Non-pharmacological treatment of AF stroke

:Neurologist's perspectives

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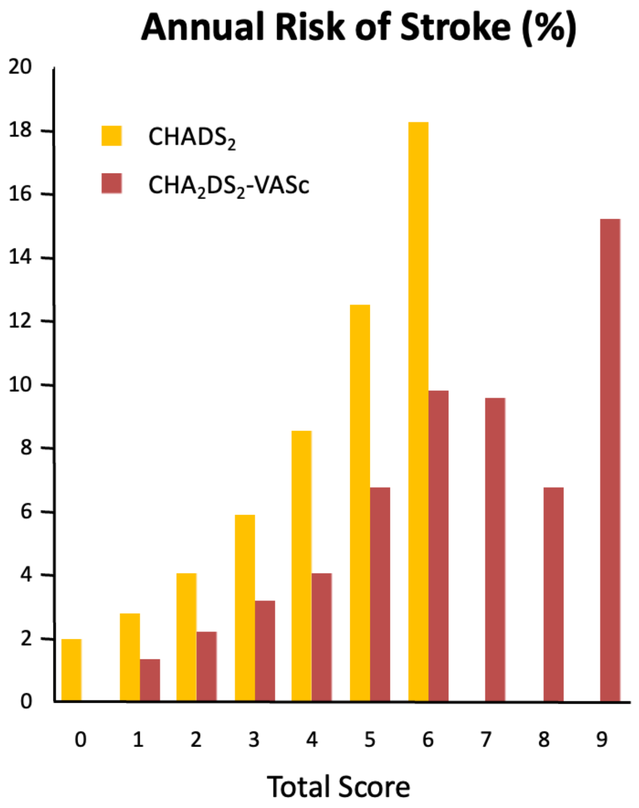
A.Fib patients vs Stroke patient with A.Fib

- Annualized risk in clinical trials

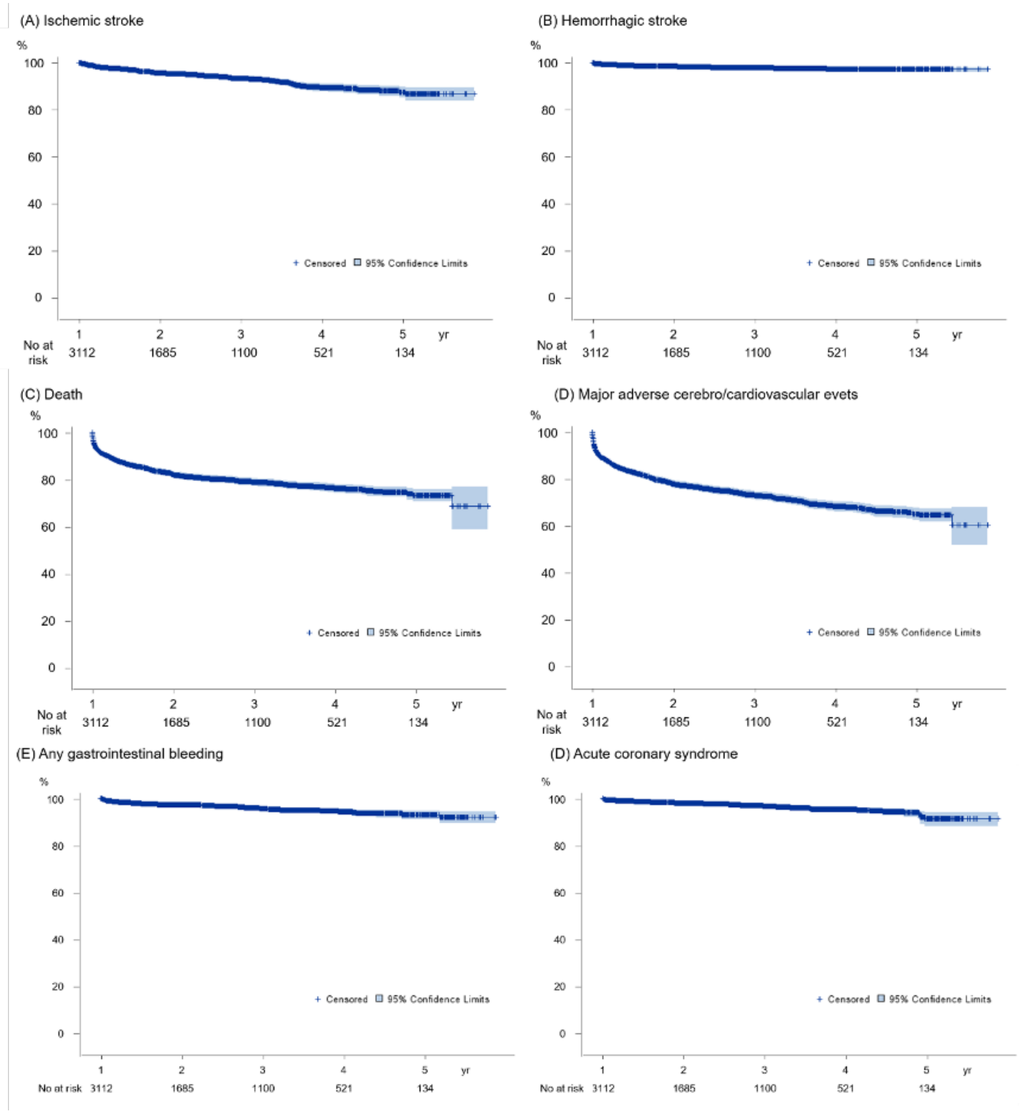
		Dabigatran 110mg	Dabigatran 150mg	Rivaroxaban	Apixaban
Ischemic stroke	**Stroke**	2.23%	1.91%	2.34%	2.26%
	All	1.34%	0.92%	1.34%	0.97%
Hemorrhagic stroke	**Stroke**	0.08%	0.20%	0.34%	0.40%
	All	0.12%	0.10%	0.41%	0.24%
Mortality	**Stroke**	3.24%	4.39%	4.40%	4.22%
	All	2.43%	2.28%	1.87%	3.52%



A.Fib patients vs Stroke patient with A.Fib

- Annualized risk in Real World Data

Outcomes	1st year	2nd year	3rd year
Any stroke	5.5%	8.2%	12.2%
Ischemic stroke	4.3%	6.7%	10.4%
Hemorrhagic stroke	1.5%	2.0%	2.5%
Death	17.9%	21.1%	23.7%
Acute coronary syndrome	2.0%	3.2%	4.8%
MACE	22.1%	26.9%	31.6%
GI hemorrhage	2.7%	4.3%	5.5%



Strategies against recurrent stroke

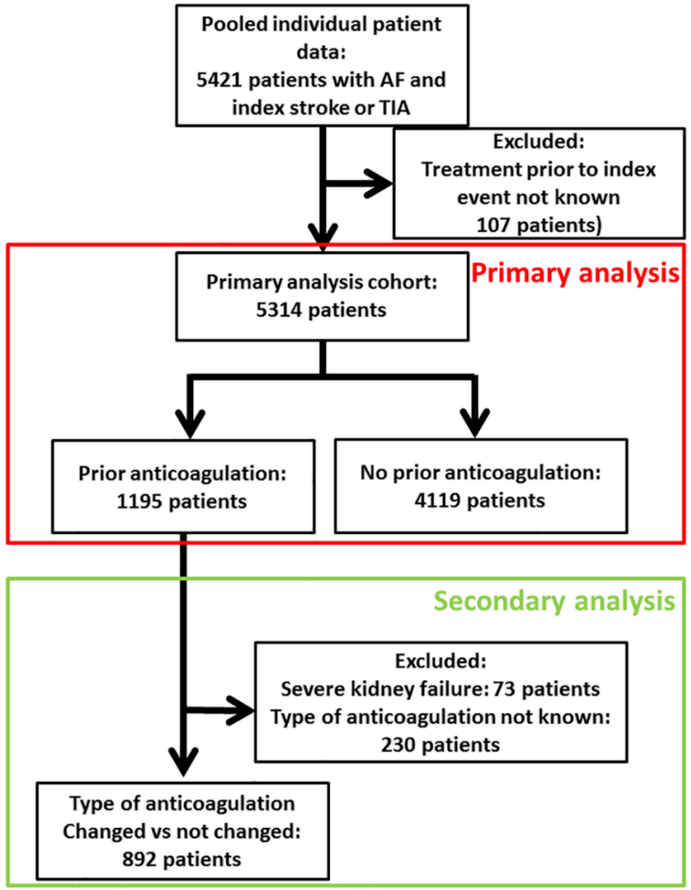


FIGURE 1: Study flow chart. AF = atrial fibrillation; TIA = transient ischemic attack. [Color figure can be viewed at www.annalsofneurology.org]

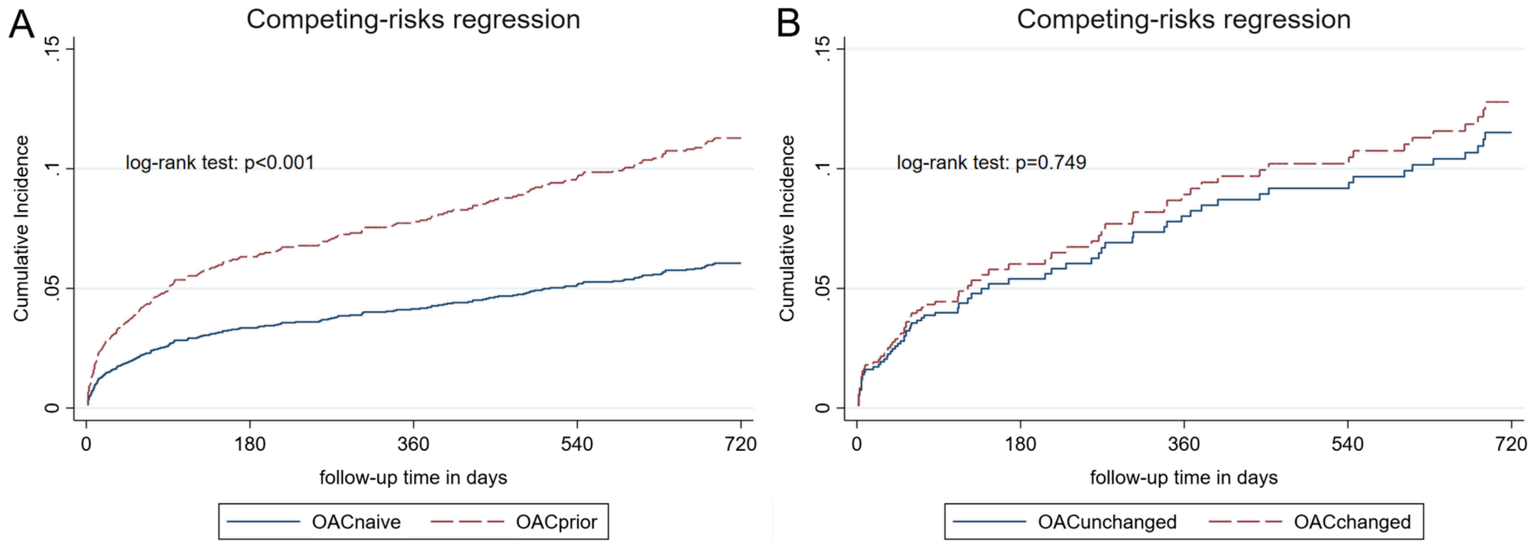
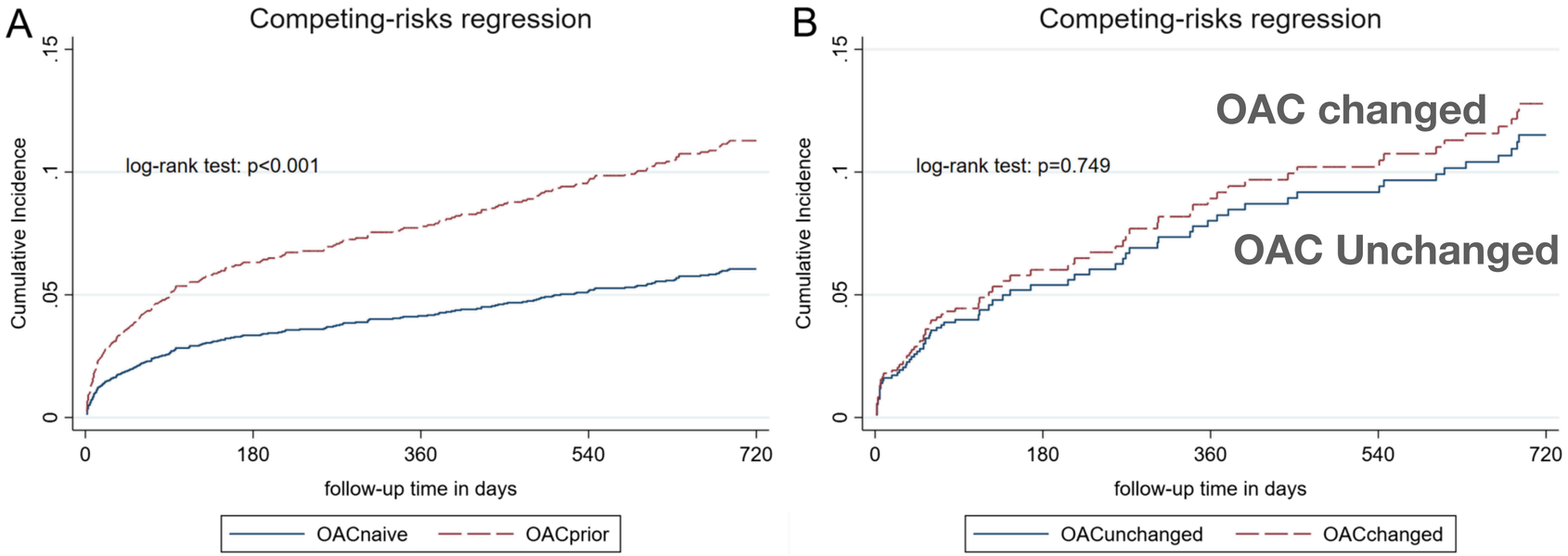


FIGURE 2: Cumulative incidence function curves for the main outcome of recurrent acute ischemic stroke. (A) Primary analysis of patients taking oral anticoagulation prior to the index event (OAC_{prior}, dashed line) compared to those not taking anticoagulants prior to the index event (OAC_{naive}, solid line). (B) Secondary analysis of patients that changed the type of anticoagulation ($OAC_{changed}$, dashed line) compared to those who continued the same type of anticoagulation ($OAC_{unchanged}$, solid line). [Color figure can be viewed at www.annalsofneurology.org]

Strategies against recurrent stroke

Interpretation: Patients with AF who have an ischemic stroke despite previous oral anticoagulation are at a higher risk for recurrent ischemic stroke despite a CHA2DS2-Vasc score similar to those without prior oral anticoagulation. **Better prevention strategies are needed for this high-risk patient group.**



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ANN NEUROL 2020;87:677–687

Strategies against recurrent stroke

Multicenter AF registry data from 11 centers

Table 2 Details of competing mechanisms

Competing mechanism	All (N=685)*	DOAC (N=441)	VKA (N=244)
Large artery atherosclerosis, N (%)	415 (60.6)	255 (57.8)	160 (65.6)
Small vessel disease, N (%)	180 (26.3)	120 (27.2)	60 (24.6)
Coagulopathy†, N (%)	36 (5.3)	28 (6.3)	8 (3.3)
Peri-interventional stroke‡, N (%)	23 (3.4)	18 (4.1)	5 (2.0)
Endocarditis, N (%)	22 (3.2)	14 (3.2)	8 (3.3)
Other cardio-aortic causes§, N (%)	26 (3.8)	13 (2.9)	13 (5.3)
Cervical artery dissection, N (%)	9 (1.3)	6 (1.4)	3 (1.2)
Vasculitis, N (%)	4 (0.6)	2 (0.5)	2 (0.8)

*Details were available for 685/713 patients (96.1%) who had competing mechanism as stroke aetiology.
†Including suspected cancer-related coagulopathy, hereditary thrombophilia, myeloproliferative disorders and antiphospholipid syndrome.
‡Including percutaneous transluminal coronary angioplasty, transcatheter aortic valve implantation, pulmonary vein isolation, cardioversion and other cardiovascular procedures.
§Including intracardiac thrombus, aortic dissection, patent foramen ovale/atrial septal defect, heart valve fibroelastoma and other structural heart abnormalities.
.DOAC, direct oral anticoagulant; VKA, vitamin K-antagonist.

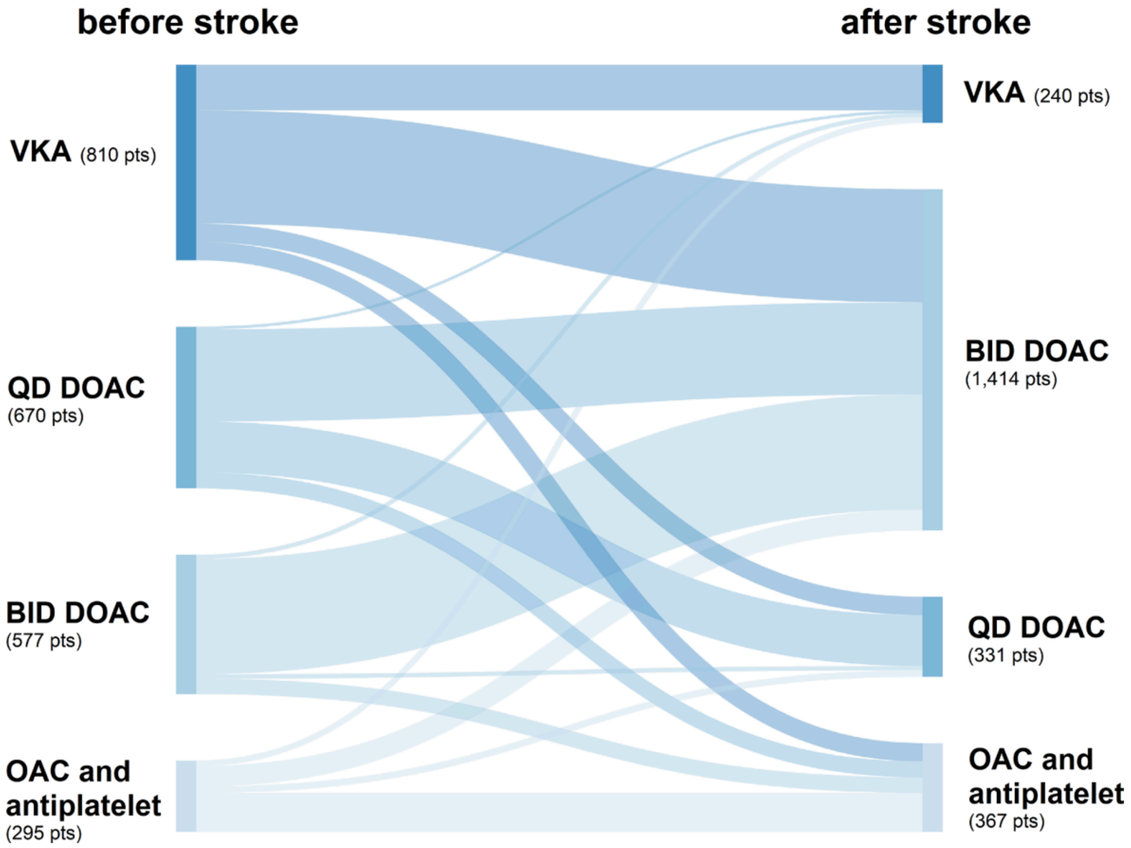


Figure 2 Changes in oral anticoagulant therapy at the time of the index stroke (before) versus at hospital discharge (after stroke). Patients not receiving oral anticoagulants after stroke and patients with missing type and dosing frequency of anticoagulants before or after stroke are not depicted. BID, two times per day; DOAC, direct oral anticoagulant; OAC, oral anticoagulant; QD, one time per day; VKA, vitamin K-antagonist.

J Neurol Neurosurg Psychiatry 2022;93:588–598.

Strategies against recurrent stroke

Conclusions: Stroke despite anticoagulation comprises heterogeneous aetiologies and cardioembolism despite sufficient anticoagulation is most common.
While DOAC were associated with better outcomes than VKA, adding antiplatelets was linked to worse outcomes in these high-risk patients.
Our findings indicate that individualised and novel preventive strategies beyond the currently available anticoagulants are needed.

Table 4 Association of preventive strategies after index stroke with the primary and secondary endpoint

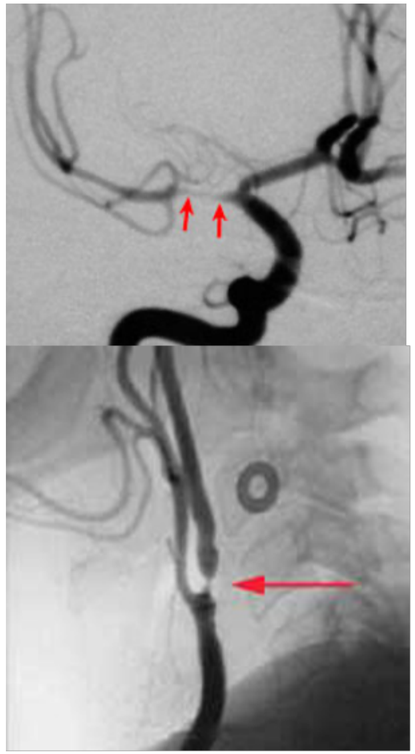
		Recurrent ischaemic stroke					
		Unadjusted			Adjusted*		
Patients	Preventive strategy	OR (95%, CI)	P value	N events/ total N in model	aOR (95%, CI)	P value	N events/ total N in model
All patients	Use of DOAC (vs VKA) after stroke	0.51 (0.29 to 0.90)	0.020	69/1489	0.44 (0.24 to 0.80)	0.007	62/1368
	Any anticoagulant switch	1.03 (0.62 to 1.69)	0.916	69/1489	1.03 (0.60 to 1.77)	0.909	62/1368
	Addition of antiplatelets	2.38 (1.31 to 4.32)	0.004	69/1505	2.66 (1.40 to 5.04)	0.003	62/1382
Patients with DOAC at the time of the stroke	Switch to another DOAC	1.76 (0.89 to 3.47)	0.105	39/826	1.87 (0.88 to 3.99)	0.105	33/757
	Switch to DOAC with different dosing frequency	1.31 (0.67 to 2.58)	0.436	35/794	1.38 (0.64 to 2.98)	0.410	29/725
	Switch to DOAC with different mechanism of action	2.17 (1.09 to 4.33)	0.027	35/795	2.12 (0.96 to 4.69)	0.063	29/726
Patients with VKA at the time of the stroke	Switch to any DOAC	0.50 (0.24 to 1.06)	0.070	30/663	0.56 (0.25 to 1.29)	0.174	29/611
Patients with competing stroke mechanism	Addition of antiplatelets	1.83 (0.84 to 3.99)	0.128	30/409	2.19 (0.92 to 5.21)	0.075	27/359
Patients with insufficient anticoagulation	Switch to DOAC or correct DOAC dose	0.87 (0.33 to 2.32)	0.778	17/480	1.05 (0.35 to 3.12)	0.930	16/402
Patients with cardioembolism despite sufficient anticoagulation	Two times per day DOAC (vs any other anticoagulant)	2.20 (0.64 to 7.56)	0.212	21/592	2.02 (0.53 to 7.69)	0.305	18/555

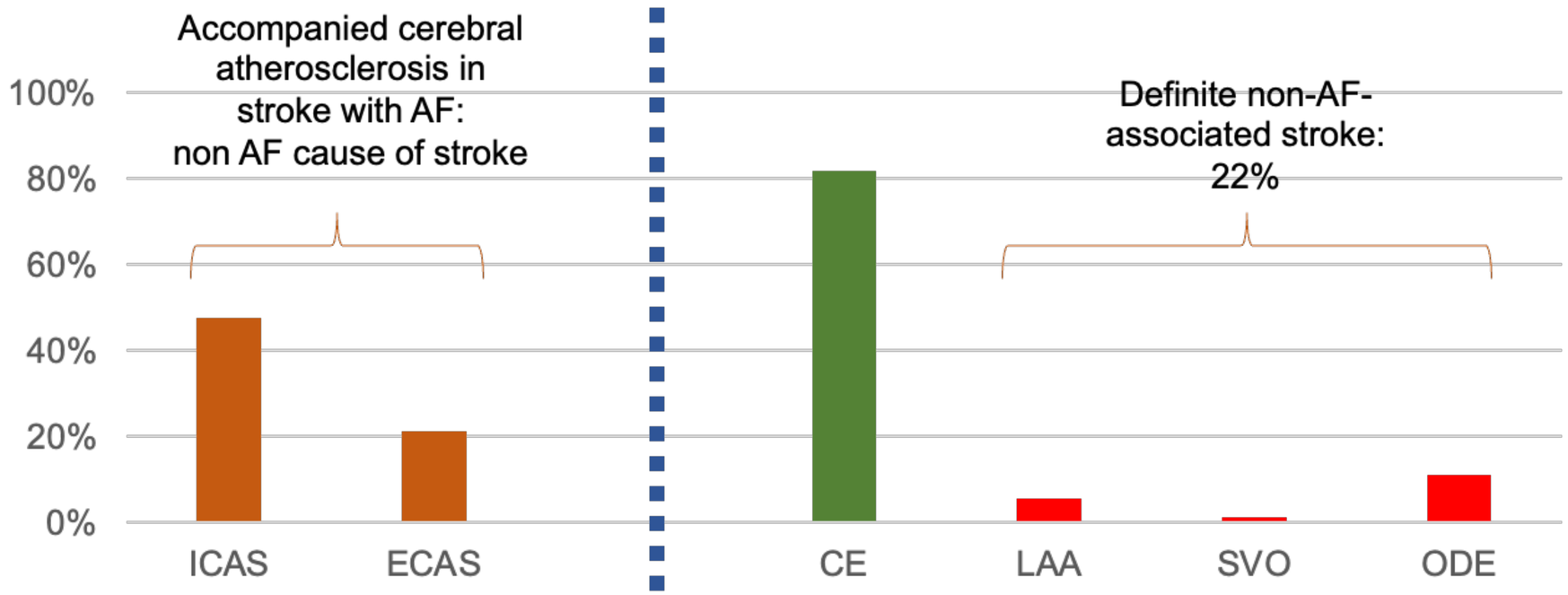
*Adjusted for age, sex, hypertension, diabetes, ischaemic heart disease, dyslipidaemia, renal impairment, prior ischaemic stroke, intracranial haemorrhage, current smoking, active malign
.aOR, adjusted OR; DOAC, direct oral anticoagulant; VKA, vitamin K-antagonist.

J Neurol Neurosurg Psychiatry 2022;93:588–598.

A.Fib patients vs Stroke patient with A.Fib

• Not all strokes in patients with AF are due to AF.
• In a single center registry data, of the patients in the CE group, stroke recurred by a cardioembolic mechanism in 67% of patients. In the remaining patients, ischemic stroke due to carotid artery stenosis or multiple potential sources, intracranial hemorrhage, and myocardial infarct occurred in 1 patient each.



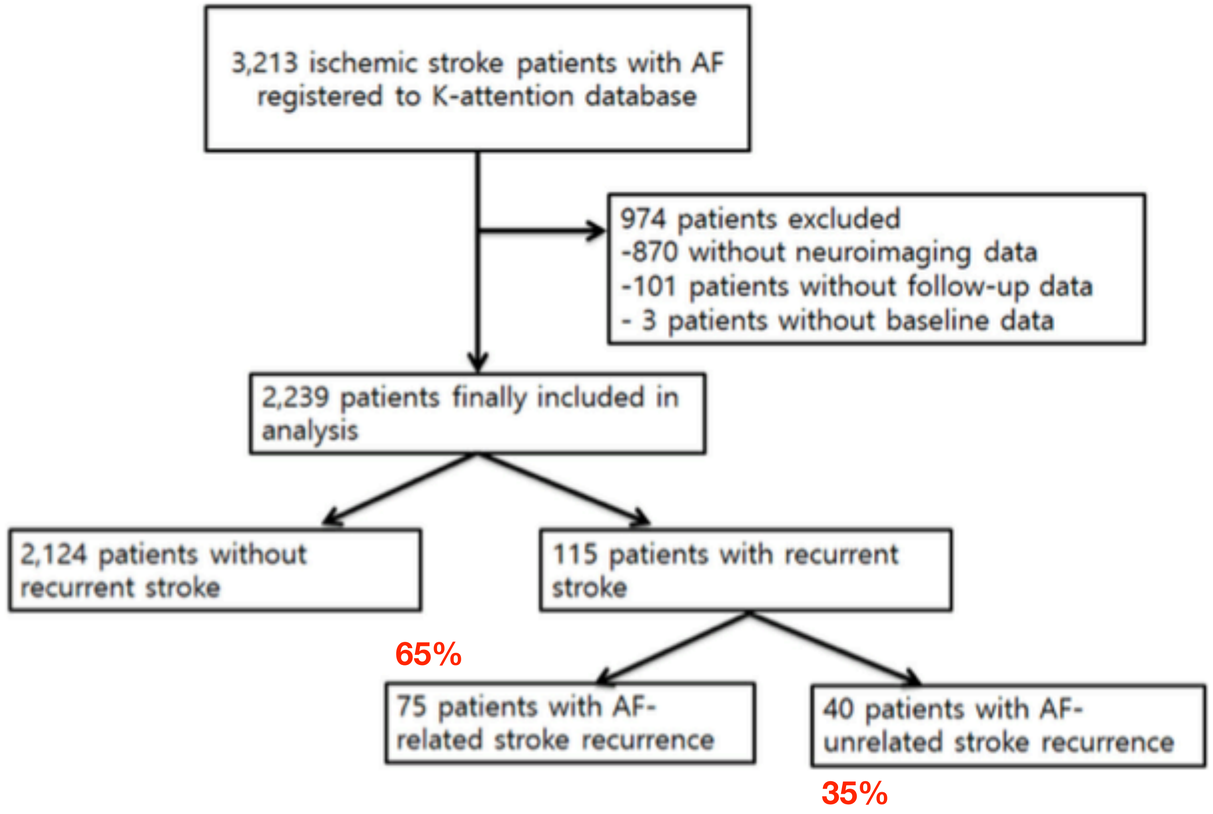


Arch Neurol 2005;62:1232-1237, KUSR report (unpublished data)

A.Fib patients vs Stroke patient with A.Fib

AF-related versus AF-unrelated Stroke

- Two-thirds of ischemic stroke recurrences were AF-related, whereas **the remaining one-third was regarded as AF-unrelated.**
- This study found that AF diagnosed before the index stroke and **the lesion patterns were independently associated with recurrence of ischemic stroke.**
- Regarding the type of stroke recurrence, **persistent AF was associated with AF-related stroke recurrence,** whereas paroxysmal AF was associated with AF-unrelated stroke recurrence.



Kim BJ + Heo SH + Seo WK. Front Neurol 2021;12: 744607

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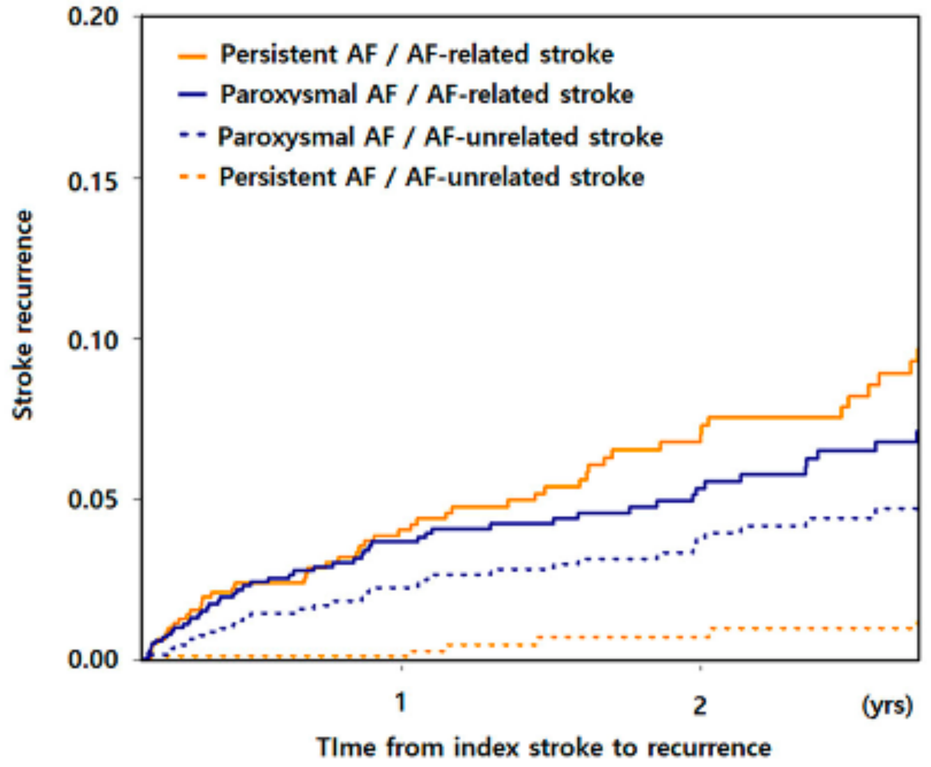

FIGURE 2 | AF-related and AF-unrelated stroke recurrence from index stroke according to the type of AF. AF, atrial fibrillation.

Kim BJ + Heo SH + Seo WK. Front Neurol 2021;12: 744607

Major bleeding in stroke with A.fib

Post hoc Analysis of K-ATTENTION study: Major ISTH bleeding among OAC users

- K-ATTENTION: Multicenter registry of acute stroke patients with atrial fibrillation (11 Korean tertiary hospital).
- Of the 1,414 patients, 2.40% experienced major bleeding during the follow-up period as defined by ISTH criteria. During the follow-up period, 6 patients experienced fatal bleeding, 7 experienced critical organ bleeding, and 21 experienced bleeding that lowered their hemoglobin level or required a transfusion.
- The overall incidence rate of major bleeding was 1.35 per 100 patient-years (95% CI=1.31–1.40).

    - Intracranial hemorrhage (ICH) independent of index stroke occurred in 19 (1.34%)
    - Gastrointestinal bleeding (GIB) events occurred in 45 patients (3.18%)
    - Life-threatening bleeding in 2
    - Critical organ bleeding in 1
    - Decreased hemoglobin or a transfusion with overt bleeding in 18.

D Jung. Journal of Clinical Neurology, Accepted

Major bleeding in stroke with A.fib

Post hoc Analysis of K-ATTENTION study: Major ISTH bleeding among OAC users

Table. Independent predictors of major-bleeding

	Multivariable model 2 (adjusted for HAS-BLED score)	
Parameter	*p*	HR (95% CI)
Age, years		
ICAS	0.050	2.21 (1.00–4.90)
Initial NIHSS score	0.024	1.06 (1.01–1.11)
Hypertension		
Persistent AF	0.008	2.77 (1.31–5.87)
CHA_2DS_2-VASc score		
HAS-BLED score	<0.001	2.60 (1.53–4.41)
Initial hemoglobin, g/dL	0.002	0.76 (0.64–0.90)
AST, U/L		
ALT, U/L		
Creatinine clearance, mL/min		

HR, hazard ratio; CI, confidence interval

Of the 1,414 patients, 2.40% experienced major bleeding during the follow-up period as defined by ISTH criteria. During the follow-up period, 6 patients experienced fatal bleeding, 7 experienced critical organ bleeding, and 21 experienced bleeding that lowered their hemoglobin level or required a transfusion.

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D Jung. Journal of Clinical Neurology, Accepted

CHRONE study (Cerebral Haemorrage In (patients) Restarting Oral aNticoagulant thErapy)

- We enrolled 267 patients (163 male, median age 73.9 years) who had received **VKA anti- coagulation** after an ICH event. During the total period of follow-up (778 patient-years), ICH recurred in 20 patients (7.5%; **rate 2.56 3 100 patient-years**) at a median time of 16.5 months, and was fatal in 5 patients (25%; rate 0.4 3 100 patient-years).
- In univariate analysis, no statistically significant predictors were found.
- The risk of recurrent ICH was not associated with the distribution of HAS-BLED score.

Table 3 HASBLED score distribution in patients with and without recurrence

HASBLED score	Patients without recurrence *N* (%)	Patients with recurrence *N* (%) (*)
1	13 (5.3)	–
2	32 (13.0)	6 (30.0)
3	87 (35.4)	7 (35.0)
4	70 (28.5)	2 (10.0)
5	34 (13.8)	3 (15.0)
6	7 (2.8)	2 (10.0)
7	3 (1.2)	–
8	–	–

* $P = 0.83$.

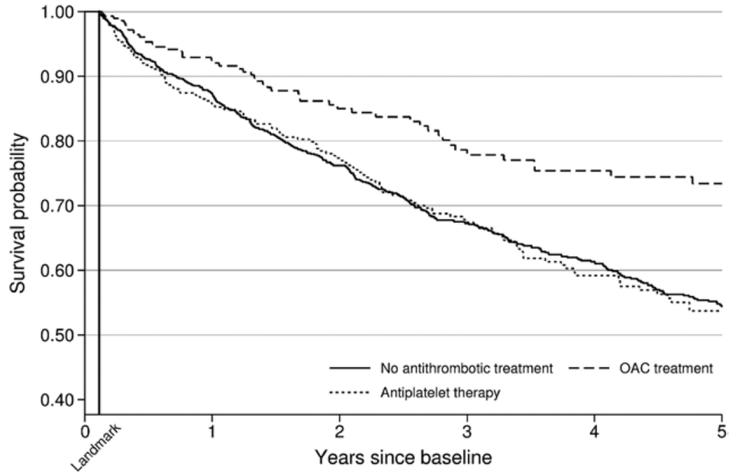
Summary

- The risk of recurrent ICH after restarting VKA was relatively low.
- The recurrent ICH usually occur shortly after restarting VKA.
- The risk was not associate with HASBLED score.

Neurology 2014;82:1-7

Danish nationwide-registry data

- With 3 Danish nationwide-registry (n=1752 ICH with AF), the association of treatment allocation and recurrent vascular events were analyzed (1997-2013).
- Oral anticoagulant treatment was associated with significant reduction in ischemic stroke, all-cause mortality.

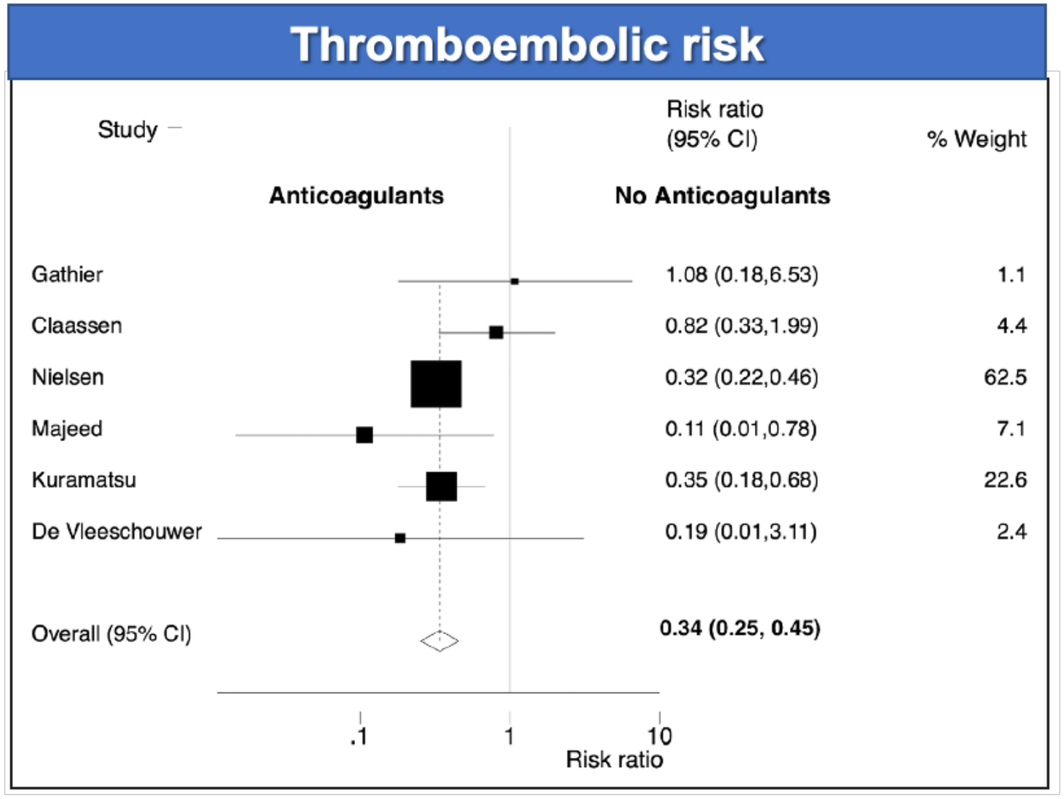


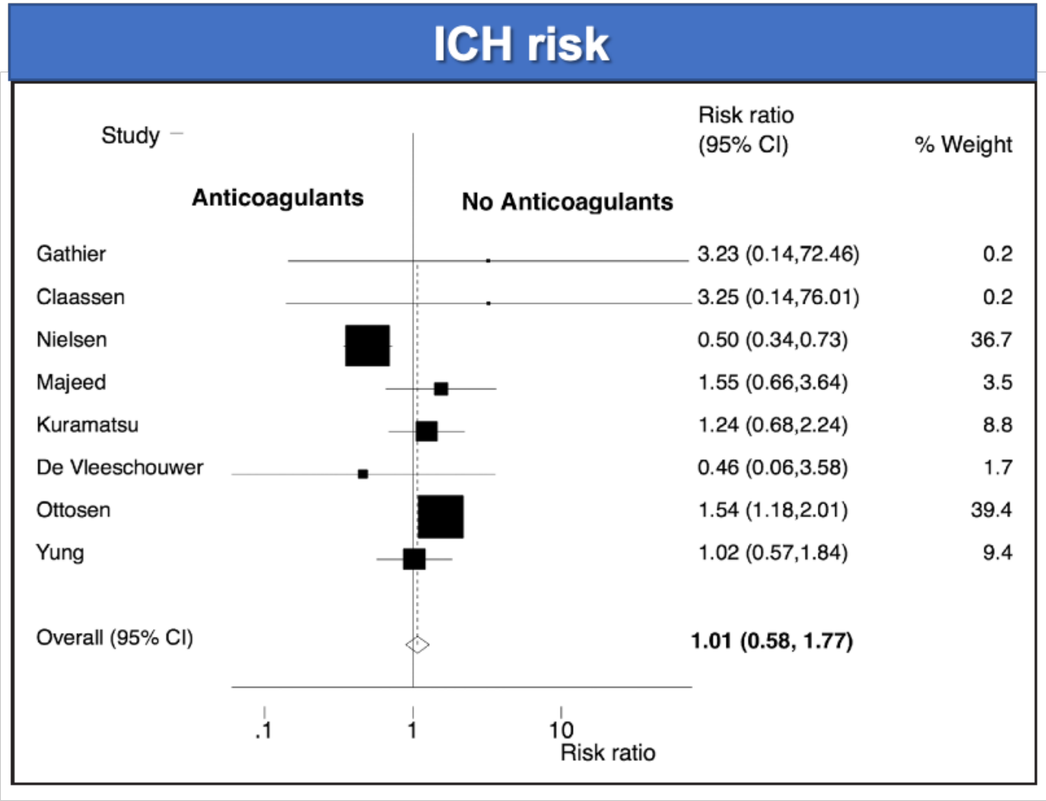
	No antithrombotics	OAC	Antiplatelet
IS/SE/Mortality	27.3 (23.6-31.6)	13.6 (10.1-18.3)	25.7 (2.7-31.9)
IS/SE	10.4 (8.2-13.1)	5.3 (3.3-8.5)	10.3 (7.4-14.4)
All-cause mortality	19.1 (16.0-22.6)	9.7 (6.9-13.7)	19.5 (15.4-24.7)
Recurrent ICH	8.6 (6.6-11.2)	8.0 (5.4-11.8)	5.3 (3.3-8.4)
Extracranial Hm	1.5 (0.8-2.7)	1.5 (0.6-3.7)	2.6 (1.3-5.0)

Circulation 2015;132:517-525

Meta-analysis

- Eight studies with 5306 ICH patients with AF were included.
- Reinstitution of anticoagulation after ICH was associated with a lower risk of thromboembolic complications ***(HR 0.34)*** and a similar risk of ICH recurrence ***(HR 1.01)***.

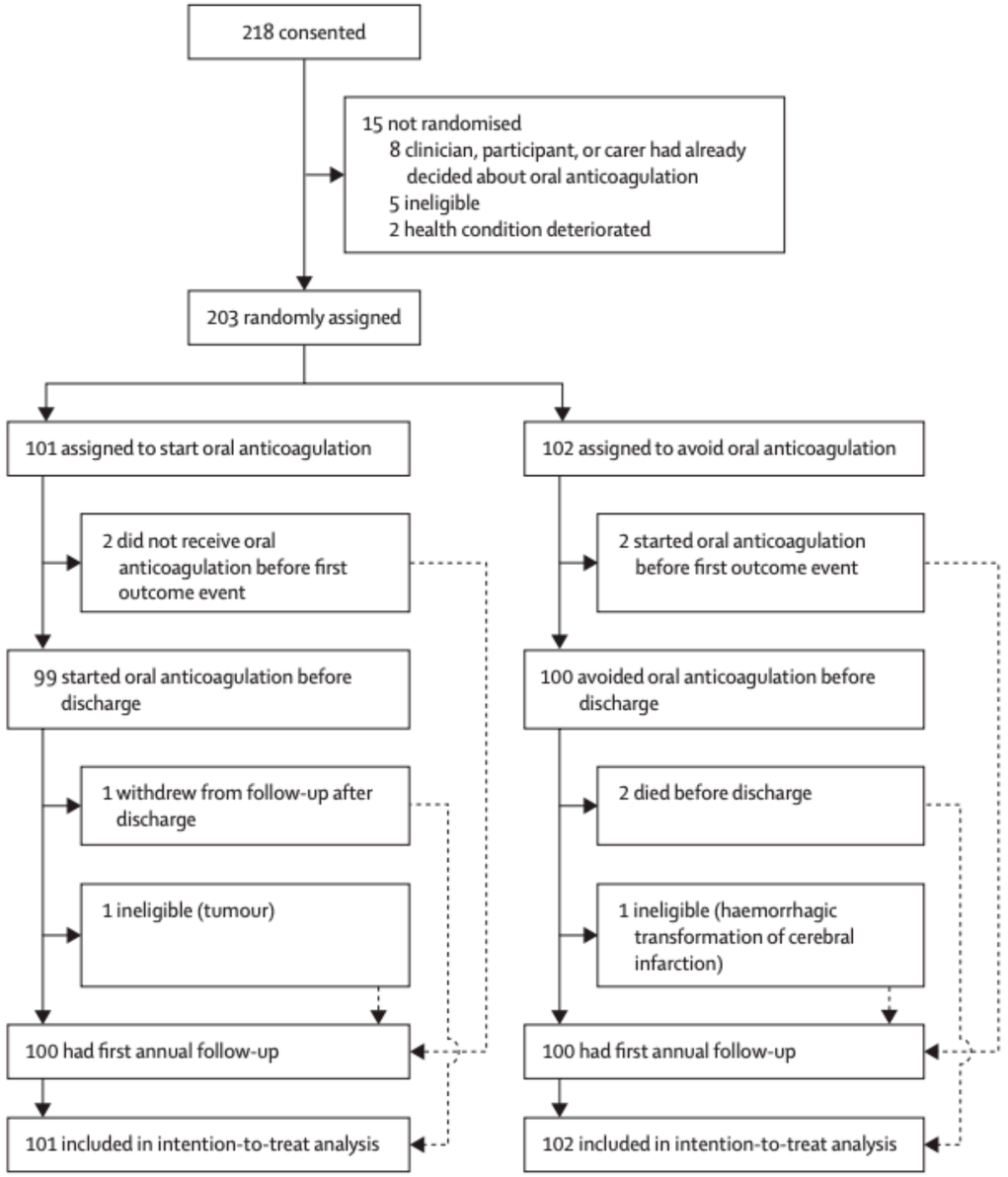




Stroke. 2017;48:314–320

SoSTART study

- SoSTART study was prospective, randomised, open-label, assessor-masked, parallel-group, pilot phase trial
- AF with ICH
- Comparing any OAC versus no OAC (none or only anti platelet agent)



Lancet Neurol 2021;20: 842-53

SoSTART study

	Start oral anticoagulation (n=101)	Avoid oral anticoagulation (n=102)	Unadjusted HR (95% CI), p value	Adjusted* HR (95% CI), p value
Primary outcome				
Recurrent symptomatic spontaneous intracranial haemorrhage	8 (8%)	4 (4%)	2·31 (0·69–7·68), p=0·173	2·42 (0·72–8·09), p=0·152
Composite secondary outcomes				
Any symptomatic major vascular event	12 (12%)	24 (24%)	0·51 (0·26–1·03), p=0·061	0·51 (0·26–1·03), p=0·060
Any stroke	11 (11%)	22 (22%)	0·53 (0·25–1·09), p=0·082	0·53 (0·25–1·09), p=0·084
Any stroke or vascular death	12 (12%)	23 (23%)	0·55 (0·27–1·10), p=0·092	0·55 (0·27–1·10), p=0·090

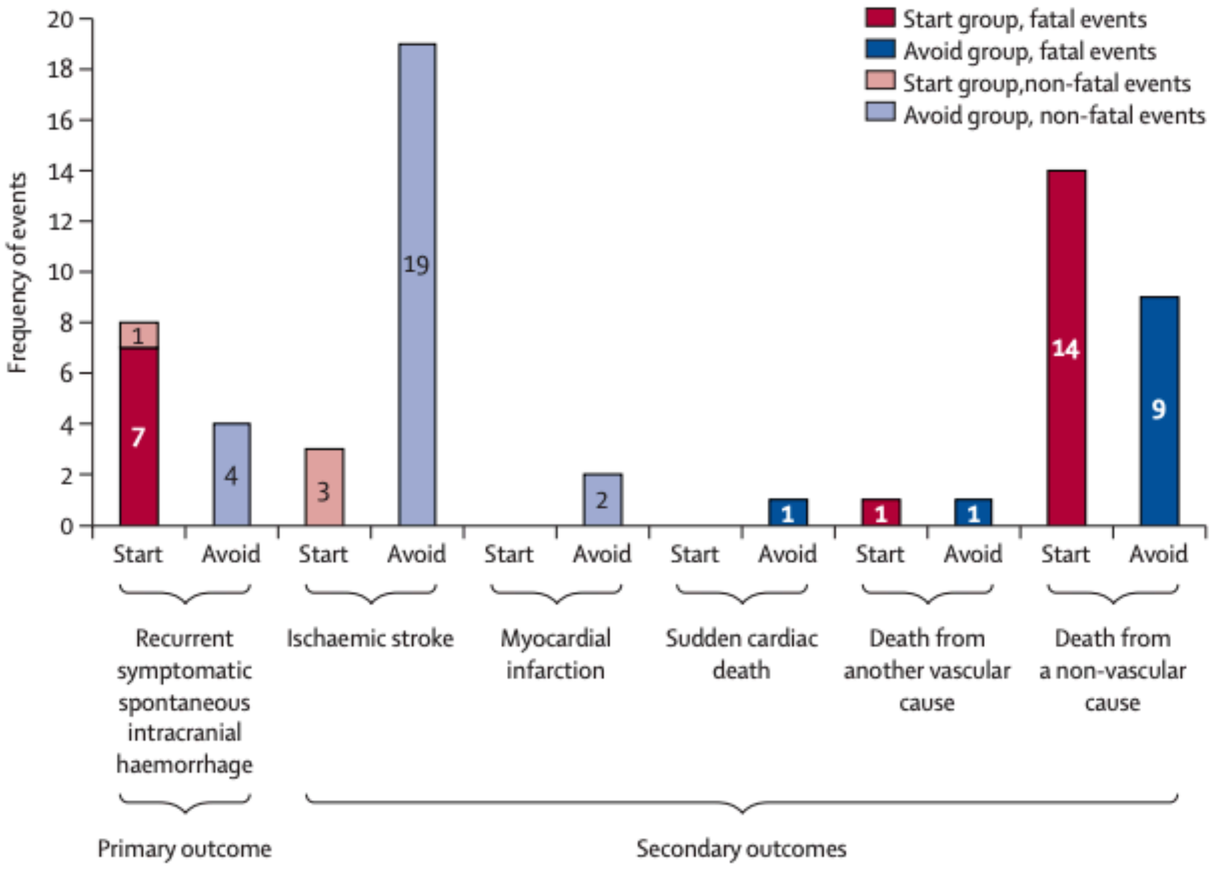
HR=hazard ratio. *Cox proportional hazards models were adjusted for two of the six minimisation variables: time since intracranial haemorrhage symptom onset (<10 weeks [reference] *vs* ≥10 weeks) and type of qualifying intracranial haemorrhage (lobar intracerebral haemorrhage *vs* non-lobar intracerebral haemorrhage and lobar intracerebral haemorrhage *vs* other); model non-convergence due to the low number of events prevented the inclusion of any more minimisation variables.

Table 2: **Risks of the first occurrence of primary and composite secondary outcome events during follow-up**

Lancet Neurol 2021;20: 842-53

SoSTART study

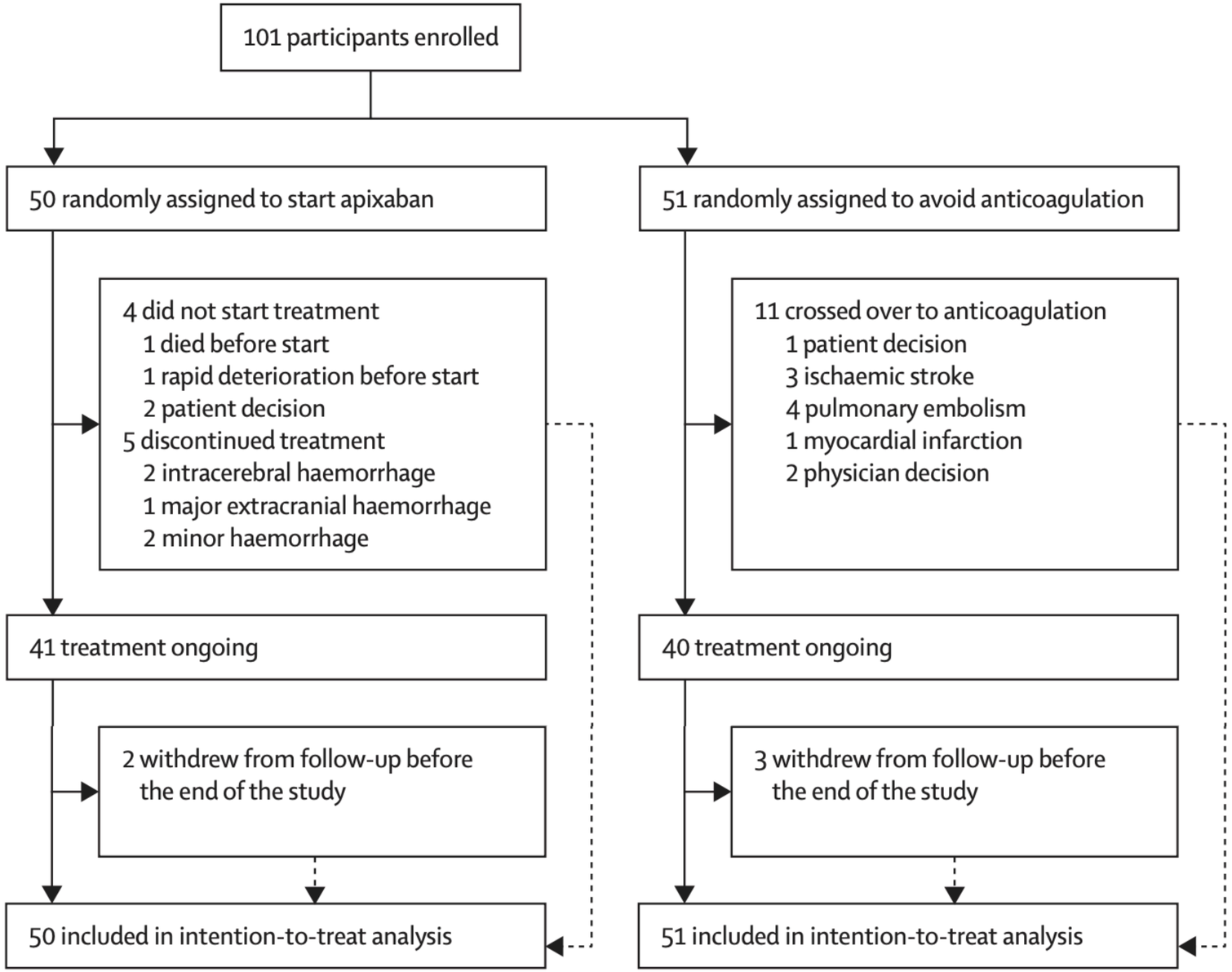
Interpretation:
Whether starting oral anticoagulation was non-inferior to avoiding it for people with atrial fibrillation after intracranial haemorrhage was inconclusive, although rates of recurrent intracranial haemorrhage were lower than expected.
In view of weak evidence from analyses of three composite secondary outcomes, the possibility that **<u>oral anticoagulation might be superior for preventing symptomatic major vascular events</u>** should be investigated in adequately powered randomised trials.



Lancet Neurol 2021;20: 842-53

APACHE-AF

- APACHE-AF was an investigator-led, prospective, randomised, open-label, phase 2 trial with blinded endpoint assessment in 16 hospitals in the Netherlands.
- AF with ICH
- Comparing apixaban versus no OAC (none or only anti platelet agent)



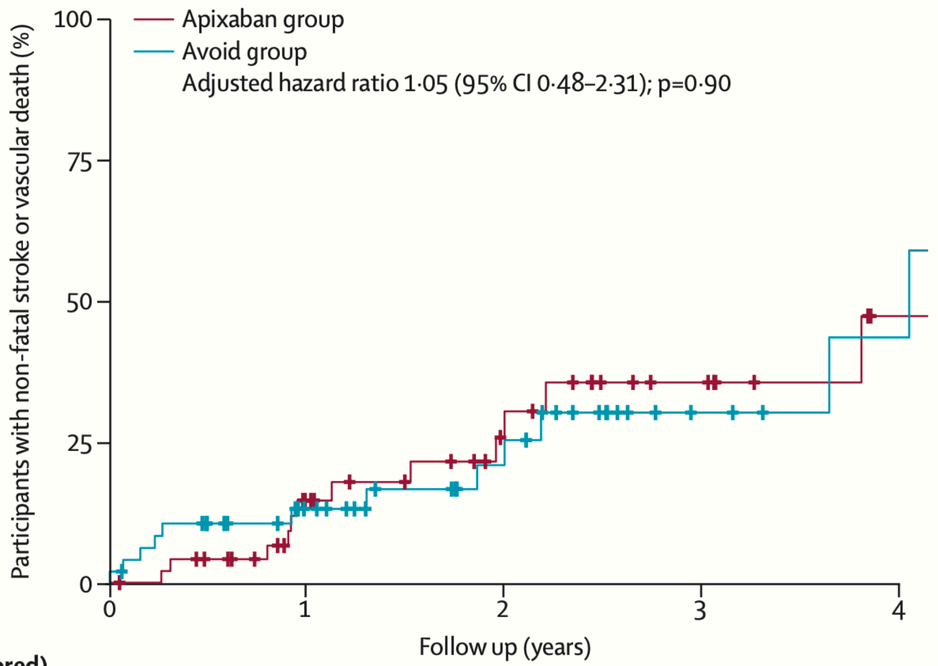
Lancet Neurol 2021;20: 907-916

APACHE-AF

	Apixaban group (n=50)	Avoid anticoagulation group (n=51)	Unadjusted analysis		Adjusted analysis	
			HR (95% CI)	p value	Adjusted HR (95% CI)	p value
Primary outcome						
Non-fatal stroke or vascular death	13 (26%)	12 (24%)	1·07 (0·49–2·34)	0·87	1·05 (0·48–2·31)	0·90
Secondary outcomes*						
Intracerebral haemorrhage	4 (8%)	1 (2%)	4·12 (0·46–36·94)	0·21	4·08 (0·45–36·91)	0·21
All major haemorrhagic events	6 (12%)	3 (6%)	2·14 (0·53–8·57)	0·29	2·11 (0·52–8·51)	0·29
Ischaemic stroke	6 (12%)	6 (12%)	0·97 (0·31–3·00)	0·96	0·96 (0·31–2·97)	0·94
All major occlusive events	6 (12%)	11 (22%)	0·46 (0·17–1·25)	0·13	0·46 (0·17–1·25)	0·13
All major vascular events according to the protocol†	14 (28%)‡	16 (31%)§	0·81 (0·39–1·66)	0·56	0·80 (0·39–1·64)	0·54
All major vascular events (myocardial infarction, stroke, or vascular death)¶	13 (26%)	13 (25%)	0·94 (0·43–2·02)	0·87	0·93 (0·43–2·00)	0·85

Lancet Neurol 2021;20: 907-916

APACHE-AF



Patients at risk (censored)					
Apixaban group	50 (0)	34 (10)	22 (19)	13 (26)	6 (32)
Avoid group	51 (0)	35 (10)	23 (20)	10 (31)	7 (33)
Cumulative number of events					
Apixaban group	0	6	9	11	12
Avoid group	0	6	8	10	11

Lancet Neurol 2021;20: 907-916

APACHE-AF trial

Interpretation:
Patients with atrial fibrillation who had an intracerebral haemorrhage while taking anticoagulants have a high subsequent annual risk of non-fatal stroke or vascular death, whether allocated to apixaban or to avoid anticoagulation.

Our data underline the need for randomised controlled trials large enough to allow identification of subgroups in whom restarting anticoagulation might be either beneficial or hazardous.

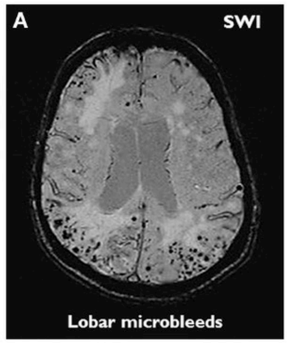
	Apixaban group (n=50)		Avoid anticoagulation group (n=51)	
	Patients with first event	All events	Patients with first event	All events
Primary outcome				
Non-fatal stroke or vascular death	13 (26%)	14	12 (24%)	12
Secondary outcomes				
Major haemorrhagic events	6 (12%)	6	3 (6%)	3
Intracerebral haemorrhage	4 (8%)	4	1 (2%)*	1
Subarachnoid haemorrhage	0	0	0	0
Traumatic intracranial haemorrhage	0	0	0	0
Major extracranial haemorrhage	2 (4%)	2	2 (4%)	2
Clinically relevant non-major bleeding	1 (2%)	1	0	0
Major occlusive events	6 (12%)	7	11 (22%)†	12
Ischaemic stroke	6 (12%)	7	6 (12%)	6
Myocardial infarction	0	0	2 (4%)	2
Pulmonary embolism‡	0	0	4 (8%)	4
Systemic embolism	0	0	0	0

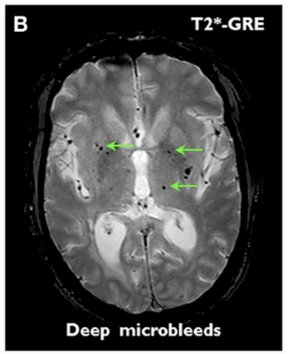
Lancet Neurol 2021;20: 907-916

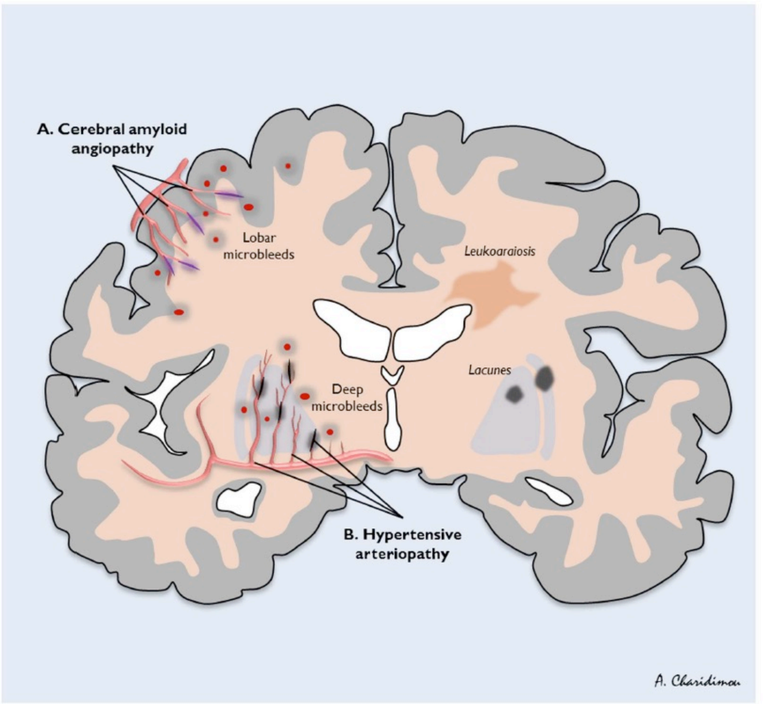
Neuroimage predictors for ICH

- Cerebral small vessel arteriopathies such as cerebral microbleeds, cerebral amyloid angiopathy are associated with OAC-associated ICH.
- The risk of recurrent bleeding after symptomatic ICH seems to be higher for lobar ICH than deep seated CMBs.

- Estimated prevalences of CAA in cognitively normal elderly was (5% to 7%), in patients with intracerebral hemorrhage (19% to 24%), and in patients with lobar intracerebral hemorrhage (50% to 57%).



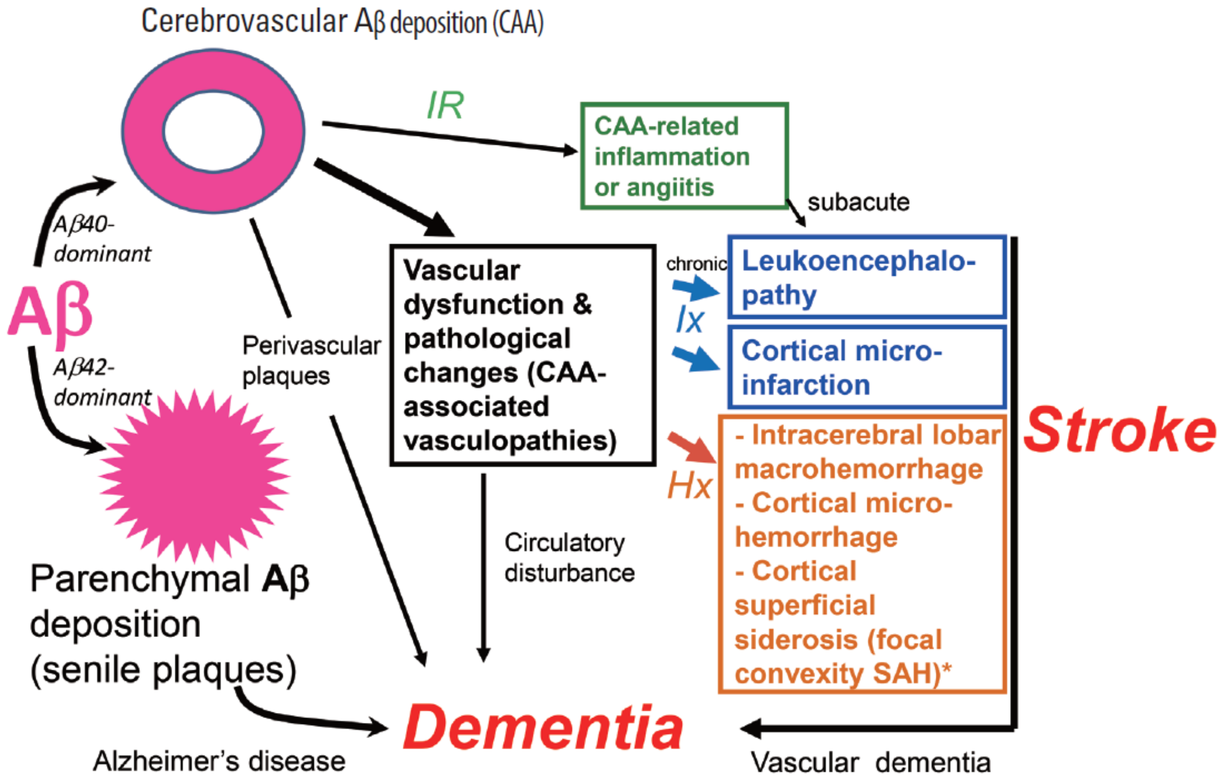




Frontier in Neurology 2012;3:133, Alzheimer's Dement.2022;18:10–28.

Cerebral amyloid angiopathy

- Cerebral amyloid angiopathy involves cerebrovascular amyloid deposition and accompany functional and pathological changes in cerebral blood vessels.
- CAA-associated vasculopathies lead to intracranial hemorrhage, ischemic changes and dementia.



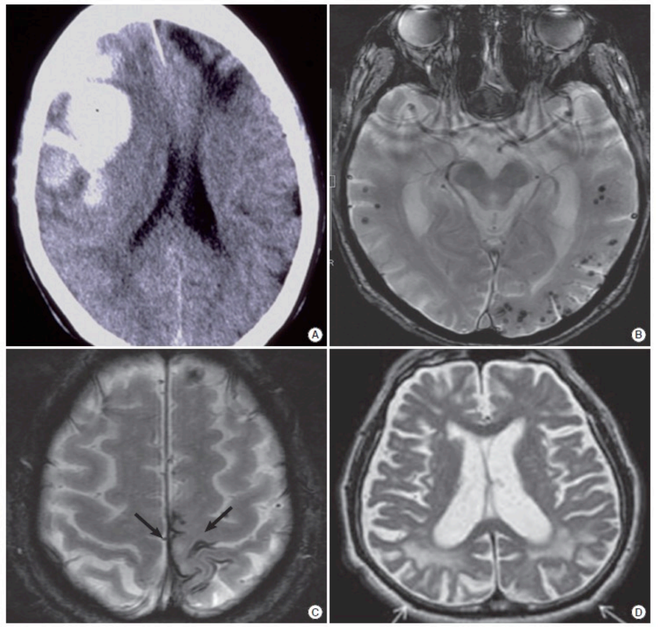


Figure 4. Imaging findings of CAA-related hemorrhages and white matter lesions. Fresh (arrow) and old (arrowhead) lobar macrohemorrhages in the frontal lobes on CT (A). Cortical microhemorrhages with lobar distribution (B) and focal subarachnoid hemorrhages (superficial siderosis) (C) on gradient echo T2*-weighted MRI. Posterior distribution of white matter hyperintensities (arrows on T2-weighted MRI) (D).

Frontier in Neurology 2012;3:133

Superficial siderosis

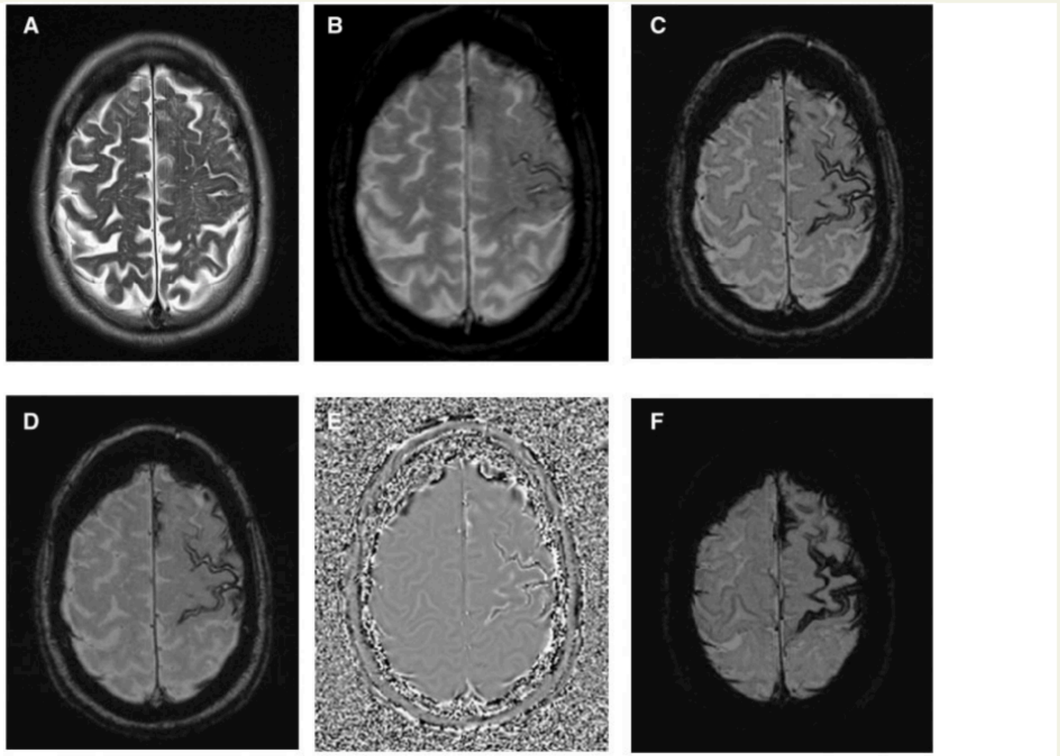


Figure 1 Detection of cSS on different MRI sequences. Axial slices through superior cerebral convexity in a patient with probable CAA. The T_2-weighted image (**A**) shows no cSS, while the T_2*-GRE (**B**) shows cSS as curvilinear low signal intensity areas on the surface of the left frontal gyri. SWI imaging (**C–F**): susceptibility-weighted image (**C**) is produced by the magnitude image (**D**) multiplied with a filtered phase image (**E**), which demonstrates more widespread and more conspicuous cSS than the T_2*-weighted GRE (**B**). The conspicuity of the cSS and of cortical veins is further enhanced in the minimum intensity projection image (**F**).

- Superficial siderosis of the CNS describes linear deposits of the blood-breakdown product haemosiderin within the subarachnoid space, the leptomeninges and the superficial layers of the cerebral or cerebellar cortices, or the spinal cord. The ICH risk at 4 years was 25% (95% CI: 7.6–28.3%) for patients without siderosis, 28.9% (95% CI: 7.7–76.7%) for patients with focal siderosis and 74% (95% CI: 44.1–95.7) for patients with disseminated cSS (log-rank test: P = 0.0031).

BRAIN 2015: 138; 2126–2139

Summary

Oral anticoagulation failure
Pharmacological failure
Comorbid diseases: atherosclerosis, RL shunt, cancer, small vessel disease
Medical condition prohibiting OAC use

High risk of bleeding
ICH
GI bleeding
Cerebral amyloid angiopathy
Fragile patients: frequent falling, Parkinsonism

Conventional strategies
Switch anticoagulation
Management co-morbid risk factors or diseases
Promoting compliance
Investigating predictor
…..

Novel strategies
Comprehensive and multidisciplinary approach
  Rhythm control
  Interventional or surgical approach
Development of novel oral anticoagulant
  FXI inhibitors etc.
…

WHAT SHOULD WE DO FOR ‘STROKE PATIENTS WITH A.FIB’