IM - ORIGINAL

Unprovoked or provoked venous thromboembolism: not the prevalent criterion to decide on anticoagulation extension in clinical practice of various countries—the prospective, international, observational WHITE study

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Background

- The guidelines recommend initial anticoagulant treatment of deep vein thrombosis (DVT) of the lower limbs and/or pulmonary embolism (PE) for at least 3–6 months in all cases.

- At the end of the maintenance period, all patients with an acute VTE event should be evaluated for their risk of recurrence and of bleeding, and the attending physician must decide what to do next.

- However, little is known about the actual practice concerning this issue in countries of different geographic areas, differing for socio-economic conditions and healthcare systems.

AIM of the study

The primary objective of the study was to assess the clinicians' decisions on the modality to manage the secondary prevention in patients after a first VTE episode, at the end of the maintenance period of anticoagulation considered standard, and the reasons guiding the physician's decision.

Methods

- WHITE was a multicenter, multinational, observational, noninterventional, investigators-initiated, no-profit, prospective study.

- 1240 patients from 79 Internal or Vascular clinical centers in 7 countries (China, Czechia, Poland, Portugal, Russia, Slovakia, and Tunisia) were involved.

- Patients of any ethnicity, male and female, aged ≥ 18 years, were eligible for the study if treated with anticoagulant therapy for 3–12 months following a documented first-ever event of provoked or unprovoked DVT of the lower limbs and/or of PE.
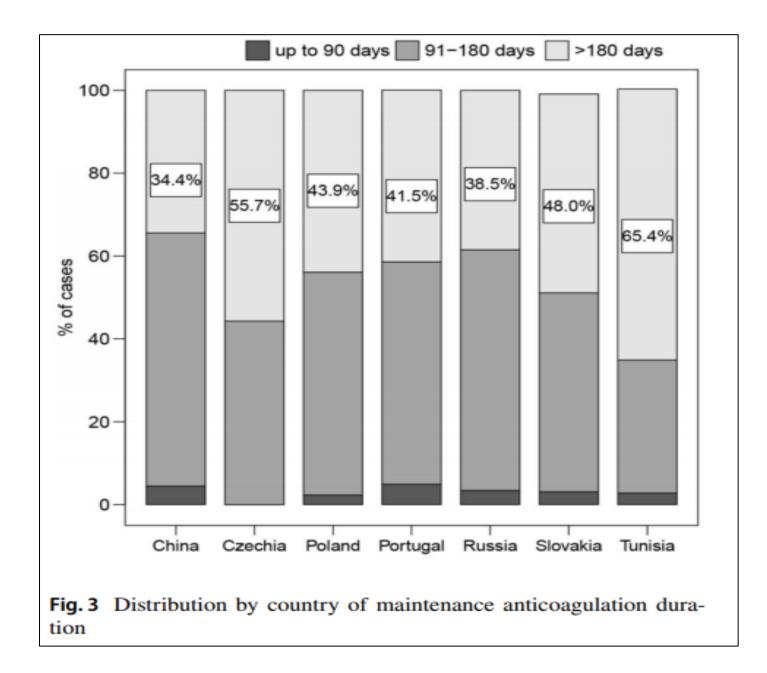
Results (I)

- The distribution of the index event was significantly different by country (P < 0.001), essentially because the rate of the reported PE in the patients included into the study in Czechia was 1.6 to 3 times greater than in all other countries (P = 0.005).

- The VTE events were classified unprovoked in 696 cases (58%) and provoked in the remaining cases.

- The distribution of treatments privileged the direct oral anticoagulants (DOACs), which were used in 86–94% of cases in China, Poland, Portugal, Russia, and Czechia, 52% in Slovakia and were not used in Tunisia, where VKAs were instead used in 86% of subjects.

Table 1 Active clinical sites and enrolled patients in each country; demographic information, clinical characteristics of included patients and type of index events

Country	Active sites, n	Patients enrolled, N. (%)	Females, N (%w)	Age, years mean±SD (N)	BMI mean±SD (N)	Hypert., N (%w)	Diabetes, N (%w)	IHD, N (%w)	CVD, N (%w)	Kidney failure, N (%w)	Smoking, N (%w)	Proximal DVT (±distal DVT) n. (%w)	Isolated distal DVT n. (%w)	PE (±DVT) n. (%w)
China	15	317 (25.6%)	162 (51.1%)	55.6±15.1 (N=317)	24.97±3.36 (N=312)	90 (28.4%)	40 (12.6%)	22 (6.9%)	14 (4.4%)	1 (0.3%)	57** (18.1%)	148 (46.7%)	134 (42.3%)	35 (11.0%)
Czechia	5	70 (5.6%)	40 (57.1%)	54.2±15.7 (N=70)	27.93±5.14 (N=67)	27 (38.6%)	8 (11.4%)	3 (4.3%)	1 (1.4%)	0 (0.0%)	16 (22.9%)	20 (28.6%)	29 (41.4%)	21 (30.0%)
Poland	20	133 (10.7%)	59 (44.4%)	56.5±16.7 (N=133)	28.38±5.12 (N=114)	57 (42.9%)	13 (9.8%)	15 (11.3%)	1 (0.8%)	7 (5.3%)	17* (12.9%)	47 (35.3%)	55 (41.3%)	31 (23.3%)
Portugal	5	41 (3.3%)	22 (55.0%)	58.8±17.9 (N=41)	28.32±4.39 (N=38)	18 (43.9%)	4 (9.8%)	2 (4.9%)	1 (2.4%)	1 (2.4%)	6 (14.6%)	24 (58.5%)	13 (31.7%)	4 (9.8%)
Russia	22	501 (40.4%)	253 (50.6%)	57.4±14.9 (N=501)	28.17±5.37 (N=499)	229 (45.7%)	48 (9.6%)	84 (16.8%)	16 (3.2%)	4 (0.8%)	111§ (24.0%)	328 (65.5%)	132 (26.3%)	41 (8.2%)
Slovakia	7	98 (7.9%)	47 (48.0%)	56.7±15.2 (N=98)	28.46±4.00 (N=97)	42 (42.9%)	9 (9.2%)	6 (6.1%)	1 (1.0%)	2 (2.0%)	11 (11.2%)	49 (50.0%)	42 (42.9%)	7 (7.1%)
Tunisia	5	80 (8.5%)	44 (55.7%)	56.4±17.4 (N=80)	29.96±5.37 (N=76)	22 (27.5%)	15 (18.8%)	4 (5.0%)	1 (1.3%)	3 (3.8%)	17* (21.5%)	36 (45.0%)	25 (31.3%)	19 (23.8%)
Total	79	1240 (100.0%)	627 (50.7%)	56.6±15.5 (N=1240)	27.49±4.99 (N=1203)	485 (39.1%)	137 (11.0%)	136 (11.0%)	35 (2.8%)	18 (1.5%)	235 (19.6%)	652 (52.6%)	430 (34.7%)	158 (12.7%)
Statistics P			0.582[b]	0.512[a]	<0.001[a]	<0.001[b]	0.288[b]	<0.001[b]	0.264[b]	0.001[b]	0.016[b]	<0.001[b]		

Results (II)

- On average, the maintenance anticoagulation had lasted approximately 6 months at the time of the decision; however, it was the shortest in China (mean±SD: 164±83 days) and the longest in Tunisia (205±68) and Czechia (196±82).

- Only very few patients (none in Czechia) received a maintenance anticoagulation for < 90 days, while a treatment for > 180 days was given to a proportion of patients ranging from 34.4% (China) to 65.4% (Tunisia).

Fig. 3 Distribution by country of maintenance anticoagulation duration

Results (III)

- In about 20% of patients, the attending physician decided to stop the anticoagulant treatment (Table 2); an extension of anticoagulation (whatever the drug used) was decided in more than half of the patients (51.3%), whereas in 28.1% of them, an antithrombotic drug (sulodexide or antiplatelet) was prescribed.

- Anticoagulation was stopped in 15.4% and 28.9% and continued in 51.7% and 49.3% of patients who had unprovoked or provoked events, respectively.

- Sex, age and the presence of cardiovascular risk factors did not significantly affect the choice of the regimen.

- The odds to continue with anticoagulation rather than stopping were higher among subjects with PE vs. those with only DVT [2.71 times (1.59–4.61; P<0.001)] and in those with concomitant diseases [1.49 (1.07–2.06; P=0.018)].

Table 3 Decisions about the treatment after the maintenance phase

Decision	Event	Unprovoked,* N=696	Provoked,* N=509	P (chi-square)	Proximal±distal DVT, N=652	PE with DVT, N=123	Isolated distal DVT, N=430	PE without DVT, N=35	P (chi-square)	All cases**, N=1240
Anticoagulant treatment was stopped, N (%)		107 (15.4%)	147 (28.9%)	<0.001	86 (13.2%)	20 (16.3%)	148 (34.4%)	1 (2.9%)	<0.001	
Anticoagulation was extended, N (%)		360 (51.7%)	251 (49.3%)	0.408	379 (58.1%)	73 (59.3%)	159 (37.0%)	25 (71.4%)	<0.001	
Antithrombotic drugs were prescribed, N (%)		229 (32.9%)	111 (21.8%)	<0.001	187 (28.7%)	30 (24.4%)	123 (28.6%)	9 (25.7%)	0.778	
Anticoagulant treatment was stopped, N (%)	Cases	107	147							255
	proximal±distal DVT	41 (38.3%)	45 (30.6%)	0.378						86 (33.7%)
	isolated distal DVT	57 (53.3%)	91 (61.9%)							148 (58.0%)
	DVT+PE	9 (8.4%)	11 (7.5%)							20 (7.8%)
	PE without DVT	–	–							1 (0.4%)
Anticoagulation was extended, N (%)	Cases	360	251							636
	proximal±distal DVT	225 (62.5%)	154 (61.4%)	0.951						379 (59.6%)
	isolated distal DVT	93 (25.8%)	66 (26.3%)							159 (25.0%)
	DVT+PE	42 (11.7%)	31 (12.4%)							73 (11.5%)
	PE without DVT	–	–							25 (3.9%)
Antithrombotic drugs were prescribed, N (%)	Cases	229	111							349
	proximal±distal DVT	130 (56.8%)	57 (51.4%)	0.191						187 (53.6%)
	Isolated distal DVT	76 (33.2%)	47 (42.3%)							123 (35.2%)
	DVT+PE	23 (10.0%)	7 (6.3%)							30 (8.6%)
	PE without DVT	–	–							9 (2.6%)

Conclusions (I)

- These data show how widespread is the current DOAC use for VTE treatment in many countries (when available) and confirm the large preference for DOACs by treating physicians and patients as well.

- In line with the international guidelines, very few patients received a maintenance anticoagulant treatment for less than the recommended 90 days; however, a consistent proportion of all patients (about 40%) were treated for >180 days before being considered for possible extension of anticoagulation.

- Anticoagulant treatment was stopped in only one-fifth of all included patients, whereas anticoagulant therapy was extended in about half of them, and an indication for continuing treatment using various antithrombotic agents was given to the remaining patients.

Conclusions (II)

- In contrast with what suggested by experts and international guidelines, the therapeutic decisions did not seem to be predominantly influenced by the unprovoked or provoked nature of the index event.

- This result indicates that many physicians in the everyday clinical practice prefer not to comply with a pretended obligation dictated by the classification as unprovoked/provoked event, but rather to try and assess the multifactorial individual recurrence risk.

- Finally, in real-life settings, physicians seem to be worried about completely stopping any treatment after the maintenance phase and limit this decision only to patients considered at low risk of recurrence.