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VENOUS DISEASE

EDITOR'S CHOICE

Recurrences and bleeding during extended treatment of patients with venous thromboembolism: results of the international, prospective, observational WHITE study

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ABSTRACT

Background: Little data are available on real-life long-term treatments after a venous thromboembolism (VTE), and on recurrent VTE or bleeds events during treatments.

Methods: We investigated the complications occurring during follow-up (FU) in VTE patients who had received the treatment decisions given by the clinical centers, active in 7 countries (China, Czechia, Poland, Portugal, Russia, Slovakia, Tunisia), which participated in the international, prospective, observational WHITE study.

Results: FU information was collected in 1004 patients, recruited by 62 clinical centers (17 centers did not participate in FU collection). Extended treatments were proposed to 811 patients: direct oral anticoagulants (DOACs) (475), sulodexide (202), antiplatelet agents (73), vitamin K antagonists (VKAs) (45), low molecular weight heparin (LMWH) (16). All specific treatments were stopped in the remaining 193 patients. Patients who during FU used treatments different than those prescribed by the local investigators (263) or for other causes (26) were excluded from analysis. 50 primary events occurred throughout 1044 years FU in 715 patients, 4.8

incidence (×100 patient-years) [3.8 for recurrences, and 0.96 for bleeding (major or clinically relevant)]. Primary event incidence differed according to treatments (LMWH=33.3, antiplatelets =7.6, VKAs = 6.1, DOACs = 4.7, sulodexide = 4.2, all treatment stopped = 2.5), and differed across the involved countries.

Conclusions: DOACs were the most used drugs for extended treatments. Overall, the rate of primary events during FU was low. The investigators identified patients at low risk of recurrence and high bleeding risk. Sulodexide use for secondary prevention deserves further studies.

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Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and/or pulmonary embolism (PE), tends to recur. The risk of recurrence differs among patients according to the nature of the index event and the characteristics of the patient. The risk of recurrence is low when the event is provoked by surgery, intermediate if provoked by a nonsurgical risk factor, and high if unprovoked.[1] Some patient characteristics are also important for assessing the risk of recurrence such as sex (the risk is higher in males, especially young ones), previous VTE events, thrombophilic alterations, the presence of important diseases (cancer), obesity and others.[2] Anticoagulant treatment is highly effective in reducing the risk of recurrence, but its protective effect is lost after discontinuation.[3, 4] The optimal duration of anticoagulant therapy after a first VTE is still matter of some debate since treatment is inevitably associated with a persistent risk of bleeding. International guidelines recommend anticoagulant treatment for no less than three months in all patients with VTE with possible extended treatment (beyond the first 3-6 months and without a pre-established date for discontinuation) for patients with unprovoked events provided their risk of bleeding is not high.[5] More recent guidelines, focusing on treatment of PE, recommend considering extended anticoagulation for patients whose index event was unprovoked or associated with a minor and transient risk factor.[6] Many vascular and family doctors, however, do not comply with these recommendations. A recent observational study showed that the decision of treating physicians to stop or extend anticoagulant treatment in VTE patients was not exclusively swayed by the secondary or unprovoked etiology of the index event but by a series of other factors, including the individual clinical conditions of patients and the presence of risk factors for either bleeding or thrombosis.[7] The multinational, prospective, observational WHITE study (WHIch decision after a first venous ThromboEmbolism),[8] which included 1240 VTE patients enrolled in 79 Internal or Vascular clinical centers in 7 countries (China, Czechia, Poland, Portugal, Russia, Slovakia, and Tunisia), aimed at analyzing how this issue was tackled in everyday clinical practice in countries where socio-economic conditions and healthcare systems differed widely. The study showed that anticoagulation was stopped in 20% of subjects and extended in about 50%, regardless of whether the event was unprovoked or provoked, while remaining patients were shifted to antithrombotic drugs (mainly sulodexide or aspirin). The present study analyzes the primary outcomes (recurrent VTE, bleeds, deaths) recorded in the WHITE Study patients during a follow-up of at least one year after the maintenance treatment phase post VTE, particularly investigating the relationship between the occurrence of events and the type of treatments recommended by the attending physicians.

Materials and methods

Study design, participants, and study population

As detailed elsewhere,[8] the WHITE study was a multicenter, multinational, observational, non-interventional, investigator-initiated, no-profit, prospective study (ClinicalTrials.gov Identifier: NCT04646993). Its aim was to evaluate the decisions taken by clinicians at the end of maintenance treatment in subjects with a first-ever DVT event of the lower limbs and/or pulmonary embolism, and to analyze the clinical events occurring during at least one year of follow-up following therapeutic decision. The

study was an independent research initiative promoted by the "Arianna Anticoagulazione" Foundation (Bologna, Italy), managed by a Core Team of vascular-expert professionals (the detailed list of the study boards and their compositions is shown in Supplementary Digital Material 1: Supplementary Table I, II). One Country Coordinator for each active country invited local clinical vascular centers to participate in the study and collaborated with local contract research organizations (CRO) to obtain authorization to the study from the national Health Authority Boards and the local Ethics Committees. Patients, aged ≥18 years, were enrolled in the study during maintenance treatment following diagnosis of a first-ever DVT and/or PE event. Patients were eligible if treated with anticoagulant therapy for 3-12 months following the VTE event. Subjects provided written informed consent before inclusion in the study. Exclusion criteria were age <18 years, thrombosis in other sites, impossibility, or unwillingness to give written informed consent (complete list of inclusion/exclusion criteria in the Protocol, available on request). Each subject had the right to refuse continuing the study at any moment and without justification. All decisions regarding the type, dose, and duration of patient treatment before and after inclusion in the study were left to the attending physician's discretion. The primary objective of WHITE study was to investigate clinician decisions on treatment management of patients at the end of the maintenance period of anticoagulation, and the reasons informing them. The results regarding the primary objective have been the object of recently published articles[8-10] The secondary objective, and subject of the present article, was the recording of thromboembolic or bleeding complications and of deaths occurring during follow-up. The protocol had aimed to set the period of follow-up after termination of standard anticoagulation at up to 2 years but, due to the general difficulties linked to the COVID-19 pandemic, it was set at least one year. Primary outcomes of the study included proximal and/or distal venous thrombotic recurrences, PE, major bleeding (MB) or clinically relevant non major bleeding (CRNMB), and death due to thrombotic or bleeding complications. Secondary outcomes were all thrombotic events in sites other than lower limb DVTs, arterial events, superficial vein thrombosis (SVT) and deaths for any cause; minor bleeds were also recorded. All the investigators who took part in the WHITE study recorded patient information in structured case report form (CRF) on a web-based central electronic database (designed and managed by Officinebit, Melide, Switzerland). The collected information was controlled by a dedicated study-monitor of the Foundation (C.M.). All patients were assigned a unique identifier, and data were anonymized before inclusion in the CRF.

Statistical analysis

All variables were summarized using the usual descriptive techniques. Demographic and clinical variables were compared, when needed, with the χ^2 test for nominal variables, and *t*-test or ANOVA for the continuous variables. The impact of demographic and prognostic factors (including country) on choice was tested by multivariable logistic regression analysis. Data were analyzed with SPSS version 24 (SPSS Inc., Chicago, IL, USA) integrated for specific items with R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

The present report analyzes the follow-up information gathered from patients included in the WHITE study from 62 clinical sites in the seven countries involved (the detailed list of the participating centers is shown in Supplementary Digital Material 2: Supplementary Text File 1). Seventeen out of the 79 clinical centers, originally participating in the study, decided against taking part in the second phase of the study (regarding the follow-up after the treatment decision) and did not collect data on follow-up of their patients. Information on follow-up (for at least one year) was collected from 1004 patients (510 females) out of the 1240 originally included in the WHITE study. The mean (±SD) age of patients was 56 (±16) years. Their demographic information and clinical characteristics are reported in Table I. The index events were classified by treating physicians as unprovoked or provoked in 581 (57.9%) and 423 (42.1%) patients, respectively. The classification differed significantly across countries ($P<0.001$; χ^2), with the proportion of provoked VTE significantly above average in the Czech Republic and China. The index event was proximal DVT (±distal DVT) in 54.3%, isolated distal DVT in 31.7%, DVT+PE in 10.6%, and isolated PE in 3.4% of patients investigated. Many patients (N. 711 [70.8%]) were given compression ultrasonography (CUS) of lower limb deep veins on average 15 days (95% CI: 12-18) before the decision visit (approximately 6 months of anticoagulation after the index events). Residual vein obstruction (RVO) was detected in 491 (69.0%) patients, more frequently in the popliteal veins. The proportion of subjects with RVO did not differ according to whether index events were classified as unprovoked or provoked.

Table I.—*Demographic information and clinical characteristics of the 1004 patients with follow-up included in the WHITE study.*

Country	Females, N. (%)	Age, years, mean±SD	BMI, mean±SD (N)	Hypertension, N. (%)	Diabetes, N. (%)	IHD, N. (%)	CVD, N. (%)	CRF, N. (%)	Smoking, N. (%)
China, N.=258	130 (50.4%)	55±15	25.04±3.3 (254)	70 (27.1%)	32 (12.4%)	20 (7.8%)	13 (5.0%)	1 (0.4%)	46 (17.8%)
Czechia, N.=67	37 (55.2%)	55±16	27.99±5.2 (64)	27 (40.3%)	8 (11.9%)	3 (4.5%)	1 (1.5%)	0 (0.0%)	16 (23.9%)
Poland, N.=128	56 (43.8%)	56±17	28.43±5.1 (109)	56 (43.8%)	13 (10.2%)	13 (10.2%)	1 (0.8%)	6 (4.7%)	17* (13.4%)
Portugal, N.=33	19 (57.6%)	60±17	27.93±4.0 (31)	15 (45.5%)	3 (9.1%)	2 (6.1%)	1 (3.0%)	1 (3.0%)	5 (15.2%)
Russia, N.=415	215 (51.8%)	57±15	28.03±5.0 (414)	187 (45.1%)	40 (9.6%)	68 (16.4%)	12 (2.9%)	3 (0.7%)	89§ (23.7%)
Slovakia, N.=23	9 (39.1%)	57±16	28.27±2.8 (22)	13 (56.5%)	2 (8.7%)	2 (8.7%)	0 (0.0%)	0 (0.0%)	1 (4.3%)
Tunisia, N.=80	44 (55.0%)	56±17	29.96±5.4 (76)	22 (27.5%)	15 (18.8%)	4 (5.0%)	1 (1.3%)	3 (3.8%)	17* (21.5%)
Total, N.=1004	510 (50.8%)	56±16	27.44±4.8	390 (38.8%)	113 (11.3%)	112 (11.2%)	29 (2.9%)	14 (1.4%)	191 (19.8%)
Statistics (P value)	0.460[b]	0.748[a]	<0.001[a]	<0.001[b]	0.378[b]	0.001[b]	0.224[b]	0.005[b]	0.058[b]

Percentage (%) denotes percent within country, *i.e.*, proportion of the total number of subjects recruited in that country with the indicated characteristic.
BMI: Body Mass Index in kg/m^2; IHD: ischemic heart disease; CVD: cerebrovascular disease; CRF: chronic renal failure.
*One case N/A; §39 cases N/A; [a]ANOVA; [b]χ^2.

Treatment decision for extended phase (during follow-up)

Treatments prescribed at the end of maintenance period were often different to those used during maintenance phase (Table II). The decision to continue anticoagulation treatment was taken in 536 patients (53.4%), with DOACs used in most cases (475 [88.6%]), followed by VKAs (45) and LMWH (16). All specific treatments were stopped in 193 patients (19.2%), whereas treatment was shifted to antithrombotic drugs in 275 (27.4%) cases. Overall, there was a reduction in the prescription of DOACs, VKAs, and LMWH, whereas the prescription of antithrombotic agents (sulodexide [202] and antiplatelet agents [73]) increased. The decision to stop treatment during follow-up was more frequent in patients whose index event was provoked (P<0.0001), in cases of isolated distal DVT *vs.* all other sites (P<0.0001) and in patients without RVO (P<0.0001) (Table III).

Outcomes during follow-up

Following pre-established criteria for analyzing outcomes during follow-up, patients (N. 263), who during follow-up used treatments different to those prescribed by the local investigators, were censored since they did not complete follow-up using the treatment prescribed by the local investigator. Subjects who were pregnant (N. 2) or were lost to follow-up (N. 24; 2.4%) were also censored. No primary outcomes were recorded in any of these patients. Seven hundred and fifteen patients continued during follow-up the treatment prescribed by the treating investigators. Overall (Table IV), across a follow-up of 1044 years (mean±SD = 533±254 days), a total of 50 primary outcomes occurred (4.8×100 patient-years); 40 events were venous thrombotic recurrences (3.8×100 patient-years), whereas 5 MB and 5 CRNMB events were recorded (0.96×100 patient-years). Secondary outcomes during follow-up were: 2 superficial vein thromboses, 4 arterial events and 12 minor bleeds; 32 deaths occurred (22 for COVID-19 infection, 5 for cancer, 1 for acute myocardial infarction, 1 for acute heart failure, and 3 for unspecified reasons), while no deaths were attributable to thrombotic or bleeding events. The incidence of primary outcomes was not homogeneous across patients treated differently during follow-up (Table IV): the incidence of recurrence was highest in patients receiving LMWH (33.3×100 patient-years), followed by that in

Table II.—*Treatment changes from maintenance and extended treatment phases.*

Treatments during follow-up, N	Treatments during maintenance phase, N.				
	DOACs, N.=819	VKAs, N.=139	LMWH, N.=29	Sulodexide, N.=5	Antiplatelets*, N.=12
DOACs, N.=475	454	16	2	/	3
VKAs, N.=45	2	43	/	/	/
LMWH, N.=16	1	/	15	/	/
Sulodexide, N.=202	163	25	9	5	/
ASA, N.=68	39	21	1	/	7
Clopidogrel, N.=5	3	/	/	/	2
All specific treatments stopped, N.=193	157	34	2	/	/

*Ten patients were treated with ASA, and 2 patients with clopidogrel.

TABLE III.—*Treatments prescribed at the end of maintenance phase to the 1004 patients with follow-up. The treatments are related to the nature (unprovoked/provoked), site of index events, and presence/absence of residual vein obstruction at compression ultrasonography investigation performed at the end of maintenance phase in 711 patients.*

	DOACs, N.=475 (47.3%)	VKAs, N.=45 (4.5%)	LMWH, N.=16 (1.6%)	Sulodexide, N.=202 (20.1%)	Antiplatelets*, N.=73 (7.3%)	All treatments stopped, N.=193 (19.2%)
Unprovoked, N.=581	282 (48.5)	24 (4.1)	2 (0.3)	145 (25.0)	44 (7.6)	84 (14.5)
Provoked, N.=423	193 (45.6)	21 (4.9)	14 (3.3)	57 (13.5)	29 (6.9)	109 (25.8)
Proximal DVT, N.=546	282 (51.7)	29 (5.3)	10 (1.8)	128 (23.4)	26 (4.8)	71 (13.0)
Isolated distal DVT, N.=318	109 (34.3)	10 (3.1)	5 (1.6)	57 (17.9)	33 (10.4)	104 (32.7)
DVT+PE, N.=106	63 (59.4)	3 (2.8)	1 (0.9)	15 (14.2)	7 (6.6)	17 (16.1)
Isolated PE, N.=34	21 (61.8)	3 (8.8)	0 (0.0)	2 (5.9)	7 (20.6)	1 (2.9)
RVO#						
Yes, N.=491	279 (56.8)	20 (4.1)	5 (1.0)	106 (21.6)	24 (4.9)	57 (11.6)
No, N.=220	45 (20.5)	5 (2.3)	3 (1.4)	67 (30.4)	22 (10.0)	78 (35.4)

Data are shown as N. (%).
DOAC: direct oral anticoagulants; DVT: deep vein thrombosis; LMWH: low molecular weight heparin; PE: pulmonary embolism; VKAs: vitamin K antagonists; RVO: residual vein obstruction; CUS: compression ultrasonography investigation.
#CUS was done in 711 patients; *68 patients treated with ASA; 5 patients treated with clopidogrel.

TABLE IV.—*Overall incidence of outcomes occurring during follow-up in the 715 patients who continued the same treatment prescribed by the participant clinical centers. Patients censored (N. 289) for having shifted to treatments different than prescribed, or for other causes, are not included in the analysis.*

	All patients, N.=715, FU=1044 y	DOACs, N.=310, FU=426 y	VKAs, N.=30, FU=49 y	LMWHs, N.=11, FU=15 y	Sulodexide, N.=154, FU=237 y	Antiplatelets*, N.=45, FU=79 y	All treatments stopped, N.=165, FU=238 y
All primary outcomes	50 (4.8)	20 (4.7)	3 (6.1)	5 (33.3)	10 (4.2)	6 (7.6)	6 (2.5)
Venous thrombotic events#	40 (3.8)	17 (4.0)	1 (2.0)	5 (33.3)	10 (4.2)	5 (6.3)	2 (0.8)
Major bleeding events	5 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.3)	4 (1.7)
CRNMB	5 (0.5)	3 (0.7)	2 (4.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Secondary outcomes							
Superficial vein thromboses	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)	0 (0.0)	0 (0.0)
Arterial events	4 (0.4)	1 (0.2)	1 (2.0)	0 (0.0)	2 (0.8)	0 (0.0)	0 (0.0)
Minor bleeding events	12 (1.1)	9 (2.1)	1 (2.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.4)
Death**							
Cancer	5 (0.5)	2 (0.5)	0 (0.0)	1 (6.7)	2 (0.8)	0 (0.0)	0 (0.0)
Other	27§ (2.6)	21 (4.9)	1 (2.0)	0 (0.0)	1 (0.4)	0 (0.0)	4 (1.7)

Data are shown as N (×100 pt-y).
*Forty received ASA, and 5 clopidogrel; #including proximal or distal DVT, DVT+PE, isolated PE; **no death was attributed to thrombotic or bleeding events; §22 patients died for COVID-19 infection; 2 for arterial disease; 3 for unspecified cause.

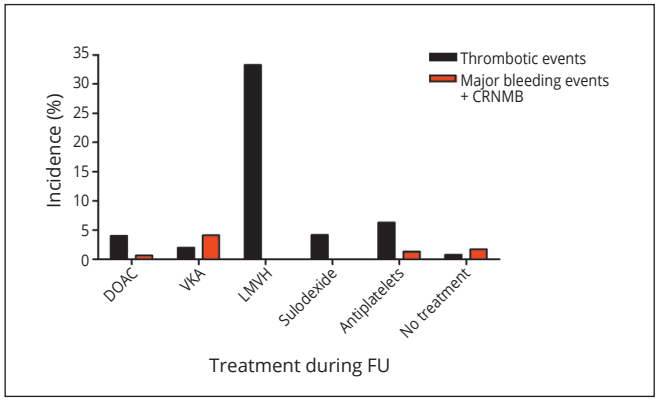

Figure 1.—Incidence of primary outcomes (thrombotic and bleeding events) recorded in the patients during follow-up in relation to the treatment. FU: follow-up.

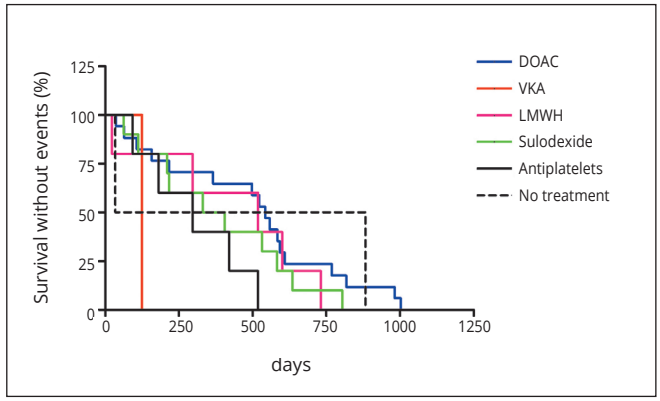

Figure 2.—Kaplan-Meier curve for venous thrombotic events recorded during follow-up in the patients in relation to the different treatments received.

TABLE V.—*Number and incidence (×100 pt-y) of primary outcomes occurred during follow-up in the 715 patients who used during follow-up the same treatment prescribed at the end of the maintenance phase.*

Country	Variables	All patients	DOACs	VKAs	LMWH	Sulodexide	Antiplatelets	All treatments stopped
China	Number of patients	213	128	6	3	18	12	46
	FU, years	278	161	8	5	27	18	59
	Outcomes, N (×100 pt-y)	17 (6.1)	14 (8.7)	0 (0.0)	1 (20.0)	1 (3.7)	0 (0.0)	1 (1.7)
Czechia	Number of patients	52	5	0	1	15	7	24
	FU, years	97	10	0	0.06	27	15	46
	Outcomes, N. (×100 pt-y)	7 (7.2)	0 (0.0)	0 (0.0)	1 (1666.6)	3 (11.1)	1 (6.7)	2 (4.3)
Poland	Number of patients	70	37	1	5	14	6	7
	FU, years	116	64	2	7	20	10	14
	Outcomes, N. (×100 pt-y)	11 (9.5)	3 (4.7)	0 (0.0)	2 (28.6)	3 (15.0)	3 (30.0)	0 (0.0)
Portugal	Number of patients	17	10	1	0	0	1	5
	FU, years	23	15	1	0	0	1	4
	Outcomes, N. (×100 pt-y)	2 (8.7)	1 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)
Russia	Number of patients	291	128	7	1	89	5	61
	FU, years	401	172	14	1	130	8	77
	Outcomes, N. (×100 pt-y)	7 (1.7)	2 (1.2)	1 (7.1)	0 (0.0)	1 (0.7)	0 (0.0)	3 (3.9)
Slovakia	Number of patients	16	1	0	0	15	0	0
	FU, years	32	3	0	0	29	0	0
	Outcomes, N. (×100 pt-y)	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.4)	0 (0.0)	0 (0.0)
Tunisia	Number of patients	56	1	15	1	3	14	22
	FU, years	98	1	24	2	5	28	38
	Outcomes, N. (×100 pt-y)	5 (5.1)	0 (0.0)	2 (8.3)	1 (50.0)	1 (20.0)	1 (3.6)	0 (0.0)
P value (χ^2 test)		0.001	0.117	0.875	0.482	0.004	0.005	0.645

FU: follow-up; pt-y: patient-years.

patients treated with antiplatelets (6.3×100 patient-years), sulodexide (4.2×100 patient-years), and DOACs (4.0×100 patient-years); it was lowest in patients who stopped all forms of treatment (0.8×100 patient-years) (Figure 1). Figure 2 shows the Kaplan-Meier curves of venous thrombotic events occurring during follow-up in relation to the different treatments. The rates of primary outcomes differed significantly across the countries (Table V), ranging from 1.7×100 patient-years for patients in Russia, to 9.5×100 patient-years for those enrolled in Poland.

Discussion

The international, prospective, observational WHITE study aimed at analyzing: 1) which treatment decisions were taken by participant clinicians (and the reasons for the decisions) regarding extension of treatment after initial and maintenance phases in subjects with a first-ever event of DVT of the lower limbs and/or pulmonary embolism across 7 countries; and 2) which complications (thrombotic or hemorrhagic) occurred after the treatment decision during follow-up of patients, and the relationship between complications and treatments taken by patients. The results of part 1) of the study have been described elsewhere,[8-10] while the present report deals with the complications occurring during follow-up of patients. Of the 1004 patients whose follow-up information was collected on the central database at the end of the study (December 2021), 263 (26.2%) had changed the treatment prescribed by the investigators at the end of the maintenance phase; these patients were excluded from further analysis. These data indicate a widespread tendency of patients (or physicians) to shift from one treatment to another long term after a VTE event. Overall, 50 primary outcomes (including venous thrombotic recurrences, MB, and CRNMB) occurred during the 1044 years of follow-up of the 715 patients who stuck to the same treatment prescribed by the treating participant, for a cumulative incidence of 4.8×100 patient-years. DOACs were the most frequently prescribed drugs for extended treatment among patients included in the study; this confirms the large and increasing use of these anticoagulant agents for acute and long-term treatment of VTE patients in many countries.[8] The use of DOACs was not dependent on the unprovoked or provoked nature of the index events and was lower in patients presenting with isolated distal DVT and in those without residual vein obstruction. The incidence of recurrent thrombotic events in patients receiving extended treatment with DOACs was 4.0×100 patient-years, with only 3 bleeding events (all CRNMB). Despite the much longer follow-up in the present study, the rate

of recurrent VTE events in patients extending anticoagulation with a DOAC was not much higher than that recently reported in a single-country study (Italy) in VTE patients treated with DOACs (4.0 *vs.* 2.9×100 patient-years, respectively).[11] The incidence of primary outcomes was highest in patients (just 11) treated long-term with LMWH (33.3×100 patient-years), followed by those receiving antiplatelet drugs (7.6×100 patient-years), or VKAs (6.1×100 patient-years). These findings can, at least in part, be accounted for by the specific clinical conditions of the relatively low number of selected patients. While the very high rate of events among patients treated with LMWH might be expected, given that this extended treatment is especially used in patients with cancer-associated VTE, it is clear that antiplatelet agents are not so good for extended treatment since they are associated with a high rate of thrombotic events (6.3×100 patient-years) and of bleeding events (1.3×100 patient-years). An important result of this study was the very low rate of recurrence (0.8×100 patient-years) in patients stopping all forms of treatment - the lowest of all. A recent systematic review and meta-analysis of studies on VTE patients after unprovoked index events[12] reported a rate of VTE recurrence of 10.1% one year after discontinuing anticoagulation. To try to understand the reasons for such a big difference, it needs to be borne in mind that: first, the present study included a significant proportion of patients whose index events were provoked; second, almost 28% of the 715 patients received antithrombotic therapy during follow-up with sulodexide or antiplatelet drugs instead of simply stopping all treatment. These therapies may have helped lower the rate of VTE recurrence. While, in patients who had stopped all forms of treatment, the rate of recurrence was low, the rate of major bleeding was the highest (1.7×100 patient-years). These seemingly contrasting results indicate that treating clinicians were able to stop any treatment in patients they considered at high risk of bleeding or at very low risk of VTE recurrence; they often chose treatments different from anticoagulation (with a lower risk of bleeding) for secondary prevention in patients potentially at a persistent – though not very high – risk of VTE recurrence. Un unexpected result of the present study was the relatively high number of patients who received sulodexide for extended treatment (154/715, 21.5%). Except for Portugal, sulodexide was prescribed by the centers of all participant countries, especially Russia where more than 30% of patients received the drug. Our results show that the incidence of VTE recurrence in patients receiving sulodexide (4.2×100 patient-years) was almost the same as in patients treated with DOACs, without any bleeding complications. These data seem to be in line with the good results obtained in the SURVET trial,[13] where sulodexide, compared to placebo, halved the rate of VTE recurrences without major bleeding complications Furthermore, two recent meta-analyses have confirmed that sulodexide can be a good option for secondary prevention of VTE.[14, 15]

Limitations of the study

This study has important limitations. The participating clinical centers operated in seven countries that differed one from the other for socio-economics conditions and healthcare systems (including drug reimbursement policies) that were impossible to adjust for. The number of patients included in each country and examined for occurrence of events during follow-up is so limited that it is impossible to draw general conclusions on clinical practice in each country. This was an observational study, and all the treatment decisions were left to the attending physicians. Unfortunately, large part of the study was performed during the COVID-19 pandemic that may have influenced for many aspects the study. For all these reasons, the interpretation of our findings requires caution. We believe, however, that the study has also merits. In a "globalized" world, an effort to assess what is the prevalent approach to manage VTE patients, especially for secondary prevention, in the real-world setting of different countries is of value; furthermore, comparison of everyday therapeutic procedures used in the countries helps standardizing clinical practice. In summary, the most frequently used treatment in the 715 patients completing follow-up and sticking with the treatment proposed by the participant investigators was extended anticoagulant therapy with DOACs (43.3% of all patients); very few patients used other anticoagulants (VKAs [4.2%] or LMWH [1.5%]). The recommendation to stop all forms of treatment was given to 23.1% of patients, while the rest received a prescription of sulodexide (21.5%) or antiplatelet drugs (6.3%). During the 1044 years follow-up the overall incidence of primary outcomes was below 5%. Altogether, participant clinicians were able to identify patients at low risk of recurrence and at high risk of bleeding, and to stop treatment in these patients. Patients who received extended treatment with DOACs or sulodexide had a low and similar incidence of recurrent VTE without major bleeding complications.

Conclusions

Based on this prospective observation, an individual approach to the VTE risk of recurrence and of bleeding, to-

gether with an implementation of DOACs and sulodexide in the long-term antithrombotic therapy, seems to be effective and safe in the real-world setting. Further prospective management studies are needed to identify the best use of anticoagulants (DOACs) or antithrombotics (sulodexide) for secondary prevention in real-life conditions in patients after a VTE event.

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