated benefit in terms of ischaemic events likely to have been prevented, we used estimates of relative risk derived from previous meta-analyses of trials of aspirin use versus control in secondary prevention of vascular events:[1] i.e. a 20% relative reduction in ischaemic events and a doubling in major bleeds. Aspirin-preventable vascular events included myocardial infarction, sudden cardiac death and non-fatal ischaemic stroke. This analysis was stratified by age, assuming the relative effects of aspirin were independent of age.

Sensitivity analyses

1. Age-specific bleeding risks

Primary analyses included all bleeding events irrespective of antiplatelet medication change during follow-up. However, sensitivity analyses were also performed for bleeding risk censoring patients when antiplatelet medication was stopped, and with exclusion of bleeds that occurred during periods of dual treatment with aspirin plus clopidogrel.

2. Comparing the long-term risks of major bleeding and risks of recurrent ischaemic events

Primary analyses included all events during follow-up. However sensitivity analyses were also performed excluding bleeding and ischaemic events <90 days after the index event or censoring at the time of either a first major bleed or a first ischaemic event.

3. Estimated NNT for PPI use

Primary analyses included all patients. However, sensitivity analyses were also performed for NNTs for PPI use in patients without history of peptic ulcer and for patients not premorbidly on any gastric protection agents.

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Web appendix Methods - Criteria and risk scores used in the study

CURE criteria

Major bleeding

- Life-threatening (fatal, intracranial, requiring surgical intervention, results in substantial hypotension requiring the use of intravenous inotropic agents)
  - ✓ Hemoglobin decrease ≥5 g/dL or required ≥4 U of blood
- Other major bleeding
  - ✓ Transfusion of 2–3 U, intraocular

Non-major bleeding

- Led to discontinuation of study drug

Reference

Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001; 345: 494-502.

ABCD^2 score for risk stratification of transient ischaemic attack (TIA)

Factor	Points
Age≥60	1
Blood pressure≥140/90mmHg	1
Clinical features	
Unilateral weakness	2
Speech disturbance without weakness	1
Other symptoms	0
Duration of symptoms	
<10min	0
10-59min	1
≥60min	2
History of diabetes	1

Reference

Johnston SC, Rothwell PM, Nguyen-Huynh MN, et al. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. Lancet 2007; 369: 283–92.

Reduction of Atherothrombosis for Continued Health (REACH) registry score

Factor	Points			
Age/years	45-54	55-64	65-74	75+
	0	2	4	6
Peripheral arterial disease	No	Yes		
	0	1		
Congestive heart failure	No	Yes		
	0	2		
Diabetes	No	Yes		
	0	1		
Hypercholesterolaemia	No	Yes		
	1	0		
Hypertension	No	Yes		
	0	2		
Smoking	Never	Former	Current	
	0	1	2	
Antiplatelet agents	None	Aspirin	Other	Both
	0	1	2	4
Oral anticoagulants	No	Yes		
	0	4		

Reference

Ducrocq G, Wallace JS, Baron G, et al. Risk score to predict serious bleeding in stable outpatients with or at risk of atherothrombosis. Eur Heart J 2010; 31: 1257-65.

Web appendix Additional discussion of PPI related harms

We did not attempt to estimate the number-needed-to-harm in relation to potential adverse effects of long-term PPI use. In the absence of large randomised trials of long-term treatment, reliable estimation of any hazard is difficult. Although the clinical significance of the pharmacodynamics interaction of some PPIs and clopidogrel is unclear,[1] there is some evidence of a short-term risk of respiratory infection (approx. 2 per 1000-person-years),[1] but there is uncertainty about a causal link with PPI use,[2] and there is no evidence of any increase in relative hazard with age.[3] However, PPI use does reduce magnesium levels, which requires screening at baseline and during follow-up,[4] and might be more problematic in patients on diuretics. Other rare adverse effects include an increased risk of C. Difficile infection.[1]

For patients aged less than 75 years, given the relatively high NNT, and current concern about complications of long-term PPI use, the benefit of routine co-prescription is less clear. It is also unclear whether a PPI should be started when patients who have been well on long-term antiplatelet treatment reach age 75 years. Consistent with our previous findings,[5] we showed that the overall bleeding risk on antiplatelet treatment at younger ages seemed to decrease over long-term follow-up, either because high-risk patients stop treatment, go on to PPI, or possibly due to adaption to local effects in the stomach with chronic use.[6] However, in our study, 87% patients were still on antiplatelet treatment after 5 years and only about one third were on a PPI or H2-AR.

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