ACUTE ISCHEMIC STROKE OUTCOME AND PRECEDING ANTICOAGULATION: DIRECT ORAL ANTICOAGULANTS VERSUS VITAMIN K ANTAGONISTS

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INTRODUCTION

- Data on the severity of AIS while taking DOAC medication is scarce.
- Hence , the aim of this study is to o explore the outcome of AIS in patients pretreated with vitamin-K-antagonists (VKA) and DOAC .

METHODS

- This is a single-center observational study
- in S~ao Jo~ao Hospital Center
- January 2016 and August 2018
- had AIS
- were on oral anticoagulants (OAC) and the rationale for anticoagulation was nonvalvular AF
- excluded patients : with transient ischemic attacks, stroke mimics, noncerebral ischemic events, and missing information on OAC medication

* therapeutic anticoagulation means :

- INR greater than 1.7
- specific drug activity greater than 50 ng/mL

* If no specific drug activity was available in patients taking DOAC, it was defined as an appropriate dose according to age, weight, and renal function.

* Patients were considered for intravenous thrombolysis with recombinant tissue-type plasminogen activator if :

- INR was less than or equal to 1.7 in patients taking VKA
- plasma drug level was less than 50 ng/mL (or last administered over 48 hours) in patients taking DOAC.

* Endovascular therapy was performed independently of anticoagulation levels in patients with large vessel occlusion

OUTCOMES:

- In-hospital mortality
- neurologic improvement at discharge of stroke unit and good functional outcome 90 days after AIS
- We defined neurologic improvement as NIHSS reduction of at least 4 (compared to NIHSS at hospital admission) and a good functional outcome 90 days after AIS as mRS less than or equal to 2.

RESULTS

- 73 patients pretreated with DOAC
- 83 pretreated with VKA suffering an AIS
- Among patients taking DOAC, 28 of 73 (38.4%) used rivaroxaban, 28 of 73 (38.4%) dabigatran, 17 of 73 (23.2%) apixaban, and there were no patients on edoxaban.
- DOAC activity was available in 35 of 73 (47.9%) of patients and was less than 50 ng/mL in 15 of 35 (42.8%).
- INR on admission was available in all patients pretreated with VKA (83 of 83) and was infratherapeutic (INR 1.7) in 41 of 83 (49.4%).

Baseline chaBaseline characteristics and treatment variables were similar between groups, whereas mortality and mRS 90 days after AIS outcomes were significantly better in the DOAC group.

	AVK (n = 83)	DOAC (n = 73)	*P* value
Age (median)	79.0 (72.0-79.0)	78.0 (72.0-84.0)	.890
Sex (male)	32/83 (38.6%)	29/73 (39.7%)	.999
Prestroke independence (mRS 0-2)	79/83 (95.2%)	67/73 (91.8%)	.517
Previous stroke/AIT	39/83 (47.0%)	25/73 (34.2%)	.142
Hypertension	65/83 (78.3%)	63/73 (86.3%)	.216
Diabetes Mellitus	25/83 (30.1%)	20/73 (27.4%)	.727
Dyslipidaemia*	53/83 (63.9%)	52/72 (72.2%)	.304
Obesity*	24/81 (29.6%)	21/72 (29.1%)	.999
Smoker* (previous or current)	12/81 (14.8%)	12/73 (16.4%)	.824
GFR at admission (Cockcroft Gault formula)	77.5 (50.5-84.9)	71.3 (54.7-98.9)	.519
Infra-therapeutic anticoagulation	41/83 (49.4%)	42/73 (57.5%)	.338
Stroke severity			
NIHSS at admission (median)	13.0 (4.0-20.0)	11.0 (4.0-17.0)	.435
NIHSS > 10 at admission	44/83 (53.0%)	38/73 (52.1%)	.999
Hospital stay (d)	10 (5-31)	7.5 (4-23)	.477
Stroke unit stay (d)	2 (2-4)	2 (2-4)	.601
Etiology of AIS			
Cardioembolism	61/83 (73.5%)	50/73 (68.5%)	
Large artery	2/83 (2.4%)	1/73 (1.4%)	
Small vessel	2/83 (2.4%)	2/73 (2.7%)	
Undetermined	15/83 (18.1%)	16/73 (21.9%)	
Other determined	1/83 (1.2%)	1/73 (1.4%)	
Investigation nonperformed	2/83 (2.4%)	3/73 (4.1%)	
Reperfusion therapy	42/83 (50.6%)	33/73 (45.2%)	.524
Thrombolysis	8/83 (9.8%)	3/73 (4.1%)	
Endovascular revascularization	29/83 (35.4%)	29/73 (39.7%)	
Thrombolysis + EVT	5/83 (6.1%)	1/73 (1.4%)	
Hemorrhagic transformation	15/83 (18.1%)	9/73 (12.3%)	.378
PH2	8/83 (9.6%)	3/73 (4.1%)	.221
Neurologic improvement in Stroke Unit (NIHSS reduction of at least 4)	23/83 (27.7%)	27/73 (37.0%)	.233
Transferred to another hospital	23/83 (27.7%)	30/73 (41.1%)	.091
Duration of hospital stay†	10 (5-33)	7 (4-23)	.495
Mortality 90 days after stroke*			
During hospital admission	**11/79 (13.9%)**	**2/71 (2.8%)**	**.019**
After hospital-discharge	0/68	0/69	
Good functional status 90 days after AIS* (mRS 0-2)	**23/73 (31.5%)**	**32/62 (51.6%)**	**.043**

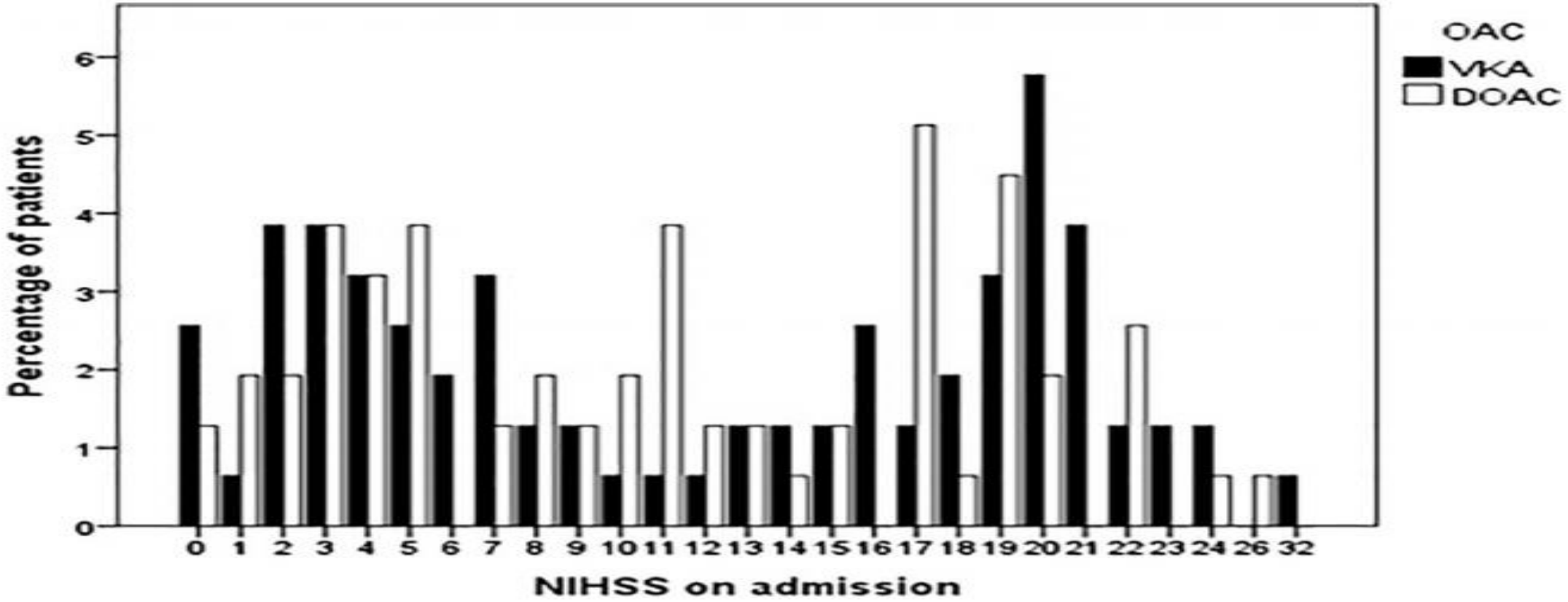

Figure 1. *Severity of stroke grouped in patients according to OAC therapy. Stroke severity in patients taking VKA (median 13, interquartile range (IQR) 4-20) was equal to patients taking DOAC (median 11, IQR 4-17) on univariate analysis (Mann-Whitney U test, P = .435). Abbreviations: DOAC, direct oral anticoagulant; OAC, oral anticoagulation; VKA, vitamin-K-antagonist.*

Table 2. *Predictors of mortality analysis—Univariate (chi-square test and Mann-Whitney U test) and multivariate (binary logistic regression)*

	Univariate *P* value	Multivariate	
		OR (95%CI)	*P* value
Age	.761	1.044 (0.94-1.15)	.404
Sex (male)	.768	1.060 (.16-9.98)	.952
Prestroke independence (mRS 0-2)	.313	–	.999
Previous stroke/TIA	.380	.524 (0.10-2.83)	.454
Hypertension	.618	.973 (0.13-7.42)	.979
Diabetes mellitus	.816	1.011 (0.16-6.29)	.990
Dyslipidaemia*	.169	.580 (0.10-3.51)	.553
Obesity*	.945	1.834 (0.32-10.42)	.494
Smoker* (previous or current)	.691	.976 (0.5-20.30)	.988
Anticoagulant (VKA)	**.019**	**12.616 (1.19-133.64)**	**.035**
GFR at admission (Cockcroft Gault formula)	.193		
Hemorrhagic transformation†	**.001**		
PH2	**<.001**	**7.516 (1.308-43.199)**	**.024**
Reperfusion therapy	.773		
Infratherapeutic anticoagulation	.788		
Stroke severity (NIHSS at admission >10)	**.002**	–	.997

Abbreviations: GFR, glomerular filtration rate; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; PH2, parenchymal hematoma type 2; TIA, transitory ischemic accident; VKA, vitamin K antagonists.

P-value multivariate analysis, hemorrhagic transformation .198.

*variable with missing data.

†An alternative multivariate model with hemorrhagic transformation (all subtypes instead of just PH2) was also performed, but statistical significance was not obtained ($P = .198$).

Table 3. *Predictors of neurologic improvement analysis—Univariate (chi-square test and Mann-Whitney U test) and multivariate (binary logistic regression)*

	Univariate *P* value	Multivariate	
		OR (95%CI)	*P* value
Age	.849	1.012 (.97-1.06)	.627
Sex (male)	.386	.790 (.30-2.03)	.624
Prestroke independence (mRS 0-2)	.503	.516 (.05-5.06)	.570
Previous stroke/AIT	.864	1.177 (.53-2.61)	.688
Hypertension	.659	.864 (.30-2.47)	.785
Diabetes mellitus	.450	.602 (0.24-1.5)	.274
Dyslipidaemia*	.358	.692 (.28-1.69)	.420
Obesity*	.562	1.320 (.52-3.34)	.558
Smoker* (previous or current)	.482	1.232 (.34-4.49)	.752
Anticoagulant (AVK)	.233		
GFR at admission (Cockcroft Gault formula)	.257		
Hemorrhagic transformation	.816		
PH2	.107		
Reperfusion therapy	**<.001**	**3.969 (1.42-11.11)**	**.009**
Infra-therapeutic anticoagulation	.844		
Stroke severity (NIHSS at admission >10)	**<.001**	2.443(.896-6.656)	.081

Abbreviations: GFR, glomerular filtration rate; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; PH2, parenchymal hematoma type 2; TIA, transitory ischemic accident; VKA, vitamin K antagonists.

*variable with missing data.

Table 4. *Predictors of good functional outcome analysis—Univariate (chi-square test and Mann-Whitney U test) and multivariate (binary logistic regression)*

	Univariate *P* value	Multivariate	
		OR (95%CI)	*P* value
Age	.059	.973 (.92-1.03)	.329
Sex (male)	.232	1.639 (.58-4.66)	.354
Prestroke independence (mRS 0-2)	**.041**	—	.999
Previous stroke/AIT	.610	.984 (.39-2.47)	.972
Hypertension	.397	.926 (.29-2.92)	.894
Diabetes mellitus	.579	2.260 (.79-6.47)	.129
Dyslipidaemia*	.471	.510 (.18-1.44)	.203
Obesity*	.715	.713 (.27-1.91)	.502
Smoker* (previous or current)	.165	.720 (.18-2.83)	.720
Anticoagulant (AVK)	**.023**	**.212 (.08-.58)**	**.003**
GFR at admission (Cockcroft Gault formula)	.638		
Hemorrhagic transformation†	**.002**		
PH2	**.008**	—	.999
Reperfusion therapy	.063		
Infratherapeutic anticoagulation	.556		
Stroke severity (NIHSS at admission >10)	**<.001**	**.101(.037-.279)**	**<.001**

for functional outcome 90 days after AIS, pretreatment with VKA (OR .212, P = .003, 95%CI .08-.58) and severe (NIHSS > 10 on admission) stroke severity (.101, P < .001, 95%CI .037- .279) were negatively associated with good functional outcome

DISCUSSION

- Infratherapeutic levels and/or inappropriate low dose of OAC was similar between the 2 groups and was not associated with stroke severity or any of the outcomes
- Preceding DOAC therapy as compared to VKA was associated with lower rates of short-term mortality and better functional outcome at 3 months.
- Subtype PH2 of hemorrhagic transformation was associated with short-term mortality, and lower stroke severity was associated with good functional outcome at 3 months.
- reperfusion therapy was associated with neurologic improvement during stroke unit stay but not with functional outcome
- Despite being associated with hemorrhagic transformation, reperfusion therapy was not associated with short-term mortality

- In this sample, the major limitations are the absence of drug levels in 52.0% of patients taking DOAC and the impossibility to check for therapy compliance, given the inherent limitations of a retrospective study.
- In this study, DOAC pretreatment was associated with lower mortality and good functional outcome 90 days after AIS, when compared to VKA. The in-hospital care was similar in both groups, and the duration of hospital stay was also similar, so these results cannot be attributed to that.
- Despite the association between reperfusion therapy and hemorrhagic transformation and that the later was associated with higher mortality, the PH2 hemorrhagic subtype and mortality were not significantly increased with reperfusion therapy, reinforcing the added value of this therapy.

CONCLUSIONS

- Nonvalvular atrial fibrillation patients pretreated with DOAC admitted for AIS had a better outcome
- when compared to VKA, although stroke severity was similar between groups.