Cerebral Ischemia in Patients on Non-Vitamin-K-Dependent Oral Anticoagulants: Through Plasma-Levels on Admission are Associated with Stroke Severity

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Background: Non-Vitamin-K-dependent oral anticoagulants (NOAC) are increasingly common in primary and secondary prevention of ischemic stroke. If an ischemic stroke occurs under NOAC-therapy, the severity and clinical course might be affected by the quality of anticoagulation at the time of stroke onset, but clinical data are limited.

Methods: Data from our prospective observational registry including all patients admitted with acute cerebral ischemia while taking oral anticoagulants between November 2014 and October 2017 were investigated. **Functional through plasma-levels** were measured in NOAC-patients using the calibrated Xa-activity (Apixaban, Rivaroxaban, Edoxaban) or the Hemoclot-essay (Dabigatran). The activity of anticoagulation was categorized into **low (<50ng/ml)**, **intermediate (50-100ng/ml)**, or **high (>100ng/ml)** and its association with clinical and imaging characteristics were investigated.

Results: Of 234 patients treated with NOAC on admission, functional through plasma-levels were available in 177 subjects (75.6%).

Plasma-levels were found to be **low** in 49 (27.7%), **intermediate** in 41 (23.2%), and **high** in 87 patients (49.2%). Patient groups were similar for relevant demographic parameters. Patients with **low plasma-levels** had significantly **higher scores on the NIHSS-scale on admission** (median 8 (IQR 3-15) vs. 4 (1-11) vs. 3 (0-8); p=0.005) and had a **higher risk of persisting neurologic deficits or cerebral infarction on imaging** (diagnosis stroke: 42 (85.7%) vs. 31 (75.6%) vs. 47 (54.0%); p<0.001). In addition, **occlusion of a large cerebral vessel was more frequent with low plasma-levels** (23 (46.9%) vs. 9 (22.0%) vs. 13 (14.9%); p<0.001).

Patients with **large vessel occlusion (LVO)** (n=45) on admission were **younger** (median 77.0 years (IQR 72.5-83.0) vs. 81.0 (77.0-86.0); p=0.003), had a **better renal function** (normal renal function on admission 68.9% vs. 49.2%; p=0.023), and **presented earlier to the hospital** than patients without large vessel occlusion (within 4.5 hours post symptom onset 66.7% vs. 43.5%; p=0.008 / within 12 hours post symptom onset 100.0% vs. 90.9%; p=0.038).

In patients presenting with **LVO** through plasma-levels on admission were **more often** categorized **low** (51.1% vs. 19.7%; p<0.001) and **less often** categorized **high** (28.9% vs. 56.1%; p=0.002) compared to patients without LVO.

In multivariate logistic regression analyses **low though plasma-level** was independently associated with **higher odds** of **LVO** on admission (3.84 (95% CI 1.80-8.20); p=0.001).

Conclusion: Through plasma-levels of NOAC on admission are associated with stroke severity. Low NOAC-plasma-levels on admission were independently associated with higher odds of large vessel occlusion on admission.

Occurrence of diagnosis stroke or TIA and LVO in patients categorized to plasma-levels low, intermediate and high.
Diagnosis stroke: 42 (85.7%) vs. 31 (75.6%) vs. 47 (54.0%); p<0.001
Diagnosis TIA: 7 (14.3%) vs. 10 (24.4%) vs. 40 (46.0%); p<0.001
LVO: 23 (46.9%) vs. 9 (22.0%) vs. 13 (14.9%); p<0.001

Median NIHSS on admission in patients categorized to plasma-levels low, intermediate and high.
NIHSS: median 8 (IQR 3-15) vs. 4 (1-11) vs. 3 (0-8); p=0.005

	No Large Vessel Occlusion on Admission (n=132)	Large Vessel Occlusion on Admission (n=45)	p-value
Age	81.0 (77.0-86.0)	77.0 (72.5-83.0)	0.003
Median (IQR)			
Male sex	60 (45.5)	24 (53.3)	0.361
n (%)			
Arterial hypertension	124 (93.9)	42 (93.3)	1.000
n (%)			
Diabetes mellitus	44 (33.3)	12 (26.7)	0.406
n (%)			
Hypertlipidemia	95 (72.0)	29 (64.4)	0.341
n (%)			
Normal renal function	65 (49.2)	31 (68.9)	0.023
n (%)			
CHA ₂ DS ₂ -VAsC	6.0 (5.0-7.0)	6.0 (5.0-7.0)	0.175
Median (IQR)			
NIHSS	3.0 (1.0-5.75)	15.0 (9.0-18.5)	<0.001
Median (IQR)			
NOAC-dosis low	67 (50.8)	21 (46.7)	0.728
n (%)		Data missing in 1 patient	
IV-Thrombolysis	3 (2.3)	14 (31.1)	<0.001
n (%)			
Endovascular treatment	0 (0.0)	25 (55.6)	<0.001
n (%)			
Plasma-level low	26 (19.7)	23 (51.1)	<0.001
n (%)			
Plasma-level intermediate	32 (24.2)	9 (20.0)	0.560
n (%)			
Plasma-level high	74 (56.1)	13 (28.9)	0.002
n (%)			
Time frame <4.5h	58 (43.9)	30 (66.7)	0.008
n (%)			
Time frame <12h	120 (90.9)	45 (100.0)	0.038
n (%)			

Baseline characteristics and therapy (LVO on admission vs. no LVO on admission).

Variable	Univariable analyses	
	OR (95% CI)	p-value
Age	0.94 (0.91-0.98)	0.006
Male sex	1.37 (0.70-2.70)	0.362
CHA ₂ DS ₂ -VAsC	0.84 (0.66-1.06)	0.143
Pre-mRS	0.83 (0.65-1.06)	0.132
NOAC low	0.89 (0.45-1.75)	0.728
Normal renal function	2.28 (1.11-4.68)	0.024
Plasma-level low	4.26 (2.06-8.80)	<0.001
Plasma-level intermediate	0.78 (0.34-1.80)	0.561
Plasma-level high	0.32 (0.15-0.66)	0.002

Variable	Multivariable analyses (Plasma-level low)		Multivariable analyses (Plasma-level high)	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	0.96 (0.77-0.96)	0.077	0.95 (0.91-0.99)	0.021
Normal renal function	2.10 (0.98-4.51)	0.057	1.79 (0.84-3.79)	0.130
Plasma-level low	3.84 (1.80-8.20)	0.001	--	--
Plasma-level high	--	--	0.35 (0.17-0.75)	0.007

Univariable and multivariable logistic regression analyses depicting the association of baseline characteristics and trough plasma-level with occurrence of large vessel occlusion on admission.