Effectiveness and safety of oral anticoagulants in the treatment of acute venous thromboembolism: A nationwide comparative cohort study in France

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Abstract:

Introduction: Data from clinical trials indicate that direct oral anticoagulants (DOACs) are non-inferior 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.

Materials and Methods: This observational study used French national claims data of adult, treatment-naive patients diagnosed with VTE (majority PE) who were hospitalized and treated for VTE with a DOAC (apixaban or rivaroxaban) or VKAs during 2013–2018. 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: 58137 patients were included (10775 VKAs, 10440 apixaban, 36922 rivaroxaban). Propensity score-matched cohort sizes were 7503 for apixaban and 9179 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 (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]).

Conclusions: 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.

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Appendix A. Propensity score

\[ \text{Logit } \hat{\psi}, \]

where \( Z = 1 \) or 0 according to if the patient is on direct anticoagulants (apixaban and rivaroxaban separately) or reference drug (vitamin K antagonists [VKAs] or low-molecular weight heparin), and \( X_1 \) and \( X_2 \) are baseline characteristics. The random error \( \epsilon \) was assumed to be independent of \( Z, X_1, \) and \( X_2. \)

The propensity score acts as a balancing score between the cohorts. After calculating the propensity score, the distribution of the propensity scores were reviewed.

First, the means and proportions of baseline variables were compared. The standardized difference compared the difference in means in units of the standard deviation. If the standardized difference was less than 10%, the covariates were considered balanced. For continuous variables, the balance of the distribution was also assessed. The high-order movements and interactions between variables should be similar between cohorts. The standardized difference was used to compare the mean of the square of continuous variables. Graphical comparisons of the distribution of continuous variables were completed. Since the graphical approach can be subjective, a numerical method for comparing the distribution of continuous baseline covariates was completed. Kolmogorov-Smirnov test allows a comparison of the distribution of a continuous variable between two independent groups.
Appendix B. Construction of the IPTW scores

After calculating the propensity score (detailed method in Appendix A), the distribution of the propensity scores were reviewed. Each patient was weighted by the inverse of the probability of their treatment option (weight=1/propensity score if the patient was on DOAC or weight = 1/(1- propensity score) if the patient was on VKA).

If a treated patient had a very low propensity score, a very large weight was generated. Large weights can increase the variability of estimated treatment effect. In order to address this, the weights were stabilized. In order to stabilize the weights, the treatment option and control weights were multiplied by a constant, equal to the expected value of being in the treatment or comparison cohorts. This reduced the variability of the weights and reduced the variance of the treatment effect estimates.

The distribution of the stabilized weight was reviewed. In cases of extreme outliers, the large weights were set to a less extreme value (recoding all weights that were greater than the 99th percentile to the 99th value).

First, the means and proportions of baseline variables were compared. The standardized difference compared the difference in means in units of the standard deviation. If the standardized difference was less than 10%, the covariates were considered balanced. For continuous variables, the balance of the distribution was also assessed. The high-order movements and interactions between variables should be similar between cohorts. The standardized difference was used to compare the mean of the square of continuous variables. Graphical comparisons of the distribution of continuous variables was completed. Side-by-side boxplots and empirical cumulative
distribution functions were used to compare the distribution of continuous covariates in the unweighted and weighted samples. Since the graphical approach can be subjective, a numerical method for comparing the distribution of continuous baseline covariates was completed. The Kolmogorov-Smirnov test allowed for a comparison of the distribution of a continuous variable between two independent groups.
Effectiveness and safety of oral anticoagulants in the treatment of acute venous thromboembolism: A nationwide comparative cohort study in France

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Summary Table

1. What is known on 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 to 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.

2. 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 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.
Abstract

Introduction: Data from clinical trials indicate that direct oral anticoagulants (DOACs) are non-inferior 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.

Materials and 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 2013–2018. 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: 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 (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]).
Conclusions: 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.

Keywords: venous thromboembolism, anticoagulant agents, apixaban, rivaroxaban, bleeding

Abbreviations: DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; HR, hazard ratio; ICD-10, International Classification of Diseases, Tenth Revision; INR, International normalized ratio; IPTW, inverse probability treatment weighting; LMWH, low molecular weight heparin; PE, pulmonary embolism; PS, propensity score; VKA, vitamin K antagonist; VTE, venous thromboembolism

Introduction

Deep vein thrombosis (DVT) and pulmonary embolism (PE), collectively referred to as venous thromboembolism (VTE), affect approximately 10 million people worldwide.\textsuperscript{1-3} Overall global incidence rate of VTE is 115 to 269 per 100000.\textsuperscript{4} Annual incidence rates range from 39 to 115 for PE and 53 to 162 for DVT per 100000 population.\textsuperscript{4-6} Data from the US 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.\textsuperscript{7} One quarter of these patients have a recurrence within 5 years and over one-third have a recurrence within 10 years.\textsuperscript{8}

The goal of VTE treatment is to prevent its recurrence over the long-term by resolving and preventing extension of the clot.\textsuperscript{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 in order 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 non-inferior 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 Cardiology³ recommends using DOACS over VKAs for first-line treatment of VTE. Similarly, the American College of Chest Physicians¹⁶ and the American Society of Hematology¹⁷ suggests 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 is also needed because the risk-benefit ratio of DOACs may differ in a non-clinical trial population.¹⁸,¹⁹ Three recent matched-cohort studies of US 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 non-major bleeding, and recurrent VTE.²⁰-²² The current study further extends the US 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.
Materials and 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), which covers 99% of the French population. 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, 25 July 2012; PE, transparency committee, 12 June 2013) and apixaban (PE and DVT, transparency committee, 1 April 2015) in this indication in France. VTE was identified through ICD-10 diagnoses of hospital stay (see Supplemental Table 1 for ICD-10 codes for a diagnosis of VTE) and VTE diagnostic procedure (see Supplemental Table 2 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 ≥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/low molecular weight heparin (LMWH) bridging or VKA only cohort, if patients used VKA and had a reimbursement for LMWH within 14 days before or after VKAs initiation, then their first VKA reimbursement date were 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 (Supplemental Table 3). 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 Supplemental Table 4 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 Supplemental Table 2 for list of procedures to diagnose DVT and PE). Other outcomes of interest included gastrointestinal bleeding, intracranial bleeding, and other bleeding (see Supplemental Table 4 for bleeding codes).
A sensitivity analysis was performed for bleeding requiring hospitalization, all ICD-10 codes or transfusions (Supplemental Table 4. 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, NC, USA). 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 multinominal logistic derived for each of the treatment comparisons of interest (VKA as reference treatment for VTE population) (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 Supplemental Table 5 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 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).
In order to compare risk, the cumulative incidence rate for clinical outcomes censored at 6 months (including 95% confidence interval 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. 95% confidence intervals were calculated using a previously published method.\textsuperscript{28} If the confidence interval did not include the null hypothesis value ("1"), the results were considered to be statistically significant.\textsuperscript{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 alpha 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 (\textbf{Appendix B}). IPTW also uses PS to obtain estimates of the average treatment effect.\textsuperscript{30} The propensity score was calculated using the same formula as PS matching (\textbf{Appendix A}). After IPTW, incidence rates were calculated as the number of events per
100 person-years for bleeding requiring hospitalization, first recurrent VTE and all-cause death. The Cox proportional hazard model was used to compared 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 = 10440), rivaroxaban (n = 36922), or VKA only or LMWH to VKA bridging (n = 10775) within 30 days after their index VTE encounter (Figure 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 (Supplemental Table 6). 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, 7503 patients were included in each of the cohorts for the apixaban vs. VKA comparison and 9179 in each of the cohorts for the rivaroxaban vs. VKA comparison (Table 1). Demographic characteristics were similar for the two cohorts in the apixaban vs VKA comparison and in the rivaroxaban vs. 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 (Supplemental Table 7).

**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 vs. apixaban and VKA vs. 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 10440 prescribed apixaban, 36922 prescribed rivaroxaban, and 10775 prescribed VKAs (Supplemental Table 8). The number of patients and crude event incidence rate (rate per 100 Person Year (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. 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. 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 (Supplemental Table 9). 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 (Supplemental Table 9). 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 vs. 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 (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)]) (Supplemental Table 9, Figure 2,
and Figure 4). 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 (Supplemental Table 10 and Supplemental Figure 1).

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 (Supplemental Table 11).

VKA vs. 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))] (Supplemental Table 9, Figure 3, and Figure 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 (Supplemental Table 10 and Supplemental Figure 1).

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 PS matching group (Supplemental Table 11).

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 US claims-based study, 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

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.\textsuperscript{31} Similarly, a US claims database study showed that major bleeding, clinically relevant non-major bleeding, and recurrent VTE were all lower with apixaban than warfarin, even though patients in the current study were older.\textsuperscript{20}

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 non-inferior to conventional therapy for recurrent VTE.\textsuperscript{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 non-major 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 non-major bleeding were significantly lower with rivaroxaban than VKAs.\textsuperscript{34} As in the current study, the rate of all-cause death was significantly lower with rivaroxaban than 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 US 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. 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.

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 to 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.

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.

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 healthcare, unlike in the US. 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 that 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 INR (International normalized ratio) 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 \(^\text{42}\). 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 10775 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.\(^\text{20-22}\) To our knowledge, this is the first nation-wide European observational study evaluating the safety and effectiveness of both apixaban and rivaroxaban compared to 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.
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Conflicts of Interest

LB has received personal fees and non-financial support from Aspen, Bayer, Bristol Myers Squibb, Pfizer, and LEO Pharma, non-financial support from Daiichi-Sankyo. GG, AK and NQ are employees of Certara, who were paid consultants to BMS and Pfizer in connection with the conduct of this study. JC, AM and RM are employees and shareholders of Pfizer.

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**Figure 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.
Figure 2. Kaplan-Meier Curves for A) Bleeding requiring hospitalization, B) All-cause Death, and C) First-recurrent VTE at 6 months: Apixaban vs. VKAs. VKA, vitamin K antagonist; VTE, venous thromboembolism.

Figure 3. Kaplan-Meier Curves for A) Bleeding requiring hospitalization, B) All-cause Death, and C) First-recurrent VTE at 6 months: Rivaroxaban vs. VKAs. VKA, vitamin K antagonist; VTE, venous thromboembolism.

Figure 4. 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. CI, confidence interval; HR, hazard ratio; PS, propensity score; VKA, Vitamin K antagonist; VTE, venous thromboembolism. Adjustment on NSAIDS, antiplatelets and strong inhibitors (time dependent).

Supplemental Figure 1. Forest Plots of Hazard Ratios for Bleeding requiring hospitalization, All-cause Death, and First-recurrent VTE at 6 Months for A) Apixaban vs. VKAs and B) Rivaroxaban vs. VKAs: IPTW Analysis. CI, confidence interval; HR, hazard ratio; IPTW, Inverse-probability weighting treatment; NSAIDS, non-steroidal anti-inflammatory drugs; VKA, Vitamin K antagonist; VTE, venous thromboembolism. Adjustment on age, NSAIDS, antiplatelets and strong inhibitors (time dependent).
### Supplemental Table 1. ICD-10 Codes for a Diagnosis of VTE

| Description                                                                 | ICD-10   |
|-----------------------------------------------------------------------------|----------|
| **Deep venous thrombosis (DVT)**                                            |          |
| Phlebitis and thrombophlebitis of femoral vein                             | I80.1xxx |
| Phlebitis and thrombophlebitis of other deep vessels of lower extremities  | I80.2xxx |
| Phlebitis and thrombophlebitis of lower extremities, unspecified            | I80.3xxx |
| Phlebitis and thrombophlebitis of unspecified site                         | I80.9xxx |
| Thrombophlebitis migrans                                                  | I82.1xxx |
| Embolism and thrombosis of vena cava                                       | I82.2xxx |
| Embolism and thrombosis of other specified veins                           | I82.8xxx |
| Embolism and thrombosis of unspecified vein                                | I82.9xxx |
| **Pulmonary embolism (PE)**                                                |          |
| PE with mention of acute core pulmonale                                    | I26.0xxx |
| PE without mention of acute core pulmonale                                 | I26.9xxx |

Abbreviation: ICD-10, International Classification of Diseases
| Event                        | VKA vs. apixaban | VKA vs. rivaroxaban |
|------------------------------|------------------|--------------------|
|                              | VKA (N=10,510)   | Apixaban (N=10,223) | VKA (N=10,510) | Rivaroxaban (N=35956) |
| Bleeding requiring hospitalization n (%) | 208 (1.98) | 81 (0.79) | 208 (1.98) | 409 (1.14) |
| Incidence per 100 PY (95% CI) | 5.22 (4.53-5.98) | 1.80 (1.43-2.24) | 5.22 (4.53-5.98) | 2.60 (2.36-2.87) |
| HR a (95% CI)                | - | 0.42 (0.33-0.55) | - | 0.77 (0.64-0.93) |
| All-cause death n (%)        | 487 (4.63) | 212 (2.07) | 487 (4.63) | 420 (1.17) |
| Incidence per 100 PY (95% CI) | 12.22 (11.16-13.36) | 4.72 (4.10-5.40) | 12.22 (11.16-13.36) | 2.67 (2.42-2.94) |
| HR a (95% CI)                | - | 0.77 (0.66-0.90) | - | 0.668 (0.58-0.78) |
| First recurrent VTE n (%)    | 197 (1.87) | 150 (1.47) | 197 (1.87) | 679 (1.89) |
| Incidence per 100 PY (95% CI) | 4.94 (4.28-5.68) | 3.34 (2.82-3.92) | 4.94 (4.28-5.68) | 4.32 (4-4.66) |
| HR a (95% CI)                | - | 0.70 (0.57-0.87) | - | 0.82 (0.70-0.96) |

Abbreviations: CI, confidence interval; HR, hazard ratio; IPTW, inverse probability treatment weighting; LMWH, low molecular weight heparin; PY, person-years; VKA, vitamin K antagonist; VTE, venous thromboembolism

a Hazard ratio (95%CI) adjusted on age (as a strata), NSAIDS, antiplatelets and strong inhibitors (time dependent)
Supplemental Table 11. Sensitivity Analysis, Bleeding requiring hospitalization, all ICD-10 Codes and Transfusion

| Analysis/time point            | VKA vs. apixaban | Apixaban (N=7503) | VKA vs. rivaroxaban | Rivaroxaban (N=9179) |
|-------------------------------|------------------|-------------------|---------------------|----------------------|
|                               | VKA (N=7503)     |                   | VKA (N=9179)        |                      |
| PS matching, 6 months         |                  |                   |                     |                      |
| n (%)                         | 235 (3.13)       | 169 (2.25)        | 322 (3.51)          | 323 (3.52)           |
| Incidence per 100 PY (95% CI)| 8.29 (7.26-9.42) | 5.15 (4.40-5.99)  | 9.24 (8.26-10.31)   | 8.13 (7.27-9.07)     |
| HR (95% CI)                   | -                | 0.62 (0.51-0.76)  | -                   | 0.89 (0.76-1.04)     |

Abbreviations: CI, confidence interval; HR, hazard ratio; ICD 10, International Classification of Diseases, Tenth Revision; LMWH, low molecular weight heparin; PS, propensity score; PY, person-years; VKA, vitamin K antagonist; VTE, venous thromboembolism
Supplemental Table 2. List of Procedures for Diagnosis of PE and DVT

| Category | Description | CCAM procedure code |
|----------|-------------|---------------------|
| **Procedures for diagnosis of Pulmonary embolism** | | |
| Pulmonary angiography | Artériographie sélective du tronc et/ou des branches de l’artère pulmonaire, par voie veineuse transcutanée | DFQH001 |
| Lung scan | Scanographie du thorax, avec injection intraveineuse de produit de contraste | ZBQH001 |
| **Venous ultrasonography** | | |
| (echographie veineuse) | Échographie-doppler des veines des membres inférieurs et des veinesiliaques, pour recherche de thrombose veineuse profonde | EJQM003 |
| | Échographie-doppler de la veine cave inférieure et de ses affluents | DHQM002 |
| | Échographie-doppler des veines des membres inférieurs et des veinesiliaques, sans marquage cutané | EJQM004 |
| | Échographie-doppler des veines des membres supérieurs | EFQM001 |
| | Échographie-doppler des veines des membres inférieurs, avec marquage cutané ou cartographie hémodynamique | EJQM001 |
| **Contrast venography** | | |
| Phlébographie sélective de plusieurs branches des veinesiliaques communes et/ou de la veine cave inférieure, par voie veineuse transcutanée | DHQH001 |
| Phlébographie de la veine cave inférieure [Cavographie inférieure], par voie veineuse transcutanée | DHQH002 |
| Phlébographie de la veine cave supérieure [Cavographie supérieure], par injection intraveineuse transcutanée | DHQH003 |
| Phlébographie sélective d’une branche de la veine iliaque commune ou de la veine cave inférieure, par voie veineuse transcutanée | DHQH004 |
| Phlébographie des veines iliaque et cave inférieure [iliocavographie], par injection intraveineuse transcutanée fémorale unilatérale ou bilatérale | DHQH005 |
| Phlébographie hypersélective d’une branche de la veine iliaque commune ou de la veine cave inférieure, par voie veineuse transcutanée | DHQH007 |
| **CTPA scan** | | |
| (Angioscanner-angioCT) | Scanographie des vaisseaux du thorax et/ou du coeur, avec scanographie des vaisseaux de l'abdomen et/ou du petit bassin [Angioscanner thoracique avec angioscanner de l'abdomen et/ou du pelvis] | ECQH011 |
| | Scanographie des vaisseaux du thorax et/ou du coeur [Angioscanner thoracique] | ECQH010 |
| | Scanographie des vaisseaux des membres supérieurs [Angioscanner des membres supérieurs] |EKQH001 |
| | Scanographie des vaisseaux des membres inférieurs [Angioscanner des membres inférieurs] | EMQH001 |
### Procedures for diagnosis of deep venous thromboembolism

| Procedure                | Description                  |
|--------------------------|------------------------------|
| Venous ultrasonography   | See list above               |
| Contrast venography      | See list above               |

Abbreviations: CCAM, *Classification Commune des Actes Médicaux*; CTPA, computerized tomography pulmonary angiogram; DVT, deep vein thrombosis; PE, pulmonary embolism.
### Supplemental Table 3. Anticoagulant dosing schedule

| Drug      | Timing                                      | Dosing plan       |
|-----------|---------------------------------------------|-------------------|
| Apixaban  | 0 - 7 days after DVT/ PE date               | 10 mg twice daily |
|           | +7 days to 6 months after DVT/PE date       | 5 mg twice daily  |
|           | +6 months after DVT/PE date                 | 2.5 mg twice daily|
| Rivaroxaban| 0 – 21 days after DVT/PE date               | 15 mg twice daily |
|           | >21 days after DVT/PE date                  | 20 mg once daily  |
|           | >6 months DVT/PE date                       | 10 or 20 mg once daily |

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism
### Supplemental Table 4. ICD-10 Codes for Bleeding Leading to Hospitalization

| Bleeding site                  | ICD-10 Codes                                                                 |
|-------------------------------|-------------------------------------------------------------------------------|
| Intracranial                  |                                                                              |
| Intracranial hemorrhage       | I60 to I62                                                                    |
| Epidural hemorrhage           | S064                                                                         |
| Traumatic subdural hemorrhage | S065                                                                         |
| Traumatic subarachnoid hemorrhage | S066                                                                       |
| Gastrointestinal              |                                                                              |
| Oesophageal varices with bleeding | I850                                                                       |
| Gastro-oesophageal laceration-hemorrhage syndrome | K226                                                                       |
| Gastric ulcer/duodenal ulcer/peptic ulcer/gastrojejunal ulcer with hemorrhage | K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286 |
| Acute hemorrhagic gastritis   | K290                                                                         |
| Hemorrhage of anus and rectum | K625                                                                         |
| Hematemesis                   | K920                                                                         |
| Melaena                       | K921; Gastrointestinal hemorrhage, unspecified: K922                        |
| Uterine and vaginal bleeding  |                                                                              |
| N92.0 Menorrhagia (primary)   |                                                                              |
| N92.0 Excessive and frequent menstruation with regular cycle |                                                                            |
| N92.1 Excessive and frequent menstruation with irregular cycle |                                                                            |
| N92.2 Excessive menstruation at puberty |                                                                            |
| N92.3 Ovulation bleeding      |                                                                              |
| N92.4 Excessive bleeding in the premenopausal period |                                                                            |
| N92.5 Other specified irregular menstruation |                                                                            |
| N92.6 Irregular menstruation, unspecified |                                                                            |
| N93 Other abnormal uterine and vaginal bleeding |                                                                            |
| N93.0 Postcoital and contact bleeding |                                                                            |
| N93.8 Other specified abnormal uterine and vaginal bleeding |                                                                            |
| N93.9 Abnormal uterine and vaginal bleeding, unspecified |                                                                            |
| N95.0 Postmenopausal bleeding |                                                                              |
| N95.8 Other specified menopausal and perimenopausal disorders |                                                                            |
| N95.9 Unspecified menopausal and perimenopausal disorder |                                                                            |
| Overall bleeding              |                                                                              |
| Acute posthemorrhagic anemia  | D62                                                                          |
| – **Intraocular bleeding**    |                                                                              |
| Retinal hemorrhage            | code H356                                                                     |
| Vitreous hemorrhage           | code H431                                                                     |
| Vitreous hemorrhage in diseases classified elsewhere | code H450                  |
| – Otorrhagia                  | code H922                                                                     |
| – **Respiratory bleeding**    |                                                                              |
| Hemothorax                    | code J942                                                                     |
| Hemorrhage from respiratory passages | R04                      |
| Recurrent and persistent hematuria | code N02                   |
| Unspecified hematuria         | code R31                                                                     |
| Hemoperitoneum                | code K661                                                                     |
| – **Intra articular bleeding**|                                                                              |
| Hemarthrosis                  | code M250                                                                     |
| – **Other bleeding**          |                                                                              |
| Hemorrhage, not elsewhere classified | code R58                   |
| Traumatic secondary and recurrent hemorrhage | code T792                |
| Haemoptysis code R042         |                                                                              |
| Haemorrhage from other sites in respiratory passages code R048 |                                                                            |
| Haemorrhage from respiratory passages, unspecified code R04.9 |                                                                            |
| Condition                                                                 | ICD Code(s) |
|-------------------------------------------------------------------------|-------------|
| Epistaxis                                                                | R040        |
| Intracranial hemorrhage                                                | I60 to I62  |
| Epidural hemorrhage                                                     | S064        |
| Traumatic subdural hemorrhage                                           | S065        |
| Traumatic subarachnoid hemorrhage                                       | S066        |
| Oesophageal varices with bleeding                                       | I850        |
| Gastro-oesophageal laceration-hemorrhage syndrome                       | K226        |
| Gastric ulcer/duodenal ulcer/peptic ulcer/gastrojejunal ulcer with hemorrhage | K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286 |
| Acute hemorrhagic gastritis                                             | K290        |
| Hemorrhage of anus and rectum                                           | K625        |
| Hematemesis                                                             | K920        |
| Melaena                                                                 | K921        |
| Gastrointestinal hemorrhage, unspecified                               | K922        |
| N92.0 Menorrhagia (primary)                                             |             |
| N92.0 Excessive and frequent menstruation with regular cycle           |             |
| N92.1 Excessive and frequent menstruation with irregular cycle         |             |
| N92.2 Excessive menstruation at puberty                                |             |
| N92.3 Ovulation bleeding                                                |             |
| N92.4 Excessive bleeding in the premenopausal period                   |             |
| N92.5 Other specified irregular menstruation                            |             |
| N92.6 Irregular menstruation, unspecified                              |             |
| N93 Other abnormal uterine and vaginal bleeding                         |             |
| N93.0 Postcoital and contact bleeding                                   |             |
| N93.8 Other specified abnormal uterine and vaginal bleeding            |             |
| N93.9 Abnormal uterine and vaginal bleeding, unspecified               |             |
| N95.0 Postmenopausal bleeding                                           |             |
| N95.8 Other specified menopausal and perimenopausal disorders          |             |
| N95.9 Unspecified menopausal and perimenopausal disorder               |             |

Abbreviations: ICD-10, International classification of diseases
### Supplemental Table 5. Covariates

| Covariate                          | Operational Definition                                                                 | Time Period for Assessment          |
|-----------------------------------|----------------------------------------------------------------------------------------|-------------------------------------|
| **Demographic and Administrative Information** |                                                                                        |                                     |
| **Index year**                    | Calendar year of the index date. Categorical (by each calendar year)                    | At index                            |
| **Age at index date**             | Age in years as of the index date, using the formula below: Age at index date = (index date – birth date + 1) / 365.25. Described as continuous and categorical (by age group): 18-54, 55-64, 65-74, 75-79, and ≥80 years. | At index                            |
| **Gender**                        | Categorical: Male, female, missing                                                    | At index                            |
| **Duration of total follow up time available** | Continuous (mean, SD, min, 25th percentile, median, 75th percentile, max) | During follow-up (exclusive the index date) |
| **Time from VTE to index AC (days)** | Continuous (mean, SD, min, 25th percentile, median, 75th percentile, max) | During the baseline period (inclusive of the index date) |
| **Long Term Disease status**      | LTD status (yes/no) Type of severe and costly chronic disease indicated by a ICD-10 code diagnosis | During the baseline period (exclusive of index date) |
| **Ecological deprivation index**  | Described as categorical (quintiles)                                                  | Based on zone of residence at VTE event diagnosis |
| **Location at the time of VTE diagnosis** | Hospital or physician area at VTE diagnosis (department code)                      | During the baseline period (exclusive of index date) |
| **Clinical Comorbidities (Charlson)** |                                                                                        |                                     |
| **Myocardial infarction**         | Presence of any ICD-10 diagnoses of hospital stay or LTD code Categorical (yes/no) Additional proxies through drug markers or medical procedures were used whenever possible to calculate comorbid disease scores | During the baseline period (exclusive of the index date) |
| **Congestive heart failure**      |                                                                                        |                                     |
| **Peripheral vascular disease**    |                                                                                        |                                     |
| **Cerebrovascular disease**        |                                                                                        |                                     |
| **Dementia**                      |                                                                                        |                                     |
| **Chronic pulmonary disease**      |                                                                                        |                                     |
| **Connective tissue disease**      |                                                                                        |                                     |
| **Ulcer disease**                 |                                                                                        |                                     |
| **Rheumatic disease**              |                                                                                        |                                     |
| **Diabetes**                      |                                                                                        |                                     |
| **Diabetes with end-organ damage** |                                                                                        |                                     |
| **Mild liver disease**             |                                                                                        |                                     |
| **Moderate or severe liver disease** |                                                                                        |                                     |
| **Hemiplegia**                    |                                                                                        |                                     |
| **Moderate or severe renal disease** |                                                                                        |                                     |
| Any malignancy, including lymphoma and leukaemia, except non-melanoma skin cancer of skin |  |  |
|---|---|---|
| Metastatic solid tumour |  |  |
| AIDS/ HIV |  |  |
| CCI score (adjusted for age) | Estimated based on the updated CCI weights as described by Bannay et al. 2016,36 Continuous (mean, SD, min, 25th percentile, median, 75th percentile, max) and categorical (1, 2, 3, ≥4). | During the baseline period (exclusive of the index date) |
| Other Comorbidities/Procedures |  |  |
| Anemia | Presence of any relevant ICD-10 code Categorical (yes/no) | During the baseline period (exclusive of the index date) |
| Central Venous Catheter |  |  |
| Coagulation Defects |  |  |
| Hyperlipidemia |  |  |
| Obesity |  |  |
| Rheumatologic disease |  |  |
| Sleep apnea |  |  |
| Spinal cord injury |  |  |
| Thrombophilia |  |  |
| Varicose Veins |  |  |
| Recent history of falls |  |  |
| Fracture/trauma involving the lower extremities |  |  |
| HIV/ AIDS |  |  |
| Cerebrovascular disease |  |  |
| Ischemic heart disease |  |  |
| Dementia |  |  |
| Hemiplegia or paraplegia |  |  |
| Pneumonia |  |  |
| Interstitial pneumonia |  |  |
| Chronic Obstructive Pulmonary Disease |  |  |
| Asthma |  |  |
| Congestive heart failure |  |  |
| Diabetes |  |  |
| Renal disease |  |  |
| Liver disease |  |  |
| Peptic ulcer disease |  |  |
| Inflammatory bowel disease |  |  |
| Peripheral vascular disease |  |  |
| Baseline bleed |  |  |
| Selected surgeries |  |  |
| Other baseline medications |  |  |
| Covariate                                      | Description                                                                 | Time Period                                                                 |
|-----------------------------------------------|-----------------------------------------------------------------------------|----------------------------------------------------------------------------|
| **ACE inhibitors/ ARBs, antiarrhythmic**      | Presence of any relevant ATC code Categorical (yes/no)                      | 3 months prior to and including index date                                   |
| Statin                                         |                                                                             |                                                                            |
| Antiarrhythmic                                 |                                                                             |                                                                            |
| Aromatase inhibitors                           |                                                                             |                                                                            |
| Beta blockers                                  |                                                                             |                                                                            |
| Erythropoiesis stimulating agents             |                                                                             |                                                                            |
| Gastroprotective agents                        |                                                                             |                                                                            |
| SERMs                                          |                                                                             |                                                                            |
| Antiplatelet                                   | Presence of any relevant ATC code Categorical (yes/no)                      | At index date ± 90 days and during entire follow-up period (inclusive of the index date) |
| Hormone therapy                               |                                                                             |                                                                            |
| NSAIDs                                         |                                                                             |                                                                            |
| Strong inhibitors of both CYP3A4 and P-gp      |                                                                             |                                                                            |
| HIV protease inhibitors                        |                                                                             |                                                                            |
| Anticonvulsant strong inducer of hepatic enzymes |                                                                             |                                                                            |
| **Cancer-related variables**                  |                                                                             |                                                                            |
| Cancer site                                    | Any malignancy except non-melanoma skin cancer (yes/no)                     | During the baseline period and until 30 days after index date               |
| Cancer type                                    | History of cancer (yes/no)                                                  |                                                                            |
|                                               | Active cancer (yes/no)                                                      |                                                                            |
|                                               | Risk of incident VTE according to Khorona high risk score.                   |                                                                            |
| Cancer-related treatment                       | Reimbursement for chemotherapy (yes/no)                                     | Baseline period and until 30 days after index date                          |
|                                               | Reimbursement for radiation (yes/no), Reimbursement for hormonotherapy (yes/no), Reimbursement for immunotherapy (yes/no). |                                                                            |

Covariates were assessed during the baseline period (during 24 months prior to and on the index date) using ICD-10 codes (principal or associated) and/or procedure and/or ATC codes, as relevant. ATC codes from reimbursement database were also used for some comorbidities, if applicable and where data were available. All comorbidities were coded as binary indicator variables (yes/no). Presence of a record of relevant codes were coded as “yes”. Absence of codes for a specific condition were presumed as the absence of the disease (i.e. coded as “no”). In the inpatient setting, diagnoses were assumed to occur at the admission date (and not the discharge date) associated with a specific hospital spell. Abbreviations: AC, anticoagulant; AIDS, acquired
immunodeficiency syndrome; ATC, Anatomical Therapeutic Chemical; CCI, Charlson Comorbidity Index; HIV, human immunodeficiency virus; ICD-10, International Classification of Diseases, 10th Revision; NSAID, non-steroidal anti-inflammatory drug; OAC, oral anticoagulant; SD, standard deviation; SERMs, selection estrogen receptor modulators; VTE, venous thromboembolism.
## Supplemental Table 6. Patient Characteristics in the Full Population (Pre-PS Adjustment)

| Characteristic                                      | Apixaban vs VKA | Rivaroxaban vs VKA | Std difference | Std difference |
|-----------------------------------------------------|-----------------|--------------------|----------------|----------------|
|                                                     | VKA (N = 10775) | Apixaban (N = 10440) |                 |                |
| DVT only *, n (%)                                   | 3820 (35.5)     | 2598 (24.9)        | -23.18         |                |
| Age at index (y), mean (SD)                         | 70.9 (18.4)     | 65.5 (17.6)        | -30.17         |                |
| Sex, male, n (%)                                   | 4282 (39.7)     | 4931 (47.2)        | -15.16         |                |
| Charlson Comorbidity Index b, n (%)                 |                 |                    |                |                |
| 0-<1                                                | 3928 (36.5)     | 5608 (53.7)        | 35.23          |                |
| 1-<2                                                | 2488 (23.1)     | 2424 (23.2)        | 0.30           |                |
| 2-<3                                                | 1933 (17.9)     | 1287 (12.3)        | -15.71         |                |
| 3-<4                                                | 1074 (10.0)     | 548 (5.3)          | -17.87         |                |
| 4 or more                                           | 1352 (12.6)     | 573 (5.5)          | -24.83         |                |
| Comorbidities b, n (%)                              |                 |                    |                |                |
| AIDS/HIV                                            | 62 (0.6)        | 13 (0.1)           | -7.64          |                |
| Anemia                                              | 1467 (13.6)     | 823 (7.9)          | -18.58         |                |
| Any renal disease                                   | 1588 (14.7)     | 491 (4.7)          | -34.37         |                |
| Any tumor                                           | 419 (3.9)       | 276 (2.6)          | -7.01          |                |
| Asthma                                              | 271 (2.5)       | 241 (2.3)          | -1.35          |                |
| Baseline bleed, all diagnosis                       | 784 (7.3)       | 549 (5.3)          | -8.33          |                |
| Chronic pulmonary disease                           | 1640 (15.2)     | 966 (9.3)          | -18.29         |                |
| Coagulation defects                                 | 549 (5.1)       | 256 (2.5)          | -13.9          |                |
| Connective tissue disease                           | 293 (2.7)       | 157 (1.5)          | -8.46          |                |
| Dementia                                            | 2732 (25.4)     | 1652 (15.8)        | -23.74         |                |
| Diabetes                                            | 1704 (15.8)     | 1354 (13.0)        | -8.11          |                |
| Diabetes with end organ damage                      | 269 (2.5)       | 109 (1.0)          | -11.03         |                |
| Fracture / trauma involving the lower extremities   | 324 (3.0)       | 141 (1.4)          | -11.36         |                |
| Hemiplegia or paraplegia                            | 364 (3.4)       | 255 (2.4)          | -5.57          |                |
| Condition                              | n (%)       | 95% CI       | OR   | 95% CI     | p-value |
|----------------------------------------|-------------|--------------|------|------------|---------|
| Hyperlipidemia                         | 565 (5.2)   | 552 (5.3)    | 0.2  | 565 (5.2)  | -3.14   |
| Inflammatory Bowel Disease             | 73 (0.7)    | 53 (0.5)     | -2.21| 73 (0.7)   | -3.08   |
| Interstitial pneumonia                 | 97 (0.9)    | 60 (0.6)     | -3.81| 97 (0.9)   | -5.98   |
| Mild liver disease                     | 291 (2.7)   | 215 (2.1)    | -4.21| 291 (2.7)  | -4.23   |
| Myocardial infarction                  | 535 (5.0)   | 388 (3.7)    | -6.13| 535 (5.0)  | -12.82  |
| Obesity                                | 1446 (13.4) | 1384 (13.3)  | -0.48| 1446 (13.4)| -1.17   |
| Peripheral Vascular disease            | 634 (5.9)   | 393 (3.8)    | -9.9 | 634 (5.9)  | -14.77  |
| Pneumonia                              | 1107 (10.3) | 871 (8.3)    | -6.65| 1107 (10.3)| -9.77   |
| Recent history of falls                | 518 (4.8)   | 336 (3.2)    | -8.1 | 518 (4.8)  | -16.86  |
| Rheumatologic disease                  | 1193 (11.1) | 941 (9.0)    | -6.85| 1193 (11.1)| -11.3   |
| Selected surgeries                     | 872 (8.1)   | 617 (5.9)    | -8.56| 872 (8.1)  | -6.73   |
| Sleep apnea                            | 376 (3.5)   | 382 (3.7)    | 0.91 | 376 (3.5)  | -1.42   |

Concomitant Treatment

| Condition                              | n (%)       | 95% CI       | OR   | 95% CI     | p-value |
|----------------------------------------|-------------|--------------|------|------------|---------|
| ACE inhibitors/ ARBs, antarrhythmic    | 2007 (18.6) | 1537 (14.7)  | -10.49| 2007 (18.6)| -19.28  |
| Anticonvulsant strong inducer of hepatic enzymes | 144 (1.3) | 91 (0.9)     | -4.45| 144 (1.3)  | -4.82   |
| Antiplatelet                           | 2431 (22.6) | 1809 (17.3)  | -13.13| 2431 (22.6)| -25.3   |
| Erythropoiesis stimulating agents      | 118 (1.1)   | 17 (0.2)     | -11.81| 118 (1.1)  | -12.79  |
| HIV protease inhibitors                | 28 (0.3)    | 2 (0.0)      | -6.45| 28 (0.3)   | -6.15   |
| Hormone therapy                        | 370 (3.4)   | 472 (4.5)    | 5.57 | 370 (3.4)  | 13.32   |
| NSAIDs                                 | 3338 (31.0) | 3270 (31.3)  | 0.74 | 3338 (31.0)| 0.72    |
| SERMs                                  | 1365 (12.7) | 1051 (10.1)  | -8.2 | 1365 (12.7)| -11.43  |

Abbreviations: ACE, angiotensin Converting Enzyme; ARBs, angiotensin receptor blockers; DVT, deep vein thrombosis; SERMs, selective estrogen receptor modulators; AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; LMWH, low molecular weight heparin; NSAIDs, non-steroidal anti-inflammatory drugs; PS, propensity score; SD, standard deviation; Std, standardized; VKA, vitamin K antagonist

* vs PE with or without DVT
b Evaluated 24 months before index date, exclusive of index date

c 3 months prior to index date, exclusive of index date
| Characteristic                        | VKA vs. apixaban | VKA vs. rivaroxaban | Std difference | Std difference |
|--------------------------------------|-----------------|---------------------|----------------|----------------|
|                                      | (N = 10510)     | (N = 10223)         |                | (N = 10510)    | (N = 35956)    |
| DVT only c, n (%)                    | 3759 (30.5)     | 2552 (30.0)         | -0.05          | 3759 (27.9)    | 9032 (27.4)    |
| Age at index (y), mean (SD)          | 68.1 (19.29)    | 68.1 (17.14)        | -0.06          | 61.4 (20.31)   | 62.4 (17.61)   |
| Sex, male, %                         | 43.74           | 43.69               | -0.09          | 49.61          | 48.96          |
| Charlson comorbidity index d,e, n (%)|                 |                     |                | (N = 10510)    | (N = 35956)    |
| 0-<1                                 | 3835 (45.1)     | 5504 (45.6)         | 1.14           | 3835 (56.1)    | 22260 (56.4)  |
| 1-<2                                 | 2422 (23.0)     | 2378 (23.3)         | 0.57           | 2422 (21.3)    | 7643 (21.7)   |
| 2-<3                                 | 1893 (15.2)     | 1256 (15.2)         | -0.04          | 1893 (12.0)    | 3563 (11.7)   |
| 3-<4                                 | 1048 (7.6)      | 532 (7.3)           | -1.13          | 1048 (5.3)     | 1381 (5.2)    |
| ≥4                                   | 1312 (9.1)      | 553 (8.6)           | -1.73          | 1312 (5.4)     | 1109 (5.1)    |
| Comorbidities d,e, n (%)             |                 |                     |                | (N = 10510)    | (N = 35956)    |
| AIDS/HIV                             | 60 (0.4)        | 13 (0.3)            | -1.93          | 60 (0.3)       | 59 (0.3)      |
| Anemia                               | 1422 (10.7)     | 790 (10.2)          | -1.77          | 1422 (7.1)     | 1687 (6.6)    |
| Any renal disease                    | 1543 (9.7)      | 467 (8.8)           | -3.31          | 1543 (5.4)     | 951 (5.0)     |
| Any tumor                            | 409 (3.3)       | 274 (3.3)           | -0.17          | 409 (2.6)      | 764 (2.5)    |
| Asthma                               | 264 (2.4)       | 238 (2.4)           | 0.02           | 264 (2.3)      | 758 (2.2)    |
| Baseline bleed, all diagnosis        | 765 (6.4)       | 535 (6.2)           | -0.77          | 765 (5.3)      | 1440 (4.8)   |
| Chronic pulmonary disease            | 1605 (12.3)     | 951 (12.1)          | -0.7           | 1605 (9.6)     | 2894 (9.6)   |
| Coagulation defects                  | 535 (3.8)       | 252 (3.6)           | -1.37          | 535 (3.4)      | 912 (3.1)    |
| Connective tissue disease            | 287 (2.1)       | 155 (2.1)           | -0.38          | 287 (1.7)      | 430 (1.6)    |
| Dementia                             | 2677 (20.7)     | 1624 (20.4)         | -0.72          | 2677 (14.7)    | 4244 (14.9)  |
| Diabetes                             | 1630 (14.1)     | 1297 (14.0)         | -0.26          | 1630 (11.2)    | 3539 (11.1)  |
| Diabetes with end organ damage       | 251 (1.7)       | 100 (1.6)           | -0.53          | 251 (1.0)      | 192 (0.9)    |
| Fracture/3                            | 320 (2.2)       | 140 (2.1)           | -0.7           | 320 (1.6)      | 377 (1.5)    |
| Condition                        | n (%)     | n (%)     | p-value | n (%)     | n (%)     | p-value |
|---------------------------------|-----------|-----------|---------|-----------|-----------|---------|
| Trauma involving the lower      | 356 (2.9) | 247 (2.9) | 0.04    | 356 (2.3) | 630 (2.2) | -0.87   |
| Extremities                     |           |           |         |           |           |         |
| Hemiplegia or paraplegia        | 558 (5.4) | 548 (5.5) | 0.32    | 558 (5.0) | 1675 (4.9) | -0.49   |
| Hyperlipidemia                  | 73 (0.6)  | 49 (0.6)  | 0.33    | 73 (0.7)  | 164 (0.5)  | -1.57   |
| Inflammatory bowel disease      | 94 (0.7)  | 59 (0.7)  | 0.1     | 94 (0.5)  | 151 (0.5)  | 0.04    |
| Interstitial pneumonia          | 288 (2.4) | 212 (2.4) | 0.12    | 288 (2.3) | 741 (2.2)  | -0.58   |
| Mild liver disease              | 527 (4.4) | 384 (4.3) | 0.34    | 527 (3.2) | 923 (3.1)  | -0.63   |
| Myocardial infarction           | 1406 (13.5) | 1341 (13.5) | 0.17 | 1406 (14.4) | 4681 (13.2) | -3.41   |
| Obesity                         | 616 (4.8) | 382 (4.8) | 0.42    | 616 (3.7) | 1035 (3.6) | -0.52   |
| Peripheral vascular disease     | 1084 (9.4) | 859 (9.3) | 0.53    | 1084 (8.5) | 2707 (8.2) | -1.19   |
| Pneumonia                       | 509 (4.1) | 332 (4.1) | 0.18    | 509 (2.6) | 654 (2.5)  | -0.52   |
| Recent history of falls         | 1160 (10.1) | 925 (10.1) | 0.08 | 1160 (8.5) | 2812 (8.6) | 0.12    |
| Rheumatologic disease           | 864 (7.1) | 612 (7.1) | 0.1     | 864 (7.1) | 2313 (6.9) | -0.58   |
| Selected surgeries              | 370 (3.6) | 379 (3.6) | 0.05    | 370 (3.6) | 1167 (3.3) | -1.38   |
| Sleep apnea                     | 1955 (16.7) | 1504 (16.6) | 0.2  | 1955 (13.2) | 4723 (13.2) | 0.09    |
| Concomitant treatment *, n (%)  | 142 (1.1) | 89 (1.2)  | 0.12    | 142 (1.1) | 297 (1.0)  | -0.94   |
| ACE inhibitors/ARBs, antiarrhythmic |        |           |         |           |           |         |
| Anticonvulsant strong inducer of hepatic enzymes | 2369 (20.0) | 1776 (20.0) | 0.13 | 2369 (15.0) | 4665 (15.1) | 0.24    |
| Antiplatelet stimulating agents | 115 (0.6) | 16 (0.3)  | 4.42    | 115 (0.3) | 38 (0.2)   | -2.16   |

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|                | Weightedmean (standarddeviation) | Weighted percentage | p-value | Weightedmean (standarddeviation) | Weighted percentage | p-value |
|----------------|----------------------------------|---------------------|---------|----------------------------------|---------------------|---------|
| **HIV protease inhibitors** | 27 (0.1) | 2 (0.1) | -3.04 | 27 (0.1) | 10 (0.1) | -0.44 |
| **Hormone therapy** | 350 (3.8) | 459 (3.9) | 0.54 | 350 (5.3) | 2244 (5.6) | 1.3 |
| **NSAIDs** | 3263 (31.4) | 3214 (31.4) | -0.02 | 3263 (31.1) | 11289 (31.3) | 0.43 |
| **SERMs** | 1353 (11.5) | 1040 (11.4) | -0.14 | 1353 (10.1) | 3313 (10.0) | -0.33 |

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

a Weighted mean (standard deviation) or weighted percentages are presented in the post IPTW population, patients with missing PS were excluded

b Stabilized IPTW weight higher than the 99th percentile are recoded and putted to the 99th percentile: 3.09 in the VKA - rivaroxaban population and 2.36 in the VKA - apixaban population

c vs. PE with or without DVT

d Evaluated in the 24 months prior to index date, exclusive of index date

e For co-morbidities, the IPTW percentages are weighted and were therefore calculated as the mean of the stabilized weight multiplied by the variable of interest

f 3 months prior to index date, exclusive of index date
### Event and Incidence Rates

| Event                                      | Apixaban (N=10440) | Rivaroxaban (N=36922) | VKA (N=10775) |
|--------------------------------------------|---------------------|------------------------|---------------|
| **Bleeding**                               |                     |                        |               |
| Bleeding requiring hospitalization         |                     |                        |               |
| n (%)                                      | 85 (0.81)           | 426 (1.15)             | 213 (1.98)    |
| Incidence per 100 PY (95% CI)              | 1.85 (1.50-2.29)    | 2.64 (2.41-2.90)       | 5.21 (4.57-5.94) |
| **Gastrointestinal bleeding, principal diagnosis** |                     |                        |               |
| n (%)                                      | 30 (0.29)           | 140 (0.38)             | 66 (0.61)     |
| Incidence per 100 PY (95% CI)              | 0.65 (0.46-0.93)    | 0.87 (0.74-1.02)       | 1.61 (1.27-2.05) |
| **Intracranial bleeding, principal diagnosis** |                     |                        |               |
| n (%)                                      | 18 (0.17)           | 48 (0.13)              | 55 (0.51)     |
| Incidence per 100 PY (95% CI)              | 0.39 (0.25-0.62)    | 0.30 (0.22-0.40)       | 1.35 (1.03-1.75) |
| **Other bleeding, principal diagnosis**    |                     |                        |               |
| n (%)                                      | 37 (0.35)           | 244 (0.66)             | 94 (0.87)     |
| Risk per 100 PY (95% CI)                   | 0.81 (0.58-1.11)    | 1.51 (1.34-1.71)       | 2.30 (1.89-2.81) |
| **All-cause death**                        |                     |                        |               |
| n (%)                                      | 216 (2.07)          | 440 (1.19)             | 500 (4.64)    |
| Incidence per 100 PY (95% CI)              | 4.71 (4.13-5.36)    | 2.73 (2.49-2.99)       | 12.23 (11.26-13.27) |
| **First-recurrent VTE**                    |                     |                        |               |
| n (%)                                      | 155 (1.48)          | 698 (1.89)             | 204 (1.89)    |
| Incidence per 100 PY (95% CI)              | 3.38 (2.89-3.94)    | 4.33 (4.03-4.66)       | 4.99 (4.36-5.70) |

**Supplemental Table 8.** Incidence Rates for Outcomes of Interest at 6 Months: Prior PS analysis

Abbreviations: CI, confidence interval; PY, person year
### Supplemental Table 9. Incidence and Hazard ratios for Outcomes of Interest at 6 Months: PS analysis

| Event                                | VKA vs. apixaban | VKA vs. rivaroxaban |
|---------------------------------------|------------------|---------------------|
|                                      | VKA (N=7503)     | Apixaban (N=7503)   | VKA (N=9179) | Rivaroxaban (N=9179) |
| **Bleeding**                          |                  |                     |              |                     |
| Bleeding requiring hospitalization    |                  |                     |              |                     |
| n (%)                                 | 123 (1.64)       | 62 (0.83)           | 162 (1.76)  | 158 (1.72)           |
| Incidence per 100 PY (95% CI)         | 4.34 (3.61-5.18) | 1.89 (1.45-2.42)    | 4.65 (3.96-5.42) | 3.98 (3.38-4.65)    |
| HR a (95% CI)                         | -                | 0.43 (0.32-0.59)    | -            | 0.86 (0.69-1.07)    |
| **Gastrointestinal bleeding, principal diagnosis** |                  |                     |              |                     |
| n (%)                                 | 36 (0.48)        | 21 (0.28)           | 47 (0.51)   | 67 (0.73)            |
| Incidence per 100 PY (95% CI)         | 1.27 (0.89-1.76) | 0.64 (0.40-0.98)    | 1.35 (0.99-1.79) | 1.69 (1.31-2.14)    |
| HR a (95% CI)                         | -                | 0.51 (0.30-0.87)    | -            | 1.26 (0.87-1.83)    |
| **Intracranial bleeding, principal diagnosis** |                  |                     |              |                     |
| n (%)                                 | 34 (0.45)        | 15 (0.2)            | 42 (0.46)   | 23 (0.25)            |
| Incidence per 100 PY (95% CI)         | 1.20 (0.83-1.68) | 0.46 (0.26-0.75)    | 1.21 (0.87-1.63) | 0.58 (0.37-0.87)    |
| HR a (95% CI)                         | -                | 0.38 (0.21-0.70)    | -            | 0.48 (0.29-0.79)    |
| **Other bleeding, principal diagnosis** |                  |                     |              |                     |
| n (%)                                 | 55 (0.73)        | 26 (0.35)           | 74 (0.81)   | 70 (0.76)            |
| Risk per 100 PY (95% CI)              | 1.94 (1.46-2.53) | 0.79 (0.52-1.16)    | 2.12 (1.67-2.67) | 1.76 (1.37-2.23)    |
| HR a (95% CI)                         | -                | 0.41 (0.25-0.65)    | -            | 0.84 (0.61-1.17)    |
| **All-cause death**                   |                  |                     |              |                     |
| n (%)                                 | 275 (3.67)       | 192 (2.56)          | 346 (3.77)  | 245 (2.67)           |
| Incidence per 100 PY (95% CI)         | 9.70 (8.59-10.92) | 5.85 (5.05-6.74)    | 9.93 (8.91-11.03) | 6.17 (5.42-6.99)    |
| HR a (95% CI)                         | -                | 0.61 (0.51-0.65)    | -            | 0.63 (0.53-0.69)    |
| First-recurrent VTE |       |       |       |       |
|--------------------|-------|-------|-------|-------|
| n (%)              | 148 (1.97) | 112 (1.49) | 172 (1.87) | 177 (1.93) |
| Incidence per 100 PY (95% CI) | 5.22 (4.41-6.13) | 3.41 (2.81-4.11) | 4.94 (4.23-5.73) | 4.46 (3.82-5.16) |
| HR \(^a\) (95% CI) | - | 0.67 (0.52-0.85) | - | 0.91 (0.74-1.13) |

Abbreviations: CI, confidence interval; HR, hazard ratio; LMWH, low molecular weight heparin; PS, propensity score; PY, person-years; VKA, vitamin K antagonist; VTE, venous thromboembolism

\(^a\) Hazard ratio (95%CI) adjusted on NSAIDS, antiplatelets and strong inhibitors (time dependent)
Table 1. Patient Characteristics: PS-matched Cohorts

| Characteristic               | VKA vs. apixaban | VKA vs. rivaroxaban |
|-----------------------------|------------------|---------------------|
|                             | (N=7503)         | (N=7503)            | (N=9179)          | (N=9179)          |
| DVT only a, n (%)           | 2184 (29.1)      | 2220                | 2997              | 3015 (32.9)       |
|                             | (29.6)           | (68.2)              | (32.7)            | (69.3)            |
| Age at index (y), mean (SD) | 68.1 (18.9)      | 68.2                | (18.6)            | 3837              |
| Sex, male, n (%)            | 3254 (43.4)      | 314 (43.4)          | 2997              | 3015 (32.9)       |
| Charlson Comorbidity Index b, n (%) | 0.94             | 0.1                | 3802              | 3676 (40.1)       |
| 0-<1                        | 3525 (47.0)      | 3487                | (41.4)            | 750 (8.2)         |
|                             | (24.91)          | (11.2)              | (17.3)            | (1583)            |
| 1-<2                        | 1869             | 1884                | 2286              | 2262 (24.6)       |
|                             | (25.1)           | (14.9)              | (24.9)            | (2262)            |
| 2-<3                        | 1094 (14.6)      | 1120                | 1583              | 1643 (17.9)       |
|                             | (14.9)           | (14.9)              | (17.3)            | (1643)            |
| 3-<4                        | 483 (6.4)        | 492 (6.6)           | 750 (8.2)         | 832 (9.1)         |
|                             | (5.9)            | (6.9)               | (8.3)             | (8.4)             |
| ≥4                          | 532 (7.1)        | 520 (6.9)           | 758 (8.3)         | 766 (8.4)         |
| Comorbidities b, n (%)      |                 |                    |                   |                   |
| AIDS/HIV                    | 12 (0.2)         | 13 (0.2)            | 3802              | 44 (0.5)          |
|                             | (0.2)            | (0.2)               | (41.4)            | (932)             |
| Anemia                      | 706 (9.4)        | 696 (9.3)           | (10.2)            | (899)             |
|                             | (6.5)            | (6.1)               | (8.4)             | (8.9)             |
| Any renal disease           | 486 (6.5)        | 461 (6.1)           | 766 (8.4)         | 737 (8.0)         |
|                             | (6.5)            | (6.1)               | (8.4)             | (8.0)             |
| Any tumor                   | 232 (3.1)        | 251 (3.4)           | (3.69)            | (335)             |
|                             | (3.1)            | (3.4)               | (3.65)            | (3.65)            |
| Asthma                      | 183 (2.4)        | 188 (2.5)           | 235 (2.6)         | 219 (2.4)         |
|                             | (2.4)            | (2.5)               | (2.6)             | (2.4)             |
| Baseline bleed, all diagnosis | 439 (5.9)       | 446 (5.9)           | 575 (6.3)         | 591 (6.4)         |
|                             | (5.9)            | (5.9)               | (6.3)             | (6.4)             |
| Chronic pulmonary disease   | 838 (11.2)       | 855                 | 1276              |                   |
|                             | (11.4)           | (11.4)              | (11.4)            | (11.4)            |
| Coagulation defects         | 246 (3.3)        | 242 (3.2)           | (3.69)            | (3.65)            |
|                             | (3.3)            | (3.2)               | (3.69)            | (3.65)            |
| Connective tissue disease   | 142 (1.9)        | 147 (2.0)           | 226 (2.5)         |                   |
|                             | (1.9)            | (2.0)               | (2.5)             | (2.5)             |
| Dementia                    | 1421 (18.9)      | 1457                | 2036              |                   |
|                             | (19.4)           | (20.0)              | (22.2)            | (2120)            |
| Diabetes                    | 1068 (14.2)      | 1052                | 1337              |                   |
|                             | (14.0)           | (14.0)              | (14.6)            | (1356)            |

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| Condition                                      | c   | n (%)  | p-value | Odds Ratio | 95% CI  | p-value | Odds Ratio | 95% CI  | p-value | Odds Ratio | 95% CI  | p-value | Odds Ratio | 95% CI  |
|------------------------------------------------|-----|--------|---------|------------|---------|---------|------------|---------|---------|------------|---------|---------|------------|---------|
| Diabetes with end organ damage                 | 95  | (1.3)  | 0.94    | 0.12       | 139     | (1.5)   | 0.86       | -0.27   |          |            |         |          |            |         |
| Fracture/trauma involving the lower extremities| 137 | (1.8)  | 0.67    | 0.71       | 208     | (2.3)   | 0.73       | -0.51   |          |            |         |          |            |         |
| Hemiplegia or paraplegia                      | 218 | (2.9)  | 0.88    | -0.24      | 300     | (3.3)   | 0.29       | -1.56   |          |            |         |          |            |         |
| Hyperlipidemia                                 | 412 | (5.5)  | 0.42    | 1.3        | 483     | (5.3)   | 0.74       | -0.49   |          |            |         |          |            |         |
| Inflammatory Bowel Disease                    | 41  | (0.6)  | 0.74    | -0.53      | 55      | (0.6)   | 0.52       | -0.96   |          |            |         |          |            |         |
| Interstitial pneumonia                         | 51  | (0.7)  | 0.77    | -0.48      | 70      | (0.8)   | 0.33       | -1.44   |          |            |         |          |            |         |
| Mild liver disease                             | 176 | (2.3)  | 0.74    | 0.53       | 248     | (2.7)   | 0.96       | 0.07    |          |            |         |          |            |         |
| Myocardial infarction                          | 316 | (4.2)  | 0.72    | -0.59      | 403     | (4.4)   | 0.29       | -1.57   |          |            |         |          |            |         |
| Obesity                                        | 1029(13.7) | (13.3) | 0.43    | 1.29       | (13.4)  | 1314     | (14.3)     | 0.084   | -2.55    |            |         |          |            |         |
| Peripheral vascular disease                    | 347 | (4.6)  | 0.85    | 0.32       | 472     | (5.1)   | 0.14       | -2.17   |          |            |         |          |            |         |
| Pneumonia                                      | 677 | (9.0)  | 0.82    | 0.37       | 873     | (9.5)   | 0.74       | -0.48   |          |            |         |          |            |         |
| Recent history of falls                        | 274 | (3.7)  | 0.39    | -1.4       | 362     | (3.9)   | 1          |         |          |            |         |          |            |         |
| Rheumatologic disease                          | 757 | (10.1) | 0.89    | 0.22       | (10.3)  | 975      | (10.6)     | 0.44    | -1.14    |            |         |          |            |         |
| Selected surgeries                             | 546 | (7.3)  | 0.51    | 1.09       | 739     | (8.1)   | 0.44       | -1.15   |          |            |         |          |            |         |
| Sleep apnea                                    | 276 | (3.6)  | 0.9     | 0.21       | 328     | (3.6)   | 0.91       | -0.18   |          |            |         |          |            |         |
| Concomitant Treatment c, n (%)                 |     |        |         |            |         |         |            |         |          |            |         |          |            |         |
| ACE inhibitors/ARBs, antiarrhythmic             | 1234| (16.5) | 0.83    | -0.36      | 1576    | (17.2)  | 0.68       | -0.61   |          |            |         |          |            |         |
| Anticonvulsant strong inducer of hepatic enzymes| 84  | (1.1)  | 0.94    | 0.13       | 125     | (1.4)   | 0.85       | -0.28   |          |            |         |          |            |         |
| Antiplatelet                                   | 1492| (19.9) | 0.78    | -0.47      | (20.7)  | 1951     | (21.3)     | 0.36    | -1.34    |            |         |          |            |         |
| Erythropoiesis stimulating agents              | 24  | (0.3)  | 0.15    | 2.36       | 29      | (0.3)   | 0.8        | -0.38   |          |            |         |          |            |         |
| HIV protease inhibitors                        | 1   | (0.01) | 0.56    | -0.94      | 13      | (0.1)   | 0.39       | 1.26    |          |            |         |          |            |         |
| Hormone therapy                                | 297 | (4.0)  | 0.52    | 1.04       | 341     | (3.7)   | 0.21       | 1.86    |          |            |         |          |            |         |
| NSAIDs                                         | 2398|        |         |            | 2831    |         |            |         |          |            |         |          |            |         |
| SERMs                                          | 2367| (31.6) | 0.59    | -0.89      | (30.8)  | 2887     | (31.2)     | 0.57    | -0.85    |            |         |          |            |         |
| **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, non-steroidal anti-inflammatory drug; PS, propensity score; SD, standard deviation; SERM, selective estrogen receptor modulators; Std, Standardized; VKA, vitamin K antagonist; VTE, venous thromboembolism

a vs. PE with or without DVT

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

c 3 months prior to index date, exclusive of index date
Table 2. Index Therapy Characteristics: PS-matched Cohorts

| Characteristic                              | VKA vs. apixaban | VKA vs. rivaroxaban |
|---------------------------------------------|------------------|---------------------|
|                                             | VKA (N = 7503)   | Apixaban (N = 7503) | VKA (N = 9179) | Rivaroxaban (N = 9179) |
| Median follow-up (days)                     | 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 \(^c\)                | 5136 (68.5)      | 5839 (77.8)         | 6338 (69.1)    | 7103 (77.4)       |
| Switching \(^d\)                            | 1954 (26.0)      | 744 (9.9)           | 2344 (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                                        | —                | 6923 (92.3)         | —              | —                 |
| 2.5 and 5 mg                                | —                | 78 (1.0)            | —              | —                 |
| Rivaroxaban                                  |                  |                     |                |                   |
| 10 mg                                       | —                | —                   | —              | 106 (1.2)         |
| 15 mg                                       | —                | —                   | —              | 3213 (35.0)       |
| 20 mg                                       | —                | —                   | —              | 914 (10.0)        |
| 15 and 20 mg                                | —                | —                   | —              | 4864 (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. Non-persistence 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 one day after the last reimbursement date of the index treatment and within 30 days after the estimated end of supply of the index drug.
