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ORIGINAL COMMUNICATION

Stroke severity in patients with preceding direct oral anticoagulant therapy as compared to vitamin K antagonists

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Abstract

Background Although direct oral anticoagulants (DOAC) have proven at least equally effective in the prevention of acute ischemic stroke (AIS) in patients with atrial fibrillation as compared to the vitamin K antagonists (VKA), no reliable data on the severity of AIS of DOAC patients as compared to VKA is available.

Methods Using a prospectively collected cohort of AIS patients, we performed univariate and multivariate (displayed as adjusted Odds Ratios, OR and 95% confidence intervals, 95% CI) analyses regarding the severity of AIS in patients with preceding DOAC ($N=210$) versus VKA ($N=173$) therapy. Additionally, we provide a sensitivity analysis considering only patients with warranted therapeutic anticoagulation activity.

Findings In a comprehensive stroke center population, the frequency of AIS under DOAC was multiple times higher than previously reported at around 6% of all AIS and steadily increasing. National Institute of Health Stroke Scale (NIHSS) in VKA patients (median 7, IQR 2–14) was equal to DOAC (median 5, IQR 2–16) on univariate analysis ($P=0.229$). According to the multivariable linear logistic regression analysis adjusting for confounders of severe stroke, VKA was not significantly associated with higher NIHSS scores (β − 0.165, 95% CI − 1.874 to 1.545, $P=0.850$) as compared to DOAC. Also in the sensitivity analysis considering only patients with warranted therapeutic OAC therapy, VKA was not significantly associated with higher NIHSS scores (β − 1.392, 95% CI − 3.506 to 0.721, $P=0.195$) as compared to DOAC. However, VKA as compared to DOAC was significantly associated with lower rates of good functional outcome at three months (0.527, 95% CI 0.300–0.928), but not with increased mortality (aOR 1.825, 95% CI 0.780–4.273).

Interpretation Ischemic stroke in patients taking DOAC is an important and frequent scenario. Stroke severity in our real world population dataset is equal in patients taking VKA and DOAC, also in the case of warranted anticoagulation therapy. Preceding VKA as compared to DOAC was associated with lower rates of good functional outcome without excess mortality, but a causal relationship cannot be proven by our study design.

Keywords Acute ischemic stroke · DOAC · Atrial fibrillation · Anticoagulation · Severity · NIHSS

Introduction

Direct oral anticoagulants (DOAC) have proven at least equally effective in the prevention of acute ischemic stroke (AIS) in patients with atrial fibrillation (AF) as compared to the vitamin K antagonist (VKA) warfarin [1] and are recommended in stroke prevention as the oral anticoagulation (OAC) of choice [2]. The net clinical benefit of DOAC treatment as compared to VKA arises mainly from a reduced risk of intracranial hemorrhage (ICH). AIS in the setting of AF is more often disabling and entails an increased mortality compared with stroke in patients without AF [3]. Despite a pronounced preventive reduction of AIS by OAC [2], AIS still

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occurs with an estimated rate of 1–2% per year in patients taking a DOAC [4]. Nevertheless, data on severity of AIS while taking DOAC medication are sparse [5–8].

In the randomized controlled trials, data on severity of ischemic stroke events was not presented [9–12] and real world data are conflicting and limited by arbitrary dichotomization of NIHSS scores and the fact that no laboratory assessment of OAC activity or information on compliance for DOAC was available [5, 13, 14].

Hence, we aimed to explore the severity of AIS in patients in a prospectively collected cohort of stroke patients consecutively admitted to our comprehensive university stroke center prescribed with OAC. Additionally, we present a sensitivity analysis considering only patients with warranted therapeutic VKA and DOAC activity on admission as well as atrial fibrillation as OAC indication.

Methods

Study design and participants

This single-centre observational study includes patients of the Swiss Stroke Registry admitted to the comprehensive university stroke center of Bern for treatment of AIS between January 2015 and August 2018. Patients were included in this analysis if they had (a) an AIS according to WHO criteria, [15] (b) available information on anticoagulation therapy prior to stroke onset, and (c) available information on NIHSS on admission. We excluded patients with transient ischemic attacks, stroke mimics, non-cerebral ischemic events, refusal of further use of biological data and missing information on OAC medication from this analysis. The study has been approved by the local ethics committee of Bern (KEK 231/14).

We grouped patients according to strata of OAC prescription (VKA, DOAC) at the time point of symptom onset. Antiplatelet prescription did not affect group assignment. For the sensitivity analysis, we further defined warranted therapeutic anticoagulation as INR > 1.7 in VKA patients or specific drug activity > 50 ng/mL in patients taking DOAC [16–20]. If no specific drug activity was available in patients taking DOAC, therapeutic anticoagulation was defined as reported previously (DOAC VKA MT) (Suppl Table 1).

We assessed the following information from the registry and in case of missing items in the medical records: demographic variables (age, sex, prestroke dependence = modified Rankin Scale (mRS) 3–5), cardiovascular risk factors, clinical parameters (blood pressure, National Institutes of Health Stroke Scale (NIHSS), onset type, TOAST-etiology, antithrombotic, antihypertensive and lipid lowering medication before admission, imaging type, laboratory parameters [cholesterol, glucose, creatinine, international normalized ratio INR, thrombin time, activated partial thromboplastin time (aPTT)] and type of acute treatment [intravenous thrombolysis (IVT) and endovascular therapy (EVT)]. To compare predictors of severe stroke, we split the cohort in half and defined severe stroke as NIHSS ≥ 6 points. We defined good functional outcome as mRS ≤ 2 at three months.

Outcomes

The primary endpoint of this analysis was the NIHSS score on admission, which was assessed by local treating physicians on admission. Secondary outcomes at three months consisted of all-cause mortality and good functional outcome at three months. For evaluation of functional outcome, we applied the mRS in routinely scheduled clinical visits or standardized telephone interviews.

Statistical analysis

We compared the two OAC groups (VKA vs. DOAC), patients with NIHSS 0–5 and NIHSS 6–42, patients with therapeutic and infra-therapeutic OAC and patients with reduced dose DOAC vs full dose DOAC using appropriate statistical measures (χ^2 test for categorical variables, Fisher's exact test for categorical variables, Mann–Whitney U test for non-normally continuous or ordinally scaled variables, and Welch's t test for independent normally distributed data). We used univariate χ^2 testing to identify baseline predictive factors of stroke severity. We selected variables from univariate analysis with a P value < 0.10 (statistical criterion), analyzed (multi)collinearity between variables and hence selected variables for the final multivariate model. For the primary analysis the association of OAC type (VKA versus DOAC) with all outcome parameters was assessed using multivariable linear and binary logistic regression adjusting for the following confounders: age (continuous), sex (categorical), pre-stroke dependence (categorical), systolic blood pressure (ordinal, adjusted odds ratio (aOR) per mmHg increase), cardioembolic stroke etiology (categorical), lipid lowering drugs (categorical), previous TIA (categorical), congestive heart failure (categorical) and admission glucose (linear, adjusted odds ratio (aOR) per mmol/L increase). Patients with missing data items were excluded from the multivariate analysis. For the sensitivity analysis, the same model was used considering only patients with warranted therapeutic OAC activity or atrial fibrillation as OAC indication on admission. We used a level of significance of 0.05.

Before starting the analysis, a power calculation was performed to estimate the yield of the available dataset. For this purpose, the values of stroke severity in the biggest available dataset of acute ischemic stroke in patients taking VKA (mean 5.3, SD 5.19) and DOAC (mean 4.0, SD 7.41)

were converted assuming Gaussian distribution as described earlier [21]. Power was calculated using a two-sample one-sided comparison of the mean of stroke severity with a type I error rate of $\alpha = 0.05$ [22].

Results

Between January 2015 and August 2018 and after exclusion of patients (Suppl Table 2), there were 210 DOAC patients and 173 VKA patients suffering AIS. Overall, 10.4% of all AIS patients had a current prescription of OAC prior to stroke onset (DOAC 5.7%, VKA 4.7%). The number of patients hospitalized with AIS under DOAC is steadily increasing in our comprehensive stroke center in the last years, reaching 3.9% in 2015, 4.6% in 2016 and 5.8% of all AIS patients in 2017 (Fig. 1) whereas the rate of AIS under VKA decreased steadily.

Of all OAC patients with AIS, in all 383/383 (100%) information on NIHSS was available and 294/383 (76.8%) had documented 90-day mRS follow-up. Either documented information on compliance or a reliable assessment of DOAC activity was available in 167/210 (79.5%) of patients taking DOAC. INR was available in all patients taking VKA. 326/383 (85.1%) patients were included in the multivariate analysis for stroke severity, 254/383 (66.3%) in the multivariate analysis for functional outcome/mortality and 203/225 (90.2%) of patients were included in the sensitivity multivariate analysis for stroke severity. Missing blood pressure ($N = 23$) and glucose ($N = 26$) were the main missing data items for the primary outcome of stroke severity.

Baseline characteristics and univariate comparisons of patients according to OAC status before AIS are presented in Table 1. Patients with DOAC had less often congestive heart failure and slightly better renal function. Otherwise, groups were comparable for baseline and treatment variables. The NIHSS scores according to OAC group are presented in Fig. 2 (Suppl Fig. 1 for patients with warranted therapeutic activity only).

Univariate analysis

Stroke severity in VKA patients (median 7, IQR 2–14) was equal to DOAC (median 5, IQR 2–16) on univariate analysis ($P = 0.229$). Patients with severe stroke (NIHSS 6–42) as compared to mild stroke (NIHSS 0–5) were older, more often female, more often dependent before stroke onset, had a lower systolic blood pressure on admission, more often cardioembolic stroke etiology, less often lipid lowering agents prescribed before stroke onset, less often a previous TIA, less often dyslipidemia, more often congestive heart failure, peripheral artery disease and higher admission glucose levels (Table 2). In VKA patients with therapeutic OAC, NIHSS on admission was lower as compared to subtherapeutic VKA. In DOAC patients with therapeutic anticoagulation activity, NIHSS on admission was numerically lower with borderline significance (Fig. 3). NIHSS was numerically lower in full dose DOAC prescription as

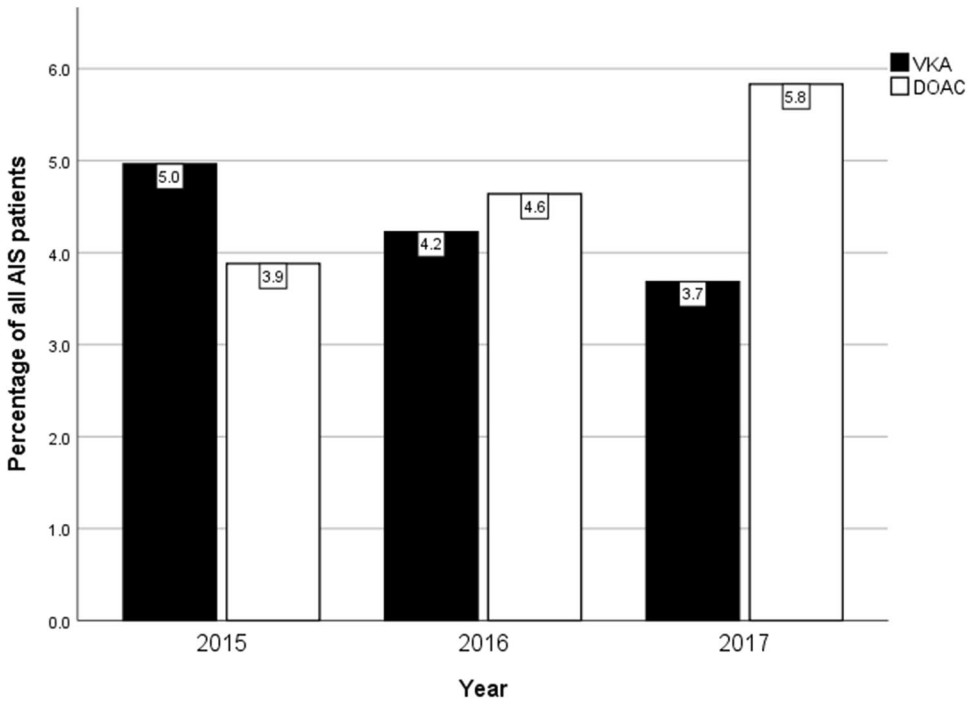

Fig. 1 Percentages of patients with acute ischemic stroke in our comprehensive university stroke center in the last 3 years. Whereas the percentage of all AIS patients with preceding VKA is steadily decreasing, the rate of AIS patients with preceding DOAC therapy is on the rise

Table 1 Baseline characteristics comparing patients with vitamin K antagonist pretreatment and patients with non-vitamin K antagonist oral anticoagulants pretreatment with data of all patients and the patient subgroups with warranted therapeutic anticoagulation activity

	DOAC ($n=210$)	VKA ($n=173$)	*P*	Available	DOAC therapeutic ($n=123$)	VKA therapeutic ($n=102$)	*P*	Available
Clinical items								
Age (years)	79 (69–85)	80 (73–85)	0.408	383	78 (68–84)	80 (71–85)	0.584	225
Sex (female)	89/209 (42.6%)	69/173 (39.9%)	0.604	382	50/123 (40.7%)	34/102 (33.3%)	0.271	225
BMI (kg/m^2)	26 (23–29)	26 (24–29)	0.854	296	26 (24–29)	26 (24–29)	0.666	185
Pre stroke dependence (mRS 3–5)	23/207 (11.1%)	20/173 (11.6%)	1.000	380	17/123 (13.8%)	14/102 (13.7%)	1.000	225
Blood pressure, systolic (mmHg)	161, SD 31	159, SD 29	0.318	360	162, SD 30	162, SD 27	0.923	218
Blood pressure, diastolic (mmHg)	85, SD 21	89, SD 23	0.099	360	85, SD 21	89, SD 21	0.166	218
Onset			0.107	378			0.26	223
Unknown	69/207 (33.3%)	48/171 (28.1%)			39/122 (32.0%)	26/101 (25.7%)	8	
Known	103/207 (49.8%)	103/171 (60.2%)			58/122 (47.5%)	59/101 (58.4%)		
Wake up	35/207 (16.9%)	20/171 (11.7%)			25/122 (20.5%)	16/101 (15.8%)		
Time to admission, hours	3.4 (1.7–11.7)	3.5 (1.7–8.7)	0.619	337	3.4 (1.8–11.8)	4.0 (1.8–10.8)	0.614	204
Medication								
Antiplatelet, additional			0.438	376			0.590	221
Mono	28/206 (13.6%)	31/170 (18.2%)			21/121 (17.4%)	20/100 (20%)		
Dual	2/206 (1.0%)	1/170 (0.6%)			1/121 (0.8%)	0		
Lipid lowering	85/209 (40.7%)	69/172 (40.1%)	0.917	381	54/123 (43.9%)	42/101 (41.6%)	0.787	224
Antihypertensives	171/210 (81.4%)	147/172 (85.5%)	0.336	382	100/123 (81.3%)	86/101 (85.1%)	0.479	224
Rivaroxaban	153/210 (73%)							
Apixaban	42/210 (20%)							
Dabigatran	9/210 (4%)							
Edoxaban	6/210 (3%)							
Risk factors								
Previous stroke	66/208 (31.7%)	50/171 (29.2%)	0.655	379	44/122 (36.1%)	32/102 (31.4%)	0.482	224
Previous TIA	23/208 (11.1%)	16/171 (9.4%)	0.615	379	19/199 (15.6%)	10/102 (9.8%)	0.234	224
History of ICH	2/208 (1.0%)	5/170 (2.9%)	0.251	378	1/122 (0.8%)	1/101 (1.0%)	1.000	223
Arterial hypertension	181 (87.0%)	148/171 (86.5%)	1.000	379	104/122 (85.2%)	87/102 (85.3%)	1.000	224
Diabetes	40/208 (19.2%)	41/170 (24.1%)	0.259	378	24/122 (19.7%)	27/101 (26.7%)	0.262	223
Dyslipidemia	143/206 (69.4%)	116/169 (68.6%)	0.911	375	87/121 (71.9%)	68/101 (67.3%)	0.467	222
Smoking	35/195 (17.9%)	20/158 (12.7%)	0.187	353	19/116 (16.4%)	9/93 (9.7%)	0.220	209
Atrial fibrillation	147/208 (70.7%)	121/173 (69.9%)	0.911	381	82/122 (67.2%)	67/102 (65.7%)	0.887	224
Congestive heart failure	37 (17.9%)	46/170 (27.1%)	0.034	377	24/121 (19.8%)	25/102 (24.5%)	0.421	223
LVEF > 30%	4/124 (3.2%)	6/134 (4.5%)	0.751	258	2/63 (3.2%)	4/80 (5.0%)	0.694	143
Prosthetic heart valve	0	0		383	0	0		225
Peripheral artery disease	17/206 (8.3%)	14/169 (8.3%)	1.000	375	8/121 (6.6%)	7/101 (6.9%)	1.000	222
Laboratory								
Admission glucose (mmol/L)	6.4 (5.6–7.5)	6.5 (5.6–8.1)	0.599	357	6.5 (5.7–7.7)	6.5 (5.6–8.2)	0.756	212
Cholesterol, total	4.5 (3.7–5.2)	4.4 (3.8–5.2)	0.706	330	4.4 (3.7–5.4)	4.4 (3.8–5.3)	0.947	195
Cholesterol, LDL	2.4 (1.8–3.1)	2.4 (1.9–3.3)	0.603	328	2.4 (1.8–3.2)	2.4 (1.8–3.4)	0.565	193
Creatinine, µmol/L	86 (71–103)	90 (76–111)	0.029	375	87 (72–102)	91 (75–110)	0.123	222

Table 1 (continued)

	DOAC ($n=210$)	VKA ($n=173$)	*P*	Available	DOAC therapeutic ($n=123$)	VKA therapeutic ($n=102$)	*P*	Available
Imaging				303				
MRI	87/154 (56.5%)	69/149 (46.3%)	0.085		47/83 (56.6%)	46/86 (53.5%)	0.75	169
CT	67/154 (43.5%)	80/149 (53.7%)			36/83 (43.4%)	40/86 (46.5%)	8	
Treatment								
IVT use			0.122	382	3/123 (2.4%)	0/101	0.25	224
Bridging transfer	5/210 (2.4%)	4/172 (2.3%)					4	
After admission to center	7/210 (3.3%)	14/172 (8.1%)						
EVT	78/209 (37.3%)	67/172 (39.0%)	0.752	381	42/123 (34.1%)	32/102 (31.4%)	0.672	225
Hospital stay, days	4 (2–6)	4 (2–9)	0.294	362	4 (2–6)	5 (2–10)	0.319	220
Etiology			0.495	378			0.52	224
Cardioembolism	102/209 (48.8%)	96/172 (55.8%)			60/122 (49.2%)	47/102 (46.1%)	2	
Dissection	0	1/172 (0.6%)			12/122 (9.8%)	11/102 (10.8%)		
Large artery	23/209 (11.0%)	18/172 (10.5%)			19/122 (15.6%)	18/102 (17.6%)		
More than one etiology	35/209 (16.7%)	22/172 (12.8%)			9/122 (7.4%)	6/102 (5.9%)		
Other determined	16/209 (7.7%)	10/172 (5.8%)			2/122 (1.6%)	1/102 (1.0%)		
Small vessel	4/209 (1.9%)	1/172 (0.6%)			2/122 (1.6%)	0		
Unknown despite complete	14/209 (6.7%)	7/172 (4.1%)			10/122 (8.2%)	5/102 (4.9%)		
Unknown with incomplete	13/209 (6.2%)	16/172 (9.3%)			8/122 (6.6%)	14/102 (13.7%)		

DOAC direct oral anticoagulants, *VKA* vitamin K antagonist anticoagulant, *BMI* body mass index, *mRS* modified Rankin Scale, *TIA* transient ischemic attack, *ICH* intracranial hemorrhage, *MRI* magnetic resonance imaging, *CT* computer tomography, *IVT* intravenous thrombolysis, *IAT* intraarterial treatment

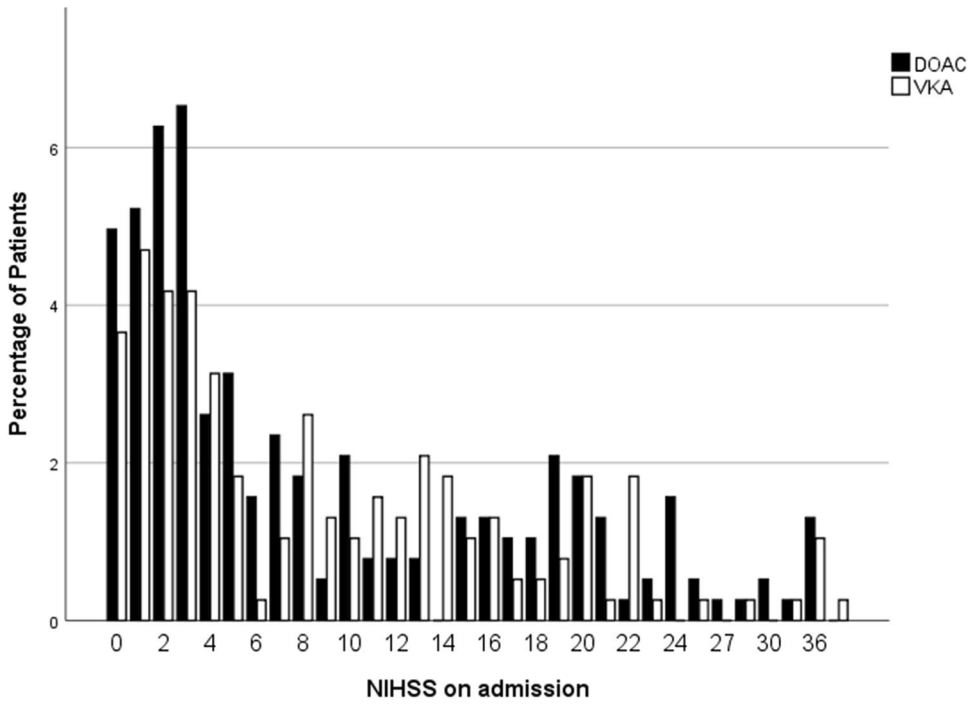

Fig. 2 Severity of Stroke grouped in patients with DOAC and VKA medication. Stroke severity in VKA patients (median 7, IQR 2–14) was equal to DOAC (median 5, IQR 2–16) on univariate analysis (Mann–Whitney *U* test, $P=0.229$)

Table 2 Characteristics comparing patients with mild and severe stroke

	NIHSS 0–5 ($n=193$)	NIHHS > 5 ($n=190$)	P	Available
Clinical items				
Age (years)	78 (66–84)	81 (74–86)	0.002	383
Sex (female)	67/192 (34.9%)	91/190 (47.9%)	0.013	382
BMI (kg/m^2)	26 (24–29)	26 (23–29)	0.762	296
Pre stroke dependence (mRS 3–5)	15/192 (7.8%)	28/188 (14.9%)	0.035	380
Blood pressure systolic (mmHg)	163, SD 30	158, SD 29	0.105	360
Blood pressure diastolic (mmHg)	86, SD 21	87, SD 22	0.547	360
Onset			0.399	378
Unknown	63/190 (33.2%)	54/188 (28.7%)		
Known	97/190 (51.1%)	109/188 (58.0%)		
Wake up	30/190 (15.8%)	25/188 (13.3%)		
Etiology			0.001	378
Non-cardioembolic	110/193 (57.0%)	83/193 (43.0%)		
Cardioembolism	75/190 (39.5%)	115/190 (60.5%)		
Medication				
Antiplatelet, additional			0.788	376
Mono	31/189 (16.4%)	28/187 (15.0%)		
Dual	1/189 (0.5%)	2/187 (1.1%)		
Lipid lowering	88/192 (45.8%)	66/189 (34.9%)	0.037	381
Antihypertensives	159/193 (82.4%)	159/189 (84.1%)	0.683	382
Anticoagulation			0.412	383
DOAC	100/190 (52.6%)	110/193 (57.0%)		
VKA	90/190 (47.4%)	83/193 (43.0%)		
Risk factors				
Previous stroke	60/189 (31.7%)	56/190 (29.5%)	0.657	379
Previous TIA	26/189 (13.8%)	13/190 (6.8%)	0.029	379
History of ICH	5/188 (2.7%)	2/190 (1.1%)	0.283	378
Arterial hypertension	162/189 (85.7%)	167/190 (87.9%)	0.548	379
Diabetes	39/189 (20.6%)	42/189 (22.2%)	0.802	378
Dyslipidemia	148/186 (79.6%)	111/189 (58.7%)	< 0.001	375
Smoking	32/185 (17.3%)	23/168 (13.7%)	0.380	353
Atrial fibrillation	128/192 (66.7%)	140/189 (74.1%)	0.118	381
Congestive heart failure	33/189 (17.5%)	50/188 (26.6%)	0.035	377
LVEF > 30%	7/116 (6.0%)	3/142 (2.1%)	0.119	258
Prosthetic heart valve	0	0		383
Peripheral artery disease	8/186 (4.3%)	23/189 (12.2%)	0.008	375
Laboratory				
Admission glucose (mmol/L)	6.2 (5.5–7.3)	6.7 (5.7–8.1)	0.004	357
Cholesterol, total	4.6 (3.8–5.3)	4.4 (3.6–5.1)	0.123	330
Cholesterol, LDL	2.5 (1.8–3.3)	2.4 (1.8–3.1)	0.650	328
Creatinine, µmol/L	87 (75–106)	90 (70–109)	0.984	375

NIHSS National Institute of Health Stroke Scale, *DOAC* direct oral anticoagulants, *VKA* vitamin K antagonist anticoagulant, *BMI* body mass index, *TIA* transient ischemic attack, *ICH* intracranial hemorrhage

compared to a lowered dose (median 4, IQR 2–10 versus median 5, IQR 3–18, $P=0.074$).

Multivariate analysis

According to the multivariable linear logistic regression analysis adjusting for confounders as outlined in the methods section, VKA was not significantly associated with higher NIHSS scores (β − 0.165, 95% CI − 1.874 to 1.545,

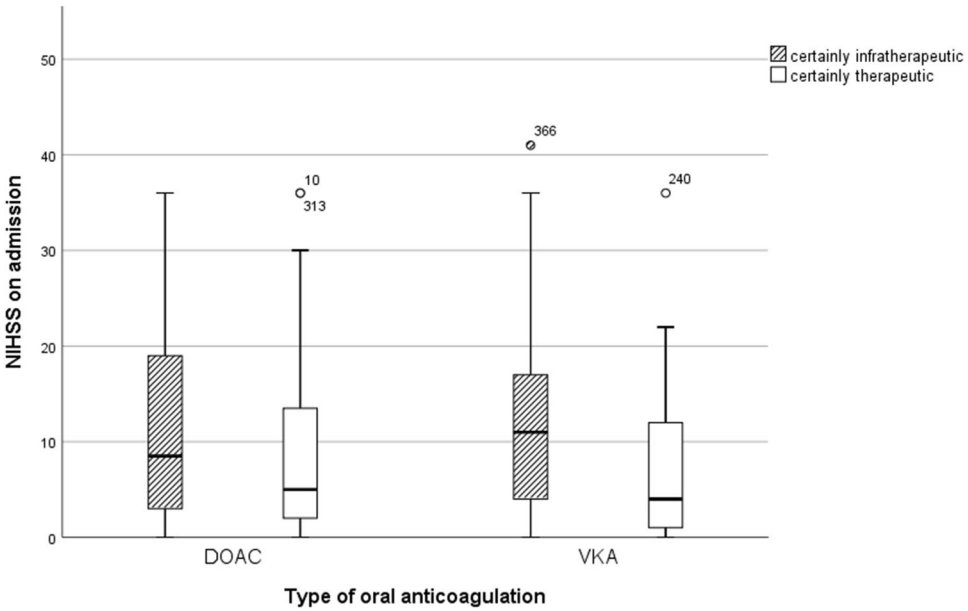

Fig. 3 Severity of Stroke according to warranted versus infratherapeutic OAC according to strata of DOAC and VKA. NIHSS in patients with VKA was significantly lower when OAC was therapeutic (median 4, IQR 1–12 vs median 11, IQR 4–17, $P < 0.001$ for Mann–Whitney U test). NIHSS in patients with DOAC was only numerically lower when OAC was therapeutic (median 5, IQR 2–15 versus median 8.5, IQR 3–19, $P = 0.096$ for Mann–Whitney U test)

$P = 0.850$) as compared to DOAC. Of the univariate predictors of severe stroke, age (β per 10 years increase 0.807, 95% CI 0.071–1.544, $P = 0.032$), heart failure (β 2.546, 95% CI 0.259–4.833, $P = 0.029$) and lipid lowering drugs (β − 2.196, 95% CI − 4.046 to − 0.347, $P = 0.020$) were significantly associated with NIHSS scores (Table 3). The associations for admission glucose (β per 1 mmol/L 0.331, 95% CI − 0.038 to 0.699, $P = 0.078$) and cardioembolic stroke (β 1.659, 95% CI − 0.082 to 3.399, $P = 0.062$) approached significance. Also in the sensitivity analysis considering only patients with warranted therapeutic OAC therapy, VKA was not significantly associated with higher NIHSS scores (β − 1.392, 95% CI − 3.506 to 0.721, $P = 0.195$) as compared to DOAC. Neither when only considering patients with AF as OAC indication, VKA was significantly associated with higher NIHSS scores (β 1.136, 95% CI − 0.893 to 3.166, $P = 0.271$) as compared to DOAC. In addition, when only considering patients with AF as OAC indication and additionally warranted therapeutic anticoagulation on admission, VKA was not significantly associated with higher NIHSS scores (β − 0.222, 95% CI − 2.736 to 2.292, $P = 0.862$) as compared to DOAC. The power calculation revealed, that our study had a 65% power to proof superiority of DOAC to reduce stroke severity as compared to VKA.

For the secondary outcomes, VKA as compared to DOAC was significantly associated with lower rates of good functional outcome at three months (0.527, 95% CI 0.300–0.928), but not mortality (aOR 1.825, 95% CI 0.780–4.273). When only considering patients with warranted therapeutic OAC activity, the association of VKA as compared to DOAC with

Table 3 Multivariate linear logistic regression analysis of predictive factors for stroke severity (NIHSS)

	Beta (β)	Significance (P)	95% Confidence intervals for beta	
			Lower limit	Upper limit
(Constant)	4.456	0.272	− 3.515	12.428
Age per 10 years increase	0.807	0.032	0.071	1.544
Male sex	− 1.496	0.101	− 3.284	0.292
Prestroke independence (mRS 0–2)	0.056	0.967	− 2.619	2.731
First systolic blood pressure per 1 mmHg	− 0.024	0.101	− 0.053	0.005
Cardioembolic stroke etiology	1.659	0.062	− 0.082	3.399
Lipid lowering drug prescription before admission	− 2.196	0.020	− 4.046	− 0.347
Previous TIA	− 1.336	0.351	− 4.148	1.477
Heart failure	2.546	0.029	0.259	4.833
Glucose on admission per 1 mmol/L	0.331	0.078	− 0.038	0.699
VKA versus DOAC	− 0.165	0.850	− 1.874	1.545

NIHSS National Institute of Health Stroke Scale, *mRS* modified Rankin Scale, *TIA* transient ischemic attack

lower rates of good functional outcome approached significance (0.519, 95% CI 0.254–1.061), whereas there was no significant association for mortality (aOR 1.546, 95% CI 0.549–4.352) as compared to DOAC.

Discussion

The comparison of patients with acute ischemic stroke under VKA versus DOAC in our real world dataset revealed the following main findings:

(1) Stroke severity in real world patients is equal in patients taking VKA and DOAC. (2) This finding holds also true in case of warranted anticoagulation therapy. (3) In a comprehensive stroke center population, the frequency of AIS under DOAC was multiple times higher than previously reported at around 6% of all AIS and steadily increasing. (4) Preceding VKA as compared to DOAC might be associated with lower rates of good functional outcome at 3 months whereas there was no difference in mortality. (5) There is need of improvement for reliable assessment of compliance and adequate laboratory diagnosis of DOAC activity.

Previous estimates assessed the prevalence of DOAC pretreatment in AIS at around 1% [23, 24]. Even factoring in the allocation bias because of a comprehensive stroke center population, the rate of almost 6% was clearly higher than expected. This number is likely to increase further as additional indications are established and there are ongoing studies using DOAC as secondary prevention in AIS patients without proven atrial fibrillation [25]. The decreasing number of VKA patients admitted to our stroke center in the last three years reflects the transition of secondary prevention in AF patients from VKA towards DOAC and additional indications for DOAC use.

In the randomized controlled trials, full dose dabigatran, apixaban, and rivaroxaban were associated with a numeric reduction of fatal/disabling stroke, but the studies did not specify if the disabling strokes were ischemic or hemorrhagic [9–11]. For edoxaban no difference of disabling or fatal stroke was observed in the full dose group and even an increased number of disabling or fatal stroke was observed in the reduced dose group [12]. Importantly, also in the biggest available real world dataset of the Get with the Guidelines registry, stroke severity while on a DOAC was equal to stroke severity while on therapeutic VKA [13]. Two previous studies found that both therapeutic VKA and DOAC therapy lowered the chances of severe AIS defined as National Institutes of Health Stroke Scale (NIHSS) > 10 points as compared to no OAC, but did not provide a direct comparison of both OAC types [5, 14]. Furthermore, the results from both studies were limited by arbitrary dichotomization of NIHSS scores and the fact that no laboratory assessment of OAC activity or information on compliance for DOAC was available. Simultaneously, doubts have been casted regarding the potential benefit of DOAC as compared to VKA in the prevention of AIS in real world data [26–28], especially in the setting of dose reductions and stretched indications for DOAC therapy.

In contrast to the randomized controlled trials, our study reports a similar stroke severity of AIS in real world VKA and DOAC patients. The sensitivity analysis comparing only patients with warranted anticoagulation activity and only patients with atrial fibrillation as OAC indication did not influence this finding. Our point estimates suggesting that VKA might even be associated with less severe stroke, especially when OAC was certainly therapeutic are in accordance with the findings of Hellwig et al. where the odds of VKA as compared to controls to prevent severe stroke was even more pronounced than for DOAC [5]. This fits with real world data indicating no significant differences between DOAC and VKA for prevention of AIS [26, 28].

In agreement with previous findings, our study confirms that therapeutic OAC reduces stroke severity as compared to infratherapeutic range, although findings were only significant for VKA patients in our cohort [6, 29]. The low rate of available specific anticoagulation assessment and missing information on DOAC compliance status probably best explain the lack of significance in the DOAC group.

Strengths and limitations

This study has the inherent limitations of a single-center retrospective analysis, although data was collected prospectively. NIHSS scores on admission were rated by treating physicians who were not all certified for NIHSS rating. Although baseline characteristics of the VKA and DOAC group were surprisingly homogeneous, we might have missed confounding baseline variables influencing the physicians' choice of OAC and affecting stroke severity and functional outcome. Our power was limited to about 65% by the fixed number of patients within our registry. Due to the limited number of AIS with preceding Apixaban and Edoxaban treatment, our findings should not be extrapolated to those substances. Thrombus formation due to infratherapeutic OAC can occur long before AIS symptom onset. However, we had no information on DOAC compliance or INR control in the months before AIS admission. Therefore, the findings have to be replicated in further cohorts of AIS, ideally by publishing the severity (NIHSS) of AIS patients with recurrent events in the randomized controlled trials, but also further real world registries.

Conclusions

Stroke severity seems to be equal in real world patients taking VKA and DOAC, also in case of warranted anticoagulation therapy. In a comprehensive stroke center, the overall

rate of DOAC pretreatment in AIS patients was at around 6% and steadily increasing emphasizing the importance of this clinical situation. Future studies should reliably differentiate between therapeutic and non-therapeutic OAC in not only VKA, but also DOAC patients, as those populations are heterogeneous. Future studies should explore if preceding VKA as compared to DOAC is truly associated with lower rates of good functional outcome.

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Compliance with ethical standards

Conflicts of interest Mr. Meinel has received travel grants from Pfizer. Mr. Kaesmacher has received travel grants from Pfizer and Stryker. Dr. Fischer is a consultant for Medtronic, CSL Behring and Stryker, outside the submitted work. Marcel Arnold received speaking fees and honoraria for scientific advisory boards from Covidien and Medtronic, outside the submitted work. All other authors have nothing to disclose.

Ethical standard This study has been approved by the appropriate ethics committee and performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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