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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

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ABSTRACT

Objective The proportion and characteristics of Italian patients affected by venous thromboembolism (VTE) treated with direct oral anticoagulants (DOACs) or vitamin K antagonists (VKAs), and complications occurring during follow-up.

Design 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 2962 years of follow-up were analysed.

Setting About 60 Italian anticoagulation and thrombosis centres participated in the observational START2-Register

Participants 2728 adult patients with VTE of a lower limb and/or pulmonary embolism (PE), with a follow-up after the initial phase treatment.

Interventions Patients could receive DOACs or VKAs; both prescribed by the National and Regional Health Systems for patients with VTE.

Outcomes measures Efficacy: rate of VTE recurrence (all thrombotic complications were also recorded). Safety: the rate of major and clinically relevant non-major bleeding events.

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 (HR 2.15 (1.14–4.06), p=0.018); the difference was almost completely due to recurrences occurring during extended treatment (2.73% DOAC vs 0.49% VKA, p<0.0001). All-cause mortality was higher in VKA-treated (5.9%) than in DOAC-treated patients (2.6%, p<0.001).

Conclusion Italian centres 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.

Strengths and limitations of this study

- The Survey on anticoagulaTed pAtients RegisTer (START2-Register) is an observational, prospective, multicentre study dedicated to collecting and analysing the clinical history of patients receiving anticoagulant or antithrombotic treatment in everyday clinical practice.
- All diagnostic and therapeutic decisions for patients included in the Register are left to the attending physicians.
- This study analysed patients included in the START2-Register for deep vein thrombosis of lower limbs and/or pulmonary embolism.
- As its aim was to investigate clinical follow-up, only those patients with a follow-up beyond the initial phase of anticoagulation treatment were analysed.
- Only patients included in the Register since January 2014 were assessed since in our country direct oral anticoagulants have only been allowed and reimbursed by the National and Regional Health Systems for treatment of venous thromboembolism as of that date.

INTRODUCTION

Venous thromboembolism (VTE), that includes deep vein thrombosis (DVT) of lower extremities and/or pulmonary embolism (PE), has long been treated with parenteral anticoagulant drugs overlapped with and followed by long-term oral administration of

vitamin K antagonists (VKA). According to the results of several randomised clinical trials, published between 2008 and 2013, four novel direct oral anticoagulants (DOACs)—dabigatran, rivaroxaban, apixaban and edoxaban—were found to be as effective and safe as standard therapy for the acute and long-term treatment of VTE.[1–6] In subsequent years, two of these agents (apixaban and rivaroxaban), proved to be useful in lower dosages for extended VTE therapy.[7] Beyond clinical trials, some real-life studies have also confirmed the validity of these agents for VTE treatment in clinical practice.[8–11] DOAC use in patients with VTE has sharply increased in the last few years,[12] confining standard anticoagulant treatment with parenteral drugs and VKAs in selected patient populations (eg, those with a phospholipid syndrome, cancer-associated thrombosis or serious renal insufficiency).

The present study analysed the baseline characteristics, type of anticoagulant treatment and follow-up of consecutive VTE patients included in the prospective, observational multicentre Survey on anticoagulaTed pAtients RegisTer (START2-Register) study. For this purpose, we only analysed patients included in the registry as of January 2014 when DOAC use for patients with VTE was allowed and reimbursed by the Italian health system.

MATERIALS AND METHODS

The START2-Register

As detailed elsewhere,[13] the START2-Register (ClinicalTrials.gov identifier: NCT02219984) is an observational, multicentre, dynamic cohort study that includes adults (≥18 years) starting anticoagulation therapy, whatever the indication for treatment and drug/dosage used. The present article only reports on patients included for VTE. The aim of the START2-Register is to collect data on the effectiveness and safety of anticoagulant treatments, on the determinants of adverse events in patients who are anticoagulated, and on their quality of life and compliance to treatment. Authorisation to set up the registry was obtained from the Ethical Committee of the University Hospital 'S. Orsola-Malpighi', Bologna, Italy, in October 2011 (n=142/2010/0/0ss). The same institution is charged with deploying and upkeeping the registry central database. The registry is one of the activities of the 'Arianna Anticoagulazione' Foundation (Bologna, Italy). Public and private institutions, companies and individuals interested in the issue of anticoagulant treatment (manufacturers of drugs or other goods and services) are asked by the Executive Committee of the registry to help fund the registry via unrestricted grants without any right to access the database. Members of the Executive Committee do not receive any payment or fee for their work. The registry is open to all physicians (called participants) prescribing anticoagulant therapy and who agree to the registry protocol. Participants should obtain approval from their local Institution Review Board. Participants are required to enrol their patients consecutively or randomly, with the timing of enrolment left to the discretion of each participant, without any exclusion criteria other than life-expectancy or geographical inaccessibility. Patients were enrolled only after giving their written informed consent and the study was conducted according the ethical principles for medical research as set out in the Declaration of Helsinki. Patients or the public were not involved in the design, conduct, reporting or dissemination plans of our research. The correctness and completeness of the data collected anonymously in the central electronic database are checked by a trained and dedicated monitor of the study, who also solicits participating centres to contact, for the purpose of the study, patients lost to follow-up through a telephone call or their general practitioner. The study was carried out and reported according to the 'Strengthening the Reporting of Observational Studies in Epidemiology' guidelines for observational studies.[14]

Study population

All the patients (aged at least 18 years) included in the START2-Register from January 2014 until June 2018 for a DVT episode of a lower limb and/or PE, and for whom follow-up was available, were analysed for the present report. In that time frame, either standard anticoagulant therapy or DOACs were prescribed by the National and Regional Health Systems for initial, long-term and extended anticoagulant treatment in patients with VTE.

Data collection

All participants in the START2-Register are required to connect to the central electronic database, accessible on the web and protected by means of individual passwords. Information is recorded in a structured case report form and involves baseline characteristics of included patients with VTE and their follow-up. Baseline characteristics of patients included in the present study were: (a) demographic, body weight, laboratory routine data, medical history (VTE episodes, hypertension, diabetes mellitus, heart failure, coronary artery disease, peripheral artery disease, atrial fibrillation, previous stroke or transient ischaemic attack or systemic embolism, chronic pulmonary disease, gastrointestinal disease, thyroid disease, previous clinically relevant bleeding, malignancy, renal and liver function, and alcohol abuse); (b) characteristics of the index VTE event and presence of risk factors (RF); (c) anticoagulant agents used and their dosages or the intended therapeutic range (2.0–3.0 international normalised ratio (INR) in all cases receiving VKAs) and concomitant medications (especially antiplatelet drugs). The quality of anticoagulation laboratory control for VKA-treated patients was assessed by calculating the time spent within the INR range 2.0–3.0 (time in therapeutic range, TTR), using Rosendaal's method.[15]

Serum creatinine levels were measured by local hospital laboratories, and creatinine clearance was calculated by the Cockcroft-Gault formula.[16] Renal failure was defined according to National Kidney Foundation stratification.[17]

Information was collected about the nature and site of VTE events. The nature of index events was considered: (a) idiopathic, when not temporally associated with any potential triggering conditions or RF; (b) associated with weak RF, such as minor arthroscopic or laparoscopic general surgery, pregnancy or puerperium, contraceptive or replacement hormonal therapy, long trip, minor trauma, stay in hospital or reduced mobility (not complete immobilisation); (c) provoked by transient major RF, when in association with one of the following conditions occurring within 3 months of VTE diagnosis, viz major surgery with general or spinal anaesthesia, lower limb fracture, casting or no weight bearing for ≥3 days and bed-bound for >3 days due to acute illness; (d) provoked by permanent major RF, when associated with paraplegia, active cancer, chronic active inflammatory disease (eg, intestinal inflammatory disease) or other serious chronic diseases, serious inherited thrombophilic alterations, antiphospholipid syndrome, severe post-thrombotic syndrome or presence of cava filter. The Charlson's weighted comorbidity index score, combining both age and comorbidity, was calculated.[18]

The site of events was classified in: (a) cases with DVT (proximal or isolated distal) without diagnosed PE; (b) PE+DVT, including all cases with objectively documented PE, either symptomatic or incidentally diagnosed, associated with the presence of a DVT (proximal or distal); (c) isolated PE, when the symptomatic or incidentally diagnosed PE was documented in the absence of a DVT. Cases with incidentally diagnosed subsegmental PE were excluded from analysis.

Follow-up data

For the scope of the present analysis, follow-up was considered from the inclusion of patients until December 2018, or until a permanent cessation of anticoagulant treatment, the last follow-up available in patients who subsequently were lost to follow-up or declined to further participate in the START2-Register, or occurrence of major bleeding (MB), thrombotic complications or death, whichever came first. During follow-up, detailed clinical reports of any relevant clinical outcome occurring in enrolled patients were collected. MB was defined according to the International Society on Thrombosis and Haemostasis criteria.[19] Clinically relevant non-MB (CRNMB) events were defined as any overt bleeding requiring a medical intervention and/or treatment discontinuation, not meeting any of the criteria for MB.[20] Thromboembolic events were recorded and defined as clinically verified recurrent VTE episodes, venous thrombosis in different sites, superficial vein thrombosis, stroke/arterial thromboembolism/transient cerebral ischaemic attack, or myocardial infarction. Bleeding and thrombotic events were included in the present analysis if occurring during anticoagulation treatment.

Patient and public involvement

Patient participation in the START2-Register is also promoted by associations of anticoagulated patients (Associazione Italiana Pazienti Anticoagulati) active in several Italian towns. Though patients were not involved in designing the present study, they are informed of results stemming from the START2-Register. The Arianna Anticoagulazione Foundation, promoter of the Register, also owns and manages a website (https://www.anticoagulazione.it/) which is open to Italian professionals, patients and caregivers who are interested in anticoagulant/antithrombotic treatment. The main results of the studies and their clinical significance are described on the site. The Foundation also holds an annual national meeting (usually in Bologna, Northern Italy), open to professionals and patients, where issues linked to anticoagulant/antithrombotic treatment are discussed and results presented and commented.

Statistical analysis

Continuous variables are expressed as median with IQR. Categorical variables are expressed as frequencies and percentages. The number of bleeding and thrombotic events was expressed as percentage (with 95% CIs) and incidence rate, calculated as the number of events per 100 patient-years of observation. Differences between groups were assessed using the χ^2 test with Yates' correction for categorical variables and the Mann-Whitney U test for continuous variables. Kaplan-Meier survival curves were plotted to estimate the cumulative incidence of bleeding and thrombotic events; HRs and their 95% CIs were calculated. The data were analysed with the use of Prism software (V.8.4.0, GraphPad Software, San Diego, California, USA), SPSS software for Windows, V.25 (SPSS) and Stata V.14 statistical software package (StataCorp, College Station, Texas, USA).

RESULTS

Baseline characteristics

From January 2014 to June 2018, 4298 patients were included in the START2-VTE-Register for occurrence of a venous thromboembolic episode. For the present report, only patients included for a DVT episode of a lower extremity and/or PE and treated with chronic oral anticoagulants (either a DOAC or VKA) were analysed, provided they had a follow-up after the initial phase treatment. As shown in figure 1, 619 patients were excluded for thrombosis at different sites and 175 because treatments given were different than oral anticoagulants. A further 776 patients were excluded because only baseline and initial treatment information was available, without subsequent follow-up visits. Finally, 2728 patients were included in this study, of whom 558 (20.5%) were treated with VKA (VKA cohort; warfarin in 98.4% of cases) and 2170 with a DOAC (DOAC cohort). The baseline characteristics of patients and type and nature of index event are shown in table 1. The following conditions were more frequent in VKA-treated

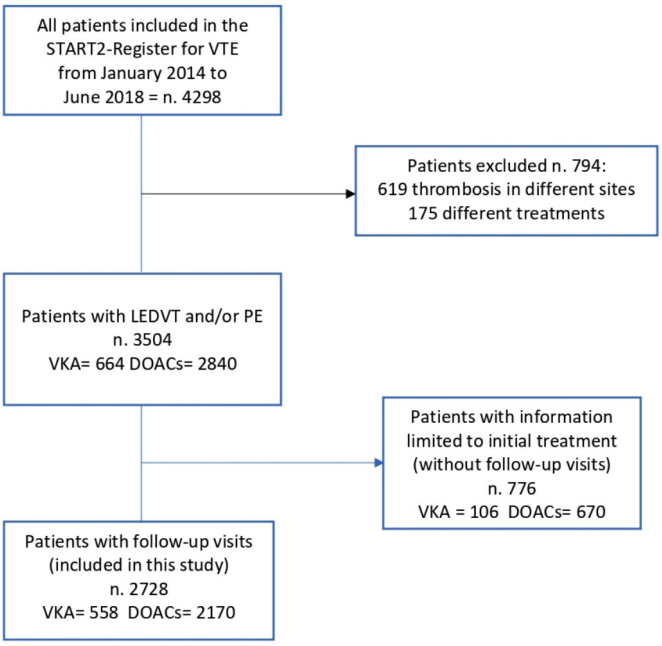

Figure 1 Patient flowchart. DOACs, direct oral anticoagulants; LEDVT, lower extremity deep vein thrombosis; PE, pulmonary embolism; START2-Register, Survey on anticoagulaTed pAtients RegisTer; VKA, vitamin K antagonist; VTE, venous thromboembolism.

versus DOAC-treated patients: impaired renal function, index events that were idiopathic or associated with weak RF or were cancer-associated, a presentation as PE and co-treatment with an antiplatelet agent. The Charlson's comorbidity score was significantly higher in VKA-treated than in DOAC-treated patients. The most frequently used DOAC was rivaroxaban (60.7%), that was the first DOAC admitted for VTE clinical indication and reimbursed by the National Health System in our country, followed by apixaban (23.1%), dabigatran (8.7%) and edoxaban (7.5%), the last available for this indication. After the initial treatment phase, 266 (12.3%) patients in the DOAC cohort received low doses of the corresponding drug (see details on the used low doses in table 1).

Events during follow-up

As shown in table 2, the follow-up was significantly longer for VKA-treated than DOAC-treated patients (p<0.001). The quality of laboratory anticoagulation control in VKA-treated patients (percentage of time spent within the therapeutic range 2.0–3.0 INR, TTR) in the whole period of observation, including the first 3 months of treatment, was 63%±20%. Anticoagulation of between 90 and 180 days was more frequent in DOAC-treated patients, whereas more VKA patients received a treatment for >180 days. During a total follow-up of 2962 years, 82 MB+CRNMB events (2.8% patient-years) occurred across the whole set of patients, without any difference between the two cohorts (table 2), with a cumulative occurrence similarly distributed between the cohorts during follow-up (figure 2A).

As reported in table 2, 67 thrombotic events (2.9% patient-years) occurred in the DOAC cohort (52 and 15 of venous and arterial type, respectively; 2 fatal), whereas 6 thrombotic events (0.9% patient-years, p=0.003) occurred in the VKA cohort (5 venous and 1 fatal stroke). The rates of thrombotic events in DOAC cohort were not significantly different to those in VKA cohort up to 180 days of treatment but became markedly higher after 180 days (2.73% vs 0.49%, in patients treated with DOAC and VKA, respectively; p<0.0001) (figure 3). The majority of thrombotic events in the DOAC cohort occurred, in fact, during extended treatment (2.73% beyond vs 0.64% before 180 days; p<0.0001). The HR for incidence of thrombotic events in DOAC cohort versus VKA cohort was 2.28 (95%CI 1.32 to 3.95), p=0.003. In particular, the cumulative occurrence of venous thrombotic events was significantly higher in DOAC cohorts than in VKA cohorts (HR 2.15 (1.14–4.06), p=0.018) (figure 2B), whereas that of arterial events was not statistically different. The incidence of thrombotic events was not different in patients treated with DOAC who received standard or low doses of the drug (table 2).

Over the study, 39 patients were lost to follow-up (more frequently VKA-treated vs DOAC-treated patients (p=0.0016)), while two patients withdrew their consent to participate in the START2-Register. The total mortality during treatment was significantly higher in VKA versus DOAC cohort (5.9% vs 2.6%, respectively; p<0.001). The difference was mainly due to the significantly higher number of deaths attributed to causes other than anticoagulant treatment (table 2).

DISCUSSION

The present study analysed baseline conditions and clinical course during follow-up of patients with VTE included in a prospective, observational registry during a period when both DOACs and VKAs were available for initial, long-term and extended treatment, and reimbursed by Italy's National or Regional Health Services. Important results of this study, which we believe may represent what happens in routine clinical practice in our country, are the following. The participating centres, expert in managing anticoagulation, prescribed DOACs to a large majority of patient (approximately 80%) at the discretion of attending physicians. Among the remaining patients, treated with VKAs, the prevalence of serious or moderate renal insufficiency, PE or cancer and co-treatment with antiplatelet drugs was significantly higher than in the DOAC cohort, and the Charlson's comorbidity score was also higher. During follow-up, the incidence of overall bleeding events (MB+CRNMB) did not differ between the two treatment cohorts. Conversely, the incidence of all thrombotic complications was higher in the DOAC versus VKA cohort (2.9 vs 0.9% patient-years, respectively; p=0.003), the difference being relevant in terms of venous thromboembolic events (2.4% vs 0.90% patient-years,

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)

*The use of rivaroxaban 10 mg per day for extended VTE treatment was approved by Italian Health System Authorities (AIFA) and reimbursed only in March 2019 (not available at the time of the present study).
DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; NS, not statistically significant; PE, pulmonary embolism; RF, risk factors; VKA, vitamin K antagonist; VTE, venous thromboembolism.

Table 2 Bleeding and thromboembolic complications recorded during follow-up

	DOAC n=2170	VKA n=558	P value
Total follow-up, days	2295	667	
Follow-up, median (IQR), years	0.81 (0.41–1.47)	1.01 (0.48–1.64)	0.001
Quality of laboratory control in VKA-treated patients (TTR), mean±SD%		63%±20%	
Lost to follow-up, n (%)	23 (1.1)	16 (2.9)	0.0016
Duration of treatment, n (%)			
≤90 days	360 (16.6)	85 (15.3)	NS
91–180 days	351 (16.2)	66 (11.8)	0.01
>180 days	1459 (67.2)	407 (72.9)	0.01
Major bleeding and CRNMB, n (% patient-years)	**61** (2.7)	**21** (3.1)	NS
Major bleeding, n (%)	28 (1.3)	8 (1.4)	NS
ICH	6	3	
GIH	11	2	
Other	11	3	
Fatal	3 (2 ICH, 1 GIH)	2 (ICH)	
Thrombotic events, n (% patient-years)	**67** (2.9)	**6** (0.9)	0.003
Standard-dose DOAC, n=1905 (FU: 2022 years)	60 (3.0)		
Low-dose DOAC, n=265 (FU: 273 years)	7 (2.6)		
Venous events, n (%)	52 (2.4)	5 (0.90)	0.027
DVT±PE	40	2	
Isolated PE	4	1	
Superficial vein thrombosis	8	2	
Arterial events, n (%)	15 (0.69)	1 (0.18)	NS
TIA	3	–	
Stroke/peripheral embolism	5	1	
AMI	7	–	
Fatal	2 (AMI, stroke)	1 (stroke)	
Deaths during follow-up, n (%)	**56 (2.6)**	**33 (5.9)**	<0.001
Major bleeding	3	2	
Stroke/ischaemic heart disease	2	1	
Sudden death	10	4	
Cancer	12	3	
Not due to anticoagulation treatment	23 (41.1)	23 (69.7)	0.01
Other	6	–	
Patients who discontinued the treatment, n (%)	**747 (34.4)**	**192 (34.4)**	NS

AMI, acute myocardial infarction; CRNMB, clinically relevant non-major bleeding; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; FU, follow-up; GIH, gastrointestinal haemorrhage; ICH, intracranial haemorrhage; NS, not statistically significant; PE, pulmonary embolism; TIA, transient cerebral ischaemic attack; TTR, Both expansion are correct: the first refers to general definition and correctly it was placed in method section; the second expansion at the bottom of the table refers to patients analysed in our study with a specific INR and for a wel defined period of time
.0–3.0 INR) since the inclusion in the registry of vitamin K antagonists-treated patients; VKA, vitamin K antagonist.

p=0.027). Overall mortality was higher among patients treated with VKAs (5.9% vs 2.6%, p<0.001).

The present study clearly shows that Italian centres prefer DOACs to treat most patients with VTE though they still prescribe VKAs to a minority of patients, including those with symptomatic PE and additional comorbidities, such as renal failure or cancer. The higher prevalence of patients with these characteristics among the VKA-treated patients suggests that the attending physicians still prefer VKA treatment for clinically serious patients. This is also confirmed by the higher mortality recorded in the VKA cohort, which in the majority of cases (about

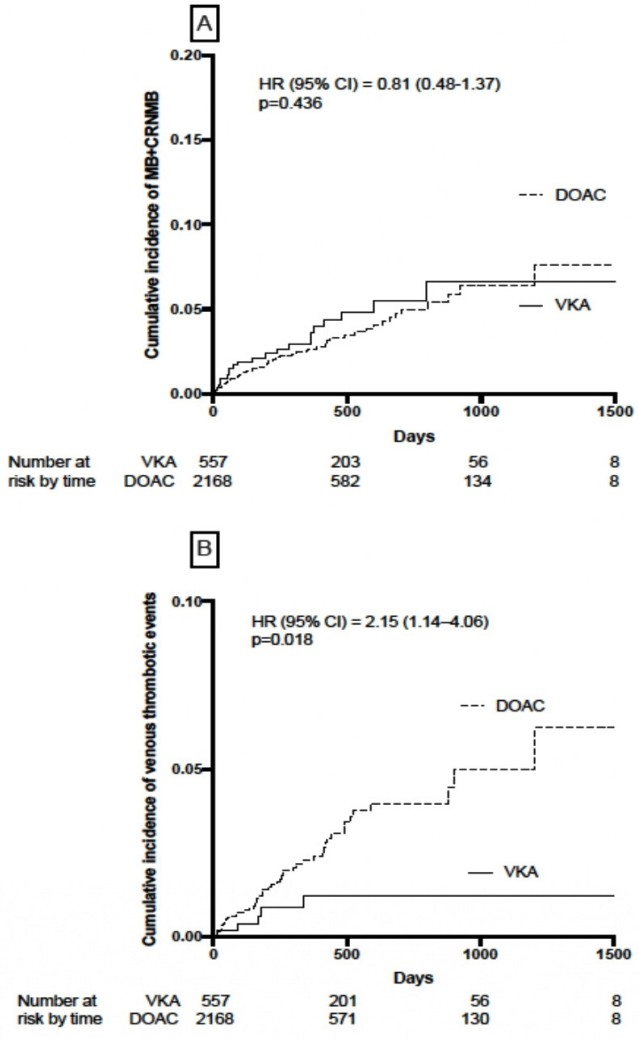

Figure 2 Kaplan-Meier cumulative event rates for bleeding events and venous thromboembolic recurrences in patients treated with DOAC or VKA. CRNMB, clinically relevant non-major bleeding; DOAC, direct oral anticoagulant; MB, major bleeding; VKA, vitamin K antagonist.

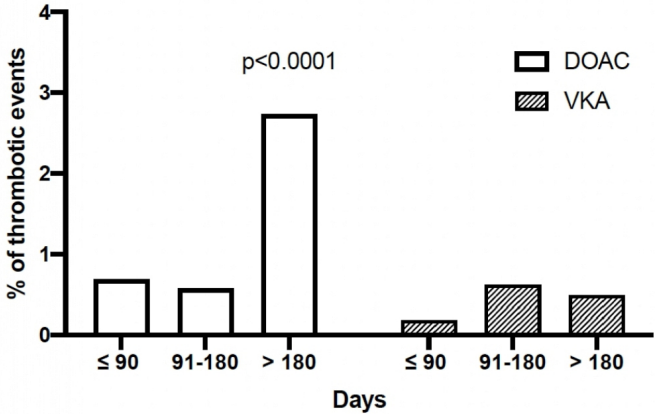

Figure 3 Incidence of thrombotic events grouped according to three time intervals of treatment with DOAC or VKA; the shown statistical significance is for the comparison between the rates recorded after 180 days of treatment with DOAC versus VKA. DOAC, direct oral anticoagulant; VKA, vitamin K antagonist.

70%) was induced by causes other than VTE complications (table 2).

Unlike results in the phase III trials addressing the suitability of DOAC for treating VTE,[21] the rate and severity of bleeding events in the present study were quite similar across the two cohorts (table 2).

A relevant and unexpected finding of our enquiry was the significantly higher rate of thrombotic complications found in DOAC-treated versus VKA-treated patients. We acknowledge that the rate of 2.9% patient-years of thrombotic complications recorded in the DOAC-treated patients is consistent with that reported in most available clinical studies. Indeed, in phase III clinical trials, the rate of the primary efficacy outcomes in DOAC ranged between 1.8% and 3.2%,[22] the rate of recurrent VTE being consistently around 2.0%.[21] A lower rate of recurrence (1.4%) was recently reported in the international, prospective XALIA study addressing the value of rivaroxaban.[8] Interestingly, when the distribution of events during follow-up was analysed, we found that the remarkable difference in thrombotic rates between DOAC-treated and VKA-treated patients was mainly accounted for by the events occurring after the first 6 months of treatment (2.73% vs 0.49% patient-years in patients treated with DOAC and VKA, respectively; p<0.0001). In contrast, during the first 180 days of treatment, we failed to find any appreciable difference between the two cohorts. We suggest these findings may mainly be attributable to the decrease in patient compliance to DOAC therapy after the initial period, an event less likely to occur in patients on VKA due to closer monitoring via periodic INR checks. It is realistic to suppose that periodic visits, key to boosting patient adherence to therapy, are less frequent in DOAC-treated patients, even if managed by anticoagulation clinics. Other factors, however, may have contributed to these findings. First, in patients with atrial fibrillation treated with low-dose edoxaban, a recent report found prevention of thrombotic complications was less effective when creatinine clearance was high (>95 mL/min).[23] While that report was only limited to the use of low-dose edoxaban, we did not want to exclude such an eventuality and so compared patients with creatinine clearance above (>90 mL/min) or below that level, but did not find any difference in the incidence of venous thrombotic events (data not shown). Second, in line with the well-known high interindividual variability in drug blood levels among DOAC-treated patients, a recent cohort study in DOAC-treated patients with atrial fibrillation showed that thrombotic complications occurred particularly in patients who had very low C-trough levels.[24] We do not have data on blood DOAC levels of investigated VTE patients, and therefore cannot comment on this potential factor. Finally, in principle, we cannot exclude the possibility that DOAC doses may have been reduced in some patients after the first 6 months of treatment and not timely signalled in the database, a factor that may also have played a role in our results.

Strengths and limitations

Our study has limitations. We analysed patient information collected in a prospective observational registry in which all the therapeutic decisions were left to the attending physicians. Furthermore, the time interval of the study was chosen to allow all included patients to receive either VKAs or DOACs for their treatment. However, the use of DOACs for VTE was still only a recent occurrence in Italy at the time. It is likely that some therapeutic decisions would be different today, in particular, a larger use of low-dose regimens in DOAC-treated patients. Finally, during the study, it was impossible to collect data on the adherence of DOAC-treated patients to the prescribed therapeutic regimens, whereas the persistence to treatment was assured. A recent population study in UK primary care confirmed the importance of lower rates of adherence and persistence to DOAC patients treated for atrial fibrillation.[25] Though we do not have confirmatory data, we too attribute the high rates of DOAC-associated thrombotic complications recorded in the study during extended VTE therapy chiefly to adherence problems.

CONCLUSION

In conclusion, our study shows that the Italian clinical centres participating in the START2-Register treat the large majority of acute VTE patients with DOACs, and generally limit the use of VKAs to a minority of patients, especially in the case of those who have more serious clinical conditions. Bleeding complications during follow-up occurred to almost the same degree in VKA-treated and DOAC-treated patients. On the contrary, recurrent VTE events were more frequent in DOAC-treated patients, a difference that was almost completely due to a high rate of events occurring late during follow-up (>180 days of treatment). Although the interpretation of our findings requires a degree of caution due to the big differences in baseline characteristics between the two study cohorts and the failure to adjust for them, our results underline the importance of periodic patient visits even during extended therapy in DOAC-treated patients to get across the need for their complete adherence to the therapy and to avoid later complications.

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REFERENCES

1 Schulman S, Kearon C, Kakkar AK, *et al*. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med* 2009;361:2342–52.
2 Bauersachs R, Berkowitz SD, Agnelli G, *et al*. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med* 2010;363:2499–510.
3 Davidson BL, Misselwitz F, Gallus AS, *et al*. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med* 2012;366:1287–97.

4 Agnelli G, Buller HR, Cohen A, *et al*. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med* 2013;369:799–808.
5 Agnelli G, Buller HR, Cohen A, *et al*. Apixaban for extended treatment of venous thromboembolism. *N Engl J Med* 2013;368:699–708.
6 Büller HR, Décousus H, Schwocho L, *et al*. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med* 2013;369:1406–15.
7 Wang K-L, van Es N, Cameron C, *et al*. Extended treatment of venous thromboembolism: a systematic review and network meta-analysis. *Heart* 2019;105:545–52.
8 Ageno W, Mantovani LG, Haas S, *et al*. Safety and effectiveness of oral rivaroxaban versus standard anticoagulation for the treatment of symptomatic deep-vein thrombosis (XALIA): an international, prospective, non-interventional study. *Lancet Haematol* 2016;3:e12–21.
9 Schulman S. Accumulating data on rivaroxaban for venous thromboembolism in clinical practice. *Thromb Haemost* 2017;117:117.
10 Imberti D, Barillari G, eXperience VTE Italian Group. Real-Life management of venous thromboembolism with rivaroxaban: results from experience VTe, an Italian epidemiological survey. *Clin Appl Thromb Hemost* 2018;24:241–7.
11 Weycker D, Li X, Wygant GD, *et al*. Effectiveness and safety of apixaban versus warfarin as outpatient treatment of venous thromboembolism in U.S. clinical practice. *Thromb Haemost* 2018;118:1951–61.
12 Riva N, Ageno W. Which patients with venous thromboembolism should receive non-vitamin K antagonist oral anticoagulants? the majority. *Blood Transfus* 2015;13:181–3.
13 Antonucci E, Poli D, Tosetto A, *et al*. The Italian START-Register on anticoagulation with focus on atrial fibrillation. *PLoS One* 2015;10:e0124719.
14 von Elm E, Altman DG, Egger M, *et al*. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med* 2007;147:573–7.
15 Rosendaal FR, Cannegieter SC, van der Meer FJ, *et al*. A method to determine the optimal intensity of oral anticoagulant therapy. *Thromb Haemost* 1993;69:236–9.
16 Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;16:31–41.
17 National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis* 2002;39:S1–266.
18 Charlson ME, Pompei P, Ales KL, *et al*. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–83.
19 Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 2005;3:692–4.
20 Kaatz S, Ahmad D, Spyropoulos AC, *et al*. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. *J Thromb Haemost* 2015;13:2119–26.
21 van Es N, Coppens M, Schulman S, *et al*. Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials. *Blood* 2014;124:1968–75.
22 Palareti G. Direct oral anticoagulants and bleeding risk (in comparison to vitamin K antagonists and heparins), and the treatment of bleeding. *Semin Hematol* 2014;51:102–11.
23 Yu HT, Yang P-S, Kim T-H, *et al*. Impact of renal function on outcomes with edoxaban in real-world patients with atrial fibrillation. *Stroke* 2018;49:2421–9.
24 Testa S, Paoletti O, Legnani C, *et al*. Low drug levels and thrombotic complications in high-risk atrial fibrillation patients treated with direct oral anticoagulants. *J Thromb Haemost* 2018;16:842–8.
25 Banerjee A, Benedetto V, Gichuru P, *et al*. Adherence and persistence to direct oral anticoagulants in atrial fibrillation: a population-based study. *Heart* 2020;106:119–26.