Fattori predittivi di emorragia intracranica in corso di terapia con anticoagulanti orali diretti per la prevenzione di ictus ischemico

Background

- Clinical trials on stroke prevention in patients with atrial fibrillation (AF) have consistently shown benefits from either warfarin or non–vitamin K antagonist oral anticoagulants (NOACs).
- However, these patients are known to experience anticoagulation-related intracerebral hemorrhage (ICH).

BRIEF REPORT

Risk Factors for Intracerebral Hemorrhage in Patients With Atrial Fibrillation on Non–Vitamin K Antagonist Oral Anticoagulants for Stroke Prevention

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Aim of the study

The aims of this prospective, multicenter, multinational, unmatched, case-control study were:

- to investigate for risk factors that could predict ICH occurring in patients with atrial fibrillation during NOAC treatment
- to evaluate the role of CHA2DS2-VASc and HAS-BLED scores in the same setting.

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Methods

- Cases were consecutive patients with atrial fibrillation who had ICH during NOAC treatment (N= 419).
- Controls were consecutive patients with atrial fibrillation who did not have ICH during NOAC treatment (N=1526).
- As within the CHA2DS2-VASc and HAS-BLED scores there are some risk factors in common, several multivariable logistic regression models were performed to identify independent prespecified predictors for ICH events.

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Characteristics of the Cases and Controls

	Cases (n=419)	Controls (n=1526)	*P* value
Age, y; mean	78.8±8.1	76.0±10.3	0.0001
Women	184 (43.9%)	690 (45.2%)	0.7
Weight, kg; mean	76.0±14.1	74.7±15.8	0.07
Duration of therapy, mo; mean	20.0±14.6	27.4±15.6	0.0001
Deep hemorrhage	277 (66.1%)		
Apixaban	151 (36.1%)	535 (35.1%)	0.7
Dabigatran	71 (16.9%)	332 (21.8%)	0.03
Edoxaban	32 (7.6%)	15 (0.9%)	0.0001
Rivaroxaban	165 (39.4%)	644 (42.2%)	0.2
Label low-dose NOACs	100 (23.9%)	447 (29.3%)	0.03
Nonlabel low dose	30 (7.2%)	134 (8.8%)	0.3
Nonlabel high dose	14 (3.3%)	18 (1.2%)	0.004
Creatinine clearance, mean	68.3±26.0	77.5±26.4	0.0001
CHA_2DS_2VASc score, median (IQR)	4.0 (2.0)	4.0 (2.0)	0.9
0	0	28 (1.9%)	
1	2 (0.5%)	74 (4.8%)	
2	30 (7.1%)	145 (9.5%)	
3	87 (20.8%)	242 (15.8%)	
4	111 (26.5%)	388 (25.4%)	
5	91 (21.7%)	285 (18.7%)	
6	57 (13.6%)	232 (15.2%)	
7	28 (6.7%)	102 (6.7%)	
8	13 (3.1%)	27 (1.8%)	
9	0	3 (0.2%)	

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Characteristics of the Cases and Controls

	Cases (n=419)	Controls (n=1526)	*P* value
HAS-BLED score, median (IQR)	3.0 (2.0)	3.0 (1.0)	0.7
0	1 (0.2%)	66 (4.3%)	
1	17 (4.0%)	189 (12.4%)	
2	165 (39.4%)	396 (26.0%)	
3	155 (37.0%)	429 (28.1%)	
4	66 (15.8%)	370 (24.2%)	
5	15 (3.6%)	68 (4.5%)	
6	0	8 (0.5%)	
Hypertension	361 (86.2%)	1320 (86.5%)	0.9
Diabetes	98 (23.4%)	313 (20.5%)	0.2
Hyperlipidemia	201 (47.9%)	562 (36.8%)	0.0001
Statin therapy	167 (39.8%)	498 (32.6%)	0.006
Alcohol abuse	44 (10.5%)	187 (12.2%)	0.3
Current smoker	45 (10.7%)	117 (7.7%)	0.06
Congestive heart failure	78 (18.6%)	348 (22.8%)	0.08
History stroke/TIA	135 (32.2%)	504 (33.0%)	0.7
Myocardial infarction/angina pectoris	103 (24.6%)	337 (22.1%)	0.3
Peripheral artery disease	56 (13.4%)	97 (6.3%)	0.0001
Paroxysmal AF	190 (45.3%)	460 (30.1%)	0.0001
Concomitant antiplatelet therapy	54 (12.9%)	51 (3.3%)	0.0001
History of severe bleeding	42 (10.0%)	152 (10.0%)	1.0
Active malignancy	43 (10.3%)	84 (5.5%)	0.001
High risk of fall	105 (25.0%)	274 (17.9%)	0.002
White matter changes	271/407 (66.6%)	407/1254 (32.5%)	0.0001
Platelets per mL, mean	217 200±68 900	219 000±71 000	0.6

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Results

Independent predictors of ICH	Variables inversely associated with the risk of ICH
• Increasing age • Concomitant use of antiplatelet agents • Active malignancy • High risk of fall • Hyperlipidemia • Low clearance of creatinine • Peripheral artery disease • White matter changes	• Low doses of NOACs (given according to label or not) • Congestive heart failure

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Characteristics of the patients with deep or lobar ICH

	Deep (n=277)	Lobar (n=142)	p
Age (years), mean	78.7±8.1	79.2±8.1	0.2
Males	162 (58.5%)	73 (51.4%)	0.1
Apixaban	101 (36.5%)	50 (35.2%)	0.8
Dabigatran	36 (13.0%)	34 (23.9%)	0.004
Edoxaban	19 (6.8%)	13 (9.1%)	0.4
Rivaroxaban	121 (43.7%)	45 (31.7%)	0.01
Hypertension	245 (88.4%)	114 (80.3%)	0.02
Diabetes Mellitus	62 (22.4%)	35 (24.6%)	0.6
Hyperlipidemia	155 (56.0%)	75 (52.8%)	0.5
Alcohol abuse	31 (11.2%)	13 (9.2%)	0.4
Current smoker	28 (10.1%)	17 (12.0%)	0.4
Congestive heart failure	55 (19.8%)	23 (16.2%)	0.3
History stroke/TIA	81 (29.2%)	53 (37.3%)	0.09
Myocardial infarction/angina pectoris	71 (25.6%)	32 (22.5%)	0.4
Peripheral artery disease	37 (13.3%)	19 (13.4%)	1.0
Concomitant antiplatelet therapy	37 (13.3%)	17 (12.0%)	0.8
History of severe bleeding	27 (9.7%)	15 (10.6%)	0.6
Active malignancy	26 (9.4%)	17 (12.0%)	0.2
High risk of fall	74 (26.7%)	31 (21.8%)	0.2
White matter changes	190 (68.6%)	79 (55.6%)	0.008

Multivariable analysis (model including HAS-BLED score): predictive factors for ICH

	OR (95% CI)	P
Standard dose	Reference	
Non-label high dose NOACs	1.76 (0.80-3.88)	0.1
Label low dose	0.74 (0.56-0.91)	0.03
Non-label low dose	0.61 (0.38-0.98)	0.04
HAS-BLED score	1.00 (0.90-1.11)	0.9
Females	0.95 (0.75-1.22)	0.6
Hyperlipidemia	2.23 (1.71-2.90)	0.0001
Diabetes mellitus	1.09 (0.82-1.43)	0.5
Current smoker	1.18 (0.80-1.76)	0.3
History of myocardial infarction	1.07 (0.81-1.42)	0.6
Peripheral artery disease	2.18 (1.50-3.17)	0.0001
Platelet count	0.99 (0.99-1.00)	0.4
Statin therapy	1.16 (0.88-2.75)	0.3
Active malignancy	1.84 (1.22-2.78)	0.003
High risk of fall	1.48 (1.12-1.96)	0.005

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Multivariable analysis (model including CHA2DS2VASc score): predictive factors for ICH

	OR (95% CI)	P
Standard dose	Reference	
Non-label high dose NOACs	0.61 (0.21-1.80)	0.3
Label low dose	0.52 (0.37-0.72)	0.0001
Non-label low dose	0.48 (0.28-0.82)	0.008
CHA_2DS_2VASc score	1.02 (0.93-1.11)	0.6
Alcohol abuse	0.93 (0.62-1.38)	0.7
Hyperlipidemia	2.48 (1.85-3.34)	0.0001
Current smoker	0.89 (0.55-1.43)	0.6
Creatinine clearance	0.98 (0.97-0.99)	0.0001
Statin therapy	1.33 (0.96-1.81)	0.08
Platelet count	0.99 (0.99-1.00)	0.2
Concomitant antiplatelet therapy	3.37 (2.07-5.49)	0.0001
History of major bleeding	1.05 (0.68-1.61)	0.8
Active malignancy	1.46 (0.91-2.35)	0.1
High risk of fall	1.37 (1.00-1.87)	0.04

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Multivariable analysis (model including risk factors, white matter changes and excluding HAS-BLED and CHA_2DS_2VASc scores): predictive factors for ICH

	OR (95% CI)	P
Standard dose	Reference	
Non-label high dose NOACs	0.53 (0.17-1.62)	0.2
Label low dose	0.42 (0.30-0.60)	0.0001
Non-label low dose	0.47 (0.27-0.83)	0.009
Age	1.04 (1.02-1.06)	0.0001
Females	0.8 (0.60-1.05)	0.1
Hypertension	0.90 (0.60-1.35)	0.6
Diabetes mellitus	1.18 (0.86-1.61)	0.2
Hyperlipidemia	2.66 (1.96-3.61)	0.0001
History of myocardial infarction	0.88 (0.63-1.23)	0.4
Peripheral artery disease	1.23 (0.77-1.98)	0.3
Congestive heart failure	0.56 (0.40-0.79)	0.001
History of stroke/TIA	0.86 (0.65-1.14)	0.3
Alcohol abuse	1.00 (0.66-1.51)	0.9
Creatinine clearance	0.98 (0.97-0.99)	0.0001
Current smoker	1.14 (0.69-1.88)	0.6
History of major bleeding	1.04 (0.67-1.62)	0.8
Statin therapy	1.26 (0.90-1.75)	0.1
Platelet count	0.99 (0.99-1.00)	0.4
Concomitant antiplatelet therapy	3.54 (2.07-6.07)	0.0001
Active malignancy	1.46 (0.91-2.37)	0.1
High risk of fall	1.31 (0.95-1.80)	0.1

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Limitations

- Observational and neither individual NOACs nor their doses were randomized
- Other pharmacological treatments besides NOACs except antiplatelets were not investigated. In fact, this limitation might be considered a serious shortcoming, in that it might hinder the interpretation of these data.
- Compliance information was provided by the patients themselves or the caregiver, no laboratory assessment of the anticoagulant status during the event.

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Conclusions

- In patients with AF treated with NOACs, age, concomitant use of antiplatelet agents, the presence of an active malignancy, high risk of fall, hyperlipidemia, low clearance of creatinine, peripheral artery disease, and white matter changes on neuroimaging were associated with increased risk of ICH.
- Low doses of NOACs (given according to label or not) and congestive heart failure were inversely associated with the risk of ICH.
- The HAS- BLED and CHA2DS2-VASc scores performed poorly in predicting ICH.

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