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ORIGINAL ARTICLE

Low drug levels and thrombotic complications in high-risk atrial fibrillation patients treated with direct oral anticoagulants

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Background

- DOACs are administered at a fixed dose in relation to clinical indications, individual characteristics, and renal function, without current indications for dose adjustment based on laboratory testing.
- However, high inter-individual variability in drug blood levels has been shown with all DOACs, and post hoc analyses of phase III trial results showed an association between DOAC plasma levels and thrombotic and bleeding complications during follow-up.

AIM OF THE STUDY

To evaluate a possible relationship between DOAC C-trough anticoagulant levels, measured at steady state within the first month of treatment, and thromboembolic events observed during 1 year of follow-up.

Methods (I)

- Observational multicenter study in patients with NVAF treated with dabigatran, rivaroxaban, or apixaban.
- Four anticoagulation clinics (Ancona, Bologna, Cremona, and Padova) affiliated with the Italian Federation of Anticoagulation Clinics (FCSA) and participating in the START Registry.
- 565 consecutive naive patients with NVAF, aged > 18 years, seen at the anticoagulation clinics from 1 January 2015 to 31 December 2015, were enrolled in the study.

Methods (II)

- Baseline characteristics were recorded in a structured database.
- Follow-up, as defined by FCSA guidelines, included clinical evaluation within the first month and then every 3 months for 1 year.
- All bleeding and thromboembolic complications were registered for 1 year of follow-up.
- Plasma samples were collected within the first 15–25 days of treatment at C-trough level, obtained at 12 h from the last dose intake for dabigatran and apixaban, and at 24 h from the last dose intake for rivaroxaban.

Results (I)

Table 1 Main clinical characteristics, thrombotic complications and direct oral anticoagulant (DOAC) plasma levels at C-trough for: all patients, patients with thrombotic complications, and patients without thrombosis

	Dabigatran	Rivaroxaban	Apixaban	Total
Patients (*n*)	185	172	208	565
Age (years), median (range)	78 (44–94)	82 (57–97)	80 (49–94)	80 (44–97)
Gender (M/F), *n*	105/80	95/77	115/93	315/250
BMI, median (range)	26.9 (17.4–43.3)	25.5 (16.6–34.7)	26.2 (16.4–40.1)	26.2 (16.4–43.3)
Daily dose of drug (no. of patients)	2 × 150 mg (82) 2 × 110 mg (103)	20 mg (100) 15 mg (72)	2 × 5 mg (154) 2 × 2.5 mg (54)	–
Creatinine clearance (mL min^{-1} 1.73 m^{-2}), median (range)	70.5 (39–149)	66.5 (36–117)	69.0 (33–117)	69.0 (33–149)
CHA_2DS_2VASc score, median (range)	3 (0–7)	3 (0–7)	3 (0–9)	3 (0–9)
DOAC plasma levels (ng mL^{-1}), median (range)				
All patients	82 (36–324)	39 (17–273)	111 (22–515)	–
Patients with thrombosis	67 (36–91)	28 (23–39)	79 (45–113)	–
Patients without thrombosis	82 (36–324)	39 (17–273)	111 (22–515)	–
Thrombosis, *n* (%)	5 (2.7) (4 Strokes, 1 AMI)	3 (1.7) (2 AMI, 1 TIA)	2 (1.0) (1 DVT, 1 Systemic Embolism)	10 (4 Strokes, 3 AMI, 1 TIA, 1 DVT, 1 Systemic Embolism)

BMI, body mass index; F, female; M, male.

Results (II)

- During 1 year of follow-up, 10 thromboembolic events were observed, with an incidence of 1.8% (95% CI 0.8–3.2) of the total population.
- All 10 thromboembolic complications occurred after the first 6 months of treatment in patients whose C-trough drug levels were in the lowest level class calculated for each drug.
- The 10 patients with thromboembolic complications had a mean CHA2DS2-VASc score that was significantly higher than that of the entire study population: 5.3 (95% CI 4.3–6.3) versus 3.0 (95% CI 2.9–3.1); $P < 0.0001$.

Table 2 Thromboembolic complications, CHA_2DS_2-VASc score, and direct oral anticoagulant (DOAC) C-trough levels

Patient	Drug	Daily dose	CHA_2DS_2-VASc score	ASA	Amiodarone	CrCl (mL min^{-1} 1.73 m^{-2})	DOAC C-trough (ng mL^{-1})	Thromboembolic complication
1	Dabigatran	150 mg × 2	5	Yes	Yes	79	36	Stroke
2	Dabigatran	110 mg × 2	7	No	No	67	67	Stroke
3	Dabigatran	110 mg × 2	3	No	Yes	53	53	Stroke
4	Dabigatran	110 mg × 2	4	No	No	67	78	Stroke
5	Dabigatran	150 mg × 2	7	No	No	76	91	AMI
6	Rivaroxaban	20 mg	7	No	No	69	39	TIA
7	Rivaroxaban	15 mg	5	No	No	56	23	AMI
8	Rivaroxaban	15 mg	5	No	No	47	28	AMI
9	Apixaban	2.5 mg × 2	6	Yes	No	44	113	Systemic embolism
10	Apixaban	5 × 2 mg	4	No	No	79	45	DVT

AMI, acute myocardial infarction; ASA; acetylsalicylic acid; CrCl, creatinine clearance; DVT, deep vein thrombosis; TIA, transient ischemic attack.

Discussion

- For all DOACs, the study confirmed the high inter-individual variability as regards the plasmatic concentration of the anticoagulant drugs.
- The combination of high cardiovascular risk with low anticoagulant levels of DOACs may expose patients to a greater risk of thrombotic complications.
- These data support the concept of assessing the anticoagulant levels at steady state, in selected patients, as a tool to contribute to efforts to achieve more effective and safer anticoagulation with DOACs.