Timing of anticoagulation after cardioembolic stroke associated with atrial fibrillation

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Disclosures (last two years)

Speaker bureaux:
- Bristol-Myers Squibb (Caravaggio)
- Pfizer (Caravaggio)

Study steering committees
- Anthos (Aster – Magnolia)
- Daiichi Sankyo (Cope)
- sanofi (Omero)

No conflict of interest with implications with the current presentation

My talk today

Timing of anticoagulation after cardioembolic stroke associated with Atrial Fibrillation

Why is it a such a critical clinical issue?

What's the anticoagulant to be preferred

Recently published or ongoing studies

Management (treatment) implications

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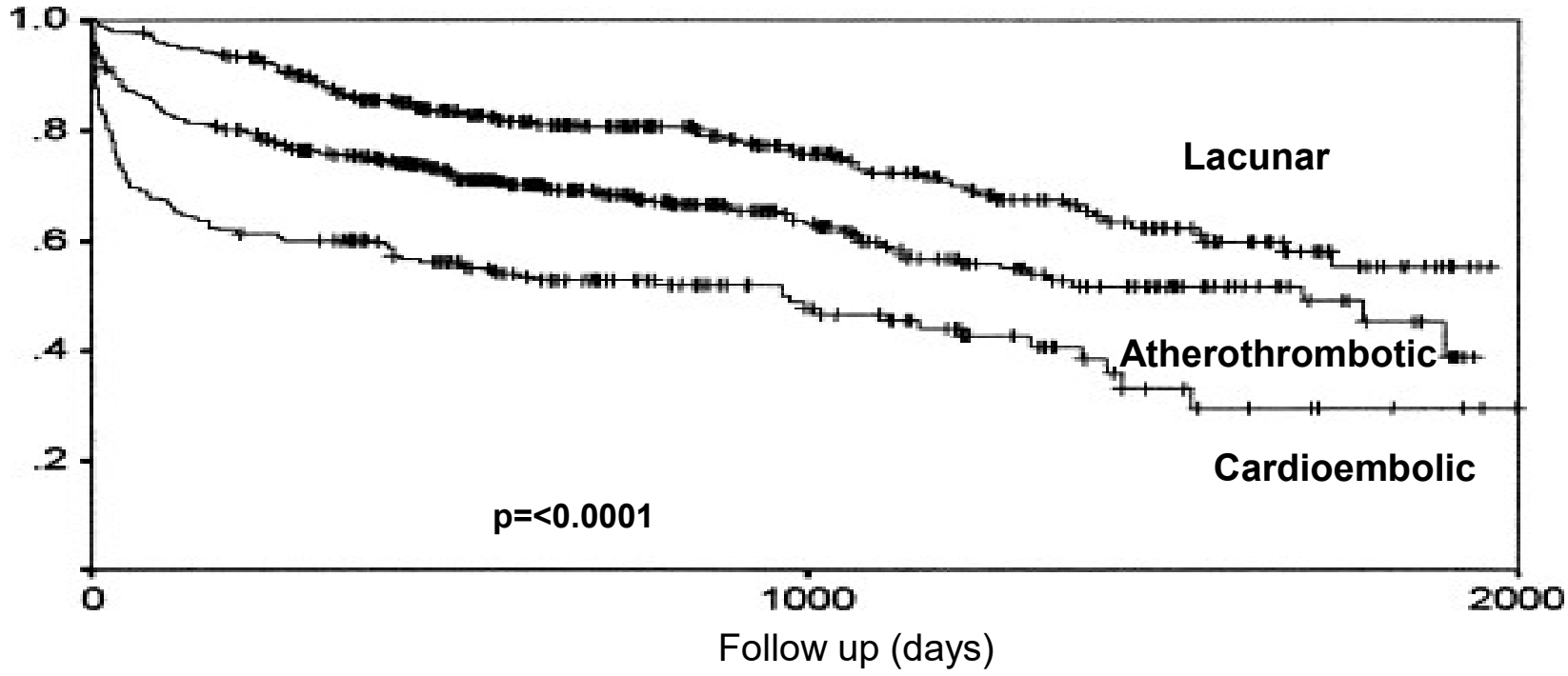
Survivors after a first-ever stroke by etiology



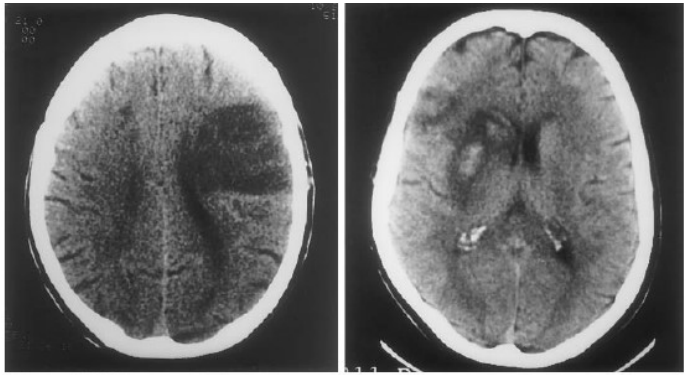
De Jong et al., J Clin Epidemiol 2003

Early risk of stroke recurrence in patients with AF

• International Stroke Trial (IST)	48 h:	4.8%
• Yasaka et al (1993)	7 d:	9.2%
• HAEST	14 d:	7.5%
• CETF		12%
• Yasaka et al (1993)		13.7%

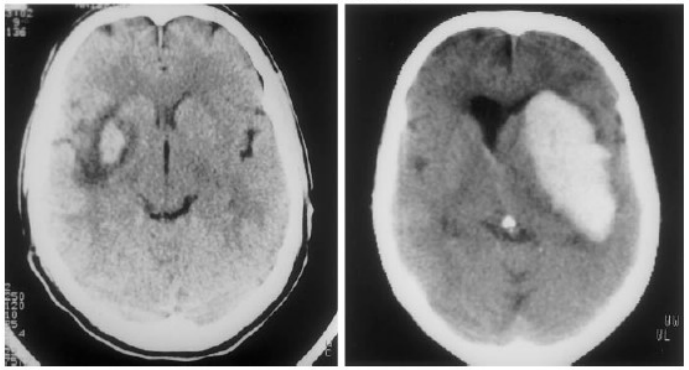
Hemorrhagic transformation of an ischemic stroke

(HI-1)
Small petechiae along the margins of the infarct



(HI-2)
More confluent petechiae within the infarcted area but without Space-occupying effect

(PH-1)
Hematoma in <30% of the infarcted area with some slight Space-occupying effect



(PH-2)
Dense hematoma >30% of the infarcted area with substantial space-occupying effect or as any hemorrhagic lesion outside the infarcted area

Fiorelli et al., Stroke 1999

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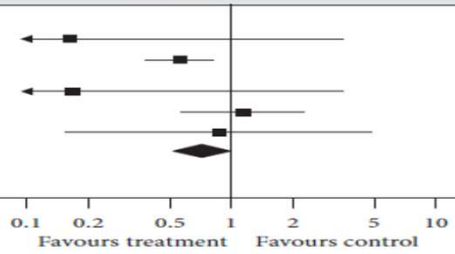
Anticoagulants within 48 for ischemic stroke

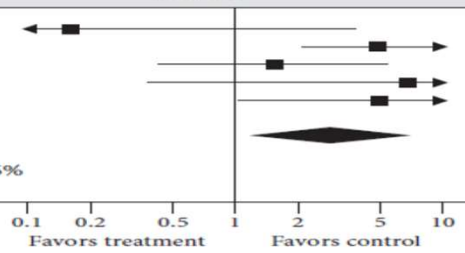
a Outcome: recurrent stroke (anticoagulants vs. aspirin or placebo)

Study or subcategory	Anticoagulants n/N	Aspirin or placebo n/N	OR (random) 95% CI	Weight %	OR (random) 95% CI
CESG [17]	0/24	2/21		1.99	0.16 (0.01–3.51)
IST heparin any dose [16]	44/1,557	79/1,612		59.81	0.56 (0.39–0.82)
TOAST [21]	0/143	2/123		2.05	0.17 (0.01–3.56)
HAEST [20]	19/224	17/225		29.92	1.13 (0.57–2.24)
TAIST [28]	4/256	2/112		6.23	0.87 (0.16–4.84)
Total (95% CI)	2,204	2,093		100.00	0.68 (0.44–1.06)
Total events: 67 (anticoagulants), 102 (aspirin or placebo)					
Test for heterogeneity: $\chi^2 = 4.77$, d.f. = 4 ($p = 0.31$), $I^2 = 16.1\%$					
Test for overall effect: $Z = 1.72$ ($p = 0.09$)					



a Outcome: hemorrhagic stroke (anticoagulants vs. aspirin or placebo)

Study or subcategory	Anticoagulants n/N	Aspirin or placebo n/N	OR (random) 95% CI	Weight %	OR (random) 95% CI
CESG [17]	0/24	2/21		7.17	0.16 (0.01–3.51)
IST heparin any dose [16]	32/1,557	7/1,612		37.99	4.81 (2.12–10.93)
HAEST [20]	6/224	4/225		25.94	1.52 (0.42–5.46)
TAIST [18]	7/256	0/112		8.16	6.76 (0.38–119.45)
Camerlingo et al. [23]	10/94	2/85		20.74	4.94 (1.05–23.23)
Total (95% CI)	2,155	2,055		100.00	2.89 (1.19–7.01)
Total events: 55 (anticoagulants), 15 (aspirin or placebo)					
Test for heterogeneity: $\chi^2 = 6.41$, d.f. = 4 ($p = 0.17$), $I^2 = 37.6\%$					
Test for overall effect: $Z = 2.34$ ($p = 0.02$)					



Paciaroni et al., Stroke 2007

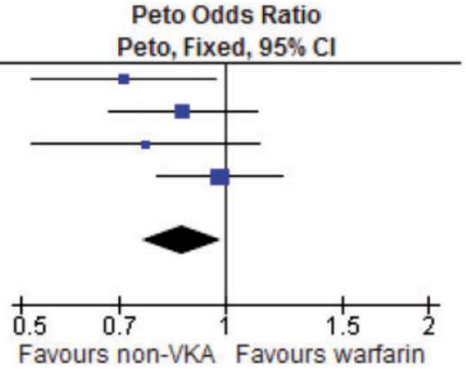
NOACs vs. AVK in secondary stroke prevention

Any stroke

Study or Subgroup	non-VKA Events	non-VKA Total	Warfarin Events	Warfarin Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
ARISTOTLE	67	1694	96	1742	18.9%	0.71 [0.52, 0.97]
ENGAGE AF-TIMI 48 (60mg)	118	1976	136	1991	28.9%	0.87 [0.67, 1.12]
RELY (150mg)	47	1233	59	1195	12.3%	0.76 [0.52, 1.13]
ROCKET-AF	171	3754	172	3714	39.8%	0.98 [0.79, 1.22]
Total (95% CI)		**8657**		**8642**	**100.0%**	**0.86 [0.75, 0.99]**
Total events	403		463			

Heterogeneity: $Chi^2 = 3.27$, $df = 3$ ($P = 0.35$); $I^2 = 8\%$

Test for overall effect: $Z = 2.10$ ($P = 0.04$)

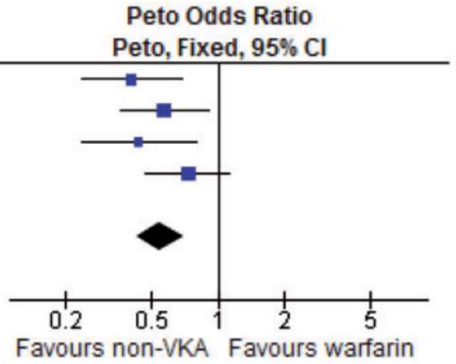


Intracranial bleeding

Study or Subgroup	non-VKA Events	non-VKA Total	Warfarin Events	Warfarin Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
ARISTOTLE	15	1694	41	1742	22.0%	0.40 [0.24, 0.68]
ENGAGE AF-TIMI 48 (60mg)	27	1976	48	1991	29.4%	0.57 [0.36, 0.90]
RELY (150mg)	13	1233	30	1195	16.9%	0.43 [0.24, 0.79]
ROCKET-AF	34	3754	46	3714	31.6%	0.73 [0.47, 1.13]
Total (95% CI)		**8657**		**8642**	**100.0%**	**0.54 [0.42, 0.70]**
Total events	89		165			

Heterogeneity: $Chi^2 = 3.60$, $df = 3$ ($P = 0.31$); $I^2 = 17\%$

Test for overall effect: $Z = 4.81$ ($P < 0.00001$)



Ntaios et al., International Journal of Stroke 2017

Clinical trials on NOACs for AFib

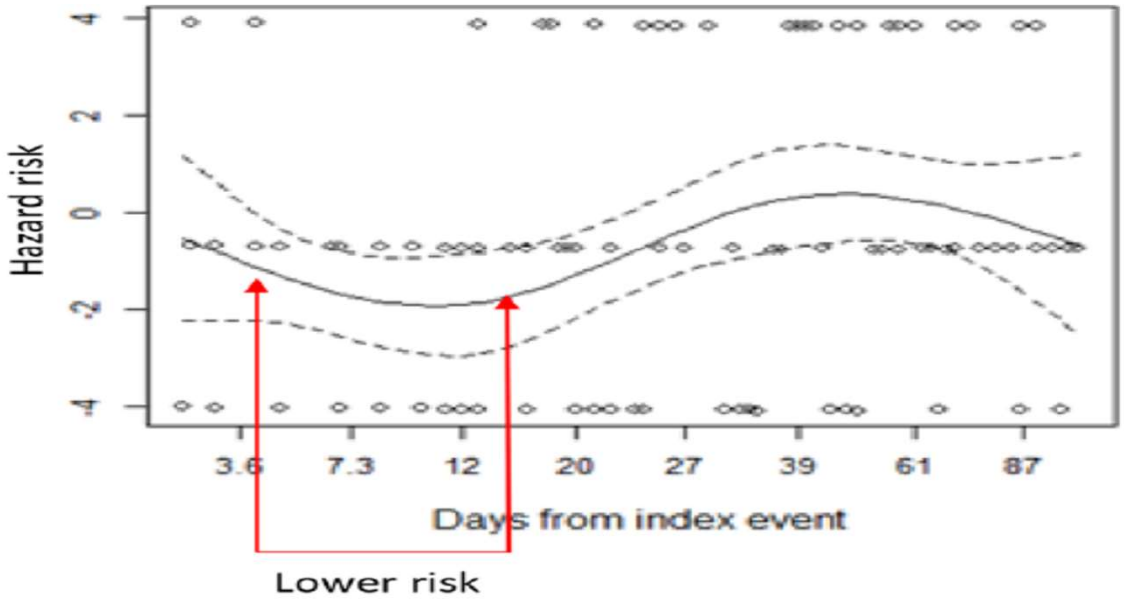
Exclusion based on timing from the index event

- ARISTOTLE: Patients with any stroke within 7 days before random assignment
- RE-LY: patients with any stroke within 14 days or severe stroke within 6 months before screening
- ROCKET AF: patients with a severe, disabling stroke within 3 months or any stroke within 14 days before randomization
- ENGAGE AF-TIMI 48: excluded patients with stroke within the previous 30 days

Easton et al., Lancet Neurol. 2012

The RAF study: Early Recurrence and Cerebral Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation. Effect of Anticoagulation and Its Timing

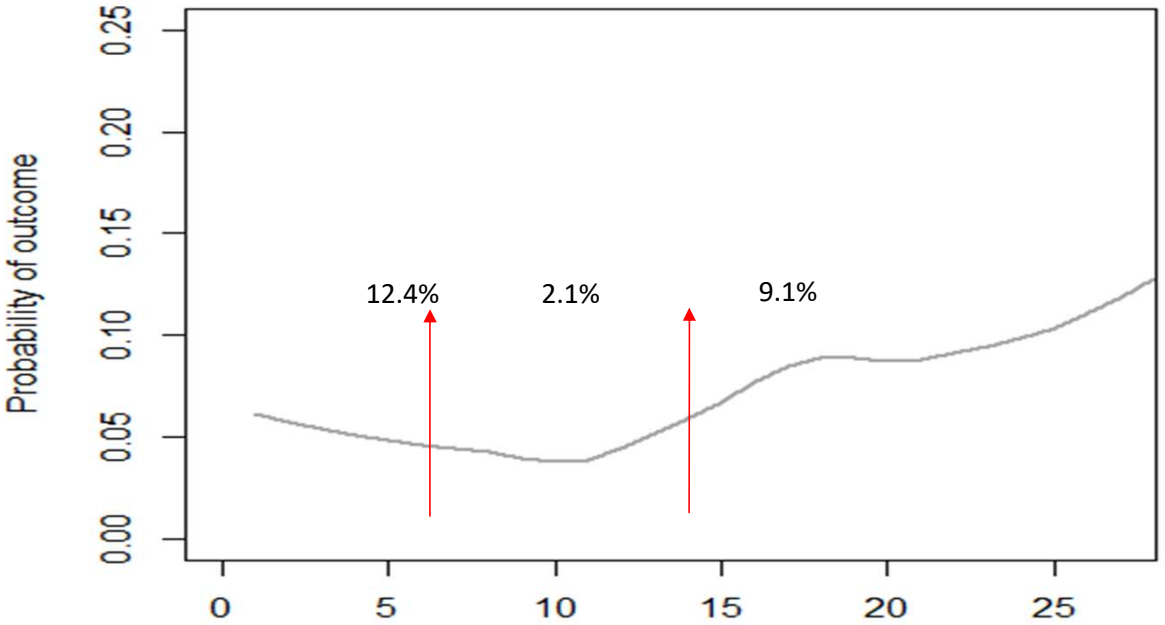
- 1029 patients with acute stroke and AF
- 77 (7.6%) ischemic recurrences (IS –TIA – SE) at 90 days
- 37 (3.6%) symptomatic ICH



Paciaroni et al., Stroke 2015

RAF NOACs study: Outcome events (ischemic and hemorrhagic) depending on the time between onset and initiation of therapy with NOACs.

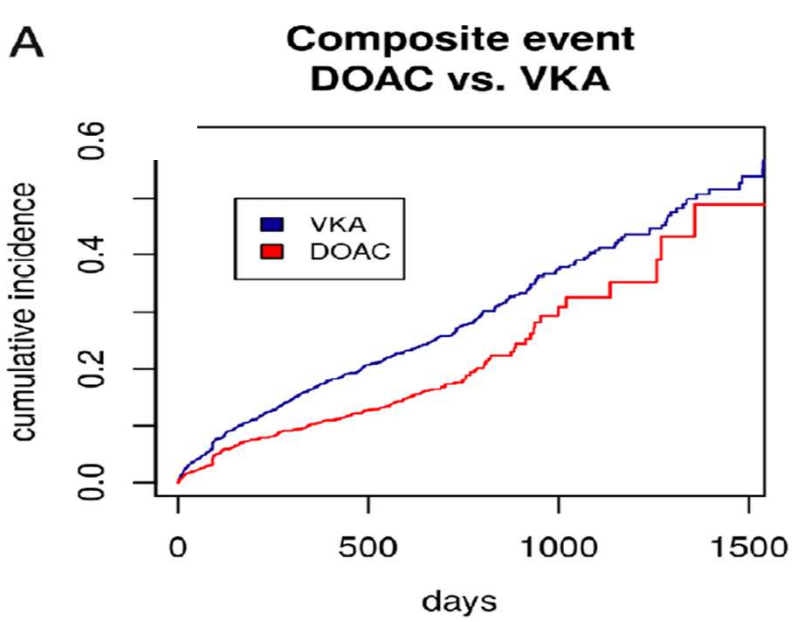
- 1127 patients with acute stroke and AF
- 32 (2.8%) ischemic recurrences (IS –TIA – SE) at 90 days
- 18 (1.6%) symptomatic ICH

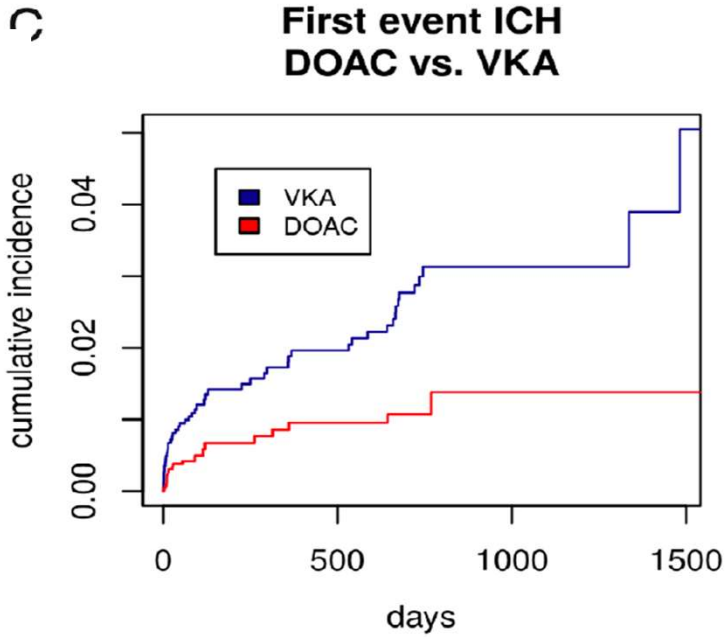


Risk of combined outcome events based upon the day of initiating NOAC

Paciaroni et al, JAHA 2017

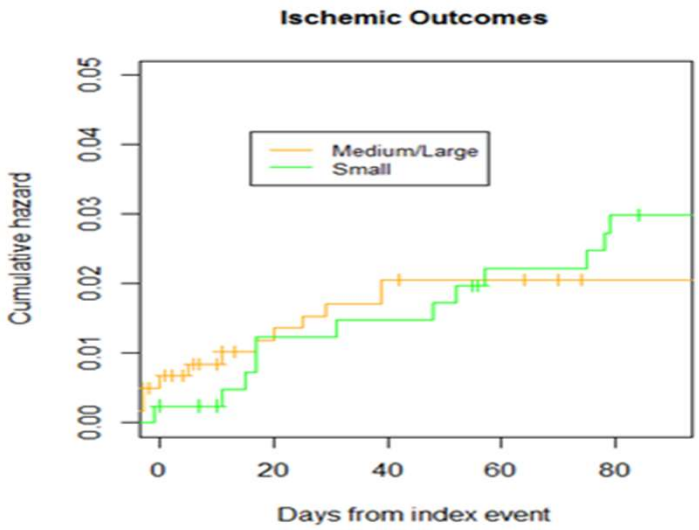
NOACs versus AVK after acute stroke in patients with AFib

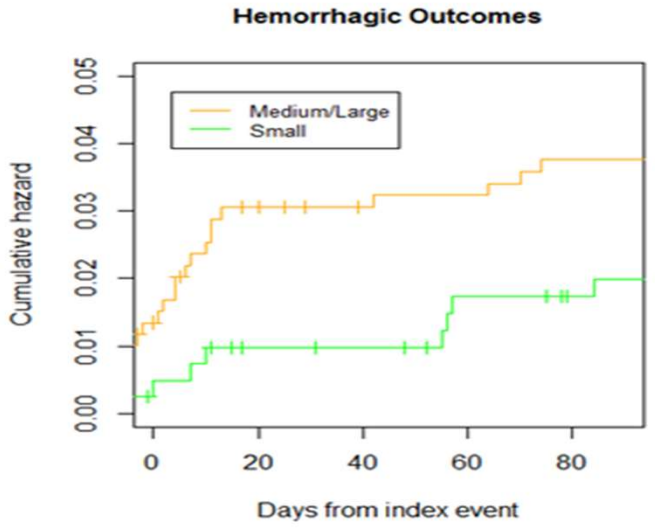




Seiffge et al., Ann Neurol 2019

RAF NOACs study: Size of ischemic lesion and risk for early recurrence and hemorrhagic transformation in DOACs treated patients





Paciaroni et al., JAHA 2017

My talk today

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Why is it a such a critical clinical issue?

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	ELAN **“Early Versus Late Initiation of Direct Oral Anticoagulants in Post-ischaemic Stroke Patients With Atrial fibrillation”**	**OPTIMAS** **“OPtimal TIMing of Anticoagulation after AF-associated acute cardiembolic ischaemic Stroke”**	**TIMING** **”Timing of oral anticoagulant therapy in acute ischemic stroke with atrial fibrillation “**	**START** **“Optimal Delay Time to Initiate Anticoagulation After Ischemic Stroke in Atrial Fibrillation”**
Planned sample size	2000	3474	3000	1500
Intervention: early start	<48 hours after symptom onset (minor and moderate stroke) or at day 6 + 1 day after symptom onset (major stroke)	≤ day 4 after ischemic stroke	≤ day 4 after ischemic stroke	Adaptive trial design: time-to-treatment delay of 3, 6, 10 or 14 days in mild/moderate. 6,10,14 or 21 days in severe
Control: **late start**	current recommendations (i.e. minor stroke after day 3 + 1 day, moderate stroke after day 6 + 1 day and major stroke after day 12 + 2 day).	between day 5 and day 14 after acute stroke	between day 5 and day 10 after acute stroke	
Estimated end of study	10/2021	2021/22	12/2020	08/2021

The Timing study

Early	0-4 days	450 patients
Delayed	5-10 days	438 patients

Planned sample size: 3000 patients

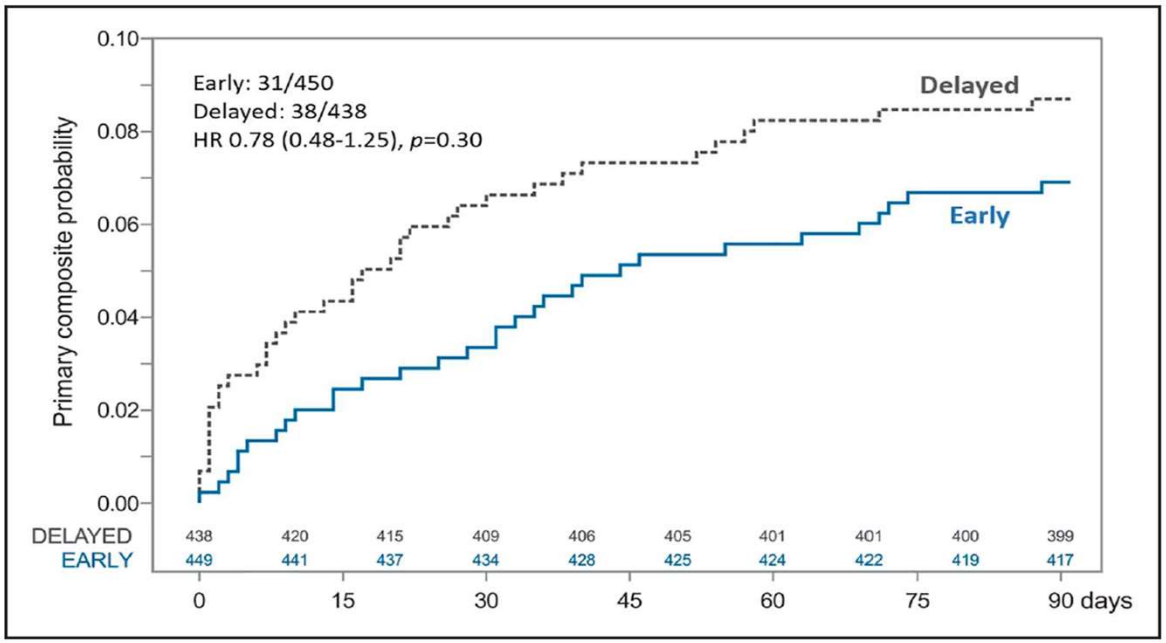


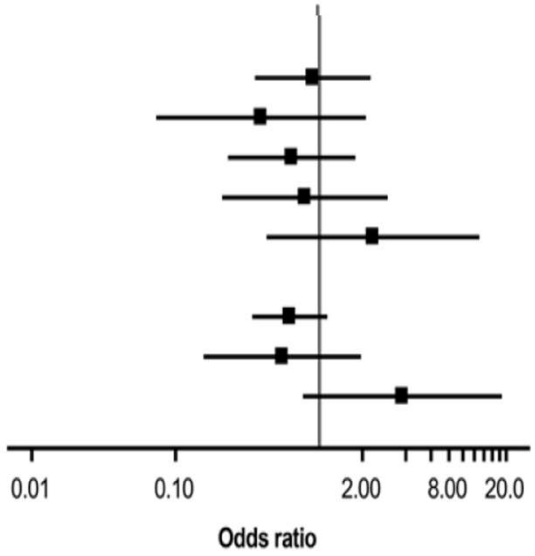
Figure 3. Time to the primary composite outcome and Cox proportional hazards analysis for early vs delayed initiation of NOAC until 90 days.

Primary outcome was a composite of ischemic stroke, symptomatic intracerebral hemorrhage, or all-cause mortality. HR indicates hazard ratio; and NOAC, non–vitamin K antagonist oral anticoagulant.

Oldegren et al., Circulation 2022

The Timing study

Variable Subgroup	Early Events/n (%)	Delayed Events/n (%)	OR (95%CI) Early vs Delayed	p-value Interaction
NIHSS on admission				
0 - 3	9/175 (5.1%)	10/176 (5.7%)	0.90 (0.36-2.27)	0.649
4 - 5	2/62 (3.2%)	5/64 (7.8%)	0.39 (0.07-2.11)	
6 - 10	7/80 (8.8%)	10/77 (13.0%)	0.64 (0.23-1.78)	
11 - 15	5/44 (11.4%)	5/36 (13.9%)	0.79 (0.21-2.99)	
>15	5/42 (11.9%)	2/37 (5.4%)	2.36 (0.43-12.99)	
Reperfusion				
None	19/289 (6.6%)	29/286 (10.1%)	0.62 (0.34-1.14)	0.103
Thrombolysis (only)	4/96 (4.2%)	7/96 (7.3%)	0.55 (0.16-1.95)	
Thrombectomy	8/65 (12.3%)	2/56 (3.6%)	3.79 (0.77-18.64)	



Oldegren et al., Circulation 2022

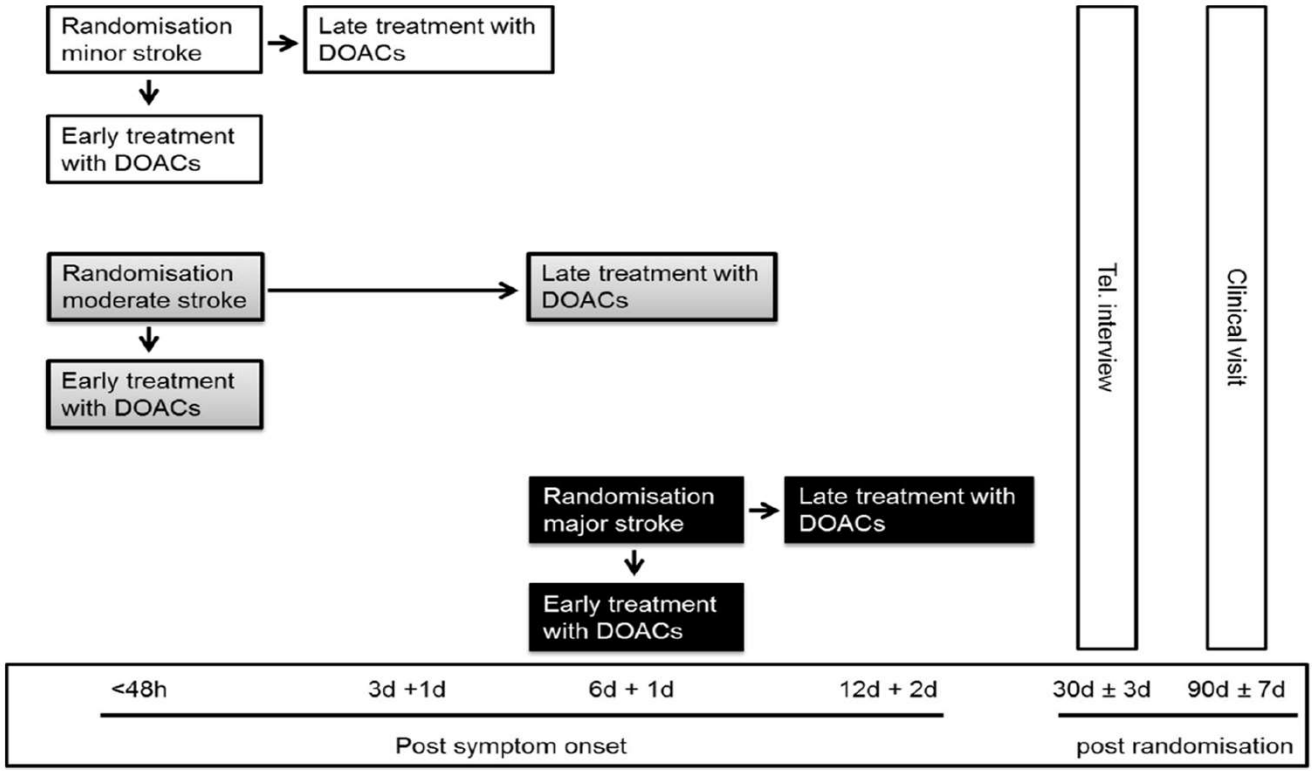
Study Protocol

EUROPEAN STROKE JOURNAL

European Stroke Journal
1–9

DOI: 10.1177/23969873221106043
journals.sagepub.com/home/eso
SAGE

Early versus Late initiation of direct oral Anticoagulants in post-ischaemic stroke patients with atrial fibrillatioN (ELAN): Protocol for an international, multicentre, randomised-controlled, two-arm, open, assessor-blinded trial

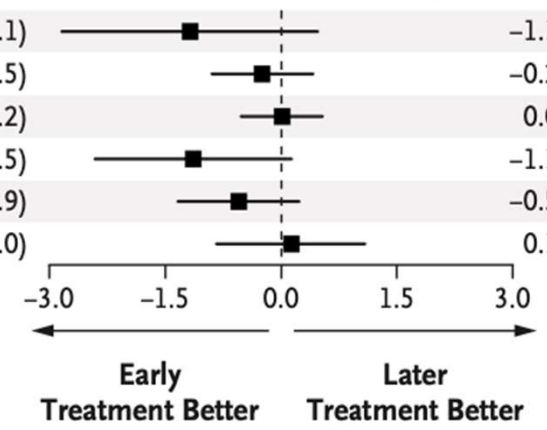


Type of DOACs

	Early (1006)	Late (1007)
Rivaroxaban	45 (4.5%)	55 (5.5%)
Dabigatran	169 (16.8%)	173 (17.2%)
Apixaban	630 (62.6%)	613 (60.9%)
Edoxaban	153 (16.2%)	150 (14.9)
Missing	4 (0.4%)	7 (0.6%)

The ELAN study

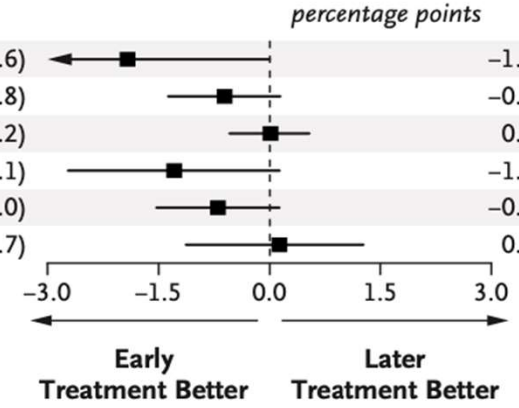
Outcome within 30 Days	Early-Treatment Group (N=984)	Later-Treatment Group (N=991)	Adjusted Risk Difference (95% CI)
	no. of events (%)		*percentage points*
Primary-outcome event	29 (2.9)	41 (4.1)	−1.18 (−2.84 to 0.47)
Major extracranial bleeding	3 (0.3)	5 (0.5)	−0.25 (−0.90 to 0.41)
Symptomatic intracranial hemorrhage	2 (0.2)	2 (0.2)	0.01 (−0.52 to 0.53)
Recurrent ischemic stroke	14 (1.4)	25 (2.5)	−1.14 (−2.41 to 0.13)
Systemic embolism	4 (0.4)	9 (0.9)	−0.55 (−1.34 to 0.23)
Death from vascular cause	11 (1.1)	10 (1.0)	0.13 (−0.84 to 1.09)



Fisher et al., N Engl J Med 2023

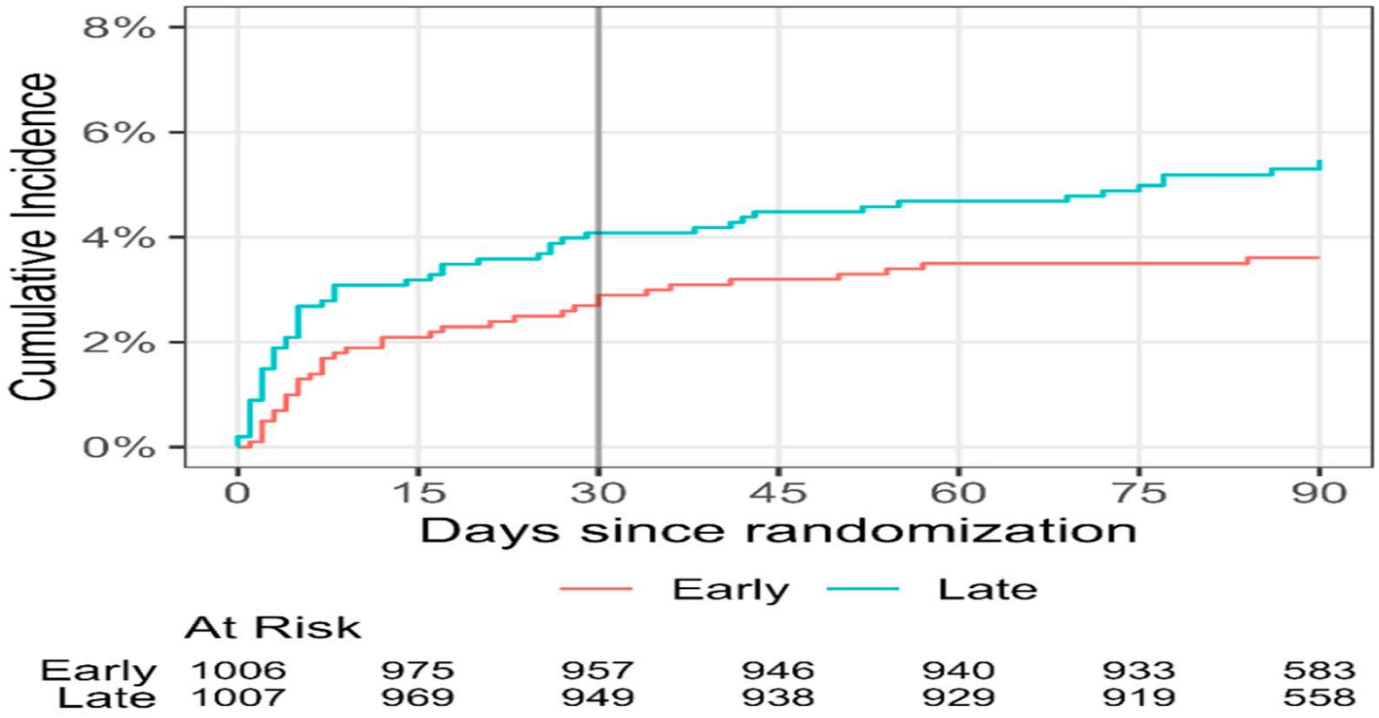
The ELAN study

Outcome within 90 Days	Early-Treatment Group (N=968)	Later-Treatment Group (N=965)	Adjusted Risk Difference (95% CI)
	no. of events (%)		*percentage points*
Primary-outcome event	36 (3.7)	54 (5.6)	–1.92 (–3.82 to –0.02)
Major extracranial bleeding	3 (0.3)	8 (0.8)	–0.61 (–1.37 to 0.14)
Symptomatic intracranial hemorrhage	2 (0.2)	2 (0.2)	0.00 (–0.54 to 0.53)
Recurrent ischemic stroke	18 (1.9)	30 (3.1)	–1.29 (–2.72 to 0.13)
Systemic embolism	4 (0.4)	10 (1.0)	–0.70 (–1.53 to 0.13)
Death from vascular cause	17 (1.8)	16 (1.7)	0.07 (–1.13 to 1.27)



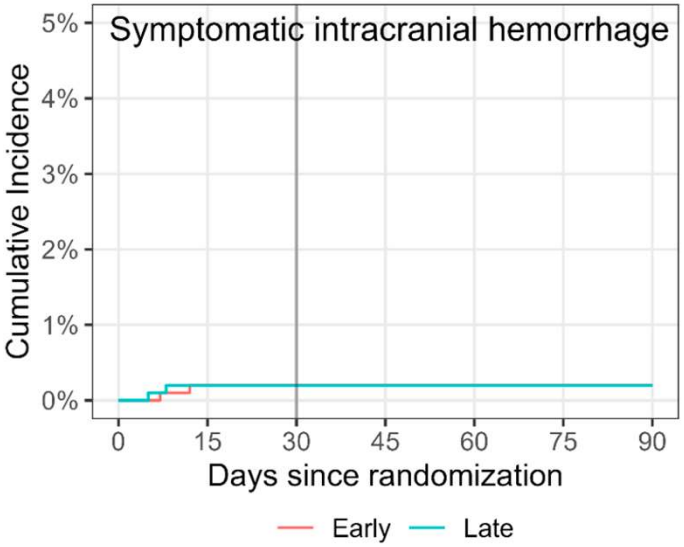
Fisher et al., N Engl J Med 2023

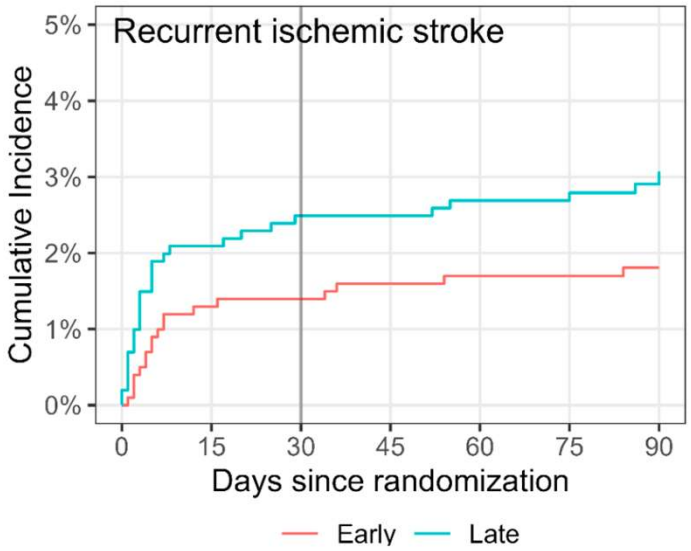
ELAN: Primary outcome at 30 and 90 days

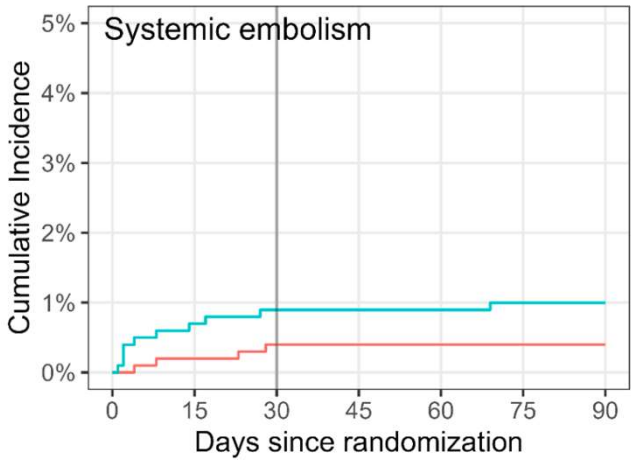


Fisher et al., N Engl J Med 2023

The ELAN study



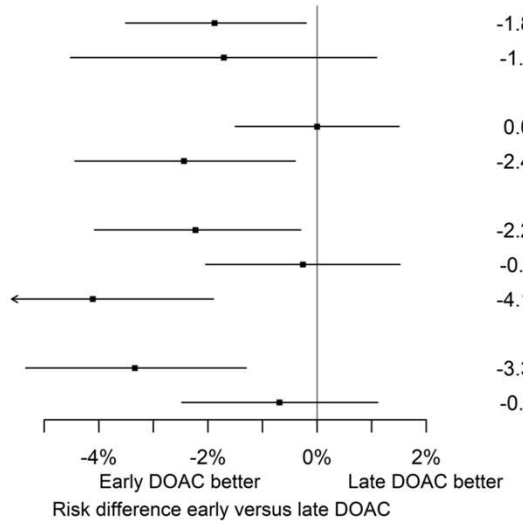




Fisher et al., N Engl J Med 2023

The ELAN study

	Early (N=968) No. of Events	Late (N=965) No. of Events	Risk Difference (95% CI)
NIHSS			
NIHSS < 10	20/808 (2.5%)	35/803 (4.4%)	-1.88% (-3.51 to -0.25)
NIHSS ≥ 10	16/160 (10.0%)	19/162 (11.7%)	-1.71% (-4.52 to 1.09)
Age			
Age < 70 years	6/223 (2.7%)	6/223 (2.7%)	0.00% (-1.50 to 1.50)
Age ≥ 70 years	30/745 (4.0%)	48/742 (6.5%)	-2.44% (-4.44 to -0.44)
Infarct size			
Minor	12/365 (3.3%)	20/362 (5.5%)	-2.23% (-4.08 to -0.38)
Moderate	15/385 (3.9%)	16/385 (4.2%)	-0.26% (-2.04 to 1.52)
Major	9/218 (4.1%)	18/218 (8.3%)	-4.11% (-6.28 to -1.94)
Sex			
Female	16/442 (3.5%)	30/431 (6.6%)	-3.34% (-5.34 to -1.33)
Male	20/526 (3.7%)	24/534 (4.4%)	-0.69% (-2.48 to 1.11)



Fisher et al., N Engl J Med 2023

My talk today

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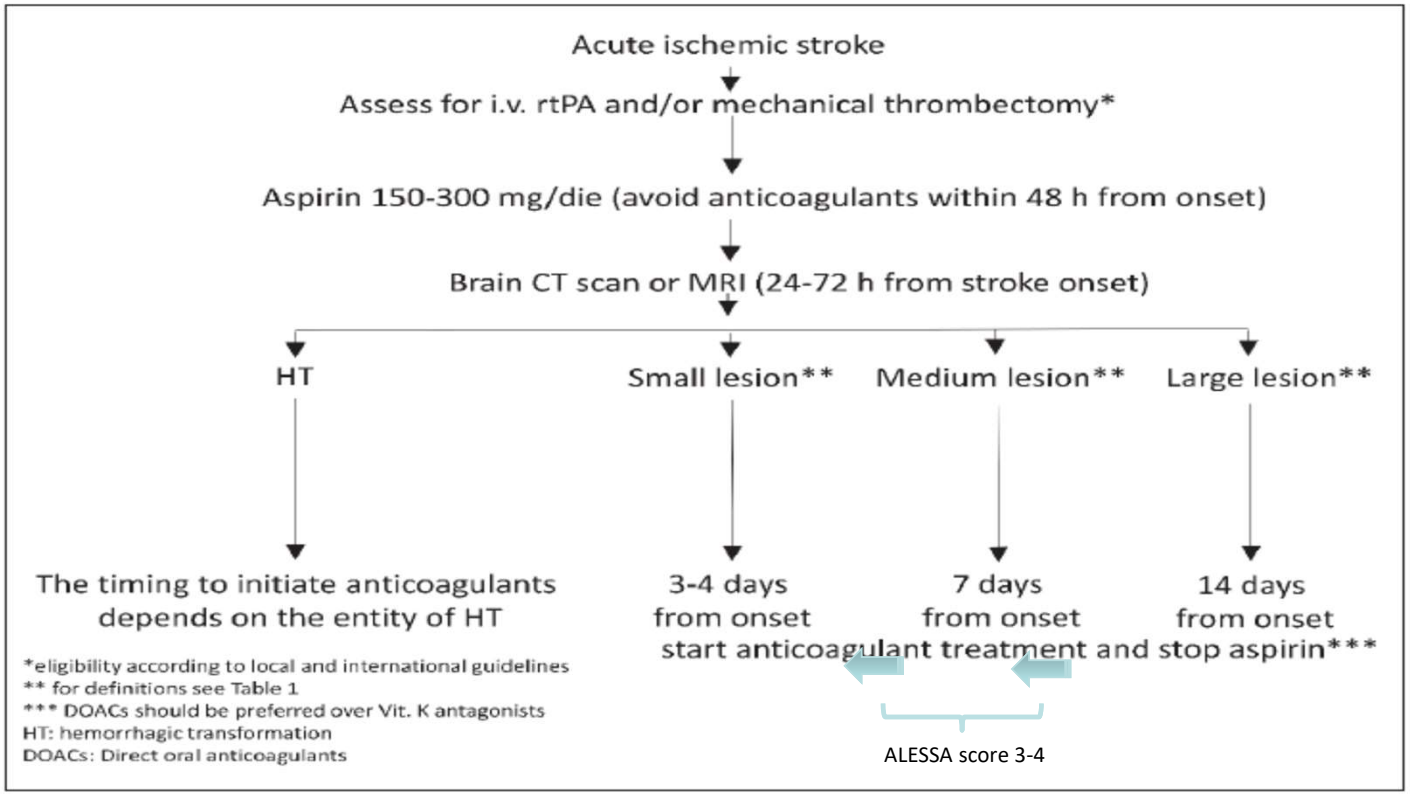
Why is it a such a critical clinical issue?

What's the anticoagulant to be preferred

Recently published or ongoing studies

Management (treatment) implications

Timing of NOAC initiation in acute stroke with AF



Paciaroni et al, Thromb Hemost 2016 (modified)

When to start anticoagulation after ischemic stroke

- **When** to start DOAC :
  - TIA — Start day 0
  - Minor/moderate stroke — Start day 0-2
  - Major stroke — Start day 7

- **How** to start anticoagulation: start all oral anticoagulants directly without heparin or LMWH-bridging

Take home messages

- Ischemic stroke in patients with atrial fibrillation is associated with a high risk of early recurrence.
- Early start of the anticoagulant treatment (within 4 days) is associated with a clinical benefit in the majority of patients,
- Treatment should be delayed in patients with large or very large ischemic lesions (7-14 days)
- DOACs should be preferred to other anticoagulants.
- Space for research remains with agents with a more favorable antithrombotic vs. hemorrhagic profile