

Stroke and Recurrent Haemorrhage Associated with Antithrombotic Treatment Following Gastrointestinal Bleeding in Patients with Atrial Fibrillation: A Nationwide Cohort Study

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Supplemental Table 1: Diagnoses, invasive and surgical procedures, and pharmacotherapy used for defining the population, concomitant medical treatment, comorbidity, and outcomes.

Population		
Non-valvular atrial fibrillation	<i>Defined from diagnosis of atrial fibrillation with the absence of diagnosis codes of valvular atrial fibrillation and mitral- or aortic valve surgery.</i>	Presence of: ICD8: 42793, 42794. ICD10: I48. Absence of: ICD8: 4240, 4241, 394-396. ICD10: I05, I06, I34, I35. NCSP: KFK, KFM.
Gastrointestinal bleeding	<i>Defined from diagnosis of ulcer and duodenal bleeding.</i>	ICD10: K250, K252, K256, K260, K262, K266, K270, K272, K276, K280, K282, K286, K290, K298A.
Apixaban	<i>Defined from ATC-code.</i>	ATC-code: B01AF02.
Rivaroxaban	<i>Defined from ATC-code.</i>	ATC-code: B01AF01.
Dabigatran	<i>Defined from ATC-code.</i>	ATC-code: B01AE07.
Vitamin K antagonist	<i>Defined from ATC-code.</i>	ATC-code: B01AA03, B01AA04.
Aspirin (acetylsalicylic acid)	<i>Defined from ATC-code.</i>	ATC-code: B01AC06, N02BA1.
ADP receptor inhibitors	<i>Defined from ATC-code.</i>	ATC-code: B01AC04, B01AC22, B01AC24
Hip or knee replacement surgery	<i>Defined from surgical procedure performed.</i>	NCSP: KNFB, KNFC, KNGB, KNGC.
Deep venous thrombosis	<i>Defined from diagnosis.</i>	ICD10: I801-I803, I809, I821-I823, I828, I829.
Pulmonary embolism	<i>Defined from diagnosis.</i>	ICD10: I26.
Concomitant medical treatment		
Dipyridamole (persantin)	<i>Defined from ATC-codes.</i>	ATC-code: B01AA
Nonsteroidal anti-inflammatory drugs	<i>Defined from ATC-codes.</i>	ATC-code: M01A, M01AX05.
Heparin	<i>Defined from ATC-codes.</i>	ATC-code: B01AB.
Proton pump inhibitors	<i>Defined from ATC-codes.</i>	ATC-code: A02BC.
H ₂ -receptor antagonist	<i>Defined from ATC-codes.</i>	ATC-code: A02BA.
Acetylsalicylic acid (aspirin)	<i>Defined from ATC-codes.</i>	ATC-code: B01AC06, N02BA01.
ADP receptor inhibitor	<i>Defined from ATC-codes.</i>	ATC-code: B01AC04, B01AC22, B01AC24.
Comorbidities		
Thromboembolism	<i>Defined from diagnosis of ischemic stroke, transient ischemic attack, or peripheral artery embolism.</i>	ICD10: I63, I64, I74, G458, G459.
Myocardial infarction	<i>Defined from diagnosis.</i>	ICD10: I21, I22.
Ischemic heart disease	<i>Defined from diagnosis.</i>	ICD10: I20-I25.
Vascular disease	<i>Defined from diagnosis of myocardial infarct and arteriosclerosis.</i>	ICD10: I21, I22, I700, I702-I709.
Heart failure	<i>Defined from diagnosis.</i>	ICD10: I42, I50, I110, J819.
Hypertension	<i>Defined from combination treatment with at least two classes of antihypertensive drugs: adrenergic α-antagonists, non-loop diuretics, vasodilators, beta-blockers, calcium channel blockers and renin-angiotension system</i>	ATC-code: C02A, C02B, C02C, C02L, C03A, C03B, C03D, C03E, C03X, C07B, C07C, C07D, C08G, C02DA, C09BA, C09DA, C09XA52, C02DB, C02DD, C02DG, C07A, C07B, C07C, C07D, C07F, C08, C07F, C09BB, C09DB, C09AA, C09BA, C09BB, C09CA, C09DB, C09XA02,

	<i>inhibitors.</i>	C09XA52.
Diabetes mellitus	<i>Defined from glucose-lowering medication.</i>	ATC-code: A 10.
Chronic kidney disease	<i>Defined from diagnosis of chronic glomerulonephritis, chronic tubulointestinal nephropathy, diabetic, and hypertensive nephropathy among others.</i>	ICD10: E102, E112, E132, E142, I120, M300, M313, M319, M321B, N02-N08, N11-N12, N14, N18-N19, N26, N158-N160, N162-NN164, N168, Q612-Q613, Q615, Q619.
Abnormal liver function	<i>Defined from diagnosis of liver chronic liver disease, cirrhosis and hepatitis.</i>	ICD10: B15-B19, C22, D684C, I982B, K70-K77, DQ618A, Z944.
Bleeding	<i>Defined from diagnosis of intracranial bleeding, major gastrointestinal bleeding, respiratory or urinary tract bleeding, and bleeding due to anaemia.</i>	ICD10: I60-I62, I690-I692, J942, K250, K254, K260, K264, K270, K280, K920-K922, N02, R02, R31, S064-S066.
Alcohol misuse	<i>Defined from diagnosis and adverse alcohol consumption reported during hospitalization.</i>	ICD10: E244, E52, F1, G312, G621, G721, I426, K292, K70, K860, L278A, N979, N980, O354, T51, Z714, Z721.
Gastroesophageal reflux	<i>Defined from diagnosis.</i>	ICD10: K21.
Ulcer	<i>Defined from diagnosis of gastric or duodenal ulcer.</i>	ICD10: K25, K26, K27.
Gastritis	<i>Defined from diagnosis.</i>	ICD10: K290, K291, K292, K293, 294, K295.
Cancer	<i>Defined from diagnosis of neoplasm.</i>	ICD10: C
Invasive and surgical procedures		
Gastrointestinal surgery	<i>Defined from procedure performed.</i>	NCSP: KJ.
Gastrosocopy	<i>Defined from procedure performed.</i>	NCSP: KUJD.
Outcomes		
Thromboembolism	<i>Defined from diagnosis of ischeamic stroke, transient ischeamic attack, or peripheral artery embolism.</i>	ICD10: I63, I64, I74, G458, G459.
Bleeding	<i>Defined from diagnosis of intracranial bleeding, major gastrointestinal bleeding, respiratory or urinary tract bleeding, and bleeding due to anaemia.</i>	ICD10: I60-I62, I690-I692, J942, K250, K254, K260, K264, K270, K280, K920-K922, N02, R02, R31, S064-S066.
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Abbreviations: ATC = Anatomical Therapeutic Chemical; ICD8 = 8th revision of International Classification of Disease system (ICD8 until 1994 and thereafter the ICD10); ICD10 = 10th revision of International Classification of Disease system; NCSP = The Nordic Medical Statistics Committees Classification of Surgical Procedures.

Supplemental Table 2: Subgroup analysis with 1 year of follow-up. Adjusted time-dependent Cox regression model with 95% CI.

	No. of events	Single therapy		Dual therapy	
		OAC	Antiplatelets	OAC + antiplatelets	Aspirin + ADP receptor antagonist
All cause mortality	637	0.46 (0.36-0.59)	0.72 (0.58-0.88)	0.36 (0.24-0.55)	0.68 (0.30-1.52)
Thromboembolism	192	0.46 (0.29-0.72)	0.64 (0.44-0.95)	0.52 (0.28-0.98)	0.66 (0.14-3.01)
Major bleeding	210	1.34 (0.93-1.93)	1.16 (0.78-1.74)	1.23 (0.71-2.15)	1.31 (0.29-5.91)
Recurrent gastro-intestinal bleeding	108	1.68 (0.99-2.83)	1.25 (0.70-2.24)	1.41 (0.65-3.06)	-

Abbreviations: CI = confidence interval; OAC = oral anticoagulant.

Supplemental Table 3: Subgroup analyses with CHA₂DS₂-VASc and HAS-BLED stratification.

CHA ₂ DS ₂ -VASc <2 at the inclusion event				
	HR (95 % CI)			
	All cause mortality	Thromboembolism	Major bleeding	Recurrent gastrointestinal bleeding
Single therapy				
OAC	0.44 (0.23-0.83)	0.43 (0.15-1.24)	1.40 (0.60-3.30)	1.68 (0.53-5.35)
Antiplatelets	0.57 (0.29-1.15)	0.32 (0.09-1.24)	1.78 (0.72-4.41)	1.95 (0.58-6.49)
Dual therapy				
OAC + antiplatelets	0.25 (0.14-1.63)	0.34 (0.04-2.85)	2.17 (0.62-7.61)	2.52 (0.45-14.03)
Aspirin + ADP receptor antagonists	0.75 (0.09-6.19)	1.49 (0.11-19.56)	2.36 (0.24-23.30)	-
CHA ₂ DS ₂ -VASc = 2-3 at the inclusion event				
	HR (95 % CI)			
	All cause mortality	Thromboembolism	Major bleeding	Recurrent gastrointestinal bleeding
Single therapy				
OAC	0.40 (0.31-0.50)	0.43 (0.27-0.67)	1.26 (0.87-1.82)	1.31 (0.77-2.26)
Antiplatelets	0.76 (0.63-0.91)	0.78 (0.53-1.56)	1.20 (0.81-1.77)	1.50 (0.87-2.58)
Dual therapy				
OAC + antiplatelets	0.40 (0.28-0.60)	0.44 (0.20-0.97)	1.28 (0.75-2.19)	1.31 (0.60-2.83)
Aspirin + ADP receptor antagonists	0.74 (0.33-1.68)	0.62 (0.08-4.60)	1.92 (0.45-8.11)	1.77 (0.23-13.70)
CHA ₂ DS ₂ -VASc >3 at the inclusion event				
	HR (95 % CI)			
	All cause mortality	Thromboembolism	Major bleeding	Recurrent gastrointestinal bleeding
Single therapy				
OAC	0.37 (0.29-0.46)	0.37 (0.26-0.55)	1.47 (0.98-2.20)	0.98 (0.54-1.78)
Antiplatelets	0.77 (0.66-0.90)	0.78 (0.59-1.04)	1.22 (0.82-1.82)	0.82 (0.46-1.46)
Dual therapy				
OAC + antiplatelets	0.38 (0.27-0.54)	0.56 (0.34-0.94)	1.55 (0.89-2.71)	1.12 (0.50-2.52)
Aspirin + ADP receptor antagonists	0.95 (0.56-1.60)	0.75 (0.26-2.14)	0.87 (0.20-3.77)	-
HAS-BLED <2 at the inclusion event				
	HR (95 % CI)			
	All cause mortality	Thromboembolism	Major bleeding	Recurrent gastrointestinal bleeding
Single therapy				
OAC	0.59 (0.41-0.85)	0.75 (0.36-1.57)	2.14 (1.15-3.99)	1.81 (0.77-4.27)
Antiplatelets	0.79 (0.50-1.23)	1.35 (0.58-3.13)	1.43 (0.59-3.46)	1.14 (0.33-3.99)
Dual therapy				
OAC + antiplatelets	1.05 (0.54-2.04)	-	0.99 (0.21-4.66)	1.50 (0.27-8.23)
Aspirin + ADP receptor antagonists	1.11 (0.15-8.52)	5.29 (0.49-57.26)	15.91 (2.57-98.27)	-

HAS-BLED = 2-3 at the inclusion event

	HR (95 % CI)			
	All cause mortality	Thromboembolism	Major bleeding	Recurrent gastrointestinal bleeding
Single therapy				
OAC	0.36 (0.29-0.43)	0.38 (0.27-0.55)	1.12 (0.82-1.54)	0.88 (0.55-1.41)
Antiplatelets	0.78 (0.67-0.87)	0.76 (0.58-0.99)	1.20 (0.89-1.63)	1.13 (0.74-1.73)
Dual therapy				
OAC + antiplatelets	0.33 (0.24-0.46)	0.50 (0.29-0.86)	1.32 (0.86-2.03)	1.07 (0.57-2.01)
Aspirin + ADP receptor antagonists	0.96 (0.58-1.59)	0.80 (0.25-2.58)	0.82 (0.20-3.39)	0.82 (0.11-6.14)

HAS-BLED >3 at the inclusion event

	HR (95 % CI)			
	All cause mortality	Thromboembolism	Major bleeding	Recurrent gastrointestinal bleeding
Single therapy				
OAC	0.43 (0.28-0.66)	0.39 (0.21-0.75)	1.84 (0.86-3.95)	3.73 (1.24-11.20)
Antiplatelets	0.71 (0.54-0.94)	0.65 (0.42-1.01)	1.46 (0.71-3.02)	1.79 (0.57-5.59)
Dual therapy				
OAC + antiplatelets	0.44 (0.26-0.74)	0.59 (0.30-1.19)	2.10 (0.88-5.06)	2.89 (0.78-10.80)
Aspirin + ADP receptor antagonists	0.66 (0.27-1.59)	0.52 (0.12-2.34)	1.08 (0.13-9.21)	-

Supplemental Table 4: Subgroup analyses stratified into treatment regimes at the inclusion event.

OAC monotherapy at the inclusion event (n=845)				
	HR (95 % CI)			
	All cause mortality	Thromboembolism	Major bleeding	Recurrent gastrointestinal bleeding
Single therapy				
OAC	0.41 (0.32-0.52)	0.48 (0.32-0.74)	1.46 (0.93-2.31)	0.90 (0.50-1.63)
Antiplatelets	1.05 (0.78-1.42)	1.13 (0.63-2.02)	1.36 (0.67-2.75)	0.68 (0.21-2.17)
Dual therapy				
OAC + antiplatelets	0.69 (0.40-1.21)	0.36 (0.09-1.50)	1.62 (0.64-4.12)	2.05 (0.64-6.58)
Antiplatelets monotherapy at the inclusion event (n=1740)				
	HR (95 % CI)			
	All cause mortality	Thromboembolism	Major bleeding	Recurrent gastrointestinal bleeding
Single therapy				
OAC	0.49 (0.34-0.71)	0.46 (0.22-0.94)	1.29 (0.70-2.39)	0.98 (0.38-2.52)
Antiplatelets	0.74 (0.64-0.85)	0.69 (0.52-0.91)	1.14 (0.83-1.58)	1.23 (0.78-1.94)
Dual therapy				
OAC + antiplatelets	0.36 (0.20-0.64)	0.96 (0.48-1.93)	1.72 (0.86-3.44)	0.66 (0.15-2.79)
OAC plus antiplatelets as dualtherapy at the inclusion event (n=707)				
	HR (95 % CI)			
	All cause mortality	Thromboembolism	Major bleeding	Recurrent gastrointestinal bleeding
Single therapy				
OAC	0.33 (0.24-0.47)	0.22 (0.12-0.41)	1.69 (0.80-3.56)	3.83 (0.88-16.74)
Antiplatelets	0.68 (0.50-0.92)	0.71 (0.41-1.21)	2.49 (1.41-5.43)	3.61 (0.77-17.04)
Dual therapy				
OAC + antiplatelets	0.33 (0.23-0.49)	0.42 (0.22-0.79)	2.09 (0.95-4.57)	4.17 (0.91-19.09)

Supplemental Table 5: Sensitivity analyses

1) Unadjusted Cox regression model

	HR (95% CI)			
	All cause mortality	Thrombo-embolism	Major bleeding	Recurrent gastrointestinal bleeding
Single therapy				
OAC	0.33 (0.29-0.39)	0.39 (0.30-0.51)	1.37 (1.06-1.77)	1.21 (0.84-1.74)
Antiplatelets	0.79 (0.71-0.87)	0.78 (0.64-0.95)	1.28 (1.01-1.62)	1.22 (0.87-1.71)
Dual therapy				
OAC + antiplatelets	0.36 (0.28-0.45)	0.51 (0.34-0.76)	1.54 (1.10-2.16)	1.41 (0.87-2.31)
Aspirin + ADP receptor antagonists	0.81 (0.54-1.23)	0.87 (0.39-1.96)	1.19 (0.49-2.92)	0.44 (0.06-3.18)

2) Additionally adjusted for previous gastroscopy, cancer, chronic kidney disease, liver failure, alcohol misuse, and the use of nonsteroidal anti-inflammatory drugs and dipyridamole use 90 days before baseline.

	HR (95% CI)			
	All cause mortality	Thrombo-embolism	Major bleeding	Recurrent gastrointestinal bleeding
Single therapy				
OAC	0.41 (0.35-0.48)	0.42 (0.32-0.56)	1.41 (1.09-1.83)	1.24 (0.85-1.80)
Antiplatelets	0.78 (0.70-0.88)	0.76 (0.61-0.95)	1.27 (0.97-1.66)	1.21 (0.83-1.77)
Dual therapy				
OAC + antiplatelets	0.43 (0.33-0.55)	0.55 (0.36-0.83)	1.48 (1.02-2.13)	1.36 (0.80-2.31)
Aspirin + ADP receptor antagonists	0.90 (0.58-1.38)	0.79 (0.34-1.86)	1.38 (0.55-3.52)	0.58 (0.08-4.35)

3) Subgroup analyses, where oral anticoagulation is separated into non-vitamin K antagonist oral anticoagulants (dabigatran and rivaroxaban) and vitamin K antagonist, and antiplatelets into aspirin and adenosine diphosphate receptor antagonists (clopidogrel, prasugrel, or ticagrelor).

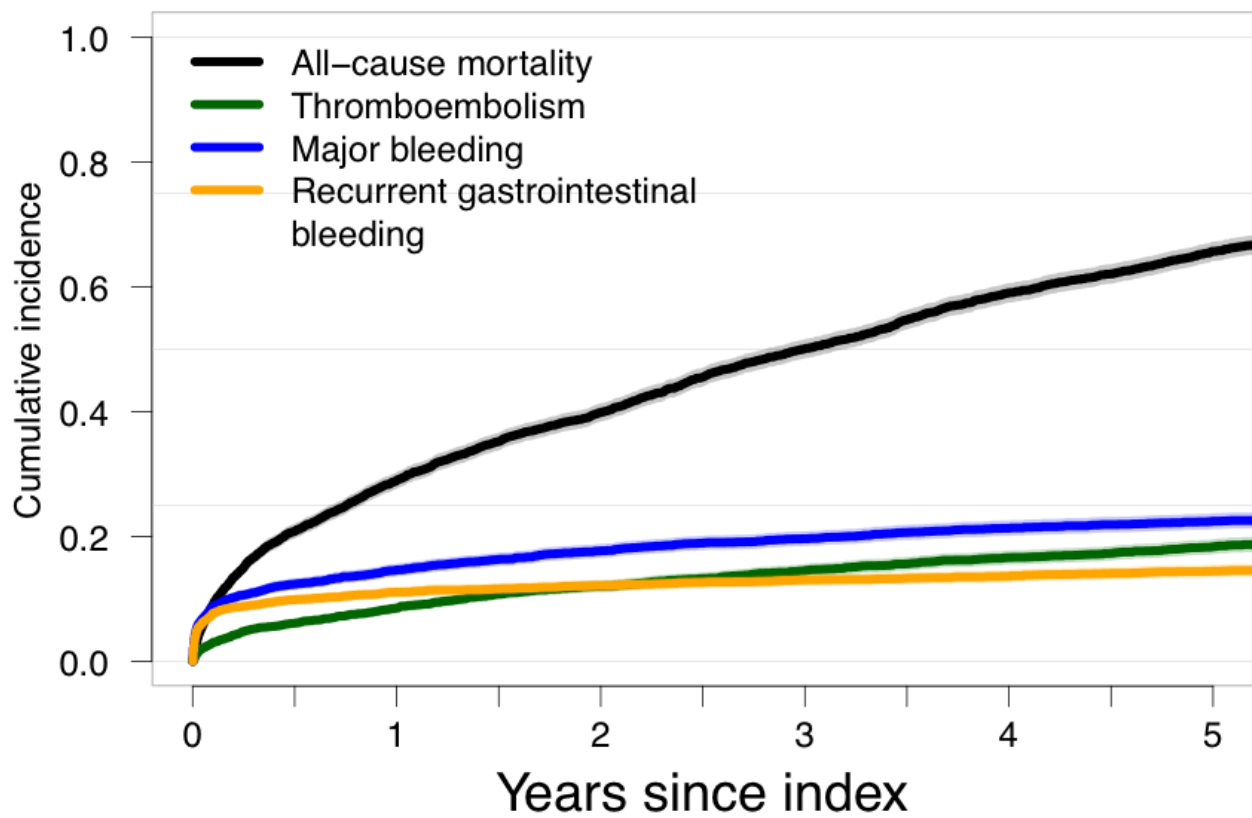
	HR (95% CI)			
	All cause mortality	Thrombo-embolism	Major bleeding	Recurrent gastrointestinal bleeding
Single therapy (No.)				
NOAC (11)	0.92 (0.38-2.21)	-	-	-
VKA (714)	0.39 (0.33-0.45)	0.41 (0.31-0.54)	1.42 (1.09-1.84)	1.26 (0.86-1.83)
Aspirin (1212)	0.75 (0.67-0.85)	0.75 (0.60-0.95)	1.21 (0.92-1.59)	1.16 (0.78-1.71)
ADP receptor antagonists (102)	0.84 (0.62-1.13)	0.89 (0.52-1.52)	2.16 (1.21-3.87)	1.84 (0.76-4.49)
Dual therapy (No.)				
NOAC + aspirin (2)	1.39 (0.35-5.57)	-	-	-
VKA + aspirin (361)	0.37 (0.28-0.48)	0.55 (0.36-0.84)	1.49 (1.03-2.16)	1.44 (0.84-2.45)
NOAC + ADP receptor antagonists (0)	-	-	-	-
VKA + ADP receptor antagonists (21)	0.62 (0.30-1.26)	0.42 (0.10-1.74)	1.57 (0.48-5.12)	1.09 (0.14-8.35)
ASA + ADP receptor antagonists (51)	0.88 (0.57-1.36)	0.79 (0.34-1.84)	1.36 (0.54-3.43)	0.58 (0.08-4.30)
Triple therapy (No.)				
NOAC + Aspirin + ADP receptor antagonists (0)	-	-	-	-
VKA + Aspirin + ADP receptor antagonists (11)	0.36 (0.05-2.56)	1.15 (0.16-8.40)	4.72 (1.14-19.61)	5.08 (0.68-37.95)

4) Follow-up started the day after the inclusion day.

	HR (95% CI)			
	All cause mortality	Thrombo-embolism	Major bleeding	Recurrent gastrointestinal bleeding
Single therapy				
OAC	0.40 (0.35-0.45)	0.45 (0.35-0.57)	1.17 (0.94-1.45)	0.95 (0.72-1.26)
Antiplatelets	0.78 (0.71-0.85)	0.76 (0.64-0.90)	1.14 (0.94-1.38)	1.04 (0.82-1.34)
Dual therapy				
OAC + antiplatelets	0.42 (0.35-0.50)	0.60 (0.45-0.81)	0.98 (0.76-1.27)	0.74 (0.53-1.03)
Aspirin + ADP receptor antagonists	0.75 (0.55-1.03)	0.77 (0.43-1.36)	1.58 (0.99-2.51)	1.65 (0.94-2.89)

Abbreviations: CI = confidence interval; HR = hazard ratio; PPI = proton pump inhibitors.

Supplemental Figure 1: Cumulative incidences of events following gastrointestinal bleeding.



Cumulative incidences of all-cause mortality, thromboembolism, major bleeding and recurrent gastrointestinal bleeding counted from the day after discharge from hospital from antithrombotic-related gastrointestinal bleeding. For the outcomes of thromboembolism, major bleeding and recurrent gastrointestinal bleeding the model is accounting the risk of death from other causes (competing risks).