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

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Supplementary material

Contents

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Supplementary methods

Study design, patient population, and data collection

Baseline clinical, neuroimaging and laboratory variables

We collected the following baseline variables: age; sex; risk factors defined in accordance with previous research,[1 2] including history of prior ischemic stroke, intracranial hemorrhage, ischemic heart disease, hypertension, diabetes mellitus, dyslipidemia, current smoking, renal impairment (defined as glomerular filtration rate <50ml/min using the creatinine-based Chronic-Kidney-Disease-Epidemiology-Collaboration equation), as well as history of bioprosthetic heart valve replacement, stenosis ≥50% or <50% in arteries supplying the territory in which the index stroke occurred (hereafter referred to as ipsilateral stenosis), active malignancy, and prestroke modified Rankin Scale (mRS); medication details at the time of the index stroke, including the type of anticoagulant, i.e., DOAC (apixaban, dabigatran, edoxaban, or rivaroxaban with their respective dosing and frequency of daily intake) or VKA (acenocoumarol, fluindione, phenprocoumon, or warfarin), as well as use of antiplatelets, statins, or antihypertensives at stroke onset; stroke characteristics, including the National Institutes of Health Stroke Scale (NIHSS) on admission, presence of large vessel occlusion (LVO), acute treatment with intravenous thrombolysis or mechanical thrombectomy, infarct pattern classified as embolic (i.e., presence of LVO, cortical infarct, or other patterns[3]) vs. nonembolic (i.e., lacunar[4]) as in prior research,[5] as well as discharge outcome on the mRS; and laboratory data, including the international normalized ratio (INR) and DOAC-specific plasma level at the time of the stroke.

Preventive treatments

We collected the following information on preventive treatments after the index stroke: use of anticoagulants (including type and dosing), antiplatelets (either alone or as add-on therapy to anticoagulation), statins, and antihypertensives at hospital discharge. Furthermore, we collected information on revascularization treatments for symptomatic ipsilateral stenosis (such as carotid endarterectomy or stenting) and nonpharmacologic prevention strategies for AF (left atrial appendage occlusion) after the index stroke.

Statistical Analyses

Secondary analyses: Association of preventive strategies with the endpoints

To explore the association of preventive strategies with the primary and secondary endpoints, we fitted univariable and multivariable logistic models adjusted for preselected common outcome predictors (i.e., age, sex, hypertension, diabetes, ischemic heart disease, dyslipidemia, renal impairment, prior ischemic stroke or ICH, current smoking, active malignancy, and use of statins or antihypertensives after stroke) with the following preventive strategies after index stroke as an independent variable:

(i) for all patients:
- use of DOAC (versus VKA). For this, we fitted all models twice, with and without the type of anticoagulant (DOAC vs. VKA) at the time of the index stroke and an interaction term anticoagulant type before*after.
- any anticoagulant switch (including VKA to DOAC, DOAC to VKA, and DOAC to another DOAC)
- new addition of antiplatelets to anticoagulants after index stroke

(ii) for patients treated with DOAC at the time of the stroke:
- switch to another DOAC
- switch to DOAC with different dosing frequency (once to twice daily or vice versa)
- switch to DOAC with different mechanism of action (thrombin to factor Xa inhibitor or vice versa)

(iii) for patients treated with VKA at the time of the stroke:
- switch from VKA to any DOAC

(iv) for patients with competing mechanism as stroke etiology:
- new addition of antiplatelets to anticoagulants after stroke

(v) for patients with insufficient anticoagulation as stroke etiology:
- DOAC dose correction (i.e., switch from reduced to full dose) or switch from VKA to DOAC after stroke

(vi) for patients with cardioembolism despite sufficient anticoagulation as stroke etiology:
- use of twice-daily DOAC (vs. any other anticoagulant) after stroke

We limited these analyses to patients for whom follow-up data were available and to those receiving oral anticoagulant therapy after the index stroke (excluding patients with antiplatelet monotherapy, parenteral anticoagulation, or no antithrombotic treatment).

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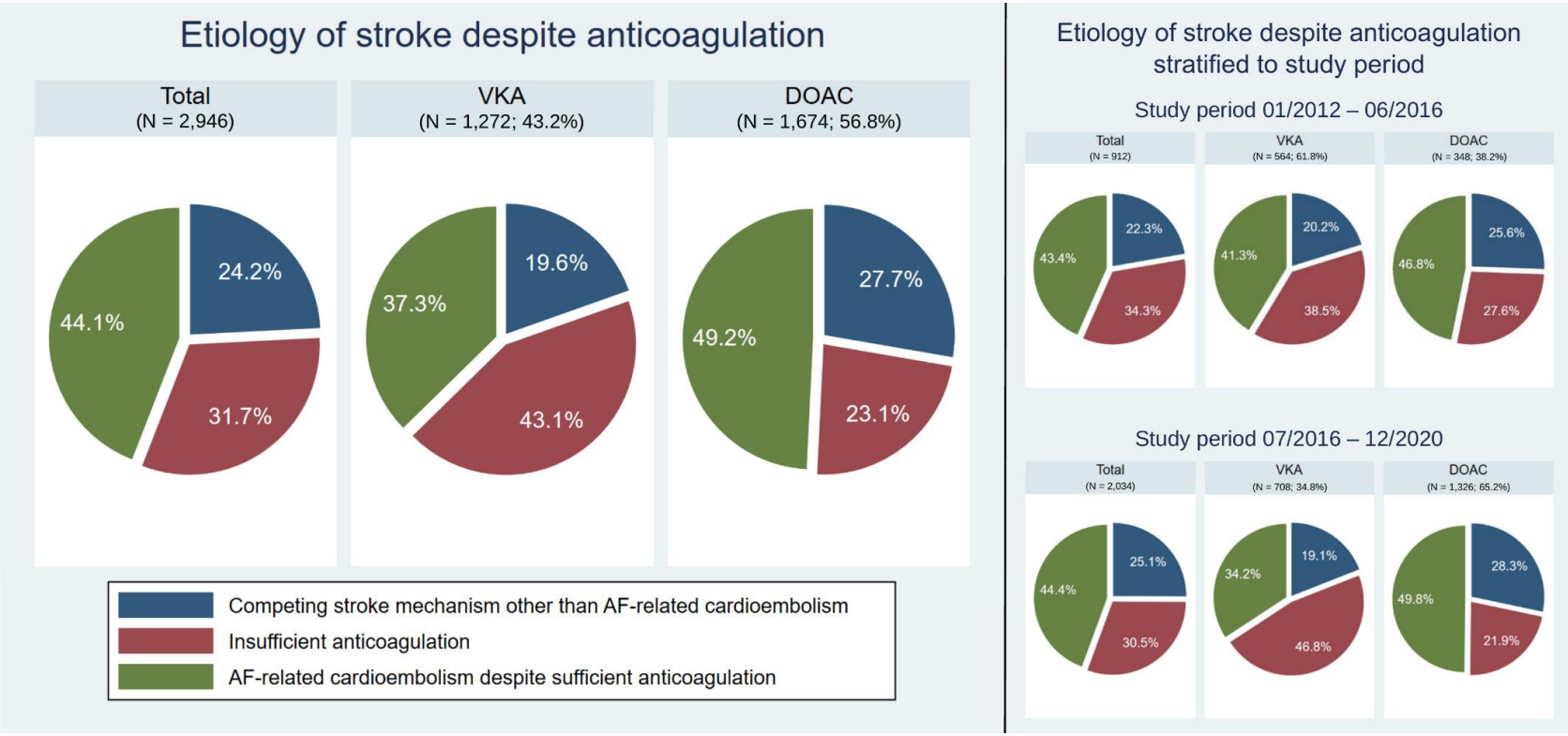
Supplementary Figure 1. Distribution of stroke etiologies in the total study population and stratified to type of anticoagulant and study period at the time of the index stroke. While the distribution of DOAC vs. VKA differed between the two study periods January 2012 to June 2016 vs. July 2016 to December 2020 (p<0.001), the distribution of stroke etiologies did not differ substantially (p=0.08).



VKA, vitamin K antagonist; DOAC, direct oral anticoagulant; AF, atrial fibrillation

Supplementary Table 1. Participating stroke centers, their contribution to the pooled dataset and complete list of collaborators

Stroke Center	Reporting period	Number of patients contributed to the analyzed pooled dataset	Complete list of collaborators
Basel, Switzerland	04/2012 – 12/2020	460	Stefan T Engelter, Philippe A Lyrer, Leo H Bonati, Christopher Traenka, Alexandros A Polymeris, Annaelle Zietz, Lilian Kriemler, Nils Peters, Gian Marco De Marchis, Sebastian Thilemann, Henrik Gensicke, Lisa Hert, Benjamin Wagner, Fabian Schaub, Louisa Meya, Nikolaos Symeon Avramiotis, Joachim Fladt, Tolga Dittrich, Urs Fisch
Berlin, Germany	01/2013 – 12/2015 01/2018 – 12/2019	438	Jan F Scheitz, Christian H Nolte, Karl Georg Haeusler, Simon Hellwig, Markus G Klammer, Simon Litmeier
Bern, Switzerland	02/2015 – 07/2020	456	Thomas R Meinel, Urs Fischer, David J Seiffge, Lorenz Grunder, Marcel Arnold, Simon Jung, Jan Gralla
Brown University, USA	01/2018 – 12/2019	50	Christoph Stretz, Shadi Yaghi, Xing (Cathy) Dai
Erlangen, Germany	04/2016 – 12/2018	334	Svenja Stoll, Ruihao Wang, Bernd Kallmünzer
George Washington University, USA	02/2016 – 12/2019	34	Christopher R. Leon Guerrero, Iman Moeini-Naghani
Heidelberg, Germany	01/2015 – 06/2018	339	Hannah Oehler, Kyra Hoelscher, Peter Ringleb, Jan C Purrucker
Lausanne, Switzerland	01/2012 – 06/2020	293	Patrik Michel, Davide Strambo, Alexander Salerno
Lugano, Switzerland	02/2014 – 08/2020	159	Giovanni Bianco, Carlo W Cereda
Mainz, Germany	09/2019 – 06/2020	87	Timo Uphaus, Klaus Gröschel
Zurich, Switzerland	01/2014 – 08/2020	296	Mira Katan, Susanne Wegener
Total	01/2012 – 12/2020	2,946	

Supplementary Table 2. Patient characteristics stratified to type of anticoagulant (DOAC vs. VKA) at the time of stroke

Characteristic	All (N=2,946)	N missing	VKA (N=1,272)	DOAC (N=1,674)	p value
Demographics					
age, median (IQR), years	81 (76-86)	0	82 (76.85-86)	80.75 (75-86)	<0.001
female sex, N (%)	1,404 (47.7%)	0	624 (49.1%)	780 (46.6%)	0.190
Risk factors					
hypertension, N (%)	2,649 (89.9%)	0	1,149 (90.3%)	1,500 (89.6%)	0.520
diabetes, N (%)	871 (29.6%)	0	362 (28.5%)	509 (30.4%)	0.250
dyslipidemia, N (%)	1,768 (60.3%)	13	791 (62.3%)	977 (58.7%)	0.047
renal impairment, N (%)	959 (33.2%)	58	457 (36.7%)	502 (30.5%)	<0.001
prior ischemic stroke, N (%)	984 (33.4%)	0	373 (29.3%)	611 (36.5%)	<0.001
history of ICH, N (%)	60 (2.0%)	0	17 (1.3%)	43 (2.6%)	0.019
ischemic heart disease, N (%)	905 (30.7%)	0	406 (31.9%)	499 (29.8%)	0.220
bioprosthetic heart valve, N (%)	151 (5.1%)	0	68 (5.3%)	83 (5.0%)	0.640
current smoking, N (%)	249 (8.8%)	103	97 (7.9%)	152 (9.4%)	0.170
active malignancy, N (%)	236 (8.1%)	15	79 (6.2%)	157 (9.4%)	0.002
prestroke mRS ≥3, N (%)	567 (22.1%)	381*	253 (23.4%)	314 (21.2%)	0.180
ipsilateral stenosis ≥50%, N (%)	452 (15.6%)	54	181 (14.6%)	271 (16.4%)	0.170
ipsilateral stenosis <50%, N (%)	496 (17.1%)	50	235 (18.8%)	261 (15.8%)	0.036
Medication details before stroke					
additional antiplatelet, N (%)	363 (12.3%)	4	162 (12.8%)	201 (12.0%)	0.540
statin, N (%)	1,354 (46.4%)	30	561 (44.8%)	793 (47.7%)	0.120
antihypertensive(s), N (%)	2,683 (91.9%)	27	1,160 (92.4%)	1,523 (91.5%)	0.380
Stroke details					
Etiology		0			
competing mechanism, N (%)	713 (24.2%)		249 (19.6%)	464 (27.7%)	<0.001
insufficient anticoagulation, N (%)	934 (31.7%)		548 (43.1%)	386 (23.1%)	
cardioembolism despite sufficient anticoagulation, N (%)	1,299 (44.1%)		475 (37.3%)	824 (49.2%)	
NIHSS on admission, median (IQR)	6 (2-14)	33	7 (3-15)	5 (2-13)	<0.001
intravenous thrombolysis, N (%)	351 (11.9%)	2	227 (17.8%)	124 (7.4%)	<0.001
endovascular treatment, N (%)	787 (26.8%)	6	340 (26.8%)	447 (26.8%)	1.000
embolic infarct pattern, N (%)	2,317 (81.7%)	111	1,036 (84.6%)	1,281 (79.6%)	<0.001
large vessel occlusion, N (%)	1,345 (46.2%)	32	628 (50.4%)	717 (43.0%)	<0.001
Laboratory parameters on admission					
INR, median (IQR)	1.4 (1.1-1.9)	100	1.8 (1.5-2.31)	1.2 (1.08-1.35)	<0.001
low anticoagulant activity, N (%)‡	957 (43.9%)	766‡	737 (58.2%)	220 (24.1%)	<0.001
Outcome at discharge					
mRS ≥3, N (%)	1,543 (63.3%)	508§	691 (64.5%)	852 (62.4%)	0.290
in-hospital death, N (%)	204 (8.4%)		104 (9.7%)	100 (7.3%)	0.035

* not collected in the center Berlin for the recruiting period 2013-2015
† not collected in the center Erlangen
‡ defined in VKA-treated patients as INR <2.0 and in DOAC-treated patients as plasma level <30ng/ml. DOAC plasma level not collected in the centers Berlin, Mainz, and George Washington University.
§ not collected in the center Mainz

VKA, Vitamin K antagonist; DOAC, direct oral anticoagulant; ICH, intracranial hemorrhage; NIHSS, National Institutes of Health Stroke Scale; INR, international normalized ratio; mRS, modified Rankin Scale

Supplementary Table 3. Preventive treatments after index stroke stratified to stroke etiology

	All (N=2,946)	N missing	**Stroke etiology**			
			Competing mechanism (N=713)	**Insufficient anticoagulation** (N=934)	**Cardioembolism despite sufficient anticoagulation** (N=1,299)	**p value**
Treatments						
Antithrombotic treatment		71				
oral anticoagulant monotherapy, N (%)	2,070 (72.0%)		404 (57.8%)	666 (73.1%)	1,000 (79.1%)	<0.001
oral anticoagulant and antiplatelets, N (%)	367 (12.8%)		198 (28.3%)	71 (7.8%)	98 (7.7%)	
antiplatelets monotherapy, N (%)	120 (4.2%)		28 (4.0%)	49 (5.4%)	43 (3.4%)	
parenteral anticoagulation, N (%)	32 (1.1%)		12 (1.7%)	10 (1.1%)	10 (0.8%)	
no treatment, N (%)	286 (9.9%)		57 (8.2%)	115 (12.6%)	114 (9.0%)	
Type of anticoagulant		80				
VKA, N (%)	315 (13.4%)		92 (15.7%)	95 (13.1%)	128 (12.2%)	0.140
DOAC, N (%)	2,042 (86.6%)		495 (84.3%)	630 (86.9%)	917 (87.8%)	
DOAC dose		199*				
full, N (%)	1,228 (66.6%)		289 (63.4%)	362 (66.2%)	577 (68.7%)	0.150
reduced, N (%)	615 (33.4%)		167 (36.6%)	185 (33.8%)	263 (31.3%)	
DOAC dosing frequency		23				
once daily, N (%)	393 (19.5%)		124 (25.3%)	145 (23.5%)	124 (13.6%)	<0.001
twice daily, N (%)	1,626 (80.5%)		367 (74.7%)	472 (76.5%)	787 (86.4%)	
DOAC mechanism of action		23				
thrombin inhibitor, N (%)	486 (24.1%)		108 (22.0%)	123 (19.9%)	255 (28.0%)	<0.001
factor Xa inhibitor, N (%)	1,533 (75.9%)		383 (78.0%)	494 (80.1%)	656 (72.0%)	
Other pharmacologic treatments						
statins, N (%)	2,126 (75.1%)	115	555 (81.3%)	643 (71.2%)	928 (74.5%)	<0.001
antihypertensives, N (%)	2,401 (84.8%)	116	592 (86.7%)	745 (82.5%)	1,064 (85.5%)	0.048
Nonpharmacologic treatments						
revascularisation treatments, N (%)	94 (3.4%)	172†	89 (13.2%)	1 (0.1%)	4 (0.3%)	<0.001
left atrial appendage occlusion, N (%)	17 (1.0%)	1,184‡	9 (1.9%)	2 (0.4%)	6 (0.8%)	0.045

* not collected in the center Lausanne
† not collected in the center Mainz
‡ not collected in the centers Berlin, Heidelberg, Lausanne and Mainz

VKA, Vitamin K antagonist; DOAC, direct oral anticoagulant

Supplementary Table 4. Association of preventive strategies after index stroke with the combined endpoint of recurrent ischemic stroke and intracranial hemorrhage

Patients	**Preventive strategy**	**Combined endpoint of recurrent ischemic stroke and ICH**					
		unadjusted			**adjusted***		
		OR [95%-CI]	**p value**	N events / total N in model	**aOR [95%-CI]**	**p value**	N events / total N in model
all patients	use of DOAC (vs. VKA) after stroke	0.50 [0.29, 0.84]	0.009	80/1,489	0.41 [0.23, 0.72]	0.002	72/1,368
	any anticoagulant switch	0.83 [0.53, 1.31]	0.425	80/1,489	0.77 [0.47, 1.25]	0.286	72/1,368
	addition of antiplatelets	2.33 [1.33, 4.08]	0.003	80/1,505	2.61 [1.43, 4.76]	0.002	72/1,382
patients with DOAC at the time of the stroke	switch to another DOAC	1.30 [0.71, 2.40]	0.398	45/826	1.28 [0.65, 2.51]	0.472	39/757
	switch to DOAC with different dosing frequency	1.08 [0.57, 2.03]	0.820	41/794	1.05 [0.52, 2.14]	0.888	35/725
	switch to DOAC with different mechanism of action	1.65 [0.86, 3.19]	0.133	41/795	1.47 [0.70, 3.11]	0.307	35/726
patients with VKA at the time of the stroke	switch to any DOAC	0.45 [0.23, 0.90]	0.023	35/663	0.45 [0.21, 0.99]	0.046	33/611
patients with competing stroke mechanism	addition of antiplatelets	1.82 [0.86, 3.84]	0.118	33/409	2.22 [0.96, 5.12]	0.061	29/359
patients with insufficient anticoagulation	switch to DOAC or correct DOAC dose	0.81 [0.33, 1.95]	0.634	21/480	0.87 [0.33, 2.25]	0.770	20/402
patients with cardioembolism despite sufficient anticoagulation	twice-daily DOAC (vs. any other anticoagulant)	1.45 [0.54, 3.94]	0.464	25/592	1.36 [0.45, 4.08]	0.586	22/555

*adjusted for age, sex, hypertension, diabetes, ischemic heart disease, dyslipidemia, renal impairment, prior ischemic stroke, ICH, current smoking, active malignancy, use of statins, use of antihypertensives

VKA, Vitamin K antagonist; DOAC, direct oral anticoagulant; ICH, intracranial hemorrhage

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