Accepted Manuscript online: 2022-01-04 Article published online: 2022-03-10

Effectiveness and Safety of Oral Anticoagulants in the Treatment of Acute Venous Thromboembolism: A Nationwide Comparative Cohort Study in France

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Thromb Haemost 2022;122:1384–1396.

Abstract

Introduction Data from clinical trials indicate that direct oral anticoagulants (DOACs) are noninferior and safer than conventional therapy (low-molecular-weight heparin followed by a vitamin K antagonist [VKA]) for treating venous thromboembolism (VTE), which includes deep vein thrombosis and pulmonary embolism (PE). This study compared the effectiveness and safety of DOACs and conventional therapy in a real-world setting.

Methods This observational study used French national claims data of adult, treatment-naïve patients diagnosed with VTE (majority PE) who were hospitalized and treated for VTE with a DOAC (apixaban or rivaroxaban) or VKAs during 2013 to 2018. Patients with active cancer were excluded. After propensity score matching for each DOAC-VKA comparison, risks of bleeding, recurrent VTE, and all-cause mortality were compared at 6 months. Cox proportional hazards regression was used to estimate adjusted hazard ratios of the endpoints.

Results A total of 58,137 patients were included (10,775 VKAs, 10,440 apixaban, 36,922 rivaroxaban). Propensity score-matched cohort sizes were 7,503 for apixaban and 9,179 for rivaroxaban. The hazard ratio (95% confidence interval) was significantly lower for apixaban than VKAs for bleeding requiring hospitalization (0.43 [0.32–0.59]), all-cause death (0.61 [0.51–0.74]), and first recurrent VTE (0.67 [0.52–0.85]). The hazard ratio was also significantly lower for rivaroxaban than VKAs for all-cause death

Keywords
- venous thromboembolism
- anticoagulants
- apixaban
- rivaroxaban
- bleeding

received
September 9, 2021
accepted after revision
November 26, 2021
published online
March 10, 2022

DOI https://doi.org/10.1055/a-1731-3922.
ISSN 0340-6245.

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(0.63 [0.53–0.74]) but not for bleeding requiring hospitalization (0.86 [0.69–1.07]) or first recurrent VTE (0.91 [0.74–1.13]).

Conclusion Apixaban was associated with superior safety and effectiveness than VKAs. All-cause mortality was lower in both DOACs than VKAs. Our results support recommendations to use DOACs over VKAs for the treatment of VTE.

Introduction

Deep vein thrombosis (DVT) and pulmonary embolism (PE), collectively referred to as venous thromboembolism (VTE), affect approximately 10 million people worldwide.[1–3] Overall global incidence rate of VTE is 115 to 269 per 100,000.[4] Annual incidence rates range from 39 to 115 for PE and 53 to 162 for DVT per 100,000 population.[4–6] Data from the United States indicate that 10 to 30% of people with VTE will die within 1 month of diagnosis, and about one-quarter of people with PE die suddenly without it being diagnosed.[7] One quarter of these patients have a recurrence within 5 years and over one-third have a recurrence within 10 years.[8]

The goal of VTE treatment is to prevent its recurrence over the long term by resolving and preventing extension of the clot.[3,9] After a VTE episode, conventional treatment has typically included heparins (low-molecular-weight heparin [LMWH] or unfractionated heparin) or fondaparinux followed by a vitamin K antagonist (VKA), such as warfarin, to prevent recurrent episodes of VTE.[3] VKAs require regular monitoring of anticoagulation and typically need heparin bridging therapy to balance the risk of bleeding with thromboembolism.[10] Direct oral anticoagulants (DOACs) are small molecules that directly inhibit clotting factors, including thrombin (dabigatran) and factor Xa (apixaban, edoxaban, and rivaroxaban).[3] Randomized controlled trials showed that DOACs are noninferior to VKAs in preventing VTE recurrence and VTE-related death but are less likely to cause intracranial bleeding, other bleeding events, and to interact with food and other drugs and are faster acting.[11–15] Accordingly, the European Society of Cardiology[3] recommends using DOACs over VKAs for first-line treatment of VTE. Similarly, the American College of Chest Physicians[16] and the American Society of Hematology[17] suggest DOACs over VKAs for the first-line treatment of VTE.

Although the clinical trial data indicate similar efficacy and better safety of DOACs over VKAs, evidence from real-world studies are needed to confirm these conclusions in the wider population and in daily clinical practice. Real-world data are also needed because the risk–benefit ratio of DOACs may differ in a nonclinical trial population.[18,19] Three recent matched-cohort studies of U.S. private health care and Medicare claims databases confirmed that safety and effectiveness were better with DOACs than conventional therapy for risks of major bleeding, clinically relevant nonmajor bleeding, and recurrent VTE.[20–22] The current study further extends the U.S. studies by comparing the real-world effectiveness and safety of the two DOACs approved for use in France for VTE (apixaban and rivaroxaban) with VKAs in a French population.

Methods

Overall Study Design and Data Source

This was a retrospective, observational, nationwide cohort study (EU PASS registration number EUPAS35888) using data extracted from the French national health data system (*Système National des Données de Santé* [SNDS]), which covers 99% of the French population.[23] Data are linked via a unique social security number to primary care, hospital, pharmacy, and death registration databases, permitting patient treatment history, treatment patterns, and hospitalizations based on International Classification of Diseases, Tenth Revision (ICD-10) codes to be tracked. The objective was to describe and compare the risk of bleeding leading to hospitalization, recurrent VTE, and all-cause death within the first 6 months after the index VTE diagnosis in adult patients receiving apixaban, rivaroxaban, or VKA.

Study Population

The analysis included adult inpatients without active cancer that had a principal diagnosis of VTE or an associated diagnosis with evidence of a diagnostic procedure for VTE from January 1, 2013 to June 30, 2018. This analysis period reflects the availability dates of rivaroxaban (DVT, price publication, July 25, 2012; PE, transparency committee, June 12, 2013) and apixaban (PE and DVT, transparency committee, April 1, 2015) in this indication in France.[24,25] VTE was identified through ICD-10 diagnoses of hospital stay (see ►**Supplementary Table S1** [available in the online version] for ICD-10 codes for a diagnosis of VTE) and VTE diagnostic procedure (see ►**Supplementary Table S2** [available in the online version] for list of procedures). Active cancer was defined as patients who have a cancer diagnosis or cancer treatment (chemotherapy, radiation, and cancer-related surgery) within 6 months before or 30 days after the index VTE diagnosis. The admission date was designated as the index VTE event date. Patients also had to have $\geq$1 reimbursement for an anticoagulant within 30 days after the date of discharge. The study population included patients who met selection criteria and received treatment with apixaban, rivaroxaban, or VKAs after their initial index encounters. In the VKA/LMWH bridging or VKA only cohort, if patients used VKA and had a reimbursement for LMWH within 14 days before or after VKA initiation, then their first VKA reimbursement date was designated as the index date. No other anticoagulant (except VKA or LMWH) could be prescribed during the following time periods: between index VTE event and initiation of VKA and for the duration of LMWH treatment if it occurred within 14 days after VKA

initiation. Patients with a VKA reimbursement within 30 days after the date of discharge for VTE events in an inpatient setting without a reimbursement for any other anticoagulant (except for LMWH as a bridging therapy) between the index VTE event and the VKA reimbursement date were classified as VKA users. The apixaban cohort consisted of patients who initiated apixaban within 30 days after the date of discharge for VTE event. The rivaroxaban cohort consisted of patients who initiated rivaroxaban within 30 days after the date of discharge for VTE event.

For DOACs, time on treatment (days of supply) was estimated using information on the number of reimbursements a patient received and on the prescribed package size, units, strength per prescription, and the European Medicines Agency dosing plan for the DOACs of interest (►**Supplementary Table S3**, available in the online version).[26,27] For VKAs, a mean daily dose was computed for all patients initiating VKAs in the study period. The mean daily dose was computed by dividing the total amount prescribed by the follow-up. Days supplied was calculated by dividing the patient's total amount dispensed by the mean daily dose. A 30-day grace period after the estimated end of the days' supply was applied for DOAC and VKA estimates.

Patients were excluded if they had a diagnosis of VTE during 24 months prior to the index date; atrial fibrillation/flutter, mechanical heart valve replacement, or mitral stenosis at the index VTE or during the 24 months preceding it; receipt of another oral or parenteral anticoagulant on the index date or during the period between the index VTE event and the index date (LMWH was allowed between the index VTE event and index date for the VKA–LMWH bridging cohort); or evidence of pregnancy at 9 months prior to the index date. In addition, patients with recording errors in the SNDS database were excluded. For this analysis, patients with active cancer 6 months prior to or 30 days after index VTE event were also excluded.

Study Outcomes

The main study outcomes included bleeding requiring hospitalization, which was a bleeding event observed during follow-up and defined as bleeding leading to hospitalization identified using a primary ICD-10 diagnosis (see ►**Supplementary Table S4** [available in the online version] for ICD-10 codes); all-cause death, which was defined as any recorded death; and first recurrent VTE, which was defined as an inpatient diagnosis of DVT or PE identified through ICD-10 codes (primary) occurring after 7 days of the index VTE event (see ►**Supplementary Table S2** [available in the online version] for a list of procedures to diagnose DVT and PE). Other outcomes of interest included gastrointestinal bleeding, intracranial bleeding, and other bleeding (see ►**Supplementary Table S4** [available in the online version] for bleeding codes).

A sensitivity analysis was performed for bleeding requiring hospitalization, all ICD-10 codes, or transfusions (►**Supplementary Table S4** [available in the online version]: ICD-10 codes for bleeding leading to hospitalization).

Statistical Analysis

All analyses were conducted using SAS Enterprise guide version 7.15 (SAS institute Inc., Cary, North Carolina, United States). Propensity score (PS) matching was used as the primary method to balance patient characteristics between the cohorts and estimated the average treatment effect for the treated. The PS was calculated using a multinomial logistic derived for each of the treatment comparisons of interest (VKA as reference treatment for VTE population) (►**Supplementary Appendix A**). The PS was defined as the probability of a patient receiving a certain treatment or not conditional on their observed baseline covariates. The list of variables included in the logistic model was based on clinical rationale (see ►**Supplementary Table S5** [available in the online version] for covariates). In case of collinearity, collinear variables were removed from the PS. Several checks were performed to ensure a good balance of PS and of covariates between apixaban and comparison groups including graphically analyzing the treatment group PS distribution and using standardized differences to balance the covariates across treatment and comparison groups. Apixaban and rivaroxaban patients were matched with those treated with VKAs using sequential pairwise nearest neighbor 1:1 matching without replacement, using the logit of PS and specified caliper of width 0.2 of standard deviation (SD) of the logit of PS. The quality of the matching was checked with absolute weighted standardized differences on the demographics and clinical covariates (standardized differences $<10\%$ indicating good balance between treatment groups).

To compare risk, the cumulative incidence rates for clinical outcomes censored at 6 months (including 95% confidence interval [CI] within each cohort) were calculated as the number of patients who experienced the event divided by the observed time at risk expressed per 100 person-years [PY]. In addition, 95% CIs were calculated using a previously published method.[28] If the CI did not include the null hypothesis value ("1"), the results were considered to be statistically significant.[29] Adjusted and unadjusted rates were computed. After PS matching, the risk for each outcome was compared between apixaban and VKA and between rivaroxaban and VKA using a Cox proportional hazard model. The proportionality assumption was checked by including the interaction between a time function and exposure (an α of 0.10 was used) and by visual inspection of the Kaplan–Meier curves. If the proportionality assumption was violated, time-varying covariates were included in the Cox proportional hazard model. The risk of the selected outcomes according to treatment of interest was investigated in time-to-event analyses using the standard Kaplan–Meier method within the first 6 months after index VTE diagnosis. Data were censored at death, end of follow-up, discontinuation, or switching of drugs, therefore only on-treatment analyses for outcomes were conducted. Only the first event of each type (recurrent VTE, bleeding, etc.) was modeled. Patients could qualify for each of the clinical events and death.

Inverse probability treatment weighting (IPTW) was used as a sensitivity analysis (►**Supplementary Appendix B**). IPTW

also uses PS to obtain estimates of the average treatment effect.[30] The PS was calculated using the same formula as PS matching (►**Appendix A**). After IPTW, incidence rates were calculated as the number of events per 100 PY for bleeding requiring hospitalization, first recurrent VTE, and all-cause death. The Cox proportional hazards model was used to compare outcomes.

Results

Patient Selection and Characteristics

Approximately 1.2 million adult patients were identified in the French national health data system with a diagnosis of VTE between January 2013 and June 2018. The study population included VTE inpatients not previously treated for VTE and prescribed apixaban ($n = 10{,}440$), rivaroxaban ($n = 36{,}922$), or VKA only or LMWH to VKA bridging ($n = 10{,}775$) within 30 days after their index VTE encounter (►**Fig. 1**).

In the full study population (prior to PS matching), the mean age (SD) was 70.9 (18.4) years and 39.7% were male in the VKA group (►**Supplementary Table S6**, available in the online version). Additionally, mean age (SD) was 65.5 (17.6) and 47.2% were male in the apixaban group, while mean age (SD) was 60.1 (17.5) and 51.4% were male in the rivaroxaban group. Patients in the VKA cohort were, on average, older, less frequently male, and more frequently had comorbidities than patients in the apixaban and rivaroxaban cohorts.

After PS matching, 7,503 patients were included in each of the cohorts for the apixaban versus VKA comparison and 9,179 in each of the cohorts for the rivaroxaban versus VKA comparison (►**Table 1**). Demographic characteristics were similar for the two cohorts in the apixaban versus VKA comparison and in the rivaroxaban versus VKA comparison. The qualifying event DVT only was found in a minority of patients (29–33%) while PE with or without DVT was found in the majority of patients. Comorbidities and concomitant treatments were also similar across the cohorts.

In the populations included in IPTW sensitivity analysis, demographics and clinical characteristics were similar across the cohorts (►**Supplementary Table S7**, available in the online version).

Use of Index and Other Therapies

Median duration of treatment was 6 months (►**Table 2**). The median follow-up at the 6-month time point in the VKA versus apixaban and VKA versus rivaroxaban cohorts was 182 days for VKA and 183 days for apixaban and rivaroxaban. The most common dosage was 5 mg for apixaban and a combination of 15 and 20 mg for rivaroxaban. Patients prescribed VKAs had the highest amount of switching (26% for both cohorts).

Risk of Bleeding, Recurrent VTE, and All-Cause Mortality in the Study Population before PS Matching

The total numbers of patients prior to PS matching were: 10,440 prescribed apixaban, 36,922 prescribed rivaroxaban, and 10,775 prescribed VKAs (►**Supplementary Table S8**, available in the online version). The number of patients and crude event incidence rate (rate per 100 PY [95% CI]) for bleeding requiring hospitalization was 0.81% (1.85 [1.50–2.29]) with apixaban, 1.15% (2.64 [2.41–2.90]) with rivaroxaban, and 1.98% (5.21 [4.57–5.94]) with VKAs. The crude incidence rate (rate per 100 PY [95% CI]) for recurrent VTE was 1.48% (3.38 [2.89–3.94]) with apixaban, 1.89% (4.33 [4.03–4.66]) with rivaroxaban, and 1.89% (4.99 [4.36–5.70]) with VKAs. The crude incidence rate (rate per 100 PY [95% CI]) for all-cause death was 2.07% (4.71 [4.13–5.36]) with apixaban, 1.19% (2.73 [2.49–2.99]) with rivaroxaban, and 4.64% (12.23 [11.26–13.27]) with VKAs.

Risk of Bleeding, Recurrent VTE, and All-Cause Mortality in PS-Matched Cohorts

In the apixaban:VKA matched cohorts, the incidence rate (rate per 100 PY [95% CI]) after PS matching for bleeding requiring hospitalization was 1.64% (4.34 [3.61–5.18]) for VKAs and 0.83% (1.89 [1.45–2.42]) for apixaban (►**Supplementary Table S9**, available in the online version). The incidence rate (rate per 100 PY [95% CI]) for first recurrent VTE was 1.97% (5.22 [4.41–6.13]) for VKAs and 1.49% (3.41 [2.81–4.11]) for apixaban. The incidence rate (rate per 100 PY [95% CI]) for all-cause death was 3.67% (9.70 [8.59–10.92]) for VKAs and 2.56% (5.85 [5.05–6.74]) for apixaban.

In the rivaroxaban:VKA matched cohorts, the incidence rate (rate per 100 PY [95% CI]) after PS matching for bleeding requiring hospitalization was 1.76% (4.65 [3.96–5.42]) for VKAs and 1.72% (3.98 [3.38–4.65]) for rivaroxaban (►**Supplementary Table S9**, available in the online version). The incidence rate (rate per 100 PY [95% CI]) for first recurrent VTE was 1.87% (4.94 [4.23–5.73]) for VKAs and 1.93% (4.46 [3.82–5.16]) for rivaroxaban. The incidence rate (rate per 100 PY [95% CI]) for all-cause death was 3.77% (9.93 [8.91–11.03]) for VKAs and 2.67% (6.17 [5.42–6.99]) for rivaroxaban.

Comparative Analyses

VKA versus Apixaban

The results, after PS matching, at 6 months showed that the risk of bleeding was significantly lower for apixaban than VKA for all measures of bleeding including bleeding requiring hospitalization (hazard ratio [HR] = 0.43 [95% CI: 0.32–0.59]), gastrointestinal bleeding (HR = 0.51 [95% CI: 0.30–0.87]), intracranial bleeding (HR = 0.38 [95% CI: 0.21–0.70]), and other bleeding (HR =0.41 [95% CI: 0.25–0.65]) (►**Supplementary Table S9,** ►**Fig. 2**, and ►**Fig. 3**). Risks were also significantly lower for apixaban than VKA for all-cause death (HR = 0.61 [95% CI: 0.51–0.74]) and first recurrent VTE (HR = 0.67 [95% CI: 0.52–0.85]).

The results of the sensitivity analysis using IPTW showed similar outcomes to the PS matching at 6 months (►**Supplementary Table S10** and ►**Supplementary Fig. S1**, available in the online version).

In the sensitivity analysis, the risk for bleeding requiring hospitalization, all ICD-10 codes or transfusion, was lower for apixaban than for VKA at 6 months in the PS-matching group (►**Supplementary Table S11**, available in the online version).

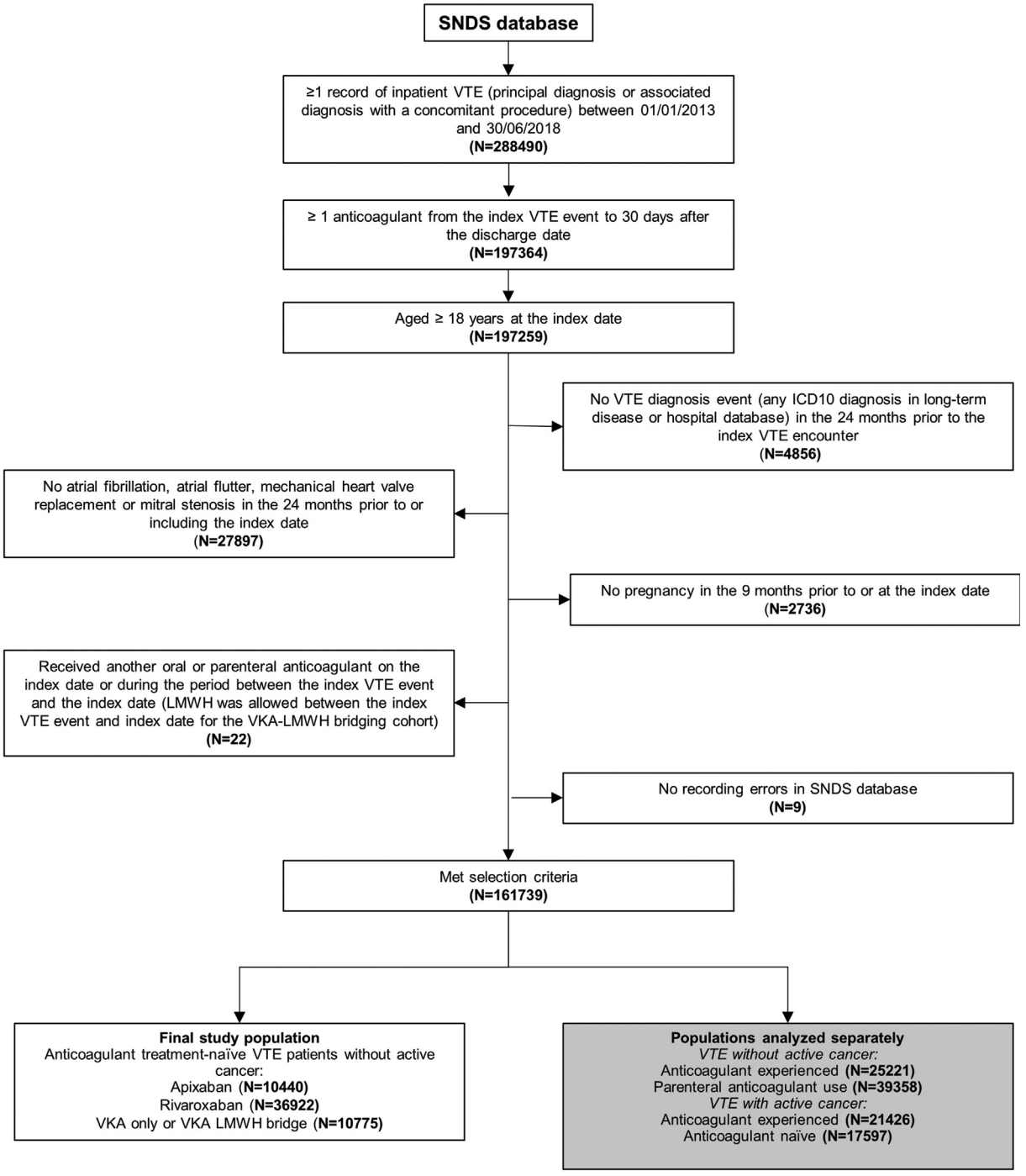

Fig. 1 Patient inclusion and exclusion criteria. ICD-10, International Classification of Diseases, Tenth Revision; LMWH, low-molecular-weight heparin; SNDS, *Système National des Données de Santé*; VKA, vitamin K antagonist, VTE, venous thromboembolism.

VKA versus Rivaroxaban

The results, after PS matching, at 6 months showed that the risk of intracranial bleeding was significantly lower for rivaroxaban than for VKA (HR = 0.48 [95% CI: 0.29–0.79]), but not for bleeding requiring hospitalization (HR = 0.86 [95% CI: 0.69–1.07]), gastrointestinal bleeding (HR = 1.26 [95% CI: 0.87–1.83]), and other bleeding (HR = 0.84 [95% CI: 0.61–1.17]) (►**Supplementary Table S9** [available in the online version], ►**Fig. 3**, and ►**Fig. 4**). Risk was significantly lower for rivaroxaban than VKA for all-cause death (HR = 0.63 [95% CI: 0.53–0.74]) but not for first recurrent VTE (HR = 0.91 [95% CI: 0.74–1.13]).

The results of the sensitivity analysis using IPTW showed that the risk was lower for rivaroxaban than VKA for bleeding requiring hospitalization, all-cause death, and first recurrent VTE at 6 months (►**Supplementary Table S10** and ►**Supplementary Fig. S1**, available in the online version).

In the sensitivity analysis, the risk for bleeding requiring hospitalization, all ICD-10 codes or transfusion, was not lower for rivaroxaban than for VKA at 6 months in the

Table 1 Patient characteristics: PS-matched cohorts

Characteristic	VKA vs. apixaban				VKA vs. rivaroxaban			
	VKA ($N=7,503$)	Apixaban ($N=7,503$)	*p*-Value	Std. difference	VKA ($N=9,179$)	Rivaroxaban ($N=9,179$)	*p*-Value	Std. difference
DVT only[a], *n* (%)	**2,184 (29.1)**	**2,220 (29.6)**	**0.52**	**−1.05**	**2,997 (32.7)**	**3,015 (32.9)**	**0.78**	**−0.42**
Age at index (y), mean (SD)	68.1 (18.9)	68.2 (16.9)	0.83	−0.36	69.3 (18.6)	68.8 (16.3)	0.06	2.76
Sex, male, *n* (%)	3,254 (43.4)	3,259 (43.4)	0.93	−0.13	3,837 (41.8)	3,777 (41.2)	0.37	1.33
Charlson comorbidity index[b], *n* (%)			0.94				0.1	
0 to <1	3,525 (47.0)	3,487 (46.5)		1.02	3,802 (41.4)	3,676 (40.1)		2.79
1 to <2	1,869 (24.91)	1,884 (25.1)		−0.46	2,286 (24.9)	2,262 (24.6)		0.61
2 to <3	1,094 (14.6)	1,120 (14.9)		−0.98	1,583 (17.3)	1,643 (17.9)		−1.72
3 to <4	483 (6.4)	492 (6.6)		−0.49	750 (8.2)	832 (9.1)		−3.18
≥4	532 (7.1)	520 (6.9)		0.63	758 (8.3)	766 (8.4)		−0.32
Comorbidities[b], *n* (%)								
AIDS/HIV	12 (0.2)	13 (0.2)	0.84	−0.33	44 (0.5)	37 (0.4)	0.44	1.15
Anemia	706 (9.4)	696 (9.3)	0.78	0.46	932 (10.2)	899 (9.8)	0.42	1.2
Any renal disease	486 (6.5)	461 (6.1)	0.40	1.37	766 (8.4)	737 (8.0)	0.43	1.15
Any tumor	232 (3.1)	251 (3.4)	0.38	−1.43	339 (3.69)	335 (3.65)	0.88	0.23
Asthma	183 (2.4)	188 (2.5)	0.79	−0.43	235 (2.6)	219 (2.4)	0.45	1.12
Baseline bleed, all diagnosis	439 (5.9)	446 (5.9)	0.81	−0.4	575 (6.3)	591 (6.4)	0.63	−0.71
Chronic pulmonary disease	838 (11.2)	855 (11.4)	0.66	−0.72	1,276 (13.9)	1,338 (14.6)	0.19	−1.93
Coagulation defects	246 (3.3)	242 (3.2)	0.85	0.3	385 (4.2)	386 (4.2)	0.97	−0.05
Connective tissue disease	142 (1.9)	147 (2.0)	0.77	−0.48	226 (2.5)	261 (2.8)	0.11	−2.37
Dementia	1,421 (18.9)	1,457 (19.4)	0.46	−1.22	2,036 (22.2)	2,120 (23.1)	0.14	−2.19
Diabetes	1,068 (14.2)	1,052 (14.0)	0.71	0.61	1,337 (14.6)	1,356 (14.8)	0.69	−0.59
Diabetes with end-organ damage	95 (1.3)	94 (1.3)	0.94	0.12	139 (1.5)	142 (1.6)	0.86	−0.27
Fracture/trauma involving the lower extremities	137 (1.8)	130 (1.7)	0.67	0.71	208 (2.3)	215 (2.3)	0.73	−0.51
Hemiplegia or paraplegia	218 (2.9)	221 (3.0)	0.88	−0.24	300 (3.3)	326 (3.6)	0.29	−1.56
Hyperlipidemia	412 (5.5)	390 (5.2)	0.42	1.3	483 (5.3)	493 (5.4)	0.74	−0.49
Inflammatory bowel disease	41 (0.6)	44 (0.6)	0.74	−0.53	55 (0.6)	62 (0.7)	0.52	−0.96
Interstitial pneumonia	51 (0.7)	54 (0.7)	0.77	−0.48	70 (0.8)	82 (0.9)	0.33	−1.44
Mild liver disease	176 (2.35)	170 (2.3)	0.74	0.53	248 (2.7)	247 (2.7)	0.96	0.07

(*Continued*)

Table 1 (*Continued*)

Characteristic	VKA vs. apixaban				VKA vs. rivaroxaban			
	VKA ($N = 7,503$)	Apixaban ($N = 7,503$)	*p*-Value	Std. difference	VKA ($N = 9,179$)	Rivaroxaban ($N = 9,179$)	*p*-Value	Std. difference
DVT only[a], *n* (%)	**2,184 (29.1)**	**2,220 (29.6)**	**0.52**	**−1.05**	**2,997 (32.7)**	**3,015 (32.9)**	**0.78**	**−0.42**
Myocardial infarction	316 (4.2)	325 (4.3)	0.72	−0.59	403 (4.4)	433 (4.7)	0.29	−1.57
Obesity	1,029 (13.7)	996 (13.3)	0.43	1.29	1,233 (13.4)	1,314 (14.3)	0.084	−2.55
Peripheral vascular disease	347 (4.6)	342 (4.6)	0.85	0.32	472 (5.1)	517 (5.6)	0.14	−2.17
Pneumonia	677 (9.0)	669 (8.9)	0.82	0.37	873 (9.5)	886 (9.7)	0.74	−0.48
Recent history of falls	274 (3.7)	294 (3.9)	0.39	−1.4	362 (3.9)	362 (3.9)	1	
Rheumatologic disease	757 (10.1)	752 (10.0)	0.89	0.22	943 (10.3)	975 (10.6)	0.44	−1.14
Selected surgeries	546 (7.3)	525 (7.0)	0.51	1.09	739 (8.1)	768 (8.4)	0.44	−1.15
Sleep apnea	276 (3.68)	273 (3.6)	0.9	0.21	328 (3.6)	331 (3.6)	0.91	−0.18
Concomitant treatment[c], *n* (%)								
ACE inhibitors/ARBs, antiarrhythmic	1,234 (16.5)	1,244 (16.58)	0.83	−0.36	1,576 (17.2)	1,597 (17.4)	0.68	−0.61
Anticonvulsant strong inducer of hepatic enzymes	84 (1.1)	83 (1.1)	0.94	0.13	125 (1.4)	128 (1.4)	0.85	−0.28
Antiplatelet	1,492 (19.9)	1,506 (20.1)	0.78	−0.47	1,901 (20.7)	1,951 (21.3)	0.36	−1.34
Erythropoiesis-stimulating agents	24 (0.3)	15 (0.2)	0.15	2.36	29 (0.3)	31 (0.3)	0.8	−0.38
HIV protease inhibitors	1 (0.01)	2 (0.03)	0.56	−0.94	13 (0.1)	9 (0.1)	0.39	1.26
Hormone therapy	297 (4.0)	282 (3.8)	0.52	1.04	341 (3.7)	374 (4.1)	0.21	−1.86
NSAIDs	2,367 (31.6)	2,398 (32.0)	0.59	−0.89	2,831 (30.8)	2,867 (31.2)	0.57	−0.85
SERMs	853 (11.4)	857 (11.4)	0.92	−0.17	1,118 (12.2)	1,130 (12.3)	0.79	−0.4

Abbreviations: ACE, angiotensin-converting enzyme; AIDS, acquired immunodeficiency syndrome; ARB, angiotensin receptor blocker; DVT, deep vein thrombosis; HIV, human immunodeficiency virus; LMWH, low-molecular-weight heparin; NSAID, nonsteroidal anti-inflammatory drug; PS, propensity score; SD, standard deviation; SERM, selective estrogen receptor modulator; Std, standardized; VKA, vitamin K antagonist; VTE, venous thromboembolism.

[a]Versus PE with or without DVT.

[b]Evaluated in the 24 months prior to the index date, exclusive of the index date.

[c]3 months prior to the index date, exclusive of the index date.

Table 2 Index therapy characteristics: PS-matched cohorts

Characteristic	VKA vs. apixaban		VKA vs. rivaroxaban	
	VKA ($N = 7,503$)	Apixaban ($N = 7,503$)	VKA ($N = 9,179$)	Rivaroxaban($N = 9,179$)
Median follow-up (d)	182	183	182	183
Treatment pattern up to 6 months, *n* (%)				
Treatment discontinuation[a]	119 (1.6)	206 (2.75)	144 (1.6)	349 (3.8)
Treatment interruption[b]	294 (3.9)	714 (9.5)	353 (3.9)	700 (7.6)
Treatment persistence[c]	5,136 (68.5)	5,839 (77.8)	6,338 (69.1)	7,103 (77.4)
Switching[d]	1,954 (26.0)	744 (9.9)	2,344 (25.5)	1027 (11.2)
Duration of treatment up to 6 months (continuous), months, median	5.95	5.95	5.95	5.95
Daily dose at treatment initiation (for DOACs only), *n* (%)				
Apixaban				
2.5 mg	-	502 (6.7)	-	-
5 mg	-	6,923 (92.3)	-	-
2.5 and 5 mg	-	78 (1.0)	-	-
Rivaroxaban				
10 mg	-	-	-	106 (1.2)
15 mg	-	-	-	3,213 (35.0)
20 mg	-	-	-	914 (10.0)
15 and 20 mg	-	-	-	4,864 (53.0)
10 and 15 mg	-	-	-	56 (0.6)
10 and 20 mg	-	-	-	14 (0.2)
10, 15, and 20 mg	-	-	-	12 (0.1)

Abbreviations: DOAC, direct oral anticoagulant; LMWH, low-molecular-weight heparin; PS, propensity score; VKA, vitamin K antagonist.
[a]For DOACs, discontinuation was defined as no evidence of index reimbursement for 30 days from the estimated end of the days of supply of the index treatment. If an all-cause hospitalization occurred during these days, the length of the hospital stay was deducted from the duration of days without refilling the treatment.
[b]Defined as a patient having a gap with no new treatment within 30 days of the estimated end of supply and index therapy being restarted >30 days after the estimated end of supply.
[c]Defined as the number of days the patient remained on the index drug with a gap of ≤30 days between the run-out date of the previous reimbursement and the following reimbursement. Nonpersistence was defined as discontinuation of index drug or switch to another anticoagulant during follow-up period.
[d]Prescription of a different anticoagulant started at least 1 day after the last reimbursement date of the index treatment and within 30 days after the estimated end of supply of the index drug.

PS-matching group (►**Supplementary Table S11**, available in the online version).

Discussion

This study showed that adults with VTE treated with apixaban had lower risks of bleeding requiring hospitalization, intracranial bleeding, gastrointestinal bleeding, other bleeding, all-cause death, and first recurrent VTE than patients treated with VKAs. Also, adults with VTE treated with rivaroxaban had lower risks of intracranial bleeding and all-cause death than patients treated with VKAs. Along with the U.S. claims-based study,[20] this further extends the results of the clinical trials to a real-world setting. The results provide further support for the established guidelines recommending the use of DOACs over conventional VTE therapies.[3,16,17]

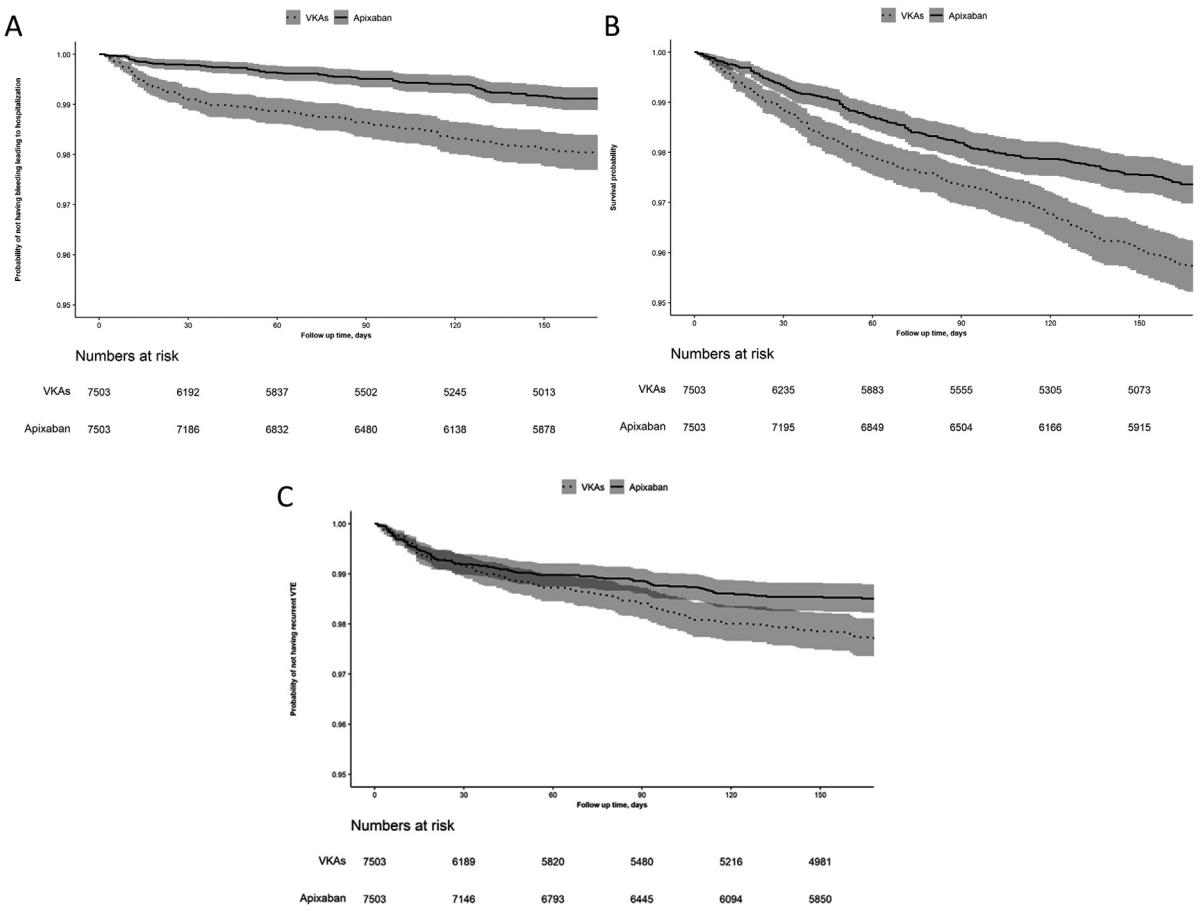

Fig. 2 Kaplan–Meier curves for (**A**) bleeding requiring hospitalization, (**B**) all-cause death, and (**C**) first recurrent VTE at 6 months: apixaban versus VKAs. VKA, vitamin K antagonist; VTE, venous thromboembolism.

The results for apixaban were similar to those of the AMPLIFY phase 3 trial for the bleeding outcome (including bleeding by site), although patients in the current study were older and did not have active cancer. In the current study apixaban was associated with a reduced risk of recurrent VTE, whereas the AMPLIFY study showed that apixaban was noninferior to conventional therapy for risk of recurrent VTE or VTE-related death.[31] Similarly, a U.S. claims database study showed that major bleeding, clinically relevant non-major bleeding, and recurrent VTE were all lower with apixaban than with warfarin, even though patients in the current study were older.[20]

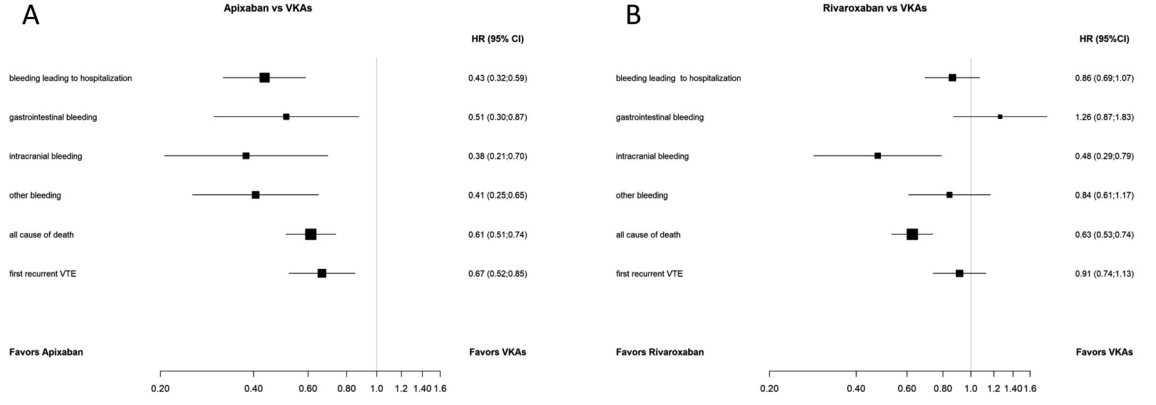

Fig. 3 Forest plots of hazard ratios for bleeding requiring hospitalization, gastrointestinal bleeding, intracranial bleeding, other bleeding, all-cause death, and first recurrent VTE at 6 months for (**A**) apixaban and (**B**) rivaroxaban: PS matching analysis. Adjustment on NSAIDs, antiplatelets, and strong inhibitors (time dependent).CI, confidence interval; HR, hazard ratio; NSAIDs, nonsteroidal anti-inflammatory drugs; PS, propensity score; VKA, vitamin K antagonist; VTE, venous thromboembolism.

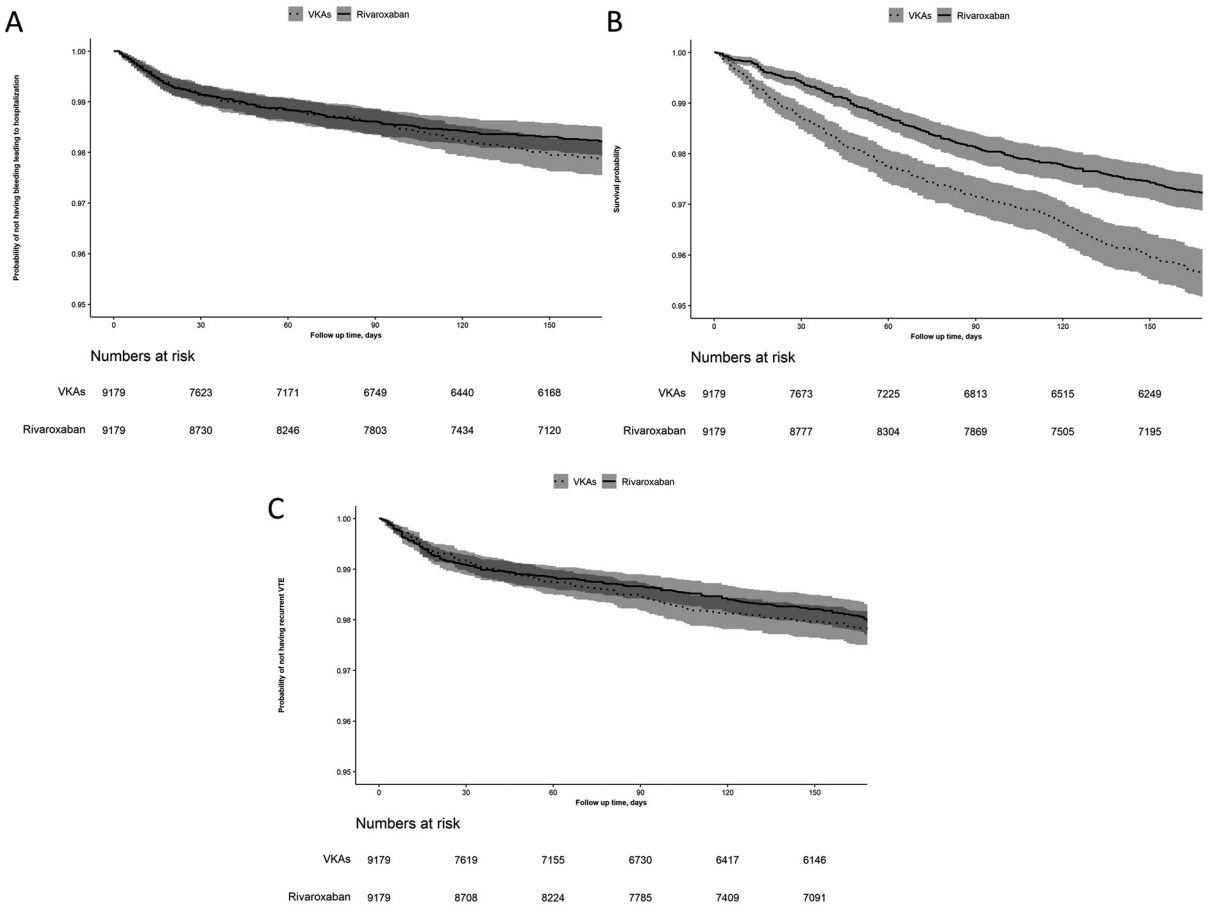

Fig. 4 Kaplan–Meier curves for (**A**) bleeding requiring hospitalization, (**B**) all-cause death, and (**C**) first recurrent VTE at 6 months: rivaroxaban versus VKAs. VKA, vitamin K antagonist; VTE, venous thromboembolism.

For rivaroxaban, our PS matching results for recurrent VTE are in line with the results of the EINSTEIN randomized clinical trials. In EINSTEIN-PE and EINSTEIN-DVT, rivaroxaban was noninferior to conventional therapy for recurrent VTE.[32,33] Superiority for VTE recurrence was not met in the EINSTEIN-PE study and not assessed in the EINSTEIN-DVT study. Results for bleeding were also generally similar although endpoints differed. In the EINSTEIN-DVT study, first major bleeding, clinically relevant nonmajor bleeding, and major bleeding did not differ between patients receiving rivaroxaban and those receiving conventional therapy, and in the EINSTEIN-PE study, major bleeding but none of the other outcomes differed between rivaroxaban and conventional therapy. In contrast, in the REMOTEV observational study, rates of major bleeding and clinically relevant nonmajor bleeding were significantly lower with rivaroxaban than with VKAs.[34] As in the current study, the rate of all-cause death was significantly lower with rivaroxaban than with VKAs in the REMOTEV observational study but not significantly lower with rivaroxaban than conventional therapy in the EINSTEIN studies. The differences in the findings could be due to the different characteristics of the study population, the treatments received, and the study design, but overall, whether rivaroxaban has a consistent benefit over VKAs requires further investigation.

In our study, the proportion of patients who switched to other anticoagulants was higher and persistence was lower in patients prescribed VKAs than in patients prescribed either apixaban or rivaroxaban. Similarly, a U.S. commercial claims database study in patients with active cancer and VTE showed that drug switching was also more frequent in patients prescribed LMWH than in patients prescribed apixaban.[35] Explanations for these results could include increased safety (less major bleeding), less food and drug interactions, and greater convenience (including no requirement for regular laboratory anticoagulation monitoring) with DOACs than with VKAs or LMWH.[36]

The results of our study were primarily based on PS matching and supported by IPTW, although IPTW findings were slightly different for rivaroxaban, possibly because of differences in populations and population sizes. For example, in the IPTW populations (compared with PS-matched populations), the patients were on average younger and had a lower comorbidity burden. In the PS matching cohort, all patients analyzed received either the intervention or the control. Thus, PS matching took into account contraindications and factors that can influence treatment decisions, such as the perception of bleeding risk and the pharmacological properties of oral anticoagulants.[37] The IPTW cohort includes a larger population but does not take into account

contraindications for individual treatments because some patients may have never received the intervention or control therapy. IPTW can also be inaccurate when overlap is poor in patient populations and may falsely indicate a difference when sample sizes are large.[38]

A strength of this study was that data were from a large national database that included roughly 99% of the French population with a single payer which limits selection bias in the study. Moreover, the patients included in the study also had access to universal health care, unlike in the United States. Additionally, our results were consistent across sensitivity analyses. To our knowledge, this is one of the largest European observational studies on DOACs and VKAs in patients with acute VTE, which provided high statistical power to detect differences. A potential limitation of this study was that it included only patients who were hospitalized because diagnostic codes and a validated algorithm for identifying outpatients with VTE were unavailable. Also, most of the patients in the current study had PE (with or without DVT). Therefore, the study excluded patients with less severe VTE and may also have excluded some patients because of missing or incorrect diagnostic codes. Another potential limitation was that treatments given to patients while in the hospital were not identified and those administered after hospital release had to be assumed based upon packaging. These issues, however, should have been similar between patient cohorts. Future work should include patients with active cancer, which was not included in the current study due to insufficient numbers. Additionally, the quality of VKA management could not be assessed in this study as international normalized ratio (INR) data are not coded in SNDS. This means that patients with significant time outside of their designated therapeutic range may be included in the analysis. Low time in therapeutic range may lead to poor outcomes in the VKA population but is reflective of real-world outcomes for patients treated with VKAs. Previous studies in France estimate inadequate INR control (as low as 50% considered to have well-controlled time in therapeutic range) in patients treated with VKAs across indications.[39–41] Furthermore, only recurrent events recorded in the hospital, and not in outpatient settings, were included which may have led to an underestimation of events. However, the approach of using hospital diagnoses maximizes the positive predictive value of identifying valid recurrent VTE events which improves the validity of the study. Moreover, the majority of patients with recurrent VTE on anticoagulant therapy are managed in the hospital and not as outpatients. Lastly, 1:1 PS matching analysis was conducted, which is the most common approach for PS matching.[42] The advantages of PS matching include being able to directly compare treated and untreated individuals. In our analysis, once a control patient was matched with an intervention patient, they were no longer available to be matched to other intervention patients. Differences in patient characteristics and the fact that there was a maximum of 10,775 patients in the control (VKA arm) resulted in patients being excluded from the primary analysis, which may have resulted in some selection bias. However, given the large numbers of patients included in this study, this did not impact the statistical powering of the study to be able to detect differences in any of the outcomes. As discussed above, results from the primary analysis are supported by IPTW analyses that included most patients.

In conclusion, the results of our study are in line with clinical trials and those of previous observational studies, both in terms of safety and effectiveness.[20–22] To our knowledge, this is the first nation-wide European observational study evaluating the safety and effectiveness of both apixaban and rivaroxaban compared with VKAs in acute VTE. Our results suggest that apixaban may offer better effectiveness and safety over VKAs for the treatment of VTE in patients without active cancer. This study also suggested some benefit of rivaroxaban over VKAs. Overall, these results support recommendations to use DOACs over VKAs for the treatment of VTE.

What is known about this topic?

- Conventional therapy (low-molecular-weight heparin followed by vitamin K antagonists) for venous thromboembolism is associated with increased risks of major bleeding.
- Results from clinical trials showed that direct oral anticoagulants were able to reduce risks of bleeding, with a similar efficacy, compared with conventional therapy.
- To complement clinical trial data, real-world evidence is needed to inform about the relative efficacy and safety of direct oral anticoagulants in a broader population.

What does this paper add?

- This retrospective study on venous thromboembolism treatments using a French national database showed that effectiveness and safety were better with direct oral anticoagulants (apixaban and rivaroxaban) than with vitamin K antagonists in patients with no active cancer.
- This study adds additional real-world evidence and complements results from clinical trials in a broader population.

Funding
This study was sponsored by Pfizer and Bristol Myers Squibb.

Conflict of Interest
L.B. has received personal fees and nonfinancial support from Aspen, Bayer, Bristol Myers Squibb, Pfizer, and LEO Pharma; nonfinancial support from Daiichi-Sankyo. G.G., A.K., and N.Q. are employees of Certara, who were paid consultants to BMS and Pfizer in connection with the conduct of this study. J.C., A.M., and R.M. are employees and shareholders of Pfizer.

Acknowledgments
Medical writing support was provided by Holly Richendrfer and Phillip S. Leventhal (Evidera) and was funded by Pfizer and Bristol Myers Squibb.

References

1 Khan F, Tritschler T, Kahn SR, Rodger MA. Venous thromboembolism. Lancet 2021;398(10294):64–77
2 Di Nisio M, van Es N, Büller HR. Deep vein thrombosis and pulmonary embolism. Lancet 2016;388(10063):3060–3073
3 Konstantinides SV, Meyer G, Becattini C, et al; ESC Scientific Document Group. 2019 ESC guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J 2020;41(04):543–603
4 Wendelboe AM, Raskob GE. Global burden of thrombosis: epidemiologic aspects. Circ Res 2016;118(09):1340–1347
5 Keller K, Hobohm L, Ebner M, et al. Trends in thrombolytic treatment and outcomes of acute pulmonary embolism in Germany. Eur Heart J 2020;41(04):522–529
6 Delluc A, Tromeur C, Le Ven F, et al; EPIGETBO study group. Current incidence of venous thromboembolism and comparison with 1998: a community-based study in Western France. Thromb Haemost 2016;116(05):967–974
7 CDC. Data and statistics on venous thromboembolism. Published 2020. Accessed June 1, 2021: https://www.cdc.gov/ncbddd/dvt/data.html
8 Khan F, Rahman A, Carrier M, et al; MARVELOUS Collaborators. Long term risk of symptomatic recurrent venous thromboembolism after discontinuation of anticoagulant treatment for first unprovoked venous thromboembolism event: systematic review and meta-analysis. BMJ 2019;366:l4363–l4363
9 McRae SJ, Ginsberg JS. Initial treatment of venous thromboembolism. Circulation 2004;110(09, Suppl 1):I3–I9
10 Wigle P, Hein B, Bloomfield HE, Tubb M, Doherty M. Updated guidelines on outpatient anticoagulation. Am Fam Physician 2013;87(08):556–566
11 Kakkos SK, Kirkilesis GI, Tsolakis IA. Editor's Choice - efficacy and safety of the new oral anticoagulants dabigatran, rivaroxaban, apixaban, and edoxaban in the treatment and secondary prevention of venous thromboembolism: a systematic review and meta-analysis of phase III trials. Eur J Vasc Endovasc Surg 2014;48(05):565–575
12 Sardar P, Chatterjee S, Mukherjee D. Efficacy and safety of new oral anticoagulants for extended treatment of venous thromboembolism: systematic review and meta-analyses of randomized controlled trials. Drugs 2013;73(11):1171–1182
13 Yeh CH, Gross PL, Weitz JI. Evolving use of new oral anticoagulants for treatment of venous thromboembolism. Blood 2014;124(07):1020–1028
14 van Es N, Coppens M, Schulman S, Middeldorp S, Büller HR. Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials. Blood 2014;124(12):1968–1975
15 Bertoletti L, Ollier E, Duvillard C, et al. Direct oral anticoagulants: current indications and unmet needs in the treatment of venous thromboembolism. Pharmacol Res 2017;118:33–42
16 Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest 2016;149(02):315–352
17 Ortel TL, Neumann I, Ageno W, et al. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. Blood Adv 2020;4(19):4693–4738
18 Moustafa F, Giorgi Pierfranceschi M, Di Micco P, et al; RIETE Investigators. Clinical outcomes during anticoagulant therapy in fragile patients with venous thromboembolism. Res Pract Thromb Haemost 2017;1(02):172–179
19 Safieddine M, Chapelle C, Ollier E, et al. Compared to randomized studies, observational studies may overestimate the effectiveness of DOACs: a metaepidemiological approach. J Clin Epidemiol 2021;130:49–58
20 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(11):1951–1961
21 Dawwas GK, Smith SM, Dietrich E, Lo-Ciganic WH, Park H. Comparative effectiveness and safety of apixaban versus warfarin in patients with venous thromboembolism. Am J Health Syst Pharm 2020;77(03):188–195
22 Coleman CI, Bunz TJ, Turpie AGG. Effectiveness and safety of rivaroxaban versus warfarin for treatment and prevention of recurrence of venous thromboembolism. Thromb Haemost 2017;117(10):1841–1847
23 Bezin J, Duong M, Lassalle R, et al. The national healthcare system claims databases in France, SNIIRAM and EGB: powerful tools for pharmacoepidemiology. Pharmacoepidemiol Drug Saf 2017;26(08):954–962
24 Haute Autorité de Santé ELIQUIS (apixaban), oral anticoagulant. Published 2015. Accessed June 28, 2021: https://www.has-sante.fr/jcms/c_2038860/fr/eliquis-apixaban-anticoagulant-par-voie-orale
25 Haute Autorité de Santé XARELTO (rivaroxaban), oral anticoagulant. Published 2013. Accessed June 28, 2021: https://www.has-sante.fr/jcms/c_1615053/fr/xarelto-rivaroxaban-anticoagulant-par-voie-orale
26 European Medicines Agency. Eliquis. Published 2021. Accessed January 9, 2022: https://www.ema.europa.eu/en/medicines/human/EPAR/eliquis#:~:text=The%20recommended%20dose%20is%20one,mg%20taken%20twice%20a%20day
27 European Medicines Agency. Xarelto. Accessed January 9, 2022https://www.ema.europa.eu/en/medicines/human/EPAR/xarelto2021
28 Rothman KJ, Greenland S. Modern Epidemiology. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2008
29 Rothman KJ. Disengaging from statistical significance. Eur J Epidemiol 2016;31(05):443–444
30 Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. Stat Med 2015;34(28):3661–3679
31 Agnelli G, Buller HR, Cohen A, et al; AMPLIFY Investigators. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med 2013;369(09):799–808
32 Bauersachs R, Berkowitz SD, Brenner B, et al; EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 2010;363(26):2499–2510
33 Büller HR, Prins MH, Lensin AW, et al; EINSTEIN–PE Investigators. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med 2012;366(14):1287–1297
34 Gaertner S, Cordeanu E-M, Nouri S, et al. Rivaroxaban versus standard anticoagulation for symptomatic venous thromboembolism (REMOTEV observational study): analysis of 6-month outcomes. Int J Cardiol 2017;226:103–109
35 Cohen A, Keshishian A, Lee T, et al. Effectiveness and safety of apixaban, low-molecular-weight heparin, and warfarin among venous thromboembolism patients with active cancer: a U.S. claims data analysis. Thromb Haemost 2021;121(03):383–395
36 Mekaj YH, Mekaj AY, Duci SB, Miftari EI. New oral anticoagulants: their advantages and disadvantages compared with vitamin K antagonists in the prevention and treatment of patients with thromboembolic events. Ther Clin Risk Manag 2015;11:967–977
37 Allan V, Ramagopalan SV, Mardekian J, et al. Propensity score matching and inverse probability of treatment weighting to

address confounding by indication in comparative effectiveness research of oral anticoagulants. J Comp Eff Res 2020;9(09): 603–614

38 Xu S, Ross C, Raebel MA, Shetterly S, Blanchette C, Smith D. Use of stabilized inverse propensity scores as weights to directly estimate relative risk and its confidence intervals. Value Health 2010; 13(02):273–277

39 Cambus JP, Magnin D, Ambid-Lacombe C, et al. Anticoagulant clinics are they effective in France? Performance evaluation of six anticoagulant clinics concerning the management of vitamin K antagonists [in French]. Rev Med Interne 2013;34(09): 515–521

40 Mahé I, Bal dit Sollier C, Duru G, Lamarque H, Bergmann JF, Drouet L. Use and monitoring of vitamin K antagonists in everyday medical practice. French results of the international ISAM study of patients with nonvalvular atrial fibrillation [in French]. Presse Med 2006;35(12, Pt 1):1797–1803

41 Cotté FE, Benhaddi H, Duprat-Lomon I, et al. Vitamin K antagonist treatment in patients with atrial fibrillation and time in therapeutic range in four European countries. Clin Ther 2014;36(09): 1160–1168

42 Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res 2011;46(03):399–424

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