Management of Patients with Ischemic Stroke Who are on Oral Anticoagulants

Magdy Selim, MD, PhD
Stroke Division
Beth Israel Deaconess Medical Center
Boston - MA

Beth Israel Deaconess Medical Center | HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

"Before we begin, full disclosure - I am man's best friend."

- **<u>NIH/NINDS/NIA/AHA Grant Support</u>:**
  - U01NS102289: Statins Use in Intracerebral Hemorrhage (SATURN) Trial
  - UF1NS120871: Statins Use in Intracerebral Hemorrhage (SATURN) MRI
  - UG3NS128397: Chronic subdural hematoma treatment with embolization vs surgery or medical management study (CHESS)

- **<u>Advisory Board/Consulting</u>:**
  - MedRhythms, Inc.
  - Loxagen, Inc.
  - Alnylam Pharmaceuticals
  - AegisCN, LLC
  - NeuGel Therapeutics, Inc. (Equity)

- **<u>Royalties</u>:**
  - UpToDate, Inc.
  - Oxford University Press

- Life-long anticoagulation is the mainstay therapy for prevention of thrombo-embolic events including ischemic stroke in patients with atrial fibrillation.
- The residual stroke risk in patients with AF on OAC is substantial, ranging from 0.7% to 2.3% per year in primary & secondary prevention, respectively.
- A significant proportion of ischemic strokes despite OAC remain unexplained and portend worse clinical outcomes.
- The management of these patients represents a challenge in everyday clinical practice.

- Patient with AF and stroke, despite OAC, are at higher risk for future stroke recurrence than patients who are naïve to OAC before their stroke.

Methods: We conducted an individual patient data pooled analysis of 7 prospective cohort studies that recruited patients with AF and recent cerebral ischemia. We compared patients taking oral anticoagulants (vitamin K antagonists [VKA] or direct oral anticoagulants [DOAC]) prior to index event (OAC_{prior}) with those without prior oral anticoagulation (OAC_{naive}). We further compared those who changed the type (ie, from VKA or DOAC, vice versa, or DOAC to DOAC) of anticoagulation ($OAC_{changed}$) with those who continued the same anticoagulation as secondary prevention ($OAC_{unchanged}$). Time to recurrent acute ischemic stroke (AIS) was analyzed using multivariate competing risk Fine–Gray models to calculate hazard ratios (HRs) and 95% confidence intervals (CIs).

Results: We included 5,413 patients (median age = 78 years [interquartile range (IQR) = 71–84 years]; 5,136 [96.7%] had ischemic stroke as the index event, median National Institutes of Health Stroke Scale on admission = 6 [IQR = 2–12]). The median CHA_2DS_2-Vasc score (congestive heart failure, hypertension, age≥ 75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65–74 years, sex category) was 5 (IQR = 4–6) and was similar for OAC_{prior} (n = 1,195) and OAC_{naive} (n = 4,119, p = 0.103). During 6,128 patient-years of follow-up, 289 patients had AIS (4.7% per year, 95% CI = 4.2–5.3%). OAC_{prior} was associated with an increased risk of AIS (HR = 1.6, 95% CI = 1.2–2.3, p = 0.005). $OAC_{changed}$ (n = 307) was not associated with decreased risk of AIS (HR = 1.2, 95% CI = 0.7–2.1, p = 0.415) compared with $OAC_{unchanged}$ (n = 585).

Interpretation: Patients with AF who have an ischemic stroke despite previous oral anticoagulation are at a higher risk for recurrent ischemic stroke despite a CHA_2DS_2-Vasc score similar to those without prior oral anticoagulation. Better prevention strategies are needed for this high-risk patient group.

ANN NEUROL 2020;87:677–687

- 22.5% of patients were taking OAC
  - 13.5% on DOAC
  - 72.% on VKA (INR <2 in 73%)
  - 14%.unknown AC type
  - 0.3% on heparins

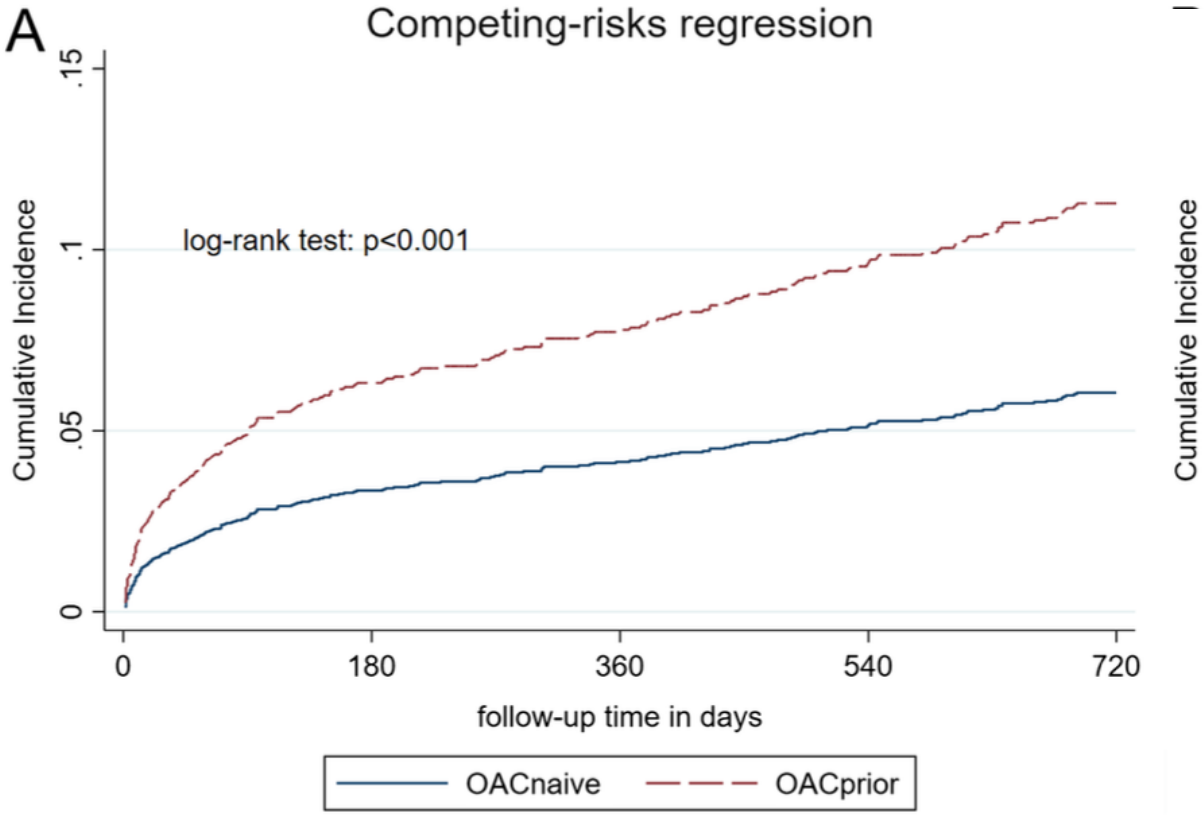


TABLE 2. Observed and Annualized Rates of Outcome Events in Patients with OAC_{prior} and OAC_{naive} and Univariate and Multivariate Analysis

	OAC_{naive}, n = 4,119		OAC_{prior}, n = 1,195		Univariate		Multivariate[a]	
	Events, n[b]	Annualized Rate (95% CI)	Events, n[b]	Annualized Rate (95% CI)	Hazard Ratio (95% CI)	*p*	Hazard Ratio (95% CI)	*p*
AIS	196	3.9 (3.3–4.4)	93	8.9 (7.3–10.8)	2.0 (1.5–2.5)	<0.001	1.6 (1.2–2.3)	0.005
ICH	69	1.4 (1.0–1.7)	21	2.0 (1.3–3.1)	1.2 (0.7–2.0)	0.426	1.1 (0.5–2.3)	0.811
Mortality	501	9.9 (9.1–10.7)	123	11.8 (9.9–13.9)	1.2 (1.0–1.5)	0.069	1.1 (0.8–1.4)	0.667

[a]Multivariate competing risk Fine–Gray analysis was adjusted for the following prespecified variables: age, sex, history of ischemic stroke other than index event, hypertension, diabetes mellitus, modest or severe kidney failure (creatinine clearance < 50ml/min), diagnosis of atrial fibrillation (known before the ischemic stroke vs diagnosed after stroke), and treatment with any oral anticoagulant after index event. Study was introduced as a shared frailty term in this analysis.

[b]n = number of patients.

AIS = acute ischemic stroke; CI = confidence interval; ICH = intracerebral hemorrhage; OAC_{naive} no anticoagulation on admission; OAC_{prior} = anticoagulation prior to admission.

FIGURE 2: Cumulative incidence function curves for the main outcome of recurrent acute ischemic stroke. (A) Primary analysis of patients taking oral anticoagulation prior to the index event (OAC_{prior}, dashed line) compared to those not taking anticoagulants prior to the index event (OAC_{naive}, solid line).

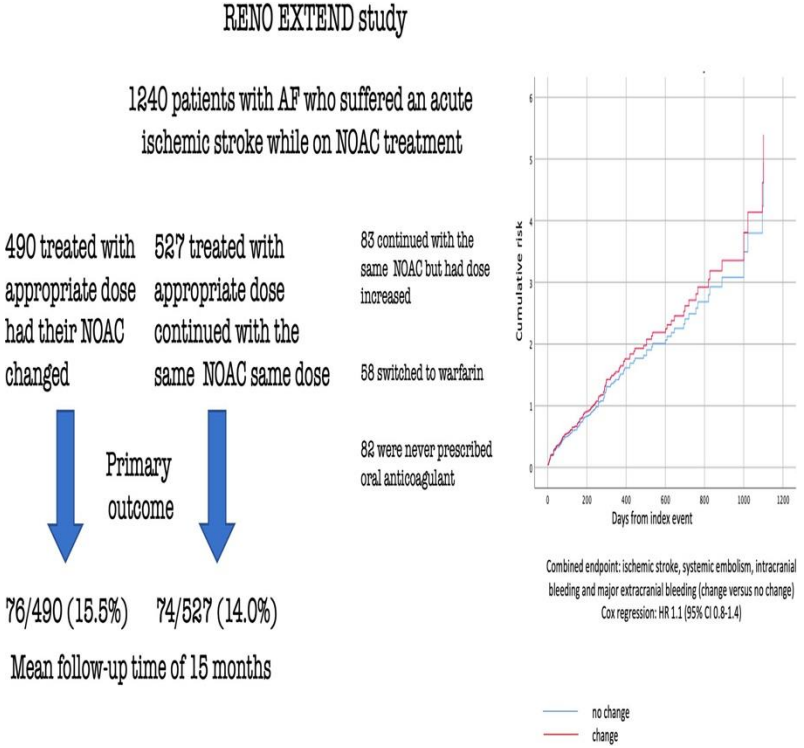
Recurrent Ischemic Stroke and Bleeding in Patients With Atrial Fibrillation Who Suffered an Acute Stroke While on Treatment With Nonvitamin K Antagonist Oral Anticoagulants: The RENO-EXTEND Study

BACKGROUND: In patients with atrial fibrillation who suffered an ischemic stroke while on treatment with nonvitamin K antagonist oral anticoagulants, rates and determinants of recurrent ischemic events and major bleedings remain uncertain.

METHODS: This prospective multicenter observational study aimed to estimate the rates of ischemic and bleeding events and their determinants in the follow-up of consecutive patients with atrial fibrillation who suffered an acute cerebrovascular ischemic event while on nonvitamin K antagonist oral anticoagulant treatment. Afterwards, we compared the estimated risks of ischemic and bleeding events between the patients in whom anticoagulant therapy was changed to those who continued the original treatment.

RESULTS: After a mean follow-up time of 15.0±10.9 months, 192 out of 1240 patients (15.5%) had 207 ischemic or bleeding events corresponding to an annual rate of 13.4%. Among the events, 111 were ischemic strokes, 15 systemic embolisms, 24 intracranial bleedings, and 57 major extracranial bleedings. Predictive factors of recurrent ischemic events (strokes and systemic embolisms) included CHA_2DS_2-VASc score after the index event (odds ratio [OR], 1.2 [95% CI, 1.0–1.3] for each point increase; P=0.05) and hypertension (OR, 2.3 [95% CI, 1.0–5.1]; P=0.04). Predictive factors of bleeding events (intracranial and major extracranial bleedings) included age (OR, 1.1 [95% CI, 1.0–1.2] for each year increase; P=0.002), history of major bleeding (OR, 6.9 [95% CI, 3.4–14.2]; P=0.0001) and the concomitant administration of an antiplatelet agent (OR, 2.8 [95% CI, 1.4–5.5]; P=0.003). Rates of ischemic and bleeding events were no different in patients who changed or not changed the original nonvitamin K antagonist oral anticoagulants treatment (OR, 1.2 [95% CI, 0.8–1.7]).

CONCLUSIONS: Patients suffering a stroke despite being on nonvitamin K antagonist oral anticoagulant therapy are at high risk of recurrent ischemic stroke and bleeding. In these patients, further research is needed to improve secondary prevention by investigating the mechanisms of recurrent ischemic stroke and bleeding.



- Competing stroke mechanisms
  - Large artery atherosclerosis
  - Small vessel disease
  - Others (dissection, drugs, etc.)
- Non-adherence/poor compliance
- Inappropriate dosing of OAC or inappropriate intake
  - For example, XARELTO® co-administration with food increases its bioavailability and it should be taken with the evening meal to reduce the potential risk of decreased efficacy of therapy.
- Reduced pharmacological efficacy
  - Use of concomitant prohibited medications
  - Genetic variability
- Other causes

Cerebrovascular disease

OPEN ACCESS

Original research

Aetiology, secondary prevention strategies and outcomes of ischaemic stroke despite oral anticoagulant therapy in patients with atrial fibrillation

Alexandros A Polymeris ,[1] Thomas R Meinel ,[2] Hannah Oehler,[3] Kyra Hölscher,[3] Annaelle Zietz,[1] Jan F Scheitz,[4] Christian H Nolte ,[4] Christoph Stretz ,[5] Shadi Yaghi ,[5] Svenja Stoll,[6] Ruihao Wang,[6] Karl Georg Häusler,[7] Simon Hellwig,[4] Markus G Klammer,[4] Simon Litmeier,[4] Christopher R Leon Guerrero,[8] Iman Moeini-Naghani,[8] Patrik Michel,[9] Davide Strambo ,[9] Alexander Salerno ,[9] Giovanni Bianco,[10] Carlo Cereda,[10] Timo Uphaus ,[11] Klaus Gröschel,[11] Mira Katan,[1,12] Susanne Wegener ,[12] Nils Peters,[1,13,14] Stefan T Engelter,[1,14] Philippe A Lyrer,[1] Leo H Bonati,[1] Lorenz Grunder,[15] Peter Arthur Ringleb,[3] Urs Fischer,[1,2] Bernd Kallmünzer,[6] Jan C Purrucker ,[3] David J Seiffge [2]

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/jnnp-2021-328391).

For numbered affiliations see end of article.

Correspondence to
David J Seiffge, Department of Neurology, Inselspital University Hospital Bern, Bern, 3010, Switzerland; david.seiffge@insel.ch

AAP and TRM contributed equally.
JCP and DJS contributed equally.

AAP and TRM are joint first authors.
JCP and DJS are joint senior authors.

For 'Presented at statement' see end of article.

Received 4 November 2021
Accepted 5 March 2022
Published Online First 8 April 2022

To cite: Polymeris AA, Meinel TR, Oehler H, *et al*. *J Neurol Neurosurg Psychiatry* 2022;**93**:588–598.

ABSTRACT

Objective To investigate the aetiology, subsequent preventive strategies and outcomes of stroke despite anticoagulation in patients with atrial fibrillation (AF).

Methods We analysed consecutive patients with AF with an index imaging-proven ischaemic stroke despite vitamin K-antagonist (VKA) or direct oral anticoagulant (DOAC) treatment across 11 stroke centres. We classified stroke aetiology as: (i) competing stroke mechanism other than AF-related cardioembolism; (ii) insufficient anticoagulation (non-adherence or low anticoagulant activity measured with drug-specific assays); or, (iii) AF-related cardioembolism despite sufficient anticoagulation. We investigated subsequent preventive strategies with regard to the primary (composite of recurrent ischaemic stroke, intracranial haemorrhage, death) and secondary endpoint (recurrent ischaemic stroke) within 3 months after index stroke.

Results Among 2946 patients (median age 81 years; 48% women; 43% VKA, 57% DOAC), stroke aetiology was competing mechanism in 713 patients (24%), insufficient anticoagulation in 934 (32%) and cardioembolism despite sufficient anticoagulation in 1299 (44%). We found high rates of the primary (27% of patients; completeness 91.6%) and secondary endpoint (4.6%; completeness 88.5%). Only DOAC (vs VKA) treatment after index stroke showed lower odds for both endpoints (primary: adjusted OR (aOR) (95% CI) 0.49 (0.32 to 0.73); secondary: 0.44 (0.24 to 0.80)), but not switching between different DOAC types. Adding antiplatelets showed higher odds for both endpoints (primary: aOR (95% CI) 1.99 (1.25 to 3.15); secondary: 2.66 (1.40 to 5.04)). Only few patients (1%) received left atrial appendage occlusion as additional preventive strategy.

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

Trial registration number ISRCTN48292829.

INTRODUCTION

Oral anticoagulation with either direct oral anticoagulants (DOAC) or vitamin K-antagonists (VKA) reduces the risk of ischaemic stroke in patients with non-valvular atrial fibrillation (AF). However, there is a substantial residual stroke risk in patients with AF despite anticoagulation ranging from 0.7% to 2.3% annually in primary and secondary prevention, respectively.[1–4] Since the introduction of DOAC, the overall use of oral anticoagulants for stroke prevention in patients with AF has increased steadily, particularly in patients with AF at the highest stroke risk.[5] Due to this development, the number of patients with AF suffering a stroke despite anticoagulation is expected to increase, too.[6 7] Accumulating evidence suggests that patients with AF and stroke despite anticoagulation are at a higher risk for future recurrence than patients who were naive to anticoagulation treatment before stroke.[8–10]

For stroke physicians, ischaemic stroke despite anticoagulation in patients with AF represents a challenge in everyday clinical practice, as its aetiology is not well-understood.[11] Competing stroke mechanisms such as large artery and small vessel disease, as well as non-adherence or inappropriately dosed anticoagulation have been discussed as potential causes of stroke despite anticoagulation,[8–11] but few data on their relative frequency exist.[6] A better understanding of the aetiology of stroke despite

Table 1 Patient characteristics stratified to stroke aetiology

Characteristic	All (N=2946)	N missing	Aetiology of stroke despite anticoagulation: Competing mechanism (N=713)	Insufficient anticoagulation (N=934)	Cardioembolism despite sufficient anticoagulation (N=1299)	P value
Laboratory parameters on admission						
INR, median (IQR)	1.4 (1.1–1.9)	100	1.4 (1.1–2.0)	1.3 (1.1–1.6)	1.4 (1.2–2.2)	<0.001
Low anticoagulant activity, N (%)‡	957 (43.9)	766§	128 (26.9)	633 (82.1)	196 (21.0)	<0.001
Low VKA activity, N (%)	737 (58.2)		96 (39.3)	528 (96.4)	113 (23.8)	<0.001
Low DOAC activity, N (%)	220 (24.1)		32 (13.8)	105 (47.1)	83 (18.1)	<0.001
DOAC plasma level, ng/mL, median (IQR)	83.9 (30–164)	761§	110.1 (54.9–193.6)	34.6 (1.0–93.5)	100.9 (44.3–192.6)	<0.001
Outcome at discharge						
mRS ≥3, N (%)	1543 (63.3)	508¶	393 (62.8)	516 (67.9)	634 (60.3)	0.004
In-hospital death, N (%)	204 (8.4)		35 (5.6)	78 (10.3)	91 (8.7)	0.007

Table 2 Details of competing mechanisms

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

Pooled data from 11 stroke centers in Switzerland, Germany & USA

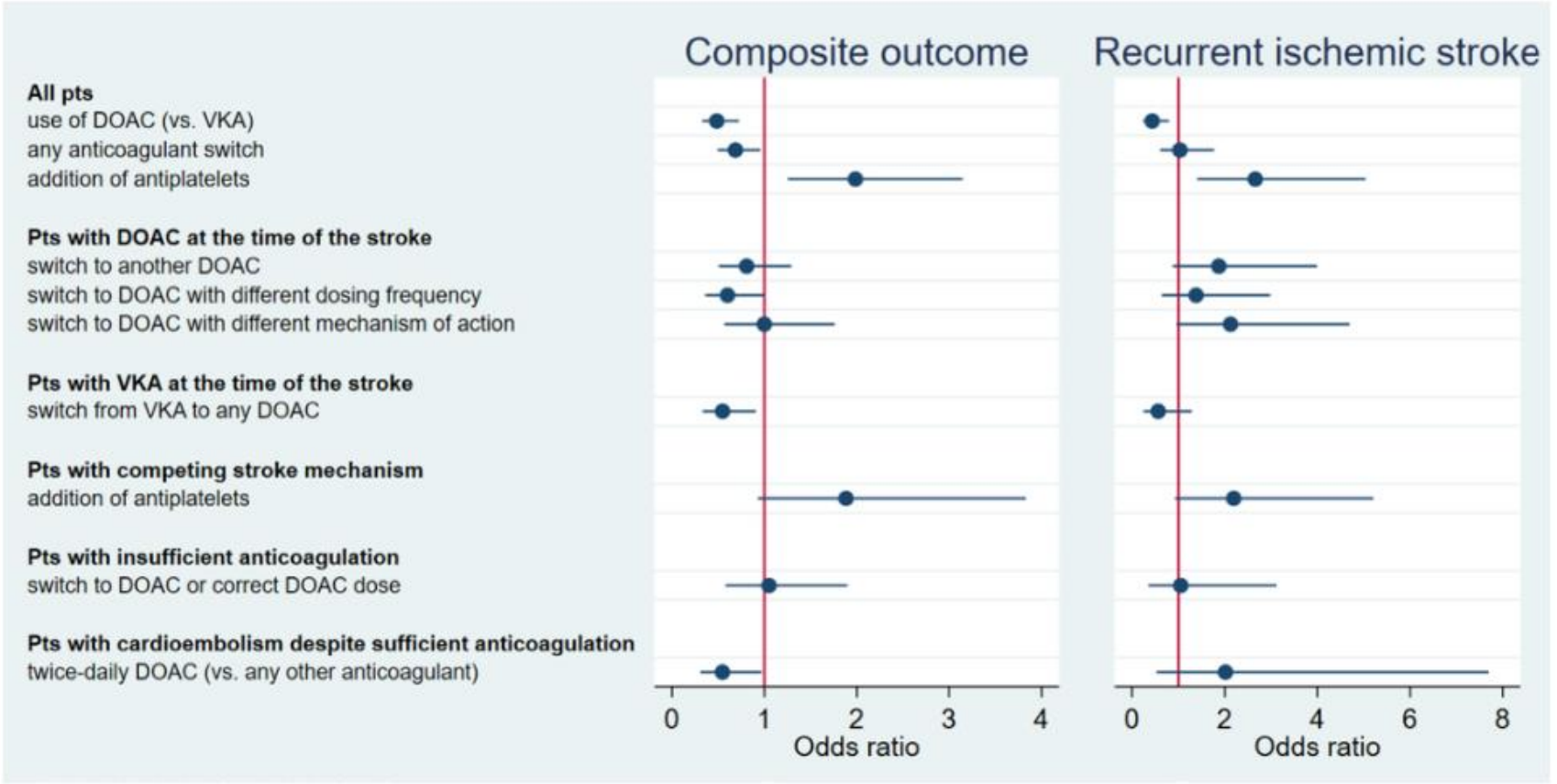


Figure 3 Association of preventive strategies after stroke despite anticoagulation with the primary and secondary endpoints from the adjusted models. DOAC, direct oral anticoagulant; Pts, patients; VKA, vitamin K-antagonist; estimates adjusted for age, sex, hypertension, diabetes, ischaemic heart disease, dyslipidaemia, renal impairment, prior ischaemic stroke, history of intracranial haemorrhage, current smoking, active malignancy, use of statins and use of antihypertensives.

- A retrospective observational study of consecutive patients diagnosed with acute ischemic stroke and preexisting use of OAC for known AF between 12/01/2017 and 03/31/2021 at the Centre Hospitalier de l'Université de Montreal.

- Data were analyzed separately as: 1) the whole cohort (all stroke patients evaluated at the CSC) and 2) local cohort (patients subsequently hospitalized at our institution).

Identified stroke mechanism		
OAC non-adherence	23 (13.3)	11 (16.9)
OAC interruption**	25 (14.5)	7 (10.8)
Inappropriate OAC dose	29 (16.8)	6 (9.2)
Undetermined breakthrough stroke	77 (44.5)	28 (43.1)
Other competing mechanism***	19 (11.0)	13 (20.0)

The Canadian Journal of Neurological Sciences (2024), 1–4
doi:10.1017/cjn.2024.3

Authors' Interpretation

- Overall, easily modifiable causes of ischemic stroke despite OAC are common.
- Strategies to improve treatment compliance, including appropriate dosing along with guideline-based risk factor and periprocedural OAC management, should be emphasized to improve secondary stroke prevention in this patient population.

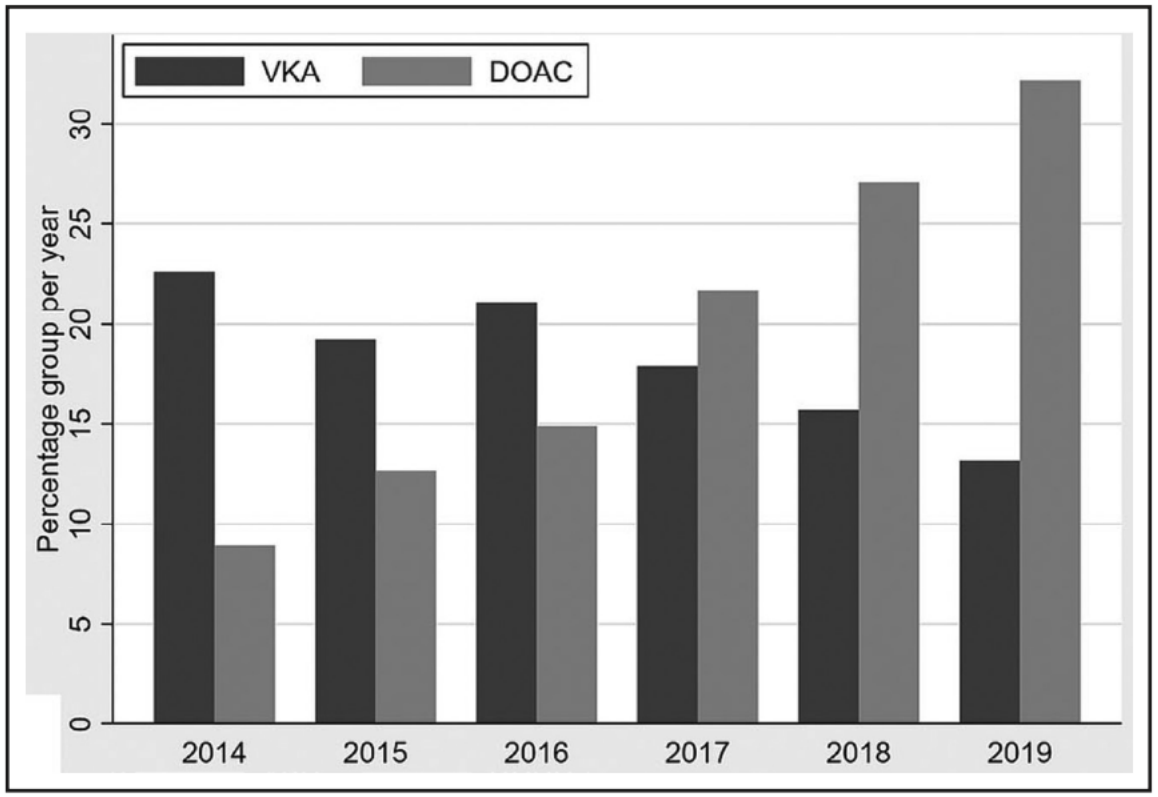


Figure. Trends in the type of anticoagulant use at the time of acute ischemic stroke among patients with atrial fibrillation between 2014 and 2019.

Stroke. 2024;55:214–225.

- The rate of ischemic stroke among patients who are on DOAC is the fastest growing category among all ischemic strokes
- Since 2014, the proportion of patients with AF & a new ischemic stroke while taking a DOAC has increased (~ 33% in 2019)
- Subgroup analyses of DOAC RCTs consistently showed a higher recurrent ischemic stroke risk in AF patients with past history of stroke/TIA

DOAC Failure

- DOAC failure" refers to a situation where a patient experiences an ischemic stroke despite being on a DOAC) medication

- Patients who experience an ischemic stroke while on a DOAC have a higher risk of experiencing another stroke, highlighting the need for careful evaluation and potential adjustments to their treatment plan

Management Strategy

1) **Reviewing adherence and dosage:** First step is to ensure the patient is taking the correct dose and adhering to the prescribed schedule.

2) **Investigating underlying causes:** Further evaluation may be needed to identify potential contributing factors like poor kidney function or other medical conditions that could impact DOAC effectiveness.

3) **Assessment of calibrated anti-Xa activity** may provide clues re: non-adherence

4) **Investigating underlying/ competing stroke mechanism:** imaging exams; TEE to exclude intracardiac thrombus, endocarditis, tumors, and evidence of severe atrial dysfunction (e.g., LA enlargement) or of thrombogenic LAA)

5) **R/O Occult hypercoagulability**

SAVAYSA® (edoxaban) tablets, for oral use
Initial U.S. Approval: 2015

WARNING: (A) REDUCED EFFICACY IN NONVALVULAR ATRIAL FIBRILLATION PATIENTS WITH CREATININE CLEARANCE (CRCL) > 95 ML/MIN

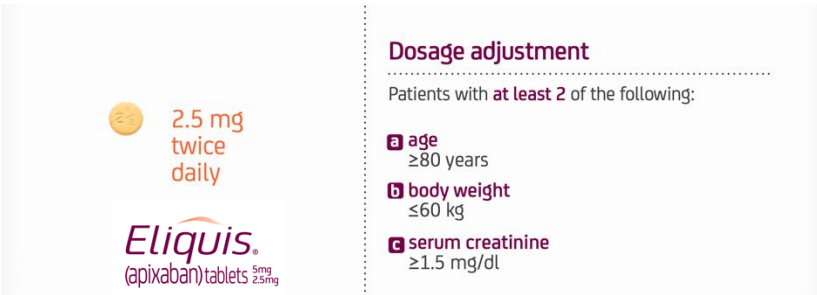
See full prescribing information for complete boxed warning.

(A) REDUCED EFFICACY IN NONVALVULAR ATRIAL FIBRILLATION PATIENTS WITH CRCL > 95 ML/MIN:
SAVAYSA should not be used in patients with CrCL > 95 mL/min. In the ENGAGE AF-TIMI 48 study, nonvalvular atrial fibrillation patients with CrCL > 95 mL/min had an increased rate of ischemic stroke with SAVAYSA 60 mg once daily compared to patients treated with warfarin. In these patients another anticoagulant should be used (5.1).

Drugs which may decrease blood levels of DOACs

- Rifampicin (P-gp inducer)
- Carbamazepine
- Phenytoin
- Phenobarbital
- Levetiracetam
- Valproate

Direct-acting oral anticoagulants (DOACs), including SAVAYSA, are not recommended for use in patients with triple positive antiphospholipid syndrome (APS). For patients with APS (especially those who are triple positive [positive for lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2-glycoprotein I antibodies]), treatment with DOACs has been associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.



Blood Tests

(Anti-Xa activity or DOAC plasma level)

- These tests may inform etiological work to determine non-adherence beyond reported compliance by patients and/or next of kin.
- However, these tests are not routinely available and calibrated anti-factor Xa activity can be difficult to interpret as there are no target levels and the absolute values expected at different time points after last DOAC intake are very heterogeneous.
- Only very low levels (<30 ng/mL) of calibrated anti-Xa activity on admission may be highly indicative of non-adherence.

Alternative Strategies

- Correct inappropriate dosing or intake
- Add aspirin
- Switch to another OAC
  - Warfarin to DOAC (apixaban or Dabigatran)
  - DOAC to DOAC
  - DOAC to warfarin
  - DOAC to LMWH
  - ? Factor XIa inhibitor(s)*
- Consider LAAO $\pm$ OAC
- Rhythm control

* There currently is not much data about the relative efficacy of Factor XIa inhibitors compared with DOACs to prevent IS among patients with NVAF

Comparing Efficacy and Safety Between Patients With Atrial Fibrillation Taking Direct Oral Anticoagulants or Warfarin After Direct Oral Anticoagulant Failure

Meng-Tsang Hsieh, MD; Chi-Hung Liu, MD, MS; Sheng-Hsiang Lin, PhD; Po-Yu Lin, MD; Yu-Ming Chang, MD; Chun-Min Wang, MD; Chih-Hung Chen, MD; Pi-Shan Sung, MD, PhD

BACKGROUND: An increased risk of recurrent stroke is noted in patients with atrial fibrillation despite direct oral anticoagulant (DOAC) use. We investigated the efficacy and safety of treatment with each of 4 different DOACs or warfarin after DOAC failure.

METHODS AND RESULTS: We retrospectively analyzed patients with atrial fibrillation with ischemic stroke despite DOAC treatment between January 2002 and December 2016. The different outcomes of patients with DOAC failure were compared, including recurrent ischemic stroke, major cardiovascular events, intracranial hemorrhage and subarachnoid hemorrhage, mortality, and net composite outcomes according to switching to different DOACs or vitamin K antagonist after index ischemic stroke. We identified 3759 patients with DOAC failure. A total of 84 patients experienced recurrent ischemic stroke after switching to different oral anticoagulants, with a total follow-up time of 14 years. Using the vitamin K antagonist group as a reference, switching to any of the 4 DOACs was associated with a 69% to 77% reduced risk of major cardiovascular events (adjusted hazard ratio [aHR], 0.25 [95% CI, 0.16–0.39] for apixaban, 0.23 [95% CI, 0.14–0.37] for dabigatran, 0.23 [95% CI, 0.09–0.60] for edoxaban, and 0.31 [95% CI, 0.21–0.45] for rivaroxaban), and a 69% to 83% reduced risk of net composite outcomes (aHR, 0.25 [95% CI, 0.18–0.35] for apixaban, 0.17 [95% CI, 0.11–0.25] for dabigatran, 0.31 [95% CI, 0.17–0.56] for edoxaban, and 0.31 [95% CI, 0.23–0.41] for rivaroxaban).

CONCLUSIONS: In Asian patients with DOAC failure, continuing DOACs after index stroke was associated with fewer undesirable outcomes than switching to a vitamin K antagonist. Alternative pharmacologic and nonpharmacologic strategies warrant investigation.

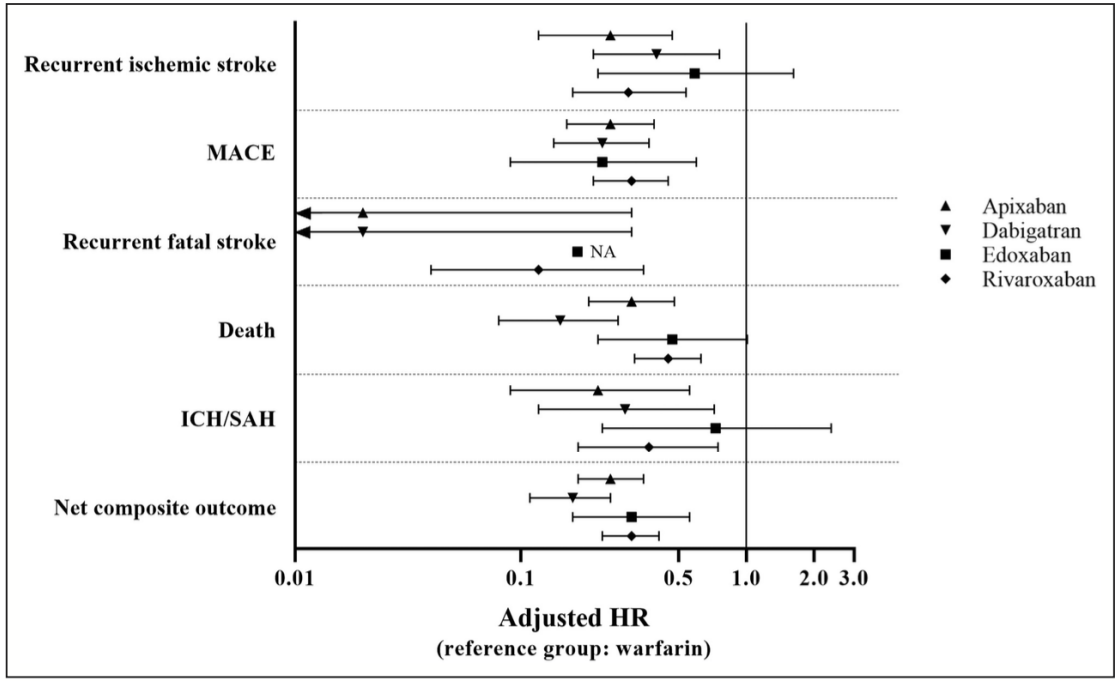


Figure. Cox model of different outcomes for patients who switched to different DOACs compared with those who switched to a VKA after DOAC failure.
Net composite outcomes: any ischemic stroke/MACE/ICH/SAH/death. DOAC indicates direct oral anticoagulant; HR, hazard ratio; ICH, intracerebral hemorrhage; MACE, major cardiovascular event; SAH, subarachnoid hemorrhage; and VKA, vitamin K antagonist.

Changing or Retaining Direct Oral Anticoagulant After Ischemic Stroke Despite Direct Oral Anticoagulant Treatment

Shin-Yi Lin, MS*; Yun-Tsz Liao, MPH*; Sung-Chun Tang, MD, PhD; Ching-Ching Claire Lin, PhD; Chi-Chuan Wang, PhD

BACKGROUND: The optimal antithrombotic strategies for patients with atrial fibrillation who experience ischemic stroke (IS) despite direct oral anticoagulant (DOAC) therapy remain inconclusive. This study compared outcomes for patients with DOAC treatment failure who changed or retained their prestroke DOAC.

METHODS AND RESULTS: This retrospective cohort study analyzed data from the National Health Insurance Research Database from 2012 to 2020. Patients with atrial fibrillation who experienced IS during DOAC therapy were assigned to either (1) the DOAC-change group: changing prestroke DOAC or (2) the DOAC-retain group: retaining prestroke DOAC. The primary outcome was a composite of recurrent IS and transient ischemic attack. The secondary outcomes included intracranial hemorrhage, major bleeding, systemic thromboembolism, and all-cause death. Propensity score–based inverse probability of treatment weighting was applied to balance the baseline characteristics between the DOAC-change and DOAC-retain groups. The Cox proportional hazards model compared the risk of outcomes between the 2 groups. In total, 1979 patients were enrolled (609 DOAC-change patients and 1370 DOAC-retain patients). The incidence rates of recurrent IS or transient ischemic attack were 7.20 and 6.56 per 100 person-years in the DOAC-change and DOAC-retain groups, respectively (hazard ratio [HR], 1.07 [95% CI, 0.87–1.30]). A nonsignificantly higher incidence rate of intracranial hemorrhage was observed in the DOAC-change group compared with the DOAC-retain group (0.75 versus 0.53 per 100-person-years; HR, 1.49 [95% CI, 0.78–2.83]). The systemic thromboembolism, major bleeding, and death rates were comparable between the DOAC-change and DOAC-retain groups.

CONCLUSIONS: Changing prestroke DOAC does not reduce the risk of recurrent cerebral ischemia in patients with atrial fibrillation who develop IS during DOAC therapy. However, future studies should continue to observe the potential trends of increased intracranial hemorrhage risk.

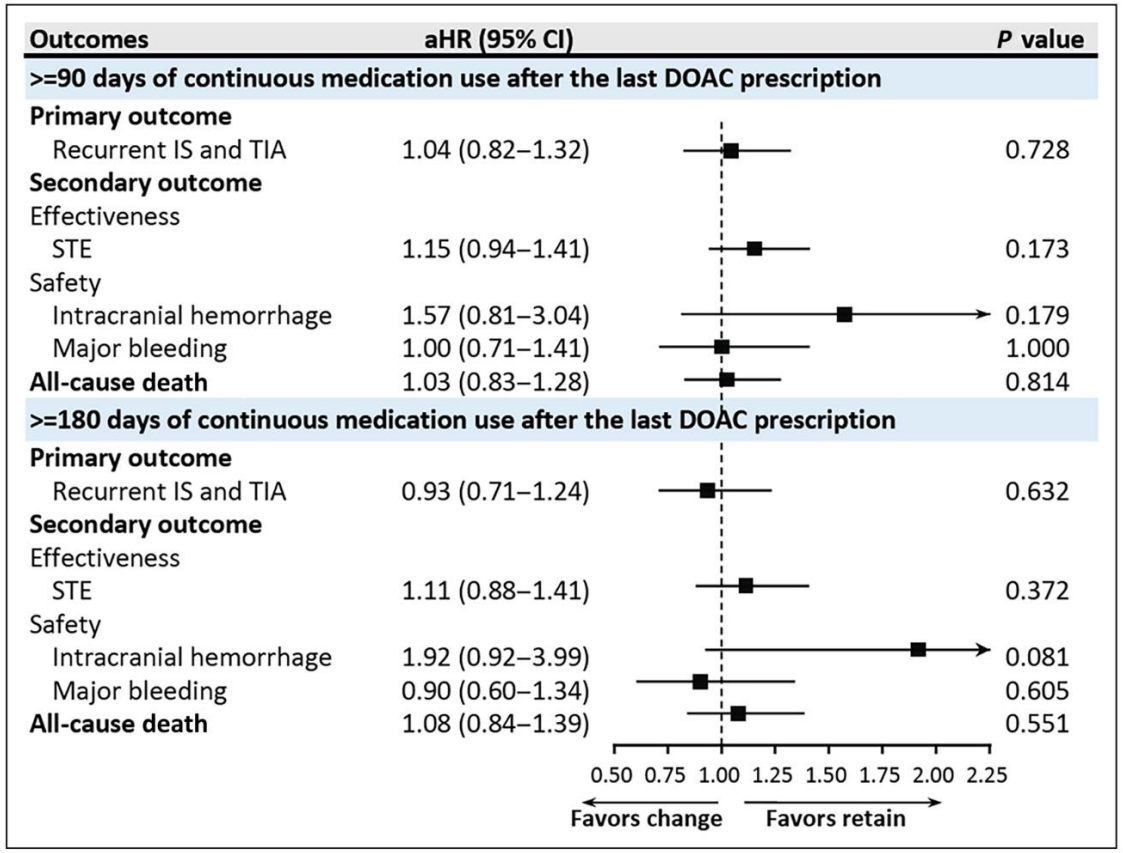


Figure 3. Hazard ratios for outcomes in patients with changed and retained prestroke DOAC (≥90 and ≥180 days of continuous medication use after the last DOAC prescription).
aHR, adjusted hazard ratio; DOAC, direct oral anticoagulant; IPTW, inverse probability of treatment weighting; IS, ischemic stroke; STE, systemic thromboembolism; and TIA, transient ischemic attack.

Association of Alternative Anticoagulation Strategies and Outcomes in Patients With Ischemic Stroke While Taking a Direct Oral Anticoagulant

Yiu Ming Bonaventure Ip, MD, Kui Kai Lau, DPhil, Ho Ko, PhD, Lucas Lau, MS, Alan Yao, MS, Grace Lai-Hung Wong, MD, Terry Cheuk-Fung Yip, PhD, Xinyi Leng, PhD, Howard Chan, PhD, Helen Chan, BSc, Vincent Mok, MD, FRCP, Yannie O.Y. Soo, MD, David Seiffge, MD,* and Thomas W. Leung, MD*

Correspondence
Dr. Leung
drtleung@cuhk.edu.hk

Neurology® 2023;101:e358-e369. doi:10.1212/WNL.0000000000207422

Abstract

Background and Objectives

Ischemic stroke despite a direct oral anticoagulant (DOAC) is increasingly common and portends a high risk of subsequent ischemic stroke. The efficacy and safety of antithrombotic regimens after the condition are unclear. We aimed to compare the outcomes of patients with ischemic stroke despite DOACs with and without an alternative antithrombotic regimen and determine the risk factors of recurrent ischemic stroke while on anticoagulation.

Methods

In a population-based, propensity score–weighted, retrospective cohort study, we compared the clinical outcomes of DOAC-to-warfarin switch, DOAC-to-DOAC switch ($DOAC_{switch}$), or addition of antiplatelet agents, with those of unchanged DOAC regimen ($DOAC_{same}$) among patients with nonvalvular atrial fibrillation (NVAF) who developed the first ischemic stroke despite a DOAC from January 1, 2015, to December 31, 2020, in Hong Kong. The primary outcome was recurrent ischemic stroke. Secondary outcomes were intracranial hemorrhage, acute coronary syndrome, and death. We performed competing risk regression analyses to compare the clinical endpoints and determined the predictors of recurrent ischemic stroke in an unweighted multivariable logistic regression model.

Results

During the 6-year study period, among 45,946 patients with AF on a DOAC as stroke prophylaxis, 2,908 patients developed ischemic stroke despite a DOAC. A total of 2,337 patients with NVAF were included in the final analyses. Compared with $DOAC_{same}$, warfarin (aHR 1.96, 95% CI 1.27–3.02, $p = 0.002$) and $DOAC_{switch}$ (aHR 1.62, 95% CI 1.25–2.11, $p < 0.001$) were associated with an increased risk of recurrent ischemic stroke. In the $DOAC_{same}$ group, adjunctive antiplatelet agent was not associated with a reduced risk of recurrent ischemic stroke. Diabetes mellitus, concurrent cytochrome P450/P-glycoprotein (CYP/P-gp) modulators, and large artery atherosclerotic disease (LAD) were predictors of recurrent ischemic stroke.

Discussion

In patients with NVAF with ischemic stroke despite a DOAC, the increased risk of recurrent ischemic stroke with switching to warfarin called for caution against such practice, while the increased ischemic stroke with DOAC-to-DOAC switch demands further studies. Adjunctive antiplatelet agent did not seem to reduce ischemic stroke relapse. Because diabetes mellitus, the use of CYP/P-gp modulators, and LAD were predictors of recurrent ischemic stroke, further investigations should evaluate whether strict glycemic control, DOAC level monitoring, and routine screening for carotid and intracranial atherosclerosis may reduce ischemic stroke recurrence in these patients.

Classification of Evidence

This study provides Class II evidence that in patients with NVAF experiencing an ischemic stroke while being treated with a DOAC, continuing treatment with that DOAC is more effective at preventing recurrent ischemic stroke than switching to a different DOAC or to warfarin.

MORE ONLINE

Class of Evidence
Criteria for rating therapeutic and diagnostic studies
NPub.org/coe

Infographic
links.lww.com/WNL/C950

Figure 2 Cumulative Incidence of (A) Ischemic Stroke, (B) Intracranial Hemorrhage, (C) Acute Coronary Syndrome, and (D) Death in Patients With Ischemic Stroke Despite Direct Oral Anticoagulant With Different Anticoagulation Strategies

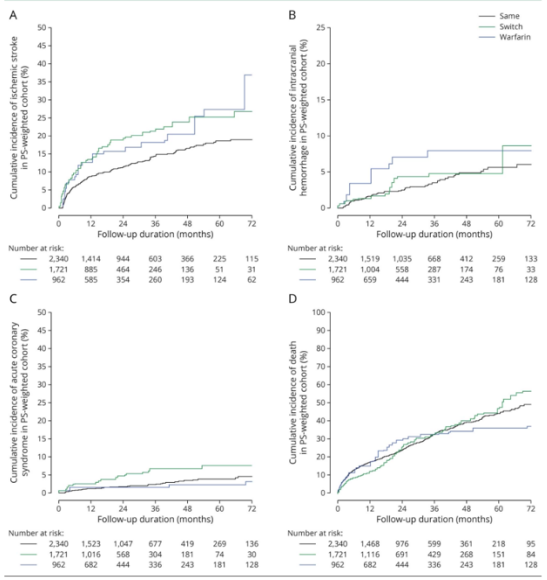
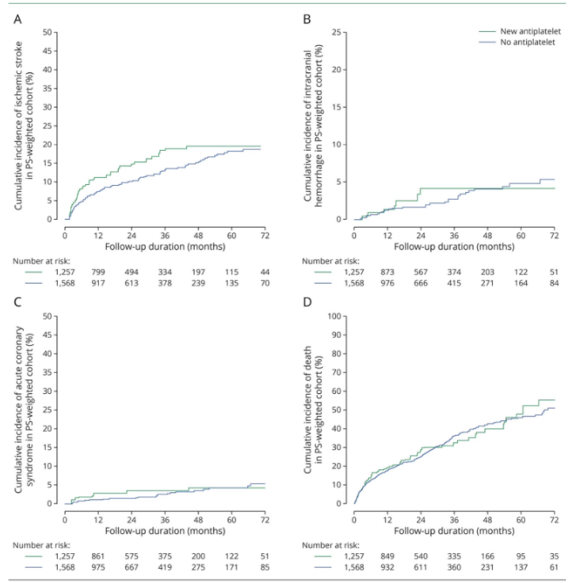
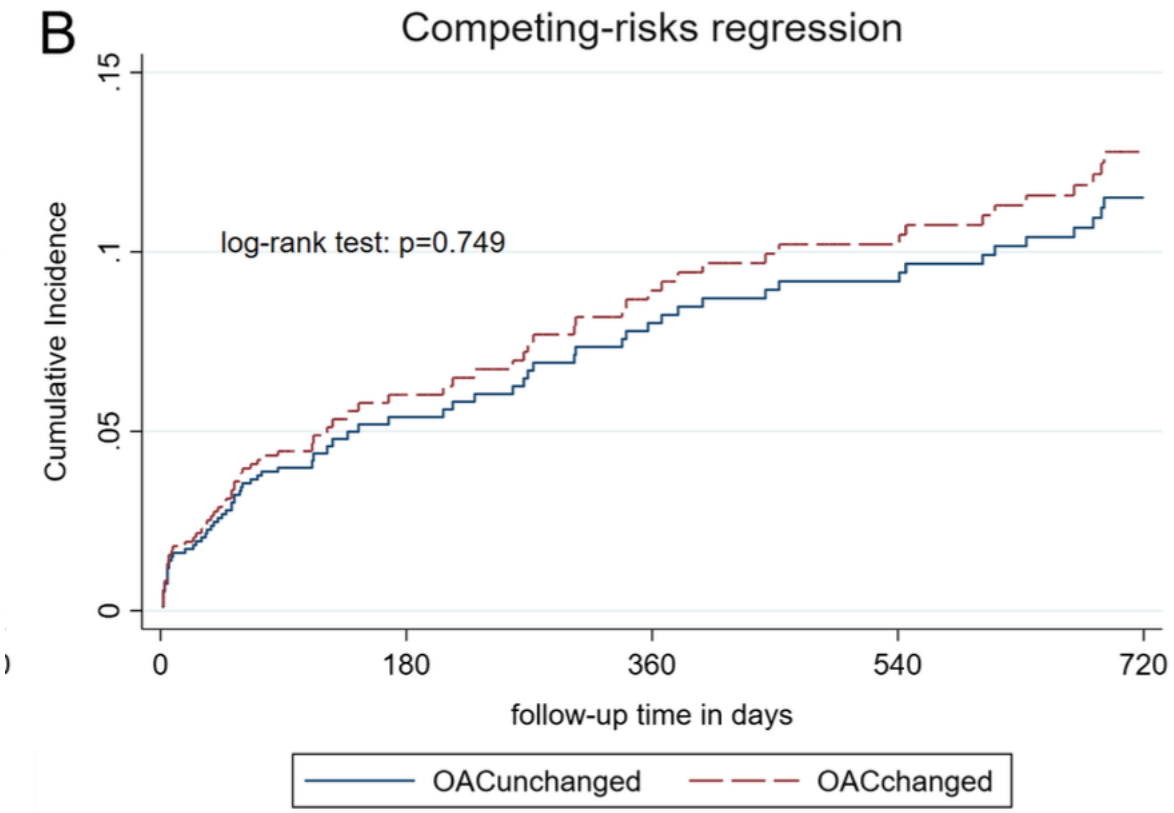


Figure 3 Cumulative Incidence of (A) Ischemic Stroke, (B) Intracranial Hemorrhage, (C) Acute Coronary Syndrome, and (D) Death in Patients With Ischemic Stroke Despite Direct Oral Anticoagulant With or Without Newly Added Antiplatelet Therapy



Methods: We conducted an individual patient data pooled analysis of 7 prospective cohort studies that recruited patients with AF and recent cerebral ischemia. We compared patients taking oral anticoagulants (vitamin K antagonists [VKA] or direct oral anticoagulants [DOAC]) prior to index event (OAC_{prior}) with those without prior oral anticoagulation (OAC_{naive}). We further compared those who changed the type (ie, from VKA or DOAC, vice versa, or DOAC to DOAC) of anticoagulation ($OAC_{changed}$) with those who continued the same anticoagulation as secondary prevention ($OAC_{unchanged}$). Time to recurrent acute ischemic stroke (AIS) was analyzed using multivariate competing risk Fine–Gray models to calculate hazard ratios (HRs) and 95% confidence intervals (CIs).
Results: We included 5,413 patients (median age = 78 years [interquartile range (IQR) = 71–84 years]; 5,136 [96.7%] had ischemic stroke as the index event, median National Institutes of Health Stroke Scale on admission = 6 [IQR = 2–12]). The median CHA_2DS_2-Vasc score (congestive heart failure, hypertension, age≥ 75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65–74 years, sex category) was 5 (IQR = 4–6) and was similar for OAC_{prior} (n = 1,195) and OAC_{naive} (n = 4,119, p = 0.103). During 6,128 patient-years of follow-up, 289 patients had AIS (4.7% per year, 95% CI = 4.2–5.3%). OAC_{prior} was associated with an increased risk of AIS (HR = 1.6, 95% CI = 1.2–2.3, p = 0.005). $OAC_{changed}$ (n = 307) was not associated with decreased risk of AIS (HR = 1.2, 95% CI = 0.7–2.1, p = 0.415) compared with $OAC_{unchanged}$ (n = 585).
Interpretation: Patients with AF who have an ischemic stroke despite previous oral anticoagulation are at a higher risk for recurrent ischemic stroke despite a CHA_2DS_2-Vasc score similar to those without prior oral anticoagulation. Better prevention strategies are needed for this high-risk patient group.

ANN NEUROL 2020;87:677–687



B) Secondary analysis of patients that changed the type of anticoagulation (OACchanged, dashed line) compared to those who continued the same type of anticoagulation (OACunchanged, solid line).

TABLE 3. Observed and Annualized Rates of Outcome Events in Patients with $OAC_{changed}$ and $OAC_{unchanged}$ and Univariate and Multivariate Analysis

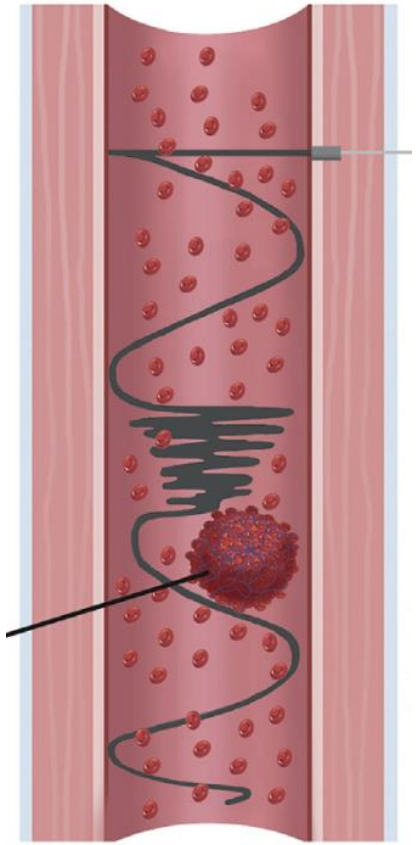
	$OAC_{changed}$, n = 307		$OAC_{unchanged}$, n = 585		Univariate		Multivariate[a]	
	Events, n[b]	Annualized Rate (95% CI)	Events, n[b]	Annualized Rate (95% CI)	Hazard Ratio (95% CI)	*p*	Hazard Ratio (95% CI)	*p*
AIS	28	8.8 (5.9–12.4)	47	8.2 (6.1–10.7)	1.1 (0.7–1.7)	0.749	1.2 (0.7–2.1)	0.415
ICH	4	1.3 (0.3–3.2)	13	2.3 (1.2–3.8)	0.6 (0.2–1.8)	0.346	0.8 (0.2–3.2)	0.793
Mortality	19	5.9 (3.6–9.1)	66	11.5 (9.0–14.4)	0.5 (0.3–0.9)	0.012	0.7 (0.4–1.2)	0.177

[a]Multivariate competing risk Fine–Gray analysis was adjusted for the following prespecified variables: age, sex, history of ischemic stroke other than index event, hypertension, diabetes mellitus, diagnosis of atrial fibrillation (known before stroke vs diagnosed after stroke), and modest kidney failure (creatinine clearance = 30–50ml/min). Study was introduced as shared frailty term in this analysis.
[b]n = number of patients.
AIS = acute ischemic stroke; CI = confidence interval; ICH = intracerebral hemorrhage; $OAC_{changed}$ = type of anticoagulant changed after index event; $OAC_{unchanged}$ = type of anticoagulant not changed after index event.

Changing the type of OAC after the index stroke was not associated with decreased risk of further ischemic strokes.

ANN NEUROL 2020;87:677–687

Nonpharmacologic Treatment Options



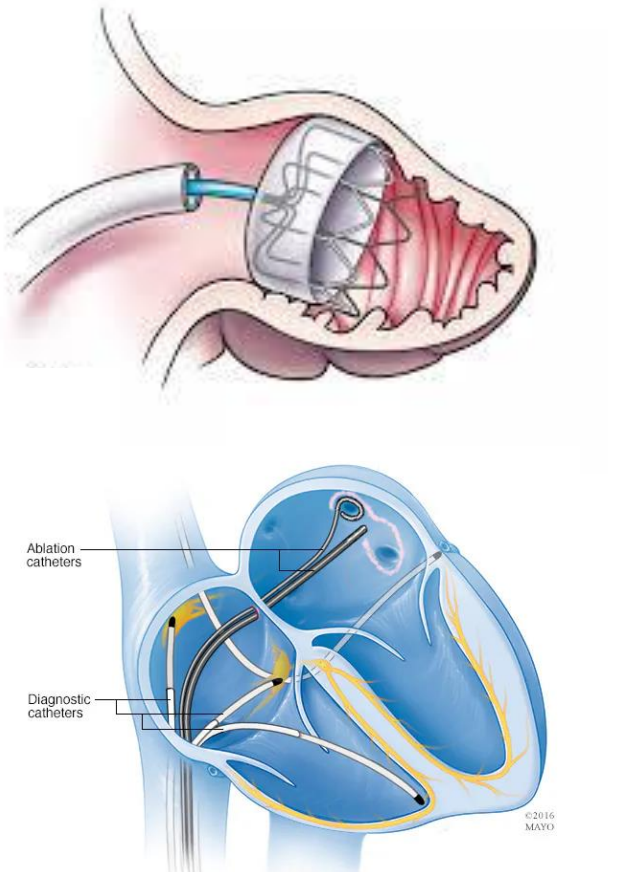


Table 1. Ischemic stroke rates reported in randomized clinical trials comparing direct oral anticoagulants and vitamin K antagonists for stroke prevention in patients with non-valvular atrial fibrillation.

First Author/ Year of Publication	Study Design	Patients No.	Age Mean	CHADS2 Score Mean	LAAC Device Implanted	Main Post-LAAC Antithrombotic Drug Regimen	Mean Follow-Up Duration (y)	Ischemic Stroke Recurrence Rate %/Patient/Year
Freixa X et al./2019 [36]	SC—RS	22	NA	NA	NA	OAC	1.8 *	2.5
Masjuan J et al./2019 [46]	MC—PS	19	72.1	5.3	ACP or Amulet	OAC + Aspirin	1.45	0
Cruz-Gonzalez I et al./2020 [35]	MC—RS	115	73.8	5.5	ACP	DAPT	1.35	2.6
Galloo X et al./2022 [45]	MC—RS	15	78.1	6	Amulet or Wachman	OAC	NA	2 events
Pracon R et al./2022 [47]	SC—PS	39	73 *	5 *	Amulet or Wachman	DAPT	1	7.7

* Median was reported instead of mean; LAAC, left atrial appendage closure; SC, single-center; MC, multicenter; RS, retrospective study; PS, prospective study; NA, not available; ACP, Amplatzer cardiac plug; OAC, oral anticoagulants; DAPT, dual antiplatelet therapy.

Significant reduction in the rate of stroke who received LAAO compared with no-occlusion group, and LAAO + OAC compared with no OAC!

The Fourth Left Atrial Appendage Occlusion Study (LAAOS-4)

ClinicalTrials.gov ID NCT05963698

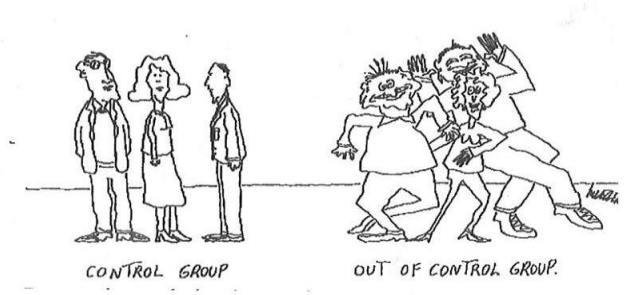
Sponsor Hamilton Health Sciences Corporation

Brief Summary

LAAOS-4 aims to determine if catheter-based endovascular left atrial appendage occlusion prevents ischemic stroke or systemic embolism in participants with atrial fibrillation, who remain at high risk of stroke, despite receiving ongoing treatment with oral anticoagulation.

Detailed Description

LAAOS-4 is a multicentre, prospective, open-label, randomized controlled trial with blinded assessment of endpoints (PROBE) to determine if catheter-based endovascular left atrial appendage occlusion prevents ischemic stroke or systemic embolism in participants with atrial fibrillation, who remain at high risk of stroke, despite receiving ongoing treatment with oral anticoagulation.

Participant Group/Arm	Intervention/Treatment
Experimental: WATCHMAN device Participants will undergo endovascular left atrial appendage occlusion with the WATCHMAN device	Device: WATCHMAN device • Participants will undergo endovascular left atrial appendage occlusion with the WATCHMAN device
No Intervention: Standard Care Participants will receive local, standard medical care	

Study Start (Actual)

2023-11-30

Primary Completion (Estimated)

2029-09-01

Study Completion (Estimated)

2029-12-01

Enrollment (Estimated)

4000

Carotid Artery Implant for Trapping Upstream Emboli

Permanent Percutaneous Carotid Artery Filter to Prevent Stroke in Atrial Fibrillation Patients

The CAPTURE Trial

Vivek Y. Reddy, MD,[a,b] Petr Neuzil, MD, PhD,[a] Tom de Potter, MD,[c] Jan van der Heyden, MD,[d] Selma C. Tromp, MD,[e] Benno Rensing, MD,[d] Eva Jiresova, MD,[a] Libor Dujka, MD,[a] Veronika Lekesova, MD[a]

ABSTRACT

BACKGROUND Patients with high stroke risk and atrial fibrillation who are unsuitable to oral anticoagulants (OACs) require other stroke prevention strategies. A novel permanent coil filter directly placed into both common carotid arteries (CCAs) was designed to capture emboli >1.4 mm in diameter.

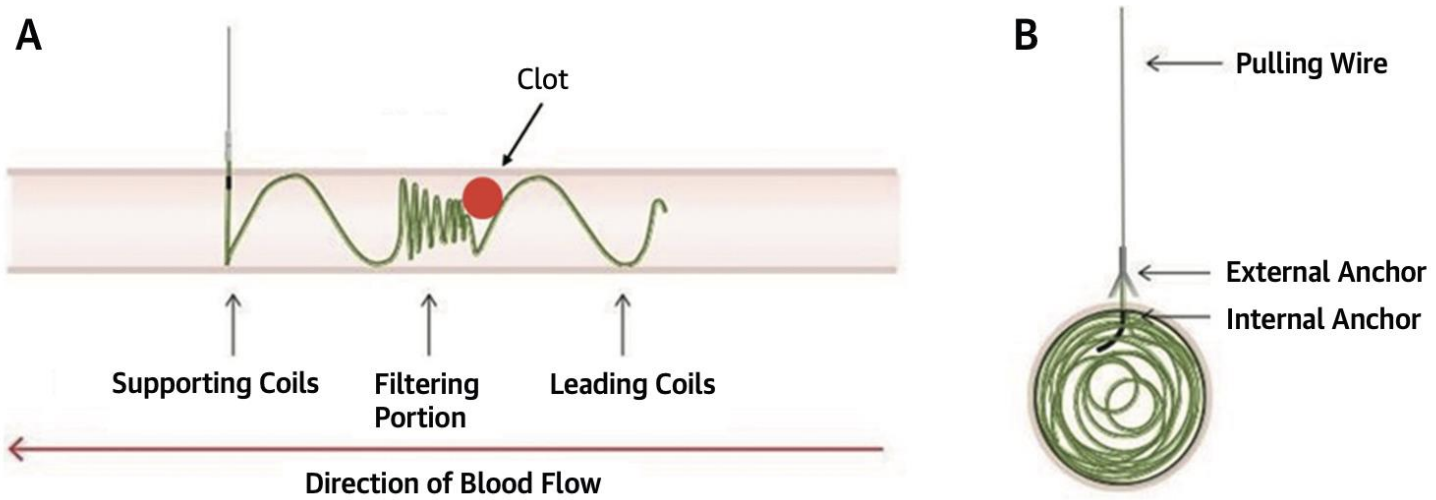
OBJECTIVES The multicenter, nonrandomized, first-in-human clinical CAPTURE (Carotid Artery Implant for Trapping Upstream Emboli for Preventing Stroke in Atrial Fibrillation Patients) trial sought to determine the feasibility and safety of bilateral CCA filter placement.

METHODS Eligible patients had atrial fibrillation, CHA_2DS_2-VASc (Congestive heart failure, Hypertension, Age 75 years, Diabetes, Stroke/transient ischemic attack, Vascular disease, Age 65 to 74 years, Sex category) ≥2, OAC unsuitability, CCA size 4.8 to 9.8 mm, and no carotid stenosis >30%. Under ultrasound guidance, after direct transcutaneous carotid puncture with a 24-gauge needle, a motorized unit expels the filter to unfurl in the artery. Patients received aspirin/clopidogrel for 3 months, and aspirin thereafter. Primary endpoints were: 1) procedural success—bilateral, properly positioned CCA filters; and 2) 30-day incidence of major adverse events—death, stroke, major bleeding, filter migration, CCA thrombus, or stenosis. Carotid ultrasounds were conducted post-procedure, pre-discharge, at 1 week, and at 1, 3, 6, and 12 months.

RESULTS At 3 centers, 25 patients were enrolled: age 71 ± 9 years, CHA_2DS_2-VASc = 4.4 ± 1.0, prior embolism in 48%. Procedure success was 92% (23 of 25 patients); 1 patient had unilateral deployment. There were no device/procedure-related major adverse events; minor puncture site hematomas/edema occurred in 5 of 25 (20%). After 6-month mean follow-up, asymptomatic thrombi were detected in 4 patients (1 bilateral, 4 unilateral), adjudicated as captured (n = 3), unclassified (n = 2), or in situ (n = 0). In all patients, the thrombi dissolved with subcutaneous heparin. In 1 patient, 2 device/procedure-unrelated minor strokes occurred.

CONCLUSIONS Permanent carotid filter placement for stroke prophylaxis is technically feasible and safe.
(Carotid Artery Implant for Trapping Upstream Emboli for Preventing Stroke in Atrial Fibrillation Patients [CAPTURE]; NCT03571789) (J Am Coll Cardiol 2019;74:829-39)

FIGURE 2 Illustration of the Carotid Coil Filter



These schematics show the filter in both side **(A)** and front **(B)** views, as well as the location of where a thrombus may be captured.

The implant is designed to exclude emboli > 1.4mm in size from reaching the anterior circulation. In AF patients, approximately 80% of strokes are total or partial anterior circulation (M1, M2 and rarely A1-2) strokes. The diameter of these branches, in the majority of cases, is > 1.5 mm

The CAPTURE trial showed the feasibility and safety of permanent carotid filter in patients with AF with high stroke risk (CHA2DS2-VASc ≤ 4 and stroke history.

Carotid Artery ImPlant for Trapping UpstReam Emboli (CAPTURE 2) for Preventing Stroke in Atrial Fibrillation Patients Taking Oral Anticoagulants

Active, not recruiting | Interventional

Location
Belgium + 7 others

Trial date
14 Apr 2019 - 23 Oct 2027

Rhythm Control

Risks and Benefits of Early Rhythm Control in Patients With Acute Strokes and Atrial Fibrillation: A Multicenter, Prospective, Randomized Study (the RAFAS Trial)

Junbeom Park, MD, PhD; Jaemin Shim, MD, PhD; Jung Myung Lee, MD, PhD; Jin-Kyu Park, MD, PhD; JoonNyung Heo, MD; Yoonkyung Chang, MD; Tae-Jin Song, MD, PhD; Dong-Hyeok Kim, MD, PhD; Hye Ah Lee, PhD; Hee Tae Yu, MD, PhD; Tae-Hoon Kim, MD, PhD; Jae-Sun Uhm, MD, PhD; Young Dae Kim, MD, PhD; Hyo Suk Nam, MD, PhD; Boyoung Joung, MD, PhD; Moon-Hyoung Lee, MD, PhD; Ji Hoe Heo, MD, PhD; Hui-Nam Pak, MD, PhD; for the RAFAS Investigators*

BACKGROUND: The purpose of the RAFAS (Risk and Benefits of Urgent Rhythm Control of Atrial Fibrillation in Patients With Acute Stroke) trial was to explore the risks and benefits of early rhythm control in patients with newly documented atrial fibrillation (AF) during an acute ischemic stroke (IS).

METHOD AND RESULTS: An open-label, randomized, multicenter trial design was used. If AF was diagnosed, the patients in the early rhythm control group started rhythm control within 2 months after the occurrence of an IS, unlikely the usual care. The primary end points were recurrent IS within 3 and 12 months. The secondary end points were a composite of all deaths, unplanned hospitalizations from any cause, and adverse arrhythmia events. Patients (n=300) with AF and an acute IS (63.0% men, aged 69.6±8.5 years; 51.2% with paroxysmal AF) were randomized 2:1 to early rhythm control (n=194) or usual care (n=106). A total of 273 patients excluding those lost to follow-up (n=27) were analyzed. The IS recurrences did not differ between the groups within 3 months of the index stroke (2 [1.1%] versus 4 [4.2%]; hazard ratio [HR], 0.257 [log-rank *P*=0.091]) but were significantly lower in the early rhythm control group at 12 months (3 [1.7%] versus 6 [6.3%]; HR, 0.251 [log-rank *P*=0.034]). Although the rates of overall mortality, any cause of hospitalizations (25 [14.0%] versus 16 [16.8%]; HR, 0.808 [log-rank *P*=0.504]), and arrhythmia-related adverse events (5 [2.8%] versus 1 [1.1%]; HR, 2.565 [log-rank *P*=0.372]) did not differ, the proportion of sustained AF was lower in the early rhythm control group than the usual care group (60 [34.1%] versus 59 [62.8%], *P*<0.001) in 12 months.

CONCLUSIONS: The early rhythm control strategy of an acute IS decreased the sustained AF and recurrent IS within 12 months without an increase in the composite adverse outcomes.

- Rhythm control therapy is an emerging approach to potentially reduce stroke recurrence beyond the effect of anticoagulation alone in patients with AF

- In RAFAS
  - Rates of stroke recurrence were lower at 12 months in the early rhythm control group (1.7%) compared with the standard care group (6.3%, p = 0.034).

  - While antiarrhythmic drugs were used early following acute stroke (<10 days), pulmonary vein ablation was performed later during the study course (>3 months), and no safety signals were observed.

Secondary Prevention of Ischemic Stroke despite adequate OAC

-Strategies and related pros and cons-

OAC Continuation

+ Standard therapy with most relevant evidence

-Diener HC et al. Lancet Neurol 2010
-Fischer U. et al. N Engl J Med 2023

− - High risk of stroke recurrence and bleeding
- No evidence that malcompliance correction improves outcomes

-Seiffge DJ et al. Ann Neurol 2020
-Polymeris AA et al. JNNP 2022
-Benz AP et al. EHJ 2023

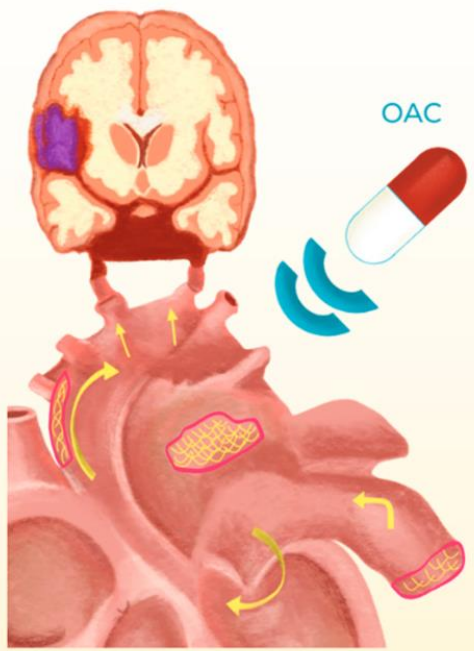
Switch to another OAC

+ Intuitively reasonable in selected scenarios: Dabigatran 150mg x 2 was the only DOAC superior to VKA in RCT

-Connolly SJ et al.. N Engl J Med 2009

− No evidence of clinical benefit

-Bonaventure YM et al. Neurology 2023
-Polymeris AA et al. JNNP 2022



Additional LAAC with or without OAC

+ Evidence of annual stroke rate reduction as compared to stroke rate predicted by score or historical rate

-Cruz-Gonzalez I et al. Rev Esp Cardiol 2020
-Freixa X et al. The Journal of invasive cardiology 2019

− Available studies are few, small and mostly retrospective

Rhythm Control

+ Evidence of efficacy in preventing stroke recurrence in patients with recent stroke regardless OAC use at the time of the event

-Park J. et al. JAHA 2022

− -Very high risk patients excluded by RCT
-No studies including patients with OAC failure

- Breakthrough stroke on OAC is not uncommon
- Only a minority of these cases (less than one-third) may be related to insufficient OAC (poor compliance or OAC underdosing)
- Initial care should firstly focus on excluding alternative reasons for stroke. BUT few cases may be related to alternative stroke mechanisms and most cases are unexplained
- There are conflicting data regarding the benefits of changing OAC regimen/type in preventing stroke recurrence
- Non-pharmacologic interventions $\pm$ OAC hold promise as potential treatment strategies for secondary stroke prevention – studies are ongoing.


THANK
YOU