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Full Length Article

Prescription patterns of direct oral anticoagulants in pulmonary embolism: A prospective multicenter French registry☆

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ABSTRACT

Background: Data regarding the use of direct oral anticoagulants (DOACs) for the treatment of acute pulmonary embolism (PE) are sparse. We conducted a prospective multicentre registry study to describe patterns of DOAC prescription for the treatment of acute PE, and the associated risk of 6-month adverse events in daily practice.
Methods: We included all PE patients discharged since the availability of DOACs for the dedicated indication of acute PE treatment. Clinical data and 6-month outcomes, including death, recurrent venous thromboembolism (VTE), bleeding, and chronic thromboembolic pulmonary hypertension (CTEPH) were recorded prospectively. Temporal trends in DOAC prescription were tested.
Results: Between 09/2012 and 04/2017, 1082 patients were included: 60.6% (n = 656) were treated with DOACs and 39.4% (n = 426) with another anticoagulant. The prescription rate of DOACs increased sharply just after their release on the market to reach a plateau over time, between 56% and 72% of the total prescription per year in PE patients (p for trend = 0.33). Active malignancy and renal function impairment were factors independently associated with non-prescription of DOACs. Overall, prescription of DOACs was appropriate in 95.3% of patients. The rate of use of non-recommended DOAC doses was 4.2% (n = 28). The rate of death, recurrent VTE, bleeding and CTEPH were 2.4%, 1.2%, 7.2%, and 1.9%, respectively in the DOAC group.
Conclusion: The choice to prescribe DOACs or not is related to patient characteristics. The overall appropriateness of prescription is high, while the rate of adverse events observed in patients treated with DOAC is low in our registry.

1. Introduction

Pulmonary embolism (PE) is the third most frequent cardiovascular disease and the most serious presentation of venous thromboembolism (VTE) [1,2]. For over five decades, PE antithrombotic treatment strategy included the use of a parenteral anticoagulant in combination with a vitamin K antagonist (VKA) until the target International Normalized Ratio of 2.0 to 3.0 was reached. However, this dual-drug

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approach is associated with some limitations, including the need to administer the parenteral agent and VKA concurrently for several days at the start of treatment, several drug- or food-interactions with VKA therapy, and the subsequent need for regular coagulation monitoring and dose adjustments during the VKA treatment [3,4]. Recently developed direct oral anticoagulants (DOACs), which are direct inhibitors of factor IIa (for dabigatran) or Xa (for rivaroxaban, apixaban and edoxaban) have been successfully tested for the treatment of VTE in large phase 3 studies [5–8]. They have been shown to be non-inferior to VKA in terms of antithrombotic effectiveness, with significantly fewer bleeding events. Moreover, DOACs have minimal drug interactions as compared with VKAs, and can be administered orally at a fixed dose without the need for routine coagulation monitoring. Based on these data, guidelines for the management of PE have validated the use of DOACs as an alternative for the treatment of VTE at the acute phase, with the same grade recommendation [3,4]. Currently, there is a paucity of real-life data about prescription patterns of DOACs in VTE [9–12].

Therefore, the aims of the present study were, in a multicenter, multidisciplinary approach, (1) to describe DOAC (and non-DOAC prescription) for the treatment of acute PE; (2) to identify patient- and physician-related factors influencing the decision to prescribe DOACs rather than other anticoagulants; (3) to evaluate the frequency of inappropriate DOAC prescription, and (4) to describe the efficacy and safety of DOACs in daily practice.

2. Material and methods

2.1. Study design

We designed a prospective, observational study, based on a multicenter registry including 11 departments in 5 centers, and covering 7 different clinical specialties (Cardiology (n = 5 departments), Vascular Medicine (n = 1), Internal Medicine/Geriatrics (n = 1), Respiratory Diseases (n = 1), Oncology (n = 1), Critical Care (n = 1), and Orthopedic Surgery (n = 1)). Inclusion criteria were all patients aged 18 years or older, with PE confirmed by computed tomography pulmonary angiography (CT-PA) or ventilation-perfusion (V/Q) scan who survived the acute phase and were discharged from the participating unit with anticoagulant therapy.

The study period encompassed September 2012 through April 2017. We chose September 2012 as the starting point of this study, corresponding to the launch date of rivaroxaban, the first DOAC to be approved on the French market for the dedicated indication of acute PE treatment. Apixaban was authorized in this indication from April 2015 onwards (edoxaban and dabigatran were not approved for the treatment of acute PE in the French market during the study period). Participation in the registry was not supposed to change the therapeutic approach in any way, and management of acute PE was at the discretion of the physicians in charge. The study was conducted in accordance with the Declaration of Helsinki. Institutional Review Board approval was obtained. Informed consent was obtained from each study participant.

Research physicians performed a medical record review at each site and abstracted data by using a standard data collection form. Physicians entered data into a dedicated database for de-identification of personal information and for partial data validation. The research physicians were also asked to ensure that recruitment was consecutive. Baseline characteristics including socio-demographic data, clinical data, imaging findings, and biological and treatment data were recorded prospectively by research physicians. In-hospital adverse events including death, causes of death, recurrent VTE, and bleeding were also recorded. Six months after the diagnosis of PE, patients returned to the hospital for a follow-up visit to record clinical status, anticoagulation treatments and outcomes (i.e., death, cause of death, recurrent VTE, bleeding, and chronic thromboembolic pulmonary hypertension (CTEPH) since hospital discharge). If the patients did not attend the hospital visit, physicians followed the sequential procedure hereafter: they performed a telephone interview with the patient, consulted the hospitalization records since discharge, contacted the patient's general practitioner by telephone, and finally, consulted the national death registry. Six-month follow-up for clinical status, treatment, and outcomes was 100% complete.

We distributed a 13-point questionnaire to one senior physician at each participating center (n = 11) to collect information on their attitudes towards DOAC or VKA strategies for the treatment of acute PE. The questionnaire was first developed by Luger et al. to evaluate physician's attitudes to oral anticoagulation prescription after acute stroke in atrial fibrillation patients [13] and adapted for use in the context of PE. The questionnaire was used to assess the frequency with which the different reasons influencing the choice of OAC for PE were cited. The questionnaire was completed at 2 timepoints: First, at baseline, just after the release of DOACs on the French market for the dedicated indication of acute PE treatment. The questionnaire was then completed again by the same physicians one year later, to explore changes over time in the reasons that influenced the choice between DOAC and VKA.

The description of appropriate and inappropriate use of DOACs is based on the international guidelines for the treatment of acute PE and includes no DOAC prescription in cancer-related VTE, in pregnant women, and in patients with severe renal insufficiency (defined by a creatinine clearance (CrCl) < 30 mL/min) [3,4]. It also includes the use of DOAC doses proven efficacious in phase III randomized trials (recommended doses: rivaroxaban 15 mg twice daily for the first 3 weeks, followed by 20 mg once daily; apixaban 10 mg twice daily for the first 7 days, followed by 5 mg twice daily) [5–7].

All adverse events were adjudicated by an independent committee. Recurrent VTE includes PE confirmed by visualization of new filling defects on CT-PA scan, or a perfusion defect involving at least 75% of a segment, with corresponding normal ventilation on V/Q scan, or diagnosis of DVT on compression ultrasonography. Bleeding events were classified according to the International Society of Thrombosis and Haemostasis criteria for major bleeding [14]. CTEPH was defined by a mean pulmonary artery pressure ≥25 mm Hg with pulmonary arterial wedge pressure ≤15 mm Hg on cardiac catheterization, and pulmonary artery obstruction seen by V-Q scan or CTPA [15].

2.2. Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD) when normally distributed, or median ± interquartile range if not normally distributed, and were analyzed with the Student *t*-test or Wilcoxon rank sum test as appropriate. Categorical variables are described as number (percentage) and were compared with the chi-square test or Fisher's exact test. Temporal trends (by periods of 3 months) in the prescription of DOACs were tested using the Jonckheere-Terpstra test for trend. The multivariable model included a missing indicator if a variable had > 10% of missing values. To investigate the independent associations of various characteristics with the prescription or non-prescription of DOACs, we constructed a hierarchical modified Poisson regression model with robust error variance, adjusted for patient and practice-level characteristics. Covariates entered into the model were all baseline characteristics including socio-demographics data, clinical and biological data and imaging findings, as well as in-hospital adverse events. Because the rate of DOAC prescription exceeded 10%, we used modified Poisson regression at all steps to estimate relative prescription rates with 95% confidence intervals (CI) directly instead of odds ratios (OR) obtained from logistic regression, which may overestimate effect differences [16]. Relative risks (RR) lower than 1 correspond to a decreased probability of DOAC prescription. Clinical symptoms and 6-month follow-up outcomes were compared between DOAC and non-DOAC groups using multivariable Cox models including baseline characteristics and in-hospital adverse events that reached a p-

Table 1
Baseline characteristics of the study population stratified by the prescription or the non-prescription of a direct oral anticoagulant at discharge for the treatment of acute pulmonary embolism.

Variables	Total (n = 1082)	Direct oral anticoagulant		p-Value
		Yes (n = 656)	No (n = 426)	
Age, years	66.2 ± 17.3	63.4 ± 18.3	70.4 ± 14.5	< 0.001
Male (%)	506 (46.8)	308 (46.9)	198 (46.5)	0.90
BMI	27.5 ± 6.3	28.1 ± 6.4	26.6 ± 6.0	< 0.001
Pre-admission anticoagulation	72 (6.6)	34 (5.2)	38 (8.9)	0.13
Co-morbidities (%)				
Diabetes	142 (13.1)	80 (12.2)	62 (14.5)	0.30
Coronary disease	154 (14.2)	71 (10.8)	83 (19.4)	< 0.001
Pulmonary disease	110 (10.2)	56 (8.5)	54 (12.7)	0.03
Prior stroke	64 (5.9)	30 (4.5)	34 (8.0)	0.02
Renal insufficiency (CrCl < 30 mL/min)	49 (4.5)	8 (1.2)	41 (9.6)	< 0.001
Neurocognitive disease	59 (5.4)	44 (6.7)	15 (3.5)	0.02
Active cancer	194 (17.9)	13 (2.0)	181 (42.5)	< 0.001
Prior bleeding	35 (3.2)	18 (2.8)	17 (4.0)	0.22
Prior VTE	266 (24.5)	153 (23.3)	113 (26.5)	0.23
Provoked PE	267 (24.6)	195 (29.7)	72 (16.9)	< 0.001
Associated DVT (%)	455 (42.0)	279 (42.5)	176 (41.3)	0.65
Clinical characteristics (%)				
HR at admission (b.p.m.)	90.3 ± 19.4	90.3 ± 19.9	90.4 ± 19.1	0.98
SBP at admission (mm Hg)	136.7 ± 23.7	138.3 ± 21.9	134.2 ± 26.1	0.005
Arterial oxyhemoglobin saturation (%)	94.0 ± 3.8	94.2 ± 3.8	93.7 ± 4.0	0.06
NYHA functional status				0.86
I	582 (53.8)	349 (53.2)	233 (54.7)	
II/III	374 (34.6)	231 (35.2)	143 (33.5)	
IV	126 (11.6)	76 (11.6)	50 (11.7)	
Syncope/lightheadedness	99 (9.1)	58 (8.8)	41 (9.6)	0.74
Initial shock	30 (2.8)	12 (1.8)	18 (4.2)	0.01
Biological data (%)				
Hemoglobin (g/dL)	13.3 ± 2.0	13.9 ± 1.6	12.4 ± 2.2	< 0.001
Platelet count ($\times 10^3$/μl)	243 ± 93	243 ± 82	242 ± 112	0.93
Creatinine clearance (mL/mn)	83.9 ± 42.8	91.0 ± 43.1	71.5 ± 39.6	< 0.001
Positive markers of myocardial injury	373 (34.5)	213 (32.4)	160 (37.6)	0.05
Echocardiographic data (%)[a]				
RV dysfunction[b]	433 (40.1)	273 (41.6)	160 (37.6)	0.18
Right heart thrombus	21 (1.9)	7 (1.1)	14 (3.3)	0.01
sPAP (mm Hg)	42.7 ± 16.7	41.3 ± 15.8	43.2 ± 12.2	0.10
sPESI (points, Q1–Q3)	1 (0–2)	1 (0–2)	2 (1–2)	< 0.001
Early mortality risk stratification				
High	47 (4.3)	20 (3.0)	27 (6.3)	< 0.001
Intermediate-high	280 (25.9)	143 (21.8)	137 (32.2)	< 0.001
Intermediate-low	391 (36.1)	188 (28.7)	203 (47.4)	< 0.001
Low	364 (33.6)	305 (46.5)	59 (13.8)	< 0.001

BMI: body mass index; CrCl: creatinine clearance; VTE: venous thromboembolic; DVT: deep vein thrombosis; PE: pulmonary embolism; HR: heart rate; SBP: systolic blood pressure; RV: right ventricle; sPAP: systolic pulmonary arterial pressure.

[a] Transthoracic echocardiographic data available for 1055 patients (97.5%).

[b] Echocardiographic criteria of RV dysfunction include RV/Left ventricle diameter ratio > 1, hypokinesia of the free RV wall; increased velocity of the tricuspid regurgitation jet; or combinations of the above.

value < 0.1 by univariate analysis. All p-values are 2-sided. A p-value of < 0.05 was considered statistically significant. Statistical analyses were performed with SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

In total, 1155 patients were admitted to the hospital with an objectively confirmed diagnosis of acute PE between September 2012 and April 2017. Seventy-one patients (6.1%) died during the hospital stay. The patients who died during the hospital course received systemic thrombolysis in 25.3% (n = 18), and extra corporeal membrane oxygenation (ECMO) in 14.1% (n = 10). Causes of in-hospital death were acute PE in 33 patients (46.7%), bleeding in 15 patients (21.1%), cancer in 16 (22.5%), and other cause of death in 7 patients (9.8%). No anticoagulant was prescribed in 2 patients (0.5%) in whom IVC filters were implanted. The remaining 1082 patients discharged from the participating institutions with an anticoagulant composed the study population. The baseline characteristics of the study population are shown in Table 1. Mean age was 66.2 ± 17.3 years, 46.8% were males. A total of 47 patients (4.3%) had high-risk PE, 280 (25.9%) had intermediate-high-risk PE, 391 (36.1%) had intermediate-low-risk PE, and 364 (33.6%) had low-risk PE [3]. At discharge, 60.6% (n = 656) were treated with DOACs and 39.4% (n = 426) received another anticoagulant regimen.

Patients who received DOACs were younger and had fewer comorbidities, including active cancer, renal insufficiency, coronary artery disease, and previous stroke as compared to those who did not receive DOACs. The rate of prior bleeding did not differ significantly between groups. Patients treated with DOACs had lower cardiac biomarkers and less frequently had shock as the initial presentation, resulting in a lower early mortality risk in this group (Table 1).

DOACs were directly started at admission in 84.3% in the DOAC group. Patients were mostly treated at admission by a parenteral anticoagulant (i.e., unfractionated heparin or low-molecular-weight heparin (LMWH)) in the non-DOAC group, as compared to the DOAC group (93.9% vs. 21.7%, respectively, p < 0.001) (Table 2). The rate of use of any in-hospital reperfusion therapy, ECMO, or inferior vena

Table 2
In-hospital course, and anticoagulant/antiplatelet regimen stratified by the prescription and the non-prescription of a direct oral anticoagulant at discharge for the treatment of acute pulmonary embolism.

Variables	Direct oral anticoagulant		p-Value
	Yes (n = 656)	No (n = 426)	
In-hospital treatments			
Anticoagulants			
Unfractionned heparin	30 (4.6)	87 (20.4)	< 0.001
LMWH	96 (14.6)	299 (70.2)	< 0.001
Fondaparinux	16 (2.5)	15 (3.5)	0.12
VKA	4 (0.6)	10 (2.3)	0.21
DOACs	510 (77.7)	15 (3.5)	< 0.001
Reperfusion therapy			
Thrombolysis	37 (5.6)	20 (4.7)	0.57
Surgical embolectomy	3 (0.5)	6 (1.4)	0.12
ECMO	3 (0.5)	5 (1.2)	0.27
Inferior vena cava filter	1 (0.1)	0 (0)	0.76
In-hospital adverse events			
Any bleeding	15 (2.3)	22 (5.2)	0.001
Major bleeding	9 (1.4)	12 (2.8)	0.03
Recurrent VTE	0 (0)	5 (1.2)	< 0.001
Anticoagulants/antiplatelet agents at discharge			
Unfractionned heparin	–	7 (1.6)	–
LMWH	–	222 (52.1)	–
Fondaparinux	–	6 (1.4)	–
VKA	–	191 (44.8)	–
Rivaroxaban	614 (93.6)	–	–
Apixaban	42 (6.4)	–	–
Antiplatelet alone	30 (4.6)	51 (12.0)	< 0.001
DAPT	0 (0)	3 (0.7)	0.06

LMWH: low-molecular weight heparin; VKA: vitamin K agonist; DOACs: direct oral anticoagulant; ECMO: extracorporeal membrane oxygenation; DAPT: dual antiplatelet therapy.

cava (IVC) filter did not differ between groups. The rate of in-hospital bleeding including both any and major bleeding was significantly higher in the group of patients discharged without DOACs ($p < 0.001$ and $p < 0.03$, respectively). None of the patients in the DOAC group and 5 patients (1.2%) in the non-DOAC group had a recurrent VTE during the hospital course (Table 2). All 5 patients who had in-hospital recurrent VTE were discharged with LMWH. At discharge, 614 patients (93.6%) were treated with rivaroxaban and 42 (6.4%) with apixaban. Most of the patients in the non-DOAC group received LMWH (53.2%) followed by VKA (43.7%). The rate of concomitant antiplatelet prescription was higher in the non-DOAC group as compared to the DOAC group (12% vs. 4.6%, $p < 0.001$) (Table 2).

After multivariable adjustment, active malignancy (RR: 0.01 [95% CI: 0.06, 0.17], $p < 0.001$) and impaired renal function (RR: 0.93 [95% CI: 0.88, 0.97], $p = 0.004$) were significantly associated with non-prescription of DOACs (Fig. 1). The prescription rate of DOACs for the treatment of acute PE increased sharply just after their release on the market, to reach a plateau over time, between 56% and 72% of the total prescriptions per year in PE patients (p for trend = 0.33) (Fig. 2).

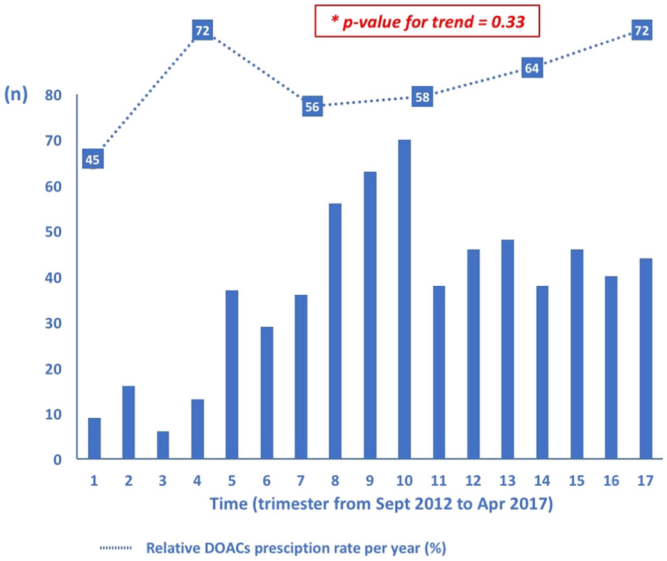

Fig. 2. Number of prescriptions (per trimester) and relative prescription rate (per year) of direct oral anticoagulants (DOACs) according to time since marketing in France. *p-value for temporal trends (by periods of 3 months) in the prescription of DOACs.

The survey of senior physicians performed at baseline (T0) in the 11 centers revealed that frequent reasons to prefer VKA over DOACs were prior VKA treatment, and the feeling that the patient was well acquainted with this anticoagulant. The most frequent reason to prefer DOACs over VKA at T0 was the presumed better risk-benefit profile for DOACs according to the results of randomized controlled trials (Fig. 3A). One year after the introduction of DOACs on the national market (T1), the main reason cited by physicians for preferring VKA over DOACs was renal insufficiency, and the potentially associated risk of accumulation. Expectation of better compliance thanks to more comfortable conditions of use with DOACs, rather than VKA, was the most common reason cited at T1 for preferring DOACs, followed by the efficacy and safety of these drugs demonstrated in clinical trials (Fig. 3B).

Overall, prescription of DOACs was appropriate in 95.3% of patients. No patient with cancer-related or pregnancy-related PE was treated with DOACs. We observed DOAC prescription in 3 patients with severe renal insufficiency (0.5%). The rate of use of non-recommended doses of DOACs was 4.2% (n = 28). Eighteen patients (2.7%) treated with rivaroxaban were given 15 mg twice daily for the first 3 weeks followed by 15 mg once daily; 3 (0.4%) patients were treated using another dose strategy. Five patients (0.8%) receiving apixaban were treated at the dose of 10 mg twice daily followed by the inappropriate

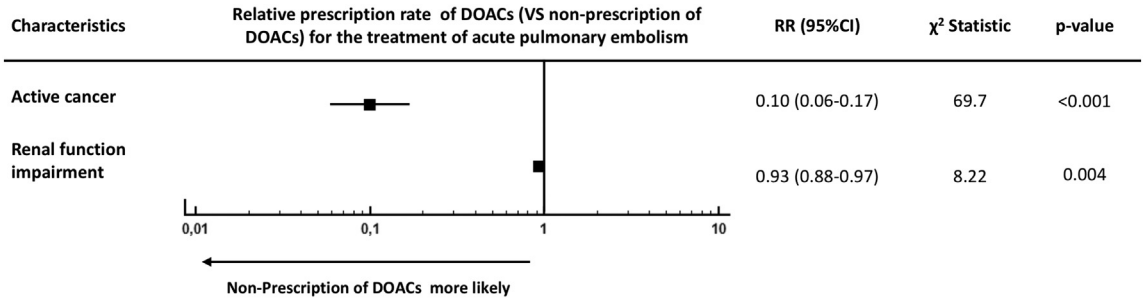

Fig. 1. Factors independently associated with direct oral anticoagulant prescription versus non-prescription for the treatment of acute pulmonary embolism. Renal function impairment is defined as a decreased creatinine clearance (per quartiles, reference Q4). DOACs: direct oral anticoagulants; RR: relative risk; CI: confidence interval.

A

Reasons to prescribe VKA rather than DOACs for pulmonary embolism					
Time	Very unfrequent				Very frequent
	0	1	2	3	4
	1) Patient's or general practitioner's (GP) concern regarding considerably higher cost of DOACs				
T0	4	2	3	2	0
T1	6	0	3	1	0
	2) Patient on VKA prior to pulmonary embolism and well-acquainted to this OAT				
T0	0	1	1	6	3
T1	0	1	4	3	3
	3) GPs might not yet be familiar with the management of DOACs				
T0	2	3	2	3	1
T1	2	4	2	2	1
	4) Fear of difficulties in the handling of hemorrhagic complications under DOAC due to the lack of an antidote				
T0	1	4	3	3	0
T1	2	4	2	3	0
	5) Multi-morbidity and cachexia of patient with potentially higher risk of drug accumulation under the use of fixed-dose DOACs				
T0	0	0	3	4	4
T1	0	0	5	3	3
	6) Regular coagulation checks by the GP might positively influence the patient's compliance				
T0	3	1	3	3	1
T1	4	0	3	4	0
	7) Recommendation of VKAs because of the patient's impaired renal function				
T0	0	1	3	4	2
T1	0	1	2	5	3

B

Reasons to prescribe DOACs rather than VKA for pulmonary embolism					
Time	Very unfrequent				Very frequent
	0	1	2	3	4
	1) Recommendation of DOAC because of the patient's preference for DOACs				
T0	1	3	2	2	3
T1	0	1	5	3	2
	2) Expectation of better compliance of self-sustaining patient due to more comfortable use without regular coagulation checks				
T0	0	1	3	3	3
T1	0	1	2	3	5
	3) Easier OAT management of immobile and multi-morbid patient by the GP without the necessity for regular coagulation checks				
T0	0	0	4	5	1
T1	0	0	2	4	4
	4) Less drug-drug- or drug-food-interaction in comparison to VKA				
T0	1	1	3	4	2
T1	0	1	4	2	4
	5) Easier OAT management in comparison to VKA e.g. in the context of elective surgery				
T0	0	1	4	3	2
T1	0	0	4	4	2
	6) Presumed lower risk of severe hemorrhagic complications to VKA according to results of the clinical trials and therefore better risk-to-benefit -profile				
T0	1	2	2	2	4
T1	0	2	3	2	4

Fig. 3. Survey among senior physicians of the frequency of different reasons influencing their choice of oral anticoagulant (OAC). A 13-point questionnaire was distributed to one senior physician (n = 11) at each participating center to collect information on their attitudes towards vitamin K antagonists (VKA) and direct oral anticoagulants (DOACs) at two time points (baseline = T0 (A), and one year later = T1 (B)) to assess the frequency with which the different reasons influencing the choice of OAC for pulmonary embolism were cited. Each reason was ranked on a five-point scale from being very infrequently to frequently decisive in the choice of OAC. Answers are presented as a heat map as follows: white -answered positively by 0–10% of physicians, yellow- answered positively by 11–30%, red – answered positively by 31–50%, blue – answered positively by ≥51%. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

dose of 2.5 mg twice daily. The remaining 2 patients (0.3%) received another dose regimen of apixaban.

The 6-month follow-up data are provided in Table 3. The mean time between discharge and follow-up was 168.2 ± 12 months (541 patient-years). At 6 months, the clinical status of survivors (i.e., 640 patients in the DOAC group and 345 patients in the non-DOAC group) did not differ between groups. A total of 90.1% of patients continued DOACs, 6.2% had transitioned to other anticoagulants, and 3.8% completed 3-month anticoagulant duration treatment and no longer had anticoagulant therapy at the 6-month follow-up visit in the DOAC group. In the non-DOACs group, 17.1% of patients had transitioned to DOACs during follow-up, 46.6% were treated with VKA, and 31.8% with heparin/fondaparinux. The remaining 4.5% of patients had discontinued anticoagulant therapy between 3 months and the follow-up visit.

Overall, 97 patients died (8.9%, 17.2 per 100 patient-years) during follow-up. The adjusted rate of death was higher among patients not treated with DOACs (39.0 vs. 4.9 per 100 patient-years, p = 0.02), mainly driven by cancer-related death (75% of the causes of death in the non-DOAC group, 0.1% in the DOAC group). By multivariable analysis, the rates of recurrent VTE (3.0 vs. 2.3 per 100 patient-years), bleeding (10.6 vs. 14.5 per 100 patient-years) including major bleeding (3.3 vs. 7.9 per 100 patient-years) did not differ significantly between DOAC and non-DOAC groups (p = 0.48, p = 0.77, and p = 0.09, respectively). In total, right heart catheterization was performed in 43 patients (3.9%) including 1.8% in the DOAC group (3.6 per 100 patient-years) and 1.9% in the non-DOAC group (3.75 per 100 patient-years) (p = 0.89).

4. Discussion

The present study from a regional multicenter multidisciplinary registry provides a snapshot view of the use of DOACs for the treatment of acute PE in the real-world setting. We observed an almost immediate and substantial uptake of DOACs starting right after their release on the national market, to reach a prescription rate of currently > 70% of all PE treatments. The choice to prescribe DOACs or not is related to patient characteristics (i.e., malignancy, renal function impairment), leading to the prescription of DOACs mainly in patients with a low burden of comorbidities. Physicians reported prescribing DOACs because of their ease of use, and because of the proven efficacy and safety of these treatments. The overall appropriateness of prescription is high, while the rate of adverse events observed in patients treated with DOACs was low in our registry.

A DOAC was not prescribed at discharge in 5 patients who suffered recurrent VTE in-hospital. All of these patients were treated with LMWH at discharge. This practice is line with the 2016 CHEST guidelines, which recommend switching to LMWH to treat recurrent VTE occurring on oral anticoagulant therapy, or increasing the dose of LMWH by about one-quarter to one-third in patients on LMWH therapy, at least temporarily (Grade of recommendation: 2C) [17].

The rate of DOAC use is somewhat higher than that observed in previous registries. In the XALIA registry, the first published prospective non-interventional study with 5140 patients treated for acute PE between 2012 and 2014, 51% received rivaroxaban at discharge [9]. Data extracted from the Norwegian Prescription Database showed that among 30,287 patients treated for VTE, 44.4% were treated with DOACs [10]. Even lower prescription rates, of around 20%, were reported in the SWIVTER and PREFER VTE registries [11,12]. The reasons that might explain these differences include the duration of the inclusion period covered by these registries, as well as the different DOAC reimbursement dates in participating countries.

To the best of our knowledge, our study is the first to identify patient-related factors associated with prescription or non-prescription of DOACs for PE treatment. We showed that both active cancer and impaired renal function were related to non-prescription of DOACs at discharge. These findings, as well as the very low prescription rates observed in these clinical situations, underscore the awareness of

Table 3
clinical status, treatments and outcomes at time of follow-up stratified by the prescription and the non-prescription of a direct oral anticoagulant for the treatment of acute pulmonary embolism.

Variables	Direct oral anticoagulant		p-Value
	Yes (n = 640)	No (n = 345)	
Time from PE diagnosis and follow-up (days)	171 ± 11	162 ± 12	0.43
Symptoms			
Asymptomatic	425 (66.4)	226 (65.3)	0.72*
NYHA functional status			0.52*
I	32 (5.0)	23 (6.7)	
II/III	163 (26.6)	78 (24.4)	
IV	4 (0.6)	4 (1.2)	
Other symptoms	30 (4.6)	20 (4.6)	1.0
Anticoagulant			
Any anticoagulant	614 (95.2)	326 (94.5)	0.08
UFH	0 (0)	5 (1.4)	0.09
LMWH	5 (0.8)	103 (29.8)	< 0.001
Fondaparinux	1 (0.1)	2 (0.6)	0.25
VKA	35 (5.3)	161 (46.6)	< 0.001
DOAC	577 (90.1)	59 (17.1)	< 0.001
None	26 (3.8)	19 (4.5)	0.12
Outcomes	Yes (n = 656)	No (n = 426)	
Death from any cause (%)	16 (2.4)	81 (19.0)	0.02
Cause of death (%)			
Cancer	1 (0.1)	61 (14.3)	–
Recurrent VTE	1 (0.1)	1 (0.2)	–
Hemorrhage	1 (0.1)	0 (0)	–
Cardiovascular	1 (0.1)	7 (1.6)	–
Other	12 (1.9)	12 (2.8)	–
Recurrent pulmonary VTE (%)			
Any	10 (1.5)	5 (1.2)	0.48
Non-fatal	9 (1.0)	4 (0.9)	0.89
Bleeding (%)			
Any	35 (5.3)	31 (7.3)	0.77
Major bleeding	11 (1.7)	17 (4.0)	0.09
CTEPH (%)	12 (1.8)	8 (1.9)	0.89

NYHA: New-York Heart Association; UFH: Unfractionned heparin; LMWH: low-molecular weight heparin; VKA: vitamin K agonist; DOACs direct oral anticoagulants; VTE: venous thromboembolism; CTEPH: chronic thromboembolic pulmonary hypertension. Other symptoms include chest pain, syncope and leg swelling or pain.

* p-Value adjusted to baseline characteristics and the PE severity.

prescribing physicians regarding the indications and contraindications of DOACs in PE.

DOACs have no indication for the treatment of cancer-related PE [3,4,18]. Four randomized controlled trials have demonstrated that LMWH is the treatment of choice in cancer-associated VTE by reducing VTE recurrence over VKAs [19–22]. The recently published Hokusai VTE cancer randomized trial demonstrated that the rate of recurrent VTE was lower, but the rate of major bleeding was higher with edoxaban, a DOAC that inhibits Factor Xa, as compared to LMWH [23]. The use of DOACs in case of severe renal insufficiency exposes the patient to a risk of plasmatic accumulation, because there is some degree of renal clearance for all of these drugs, and this may lead to an increased risk of bleeding [24]. Moreover, there are no outcome data available regarding DOACs in patients with advanced chronic kidney disease (CrCL < 30 mL/min), and the current guidelines recommend against their prescription in such patients [3,4].

The appropriateness of DOAC prescription was good in our registry, with an overall adherence to prescription guidelines of 95.3%, including, as mentioned above, non-prescription of DOACs in cancer-related VTE and in severe kidney disease. Nevertheless, we observed a 4% rate of off-label dosing of DOACs, which could result in theoretical under-dosing. DOACs prescribed for VTE treatment do not require dose adjustment based on the patient profile (e.g., weight, creatinine clearance or age), contrary to AF treatment. Our registry was not designed to record physician attitudes towards the dosing and regimen of DOACs prescribed, but we may assume that DOAC dosing may have been based on the rules from the AF context for at least some of the patients. The impact of potential under-dosing in PE treatment is currently unclear. A recent report from the RIETE registry data showed a potential increase in the rate of recurrent VTE in patients treated with lower doses compared to those treated with doses validated in phase III randomized trials [25].

The results of the surveys completed by the physicians soon after the launch of DOACs for VTE treatment likewise highlight the strong influence of the AF experience in the physicians' prescribing attitudes, with initial concerns about the risk of drug accumulation according to the patient's clinical status, and the lack of interest for DOACs felt by the physician if the patient was already treated with VKA. Highly similar results were found with a survey analysis in the field of secondary stroke prevention in AF patients [13]. The second iteration of the survey (at T1) illustrates the change in physicians' opinions concerning DOAC use in PE treatment. At that time, their main motivations for prescribing DOACs were the demonstrated efficacy and safety of these drugs, as well as their ease of use for both the patient and the physician.

Regarding outcomes analysis, we observed similarly low rates of recurrent VTE and bleeding as those observed in the XALIA registry [9]. We cannot draw any conclusion about the significantly lower rate of death observed in the DOAC group as compared to the non-DOAC group, even though we constructed a multivariable model that included several baseline and in-hospital variables. The two groups are too different, especially in terms of the patients with active cancer and the high cancer-related mortality rate observed in the non-DOACs group.

The strengths of this study include the prospective nature, adjudication of outcomes, and a 100% complete follow-up. However, our analysis also has some limitations. First, we recorded several patient baseline characteristics, but we were unable to determine the level of frailty of patients receiving DOACs versus those receiving VKA. In a previously published registry, many physicians were reluctant to prescribe DOACs in frail patients with advanced age, multiple comorbidities, or taking numerous medications, and often prefer monitored VKA [9]. Second, the questionnaire analysis takes into account oral anticoagulation but not LMWH prescription, which represents the main prescription in the non-DOAC group. We did not prospectively record patients' preferences for the respective choice of anticoagulation in each individual case. Finally, the comparison of 6-month adverse events between DOAC and non-DOAC groups did not take into account switches from one anticoagulant to another or discontinuation of anticoagulant therapy during follow-up.

5. Conclusion

Direct oral anticoagulants rapidly achieved a dominant market share over VKA and other parenteral anticoagulants within 4 years of their approval for reimbursement and release on the market in France. The choice to prescribe DOACs or not is related to patient characteristics (i.e. active cancer and renal function impairment) as well as to the demonstrated efficacy and safety of these treatments. Overall, appropriateness is high, but issues regarding dose adjustment of DOACs deserve to be addressed. The rate of adverse events observed in patients treated with DOAC was low in our registry.

Statement of conflict of interest

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