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Prévention des risques thrombotiques après une hémorragie cérébrale

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PhIND
PHYSIOPATHOLOGY & IMAGING OF NEUROLOGICAL DISORDERS

Intracerebral haemorrhage (ICH)

- Pejorative long-term prognostic

- ICH survivors are at risk of
  - Recurrent ICH: 1- 7%/y
  - Ischaemic stroke (IS): 1- 4%/y
- Risks vary among ICH subgroups

- How to optimize secondary prevention after ICH ?
  - Balance between risk of recurrent ICH and ischemic events

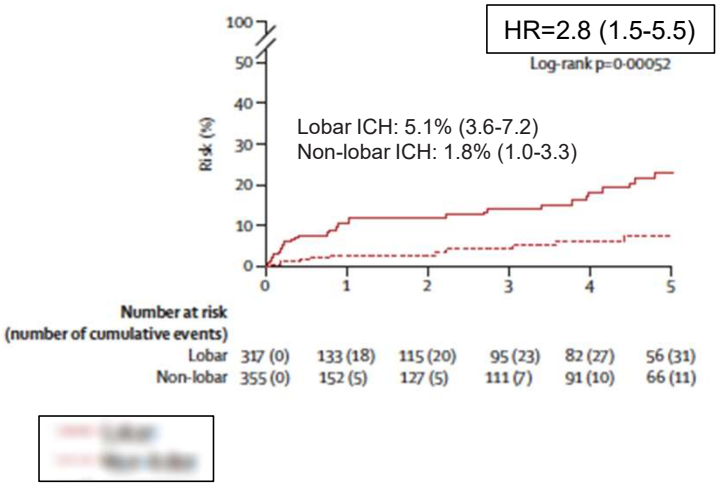
Poon MTC et al, JNNP 2014; Li L, Poon MTC et al, Lancet Neurol 2021

Risks of vascular events after ICH vary by ICH location

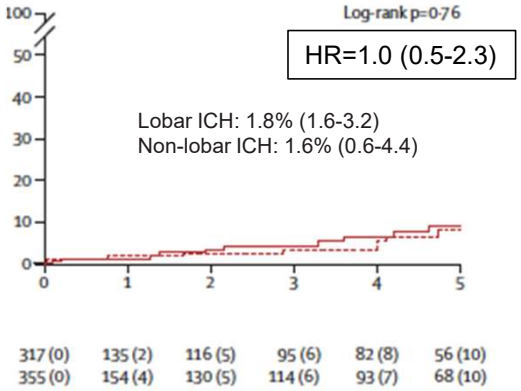
Pooled analyses of 2 <u>population-based studies</u>
674 1st ever ICHs (47% lobar ICH)
Mean age: 75y
32% Hx of occlusive vascular disease (no ≠ between lobar and non-lobar ICH)
1553 patient-years of follow-up

In lobar vs. non-lobar ICH:
-Increased risk of recurrent ICH (X2.8)
-Similar risk of IS
-Similar risk of vascular events
But inevitable biases due to observational studies

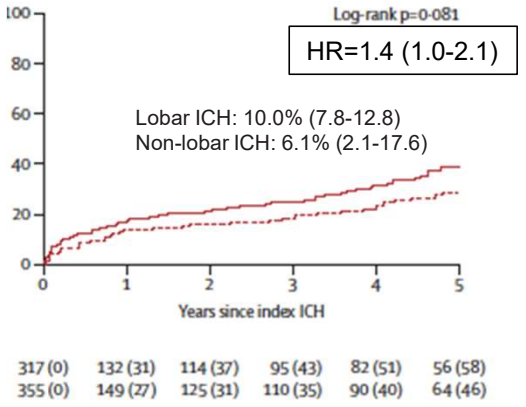
Annual rate of recurrent intracerebral haemorrhage



Ischaemic stroke (IS)



Vascular events: stroke (any type), MI or vascular death



Li L, Poon MTC et al, Lancet Neurol 2021

Whether to re-start antiplatelet therapy after ICH ?

the RESTART trial

ICH on antithrombotics (antiplatelet or anticoagulant) for (primary or secondary) prevention
Randomisation 1:1 (Re)Start monotherapy antiplatelet *vs.* Avoid antiplatelet

537 ICHs (62% lobar ICH)
2 y median follow-up
Hx of atherosclerotic disease: 71% in both arms
Hx of AF: 23% and 31%
No Hx of atherosclerotic disease or AF: 5% and 3%

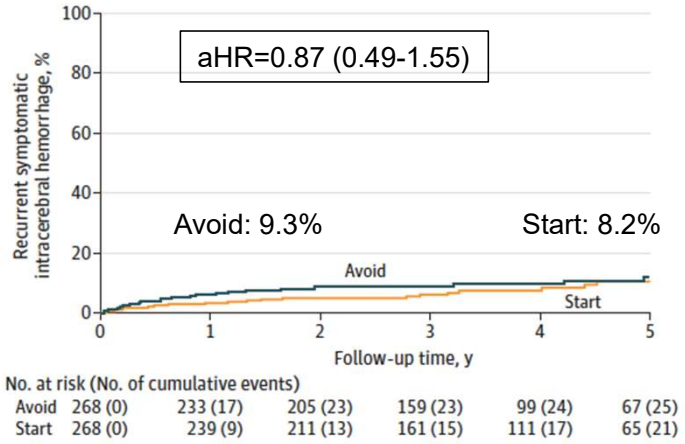
Adjustment for age and ICH location

Major occlusive vascular events
IS, MI, mesenteric ischemia, peripheral arterial occlusion, DVT/PE
Avoid: 21.3% *vs.* Start: 19.8%

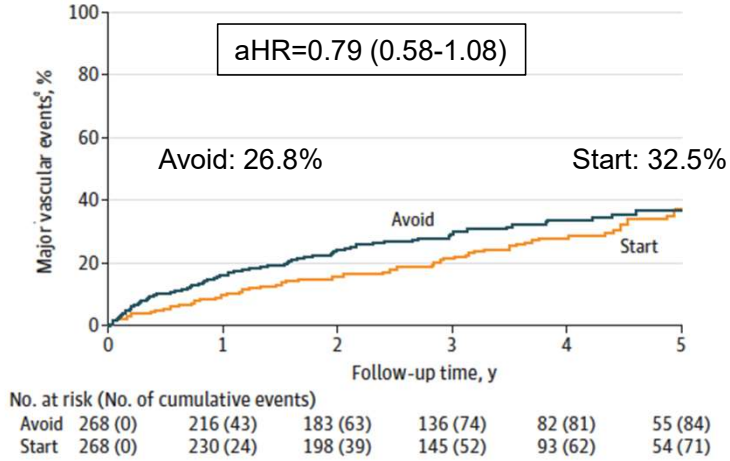
aHR=1.09 (0.75-1.59)

Lack of power: inclusion of 537/720 (75%) patients of the sample size target

Recurrent symptomatic ICH



Major vascular events: MI, stroke (any type) or vascular death



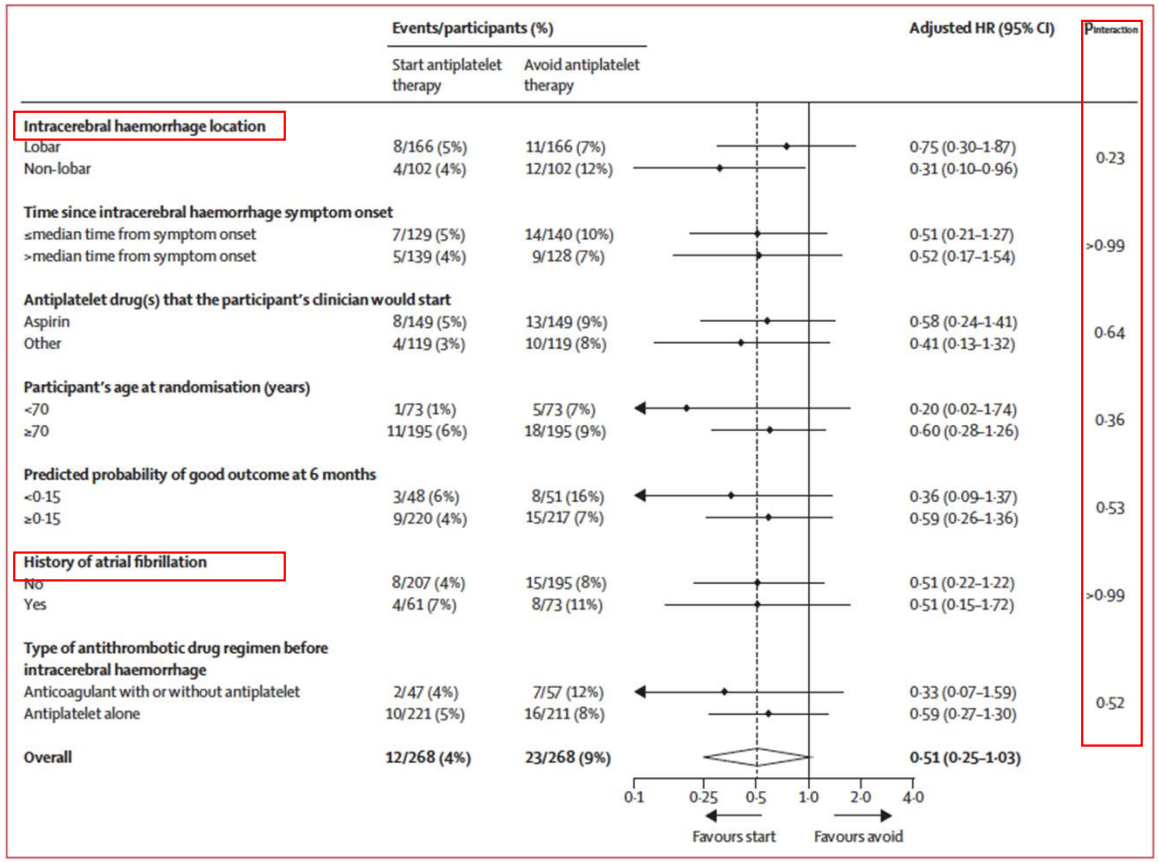
Al-Shahi Salman R et al, JAMA Neurol 2021

Whether to re-start antiplatelet therapy after ICH ?

the RESTART trial

No interaction by subgroups for the risk of rec ICH

Subgroup analyses of the risk of first recurrent symptomatic ICH



	Events/participants (%)		Adjusted HR (95% CI)	$P_{interaction}$
	Start antiplatelet therapy	Avoid antiplatelet therapy		
Intracerebral haemorrhage location				
Lobar	8/166 (5%)	11/166 (7%)	0·75 (0·30–1·87)	0·23
Non-lobar	4/102 (4%)	12/102 (12%)	0·31 (0·10–0·96)	
Time since intracerebral haemorrhage symptom onset				
≤median time from symptom onset	7/129 (5%)	14/140 (10%)	0·51 (0·21–1·27)	>0·99
>median time from symptom onset	5/139 (4%)	9/128 (7%)	0·52 (0·17–1·54)	
Antiplatelet drug(s) that the participant's clinician would start				
Aspirin	8/149 (5%)	13/149 (9%)	0·58 (0·24–1·41)	0·64
Other	4/119 (3%)	10/119 (8%)	0·41 (0·13–1·32)	
Participant's age at randomisation (years)				
<70	1/73 (1%)	5/73 (7%)	0·20 (0·02–1·74)	0·36
≥70	11/195 (6%)	18/195 (9%)	0·60 (0·28–1·26)	
Predicted probability of good outcome at 6 months				
<0·15	3/48 (6%)	8/51 (16%)	0·36 (0·09–1·37)	0·53
≥0·15	9/220 (4%)	15/217 (7%)	0·59 (0·26–1·36)	
History of atrial fibrillation				
No	8/207 (4%)	15/195 (8%)	0·51 (0·22–1·22)	>0·99
Yes	4/61 (7%)	8/73 (11%)	0·51 (0·15–1·72)	
Type of antithrombotic drug regimen before intracerebral haemorrhage				
Anticoagulant with or without antiplatelet	2/47 (4%)	7/57 (12%)	0·33 (0·07–1·59)	0·52
Antiplatelet alone	10/221 (5%)	16/211 (8%)	0·59 (0·27–1·30)	
Overall	**12/268 (4%)**	**23/268 (9%)**	**0·51 (0·25–1·03)**	

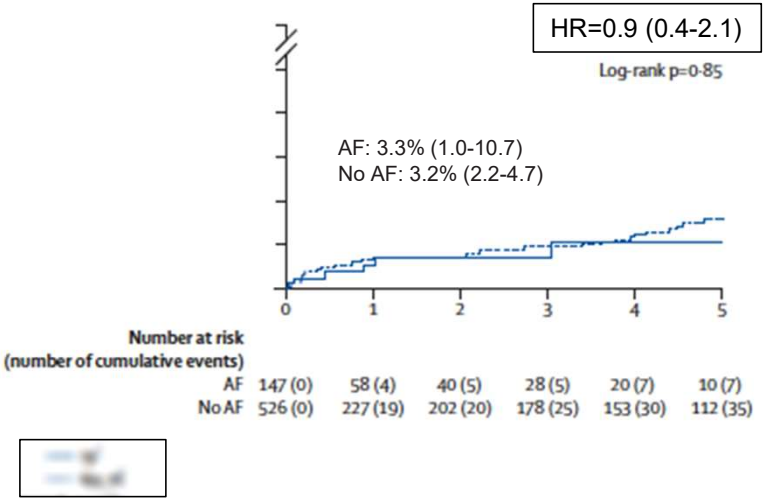
Al-Shahi Salman R et al, JAMA Neurol 2021

Risks of recurrent vascular events after ICH by history of AF

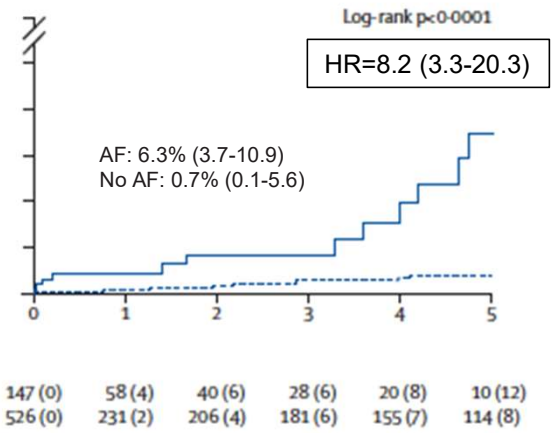
Pooled analyses of 2 population-based studies
674 1st ever ICHs (47% lobar ICH)
Mean age: 75y
22% Hx of AF (no ≠ between lobar and non-lobar ICH)
1553 patient-years of follow-up

ICH patients with AF:
-No difference in risk of rec ICH,
-Increased risk of IS and vascular events

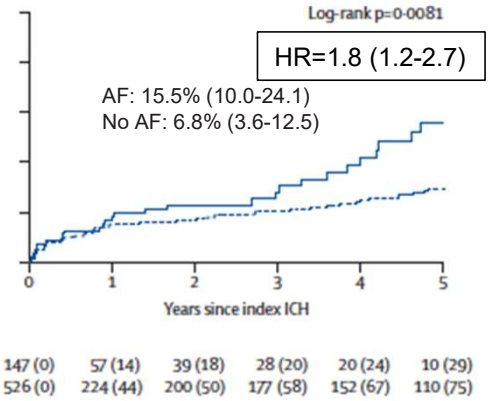
Annual rate of recurrent intracerebral haemorrhage



Ischaemic stroke



Vascular events: stroke (any type), MI or vascular death



Only in lobar ICH without AF: risk of rec ICH > IS
AF patients: risk of rec ICH, IS and vascular events is high in lobar and non-lobar ICH

Li L, Poon MTC et al, Lancet Neurol 2021

Risk of recurrent stroke with VKA-anticoagulation for AF after intracranial haemorrhage (ICrH)

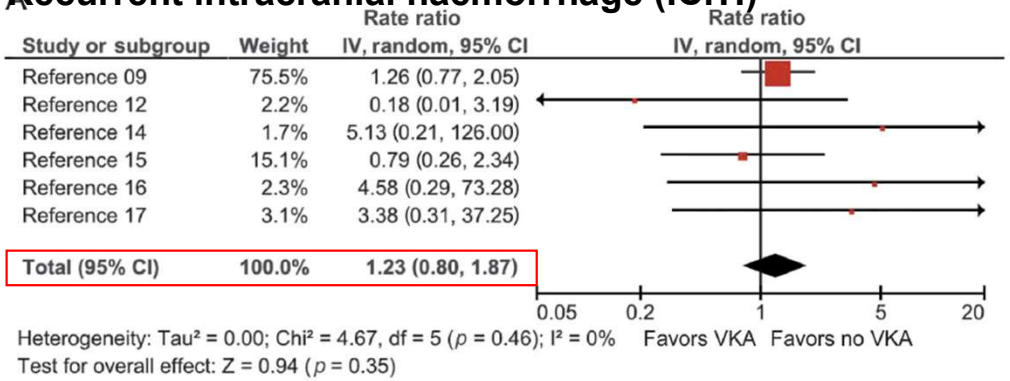
Meta-analysis of observational studies
2,452 ICHs with AF
Resumption of VKA vs. No VKA (antiplatelets or no antithrombotics)
Mean age: 76 y
41% female

Annual rate of rec ICrH
VKA: 4.6 (3.1–6.6)
No VKA: 4.0 (3.2–5.0)

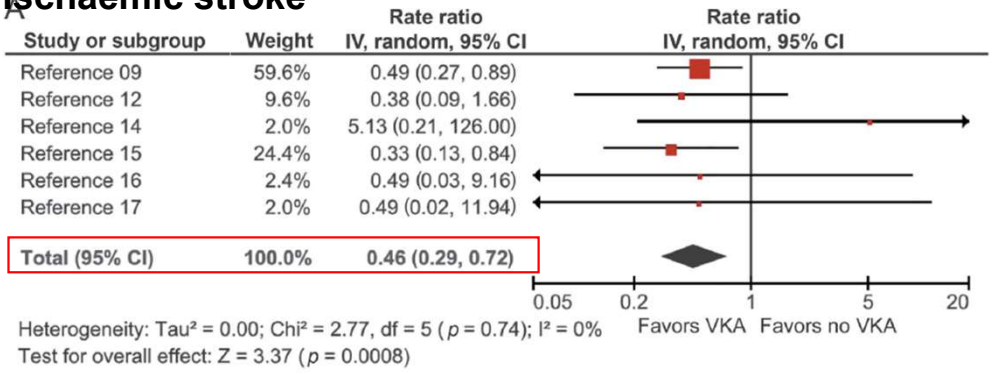
In ICH patients with AF, VKA is associated with:
-60% risk reduction in IS
-No increased risk in rec ICrH
But biases due to observational data
Physicians might not resume VKA in pts deemed to be at increased risk of rec ICH

Annual rate of IS
VKA: 3.2 (2.0–4.9)
No VKA: 7.3 (6.2–8.5)

A Recurrent intracranial haemorrhage (ICrH)



A Ischaemic stroke



Korompoki E, Poon MTC et al, Neurology 2017

Likelihood of resumption of VKA for AF after ICH

Meta-analysis of 3 prospective multicenter registries
941 ICHs on VKA at the time of ICH
with Hx of AF

Resumption of VKA vs. No VKA (antiplatelets or no antithrombotics)
Mean age: 72 y
39% female

Likelihood of resuming VKA after ICH:
-Higher CHA_2DS_2-VASC scores
-Non lobar ICH

Characteristics of Participants by Anticoagulation Resumption Status.

Variable	OAT Resumption	No OAT Resumption	p
No. of Individuals	262	679	-
Age (mean, SD) *	71.5 (8.9)	72.6 (9.4)	0.17
Sex (female)	97 (37)	258 (38)	0.85
CHA_2DS_2-VASc score ǂ	5 (5 – 6)	4 (4 – 6)	**0.012**
ICH Location			**0.003**
- Lobar	81 (31)	311 (46)	
- Non-lobar	181 (69)	368 (54)	
ICH Volume (median, IQR) ǂ	10.8 (3.4 – 24.4)	11.9 (4.3 – 26.4)	0.081
Discharge mRS (median, IQR) ǂ	3 (3 – 4)	3 (3 – 4)	0.25
Antiplatelet Agents	20 (8)	378 (56)	**< 0.001**

Murphy MP et al, Stroke 2018

VKA resumption for AF after high-risk intracerebral haemorrhage (ICH): lobar ICH and CAA

IPD meta-analysis of METRACE, MGH, ERICH registries
Incident ICHs with AF on VKA at the time of ICH
633 nonlobar ICHs and 379 lobar ICHs
Median follow-up of 48.6 months
Propensity score matching using GCS, ICH volume, IVH, discharge mRS, CHA2DS2-VASc score, and HAS-BLED score

MRI data available for 190/379 (50%) lobar ICH
Possible (n=136) and probable CAA (n=54)
Modified Boston criteria 2010

Among lobar ICH survivors
VKA resumption: long-term better functional outcome, decreased mortality and stroke recurrence

	All ICH			Nonlobar ICH			Lobar ICH		
Outcome[a]	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
Mortality	0.32	0.15–0.66	0.002[b]	0.30	0.10–0.91	0.035[b]	0.33	0.12–0.87	0.026[b]
Favorable outcome, mRS = 0–3	3.99	1.76–9.05	0.001[b]	4.10	1.24–13.57	0.022[b]	3.89	1.26–11.98	0.019[b]
All-cause stroke	0.50	0.32–0.79	0.003[b]	0.49	0.26–0.93	0.031[b]	0.51	0.26–0.99	0.047[b]
Recurrent ICH	1.10	0.96–1.26	0.20	1.10	0.94–1.28	0.23	1.21	0.86–1.70	0.27
Ischemic stroke	0.46	0.28–0.75	0.002[b]	0.44	0.22–0.90	0.025[b]	0.48	0.25–0.94	0.032[b]

Among possible and probable CAA-ICH survivors
VKA resumption: long-term decreased mortality
But lower mRS at discharge for lobar ICH who started VKA

	Possible CAA			Probable CAA		
Outcome[a]	HR	95% CI	*p*	HR	95% CI	*p*
Mortality	0.27	0.08–0.86	0.028[b]	0.30	0.10–0.92	0.037[b]
Favorable outcome, mRS 0–3	3.40	1.22–9.46	0.020[b]	3.11	1.08–8.97	0.038[b]

Biffi A et al, Ann Neurol 2017

Anticoagulation for AF in ICH patients

- 1/5 of ICH patients have AF (either previously known or newly diagnosed)
- In ICH patients with AF, observational studies suggested
  - No increase in risk of rec ICH
  - Increased risk of IS and vascular events
- But limitations of observational data
  - Selection biaises
  - Confounding
- Uncertainties remain about the benefit of resuming anticoagulant after ICH in AF patients

Horstmann S, et al. Eur J Neurol 2014
Li L, Poon MTC et al, Lancet Neurol 2021

Whether to re-start anticoagulation after ICH in AF patients ?

RCTs of oral anticoagulation for AF in ICH survivors

Trial	Stroke	Intervention vs. comparator	n	Status	Contact
APACHE-AF	ICH	Apixaban vs. no OAC	101	Closed	Klijn/vd Worp
NASPAF-ICH	ICH	NOAC vs. AP	30	Closed	Shoamanesh/Hart
SoSTART	ICrH	OAC vs. no OAC	203	Closed	Al-Shahi Salman
STATICH	ICH	OAC vs. no OAC	47/250	Open	Wyller/Rönning
A_3ICH	ICH	Apixaban vs. LAAO vs. no AT	48/300	Open	Cordonnier
PRESTIGE-AF	ICH	NOAC vs. no OAC	50/654	Open	Veltkamp
ASPIRE	ICH	Apixaban vs. aspirin	28/700	Open	Sheth/Kamel
ENRICH-AF	ICrH	Edoxaban vs. no OAC	104/1200	Open	Shoamanesh

ICH: intracerebral haemorrhage
ICrH: intracranial haemorrhage, including intracerebral haemorrhage (ICH), intraventricular haemorrhage, subarachnoid haemorrhage, or subdural haemorrhage
AP: antiplatelet therapy
AT: antithrombotic therapy

Data on June 2021

Effects of long-term anticoagulant for AF after intracranial haemorrhage: Individual participant data meta-analysis of RCTs (COCROACH)

RCT	Participants	Intervention (start OAC)	Comparator (avoid OAC)	Ratio	Primary outcome	Follow-up
SoSTART: Start or Stop Anticoagulants Randomised Trial	ICrH >24h after onset, age >17y, AF, CHA_2DS_2-VASc score ≥2 (n=201)	NOAC or vitamin K antagonist (n=100)	Antiplatelet agents or no antithrombotic agents (n=101)	1:1	Recurrent symptomatic ICH	≥12m
APACHE-AF	Anticoagulant-associated ICH 7-90d after onset, age >17y, AF, mRS<5, CHA_2DS_2-VASc score ≥2 (n=101)	Apixaban (n=50)	Antiplatelet agent or no antithrombotic agents (n=51)	1:1	Vascular death or non-fatal stroke	≥6m
NASPAF-ICH	ICH >14d after onset, age >44y, AF indicating OAC by $CHADS_{65}$ score (n=30)	NOAC (n=21)	Aspirin (n=9)	2:1	Recurrent stroke	≥6m

Al-Shahi Salman R et al, unpublished, data presented at ESOC 2022

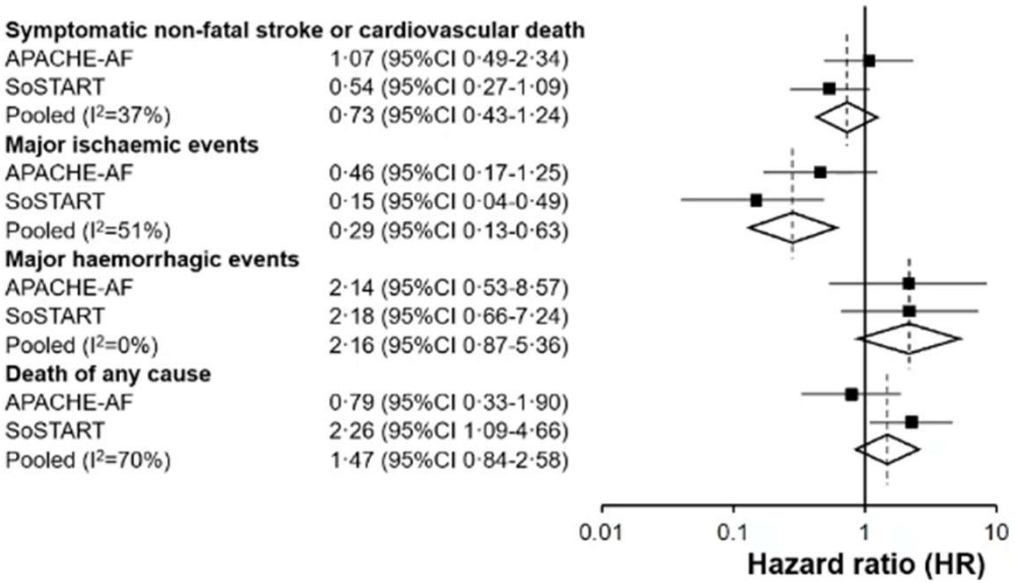
Effects of long-term anticoagulant for AF after intracranial haemorrhage: Individual participant data meta-analysis of RCTs (COCROACH)

Results: frequencies of outcomes

	Start OAC (n=150)	Avoid OAC (n=152)
Primary outcome		
Symptomatic non-fatal stroke or cardiovascular death	25 (16·7%)	35 (23·0%)
Secondary outcomes		
Major ischaemic events	9 (6·0%)	32 (21·1%)
Ischaemic stroke	9 (6·0%)	25 (16·4%)
Systemic arterial embolism	0 (0%)	0 (0%)
Pulmonary embolism	0 (0%)	4 (2·6%)
Myocardial infarction	0 (0%)	4 (2·6%)
Major haemorrhagic events	14 (9·3%)	7 (4·6%)
Intracranial haemorrhage	12 (8·0%)	5 (3·3%)
Extracranial haemorrhage	2 (1·3%)	2 (1·3%)
Death of any cause	31 (20·7%)	22 (14·5%)
Vascular death	13 (8·7%)	9 (5·9%)
Death of any other cause	18 (12·0%)	13 (8·6%)

Outcome: stroke (any type) i.e. ischaemic or heamorrhagic stroke

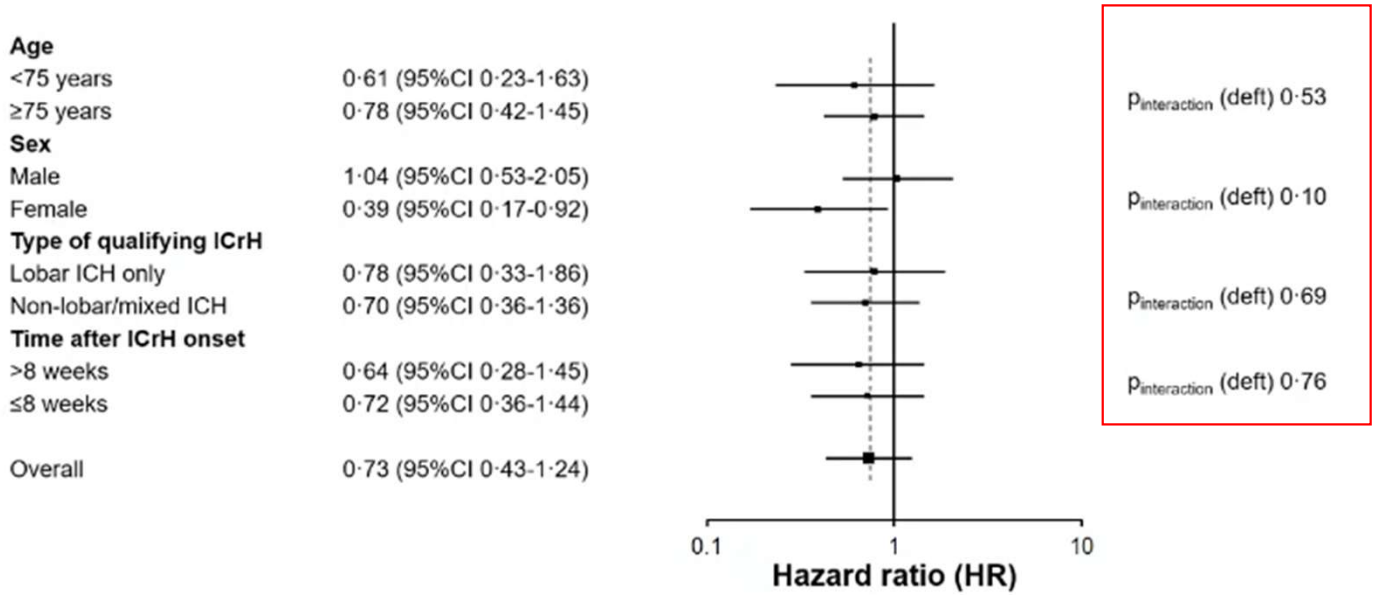
Effect of start vs avoid OAC on outcomes



Al-Shahi Salman R et al, unpublished data presented at ESOC 2022

Effects of long-term anticoagulant for AF after intracranial haemorrhage: Individual participant data meta-analysis of RCTs (COCROACH)

Effect of start vs avoid OAC on outcomes on stroke or cardiovascular death in subgroups



Al-Shahi Salman R et al, unpublished data presented at ESOC 2022

Pilot trials showed the need of phase III trials

Ongoing RCTs: various interventions and controls

RCT	Stroke	Intervention vs. comparator	Recruited / target	Contact
STATICH	ICH	OAC *vs* no OAC	57 / 250	Rønning/Sandset
A_3ICH	ICH	Apixaban *vs* LAAO *vs* no antithrombotic therapy	60 / 300	Cordonnier
PRESTIGE-AF	ICH	NOAC *vs* no OAC	125 / 654	Veltkamp
ASPIRE	ICH	Apixaban *vs* aspirin	84 / 700	Sheth/Kamel
ENRICH-AF	ICrH	Edoxaban *vs* no OAC	330 / 1,200	Shoamanesh

Recruitment data on 2nd

Should high-risk ICH patients undergo LAAO rather than oral anticoagulation (OAC) ?

- ICH patients were excluded from the RCTs of LAAO *vs*. OAC !
- Data on LAAO in ICH are only observational and limited
- Most of the RCT of LAAO *vs*. OAC used VKA as controls
- After LAAO, patients must take long-term antiplatelet therapy (and temporarily dual antiplatelet)

3 non-inferiority trials have compared LAAO *vs.* oral anticoagulation for non valvular AF

	PROTECT AF	PREVAIL	PRAGUE-17
Main inclusion criteria	Non v AF with CHADS2 score≥1	Non v AF with CHADS2 score ≥2	Non v AF with Hx of bleeding, or cardioembolic events, or CHA2DS2-VASc score≥3, and HAS-BLED score≥2
Country	USA and Europe.	USA	Czech Republic
LAAO device	WATCHMAN device	WATCHMAN device	Amulet (25%) or Watchman (75%)
After LAACO regimen	Warfarin for 45d, Then clopidogrel + aspirin for 6 months, Then aspirin alone indefinitely	Warfarin and aspirin for 45 days, If complete closure of the LAA on the 45-day TEE, clopidogrel + aspirin for 6-months, Then aspirin alone indefinitely If no complete closure of the LAA on the 45-day TEE, warfarin and aspirin for 6months When seal is adequate, aspirin alone indefinitely	Aspirin + clopidogrel for 3 months, Then aspirin alone indefinitely
Oral anticoagulation	VKA (INR 2-3)	VKA (INR 2-3)	DOAC (Apixaban 95%)

IPD meta-analysis of the PROTECT AF and PREVAIL non-inferiority trials: LAAO *vs.* VKA for non valvular AF

LAAO: procedural complications rate
-8.7% in PROTECT AF
-4.2% in PREVAIL

No ICH pt included

Non-inferiority margin: 1.75 as the upper bound for the HR
Primary outcome: (ischemic or hemorrhagic) stroke or TIA; 2) systemic embolism; or 3) cardiovascular death

TABLE 4 5-Year Patient-Level Meta-Analysis of PROTECT AF and PREVAIL (2:1 Randomization)

	Device Group (n = 732)		Control Group (n = 382)			
	No. of Events	Rate (per 100 PY)	No. of Events	Rate (per 100 PY)	Hazard Ratio (95% Confidence Interval)	p Value
Efficacy: stroke/SE/CV death	79/2,856.0	2.8%	50/1,472.8	3.4%	0.82 (0.58-1.17)	0.27
All stroke or SE	49/2,849.4	1.7%	27/1,472.9	1.8%	0.96 (0.60-1.54)	0.87
Ischemic stroke or SE	45/2,850.2	1.6%	14/1,479.1	0.95%	1.71 (0.94-3.11)	0.08
Hemorrhagic stroke	5/2,954.8	0.17%	13/1,499.0	0.87%	0.20 (0.07-0.56)	0.0022
Ischemic stroke or SE >7 days	37/2,862.1	1.3%	14/1,479.1	0.95%	1.40 (0.76-2.59)	0.28
Disabling stroke	13/2,943.0	0.44%	15/1,493.8	1.0%	0.45 (0.21-0.94)	0.03
Nondisabling stroke	31/2,879.1	1.1%	12/1,484.3	0.81%	1.38 (0.71-2.68)	0.35
CV/unexplained death	39/2,960.5	1.3%	33/1,505.2	2.2%	0.59 (0.37-0.94)	0.027
All-cause death	106/2,961.6	3.6%	73/1,505.2	4.9%	0.73 (0.54-0.98)	0.035
Major bleeding, all	85/2,748.4	3.1%	50/1,414.7	3.5%	0.91 (0.64-1.29)	0.60
Major bleeding, non-procedure-related	48/2,853.6	1.7%	51/1,411.3	3.6%	0.48 (0.32-0.71)	0.0003

Reddy VY et al, JACC 2017

The non-inferiority PRAGUE-17 trial
LAAO *vs*. DOAC for non valvular AF

LAAO: procedural complications rate 2.6/an

ICH pt included ?

Non inferiority margin: 1.469 as the upper bound for the HR
Primary outcome: (ischemic or haemorrhagic) stroke or TIA; 2) systemic embolism; 3) clinically significant bleeding; 4) cardiovascular death; or 5) a significant peri-procedural or device-related complications.

TABLE 3 Incidence of Composite Primary Endpoint and its Components in the Presence of Competing Risk (Noncardiovascular Death for Primary Endpoint and Cardiovascular Death, All-Cause Death for Other Endpoints) in the Intention-to-Treat Populations

	DOAC (n = 201)			LAAC (n = 201)					
	No. of Patients With Event	No. Events	Event Rate/Yr	No. of Patients With Event	No. Events	Event Rate/Yr	Subdistribution Hazard Ratio (95% CI)	p Value	p Value for Noninferiority
Primary endpoint	41	47	13.42	35	38	10.99	0.84 (0.53-1.31)	0.44	0.004
Cardiovascular death	15	15	4.28	11	11	3.18	0.75 (0.34-1.62)		
All stroke/TIA	9	9	2.57	9	9	2.60	1.00 (0.40-2.51)		
Ischemic stroke/TIA	8	8	2.28	9	9	2.60	1.13 (0.44-2.93)		
Systemic embolism	1	1	0.29	0	0	0.00	–		
Procedure/device related complications	–	–	–	9	9	2.60	–		
ISTH major/nonmajor bleeding	22	26	7.42	18	19	5.50	0.81 (0.44-1.52)		
ISTH major/nonmajor bleeding not related to device	22	26	7.42	12	13	3.76	0.53 (0.26-1.06)		

No difference in all cause mortality: 4.9% vs 4.3% (HR=0.88, 95%CI 0.48-1.63)

Osmancik et al, JACC 2020

In ICH survivors with indication of antithrombotic therapy

- Feasibility of trials comparing antithrombotic strategies
- Need of further large RCTs in ICH survivors
  - With atherosclerotic disease comparing starting and avoid antiplatelet therapy
  - With AF comparing starting or avoiding anticoagulation or LAAO

- Subgroup analysis
  - ICH aetiology, in particular CAA
  - BP control
  - Burden of small vessel disease
  - Additional atherosclerotic disease

PRESTIGE-AF

PREVENTION OF STROKE IN INTRACEREBRAL HAEMORRHAGE SURVIVORS WITH ATRIAL FIBRILLATION

- **Inclusion criteria:**
- ICH from 15 days to 12 months
- Non valvular AF
- CHADVASC score ≥3 in women and ≥2 in men
- mRS ≤4

- **Exclusion criteria:**
- ICH due to trauma or vascular malformation
- Absolute need for antiplatelet therapy

Randomisation:

DOAC *vs* no anticoagulation (antiplatelet therapy and preventive anticoagulation are permitted)

Contactez-moi: boulanger-ma@chu-caen.fr

Ongoing RCTs of stroke prevention for AF after ICH: LAAO *vs*. medical therapy

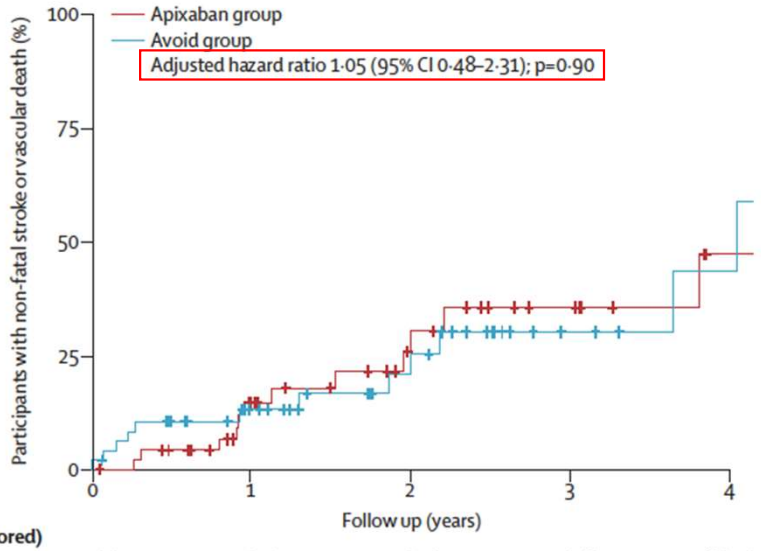
- **STROKECLOSE Trial**
- LAAO *vs.* medical therapy (VKA, non-VKA OAC, antiplatelet therapy or no antithrombotic therapy)
- ClinicalTrials.gov Identifier: NCT03463317

- **A3ICH Trial**
- LAAO *vs.* apixaban *vs*. no antithrombotic therapy
- ClinicalTrials.gov Identifier: NCT03243175

Apixaban *vs.* avoid anticoagulation after intracerebral haemorrhage (ICH) in patients with AF:
the APACHE-AF trial

Pilot phase II trial
Randomisation 1:1 Apixaban 5mg twice daily *vs.* No anticoagulation (any antiplatelet or no antithrombotic)
101 ICHs on anticoagulation at the time of ICH (14% lobar ICH)
With AF and CHA_2DS_2-VASC ≥2
2 y median follow-up

Primary outcome: non-fatal stroke (IS, rec ICH or subarachnoid haemorrhage) or vascular death



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

Annual rates
Avoid anticoagulant: 11.9% (6.2-20.8)
Apixaban: 12.6% (6.7-21.5)

Schreuder FHBM et al, APACHE-AF trial. Lancet Neurol 2021

Non-vitamin K Oral Anticoagulants in Intracerebral Hemorrhage (ICH) survivors with AF:
the NASPAF-ICH trial

Feasibility phase II trial
30 ICHs
With AF and $CHADS_2$ ≥1
Median follow-up: 15.3 months (range 10.8 months–2.8 years)
Blood pressure target <130/80 mm Hg

Randomisation 2:1 NOAC (n=21) *vs.* aspirin 81 mg daily (n=9)
Among NOAC: 76% received apixaban and 24% received dabigatran

Primary feasibility outcome: recruitment rate
Primary efficacy outcome: any stroke (*i.e.* IS or recurrent ICH)

65 patient-years of follow-up
Primary outcome:
- -NOAC: 0/21
- -Aspirin: 1/9 (11.1%) =1 major systemic haemorrhage

Shoamanesh A et al, NASPAF-ICH trial presented at ISC 2020 (unpublished)

Start or Stop Anticoagulants for AF after spontaneous intracranial haemorrhage: the SoSTART trial

Pilot non-inferiority trial
203 ICrHs not due to an underlying macrovascular cause
- 187/203 (92%) ICH (36% lobar ICH and 64% non-lobar ICH)

With AF and CHA_2DS_2-VASC ≥2
Median follow-up of 1.2 years

Randomisation 1:1 Start OAC (NOAC or warfarin) **or avoid oral anticoagulation** (antiplatelet or no antithrombotic)
Non-inferiority trial: 12% non-inferiority margin (aHR=3.2), 1-sided p=0.025 and power=90%
Planned sample size of 190 participants

Al-Shahi Salman R et al, Lancet Neurol 2021

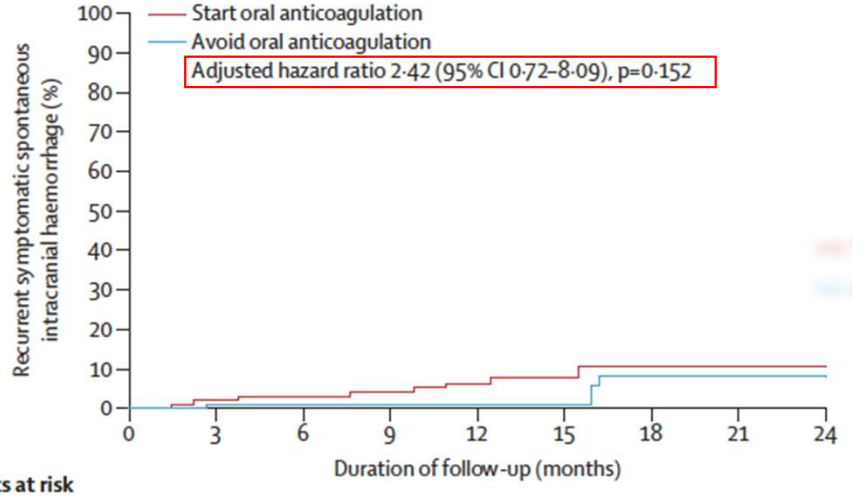
Start or Stop Anticoagulants for AF after spontaneous intracranial haemorrhage: the SoSTART trial

A pilot-phase **non-inferiority trial**
Randomisation 1:1 Start OAC (NOAC or warfarin) **or avoid oral anticoagulation** (antiplatelet or no antithrombotic)
With AF and CHA_2DS_2-VASC ≥2
Non-inferiority trial: 12% non-inferiority margin (aHR=3.2), 1-sided p=0.025 and power=90%
Planned sample size of 190 participants

203 ICrHs: 187/203 (92%) ICH (36% lobar ICH and 64% non-lobar ICH)

Primary outcome: recurrent symptomatic intracranial haemorrhage

96% adherence to allocated treatment
Average systolic BP=130mmHg
99% NOAC in the anticoagulant arm
Median follow-up of 1.2 years



Patients at risk (number censored)									
Start oral anticoagulation	101 (1)	95 (4)	90 (8)	88 (9)	65 (30)	35 (59)	26 (67)	25 (68)	14 (79)
Avoid oral anticoagulation	102 (0)	97 (4)	96 (5)	96 (5)	69 (32)	45 (56)	35 (63)	34 (64)	19 (79)
Cumulative number of events									
Start oral anticoagulation	0	2	3	4	6	7	8	8	8
Avoid oral anticoagulation	0	1	1	1	1	1	4	4	4

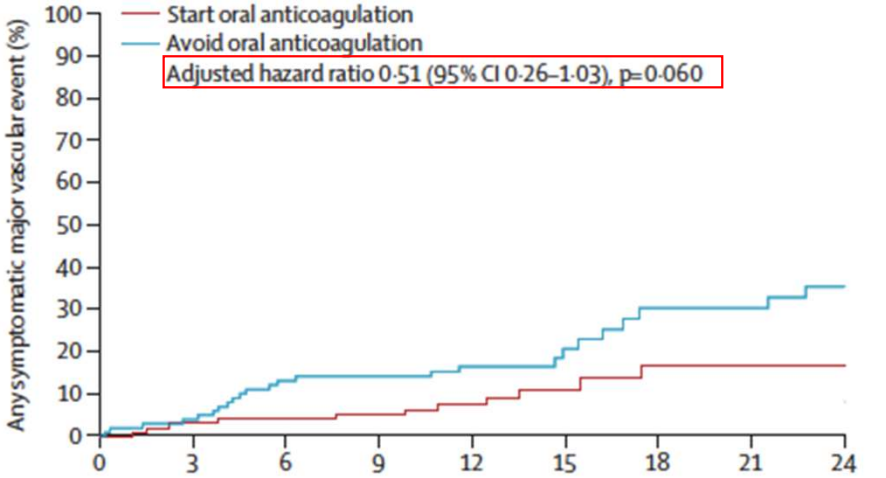
Start: n=8/101 (8%)
Avoid: n=4/102 (4%)

Non-inferiority was not met

Al-Shahi Salman R et al, Lancet Neurol 2021

Start or Stop Anticoagulants for AF after spontaneous intracranial haemorrhage: the SoSTART trial

Secondary outcome: any symptomatic major vascular event (MI, symptomatic intracranial haemorrhage, IS, symptomatic DVT)



Patients at risk (number censored)									
Start oral anticoagulation	101 (1)	94 (4)	89 (8)	87 (9)	65 (29)	34 (58)	25 (65)	24 (66)	14 (76)
Avoid oral anticoagulation	102 (0)	94 (4)	85 (4)	84 (4)	59 (27)	36 (48)	27 (53)	27 (53)	16 (62)
Cumulative number of events									
Start oral anticoagulation	0	3	4	5	7	9	11	11	11
Avoid oral anticoagulation	0	4	13	14	16	18	22	22	24

Avoid: n=24/101 (24%)

Start: n=11/101 (12%)

Al-Shahi Salman R et al, Lancet Neurol 2021