

Gestion des anticoagulants chez les patients avec AVC ischémique et fibrillation auriculaire

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Disclosures

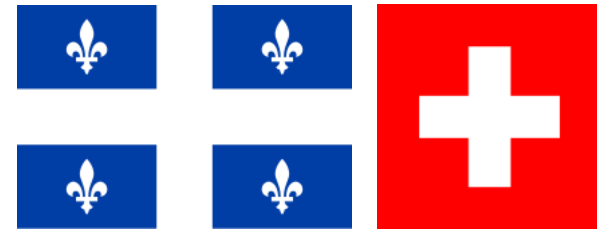
Research funding

Swiss National Science Foundation, Swiss Heart Foundation, Bangerter-Rhyner Foundation, AstraZeneca (Externally sponsored research program)

Speaker/Advisory board (used for research funding)

AstraZeneca, Pfizer, VarmX, Bioxodes, EMCREG, PHRI/Javelin/Intercept





Switzerland – Québec



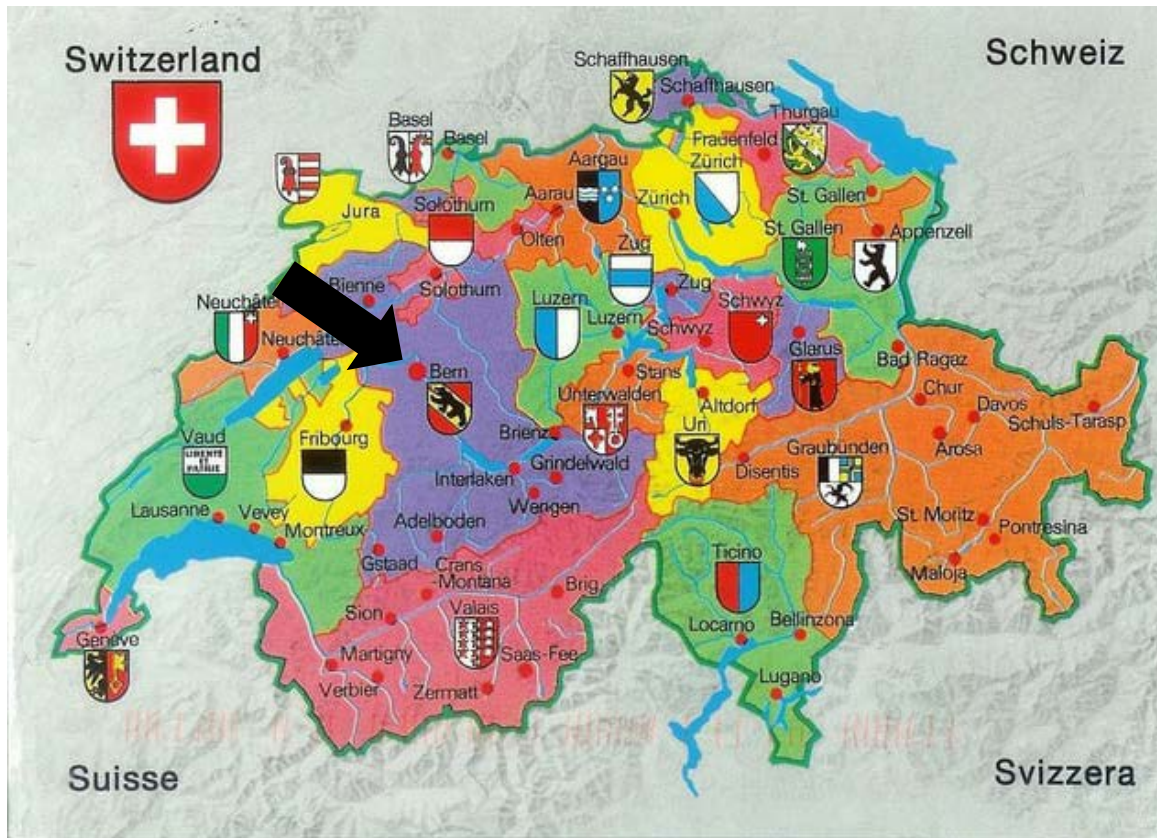
Switzerland

41 285 km²
9 060 598 inhabitants



Québec

1.542.056 km²
8.501.833 inhabitants





Ne partez pas sans moi!

Agenda

- Introduction - burden of atrial fibrillation, cardioembolism and stroke
- Management of anticoagulation in specific stroke scenarios
 - Timing of anticoagulation after a recent stroke
 - Use of IV thrombolysis in a patient on anticoagulation
 - Management of anticoagulation after a stroke despite anticoagulation therapy («breakthrough stroke»).

Atrial fibrillation, cardioembolism and ischemic stroke

- 44 million individuals have atrial fibrillation (AF) worldwide
- 1970ies: AF as possible etiology of ischemic stroke
- 20-30% of all ischemic strokes are related to AF
- Europe: approximately 240 000 AF-related ischemic strokes/year

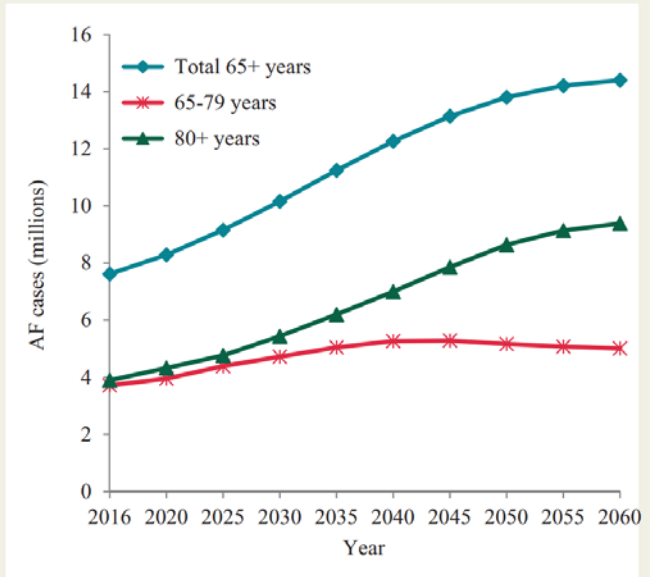
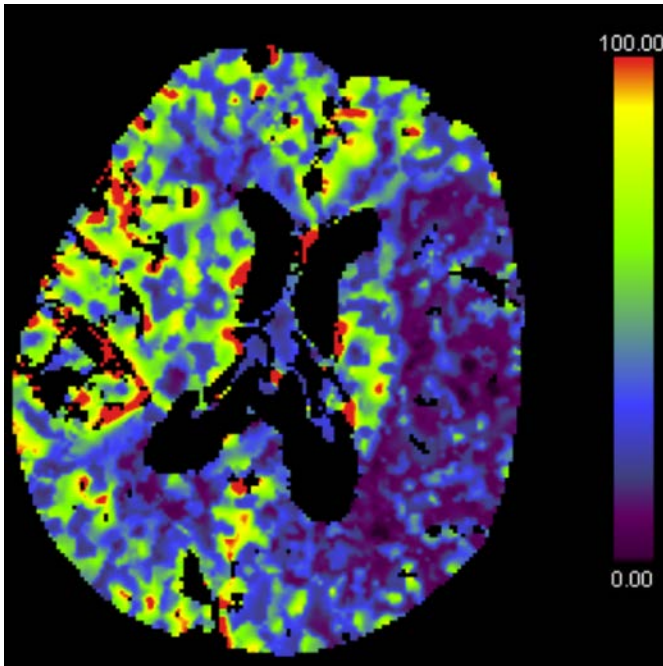
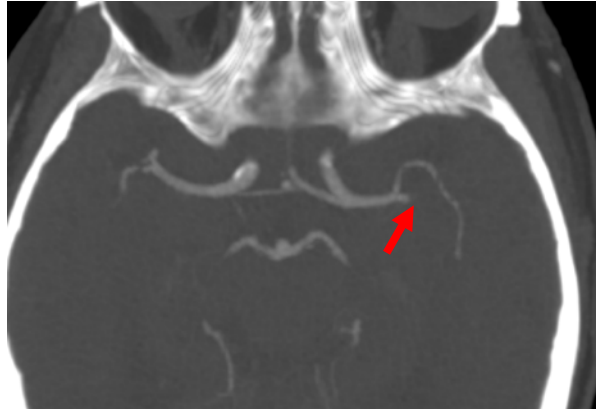


Figure 3 Projections of number of European Union elderly with atrial fibrillation between 2016 and 2060. AF, atrial fibrillation.

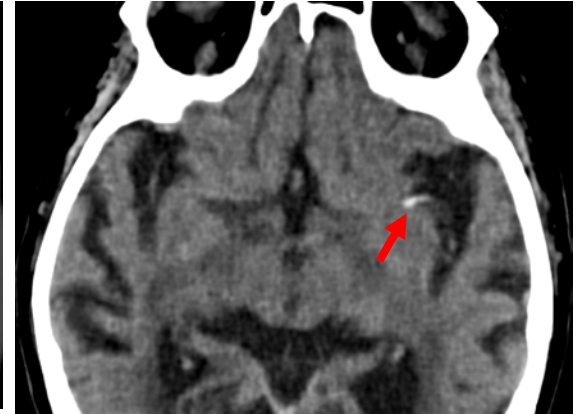
85yo lady, known AF, no anticoagulation (fear of frequent falls)
Sudden onset right side hemiparesis + aphasia, NIHSS 20 points
Onset to imaging time: 120 minutes



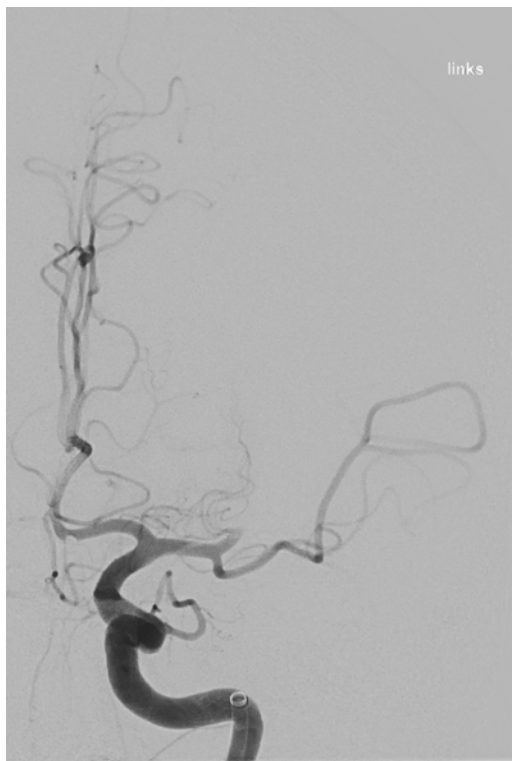
CBF



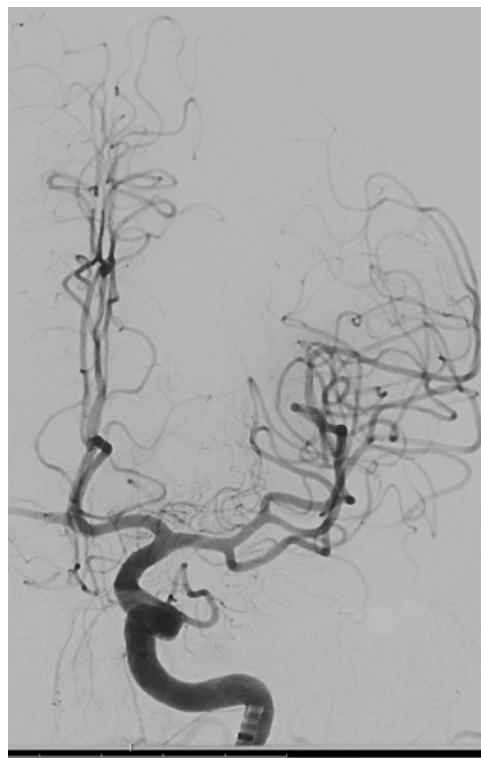
CT-A



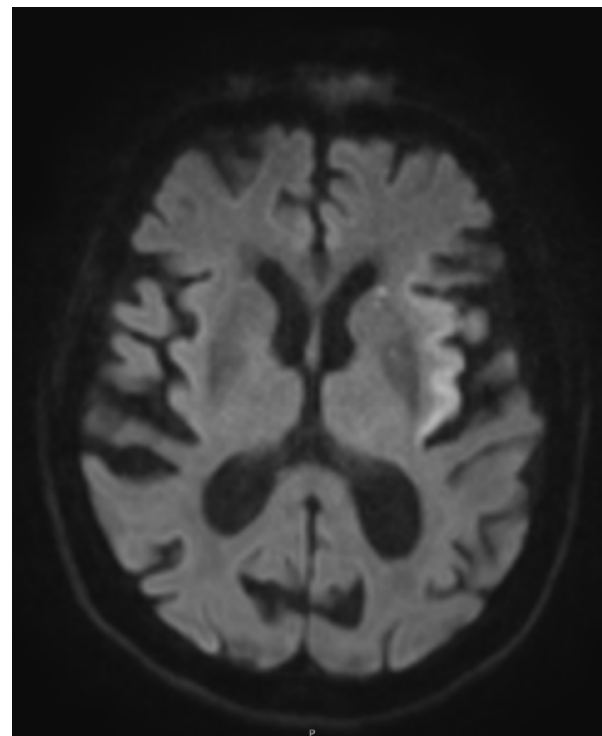
Non-contrast CT



Angio –
before thrombectomy



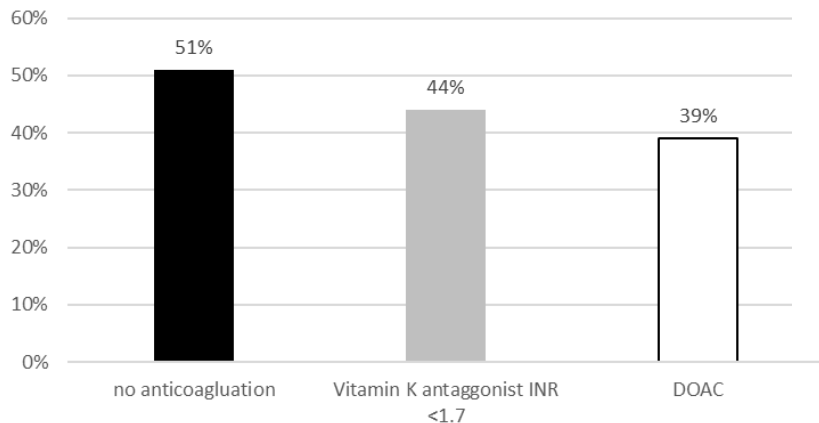
Angio –
after thrombectomy



MRI day 2

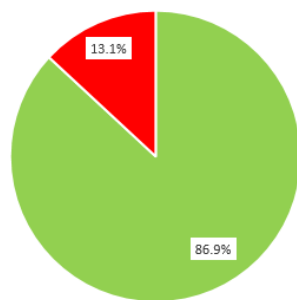
Characteristics of AF-associated stroke

Large vessel occlusion

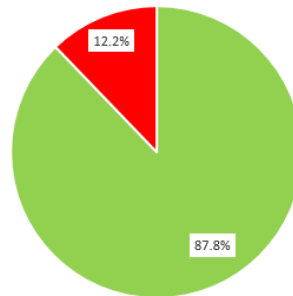


aOR (DOAC): 0.67 (95%CI 0.56-0.76)

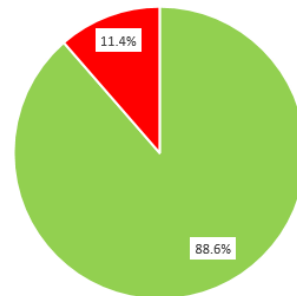
no prior anticoagulation (n=5875)



VKA (n=1496)



DOAC (n=2793)



Anterior circulation

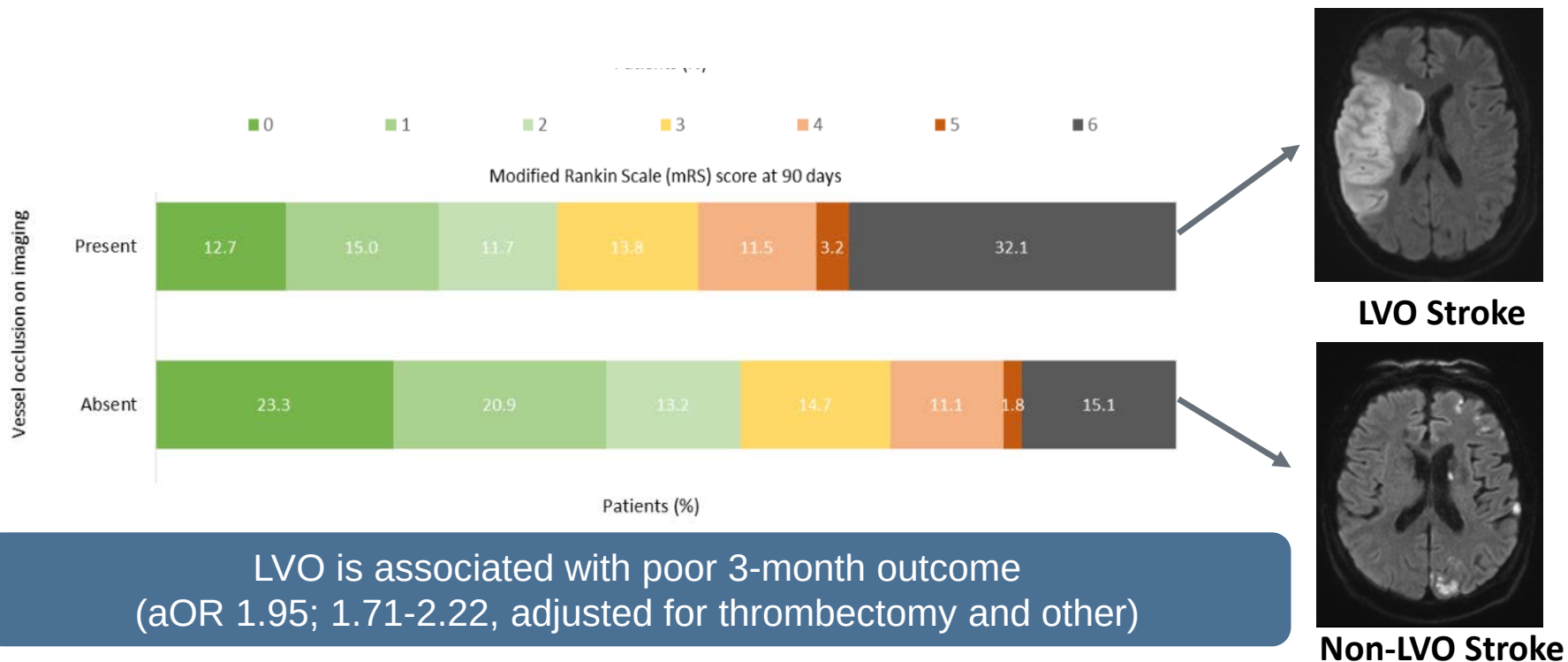


Posterior circulation

Anterior circulation
intracranial ICA 14.5%
MCA M1 34.1%
MCA M2 29.6%

AF-associated stroke: frequently large-vessel occlusion, >85% in the anterior circulation

AF-stroke with vs without large vessel occlusion



Pharmacotherapy for stroke prevention in AF

- 1980-90ies: Multiple studies with Warfarin, Aspirin and others
- 2010ies: „DOAC – trials“
 - Anti-Xa: Rivaroxaban (ROCKET-AF), Edoxaban (ENGAGE-AF-TIMI), Apixaban (ARISTOTLE)
 - Anti-IIa: Dabigatran (RE-LY)
- Anticoagulation is the cornerstone of stroke prevention:
 - Aspirin: 20% relative risk reduction
 - Warfarin: 64% relative risk reduction
 - DOACs: at least as effective as warfarin

«If you are treating even ONE patient in your practice with anticoagulation,
you should wake up once a week or so with a cold sweat»

Charles Miller Fisher (1913-2012)

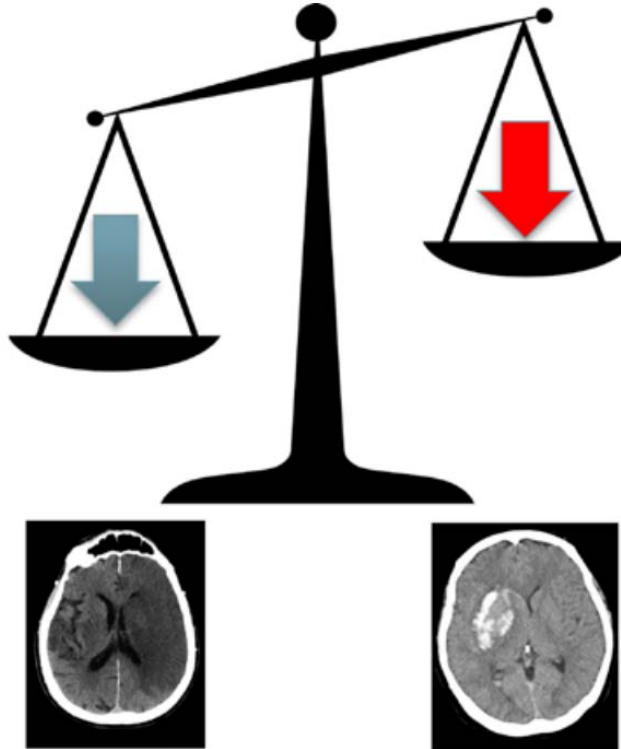


Timing of DOAC-initiation after recent AF-associated stroke

Starting OAC
late

–

risk of early
recurrent
stroke?



Starting OAC
early
–
risk of
haemorrhagic
transformation?

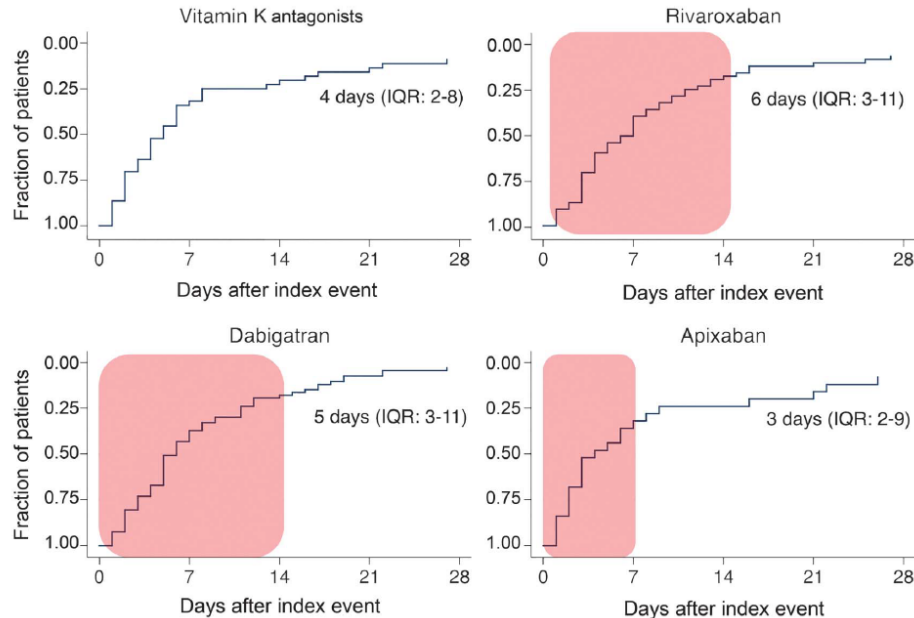
Early start of DOAC – first evidence

David J. Seiffge, MD*
Christopher Tsoukas,
MD*
Alexandros Polyzidis,
MD

ABSTRACT

Objectives: In patients with recent acute ischemic stroke (AIS) and atrial fibrillation, we assessed the starting time of direct, non-vitamin K antagonist oral anticoagulants (DOACs) for secondary prevention, the rate of intracranial hemorrhage (ICH), and recurrent ischemic events during follow-up.

Figure Time to start of OAC after the index event



Number of symptomatic
ICH with DOAC:
0

Timing of anticoagulation after recent ischaemic stroke in patients with atrial fibrillation



David J Seiffge*, David Werning*, Maurizio Paciaroni, Jesse Dawson, Steven Warrick, Thomas J Milling, Stefan T Engelke, Urs Fischer†, Bo Norving†

Study population	Patients' median age, median stroke severity, and infarct size*	Median timing of anticoagulation administration initiation	Follow-up period	Recurrent ischaemic stroke†	Intracranial haemorrhage†
Observational studies with clinical follow-up of ≥3 months					
Seiffge et al ¹⁶ (NOACISIP)	204 (155 DOAC treated) 79 years; NIHSS score 4; no information on infarct size	5 days (≤7 days for 65% [n=100] of DOAC-treated patients)	At least 3 months	7.7% per year (5.1% per year for DOAC administration ≤7 days vs 9.3% per year for DOAC administration >7 days, p=0.53)	1.3% per year
Arihiro et al ¹⁶ (SAMURAI-NVAF)	1192 (466 DOAC treated) 78 years; NIHSS score 3; 24% small, 48% medium, and 28% large infarcts	5 days for DOAC	3 months	8.5% per year (VKA) and 10.1% per year (DOAC, p=0.05)	1.2% per year (VKA) vs 0.8% per year (DOAC)
Paciaroni et al ¹⁶ (RAF-NOAC)	1127 (all DOAC treated) 76 years; NIHSS score 8; 41% small, 33% medium, and 22% large infarcts	No overall median reported (8 days for dabigatran and rivaroxaban, 7 days for apixaban)	3 months	7.8% per year	6.4% per year
Wilson et al ¹⁶	1355 (475 DOAC treated) 76 years; NIHSS score 4; 18% large infarcts	11 days (≤4 days for 26% [n=358] of patients)	90 days	5.7% per year (combined DOAC and VKA)	0.6% per year (combined DOAC and VKA)
Observational studies with clinical follow-up within 3 months or with surrogate outcome imaging markers					
Macha et al ¹⁶	243 (all DOAC treated) 78 years; NIHSS score 5; 17% small infarct or TIA, 70% medium, and 13% large infarcts	From 1.7 days for small infarct or TIA to 6.7 days for large infarcts (≤7 days for 89.7% [n=218] of DOAC-treated patients)	In hospital	Not reported	1 case of symptomatic and 2 cases of asymptomatic intracranial haemorrhage
Cappellari et al ¹⁶	147 (all DOAC treated) 79 years; NIHSS score 8; 54% small, 22% medium, and 24% large infarcts	3.3 days (≤3 days for 66% [n=97] of patients; ≤7 days for all patients)	CT scan at 7 days	No case observed	8 cases of asymptomatic intracranial haemorrhage (7 new, 1 before DOAC treatment)
Gioia et al ¹⁶	60 (all rivaroxaban treated) 74 years; NIHSS score 2; median DWI lesion volume 7.9 mL	3 days	MRI scan at 7 days	1 case	No cases of symptomatic intracranial haemorrhage, 8 cases of asymptomatic petechial haemorrhage
Deguchi et al ¹⁶	300 (186 DOAC treated) 77 years; NIHSS score 7; no information on infarct size	3 days for DOAC, 7 days for VKA	In hospital	No case observed	2 cases of intracranial haemorrhage, 1 case of extracranial haemorrhage
Observational studies with a majority of patients receiving VKAs or heparins					
Abdul-Rahim et al ¹⁶	1300 (no DOAC-treated patients) 73 years; NIHSS score 14; no information on infarct size	2 days	90 days	8.2% of patients (107 events in 1300 patients)	2.3% of patients had symptomatic intracranial haemorrhage (30 events in 1300 patients)
Paciaroni et al ¹⁶	1029 (93 DOAC treated) 77 years; NIHSS score 9; 37% small, 36% medium, and 27% large infarct	8.5 days for DOAC, 12.1 days for VKA	3 months	77 events (including TIA and systemic embolism)	37 events (including major extracranial haemorrhages)
Randomised controlled trials with patients receiving DOACs					
Hong et al ¹⁶	195 (95 rivaroxaban treated) 70 years; NIHSS score 2; median DWI lesion volume 2.6 mL	2 days	MRI scan at 4 weeks	1 case	30 new haemorrhagic lesions (all asymptomatic)

DOAC=direct oral anticoagulant. NIHSS=National Institutes of Health Stroke Scale. VKA=vitamin K antagonist. TIA=transient ischaemic attack. DWI=diffusion weighted imaging. *Although definitions of infarct size might differ slightly between studies, small infarct size was commonly defined by lesions smaller than 1.5 cm in the anterior or posterior circulation; medium infarct size by lesions in a cortical superficial branch of middle cerebral artery (MCA), in the MCA deep branch, in the internal border zone territories, in a cortical superficial branch of posterior cerebral artery, or in a cortical superficial branch of the anterior cerebral artery; large infarct size by lesions that involve the complete territory of MCA, posterior cerebral artery, or anterior cerebral artery, in two cortical superficial branches of MCA, in a cortical superficial branch of MCA associated to the MCA deep branch, or in more than one early artery territory. †Annualised event frequencies (% per year) were calculated whenever possible using published data (number of observed events divided by follow-up period).

Table 1: Summary of studies on early initiation of anticoagulant treatment in patients with recent atrial fibrillation-related ischaemic stroke

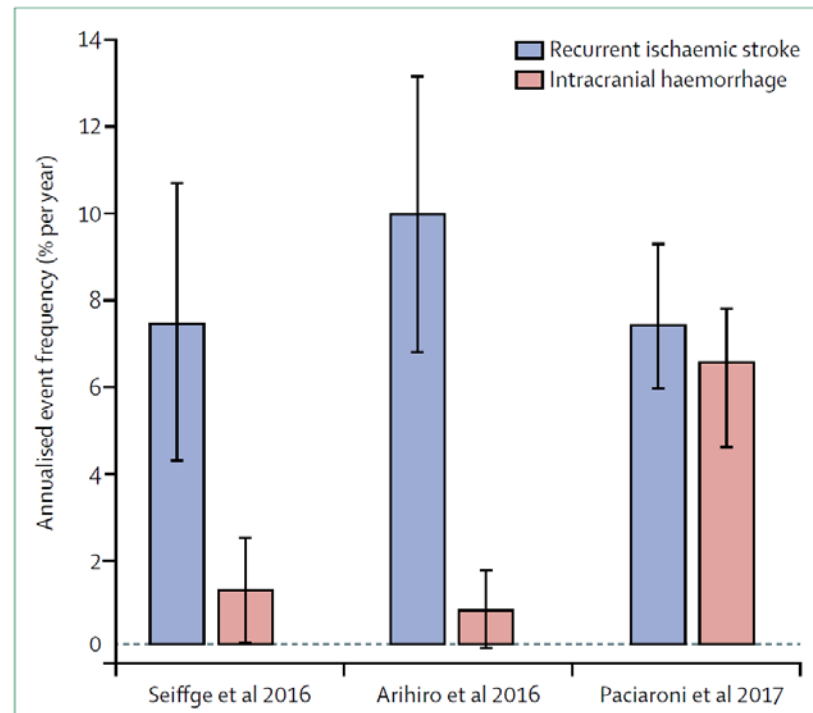


Figure 1: Risk of recurrent ischaemic stroke and intracranial haemorrhage in patients with atrial fibrillation and a recent ischaemic stroke

Seiffge et al Lancet Neurology 2018

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U. Fischer, M. Kopp, U. Strbian, M. Branca, S. Abend, S. Trelle, M. Pascariou, G. Thomaia, P. Michel, R. Nedelchev, L.H. Bonati, G. Ntanos, T. Gatzinger, E.-C. Sandert, P. Rety, R. Lemmens, P.J. Sylja, D. Aguilar de Soto, N.M. Altmann, T. Gódmann, T. Gódmann, T. Toomari, M. Truinen, H. Thapar, M. Chom, C. Cavaletto, J. Vohók, J. Závada, J. Matoušek, J. Křístek, P. Kortányi, P. Vanacker, C. Alm, G. Kishimoto, C. Kuyk, D. Hemedi, S. Poll, A. Pavia Naves, N. Caracciolo, P. Slade, J. Demerouti, A. Salerno, M. Kuehl, T. Kahles, D. Gladstone, K. Tanaka, S. Ravi, R. Hidalgo, J.D. Wering, M. Goldin, M. Cecere, E. Ferrari, S. Breyer, F. Jung, B.J. Weder, T. Taitelbaum, S. Farzi, B. Reizm-Kasprak, A. Hakani, G. Salami, C. Bassetti, J. Crulla, D.J. Seiffert, T. Vahva, J. Dawson, for the ELM Investigators¹

Articles

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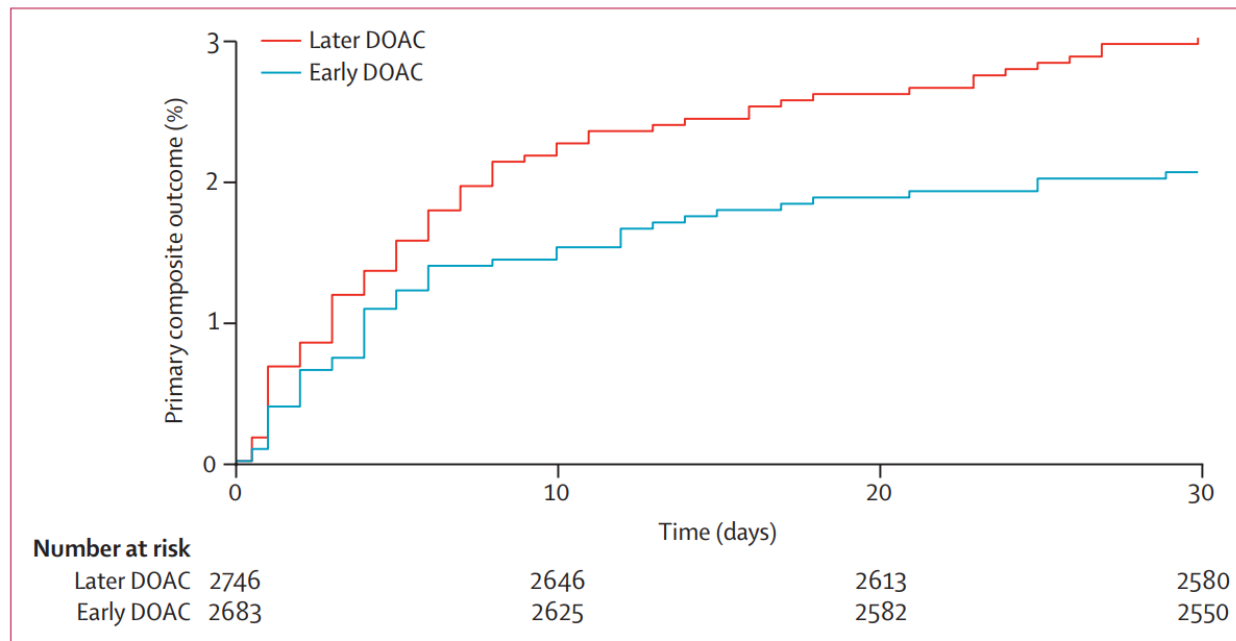
Circulation

Early Versus Delayed Non-Vitamin K Antagonist Oral Anticoagulant Therapy After Acute Ischemic Stroke in Atrial Fibrillation (TIMING): A Registry-Based Randomized Controlled Noninferiority Study

Jonas Oldgren , MD, PhD¹; Signild Åsberg , MD, PhD²; Ziad Hijazi , MD, PhD; Per Wester , MD, PhD; Maria Bertilsson, MSc
Bo Nordin , MD, PhD; for the National TIMING Collaborators

02.10.2025 17

Individual patient data meta-analysis (IPDMA) CATALYST

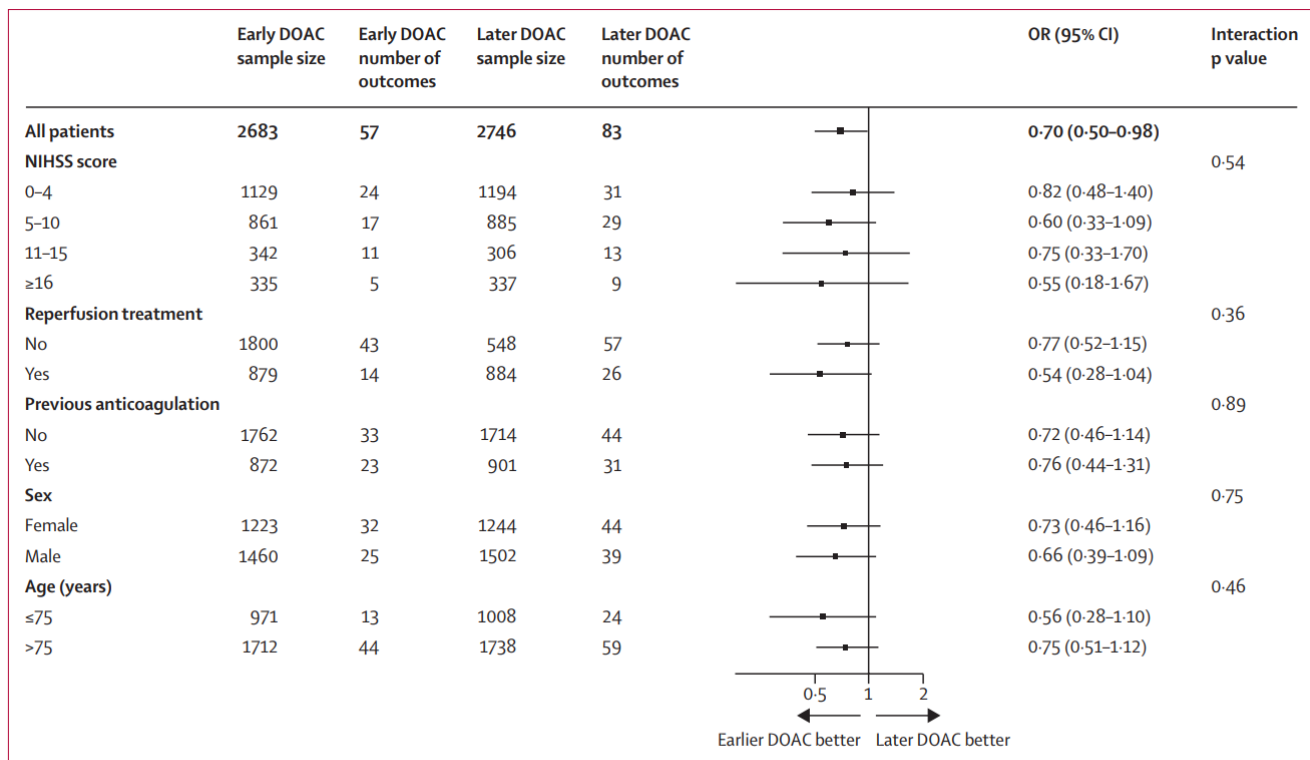


Early ≤ 4 days
Late ≥ 5 days

Figure 2: Primary composite outcome at 30 days by DOAC initiation timing (cumulative hazard)

Log-rank p value: 0.034. DOAC=direct oral anticoagulant.

- Composite endpoint:
- recurrent ischaemic stroke
 - symptomatic intracerebral haemorrhage
 - unclassified stroke



Consistent
effect in all
subgroups

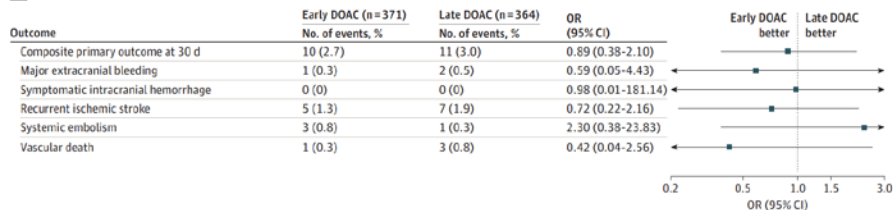
Figure 3: Primary outcome overall and by subgroups of interest

Interaction p value refers to the interaction term between early versus later DOAC and the baseline characteristic with respect to the primary outcome.

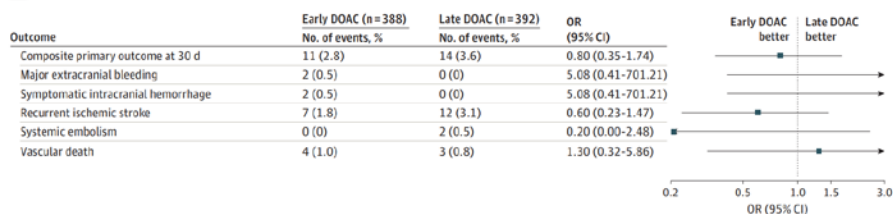
DOAC=direct oral anticoagulant. NIHSS=National Institutes of Health Stroke Scale. OR=odds ratio.

Figure 2. Unadjusted Odds Ratios (ORs) of the Primary Composite Outcome and Secondary Outcomes at 30 Days

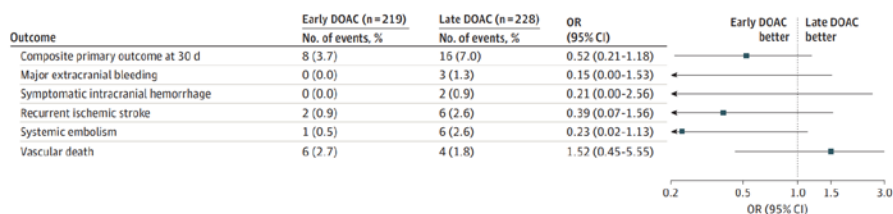
A Minor stroke



B Moderate stroke



C Major stroke



The incidences of the primary and secondary outcomes at 30 days were comparable for all infarct size groups, including minor (A), moderate (B), and major (C) stroke. DOAC indicates direct oral anticoagulation.

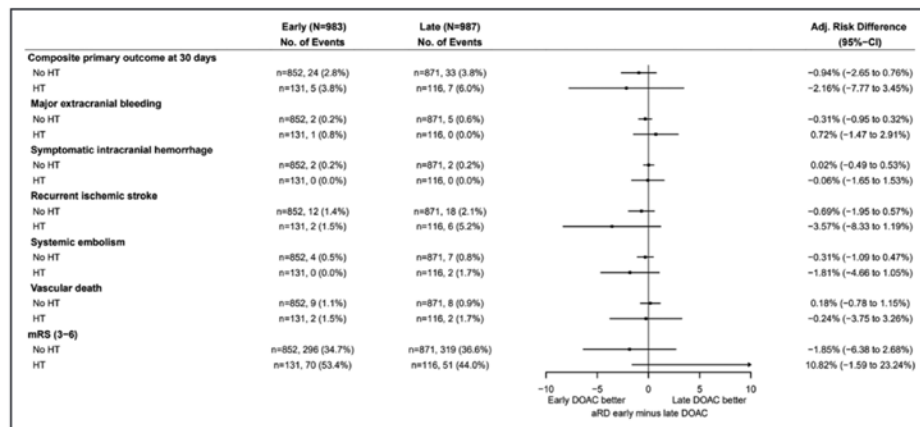


Figure 2. Primary and secondary outcomes.

Forest plots representing the adjusted risk differences (aRDs; early vs late anticoagulation) of the composite outcome, its components, and functional outcome at 30 days for participants with (1), hemorrhagic transformation (HT) and (2), no HT. DOAC indicates direct oral anticoagulation; and mRS, modified Rankin Scale.

Consistent effect regardless of stroke lesion size or haemorrhagic transformation

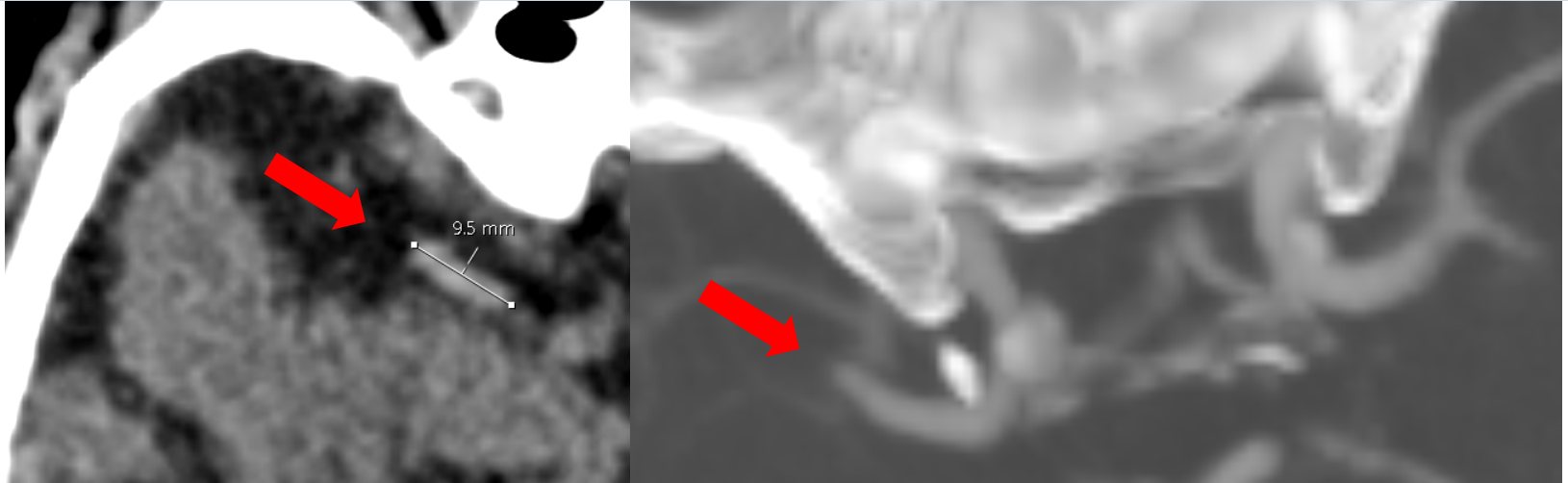
Stroke on anticoagulants – a frequent clinical scenario

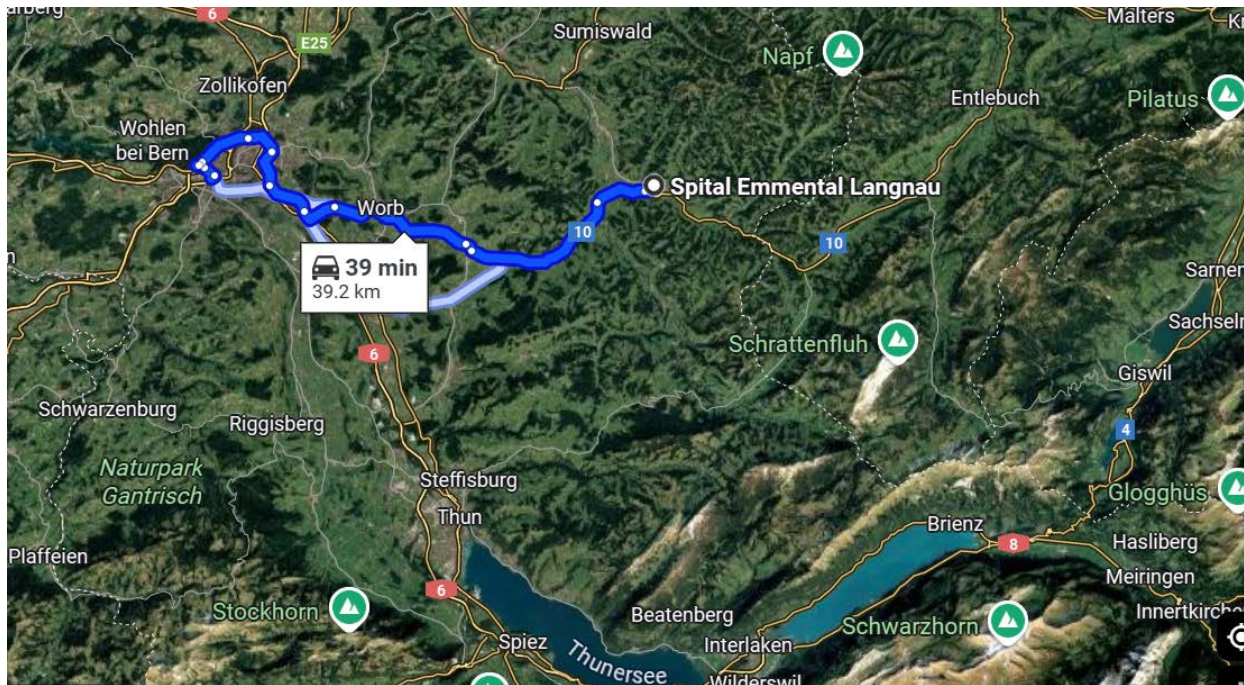
Symptoms: left side hemiparesis, NIHSS 11

Medical history: Atrial fibrillation on Apixaban 5mg, last intake 2h before stroke onset

Currently hospitalized for heart failure, medication intake under supervision

Symptom to CT time: 1h (in hospital)





estimated time to groin
puncture at Inselspital:
90-120 minutes

Vote – what would you do?

1) No IVT, send to Bern for thrombectomy

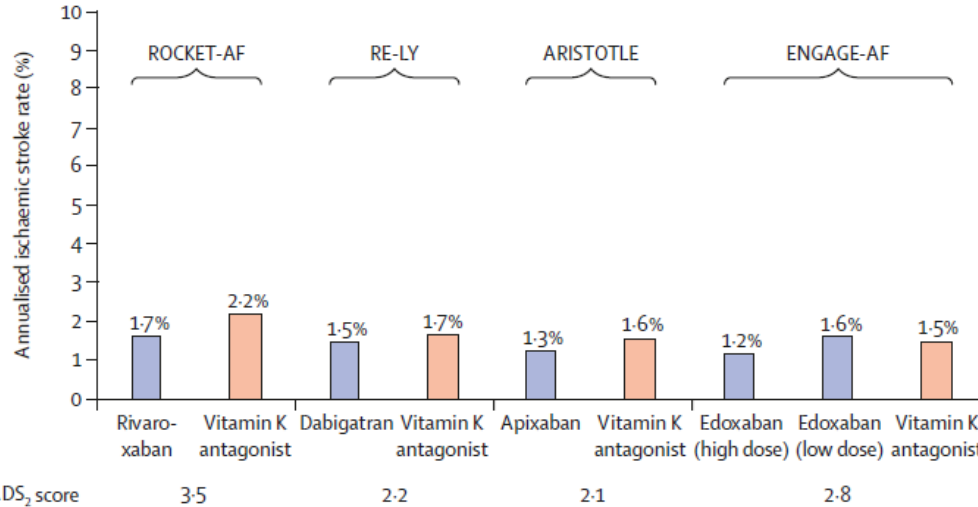
2) Start IVT, send to Bern for thrombectomy

3) Too old, too sick – keep patient in the Emmenthal



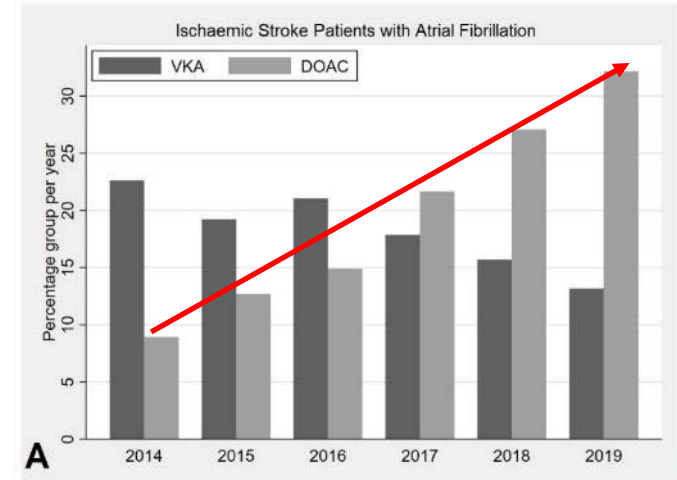
The burden of «breakthrough stroke» despite anticoagulants

Randomised controlled trials comparing direct oral anticoagulants with vitamin K antagonists



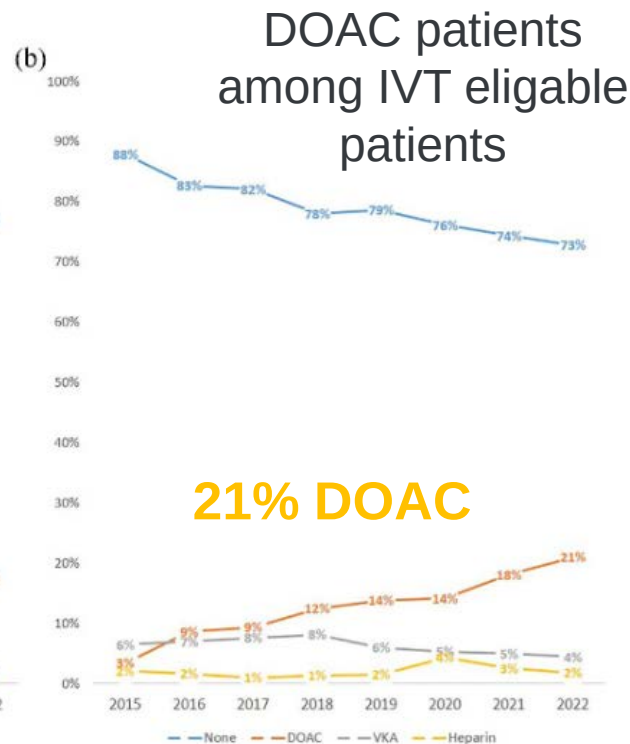
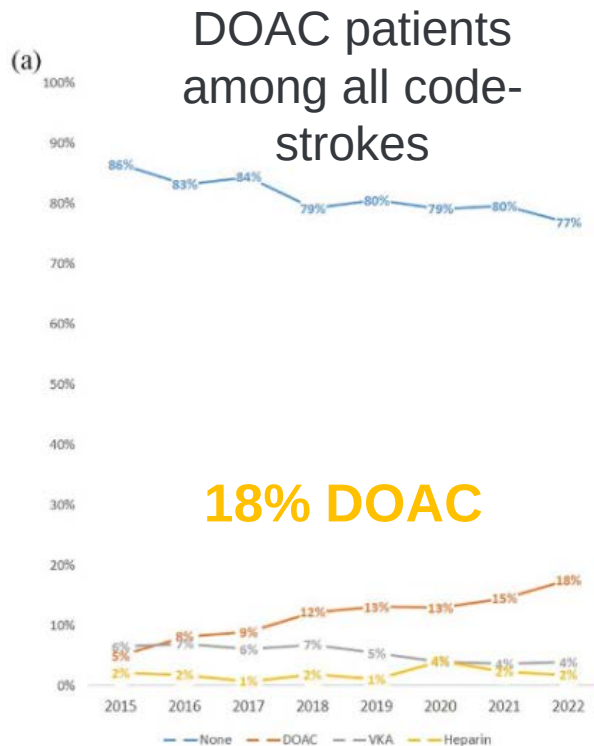
Participants with atrial fibrillation on anticoagulation therapy in large RCTs had «breakthrough» strokes at 1-2%/year

Swiss Stroke Registry



38% of all AF-strokes are «Breakthrough stroke» despite anticoagulation

The burden of breakthrough strokes despite anticoagulation



IVT in patients taking Vitamin K antagonists (VKA)

Risks of Intracranial Hemorrhage Among Patients With Acute Ischemic Stroke Receiving Warfarin and Treated With Intravenous Tissue Plasminogen Activator

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Li Liang, PhD
Eric E. Smith, MD, MPH
Lee H. Schwamm, MD
Matthew J. Reeves, PhD
DaiWai M. Olson, PhD, RN
Adrian F. Hernandez, MD, MHS
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INTRAVENOUS TISSUE PLASMINOGEN ACTIVATOR (tPA) is currently the only effective treatment to improve outcomes for acute ischemic stroke^{1,2}; however, treatment with intravenous tPA carries the risk of symptomatic intracranial hemorrhage (sICH). Of patients who receive intravenous tPA for stroke, 2.4% to 8.8%

Context Intravenous tissue plasminogen activator (tPA) is known to improve outcomes in ischemic stroke; however, patients receiving long-term chronic warfarin therapy may face an increased risk for intracranial hemorrhage when treated with tPA. Although current guidelines endorse administering intravenous tPA to warfarin-treated patients if their international normalized ratio (INR) is ≤ 1.7 or lower, there are few data on safety of intravenous tPA in warfarin-treated patients in clinical practice.

Objectives To determine the risk of symptomatic intracranial hemorrhage (sICH) among patients with ischemic stroke treated with intravenous tPA who were receiving warfarin vs those who were not and to determine this risk as a function of INR.

Design, Setting, and Patients Observational study, using data from the American Heart Association Get With The Guidelines-Stroke Registry, of 23 437 patients with ischemic stroke and with INR of 1.7 or lower, treated with intravenous tPA in 1203 registry hospitals from April 2009 through June 2011.

Main Outcome Measure Symptomatic intracranial hemorrhage. Secondary endpoints include life-threatening/serious systemic hemorrhage, any tPA complication and in-hospital mortality.

Results Overall, 1802 (7.7%) patients with stroke treated with tPA were receiving warfarin (median INR, 1.20; interquartile range [IQR], 1.07–1.40). Warfarin-treated patients were older, had more comorbid conditions, and had more severe strokes. The unadjusted sICH rate in warfarin-treated patients was higher than in non-warfarin-treated patients (5.7% vs 4.6%, $P < .001$), but these differences were not significant.

Safety of Intravenous Thrombolysis for Ischemic Stroke in Patients Treated with Warfarin

Michael V. Mazza, MD,¹ Kennedy R. Lees, MD, FRCP,² Romesh Markus, MD, FRACP,³ Risto O. Roine, MD, PhD,⁴ Raymond C. S. Seet, MD, MRCP,⁵ Nils Wahlgren, MD, PhD,¹ and Niaz Ahmed, MD, PhD,¹ for the Safe Implementation of Thrombolysis in Stroke Investigators

Objective: Controversy surrounds the safety of intravenous (IV) tissue plasminogen activator (tPA) in ischemic stroke patients treated with warfarin. The European tPA license precludes its use in anticoagulated patients altogether. American guidelines accept IV tPA use with an international normalized ratio (INR) ≤ 1.7 . The influence of warfarin on symptomatic intracerebral hemorrhage (sICH), arterial recanalization, and long-term functional outcome in stroke thrombolysis remains unclear.

Methods: We analyzed data from 45 074 patients treated with IV tPA enrolled in the Safe Implementation of Thrombolysis in Stroke (SITS) International Stroke Thrombolysis Register. A total of 768 patients had baseline warfarin treatment with INR ≤ 1.7 . Outcome measures were sICH, arterial recanalization, mortality, and functional independence at 3 months.

Results: Patients on warfarin with INR ≤ 1.7 were older, had more comorbidities, and had more severe strokes compared to patients without warfarin. There were no significant differences between patients with and without warfarin in sICH rates (adjusted odds ratio [aOR] = 1.23, 95% confidence interval [CI] = 0.72–2.11 per SITS-MOST; aOR = 1.26, 95% CI = 0.82–1.70 per European Cooperative Acute Stroke Study II) after adjustment for age, stroke severity, and comorbidities. Neither did warfarin independently influence mortality (aOR = 1.05, 95% CI = 0.83–1.35) or functional independence at 3 months (aOR = 1.01, 95% CI = 0.81–1.24). Arterial recanalization by computed tomography/magnetic resonance angiography trended higher in warfarin patients (62% [37 of 59] vs 55% [776/1475], $p = 0.064$). Recanalization approximated by disappearance at 22 to 36 hours of a baseline hypodense middle cerebral artery sign was increased (63% [124 of 196] vs 55% [3,901 of 7,099], $p = 0.022$).

Interpretation: Warfarin treatment with INR ≤ 1.7 did not increase the risk for sICH or death, and had no impact on

ORIGINAL ARTICLE

Recommendation

For patients with acute ischaemic stroke of < 4.5 h duration, who use vitamin K antagonists and have INR ≤ 1.7 we recommend intravenous thrombolysis with alteplase.

Quality of evidence: Low $\oplus\oplus$

Strength of recommendation: Strong $\uparrow\uparrow$

For patients with acute ischaemic stroke of < 4.5 h duration, who use vitamin K antagonists and have INR > 1.7 we recommend no intravenous thrombolysis.

Quality of evidence: Very Low $\oplus$

Strength of recommendation: Strong $\downarrow\downarrow$

For patients with acute ischaemic stroke of < 4.5 h duration, who use vitamin K antagonists, and for whom the results of coagulation testing is unknown, we recommend no intravenous thrombolysis.

Quality of evidence: Very low $\oplus$

Strength of recommendation: Strong $\downarrow\downarrow$

Data quality:

Retrospective cohort studies
INR cut-off ≤ 1.7 based on expert opinion

IVT in patients taking direct oral anticoagulants (DOAC)



The use of IV alteplase in patients taking direct thrombin inhibitors or direct factor Xa inhibitors has not been firmly established but **may be harmful**.† (COR III: Harm; LOE C-EO)§|| IV alteplase should not be administered to patients taking



Recommendation

For patients with acute ischaemic stroke of < 4.5 h duration, who used a NOAC during the last 48 h before stroke onset, and for whom there is no specific coagulation tests available (i.e. calibrated anti-Xa-activity for factor Xa inhibitors, thrombin time for dabigatran, or the NOAC blood concentrations), **we suggest no intravenous thrombolysis**.

Quality of evidence: Very Low ⊕

Strength of recommendation: **Strong** !!

For patients with acute ischaemic stroke of < 4.5 h duration, who used a NOAC during the last 48 h before stroke onset, and who have an anti-Xa activity < 0.5 U/ml (for factor Xa inhibitors) or thrombin time < 60 s (for direct thrombin inhibitors), there is insufficient evidence to make an evidence-based recommendation. Please see the Expert consensus statement below.

Quality of evidence: Very low ⊕

Strength of recommendation: -

For patients with acute ischaemic stroke of < 4.5 h duration, who used dabigatran during the last 48 h before stroke onset, there is insufficient evidence to make a recommendation for or against the use of the combination of idarucizumab and intravenous thrombolysis with alteplase over no intravenous thrombolysis. Please see the Expert consensus statement below.

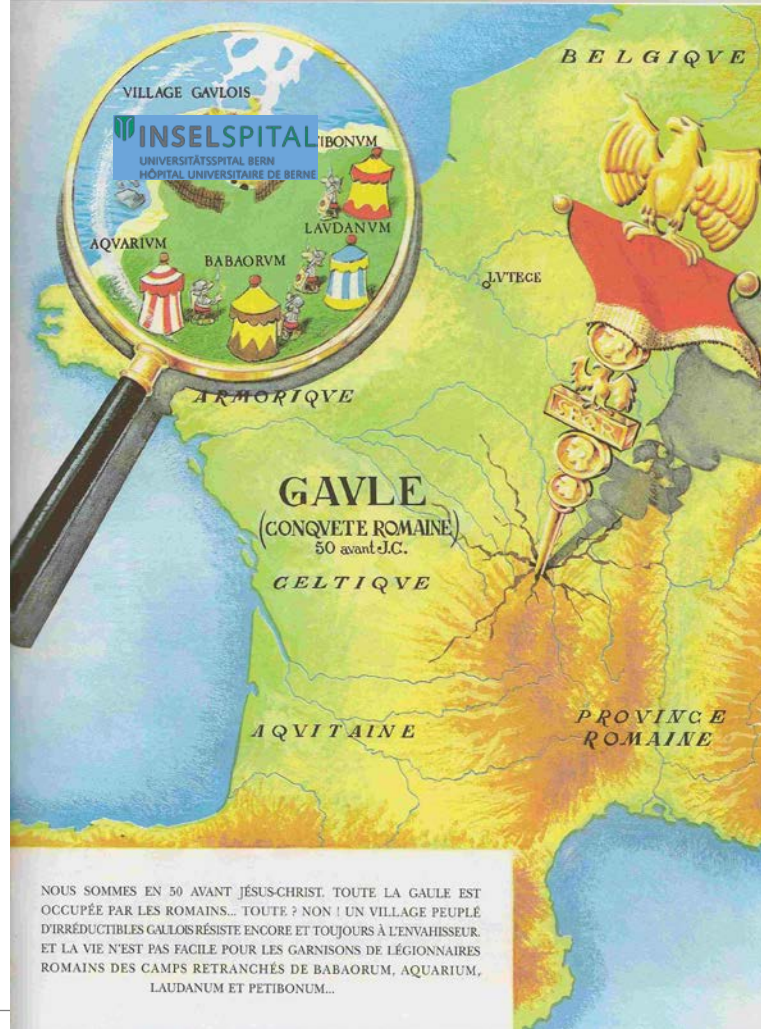
Quality of evidence: Very low ⊕

Strength of recommendation: -

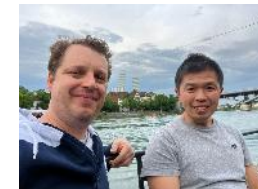
«We suggest
no
intravenous
thrombolysis»

Current international guidelines
recommend **AGAINST** the use of IVT in
patients on DOACs

There are a few brave, indomitable neurologists in Switzerland* who do use IVT in stroke patients on DOACs...



* and friends and colleagues around the globe!



Summary of evidence - 2021

Table 3 Observational studies including patients on direct oral anticoagulant (DOAC) treated with intravenous thrombolysis

Study	Number of patients (DOAC type)	Number of sICH/rate	Number of patients (comparator)	Number of sICH/rate	Comment
Heterogenous or unknown selection criteria (n=5 studies, n=475 patients)					
Xian <i>et al</i> ¹²	251 (all DOAC)	12 (4.8%)	1500 (VKA)	73 (4.9%)	No selection criteria or information on anticoagulation available
Seiffge <i>et al</i> ¹¹	78 (all DOAC)	2 (3.9%)	441 (VKA) and 8938 (no anticoagulation)	9.3% and 7.2%	Heterogenous selection criteria, all within 48 hours, partly plasma level-based
Suzuki <i>et al</i> ¹⁰	71 (all DOAC)	2%	n/a	n/a	National survey and case collection, (dosage of rt-PA: 0.6 mg/kg)
Shahjouei <i>et al</i> ¹⁴	6 (dabigatran)	0	n/a	n/a	Case collection
Meinel <i>et al</i> ³³	69 (all DOAC)	3.1%	1544 (no anticoagulation) and 156 (VKA with INR <1.7)	3.6% (no) and 4.6% (VKA)	18 of 23 centres used DOAC plasma levels for patient selection
DOAC plasma-level based approach (n=3 studies, n=36 patients)					
Marsch <i>et al</i> ⁴⁶	9 (all DOAC)	1 (4.2%)	31 VKA	1 (3.3%)	All patients <48 hours of last intake
Seiffge <i>et al</i> ²⁸	18 (rivaroxaban)	0	n/a	n/a	
Purrucker <i>et al</i> ⁸	9 (all DOAC)	0	n/a	n/a	
Idarucizumab (n=8 studies, n=236 patients)					
Beharry <i>et al</i>	13 (dabigatran)	0	n/a	n/a	Tenecteplase
Barber <i>et al</i>	51 (dabigatran)	2 (3.9%)	1285 (all non-DOA)	49 (3.8%)	
Kerner <i>et al</i>	80 (dabigatran)	0	n/a		
Küpper <i>et al</i>	7 (dabigatran)	0	n/a		
Pretnar Oblak <i>et al</i>	11 (dabigatran)	2 sICH (18.2%)	n/a	no	9 with elevated thrombin time
Giannandrea <i>et al</i>	55 (dabigatran)	3 sICH (5.5%)	n/a	n/a	
Sanak <i>et al</i>	13 (dabigatran)	1 sICH (7.6%) 2 aICH	n/a	n/a	
Fang <i>et al</i>	6 (dabigatran)	0	n/a	n/a	

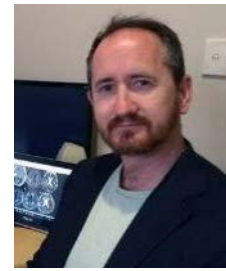
INR, international normalised ratio; sICH, symptomatic intracerebral haemorrhage; VKA, vitamin K antagonist.

No signal of harm in retrospective cohort studies

sICH rates generally low

Small sample size (<100 patients)

International collaboration: DOAC-IVT



Design: International, multi-centre, retrospective cohort study (CRD42021277825)

Study population: Patients with ischaemic stroke on prior DOAC therapy (confirmed last intake <48h) who received IVT

Main outcome: symptomatic intracerebral haemorrhage (sICH)

Secondary outcome: functional independence at 3 month (mRS 0-2)

Sensitivity analysis: Selection approach (i.e. DOAC-level-measurements, prior reversal-treatment, IVT without DOAC-level measurement nor reversal treatment or inadvertent use of IVT)



DOAC-IVT

Research

JAMA Neurology | Original Investigation

Intravenous Thrombolysis in Patients With Ischemic Stroke and Recent Ingestion of Direct Oral Anticoagulants

Thomas R. Meinel, MD, Duncan Wilson, PhD, Henrik Gensicke, MD, Jan F. Scheitz, MD, Peter Ringleb, MD, Ioana Goganau, MD, Johannes Kaesmacher, MD, Hee-Joon Bae, MD, Do Yeon Kim, MD, Pawel Kerner, MD, Kentaro Suzuki, MD, Kazumi Kimura, MD, Kosmas Macha, MD, Masatoshi Koga, MD, Shinichi Wada, MD, Valerian Altersberger, MD, Alexander Salerno, MD, Logesh Palanikumar, MD, Andrea Zini, MD, Stefano Forlivesi, MD, Lars Kellert, MD, Johannes Wischmann, MD, Espen Kristoffersen, MD, PhD, James Beharry, MD, P. Alan Barber, PhD, Jae Beom Hong, MD, Carlo Cereda, MD, Eckhard Schlemm, MBBS, PhD, Yusuke Yakushiji, MD, Sven Poli, MD, MSc, Ronen Leker, MD, Michele Romoli, MD, Marialuisa Zedde, MD, Sami Curtze, MD, Benno Ikenberg, MD, Timo Uphaus, MD, David Giannandrea, MD, Pere Cardona Portela, MD, Roland Veltkamp, MD, Annemaree Ranta, PhD, Marcel Arnold, MD, Urs Fischer, MD, Jae-Kwan Cha, MD, Teddy Y. Wu, PhD, Jan C. Purrucker, MD, MSc, David J. Seiffge, MD, and the DOAC-IVT Writing Group, for the International DOAC-IVT, TRISP, and CRCS-K-NIH Collaboration

252 (30%) received DOAC reversal



225 (27%) were selected on DOAC-levels



355 (43%) no reversal or DOAC-level check



Meinel et al JAMA Neurol 2023

Insel Gruppe – stroke, afib and anticoagulation

Table 1. Patient Baseline Characteristics

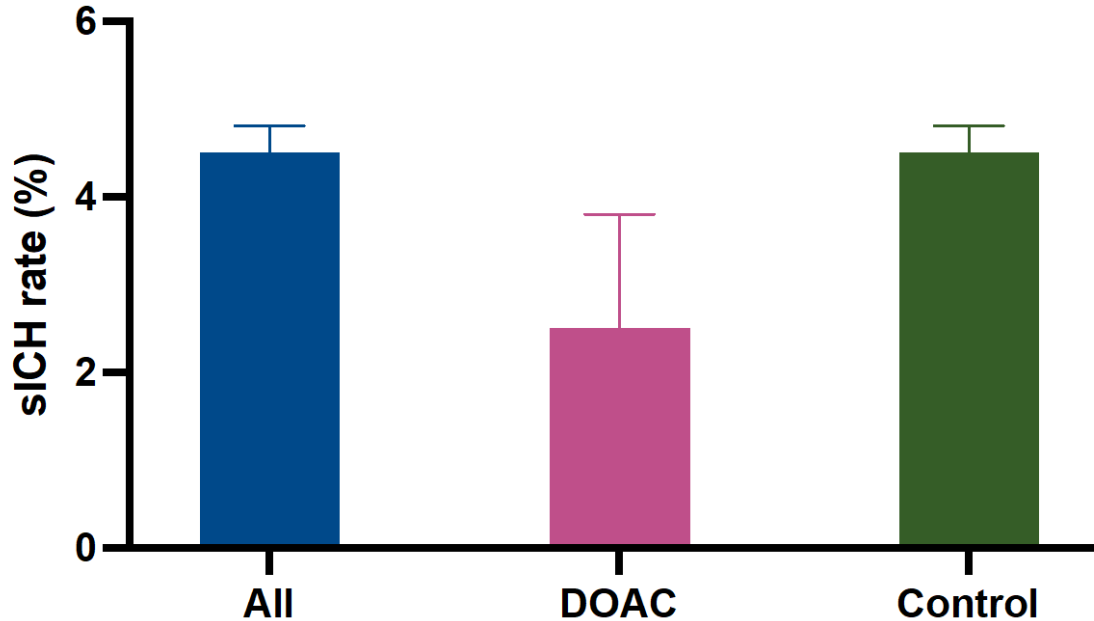
Characteristic	Total, No.	No. (%)			P value
		All patients (N = 33 207)	Controls (n = 32 375)	Patients with recent ingestion of DOACs (n = 832)	
Age, median (IQR), y	33 198	73 (62-80)	72 (62-80)	79 (71-85)	<.001
Sex					
Female	33 199	14 458 (43.5)	14 103 (43.6)	355 (42.7)	.60
Male		18 741 (56.5)	18 264 (56.4)	477 (57.3)	
Geographical region					
Europe		21 266 (64.0)	20 792 (64.2)	474 (57.0)	
Asia	33 207	6698 (20.2)	6489 (20.0)	209 (25.1)	<.001
Australia and New Zealand		5243 (15.8)	5094 (15.7)	149 (17.9)	
NIHSS score, median (IQR) ^a	32 928	9 (5-16)	9 (5-16)	11 (6-17)	<.001
Prestroke modified Rankin Scale score, median (IQR) ^b	29 059	0 (0-0)	0 (0-0)	0 (0-1)	<.001
Systolic blood pressure, mean (SD), mm Hg	29 178	154 (28)	154 (28)	154 (27)	.67
Time from symptom onset to hospital admission, median (SD), h	12 179	1.3 (0.8-2.3)	1.3 (0.8-2.3)	1.7 (1.0-2.6)	<.001
Blood glucose level, mean (SD), mg/dL	28 711	133 (48)	133 (48)	133 (45)	.77
International normalized ratio, median (IQR)	17 471	1 (1-1.1)	1 (1-1.1)	1.1 (1.02-1.2)	<.001
Risk factors and medication ^c					
Arterial hypertension	33 000	20 637 (62.5)	20 072 (62.2)	565 (75.1)	<.001
Current smoking	30 337	5891 (19.4)	5796 (19.6)	95 (12.8)	<.001
History of hypercholesterolemia	32 941	12 413 (37.7)	12 091 (37.6)	322 (43.2)	.002
Diabetes	32 978	6484 (19.7)	6311 (19.6)	173 (23.2)	.01
Antiplatelet therapy	29 884	10 471 (35.0)	10 383 (35.7)	88 (11.2)	<.001
AF	16 629	4616 (27.8)	4008 (25.1)	608 (90.1)	<.001
If taking anticoagulation, AF as reason for anticoagulation	1248	1171 (93.8)	609 (90.2)	562 (98.1)	
Type of anticoagulation used					
Dabigatran		0	0	342 (41)	
Rivaroxaban		0	0	258 (31)	<.001
Apixaban		0	0	163 (20)	
Edoxaban	33 207	0	0	68 (8)	
DOAC, not specified which agent		0	0	1 (<1)	
Vitamin K antagonists		0	0	689	
Presence of large vessel occlusion	33 069	10 970 (33.2)	10 516 (32.6)	454 (59.0)	<.001
Mechanical thrombectomy	32 833	6391 (19.5)	6106 (19.1)	285 (34.3)	<.001
Tenecteplase used (instead of alteplase)	33 199	1276 (3.8)	1225 (3.8)	51 (6.1)	<.001
Time from symptom onset to intravenous thrombolysis, median (IQR), min	29 717	138 (98-190)	138 (98-190)	153 (110-210)	<.001

Many significant differences between patients with and without prior DOAC ingestions

Patients on DOACs: older, higher NIHSS, longer onset-to-admission and to-IVT time, higher burden of risk factors

→ predictors for higher risk of sICH

DOAC-IVT: Primary outcome



adjusted OR 0.57; 95% CI 0.36 to 0.92, $p = 0.02$

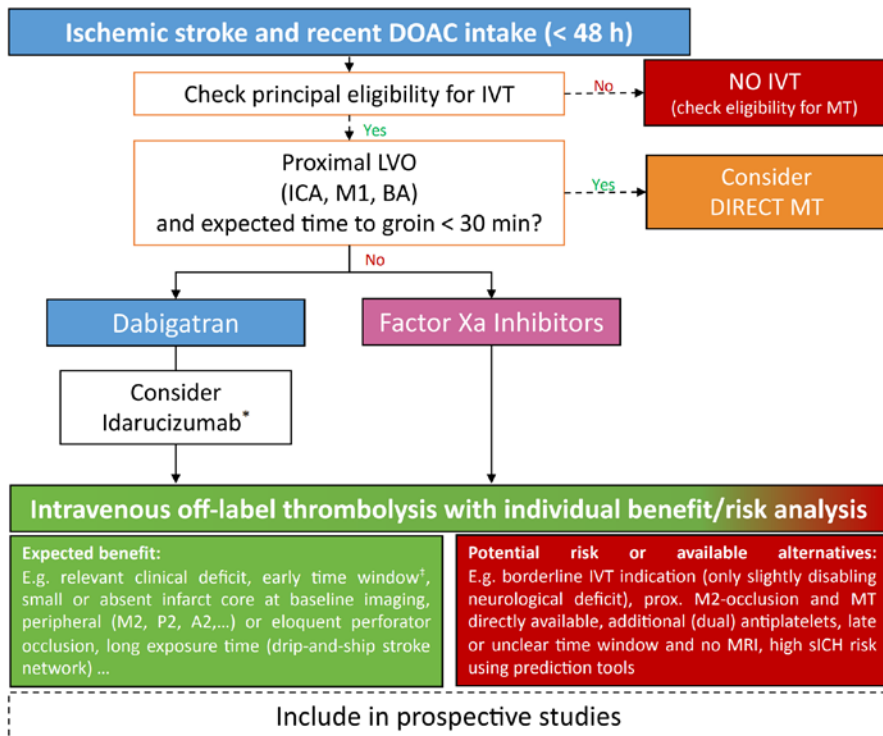
Subgroup analyses

Selection method	n	OR	95% CI	p value
Controls	32035	Reference		
DOAC level	225	0.66	0.31 to 1.40	0.28
No DOAC level nor reversal	355	0.84	0.46 to 1.53	0.56
Reversal	252	0.30	0.09 to 0.92	0.04

Patients with DOAC-levels >100ng/ml or intake <12 hours without reversal:

adjusted **OR 0.57**; (95% CI 0.23–1.42)

How we do it...



Stroke Richtlinien

des Berner Stroke Netzwerks

S. Jung, T. Meinel, P. Bücke, D. Seiffge, B. Birner, T. Horvath, M. Heldner, U. Prange, B. Volbers, H. Sarikaya, S. Muth, A. Luczkiewicz, P. Correia, A. Humm, S. Renaud, R. Bühler, J. Gralla, J. Kaesmacher, H. Mattle, M. Bühlmann, A. Angelillo-Scherrer, D. Bervini, W. Z'Graggen, A. Raabe, M. Arnold, U. Fischer für das **Stroke-Team Bern**

Anmeldung von Strokes und anderen neurologischen Notfällen via
Dienst-OA Neurologie 031 632 17 02

OA Neurologie			
Dienst OA (24/7)	6009 (031 632 17 02)	Stroke Unit	
Stroke Unit	20854	Stroke Unit AA (7-16h)	44657
Bettenstation	8792	Spätdienst (14-23h)	44659
Neuroreha Triage	4479	Pflege	43742
IB Schichtleiter	7770	WE Dienst Neuro Bettenstation	44660
Anästhesie	8555	REA MET Team	9999 5588
NRAD AA Dispatcher/MRI	23460	NRAD MR MTRA (24/7)	26200
NRAD CT AA	28447 o. 5563	NRAD CT MTRA (7-19h)	28272
NRAD OA Angiographie	23484	NRAD Angio MTRA	22448
		Notfall CT MTRA (24/7)	46201
Neurochir AA	6310	Kardiologie TA	6248
Neurochir OA	7310	Infektiologie TA	6666
Allgemeine Radiologie TA	6203	Labor Chemie	22408
UKN -OA Medizin	7520		

<https://neurologie.insel.ch/de/aerzte-und-zuweiser/richtlinien>
www.strokecenter.ch

Intravenous thrombolysis in patients with recent intake of direct oral anticoagulants – a target trial analysis after the liberalization of institutional guidelines

Is off-label intravenous thrombolysis (IVT) after recent intake of direct oral anticoagulants (DOACs) and without the application of reversal agents safe and effective?

Methods



vs.



Stroke eligible for IVT
+ DOAC intake < 48 h



Outcome:

- Symptomatic intracerebral hemorrhage (sICH)
- Radiological ICH
- Any major bleeding
- mRS 0–2 (90 days)



Results



n=49

Mean plasma level: 77 ng/ml
82% last intake < 24 h



n=49

Mean plasma level: 125 ng/ml

Outcome: IVT versus no IVT

↔ sICH (ECASS III)	0% vs. 4%
↔ sICH (NINDS)	2% vs. 9%
↔ Radiological ICH (PH 2)	2% vs. 9%
↔ All major bleeding	0% vs. 6%
↑ mRS 0–2 (90 days)	81% vs. 28%

Conclusion



IVT after recent DOAC
ingestion appears to be safe



The association of IVT with
better functional outcomes
warrants RCT data



The paradigm DOAC =
absolute IVT contraindication
might have to be questioned

ORIGINAL CONTRIBUTION

Intravenous Thrombolysis in Patients With Recent Intake of Direct Oral Anticoagulants: A Target Trial Analysis and Comparison With Reversal Agent Use

Thomas R. Meinel¹, MD; Philipp Bücke², MD; Lucio D'Anna³, MD; Giovanni Merlino⁴, MD; Diana Aguiar de Sousa⁵, MD; Sven Poli⁶; Jan C. Purrucker⁷; Davide Strambo⁸, MD; Michele Romoli⁹, MD; Gian Marco De Marchis¹⁰; Waltraud Pfeilschifter¹¹; Marialuisa Zedde¹², MD; João Pedro Marto¹³, MD; Paolo Candelaresi¹⁴, MD; Robin Lemmens¹⁵; Pasquale Scoppettuolo¹⁶, MD; Malin Wöckel, MD; Pawel Kermer¹⁷; Espen Saxhaug Kristoffersen¹⁸; Malik Ghannam¹⁹; Senta Frol²⁰, MD; Christian H. Nolte²¹; Yusuke Yakushiji, MD; Emmanuel Touzé²²; Timo Uphaus²³; Marina Mannino²⁴, MD; George Ntaios²⁵; Visnja Padjen²⁶; Nils Henninger²⁷; Freschta Zipser-Mohammadzadeh, PhD; Marisa E. Mariano, MD; Carolina Guerreiro²⁸, MD; Alessandra Burini, MD; Laura Ceccarelli, MD; Mariarosaria Valente, MD; Alexandra Gomez-Exposito²⁹, MD; Antonia Kleeberg³⁰, MD; Guillaume Thevoz, MD; Patrik Michel³¹; Gianluca Stufano³², MD; Dimitrios Vlachos³³, MD; Matthias Herrmann, MD; Bárbara Rodrigues, MD; Emanuele Spina³⁴, MD; Vincenzo Andreone, MD; Arne Allardt; Qasem N. Alshaer³⁵, MD; Christoph Riegler³⁶, MD; Takenobu Kunieda³⁷, MD; Marion Boulanger³⁸, MD; Marianne Hahn³⁹, MD; Dimitra Papadimitriou⁴⁰, MD; Jayachandra Muppa⁴¹, MD; Louise Maes⁴², MD; Anna Ranta⁴³; Alicia Tyson⁴⁴, MD; P. Alan Barber⁴⁵; Alan Davis⁴⁶, MD; Teddy Y. Wu⁴⁷, MD; Johannes Kaesmacher⁴⁸; Urs Fischer⁴⁹; David J. Seiffge⁵⁰; for the International DO-IT Collaboration*

Target trial design:

- 1) Develop a protocol of a hypothetical RCT (e.g. in/exclusion criteria, treatment groups, outcome)
- 2) Emulate the components of that protocol using the observational data

JAMA Guide to Statistics and Methods

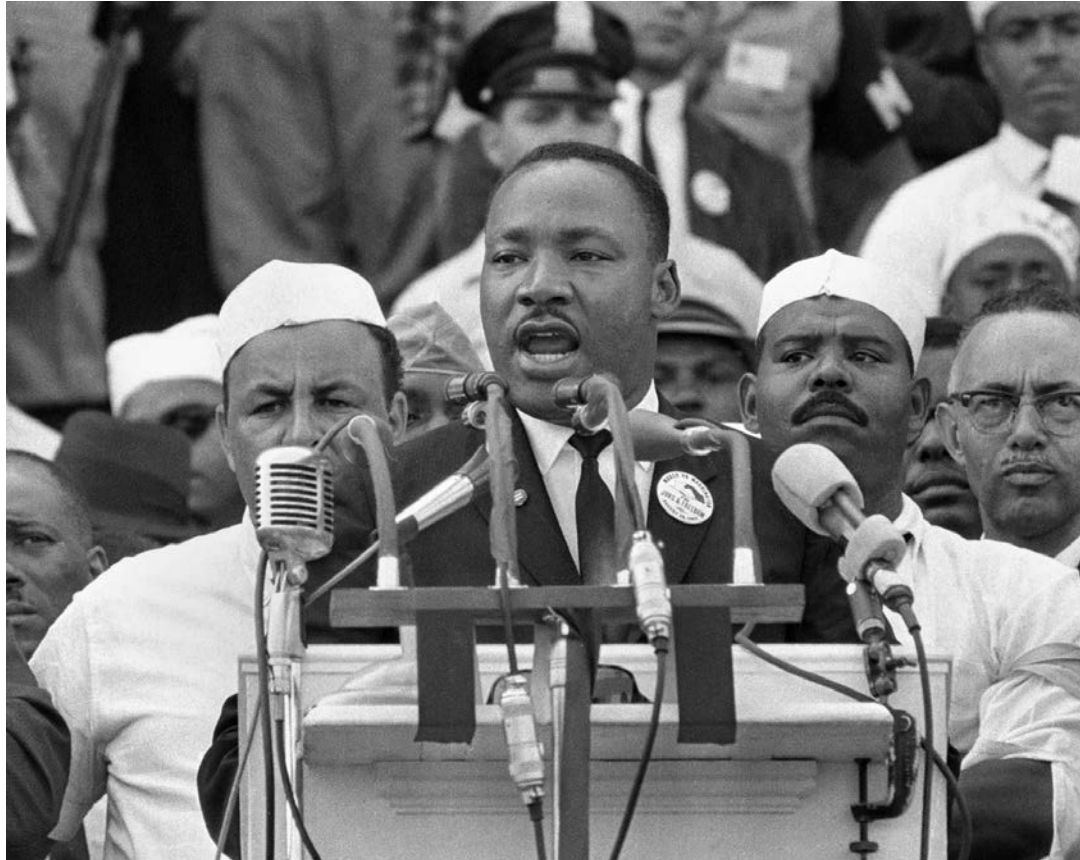
Target Trial Emulation

A Framework for Causal Inference From Observational Data

Miguel A. Hernán, MD, DrPH; Wei Wang, PhD; David E. Leaf, MD, MMSc

Table 3. Safety and Efficacy Outcomes

	Patients receiving IVT vs not receiving IVT			IVT with vs without prior reversal		
	No IVT	IVT	Adjusted difference (95% CI)	No reversal	Reversal (all Idarucizumab)	Adjusted difference, % (95% CI)
N (%)	n=1000	n=342		n=283	n=289	
Safety outcomes, n (%)						
sICH (ECASS III)*	54 (5.9%)	10 (3.0%)	−2.1% (−5.3% to +1.2)	10 (3.7%)	6 (2.1%)	−2.8% (−6.9 to +1.3)
sICH (NINDS)*	55 (6.5%)	9 (3.0%)	−1.1% (−5.2 to +2.9)			
Any radiological ICH*						
None	735 (78.1%)	264 (80.2%)	For any radiological ICH: −3.5% (−9.8 to +2.9)	213 (78.6%)	277 (96.2%)	For any radiological ICH: −16.4% (−22.9 to −10.1)
HI 1	92 (9.8%)	26 (7.9%)		21 (7.7%)	6 (2.1%)	
HI 2	47 (5.0%)	18 (5.5%)		18 (6.6%)	0 (0.0%)	
PH 1	13 (1.4%)	3 (0.9%)		2 (0.7%)	1 (0.3%)	
PH 2	22 (2.3%)	8 (2.4%)		8 (3.0%)	2 (0.7%)	
SAH	27 (2.9%)	9 (2.7%)		8 (3.0%)	2 (0.7%)	
Multiple types	5 (0.5%)	1 (0.3%)		1 (0.4%)	0 (0.0%)	
Any major bleeding†	21 (2.3%)	7 (2.3%)	+0.0% (−2.4 to +2.4)	6 (2.4%)	2 (0.7%)	−0.9% (−2.8 to +1.0)
Orolingual edemat†	0 (0.0%)	4 (1.2%)	+1.2% (+0.03 to +2.4)	4 (1.5%)	3 (1.0%)	−0.0% (−1.7 to +1.6)
Mortality (90 d)†	219 (22.7%)	47 (15.7%)	−3.3% (−9.5 to +2.9)	42 (17.1%)	5 (9.3%)	−5.5% (−15.5 to +4.6)
Efficacy outcome, n (%)†						
mRS score of 0–2 or return to baseline (90 d)	405 (43.7%)	181 (62.2%)	+14.4% (+7.1% to +21.8%)	147 (62.0%)	159 (63.9%)	−2.6% (−10.9 to +5.7)
mRS score shift analysis			aOR, 0.60 (0.45 to 0.80)			aOR, 1.32 (0.92 to 1.88)
NIHSS score difference between admission and 24 h	2 (0–7)	3 (1–7)	+0.33 (−0.58 to 1.24)	3 (0–7)	4 (1–9)	+0.05 (−1.2 to +1.2)

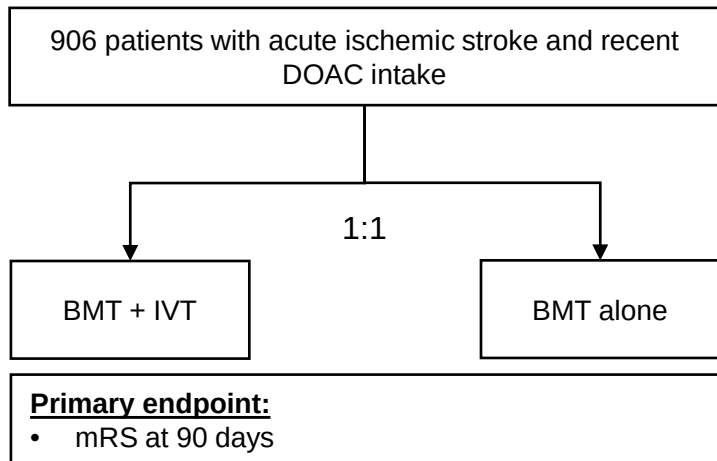




Thomas Meinel,
Bern

“Safety and Efficacy of Intravenous Thrombolysis in Patients with Ischemic Stroke and Recent Ingestion of Direct Oral Anticoagulants: DO-IT – The DOAC Intravenous Thrombolysis trial”

An international, multicenter, prospective, randomized, open label, blinded endpoint (PROBE) trial with predefined interim analyses



Sponsor-Investigator:

PD Dr. med Th. Meinel (Principal Investigator)
Prof. Dr. med. D. Seiffge (Co-Principal Investigator)
Prof. Dr. med. U. Fischer (Co-Principal Investigator)

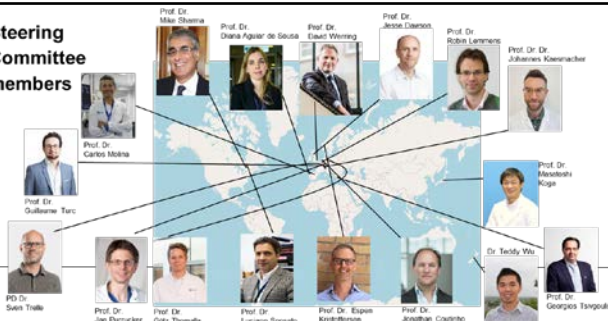
Leading Center:

Inselspital Bern, Bern University Hospital

Clinicaltrials.gov:

NCT06571149

Steering Committee members



FONDS NATIONAL SUISSE
SCHWEIZERISCHER NATIONALFONDS
FONDO NAZIONALE SVIZZERO
SWISS NATIONAL SCIENCE FOUNDATION

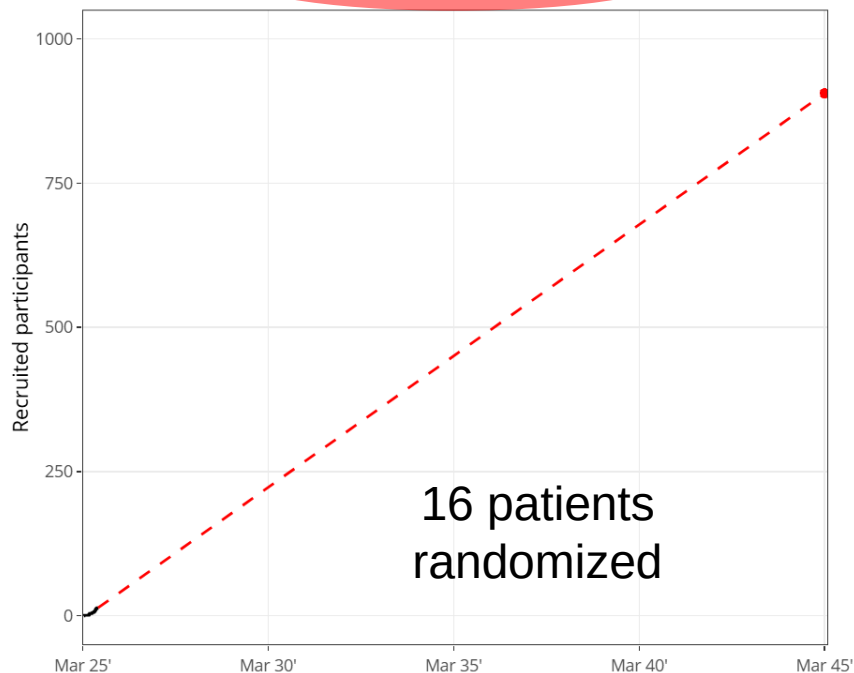


Helmut Horten Stiftung





Predicted end date: March 02, 2045



Center	First participant in	Months accruing	Participants accrued	Accrual rate (per month)
St-Gallen	05 Jun 2025	2	2	1.07
Bern	14 Mar 2025	5	8	1.73
Basel	05 May 2025	3	4	1.38
Overall	14 Mar 2025	5	14	3.02

active



Coming soon



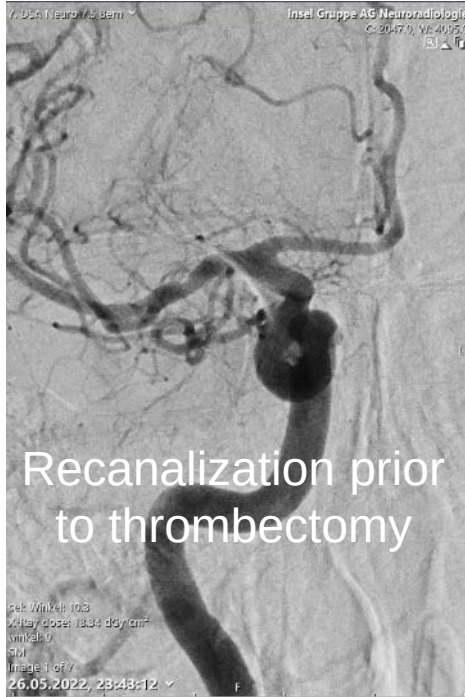
Ongoing RCTs in patients on DOAC



	DO-IT	PASSION	SIFT	DOSE (ACT-global DOAC domaine)
Trial registration	NCT06571149	not available	not available	NCT06320431
Sample size	906 patients	668 patients	300 patients	Overall 4000 patients
Centres/countries	>100 centres, global	Germany	Norway	global
Intervention	IV thrombolysis (TNK or rtPA)	TNK 0.25mg/kg	IV thrombolysis (TNK or rtPA)	2 doses of TNK (0.18 and 0.25mg/kg)
Design	PROBE	Double blinded	PROBE	Double blinded
Primary endpoint	mRS shift at 90days	mRS at 90days	early neurological improvement	?
Secondary endpoint	sICH and other	sICH mRS <2	sICH mRS at 90days	?
Status	Recruiting	Funding obtained	Recruiting	Funding obtained



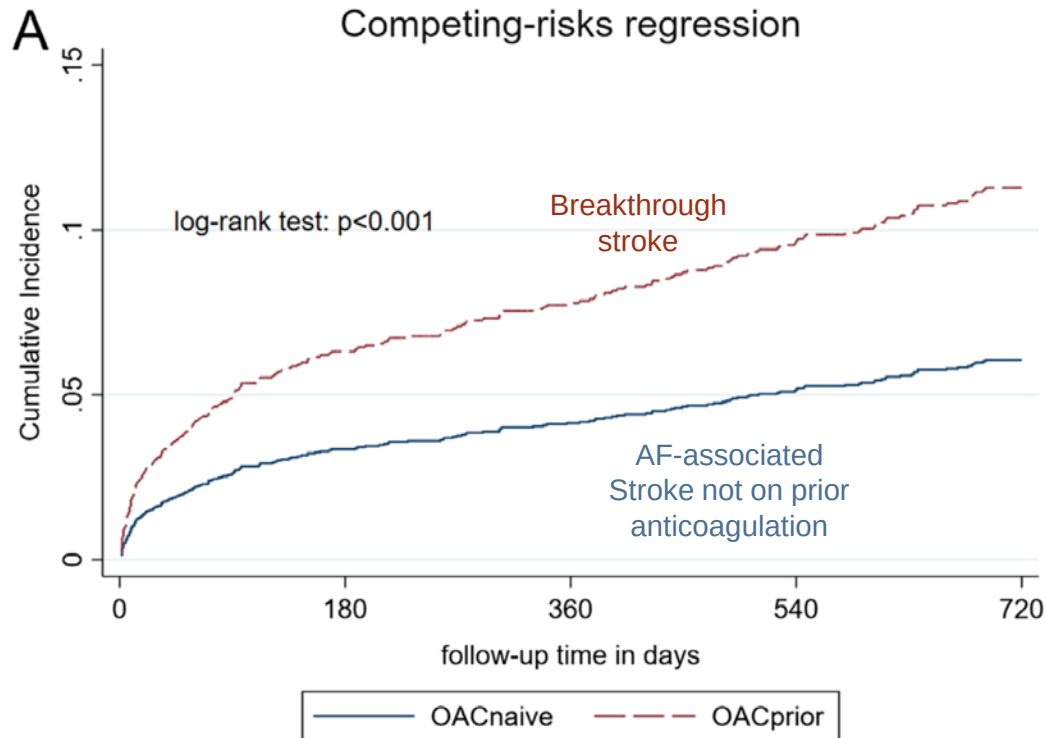
Treatment:
«drip-and-
ship»
iv rTPA
started



NIHSS day 2: 0 points
Discharged home

Follow-up CT

Breakthrough stroke: high risk of recurrence



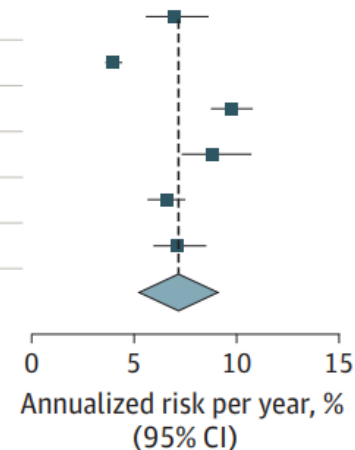
Risk of stroke recurrence after breakthrough stroke

Figure 3. Annualized Risk of Recurrence After Stroke Despite Anticoagulation

A Recurrent ischemic stroke

Study	Sample, No.	Annualized risk per year, % (95% CI)
COMBINE AF ¹⁷	1163	7.00 (5.54-8.71)
Hindsholm et al ²³	3075	3.99 (3.57-4.44)
Ip et al ²⁴	2337	9.77 (8.77-10.85)
Seiffge et al ³⁵	1195	8.90 (7.24-10.79)
Taiwan NHIRD ²⁸	1979	6.56 (5.69-7.52)
RENO-EXTEND ³²	1240	7.16 (5.93-8.56)

Overall pooled incidence, 7.20% per year
(95% CI, 5.05%-9.34%)



Aetiology of breakthrough strokes

Competing (non-AF) stroke aetiology

large artery atherosclerosis,
small vessel disease

24.2%

Medication error

Non-compliance, OAC
paused/stopped for
intervention, wrong dosage

31.7%

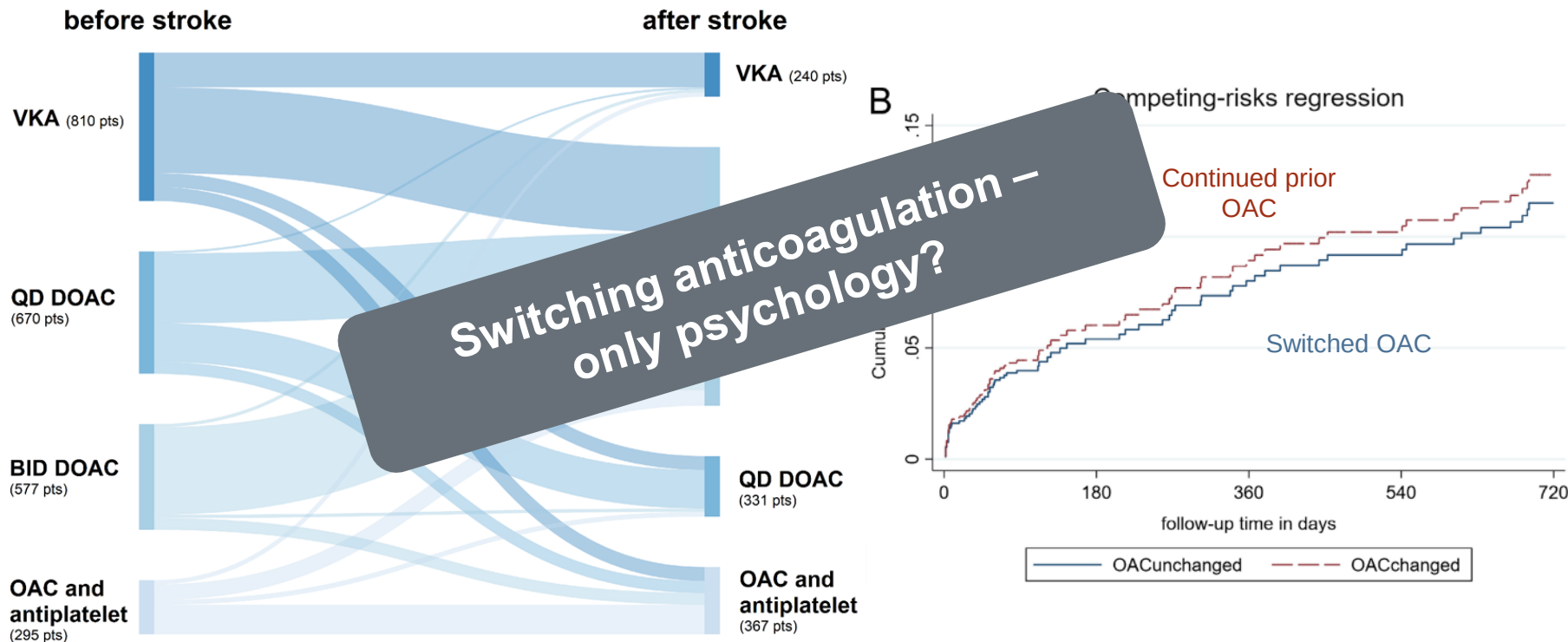
Cardioembolism despite adequate OAC

«pure» breakthrough strokes

41.4%

Data from 2946 patients with AF and
breakthrough strokes

Anticoagulation before and after a breakthrough stroke



Anticoagulation management after breakthrough stroke – East asian population

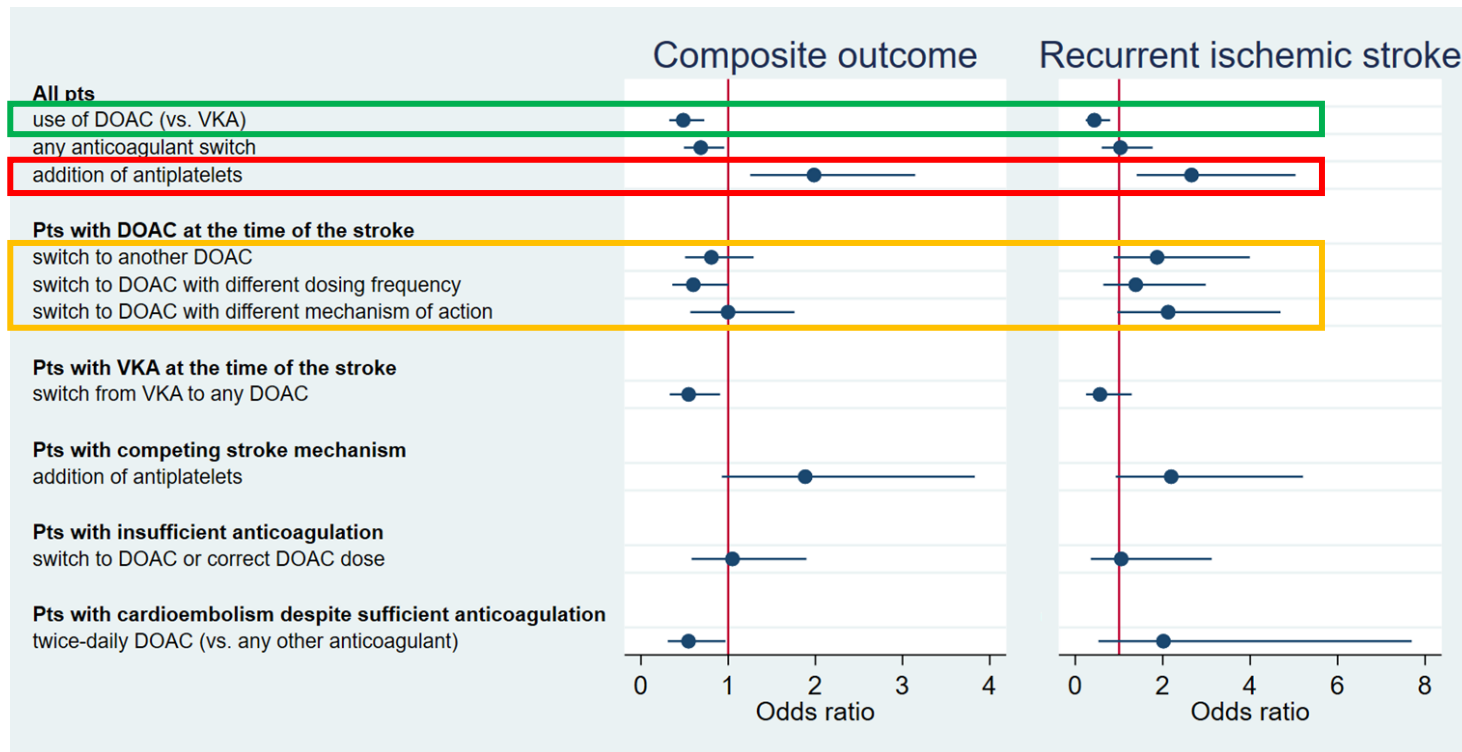
Table 2 Outcome Comparisons Among Antithrombotic Strategies After the First Ischemic Stroke Despite DOACs

	Warfarin (n = 122) vs DOAC _{same} (reference, n = 1,652)			DOAC _{switch} (n = 477) vs DOAC _{same} (reference, n = 1,652)			New antiplatelet (n = 249) vs No antiplatelet (reference, n = 1,166)		
	Median follow-up (mo)	aHR (95% CI)	p Value	Median follow-up (mo)	aHR (95% CI)	p Value	Median follow-up (mo)	aHR (95% CI)	p Value
Ischemic stroke	17	1.96 (1.27–3.02)	0.002	16	1.62 (1.25–2.11)	<0.001	17	1.28 (0.88–1.84)	0.188
Intracranial hemorrhage	19	1.51 (0.64–3.54)	0.342	18	1.06 (0.59–1.90)	0.837	19	1.20 (0.54–2.68)	0.654
ACS	20	1.69 (0.33–8.81)	0.529	18	2.18 (1.29–3.67)	0.003	19	1.71 (0.80–3.66)	0.167
Death	18	1.36 (0.92–2.01)	0.122	18	0.98 (0.81–1.19)	0.833	18	1.09 (0.84–1.41)	0.512

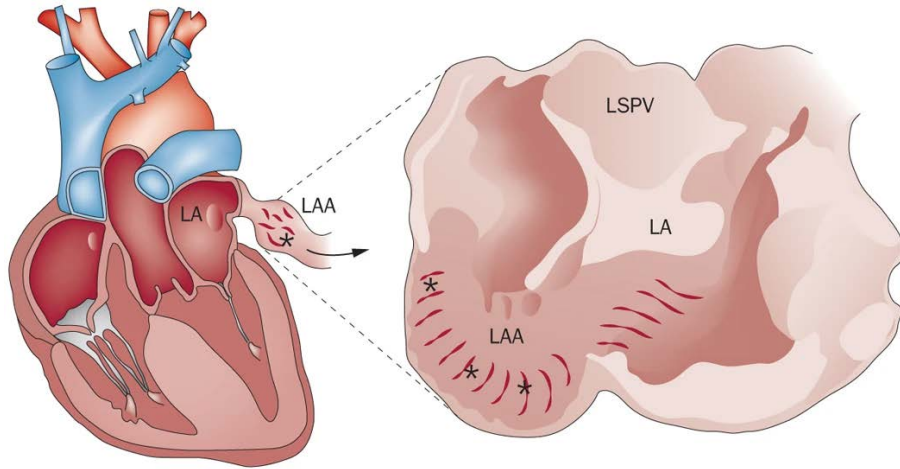
Abbreviations: ACS = acute coronary syndrome; aHR = adjust hazard ratio; CI = confidence interval; DOAC = direct oral anticoagulant.

N.B.: Comparisons between antiplatelet regimens were within the DOAC_{same} group.

Anticoagulation therapy after breakthrough stroke

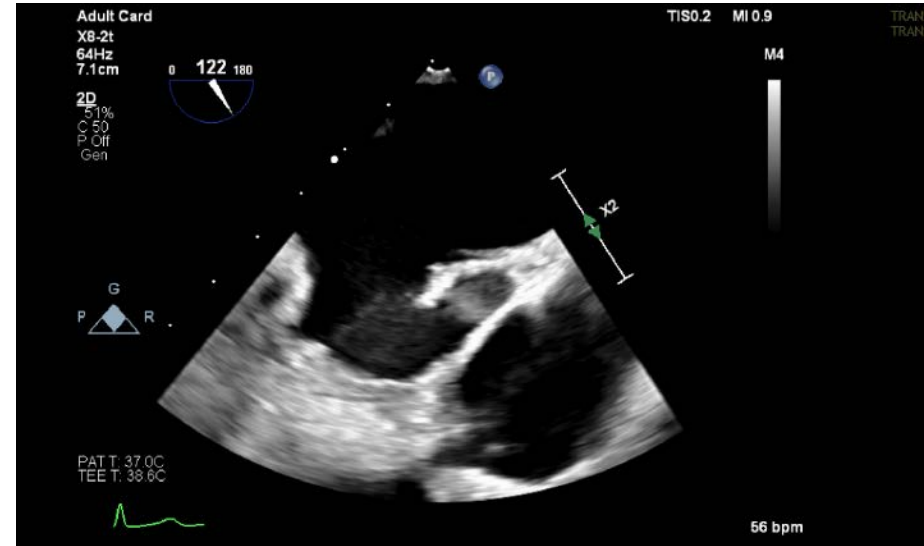


Left atrial appendage (LAA)

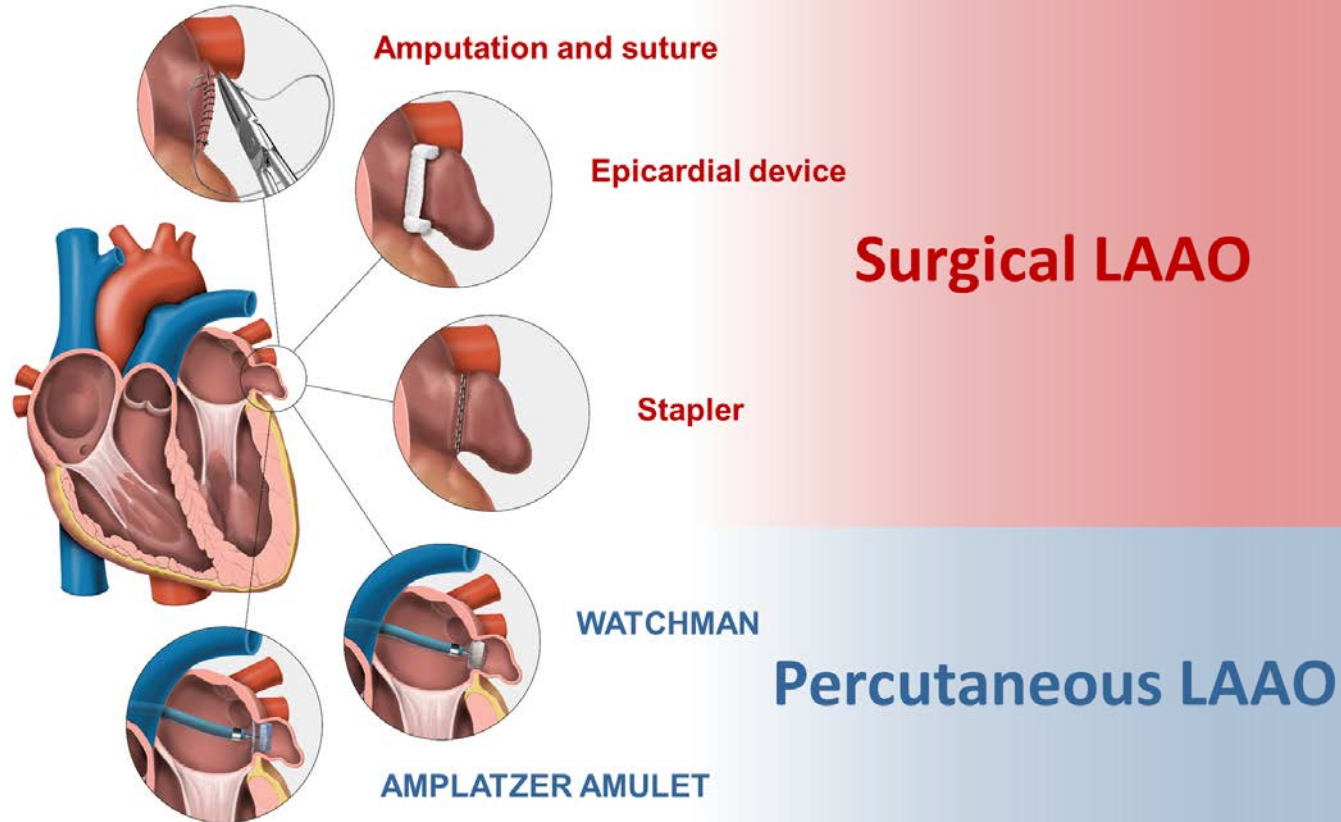


LAA:

82% of all thrombi are in the LAA in patients with AF and recent stroke



LAA thrombus in a patient with breakthrough stroke at Inselspital Bern



LAAOS-III – first evidence to combine LAAO with anticoagulation

LAAOS III

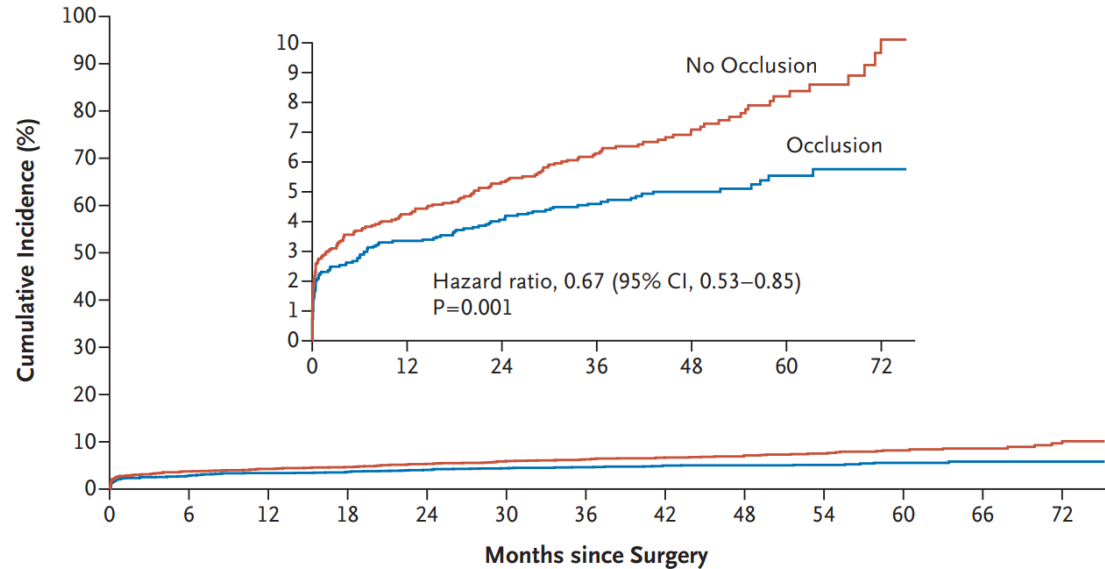
Randomised, controlled trial

Patients with AF undergoing open heart surgery

LAAO vs. no LAAO

Continue medical therapy

9% with prior stroke



2391	2134	2081	2030	1981	1897	1607	1291	1016	751	540	348	205
2379	2163	2105	2059	2020	1948	1642	1322	1046	781	550	349	199

LAAO in «breakthrough stroke» patients

Matched-cohort study

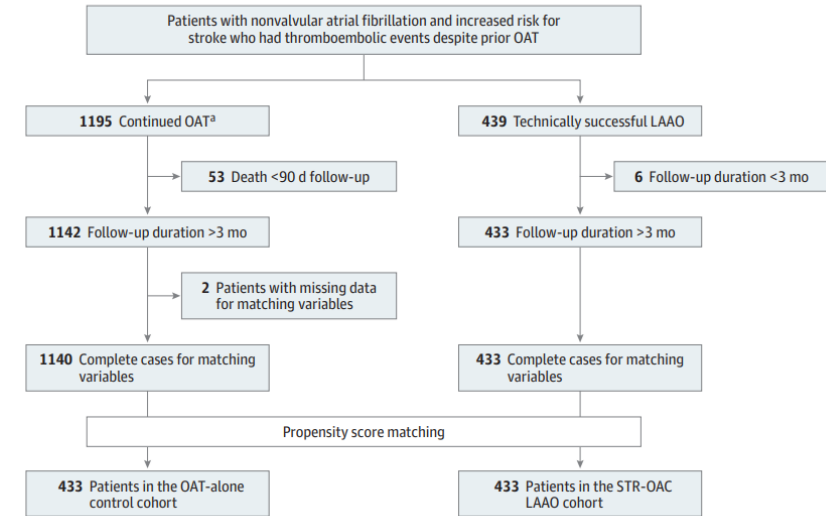
Patients with AF and breakthrough stroke who continued OAC

VS.

Patients with AF and breakthrough stroke/LAAO thrombus who received LAAO (+/- OAC)

Primary outcome:
recurrent ischemic stroke

Figure 1. Flowchart of Patient Inclusion



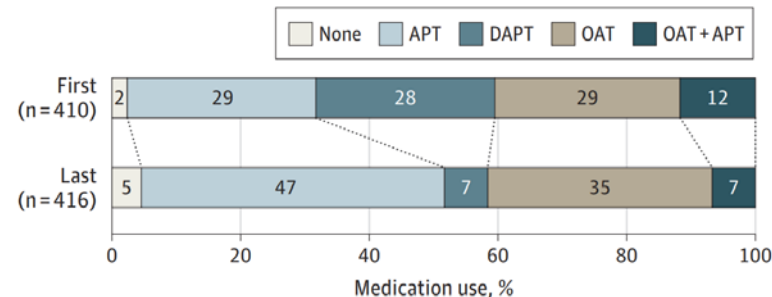
Left Atrial Appendage Occlusion vs Standard of Care After Ischemic Stroke Despite Anticoagulation

Moniek Maarse, MD, PhD; David J. Seiffge, MD; David J. Werring, MD, PhD; Lucas V. A. Boersma, MD, PhD; and the STR-OAC LAAO Group, for the RAF, RAF-DOAC, CROMIS-2, SAMURAI, NOACISP, Erlangen Registry, and Verona Registry

Table 1. Baseline Characteristics After Propensity Score Matching

Characteristic	Matched patients		P value	SMD	Unmatched patients in the OAT control cohort (n = 707), No. (%)
	STR-OAC LAAO (n = 433), No. (%)	OAT-alone control cohort (n = 433), No. (%)			
Event under OAT use (index event)			NA	NA	
Ischemic stroke	265 (61)	398 (92)			653 (92)
TIA	75 (17)	35 (8)			54 (8)
SE	16 (4)	NA			NA
LAA thrombus	77 (18)	NA			NA
OAT before index event ^a					
NOAC	242 (56)	191 (44)	.001	NA	350 (50)
VKA	216 (50)	242 (56)	.09	NA	357 (51)
OAT adequate before index event	400 (92)	246 (57)	<.001		
Age, mean (SD), y	71.8 (9.4)	72.7 (9)	.17	-0.09	80.9 (6.5)
Gender			.33	0.07	
Female	171 (39)	156 (36)			373 (53)
Male	262 (61)	277 (64)			334 (47)
AF type			NA	NA	
Paroxysmal	166 (38)	72 (17)			100 (14)
Persistent	75 (17)	158 (36)			232 (33)
Permanent	180 (42)	8 (2)			22 (3)
Not specified	12 (3)	210 (48)			353 (50)
CHA2 DS2-VASc score, mean (SD)	5 (1.6)	5.1 (1.5)	.29	-0.07	5.5 (1.4)
Hypertension	332 (76)	355 (82)	.07	-0.13	628 (89)
Diabetes	108 (25)	98 (23)	.47	0.05	319 (45)
Congestive heart failure	103 (24)	NA	NA	NA	NA
Vascular disease	172 (40)	NA	NA	NA	NA
HAS-BLED score, mean (SD)	2.8 (1.3)	NA ^b	NA	NA	NA
History of ICH	41 (10)	5 (2)	<.001	NA	11 (2)

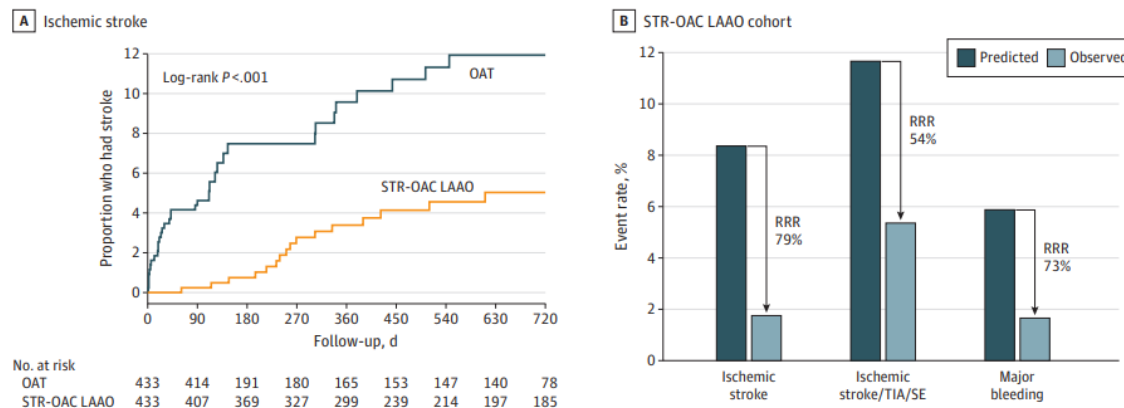
Figure 2. Medication Use for Members of the STR-OAC LAAO Cohort During the First and Last Follow-Up



APT indicates antiplatelet therapy; DAPT, dual antiplatelet therapy; OAT, oral anticoagulation therapy.

Recurrent stroke reduction in breakthrough stroke with LAAO

Figure 3. Kaplan-Meier Curves and Relative Risk Reductions (RRRs)



A, Primary outcome was ischemic stroke in the STR-OAC Left Atrial Appendage Occlusion (LAAO) group vs oral anticoagulation therapy (OAT) group (control). B, Observed annualized event rates (total number of events per patient-years of follow-up) for ischemic stroke; the composite of ischemic stroke, transient

ischemic attack (TIA), and systemic embolism (SE); and nonprocedural major bleeding were calculated and compared with predicted event rates based on CHA2 DS2-VASc and HAS-BLED scores^{21,22} for the STR-OAC LAAO cohort.

LAAO in breakthrough stroke:
percutaneous LAAO (+/-OAC) seems to have the same risk reduction as in LAAOS III

“Early Closure of Left Atrial Appendage for Patients With Atrial Fibrillation and Ischemic Stroke Despite Anticoagulation Therapy”

An international, multicentre, prospective, randomized, controlled, two-arm parallel group, blinded endpoint adjudicated, superiority, adaptive clinical trial (PROBE)

482-1000 patients with breakthrough stroke
(adaptive design)

DOAC therapy

1:1

DOAC + LAAO

Primary endpoint:

- Recurrent stroke
- Systemic embolism
- Cardiovascular death

**Sponsor-
Investigator:**

Prof. Dr. med. L. Räber, PhD (Cardiology PI)
Prof. Dr. med. D. Seiffge (Neurology PI)

Leading Center:

Inselspital Bern, Bern University Hospital

Clinicaltrials.gov:

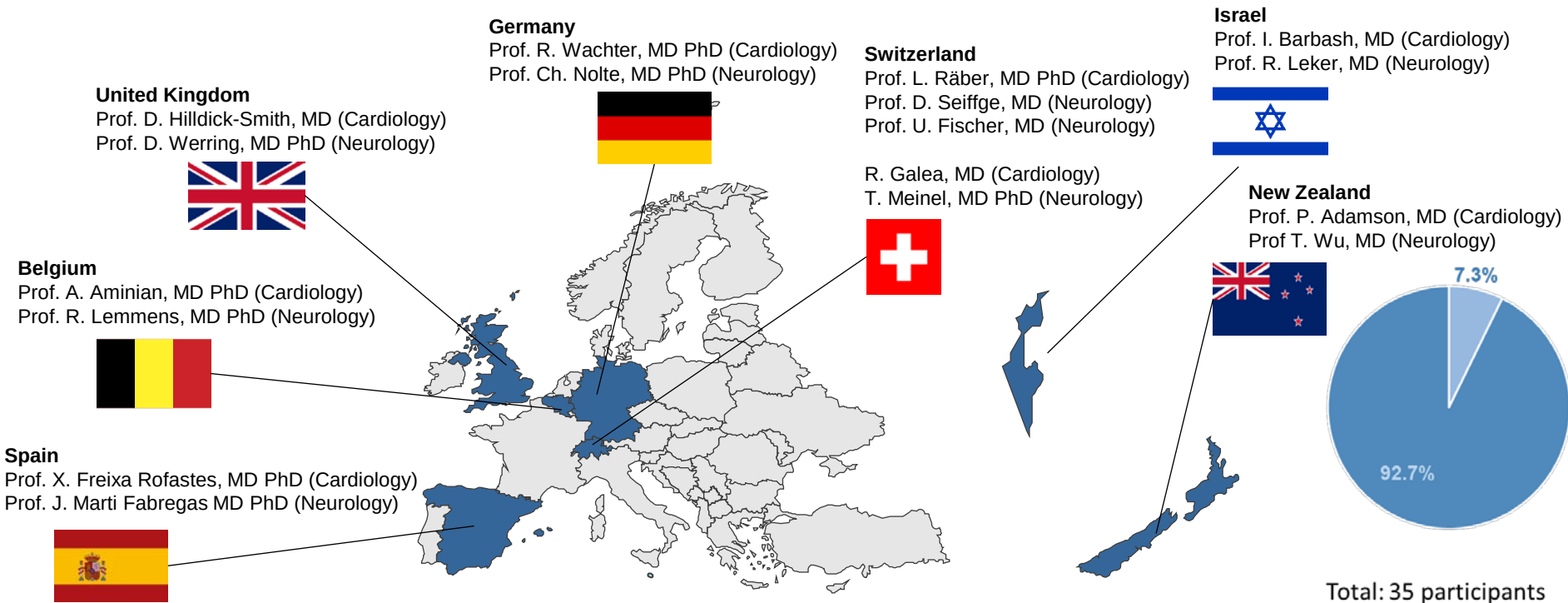
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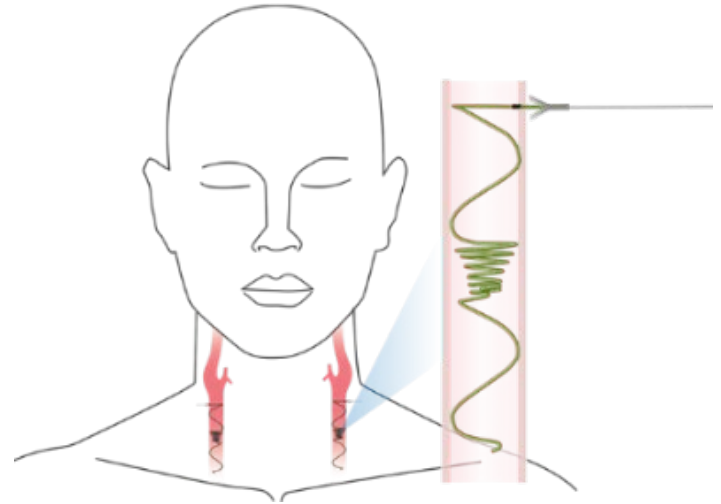
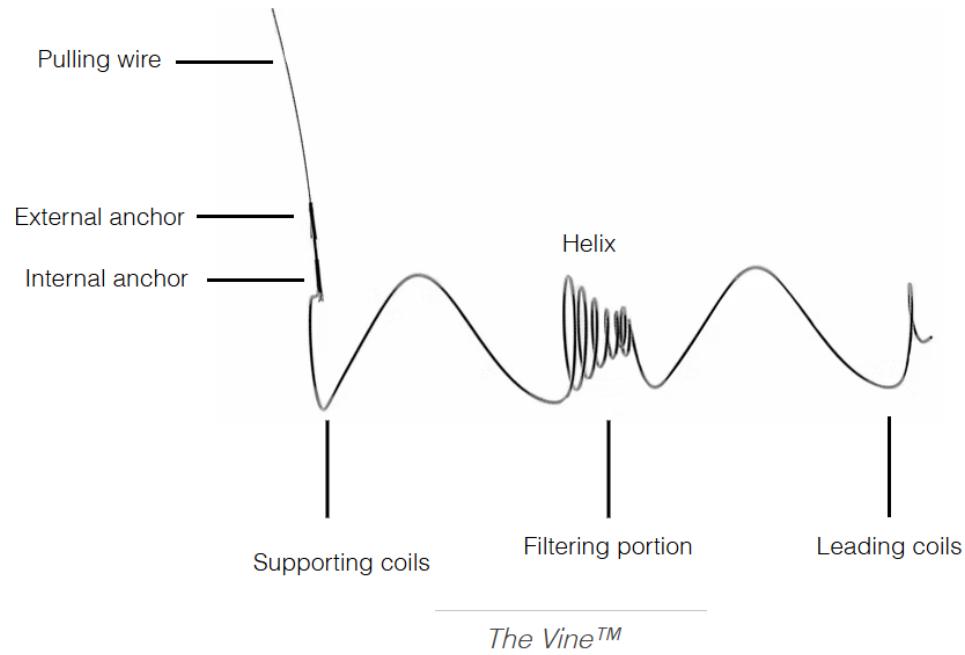
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FONDO NAZIONALE SVIZZERO
SWISS NATIONAL SCIENCE FOUNDATION

www.elapse-trial.ch

ELAPSE – an international effort



Permanent carotid coil filter



Bilaterale carotid artery filters

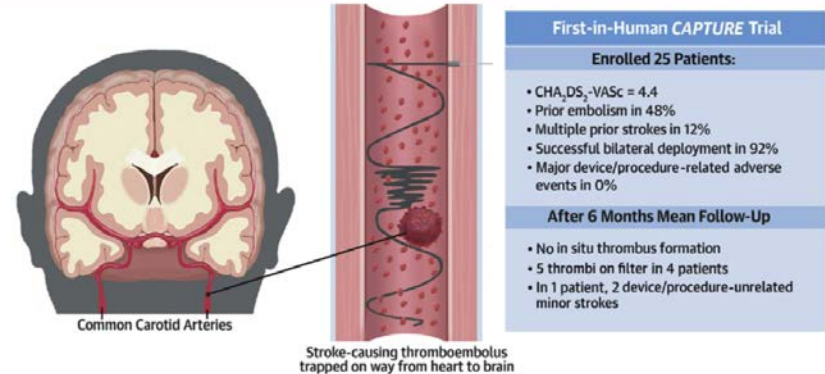
• CAPTURE 1

- First in-human study, 25 participants

• CAPTURE 2

- Safety study, 81 participants
- 2 phases (first 10 patients, second 71 patients) – major change in implant design

CENTRAL ILLUSTRATION: A Percutaneous Carotid Coil Filter for Stroke Prevention in Atrial Fibrillation



JAVELIN





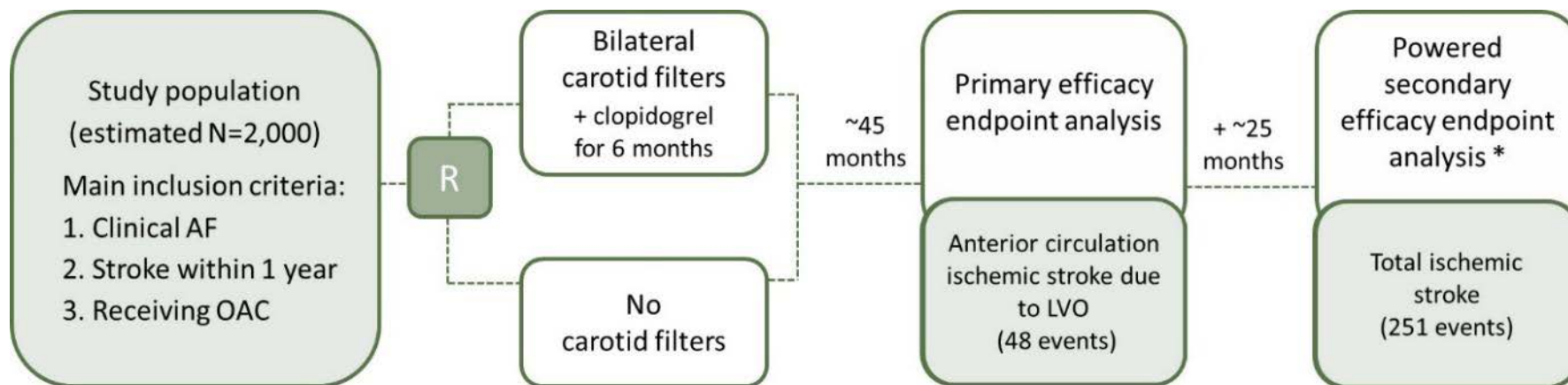
PJ Devereaux

Ashkan
Shoamanesh

Alexander Benz

“Carotid Implants for PreveNtion of STroke ReCurrEnce from Large Vessel Occlusion in Atrial Fibrillation Patients Treated with Oral Anticoagulation (INTERCEPT)”

An international, multicentre, prospective, randomized, controlled, two-arm parallel group, blinded endpoint adjudicated, superiority, adaptive clinical trial (PROBE)



	INTERCEPT (NCT05723926)	ELAPSE (NCT05976685)	LAAOS-4 (NCT05963698)
Intervention	Permanent bilateral carotid artery filter on top of DOAC therapy (plus antiplatelet therapy for 6 months)	Percutaneous left atrial appendage occlusion (any approved device) on top of DOAC therapy (plus antiplatelet therapy for 6 weeks)	Percutaneous left atrial appendage occlusion with device
Comparator	Standard DOAC therapy	Standard DOAC therapy	Local, standard medical care (any anticoagulation)
Sample size	2000 participants	482 participants (adaptive design)	4000 participants
Estimated percentage of patients with breakthrough strokes	66%	100%	Unknown (patients with breakthrough stroke are eligible among other patients at high risk of stroke)
Primary endpoint	Large vessel anterior circulation ischemic stroke	Composite of ischaemic stroke, systemic embolism, and cardiovascular death	Composite of ischaemic stroke and systemic embolism
Follow-up	44 months	Minimum 6 months, and maximum 48 months	4 years (estimated average)
Current status	Vanguard trial in preparation	First patient recruited in Q1/2024	First patient recruited in Q4/2023
DOAC=direct oral anticoagulant therapy.			
Table 3: Trials in patients with atrial fibrillation and stroke despite anticoagulation therapy			

Conclusions



- Atrial fibrillation is one of the most frequent causes of stroke
- AF-associated stroke frequently LVO and severe stroke , anticoagulation reduces risk of stroke
- **Stroke specific management:**
 - **Timing of DOAC after recent stroke:** can (should?!) be started early (<4 days, evidence from 4 RCTs!)
 - **Use of IVT in patients on DOACs:** Current guidelines recommend AGAINST use of IVT, observational data suggest low risk of sICH and potential clinical benefit (RCTs ongoing)
 - **Management after «breakthrough stroke»:** changing DOAC/adding antiplatelets is not beneficial, new options include LAAO and permanent bilateral carotid filters on top of DOAC (RCT ongoing)