OFF-LABEL DOSE REDUCTION OF DIRECT ORAL ANTICOAGULANTS

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Introduction: DOACs have probed to be safer and more effective than vitamine-K antagonist in clinical trials.

- ✓ However, dose reduce´s evidence in terms of safety and efficacy remains limited (5-25% in *ROCKET*, *ARISTOTLE*, *ENGAGE*), except for dabigatran (50% in *RE-LY*).
- ✓ Nevertheless, real life studies show low dosing is used in up to 60% of patients with DOACs, without fulfilling labelling dose reduction criteria in most cases, and therefore, risking their efficacy.
- ✓ Neurological patients´specific characteristics main explain this behaviour: they are older and have got a higher hemorrhagic risk. *But, are we, neurologists, right?*.
- ✓ The aim of our study was to analyze DOACs dose reductions.

Methods: Multicentric observational study. 2013-2017 prospective registries of neurological patients with DOACs from three University Hospitals have been analyzed.

- ✓ Baseline characteristics, doses, reason for reduction and embolic/hemorrhagic events were registered during the follow-up (mean 14,8 months, SD 10,7), in both groups, full dose and reduced dose.
- ✓ The primary objective was to evaluate reduced/low dose rate and if the adjustment was based on labeling criteria. Secondary objectives measures were incidence of embolic events and bleeding complications (regardless severity) in full dose vs reduced dose during follow-up.

Results: 165 patients included

Treatment groups

FULL DOSE n = 95
Dabigatran n=22
Rivaroxaban n=28
Apixaban n=43
Edoxaban n=2

REDUCED DOSE n = 70	According to labelling*	Estimated high hemorrhagic risk**	Unspecified reason***	% Off-label
Dabigatran n=36	27	7	2	9/36 (25%)
Rivaroxaban n=17	12	1	4	5/17 (29,4%)
Apixaban n=17	9	3	5	8/17 (47%)
Edoxaban n=0	0	0	0	0%
Total	48 (68,6%)	11 (15,7%)	11 (15,7%)	22/70 (31,4%)

Dose reduction criteria

Labelling dose reduction*	Dabigatran 110 BD	Rivaroxaban 15 OD	Apixaban 2,5 BD	Edoxaban 30 OD
Conditions	1/4	1/1	2/3	1/3
Renal clearance (ml/min)	30-49	15-49	15-29 (RCl≥1,5 mg/dl)	15-49
Age (years)	≥80		≥80	-
Weight (Kg)	-		≤60	≤60
Other drugs	verapamil			Verapamil, quinidine dronedarone, eritro micin ketoconazol
Other	HASBLED>3, gastrointestinal pathology, “75-80 years”			
Contraindicated	dronedarone, azoles ritonavir, ciclosporine, tacrolimus	dronedarone, azoles, ritonavir	azoles, ritonavir	-

High hemorrhagic risk**

Recent ischemic stroke
Previous cerebral bleed
Gastrointestinal or genitourinary bleed
Tripple antithrombotic therapy
Tumours
Comorbidity
Risk of falls
Alcoholism
Apixaban 1/3

Baseline characteristics

	FULL DOSE (n=95)	REDUCED DOSE (n=70)	<i>p</i>
Non valvular AF	98,9%	97,1%	0,3912
Previous TIA/ ischemic stroke	96,8% (3 cerebral bleeds)	87,1% (9 cerebral bleeds)	0,0177
Previous ischemic/ hemorrhagic stroke	100%	100%	-
Previously anticoagulated	60% (warfarin 96,5%)	64,3% (warfarin 88,9%)	0,5755
Age (average)	76 (37-90)	84 (50-94)	<0,0001
CHADS2-VASc (average)	5 (1-8)	6 (2-8)	0,00447
HAS-BLED (average)	3 (0-4)	3 (1-5)	0,0219
Renal clearance< 50ml/min	7,4%	34,3%	<0,0001
Antiplatelets	6,3%	5,7%	0,8729
Withdrawal	6/95 (6,3%) 5,1% annually	7/70 (10%) 8,1% annually	0,3853

Embolic events

FULL DOSE (n=95). Embolic events (EE)					
TIA	Minor stroke (NIHSS<4)	Stroke (NIHSS>5)	Other	Total EE	%EE
0	2	5	0	7	7/95 (7,3%)

p=0,5

REDUCED DOSE (n=70). Embolic events (EE)					
TIA	Minor stroke (NIHSS<4)	Stroke (NIHSS>5)	Other	Total EE	%EE
0	4	2	1	7	7/70 (10%)

Hemorrhagic events

FULL DOSE (n=95). Hemorrhagic events (HE)			
Mayor	Minor	Total EE	%EE
1	5	6	6/95 (6,3%)

p=0,3

REDUCED DOSE (n=70). Hemorrhagic events (HE)			
Mayor	Minor	Total EE	%EE
2	4	6	6/70 (8,5%)

FULL DOSE

- Embolic events
(annualized rate)
- No embolic events

REDUCED DOSE

FULL DOSE

- Hemorrhagic events
(annualized rate)
- No hemorrhagic events

REDUCED DOSE

Conclusions:

- ✓ **Off-label dose reduction resulted frequent** in our multicentric series of patients with DOACs and ischemic/hemorrhagic stroke, due to a high hemorrhagic risk assessed a priori by the neurologist.
- ✓ Dose reduced group, indeed, included **older patients, with higher embolic/hemorrhagic risk, and renal failure** was common. **Full dose** was preferred in patients with previous stroke.
- ✓ Our **annualized events´ rate were higher** than those in secondary prevention published in literature, however our series´ **embolic risk and withdrawal rate are clearly higher**.
- ✓ **No differences in vascular recurrences** were observed between groups during follow-up.