Bleeding and thrombotic complications during treatment with direct oral anticoagulants or vitamin K antagonists in venous thromboembolic patients included in the prospective, observational START2-register

Gualtiero Palareti ,[1] Emilia Antonucci,[1] Cristina Legnani,[1] Daniela Mastroiacovo,[2] Daniela Poli,[3] Paolo Prandoni,[1] Alberto Tosetto ,[4] Vittorio Pengo,[5] Sophie Testa,[6] Walter Ageno,[7] on behalf of the START2 Register Investigators

Background

- DOAC use in patients with VTE has sharply increased in the last few years, confining standard anticoagulant treatment with parenteral drugs and VKAs in selected patient populations.
- The START2-Register is an observational, multicentric, dynamic cohort study that includes adults (≥18 years) starting anticoagulation therapy, whatever the indication for treatment and drug/dosage used.

Aim of the study

To analyze the proportion and characteristics of Italian patients affected by VTE treated with DOACs or VKAs, and complications occurring during follow-up.

Methods

- A prospective cohort of 2728 VTE patients included in the Survey on anticoagulaTed pAtients RegisTer (START2-Register) from January 2014 to June 2018 was investigated.
- Characteristics of patients, type of treatment and complications occurring during follow-up were analyzed.
- Patients could receive DOACs or VKAs; both prescribed by the National and Regional Health Systems for patients with VTE.
- Efficacy endpoint: rate of VTE recurrence.
- Safety endpoint: rate of major and clinically relevant non-major bleeding events.

Table 1 Baseline characteristics of patients and of VTE events

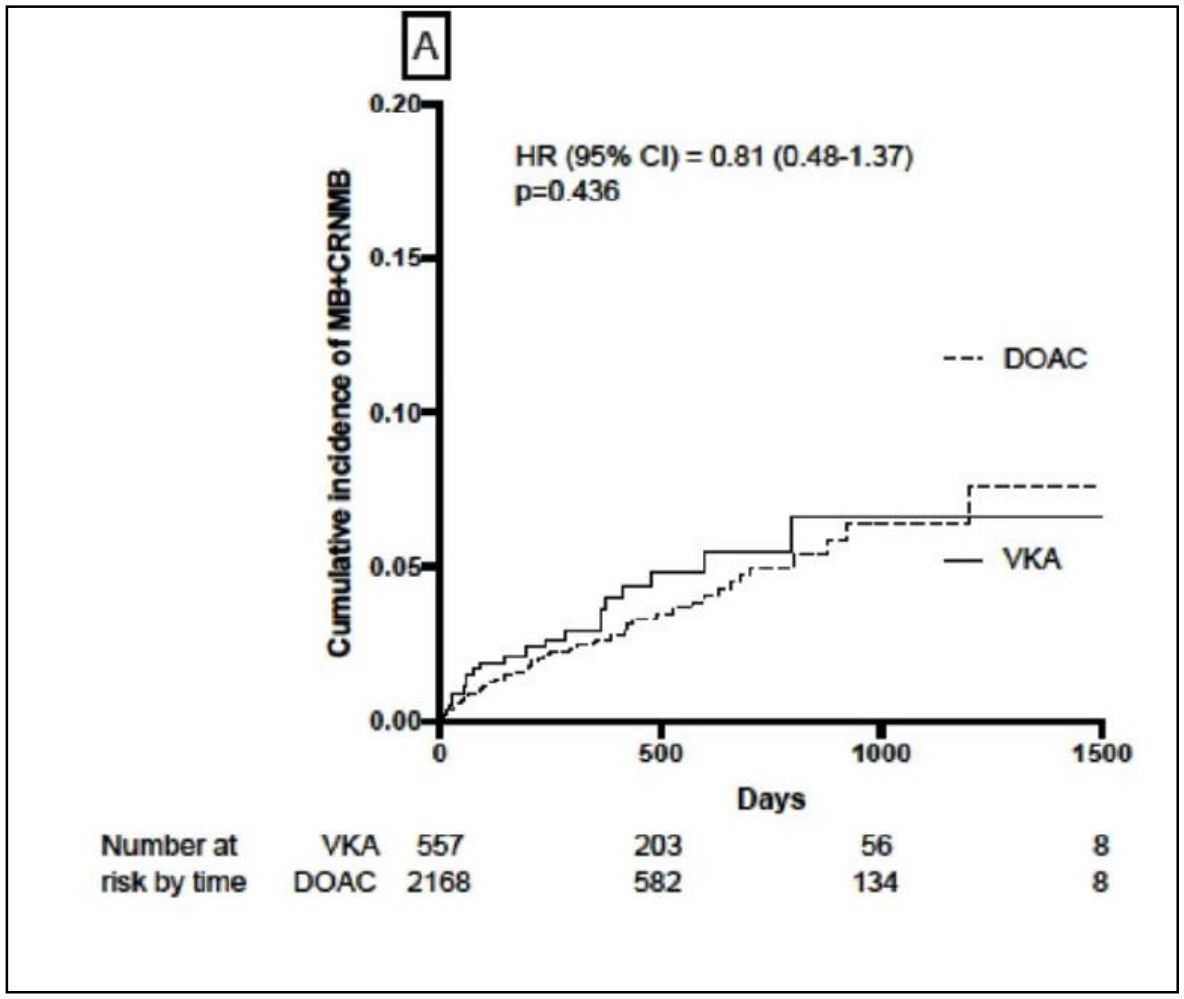
n (%)	DOAC cohort 2170 (79.5)	VKA cohort 558 (20.5)	P value
Male, n (%)	1115 (51.4)	269 (48.2)	NS
Age, median (IQR), years	68 (52–78)	69 (53–79)	NS
Age classes, n (%)			
<65 years	975 (44.9)	236 (42.3)	NS
65–74 years	503 (23.2)	130 (23.3)	NS
≥75 years	692 (31.9)	192 (34.4)	NS
Creatinine, mg/dL, median (IQR)	0.90 (0.76–1.0)	0.90 (0.75–1.1)	NS
Creatinine >1.5 mg/dL, n (%)	63 (2.9)	45 (8.1)	<0.001
Creatinine clearance, n (%)			
<30 mL/min	32 (1.5)	32 (5.7)	<0.001
30–59 mL/min	493 (22.7)	148 (26.5)	NS
60–90 mL/min	741 (34.1)	179 (32.1)	NS
>90 mL/min	890 (41.0)	199 (35.7)	0.023
Missing	14 (0.7)	–	
Type of VTE event, n (%)			
DVT	**1331 (61.3)**	**280 (50.2)**	<0.001
Proximal	1006 (75.6)	175 (62.5)	<0.001
Distal	277 (20.8)	100 (35.7)	<0.001
Missing	48 (3.6)	5 (1.8)	
DVT+PE	**460 (21.2)**	**147 (26.3)**	0.01
Proximal+PE	373 (81.1)	95 (64.6)	<0.001
Distal+PE	73 (15.9)	48 (32.7)	<0.001
Missing	14 (3.0)	4 (2.7)	NS
Isolated PE	**379 (17.5)**	**131 (23.5)**	0.001

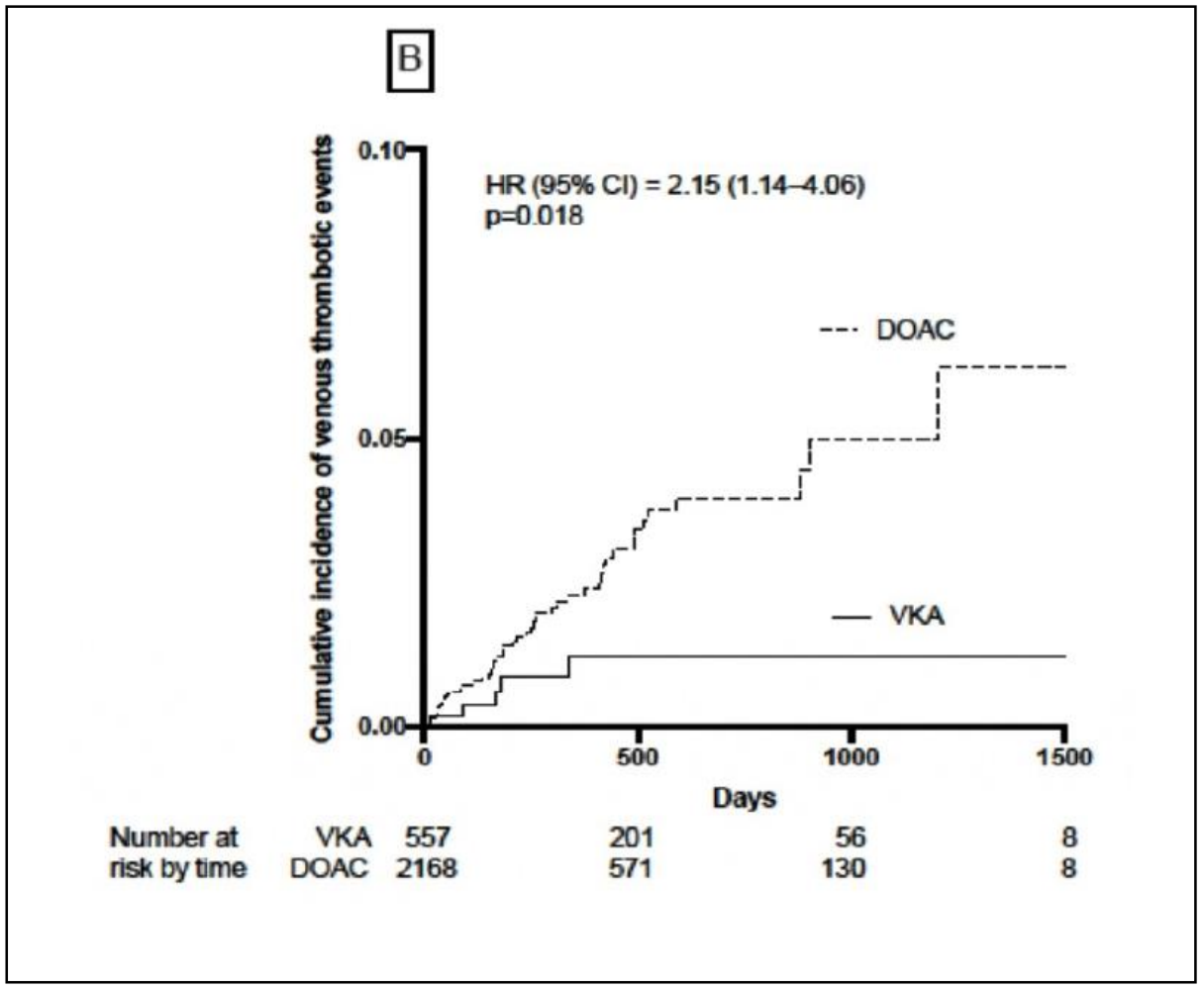
Nature of VTE events, n (%)			
Idiopathic	1429 (65.9)	394 (70.6)	0.035
Associated with weak RF	105 (4.8)	36 (6.5)	NS
Provoked by transient major RF	360 (16.6)	72 (12.9)	0.033
Provoked by permanent major RF	264 (12.2)	49 (8.8)	0.025
Cancer	94 (35.6)	31 (63.3)	0.001
Missing	12 (0.6)	7 (1.3)	NS
Charlson's score, median (IQR)	3 (2–5)	4 (2–6)	0.0001
Associated antiplatelet agents, n (%)	138 (6.4)	53 (9.5)	0.011
DOAC, all n=2170; low dose, 266 (12.3%)	**Total n (%)**	**Standard dose n (%)**	**Low dose n (%)**
Rivaroxaban (20 mg or 15 mg once daily)*	1317 (60.7)	1245 (57.4)	72 (3.3)
Apixaban (5 mg or 2.5 mg two times per day)	501 (23.1)	383 (17.6)	118 (5.4)
Dabigatran (150 mg or 110 mg two times per day)	189 (8.7)	157 (7.2)	32 (1.5)
Edoxaban (60 mg or 30 mg once daily)	163 (7.5)	119 (5.5)	44 (2.0)

Results

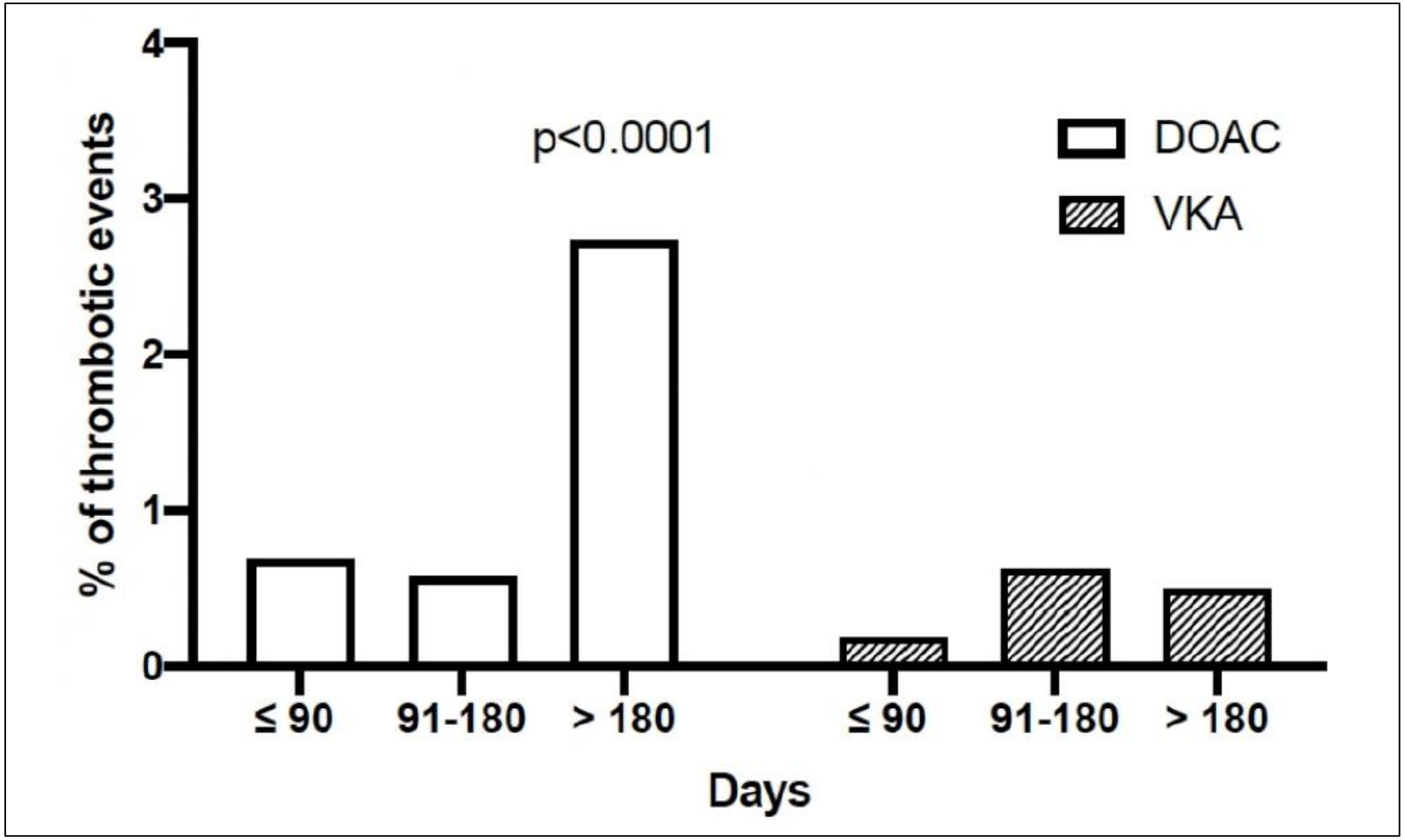
- Almost 80% of patients were treated with DOACs.
- The prevalence of symptomatic PE and impaired renal function was higher in patients receiving VKAs.
- Duration of anticoagulation was >180 days in approximately 70% of patients.
- Bleeding events were similar in both treatment groups.
- The overall eventuality of recurrence was significantly higher in DOAC cohorts versus VKA cohorts; the difference was almost completely due to recurrences occurring during extended treatment.
- All-cause mortality was higher in VKA-treated than in DOAC-treated patients.

Kaplan-Meier cumulative event rates for bleeding events (major bleeding + clinically relevant nonmajor bleeding) and venous thromboembolic recurrences in patients treated with DOAC or VKA





Incidence of thrombotic events grouped according to three time intervals of treatment with DOAC or VKA; the shown statistical significance is for the comparison between the rates recorded after 180 days of treatment with DOAC versus VKA.



Conclusions

- Italian centers treat most patients with VTE with DOACs and prefer VKA for those with more serious clinical conditions.
- Recurrences were significantly more frequent in DOAC-treated patients due to increased incidence after 180 days of treatment, probably due to reduced adherence to treatment.
- These results underline the importance of structured surveillance of DOAC-treated patients with VTE to strengthen treatment adherence during extended therapy.