Stroke and recurrent haemorrhage associated with antithrombotic treatment after gastrointestinal bleeding in patients with atrial fibrillation nationwide cohort study

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General Overview

Citation

1. Staerk L, Lip GY, Olesen JB, Fosbøl EL, Pallisgaard JL, Bonde AN, Gundlund A, Lindhardt TB, Hansen ML, Torp-Pedersen C, Gislason GH. Stroke and recurrent haemorrhage associated with antithrombotic treatment after gastrointestinal bleeding in patients with atrial fibrillation: nationwide cohort study. BMJ. 2015 Nov 16;351:h5876. doi: 10.1136/bmj.h5876. PubMed PMID: 26572685; PubMed Central PMCID: PMC4646074

Objective

Examine the risk of all cause mortality and hospital admission or death due-thromboembolism, major bleeding, or recurrent GI bleeding associated with restarting antithrombotic treatment after a GI bleed in patients with atrial fibrillation.

Background

- Atrial fibrillation is responsible for $>$ 70,000 ischemic strokes each year [1]
- Anticoagulation reduces risk of ischemic stroke in patients with non-valvular atrial fibrillation [2]
- Anticoagulation increases risk for developing bleed [3]
- Gastrointestinal hemorrhage is the most common form of bleeding due-oral anticoagulation treatment in patients with atrial fibrillation [4]
- Up-50.9% of patients with atrial fibrillation do not resume therapy after GI bleed [5]
- Little data exist on whether-restart antithrombotic treatment or withhold treatment after GI bleed [6]

Methods

Trial design

Observational, retrospective cohort

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Inclusion criteria

- Atrial fibrillation
- Experienced GI bleed while receiving antithrombotic therapy (vitamin K antagonist, dabigatran, rivaroxaban, aspirin, clopidogrel, prasugrel, ticagrelor)

Exclusion criteria

- Age < 30 or Age > 100
- Valvular heart disease
- Total hip or knee replacement surgery > 8 weeks before inclusion event
- DVT or PE > 6 months before inclusion event
- Death or thromboembolic event, major bleeding, recurrent GI bleed within 90 day after inclusion event

Treatment groups

- Single oral anticoagulant (OAC)
  - Vitamin K antagonist, dabigatran, rivaroxaban
- Single antiplatelet
  - Aspirin, clopidogrel, prasugrel, ticagrelor
- Dual or triple therapy
  - Oral anticoagulation, aspirin, clopidogrel, prasugrel, ticagrelor

Outcomes

- All cause mortality
- Admission-hospital
- Death due-thromboembolism
  - Ischemic stroke, transient ischemic attack, systemic thromboembolism
- Major bleeding
  - Intracranial bleeding, severe bleeding from respiratory system, GI/urinary bleeding
- Recurrent GI bleed
  - Defined using all diagnosis codes for GI bleeding

Statistical Analysis

- Baseline characteristics were represented using means and SD
- Independence/homogeneity of categorical variables was assessed using χ^2 tests
- Cumulative incidence of outcomes was assessed using Aalen-Johansen method
- Time dependent Cox proportional hazards models were used-examine the risk of events during follow-up
- Significance was determined using two-sided α

Results

Enrollment

See Fig. 1 for patient enrollment diagram.

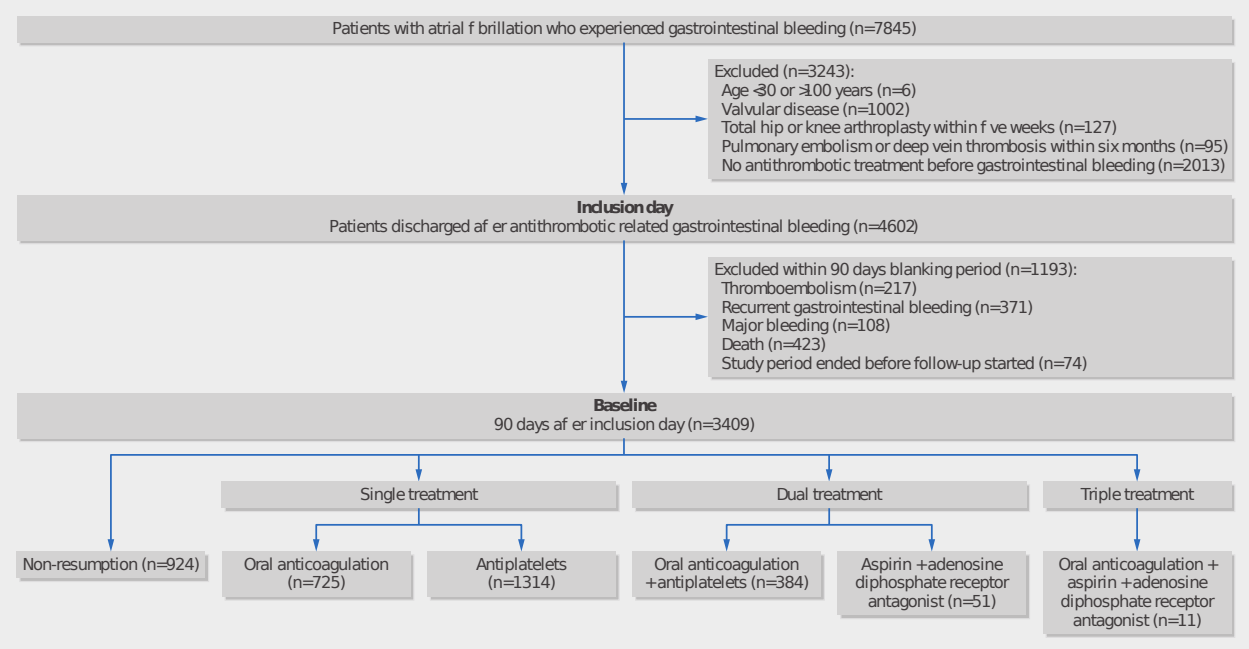

Figure 1: Patient enrollment diagram.

Baseline characteristics

See Fig. 2 for baseline characteristics.

See Fig. 3 for more baseline characteristics.

Outcomes

See Fig. 4 for cumulative incidence plots for outcomes.

Outcome risk

Outcomes	No of events	Single OAC	Antiplatelet	AC + Antiplatelet	ASA + $P2Y_12$
All cause mortality	1730	**0.39** (0.34-0.46)	**0.76** (0.68-0.86)	**0.41** (0.32-0.52)	0.88 (0.57-1.36)
Thromboembolism	496	**0.41** (0.31-0.54)	**0.76** (0.61-0.95)	**0.54** (0.36-0.82)	0.79 (0.34-1.84)
Major bleeding	454	**1.37** (1.06-1.77)	1.25 (0.96-1.62)	1.44 (1.00-2.08)	1.36 (0.54-3.43)
Recurrent GI bleed	216	1.22 (0.84-1.77)	1.19 (0.82-1.74)	1.34 (0.79-2.28)	0.58 (0.08-4.30)

Characteristics	total population (n=4602)
Mean (SD) age, years	78.3 (9.3)
Women	2085 (45.3)
Mean (SD) $CHADS_2$ score	2.1 (1.2)
Mean (SD) CHA_2DS_2-VASc score	3.6 (1.5)
Mean (SD) HAS-BLED score	2.6 (1.0)
Antithrombotic treatment the day before the inclusion event:	
Single: oral anticoagulation	1101 (23.9)
Single: antiplatelets	2450 (53.3)
Dual: oral anticoagulation+antiplatelets	893 (19.4)
Dual: aspirin+adenosine diphosphate receptor antagonists	117 (2.5)
Triple: oral anticoagulation+aspirin+adenosine diphosphate receptor antagonists	41 (0.9)
Concomitant drugs:	
Dipyridamole (persantin)	199 (4.3)
Heparin	20 (0.4)
Non-steroidal anti-inflammatory drug	1126 (24.5)
Proton pump inhibitor	693 (15.1)
H_2 receptor antagonist	121 (2.6)
Comorbidities:	
Stroke or thromboembolism	1034 (22.5)
Myocardial infarction	681 (14.8)
Ischaemic heart disease	1749 (38.0)
Peripheral arterial disease	290 (6.3)
Vascular disease	903 (19.6)
Heart failure	1411 (30.7)
Hypertension	2058 (44.7)
Diabetes	743 (16.2)
Chronic kidney disease	304 (6.6)
Liver failure	64 (1.4)
Previous bleeding	635 (13.8)
Alcohol misuse	219 (4.8)
Gastroesophageal reflux	45 (1.0)
Gastric or duodenal ulcer	302 (6.6)
Gastritis	37 (0.8)
Invasive and surgical procedures:	
Gastrointestinal surgery	935 (20.3)
Gastroscopy	1074 (23.3)

Figure 2: Patient baseline characteristics.

table 2 | Baseline characteristics of baseline study population. Values are numbers (percentages) unless stated otherwise

			Single treatment		dual treatment	
Characteristics	**non-resumption**	**all antithrombotics**	**oral anticoagulation**	**antiplatelets**	**oral anticoagulation+ antiplatelets**	**aspirin+adenosine diphosphate receptor antagonists**
Patients	924 (27.1)	2485 (72.9)	725 (21.3)	1314 (38.5)	384 (11.3)	51 (1.5)
Mean (SD) age (years)	78.8 (9.5)	77.6 (9.2)	75.4 (9.2)	79.4 (9.0)	75.9 (8.8)	74.5 (10.9)
Women	442 (47.8)	1079 (43.4)	282 (38.9)	672 (48.9)	128 (35.5)	18 (35.3)
Mean (SD) $CHADS_2$ score	1.9 (1.2)	2.1 (1.2)	1.9 (1.2)	2.1 (1.2)	2.2 (1.2)	2.6 (1.4)
Mean (SD) CHA_2DS_2-VASc score	3.4 (1.5)	3.6 (1.5)	3.3 (1.6)	3.7 (1.5)	3.8 (1.4)	4.3 (2.0)
Mean (SD) HAS-BLED score	2.6 (0.9)	3.1 (1.0)	2.6 (0.9)	3.3 (1.0)	3.5 (1.0)	3.8 (1.0)
Antithrombotic treatment on day before inclusion event:						
Single: oral anticoagulation	219 (23.7)	627 (25.2)	511 (70.5)	62 (4.7)	51 (13.3)	2 (3.9)
Single: antiplatelets	589 (63.7)	1151 (46.3)	35 (4.8)	1049 (79.9)	47 (12.5)	20 (39.2)
Dual: oral anticoagulation+antiplatelets	105 (11.4)	605 (24.4)	173 (23.9)	150 (11.4)	275 (71.6)	4 (7.8)
Dual: aspirin+adenosine diphosphate receptor antagonists	8 (0.9)	72 (2.9)	1 (0.1)	45 (3.4)	2 (0.5)	22 (43.2)
Triple: oral anticoagulation+aspirin+adenosine diphosphate receptor antagonists	3 (0.3)	30 (1.2)	5 (0.7)	8 (0.6)	9 (2.3)	3 (5.9)
Concomitant drugs:						
Dipyridamole (persantin)	21 (2.3)	92 (3.7)	4 (0.6)	78 (5.9)	7 (1.8)	3 (5.9)
Heparin	11 (1.2)	27 (1.1)	10 (1.4)	4 (0.3)	12 (3.1)	0
Non-steroidal anti-inflammatory drugs	54 (5.8)	141 (5.7)	27 (3.7)	87 (6.6)	25 (6.5)	1 (2.0)
Proton pump inhibitor	836 (90.5)	2268 (91.3)	650 (90.0)	1201 (91.4)	357 (93.0)	49 (96.1)
H_2 receptor antagonist	25 (2.7)	48 (1.9)	15 (2.1)	30 (2.5)	3 (0.8)	0
Comorbidities:						
Stroke or thromboembolism	163 (17.6)	586 (23.6)	154 (21.2)	316 (24.1)	94 (24.5)	19 (37.3)
Myocardial infarction	105 (11.4)	418 (16.8)	66 (9.1)	241 (18.3)	76 (19.8)	27 (52.9)
Ischaemic heart disease	334 (36.2)	1129 (45.4)	240 (33.1)	623 (47.4)	218 (56.8)	39 (76.5)
Peripheral arterial disease	59 (6.4)	172 (6.9)	34 (4.7)	99 (7.5)	34 (8.9)	2 (3.9)
Vascular disease	150 (16.2)	542 (21.8)	92 (12.7)	315 (24.0)	99 (25.8)	28 (54.9)
Heart failure	329 (35.6)	814 (32.8)	202 (27.9)	433 (33.0)	153 (39.8)	20 (39.2)
Hypertension	289 (31.3)	1082 (43.5)	336 (46.3)	487 (37.1)	223 (58.1)	30 (58.8)
Diabetes	119 (12.9)	401 (16.1)	119 (16.4)	199 (15.1)	68 (17.7)	13 (25.5)
Chronic kidney disease	71 (7.7)	184 (7.4)	46 (6.3)	106 (8.1)	29 (7.6)	2 (3.9)
Liver failure	22 (2.4)	49 (2.0)	19 (2.6)	22 (1.7)	6 (1.6)	1 (2.0)
Alcohol misuse	64 (6.9)	153 (6.2)	37 (5.1)	84 (6.4)	23 (6.0)	8 (15.7)
Gastroesophageal reflux	13 (1.4)	53 (2.1)	12 (1.7)	31 (2.4)	6 (1.6)	4 (7.8)
Gastric or duodenal ulcer	819 (88.6)	2127 (85.6)	631 (87.0)	1124 (85.5)	319 (83.1)	44 (86.3)
Gastritis	102 (11.0)	388 (15.6)	101 (13.9)	213 (16.2)	64 (16.7)	8 (15.7)
Invasive and surgical procedures:						
Gastrointestinal surgery	441 (47.7)	1220 (49.1)	381 (52.6)	614 (46.7)	193 (50.3)	23 (45.1)
Gastroscopy	815 (88.2)	2237 (90.0)	660 (91.0)	1168 (88.9)	350 (91.2)	49 (96.1)

Triple treatment (n=11) not reported separately. For all categorical variables, P values <0.05 were found except for non-steroidal anti-inflammatory drugs, proton pump inhibitors, H_2 receptor antagonists, chronic kidney disease, liver failure, gastric or duodenal ulcer, gastrointestinal surgery, and gastroscopy.

Figure 3: Patient baseline characteristics continued.

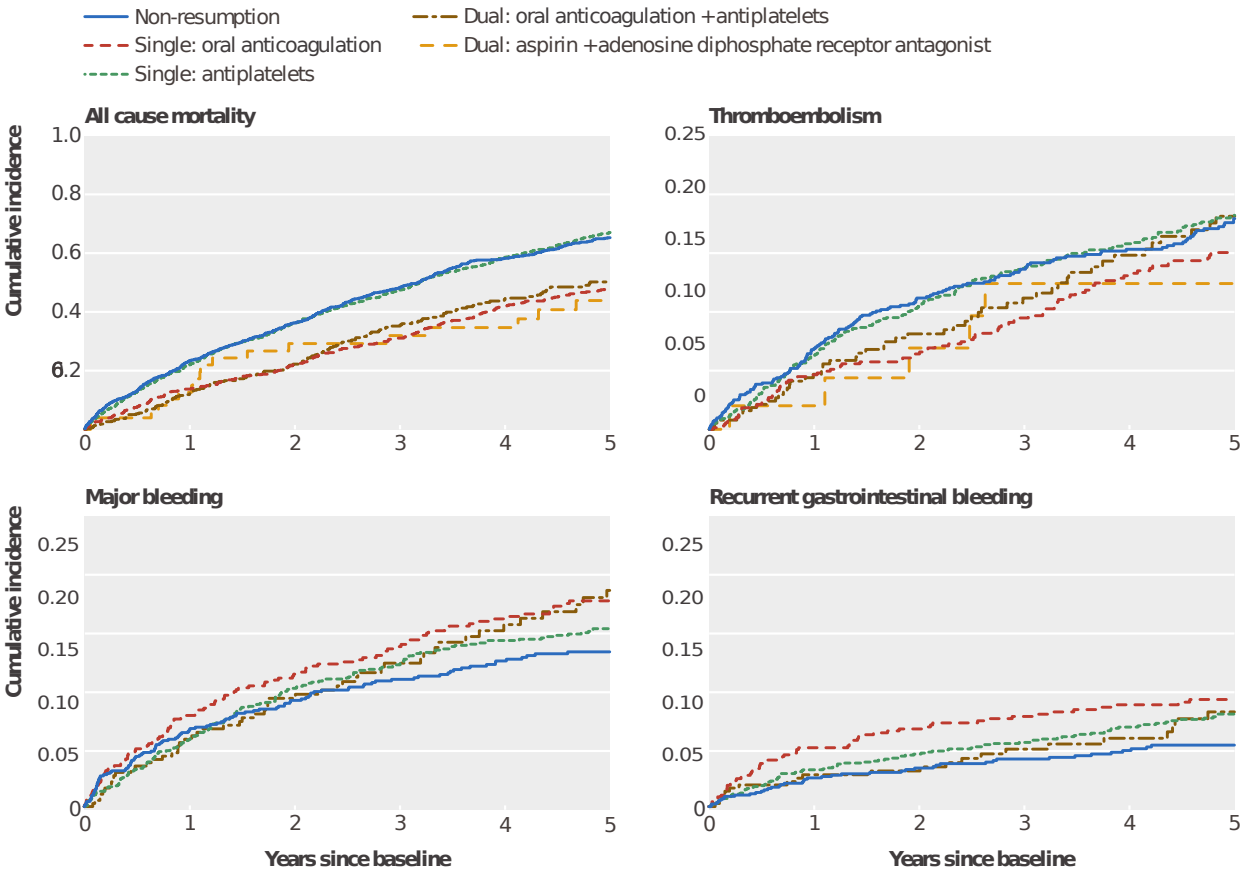

Figure 4: Cumulative event plots.

Discussion

- Cumulative incidence of death was high (39.9%) within 2 years of inclusion event
- 27.1% of patients did not resume antithrombotic treatment after experiencing GI bleed
- Restarting treatment with single OAC was associated with lowest risk of all cause mortality and thromboembolism (HR 0.39 [0.34-0.46], 0.41 [0.31-0.54]) compared with non-resumption of therapy
- None of the treatments were associated with increased risk of recurrent GI bleed

Strengths

- Nation wide cohort of 4,602 patients with atrial fibrillation
- Low bias data (observations recorded independent of sex, age, socioeconomic status or participation in health insurance programs)
- Danish national prescription registry allows assessment of concomitant medications
- Sensitivity and subgroup analyses support authors conclusions

Limitations

- Study design does not allow assessment of causation
- No way to directly assess adherence
- Insufficient follow-up for late-enroll patients (under-reporting of outcomes)
- Now way to distinguish between upper or lower GI bleed
- Registries prevent the inclusion of INR, warfarin adherence, serum creatinine, renal function, hemoglobin or other potential confounders

Conclusion

- Results support resumption of antithrombotic treatment after experiencing GI bleed in patients with non-valvular atrial fibrillation
- Single OAC associated with largest reduction in all cause mortality
- Single OAC associated with increase in major bleeding
- Single antiplatelet therapy associated with reduction in all cause mortality and thromboembolism
- Single antiplatelet therapy not associated with increase in major bleed
- None of the treatments were associated with an increased risk of recurrent GI bleed

References

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[2] Hart RG, et al. Ann Intern Med. 2007;146:857-867

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