04 April 2024

Data analysis report

Title: Association between use of direct oral anticoagulants (DOACs) and increased risk of interstitial lung disease

Administrative details of the data analysis	
Substance(s)	Edoxaban, Apixaban, Rivaroxaban, Dabigatran
Condition/ADR(s)	Interstitial lung disease
Short title of topic	ILD and DOACs
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1. List of abbreviations

MAH	*Marketing Authorisation Holder*
EMA	*European Medicines Agency*
PRAC	*Pharmacovigilance Risk Assessment Committee*

2. Milestones

Milestone	**Planned date**
Draft analysis plan circulated to Requester and Committee Members for comments	24/03/2023
Comments from Requester and Committee Members on draft analysis plan by	04/04/2023
Updated analysis plan following comments circulated by EMA to Requester and Committee Members by	21/06/2023
Analysis report by EMA circulated to Requester and Committee Members by	04/04/2024

3. Rationale and background

Interstitial lung disease (ILD) describes a heterogenous group of respiratory disorders affecting the interstitium of the lungs.[1,2] ILD may occur when an injury to the lungs triggers an abnormal healing response. The repair process is disrupted, and the tissue around the alveoli becomes scarred and thickened. Prolonged ILD may result in pulmonary fibrosis, but this is not always the case.[1,2]

Cases of interstitial lung disease (ILD) have been recently described, especially in Asian subjects, in people using direct oral anticoagulants (DOACs).[3-5] In addition, a recently published observational study suggests an increased risk of ILD in patients treated with factor Xa inhibitors (edoxaban, apixaban, rivaroxaban) as compared to warfarin users among subjects with non-valvular atrial fibrillation in Taiwan [6, 7], which triggered a new potential safety signal. A thorough review of this issue within the ongoing and upcoming PSUSA procedures for edoxaban, apixaban and rivaroxaban is expected. In this context, a real-world data (RWD) analysis was requested to better inform the PRAC on the relationship between increased risk of ILD and use of DOACs in the European population.

4. Research question and objectives

Research question

Is the use of factor Xa (FXa) inhibitors (edoxaban, apixaban and rivaroxaban) or direct thrombin inhibitor (dabigatran) associated with an increased risk of interstitial lung disease (ILD) when compared with patients treated with vitamin K antagonists (VKA), among patients with Atrial Fibrillation (AF), or Venous Thromboembolism (VTE), where VTE comprised Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE)?

Specific objectives:

To assess whether there is an association between treatment initiation with:

1. DOACs (all combined)
2. Edoxaban
3. Apixaban
4. Rivaroxaban
5. Dabigatran

and increased risk of interstitial lung disease (ILD) when compared to treatment initiation with vitamin K antagonists (VKA), among patients with AF and VTE.

5. Research methods

5.1. Study design

Propensity score matched comparative cohort studies with two-stage meta-analysis.

5.2. Data sources

The following databases were used: IQVIA™ Medical Research Data (IMRD) UK, IQVIA™ Disease Analyser Germany, and THIN® Spain and Italy. These databases have been mapped to the OMOP (Observational Medical Outcomes Partnership) CDM (Common Data Model) version 5.3. Details of the included databases can be found in the **Annex 1**.

5.3. Setting and study population

The included study population consisted of adult new users of the anticoagulants of interest (see section 5.5 on Exposures), as recorded for patients visiting general practices in UK, Germany, Spain, and Italy.

The population was stratified by indication for anticoagulation, namely for the management of atrial fibrillation (AF) or for the management of venous thromboembolism (VTE, namely deep vein thrombosis or pulmonary embolism). Indications were identified by the presence of diagnosis codes within the individual's electronic health record in the year up to the index date. Patients initiating anticoagulation with no diagnostic code for AF or VTE were not included in the analysis. For patients with multiple indications, the most recent indication (before index date) was used when the indications were recorded on different dates. When both AF and VTE were recorded on the day of the most recent indication, the patient was excluded. Patients with a recorded history of cardiac mechanical valve or mitral stenosis prior to cohort entry were excluded, as they have an indication for VKA, not DOACs.

Individuals with a diagnosis of ILD prior to cohort entry (anytime in the patient's prior history) were excluded from the cohort. A broad ILD definition was used for this exclusion to increase the validity that incident ILD events were new (see Annex for code list).

5.4. Study period

The study observation period to identify new users was from 1st of January 2010, to 31st of December 2019 (i.e., the period before COVID-19 cases emerged).

Cohort entry was defined as the date of anticoagulant initiation (**index date**). New anticoagulant use was defined as no prescription for any anticoagulant of interest in the 365 days prior to cohort entry.

Cohort exit was defined as the earliest of ILD diagnosis, death (for databases where death is captured), end of individual observability (deregistration or end of practices contributing data where these data are captured), treatment switching (for the on-treatment analysis) or end of the study period (31st December 2019). See Figure 1 for a schematic of the cohorts. For the analysis of any DOAC vs VKA, switching from one DOAC to a different DOAC or from one VKA to another VKA was not considered a switch of exposure. In contrast, switching from VKA to DOAC was considered as a censoring event for the on-treatment analyses (Section 5.6.1.2 below).

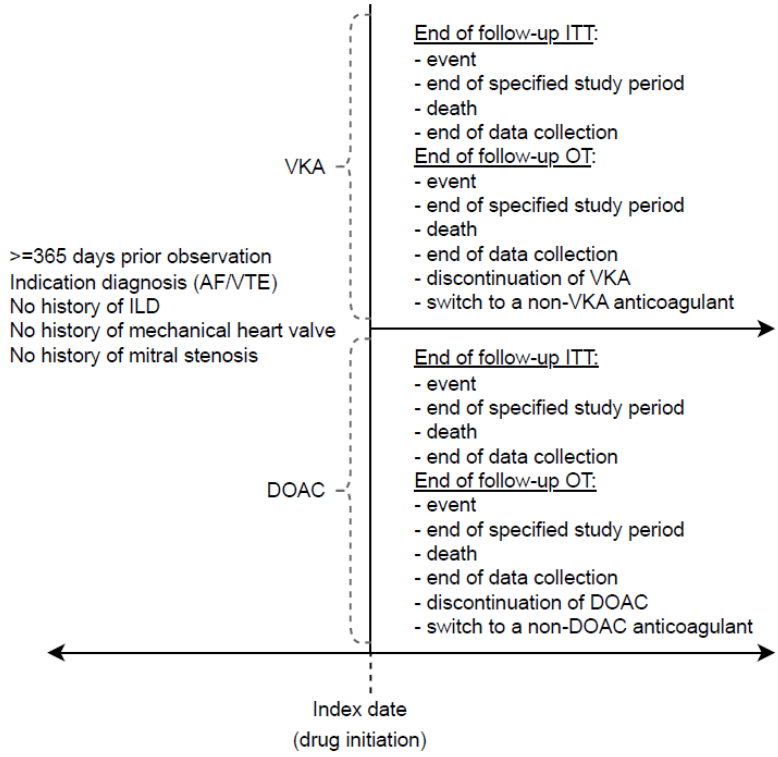

Figure 1. Cohort entry and exit criteria.

5.5. Variables

Outcome

The outcome of interest consisted of an incident diagnosis of ILD. ILD consists of a heterogenous group of conditions. The ILD phenotype is therefore a composite of different codes representing ILD in general, or as specific conditions that are classed as an ILD. Exclusion of patients with pre-existing ILD was evaluated using a composite phenotype consisting of any ILD related code. For the outcome in the analysis, a narrower definition of ILD was used, namely pulmonary fibrosis, pneumonitis, ILD specific codes, and drug induced ILD (please see Appendix for exemplar codes lists). We followed the "narrow" scope list of terms (i.e., very specific preferred terms) documented in the Introductory Guide for Standardised MedDRA Queries (SMQs) Version 25.0 [8]. We mapped these SMQ codes to SNOMED codes and used their OMOP concept IDs, and subsequently removed any codes that indicate another well-defined cause of ILD. Detailed list of codes included are shown in **Annex 2**.

Exposures

Exposures of interest consisted of VKAs (comparator, consisting of either warfarin, acenocoumarol, phenindione, or phenprocoumon), and DOACs (target, consisting of apixaban, dabigatran, edoxaban and rivaroxaban). Exposure was identified through prescriptions recorded in the electronic health record. Target exposures were evaluated by class (any DOAC) and as individual drug substances.

For the on-treatment analysis (Section 5.6.1.2 below)., patients were considered continuously exposed from cohort entry (index date) up to 30 days after the date of the last anticoagulant prescription in the patients record. In order to account for different treatment episodes over time, gaps of >90 days between anticoagulant prescriptions were considered as different treatment episodes and continuous exposure was censored 30 days after the last prescription before the gap. Detailed list of codes and terms included to identify exposure to DOACs are shown in the **Annex 2**.

Confounders

Baseline risk factors for ILD were measured including: age, sex, history of pneumonia, chronic obstructive pulmonary disease, chronic kidney disease, hepatitis C, history of tuberculosis sarcoidosis, history of autoimmune diseases, history of connective tissue disorders, history of sarcoidosis, history of cancer, exposure to medications (nitrofurantoin, sulfonamides, amiodarone, methotrexate, cyclophosphamide, dronedarone, SSRIs/SNRI antidepressants , anticonvulsants, antiplatelets, statins, angiotensin converting enzyme inhibitors (ACEI), angiotensin-II receptor blockers (ARB), thiazide diuretics and systemic fluoroquinolone antibiotics [Detailed list is shown in Annex 2]), smoking status.[9, 10] We included current smoking status as a binary variable. An individual was classed as a current smoker (1) or non-current smoker (0, i.e., other smoking status or the absence of a smoking status) based on the most recent smoking status prior to their index date. Information on prior radiotherapy and chemotherapy were not available for some patients but were included in the analysis when available. Risk factors that were not reliably identifiable including environment and occupational exposures, family history, and biologics, were not considered in the analysis.

Additionally, the incidence of ILD has changed substantially over time as well as the prescription patterns of the exposures. We therefore also accounted for calendar time in the propensity score analysis.

5.6. Statistical analysis

5.6.1.1. Brief summary of the analysis method

For the primary analysis, propensity scores were used to match new users of the target exposure (DOACs) to new users of the comparator exposure (VKAs), to control for confounding. For the secondary analysis, propensity scores were used to match new users of the individual target exposures to the comparator exposure (VKAs). For all analyses, cause-specific Cox proportional hazards models were used to estimate the relative hazard ratio of ILD after exposure accounting for mortality (where captured). Finally, random-effects meta-analysis methods were used to synthesise results across databases.

5.6.1.2. Descriptive analysis

Descriptive analyses were performed to describe the study cohorts at baseline in terms of demographic characteristics, comorbidities, and history of treatment with drugs commonly associated with ILD.

5.6.1.3. Main statistical methods

Propensity score matching was performed using a 1:1 matching of VKA users to DOAC users using a caliper width of 0.01 (see section 5.11 Protocol amendments) of the standard deviation of the logit of the propensity score.[11] We included the baseline risk factors and calendar days as predictor variables in the propensity score, where calendar year was matched exactly. Matching occurred within strata of indication (AF and VTE). Absolute standardised mean differences (SMD) for each variable were calculated before and after propensity score matching, with SMD of less than 0·1 representing successful matching. We visually checked the distributions of the propensity scores across treatment arms, within strata (indication, database).

In the propensity-matched cohort, the incidence of each study outcome was estimated between target (DOAC) and comparator (VKA) cohorts. Cause-specific Cox models were used to calculate hazard ratios for the instantaneous risk of the ILD outcome. We applied two analytical approaches: an on-treatment analysis (OT) and an intention to treat analysis (ITT as per the study by Chan et al.). For both

treatment strategies, follow-up was additionally restricted to a maximum of 1 year in a sensitivity analysis.

Random-effects meta-analysis was conducted for the AF cohort analyses when comparisons from more than two databases were available and 95% prediction intervals (PI) are provided.[12-14]

5.6.1.4. Missing data

The analysis was conducted on the assumption that an individual has a condition or prescription exposure if it is recorded in their electronic health record. No multiple imputation methods were performed. Therefore, patients with missing records for an indication were excluded from the analyses.

5.6.1.5. Sample size

The sample size was driven by the availability of individuals with exposures and outcomes within each database and no a priori sample size requirement was stipulated.

Quality control

The study was conducted according to the ENCePP code of conduct (European Medicines Agency 2018).

Standard operating procedures or internal process guidance were adhered to for the conduct of the study. These procedures included rules for secure and confidential data storage, quality-control procedures for all aspects of the study from protocol development to the reporting of the results.

All documents underwent at least one round a review by an experienced reviewer, while the results from the statistical analysis were either reviewed or checked via double coding.

The quality control of the data is the responsibility of the data holder.

Software

Sample selection and creation of the analytic variables were performed using the Instant Health Data (IHD) software (Panalgo, Boston, MA, USA). Further creation of analytic variables and statistical analyses were undertaken with R, version 4.1.2. Matching was performed with the MatchIt package.[15] Cox PH models were estimated with the coxphf package (add ref to coxphf). Other notable packages were ggplot2, cowplot and cobalt (figures), tableone (patient characterisation) and assertthat (quality control).

Protocol amendments

Propensity score

- Including calendar year as a categorical or nonlinear continuous variable was not sufficient. There were major differences in the values for the propensity scores for patients starting treatment on December 31st in one year and January 1st in the next. Therefore, we included this variable as the number of calendar days between the index date and January 1st, 2016, an arbitrary date. This continuous variable was then included using a spline with 8 dimensions.
- In some cohorts, the standard mean difference (SMD) in the propensity scores exceeded the limit of 0.10 that we set in the protocol, when using a caliper of 0.20 as defined in the protocol. We reduced the caliper to 0.01, which improved covariate balance after matching.

Cohorts analysed

- We do not present results of IRs and HRs among VT patients for THIN Spain given the very small sample size after PS matching (n=16). In addition, we do not present these results for THIN Italy among VT patients given the imbalance in the characteristics of treatment groups after PS matching.
- We do not present results of IRs and HRs in cohorts where only a single event or no events occurred, as despite the correction below, we could not obtain reliable estimates for these.

Analysis model

- We encountered non-estimable analyses, so we used Firth's bias correction to the likelihood to obtain estimates. This analysis removes first order bias and should not be considered a deviation from the analysis. [16,17]

Negative control outcomes

- We included negative control outcomes as a method to test for residual unmeasured confounding. Negative controls were identified using the OHDSI ATLAS tool that has been integrated with the LAERTES evidence base.[18] LAERTES integrates several sources of evidence for investigating the association between drugs and health outcomes of interests (HOIs) into a single data source. Evidence is sourced from spontaneous reports, scientific literature, and both American and European product labelling. Atlas then discriminates between known positive drug-HOI causal relationships and drugs not known to be associated with the outcome based upon evidence in LAERTES and their strength. This list was then screened manually to identify a limited number of potential negative outcomes to be considered.

6. Results

Details of the patient cohort attrition for each database are shown in the supplementary Tables S1-S4 contained in **Annex 3**.

6.1. New DOAC use in people with AF

In the AF cohort: 13,827 new DOAC users and 14,658 new VKA users were identified in IMRD UK; 24,646 and 11,047 respectively in IQVIA Germany; 1,135 and 8,082 respectively in THIN Spain; and 1,690 and 2,001 respectively in THIN Italy.

In all data sources there were large baseline imbalances (SMRD >0.1) in calendar year and date of index date. In IMRD UK, there were further baseline imbalances in the use of ACE inhibitors, amiodarone/dronedarone, anticonvulsants, nitrofurantoin, and SSRI/SNRI (supplementary Table S5). In IQVIA Germany, there were further baseline imbalances in use of ACE inhibitors, amiodarone/dronedarone, fluoroquinolones, statins, sulfonamides, and thiazide diuretics (supplementary Table S6). In THIN Spain, there was further baseline imbalance in age and sex, the use of ACE inhibitors, ARBs, Fluoroquinolones, SSRI/SNRI, and a prior history of kidney disease (supplementary Table S7). In THIN Italy, there were further baseline imbalances in the use of anticonvulsants, antiplatelets, fluoroquinolones, SSRI/SNRIs, statins, as well as a prior history of pneumonia and cancer (supplementary Table S8).

In the AF cohorts, 3603 per treatment group arm were propensity score matched in IMRD UK (26.1% of new DOAC users), 6140 in IQVIA Germany (24.9% of new DOAC users); 948 in THIN Spain (83.5% of new DOAC users); and 875 in THIN Italy (51.7% of new DOAC users). All included covariates were balanced with an SMD of <0.1 after propensity score matching using the reduced caliper width (supplementary Tables S5 to S8 and S11, and Figure S1).

Incidence rates in new DOAC and VKA users in matched AF cohorts

In the cohorts prepared for ITT analysis, the incidence per 10,000 person years of ILD in VKA users and DOAC users with AF was: 21.4 and 18.8 in IMRD UK; 11.1 and 11.2 in IQVIA Germany; 22.3 and 4.5 in THIN Spain; and 4.7 among VKA users in THIN Italy with no incident cases of ILD identified in the VKA cohort (Table 1). Incidence rates varied slightly in the cohorts prepared for OT analysis, which may be related to the lower number of events and available follow-up time with estimates being less precise.

Hazard ratios for incident ILD in DOAC users in matched AF cohorts

In the ITT analysis, hazard ratios for incident ILD among DOAC users compared to VKA users with AF were 0.88 (95%CI 0.51 to 1.51) in IMRD UK, 1.01 (95%CI 0.58 to 1.75) in IQVIA Germany, 0.27

(95%CI 0.03 to 1.36) in THIN Spain, and not estimable in THIN Italy (Table 2). The meta-analysed hazard ratio was 0.90 (95%CI 0.42 to 1.91, 95% PI 0.42 to 1.91). Hazard ratios for the OT analysis were 1.09 (95%CI 0.56 to 2.19) in IMRD UK and 2.36 (95%CI 0.39 to 24.29) in IQVIA Germany. No meta-analysis was performed as only two estimates were available.

The hazard ratios for incident ILD in AF cohorts when follow-up was restricted to a maximum of 365 days were similar in the ITT analysis but with a significant reduced hazard of ILD with meta-analysis (meta-analysed HR 0.74, 95% PI 0.59 to 0.93), and only imprecise estimates were available in the OT analysis (supplementary Table S9).

Hazard ratios for negative controls in DOAC users in matched AF cohorts

The cohort size, number of events and incidence rates for each negative control are shown in **Appendix File 1.** In the ITT analysis, meta-analysed hazard ratios for each negative control in DOAC users compared to VKA users with AF were: 0.85 (95%CI 0.63 to 1.16) for acquired hallux valgus; 0.86 (95%CI 0.71 to 1.05) for acute conjunctivitis; 0.75 (95%CI 0.72 to 0.79) for the common cold; 0.89 (95%CI 0.66 to 1.21) for ingrowing toenail; and 1.06 (95%CI 0.63 to 1.76) for varicella zoster infection. In the OT analysis, meta-analysed hazard ratios for each negative control were: 1.02 (95%CI 0.47 to 2.24), 1.40 (95%CI 0.83 to 2.37), 0.76 (955CI 0.54 to 1.06), 1.25 (95%CI 0.98 to 1.58) and 1.05 (95%CI 0.55 to 2.01) respectively.

Individual DOAC use in people in matched AF cohorts

The characteristics of AF patients used in the individual DOAC drug substance cohorts and their event rates are shown in **Appendix File 2** and supplementary Table S10 respectively. AF cohorts for individual DOACs were smaller and therefore incidence rates less precise, with several cohorts having zero events during follow-up.

Whilst the covariates with baseline imbalances were similar to those in the overall DOAC cohort, imbalances in calendar year of index date and days since cohort entry were greater for individual DOAC cohorts except for rivaroxaban. For the AF cohort, the largest frequency of matched patients per treatment group was with rivaroxaban in IMRD UK (n=2775), IQVIA Germany (n=5505), and THIN Italy (n=400), whilst the highest frequency of matched patients occurred with apixaban in THIN Spain (n=456). The number of cohorts that failed to pass propensity score diagnostics is shown in supplementary Table S11.

In the ITT analysis, meta-analysed hazard ratios for incident ILD among Rivaroxaban users compared to VKA users with AF were: 0.85 (95%CI 0.43 to 1.66, 95% PI 0.4 to 1.81) (supplementary Table S12). Hazard ratios for apixaban were 0.66 (95%CI 0.27 to 1.54) in IMRD UK and 1.24 (95%CI 0.62 to 2.51) in IQVIA Germany; for dabigatran were 1.03 (95%CI 0.39 to 2.71) in IMRD UK and 0.81 (95%CI 0.22 to 2.86) in IQVIA Germany; for edoxaban were 2.33 (95%CI 0.38 to 24.01) in IMRD UK and 1.57 (95%CI 0.54 to 4.91) in IQVIA Germany. No meta-analysis was performed for apixaban, dabigatran and edoxaban as fewer than three estimates were available.

Hazard ratios were not significantly different for the OT analysis that were less precise (supplementary Table S12) and when follow-up was restricted to maximum 365 days (supplementary Table S13).

6.2. New DOAC use in people with VT

In the VT cohort: 5,289 new DOAC users and 7,295 new VKA users were identified in IMRD UK; 17,083 and 9,385 respectively in IQVIA Germany; 10 and 2,005 respectively in THIN Spain; and 207 and 221 respectively in THIN Italy.

In all data sources there was a baseline imbalance (SMRD >0.1) in calendar year and date of index date. In IMRD UK, there were further baseline imbalances in the use of amiodarone/dronedarone, anticonvulsants, nitrofurantoin, SSRI/SNRI, and thiazide diuretics (supplementary Table S14). In IQVIA Germany, there was further baseline imbalance in use of ACEIs and thiazide diuretics (supplementary Table S15). No data are shown for THIN Spain and THIN Italy due to the small numbers.

Following propensity score matching in the VT cohorts 1,606 people were matched per treatment group in IMRD UK (30.4% of new DOAC users), 4,334 in IQVIA Germany (25.4% of new DOAC users),

5 in THIN Spain (50.0% of new DOAC users) and 39 in THIN Italy (18.8% of new DOAC users). The propensity score distributions for IMRD UK and IQVIA Germany after matching and all included covariates were balanced with an SMD of <0.1 (supplementary Figure S2 and supplementary Tables S14-S15). The number of cohorts that failed to pass propensity score diagnostics is shown in supplementary Table S11.

Incidence rates in new DOAC and VKA users in matched VT cohorts

In the cohorts prepared for ITT analysis, the incidence per 10,000 person years of ILD in VKA users and DOAC users with VT was: 15.9 and 23.0 in IMRD UK; and 11.1 and 11.2 in IQVIA Germany (Table 1). Incidence rates varied slightly in the cohorts prepared for OT analysis that may be related to the lower number of events and available follow-up time with estimates being less precise.

Hazard ratios for incident ILD in DOAC users in matched VT cohorts

In the ITT analysis, hazard ratios for incident ILD among DOAC users compared to VKA users with VT were 1.44 (95%CI 0.60 to 3.62) in IMRD UK and 0.56 (95%CI 0.28 to 1.08) in IQVIA Germany (Table 2). In the OT analysis, hazard ratios were 1.36 (95%CI 0.30 to 7.80) and 0.82 (95%CI 0.14 to 5.37) respectively. No meta-analysis was performed for the VT cohorts as there were only two estimates.

In the ITT analysis, hazard ratios for incident ILD in VT cohorts with restricted follow-up to maximum 365 days were HR 0.80, 95%CI 0.18 to 3.29 in IMRD UK and HR 0.48, 95%CI 0.14 to 1.40 in IQVIA Germany (supplementary Table S9).

Hazard ratios for negative controls in DOAC users in matched VT cohorts

The cohort size, number of events and incidence rates for each negative control are shown in **Appendix File 1**. In the ITT analysis, hazard ratios for negative control outcomes in DOAC users compared to VKA users with VT were not significant apart from ingrown toenail IQVIA Germany (HR 1.42, 95%CI 1.03 to 1.98) (Table 3). In the OT analysis, ingrown toenail was increased in IMRD UK (HR 3.10, 95%CI 1.17 to 10.11).

Individual DOAC use in matched VT cohorts

The characteristics of VT patients used in the individual DOAC drug substance cohorts and their event rates are shown in **Appendix File 2** and supplementary Table S10 respectively. VT cohorts for individual DOACs were even smaller than for AF cohorts and had similar limitations in terms of low precision and zero events rates.

Whilst covariates with baseline imbalances were similar as in the overall DOAC cohort, imbalances in calendar year of index date and days since cohort entry were greater for individual DOAC cohorts except for dabigatran and rivaroxaban. For the VT cohort, the largest frequency of matched patients was with rivaroxaban in IMRD UK (n=1545), IQVIA Germany (n=4206), and THIN Italy (n=9), with no matched cohorts evaluated in THIN Spain.

In the ITT analysis, hazard ratios for: apixaban were 0.79 (95%CI 0.18 to 3.24) in IMRD UK and 0.48 (95%CI 0.12 to 1.62) in IQVIA Germany; edoxaban was 0.28 (95%CI 0.03 to 1.42) in IQVIA Germany; rivaroxaban were 1.77 (95%CI 0.73 to 4.62) in IMRD UK and 0.71 (95%CI 0.36 to 1.34) in IQVIA Germany (supplementary Table S12). No estimates were estimable for dabigatran or for THIN Italy given the limited number of individuals.

Hazard ratios were not significantly different for the OT analysis (supplementary Table S12) and when follow-up was restricted to maximum 365 days (supplementary Table S13).

7. Discussion

In this multi-database study, we observed no increased risk of ILD associated with overall DOAC use compared to VKA use in patients with AF or VT. Similarly, we observed no increased risk of ILD associated with individual DOAC drug substances although limitations in sample size and precision mean it is not possible to exclude an association with individual drug substances based upon the available data.

7.1. Limitations of the research methods

Limitations of this study include the potential for missing data if exposure, outcomes, or covariates are not recorded in an individual's electronic health record. Only primary care databases were used with no linkage to hospital diagnoses that could lead to under ascertainment of outcomes.

Known risk factors for ILD were used as covariates to estimate the propensity score. However, some risk factors were not possible to include (e.g., environmental exposure) and unknown risk factors may have remained. The analysis controlled for baseline observed confounders. Complex time-varying analysis of confounders (e.g., drug exposure) was not performed and residual confounding remains possible.

Diagnostic coding for ILD is not known to have been validated in the primary care databases available. Although confirmation of the diagnoses requires specialist input; the nature of the diagnosis means that its recording in primary care records could be reasonably accurate. However, this assumption should be treated cautiously.

For privacy of the patients, the exact dates of birth and death are not recorded in the used databases. Instead, year of birth is available; and for patients whose death is registered; year of death is available. Patients were assumed to have died the day of the last record in the database, when year of death was provided. For the IMRD UK database, these dates are available for some patients, but a random error is added to these dates, leading to increased or decreased exposure time. THIN Spain and THIN Italy databases include date shifting of recordings to the start of the each week for anonymisation purposes meaning there may be short-term misclassification of exposure and/or events. However, the sample sizes provided from these two databases were limited compared to IQVIA Germany and IMRD UK.

A limited number of new DOAC users could be matched with new VKA users when calendar year and date of index date were included in the propensity score model, with uncertainty around generalisability of findings. However, prescribing patterns of DOACs and VKAs have changed significantly over the time period with the resulting strong influence on the propensity score estimation and balance. Similarly, the incidence of ILD has risen over time whilst DOAC prescribing has also increased, both patterns were observed in our study. It is uncertain whether the study by Chan *et al* accounted for calendar time when matching patients, and we did not observe an association suggestive of an increased risk of ILD.

We included selected negative controls to increase the robustness of the study. However, the absence of an association with these outcomes has not previously been demonstrated in these databases. In the AF cohorts, we observed that DOAC users had a smaller hazard of common cold on ITT analysis with a similar but not significant meta-analysis effect estimate on OT analysis. If these differences are related to residual unmeasured confounding it may suggest that the estimates for ILD in people with AF may be conservative. However, this pattern was not observed for the other negative outcomes suggesting that systematic residual unmeasured confounding is less likely to be present.

Conclusion

Our study results do not suggest that DOACs increase the risk of ILD compared to VKA users in either AF or VT patients. However, limitations in sample size may require the need for further research to confirm or refute these findings.

8. References

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Table 1. Number of person years of follow-up, events and incidence rates (IR) per 10,000 person-year for incident ILD in the new DOAC users vs new VKA users according to indication and treatment strategy in the matched cohorts.

Database	N VKA	N DOAC	Py VKA	Py DOAC	Events VKA	Events DOAC	IR VKA	IR DOAC
AF cohorts								
ITT								
IMRD UK	3603	3603	13112.12	12765.76	28	24	21.35	18.8
IQVIA Germany	6140	6140	22536.15	22307.99	25	25	11.09	11.21
THIN Spain	948	948	2244.87	2248.73	5	<5	22.27	4.45
THIN Italy	875	875	2116.41	2078.13	<5	0	4.72	0
OT								
IMRD UK	3603	3603	6495.2	8485.4	14	20	21.55	23.57
IQVIA Germany	6140	6140	900*	5000*	<5	5	11.63	9.81
THIN Spain	948	948	188.32	100*	0	<5	0	108.11
THIN Italy	875	875	397.13	1284.79	0	0	-	-
VT cohorts								
ITT								
IMRD UK	1606	1606	5043.75	4775.1	8	11	15.86	23.04
IQVIA Germany	4334	4334	15970.7	15615.67	24	13	15.03	8.32
THIN Spain	5	5	9.66	13.49	0	0	-	-
THIN Italy	39	39	71.62	69.92	0	0	0.0	0.0
OT								
IMRD UK	1606	1606	1400*	1600*	<5	<5	14.74	25.44
IQVIA Germany	4334	4334	700*	2000*	<5	<5	30.42	20.15
THIN Spain	5	5	0.82	0.4	0	0	-	-
THIN Italy	39	39	21.56	31.3	0	0	-	-

DOAC=direct oral anticoagulant. VKA=Vitamin K antagonist anticoagulant.
N=number. Py=person years. IR=incidence rate per 10,000pys.
AF=atrial fibrillation. VT=venous thromboembolism.
ITT=intention to treat. OT=on treatment.
*Rounded to avoid disclosure.

Table 2. Hazard ratios for incident ILD in new DOAC users vs new VKA users according to indication and treatment strategy in the matched cohorts.

	ITT				OT			
Database	**HR**	**95% CI lower**	**95% CI upper**	**p-value**	**HR**	**95% CI lower**	**95% CI upper**	**p-value**
AF cohorts								
IMRD UK	0.88	0.51	1.51	0.645	1.09	0.56	2.19	0.800
IQVIA Germany	1.01	0.58	1.75	0.979	2.36	0.39	24.29	0.355
THIN Spain	0.27	0.03	1.36	0.118	-	-	-	-
Meta-analysis	0.90	0.42	1.91	0.602	n/a			
VT cohorts								
IMRD UK	1.44	0.60	3.62	0.416	1.36	0.30	7.80	0.693
IQVIA Germany	0.56	0.28	1.08	0.082	0.82	0.14	5.37	0.821
Meta-analysis	n/a				n/a			

Comparison DOAC users (target treatment) vs VKA users (comparator treatment).
HR=hazard ratio. CI=confidence interval. AF=atrial fibrillation. VT=venous thromboembolism.
ITT=intention to treat. OT=on treatment. Databases without estimates not shown.
Meta-analysis=random effects. No meta-analysis was performed when only 2 estimates were available.
Hyphen=hazard ratio inestimable due to 0 count in the target, comparator cohorts or both.
n/a=not applicable.

Table 3. Hazard ratios for negative control outcomes in new DOAC users vs new VKA users by indication and treatment strategy in the matched cohorts.

Outcomes	Database	ITT HR	ITT 95% CI lower	ITT 95% CI upper	ITT p-value	OT HR	OT 95% CI lower	OT 95% CI upper	OT p-value
AF cohorts									
Acquired Hallux Valgus	IMRD UK	1.44	0.57	3.84	0.440	1.96	0.50	10.69	0.348
Acquired Hallux Valgus	IQVIA Germany	0.81	0.59	1.09	0.160	0.89	0.37	2.27	0.804
Acquired Hallux Valgus	THIN Spain	1.01	0.38	2.66	0.985	0.33	0.00	6.27	0.471
Acquired Hallux Valgus	THIN Italy	0.72	0.12	3.72	0.695	0.33	0.00	6.25	0.469
Acquired Hallux Valgus	Meta-analysis	0.85	0.63	1.16	0.194	1.02	0.47	2.24	0.937
Acute Conjunctivitis	IMRD UK	0.98	0.74	1.31	0.911	1.38	0.94	2.08	0.105
Acute Conjunctivitis	IQVIA Germany	0.78	0.57	1.06	0.109	1.27	0.42	4.50	0.679
Acute Conjunctivitis	THIN Spain	0.81	0.60	1.09	0.167	2.25	0.79	6.44	0.127
Acute Conjunctivitis	THIN Italy	0.62	0.06	4.63	0.633	0.19	0.01	2.67	0.199
Acute Conjunctivitis	Meta-analysis	0.86	0.71	1.05	0.094	1.40	0.83	2.37	0.135
Common Cold	IMRD UK	0.71	0.45	1.09	0.119	0.62	0.36	1.07	0.085
Common Cold	IQVIA Germany	0.75	0.61	0.93	0.010	0.82	0.41	1.74	0.590
Common Cold	THIN Spain	0.76	0.61	0.95	0.016	0.94	0.43	1.99	0.877
Common Cold	THIN Italy	0.86	0.26	2.72	0.800	1.02	0.20	6.21	0.979
Common Cold	Meta-analysis	0.75	0.72	0.79	0.000	0.76	0.54	1.06	0.077
Ingrown Toenail	IMRD UK	1.08	0.71	1.63	0.730	1.32	0.75	2.40	0.335
Ingrown Toenail	IQVIA Germany	0.80	0.57	1.12	0.186	0.96	0.29	4.09	0.949
Ingrown Toenail	THIN Spain	0.74	0.23	2.22	0.590	1.21	0.01	22.63	0.910
Ingrown Toenail	THIN Italy	3.08	0.16	449.30	0.458	0.79	0.04	115.33	0.888
Ingrown Toenail	Meta-analysis	0.89	0.66	1.21	0.311	1.25	0.98	1.58	0.059
Varicella	IMRD UK	1.04	0.67	1.63	0.858	1.03	0.64	1.68	0.9
Varicella	IQVIA Germany	0.86	0.62	1.18	0.342	0.86	0.48	1.57	0.626
Varicella	THIN Spain	0.59	0.24	1.34	0.207	0.44	0.08	1.71	0.242
Varicella	THIN Italy	1.01	0.21	4.75	0.991	6.88	0.67	925.6	0.115
Varicella	Meta-analysis	0.95	0.63	1.44	0.71	1.05	0.55	2.01	0.828
VT cohorts									
Acquired Hallux Valgus	IMRD UK	0.81	0.28	2.24	0.679	0.18	0.00	2.20	0.192
Acquired Hallux Valgus	IQVIA Germany	1.14	0.83	1.56	0.434	1.69	0.71	4.57	0.244
Acute Conjunctivitis	IMRD UK	1.16	0.75	1.80	0.499	0.89	0.46	1.73	0.733
Acute Conjunctivitis	IQVIA Germany	1.14	0.83	1.57	0.434	0.91	0.36	2.54	0.840
Common Cold	IMRD UK	0.89	0.38	2.01	0.771	0.83	0.25	2.82	0.762
Common Cold	IQVIA Germany	0.80	0.64	1.01	0.058	1.07	0.44	2.83	0.883
Ingrown Toenail	IMRD UK	1.58	0.87	2.94	0.132	3.10	1.17	10.11	0.022
Ingrown Toenail	IQVIA Germany	1.42	1.03	1.98	0.033	1.38	0.52	4.54	0.535
Varicella	IMRD UK	0.65	0.29	1.39	0.268	0.86	0.33	2.19	0.747
Varicella	IQVIA Germany	0.9	0.61	1.32	0.592	0.69	0.34	1.41	0.302

Comparison DOAC users (target treatment) vs VKA users (comparator treatment).
HR=hazard ratio. CI=confidence interval. AF=atrial fibrillation. VT=venous thromboembolism.
ITT=intention to treat. OT=on treatment. Databases without estimates not shown.
Meta-analysis=random-effects. No meta-analysis performed when only 2 estimates available.
Hyphen=hazard ratio inestimable due to 0 count in the target, comparator cohorts or both.

Annex 1 – Code lists

- List of codes and terms that were used for narrow and broad ILD definition:

ILD_broad and narrow list_21.06.20

- List of codes and terms that were used to identify DOACs and Vitamin K Antagonist:

DOACs - RxNorm and RxNorm Extensi

VitKAntagonists_21.06.2021.xlsx

- List of codes and terms that were used to identify AF; DVT and PE patients:

Indications - 2023 08 03.xlsx

- List of codes and terms that were used to identify exposure to co-medications:

DOAC-ILD-Covariate-Drugs_21.06.2023.

- List of codes and terms that were used to identify comorbidities and smoking:

DOAC-ILD-Covariate-Codes 2023 08 03.

- List of codes and terms that were used to identify negative controls:

Negative Controls.xlsx

Annex 2 - Data sources

IQVIA™ Medical Research Data (IMRD) UK

IQVIA™ Medical Research Data (IMRD) UK is a primary care database from the UK. GPs play a gatekeeper role in the healthcare system in the UK as they are responsible for delivering primary health care and specialist referrals. Over 98% of the UK-resident population is registered with a GP, so that GP patient records are broadly representative of the UK population in general. Patients are affiliated to a practice, which centralizes the medical information from GPs, specialist referrals, hospitalizations, and tests.

IQVIA™ Disease Analyzer Germany

IQVIA™ Disease Analyzer Germany collects computerised information from specialised and general primary care practices throughout Germany since 1992. Around 3% of general practitioners (GP) practices are included in this database, which covers all patients consulting one of these practices. Data from IQVIA™ Disease Analyzer Germany have been shown to be reasonably representative of German healthcare statistics for demographics and certain diseases and is considered one of the largest national medical databases worldwide. IQVIA™ Disease Analyzer Germany includes more than 2500 practices and 3100 physicians (13 speciality groups) representing over 15000000 patients.

The quality of IQVIA™ Disease Analyzer data is ensured by a series of continuous QA controls and data refinement. These include checking incoming data for criteria such as completeness and correctness (e.g., linkage between diagnoses and prescriptions) and standardizing certain data values such as laboratory test results to enable reliable analysis.

The Health Improvement Network (THIN®) Italy

In THIN® Italy data collection started in 2000 and this database is currently able to provide clinical monitoring data of anonymised patients managed by 500 GPs in primary care (including patients' history). The data source of THIN® Italy is electronic health care records. The entire database reaches 900000 patients, from which 500000 are currently actively followed. In order to be representative at national and macroregional level, physicians have been recruited in accordance with their distribution in terms of geographical location, age and gender.

It includes information on patient's diagnoses, test results and medication. In all countries patients are informed about the collection and anonymization of the data and they are able to opt out; in which case no data are subsequently transmitted to the THIN® database.

The Health Improvement Network (THIN®) Spain

THIN® Spain is mainly a primary care database, including practitioners (GP), specialists and pediatricians & nurses. It contains data from approximately 2000 GPs and 2400 specialists (cardiology, pulmonology, urology, etc.). THIN® Spain also includes partial information on activities related to the hospital. THIN® Spain is globally representative of the national demographics and prevalence on main chronic pathologies in Spain. It includes 3000000 individuals out of the overall population. Of these, 1800000 are active from 2014. Number of deceased patients globally varies between 8 and 9 thousand individuals per year, and number of new-borns ranges between 10 and 12 thousand individuals per year. New patients are automatically included into the database and deceased patients identified in a specific field. It includes information on patient's diagnoses; test results and medication. The database follow a very strict anonymization process. In all countries patients are informed about the collection and anonymization of the data and are able to opt out; in which case no data are subsequently transmitted to the THIN® database.

The study protocol for this study was submitted to and approved by Hospital Clinic ethics committee (Barcelona), which reviewed the data collection, protection, and anonymization processes.

Annex 3 – Supplementary tables and figures

Table S1. Cohort attrition in IMRD UK database

	DOACs cohort		VKAs cohort	
	Selected sample	**Attrition**	**Selected sample**	**Attrition**
Patients available in database anytime	5,317,853		5,317,853	--
Users of DOACs/VKAs at anytime	89,864	5,227,989	88,511	5,229,342
No previous history of broad ILD before index date	89,313	551	87,984	527
Age ≥18 years	60,565	28,748	54,773	33,211
Had a diagnosis of AF or VT recorded within 365 days before index date	39,424	21,141	31,900	22,873
Sex is recorded	39,424	0	31,899	1
Users of DOACs/VKAs during study observation period (01/01/2010 to 31/12/2019)	35,840	3,584	30,879	1,020
No previous use of DOACs before index date	26,611	9,229	30,272	607
Days at risk > 0 since index date	26,531	80	30,226	46
>= 365 days observable before index date	19,207	7,324	22,160	8,066
No history of cardiac mechanical valve and mitral stenosis	19,182	25	22,034	126
Sample included in the study				
Total sample	19,116	66*	21,953	81*
Only AF	13,827	--	14,658	--
Only VT	5,289	--	7,295	--

* Patients with both diagnosis of AF and VT recorded on the same day were excluded.
DOAC=direct oral anticoagulants. VKA=vitamin-K antagonists.
AF=atrial fibrillation. VT=venous thromboembolism.

Table S2. Cohort attrition in IQVIA DA Germany database

	DOACs cohort		VKAs cohort	
	Selected sample	**Attrition**	**Selected sample**	**Attrition**
Patients available in database anytime	41,974,403	--	41,974,403	--
Users of DOACs/VKAs at anytime	370,729	41,603,674	164,419	41,809,984
No previous history of broad ILD before index date	368,863	1,866	163,414	1,005
Age ≥18 years	236,459	132,404	128,758	34,656
Had a diagnosis of AF or VT recorded within 365 days before index date	76,048	160,411	34,450	94,308
Sex is recorded	75,940	108	34,407	43
Users of DOACs/VKAs during study observation period (01/01/2010 to 31/12/2019)	73,202	2,738	33,633	774
No previous use of DOACs before index date	64,830	8,372	32,141	1,492
Days at risk > 0 since index date	64,830	0	32,141	0
>= 365 days observable before index date	42,119	22,711	20,748	11,393
No history of cardiac mechanical valve and mitral stenosis	42,013	106	20,605	143
Sample included in the study				
Total sample	41,729	284*	20,432	173*
Only AF	24,646	--	11,047	--
Only VT	17,083	--	9,385	--

* Patients with both diagnosis of AF and VT recorded on the same day were excluded.
DOAC=direct oral anticoagulants. VKA=vitamin-K antagonists.
AF=atrial fibrillation. VT=venous thromboembolism.

Table S3. Cohort attrition in THIN® Spain database

	DOACs cohort		VKAs cohort	
	Selected sample	**Attrition**	**Selected sample**	**Attrition**
Patients available in database anytime	1,851,625	--	1,851,625	--
Users of DOACs/VKAs at anytime	12,781	1,838,844	31,696	1,819,929
No previous history of broad ILD before index date	12,758	23	31,607	89
Age ≥18 years	7,651	5,107	27,326	4,281
Had a diagnosis of AF or VT recorded within 365 days before index date	5,975	1,676	18,176	9,150
Sex is recorded	5,975	0	18,176	0
Users of DOACs/VKAs during study observation period (01/01/2010 to 31/12/2019)	4,331	1,644	18,132	44
No previous use of DOACs before index date	1,807	2,524	17,815	317
Days at risk > 0 since index date	1,807	0	17,815	0
>= 365 days observable before index date	1,147	660	10,186	7,629
No history of cardiac mechanical valve and mitral stenosis	1,145	2	10,123	63
Sample included in the study				
Total sample	1,145	0	10,087	36*
Only AF patients	1,135	--	8,082	--
Only VT patients	10	--	2,005	--

* Patients with both diagnosis of AF and VT recorded on the same day were excluded.
DOAC=direct oral anticoagulants. VKA=vitamin-K antagonists.
AF=atrial fibrillation. VT=venous thromboembolism.

Table S4. Cohort attrition in THIN® Italy database

	DOACs cohort		VKAs cohort	
	Selected sample	**Attrition**	**Selected sample**	**Attrition**
Patients available in database anytime	1,223,611	--	1,223,611	--
Users of DOACs/VKAs at anytime	29,398	1,194,213	23,399	1,200,212
No previous history of broad ILD before index date	29,383	15	23,381	18
Age ≥18 years	16,004	13,379	20,260	3,121
Had a diagnosis of AF or VT recorded within 365 days before index date	3,462	12,542	3,041	17,219
Sex is recorded	3,462	0	3,041	0
Users of DOACs/VKAs during study observation period (01/01/2010 to 31/12/2019)	3,188	274	3,011	30
No previous use of DOACs before index date	2,314	874	2,946	65
Days at risk > 0 since index date	2,314	0	2,946	0
>= 365 days observable before index date	1,904	410	2,235	711
No history of cardiac mechanical valve and mitral stenosis	1,900	4	2,228	7
Sample included in the study				
Total sample	1,897	3*	2,222	6*
Only AF	1,690	--	2,001	--
Only VT	207	--	221	--

* Patients with both diagnosis of AF and VT recorded on the same day were excluded.
DOAC=direct oral anticoagulants. VKA=vitamin-K antagonists.
AF=atrial fibrillation. VT=venous thromboembolism.

Table S5. Characteristics of new DOAC and VKA users with AF before and after propensity score (PS) matching in IMRD UK.

	Before PS matching			After PS matching		
	VKA	DOAC	SMD	VKA	DOAC	SMD
n	14658	13827		3603	3603	
ACEIs = 1 (%)	9015 (61.5)	7635 (55.2)	-0.1264	2092 (58.1)	2072 (57.5)	-0.0112
Age (median [IQR])	75.00 [68.00, 81.00]	76.00 [68.00, 83.00]	0.077	76.00 [68.00, 82.00]	75.00 [68.00, 82.00]	-0.0025
AmiodaroneOrDronedarone = 1 (%)	1402 (9.6)	456 (3.3)	-0.3509	172 (4.8)	181 (5.0)	0.014
Anticonvulsants = 1 (%)	1299 (8.9)	1962 (14.2)	0.1527	446 (12.4)	475 (13.2)	0.0231
Antiplatelets = 1 (%)	2405 (16.4)	2769 (20.0)	0.0904	728 (20.2)	740 (20.5)	0.0083
ARBs = 1 (%)	3511 (24.0)	3199 (23.1)	-0.0194	852 (23.6)	875 (24.3)	0.0151
AutoimmuneDisease = 1 (%)	521 (3.6)	556 (4.0)	0.0238	141 (3.9)	137 (3.8)	-0.0057
CalendarDays (median [IQR])	-1449.50 [-2144.00, -709.00]	565.00 [48.50, 1012.00]	2.8617	-255.00 [-542.50, 111.00]	-248.00 [-534.00, 117.00]	0.0096
Cancer = 1 (%)	2584 (17.6)	2801 (20.3)	0.0654	679 (18.8)	727 (20.2)	0.0331
Chemotherapy = 1 (%)	136 (0.9)	158 (1.1)	0.0202	36 (1.0)	37 (1.0)	0.0026
ConnectiveTissueDisease = 1 (%)	13 (0.1)	8 (0.1)	-0.0128	<5	0 (0.0)	-0.0231
COPD = 1 (%)	1354 (9.2)	1459 (10.6)	0.0428	346 (9.6)	365 (10.1)	0.0172
Cyclophosphamide = 1 (%)	<5	5 (0.0)	0.0047	<5	0 (0.0)	-0.0292
Fluoroquinolones = 1 (%)	2650 (18.1)	2602 (18.8)	0.0189	661 (18.3)	684 (19.0)	0.0163
HepatitisC = 1 (%)	9 (0.1)	11 (0.1)	0.0064	<5	<5	0
KidneyDisease = 1 (%)	4201 (28.7)	3410 (24.7)	-0.0928	931 (25.8)	948 (26.3)	0.0109
Methotrexate = 1 (%)	230 (1.6)	259 (1.9)	0.0224	66 (1.8)	62 (1.7)	-0.0082
Nitrofurantoin = 1 (%)	1585 (10.8)	2719 (19.7)	0.2227	547 (15.2)	557 (15.5)	0.007
Pneumonia = 1 (%)	673 (4.6)	977 (7.1)	0.0966	196 (5.4)	202 (5.6)	0.0065
Radiotherapy = 1 (%)	178 (1.2)	233 (1.7)	0.0366	47 (1.3)	63 (1.7)	0.0345
Sarcoidosis = 1 (%)	25 (0.2)	32 (0.2)	0.0127	6 (0.2)	6 (0.2)	0
Sex = MALE (%)	8175 (55.8)	7500 (54.2)	-0.0307	2016 (56.0)	2022 (56.1)	0.0033
Smoker = 1 (%)	700 (4.8)	650 (4.7)	-0.0035	176 (4.9)	175 (4.9)	-0.0013
SSRIOrSNRI = 1 (%)	4889 (33.4)	5548 (40.1)	0.1381	1344 (37.3)	1358 (37.7)	0.0079
Statins = 1 (%)	9110 (62.2)	8471 (61.3)	-0.0182	2194 (60.9)	2239 (62.1)	0.0256
Sulfonamides = 1 (%)	169 (1.2)	143 (1.0)	-0.0117	39 (1.1)	41 (1.1)	0.0055
ThiazideDiuretics = 1 (%)	6068 (41.4)	5091 (36.8)	-0.0949	1428 (39.6)	1435 (39.8)	0.004
Tuberculosis = 1 (%)	42 (0.3)	26 (0.2)	-0.0227	5 (0.1)	9 (0.2)	0.0256
yearOfIndexDate (median [IQR])	2012.00 [2010.00, 2014.00]	2017.00 [2016.00, 2018.00]	2.7756	2015.00 [2014.00, 2016.00]	2015.00 [2014.00, 2016.00]	0
Propensity score			2.9829			0.0108

DOAC=direct oral anticoagulants. VKA=vitamin-K antagonists.
AF=atrial fibrillation. VT=venous thromboembolism.

Table S6. Characteristics of new DOAC and VKA users with AF before and after propensity score (PS) matching in IQVIA Germany.

	Before PS matching			After PS matching		
	VKA	DOAC	SMD	VKA	DOAC	SMD
n	11047	24646		6140	6140	
ACEIs = 1 (%)	5761 (52.1)	9773 (39.7)	-0.2555	2815 (45.8)	2728 (44.4)	-0.029
Age (median [IQR])	74.00 [68.00, 80.00]	75.00 [67.00, 81.00]	0.026	75.00 [69.00, 80.00]	75.00 [69.00, 81.00]	-0.0109
AmiodaroneOrDronedarone = 1 (%)	940 (8.5)	834 (3.4)	-0.2834	340 (5.5)	338 (5.5)	-0.0018
Anticonvulsants = 1 (%)	716 (6.5)	1619 (6.6)	0.0035	410 (6.7)	368 (6.0)	-0.0276
Antiplatelets = 1 (%)	1116 (10.1)	2281 (9.3)	-0.0292	638 (10.4)	641 (10.4)	0.0017
ARBs = 1 (%)	3201 (29.0)	7080 (28.7)	-0.0055	1732 (28.2)	1699 (27.7)	-0.0119
AutoimmuneDisease = 1 (%)	830 (7.5)	1789 (7.3)	-0.0098	461 (7.5)	460 (7.5)	-6.00E-04
CalendarDays (median [IQR])	-1137.00 [-1970.50, -185.00]	496.50 [-134.00, 1007.00]	1.8327	-297.50 [-822.00, 308.00]	-291.00 [-827.00, 311.00]	0.0058
Cancer = 1 (%)	1911 (17.3)	4343 (17.6)	0.0085	1129 (18.4)	1084 (17.7)	-0.0192
Chemotherapy = 1 (%)	214 (1.9)	374 (1.5)	-0.0343	100 (1.6)	101 (1.6)	0.0013
ConnectiveTissueDisease = 1 (%)	<5	7 (0.0)	0.0007	<5	<5	0
COPD = 1 (%)	1856 (16.8)	3616 (14.7)	-0.0602	997 (16.2)	983 (16.0)	-0.0064
Cyclophosphamide = 1 (%)	<5	0 (0.0)	-0.0171	0 (0.0)	0 (0.0)	0
Fluoroquinolones = 1 (%)	2644 (23.9)	4873 (19.8)	-0.1045	1311 (21.4)	1279 (20.8)	-0.0131
HepatitisC = 1 (%)	46 (0.4)	87 (0.4)	-0.0107	27 (0.4)	21 (0.3)	-0.0165
KidneyDisease = 1 (%)	2617 (23.7)	5309 (21.5)	-0.0523	1552 (25.3)	1500 (24.4)	-0.0206
Methotrexate = 1 (%)	67 (0.6)	169 (0.7)	0.0096	33 (0.5)	27 (0.4)	-0.0118
Nitrofurantoin = 1 (%)	144 (1.3)	338 (1.4)	0.0058	85 (1.4)	93 (1.5)	0.0112
Pneumonia = 1 (%)	845 (7.6)	1714 (7.0)	-0.0273	430 (7.0)	423 (6.9)	-0.0045
Radiotherapy = 1 (%)	39 (0.4)	75 (0.3)	-0.0088	19 (0.3)	27 (0.4)	0.0237
Sarcoidosis = 1 (%)	32 (0.3)	93 (0.4)	0.0143	20 (0.3)	27 (0.4)	0.0186
Sex = MALE (%)	6005 (54.4)	12902 (52.3)	-0.0402	3278 (53.4)	3239 (52.8)	-0.0127
Smoker = 1 (%)	0 (0.0)	0 (0.0)	0	0 (0.0)	0 (0.0)	0
SSRIOrSNRI = 1 (%)	1464 (13.3)	2853 (11.6)	-0.0524	774 (12.6)	738 (12.0)	-0.0183
Statins = 1 (%)	4476 (40.5)	7926 (32.2)	-0.1789	2277 (37.1)	2209 (36.0)	-0.0237
Sulfonamides = 1 (%)	983 (8.9)	1585 (6.4)	-0.1006	477 (7.8)	475 (7.7)	-0.0013
ThiazideDiuretics = 1 (%)	2051 (18.6)	3026 (12.3)	-0.1916	907 (14.8)	886 (14.4)	-0.0104
Tuberculosis = 1 (%)	50 (0.5)	99 (0.4)	-0.0081	25 (0.4)	26 (0.4)	0.0026
yearOfIndexDate (median [IQR])	2012.00 [2010.00, 2015.00]	2017.00 [2015.00, 2018.00]	1.8002	2015.00 [2013.00, 2016.00]	2015.00 [2013.00, 2016.00]	0
Propensity score			2.9808			0.0176

DOAC=direct oral anticoagulants. VKA=vitamin-K antagonists.
AF=atrial fibrillation. VT=venous thromboembolism.

Table S7. Characteristics of new DOAC and VKA users with AF before and after propensity score (PS) matching in THIN Spain

	Before PS matching			After PS matching		
	VKA	DOAC	SMD	VKA	DOAC	SMD
n	8082	1135		948	948	
ACEIs = 1 (%)	2913 (36.0)	354 (31.2)	-0.1048	313 (33.0)	321 (33.9)	0.0182
Age (median [IQR])	77.00 [69.00, 83.00]	69.00 [59.00, 79.00]	-0.5268	72.00 [64.00, 80.00]	72.00 [64.00, 80.25]	0.0146
AmiodaroneOrDronedarone = 1 (%)	605 (7.5)	106 (9.3)	0.0637	74 (7.8)	79 (8.3)	0.0181
Anticonvulsants = 1 (%)	1162 (14.4)	148 (13.0)	-0.0397	149 (15.7)	133 (14.0)	-0.0501
Antiplatelets = 1 (%)	568 (7.0)	90 (7.9)	0.0334	71 (7.5)	81 (8.5)	0.039
ARBs = 1 (%)	3155 (39.0)	373 (32.9)	-0.1314	336 (35.4)	351 (37.0)	0.0337
AutoimmuneDisease = 1 (%)	159 (2.0)	19 (1.7)	-0.0229	26 (2.7)	15 (1.6)	-0.0904
CalendarDays (median [IQR])	353.00 [-200.00, 878.00]	563.00 [76.50, 1053.00]	0.3019	559.50 [45.00, 1039.00]	556.00 [66.00, 1046.00]	0.0054
Cancer = 1 (%)	480 (5.9)	59 (5.2)	-0.0334	46 (4.9)	54 (5.7)	0.038
Chemotherapy = 1 (%)	0 (0.0)	<5	0.0297	948 (100.0)	948 (100.0)	0
ConnectiveTissueDisease = 1(%)	0 (0.0)	0 (0.0)	0	0 (0.0)	0 (0.0)	0
COPD = 1 (%)	83 (1.0)	11 (1.0)	-0.0059	10 (1.1)	11 (1.2)	0.0108
Cyclophosphamide = 1 (%)	0 (0.0)	0 (0.0)	0	0 (0.0)	0 (0.0)	0
Fluoroquinolones = 1 (%)	2444 (30.2)	282 (24.8)	-0.1248	270 (28.5)	264 (27.8)	-0.0146
HepatitisC = 1 (%)	43 (0.5)	8 (0.7)	0.0207	<5	5 (0.5)	0.0126
KidneyDisease = 1 (%)	1013 (12.5)	89 (7.8)	-0.1746	75 (7.9)	88 (9.3)	0.051
Methotrexate = 1 (%)	78 (1.0)	10 (0.9)	-0.009	11 (1.2)	8 (0.8)	-0.0339
Nitrofurantoin = 1 (%)	131 (1.6)	14 (1.2)	-0.0351	14 (1.5)	14 (1.5)	0
Pneumonia = 1 (%)	414 (5.1)	38 (3.3)	-0.0986	38 (4.0)	38 (4.0)	0
Radiotherapy = 1 (%)	0 (0.0)	0 (0.0)	0	0 (0.0)	0 (0.0)	0
Sarcoidosis = 1 (%)	<5	<5	0.0214	0 (0.0)	<5	0.0356
Sex = MALE (%)	4230 (52.3)	747 (65.8)	0.2841	594 (62.7)	578 (61.0)	-0.0356
Smoker = 1 (%)	0 (0.0)	0 (0.0)	0	0 (0.0)	0 (0.0)	0
SSRIOrSNRI = 1 (%)	1599 (19.8)	165 (14.5)	-0.1489	161 (17.0)	154 (16.2)	-0.0209
Statins = 1 (%)	3946 (48.8)	529 (46.6)	-0.0444	467 (49.3)	477 (50.3)	0.0211
Sulfonamides = 1 (%)	165 (2.0)	19 (1.7)	-0.0286	18 (1.9)	18 (1.9)	0
ThiazideDiuretics = 1 (%)	498 (6.2)	64 (5.6)	-0.0227	60 (6.3)	59 (6.2)	-0.0046
Tuberculosis = 1 (%)	11 (0.1)	0 (0.0)	-0.0394	948 (100.0)	948 (100.0)	0
yearOfIndexDate (median [IQR])	2016.00 [2015.00, 2018.00]	2017.00 [2016.00, 2018.00]	0.285	2017.00 [2016.00, 2018.00]	2017.00 [2016.00, 2018.00]	0
Propensity score			0.5741			.0001

DOAC=direct oral anticoagulants. VKA=vitamin-K antagonists.
AF=atrial fibrillation. VT=venous thromboembolism.

Table S8. Characteristics of new DOAC and VKA users with AF before and after propensity score (PS) matching in THIN Italy.

	Before PS matching			After PS matching		
	VKA	DOAC	SMD	VKA	DOAC	SMD
n	2001	1690		875	875	
ACEIs = 1 (%)	896 (44.8)	827 (48.9)	0.0832	433 (49.5)	411 (47.0)	-0.0503
Age (median [IQR])	76.00 [70.00, 82.00]	77.00 [70.00, 83.00]	0.0531	77.00 [70.00, 83.00]	77.00 [70.00, 82.00]	-0.0311
AmiodaroneOrDronedarone = 1 (%)	136 (6.8)	148 (8.8)	0.0694	32 (3.7)	32 (3.7)	0
Anticonvulsants = 1 (%)	179 (8.9)	207 (12.2)	0.1007	101 (11.5)	97 (11.1)	-0.0139
Antiplatelets = 1 (%)	132 (6.6)	184 (10.9)	0.1378	80 (9.1)	68 (7.8)	-0.044
ARBs = 1 (%)	727 (36.3)	692 (40.9)	0.0938	326 (37.3)	331 (37.8)	0.0116
AutoimmuneDisease = 1 (%)	43 (2.1)	50 (3.0)	0.0478	24 (2.7)	23 (2.6)	-0.0067
CalendarDays (median [IQR])	-312.00 [-1145.00, 451.00]	780.00 [325.00, 1158.00]	1.8547	521.00 [13.50, 969.00]	521.00 [13.50, 976.00]	0.0097
Cancer = 1 (%)	149 (7.4)	189 (11.2)	0.1186	79 (9.0)	75 (8.6)	-0.0145
Chemotherapy = 1 (%)	0 (0.0)	0 (0.0)	0	0 (0.0)	0 (0.0)	0
ConnectiveTissueDisease = 1 (%)	<5	<5	-0.0168	0 (0.0)	0 (0.0)	0
COPD = 1 (%)	17 (0.8)	27 (1.6)	0.0597	11 (1.3)	6 (0.7)	-0.0456
Cyclophosphamide = 1 (%)	<5	<5	0.0038	0 (0.0)	<5	0.047
Fluoroquinolones = 1 (%)	700 (35.0)	772 (45.7)	0.2148	375 (42.9)	368 (42.1)	-0.0161
HepatitisC = 1 (%)	9 (0.4)	7 (0.4)	-0.0055	<5	<5	-0.0178
KidneyDisease = 1 (%)	138 (6.9)	126 (7.5)	0.0213	66 (7.5)	63 (7.2)	-0.0131
Methotrexate = 1 (%)	21 (1.0)	18 (1.1)	0.0015	9 (1.0)	8 (0.9)	-0.0111
Nitrofurantoin = 1 (%)	21 (1.0)	30 (1.8)	0.055	12 (1.4)	17 (1.9)	0.0433
Pneumonia = 1 (%)	29 (1.4)	56 (3.3)	0.1042	9 (1.0)	11 (1.3)	0.0128
Radiotherapy = 1 (%)	0 (0.0)	0 (0.0)	0	0 (0.0)	0 (0.0)	0
Sarcoidosis = 1 (%)	0 (0.0)	0 (0.0)	0	0 (0.0)	0 (0.0)	0
Sex = MALE (%)	1033 (51.6)	850 (50.3)	-0.0266	444 (50.7)	434 (49.6)	-0.0229
Smoker = 1 (%)	0 (0.0)	0 (0.0)	0	0 (0.0)	0 (0.0)	0
SSRIOrSNRI = 1 (%)	231 (11.5)	263 (15.6)	0.1108	117 (13.4)	115 (13.1)	-0.0063
Statins = 1 (%)	694 (34.7)	679 (40.2)	0.1121	343 (39.2)	345 (39.4)	0.0047
Sulfonamides = 1 (%)	85 (4.2)	101 (6.0)	0.0729	56 (6.4)	53 (6.1)	-0.0145
ThiazideDiuretics = 1 (%)	218 (10.9)	190 (11.2)	0.011	108 (12.3)	95 (10.9)	-0.047
Tuberculosis = 1 (%)	<5	9 (0.5)	0.0594	<5	<5	0
yearOfIndexDate (median [IQR])	2015.00 [2012.00, 2017.00]	2018.00 [2016.00, 2019.00]	1.8246	2017.00 [2016.00, 2018.00]	2017.00 [2016.00, 2018.00]	0
Propensity score			1.8474			0.007

DOAC=direct oral anticoagulants. VKA=vitamin-K antagonists.
AF=atrial fibrillation. VT=venous thromboembolism.

Figure S1. Propensity score (PS) distributions for matched AF cohorts.

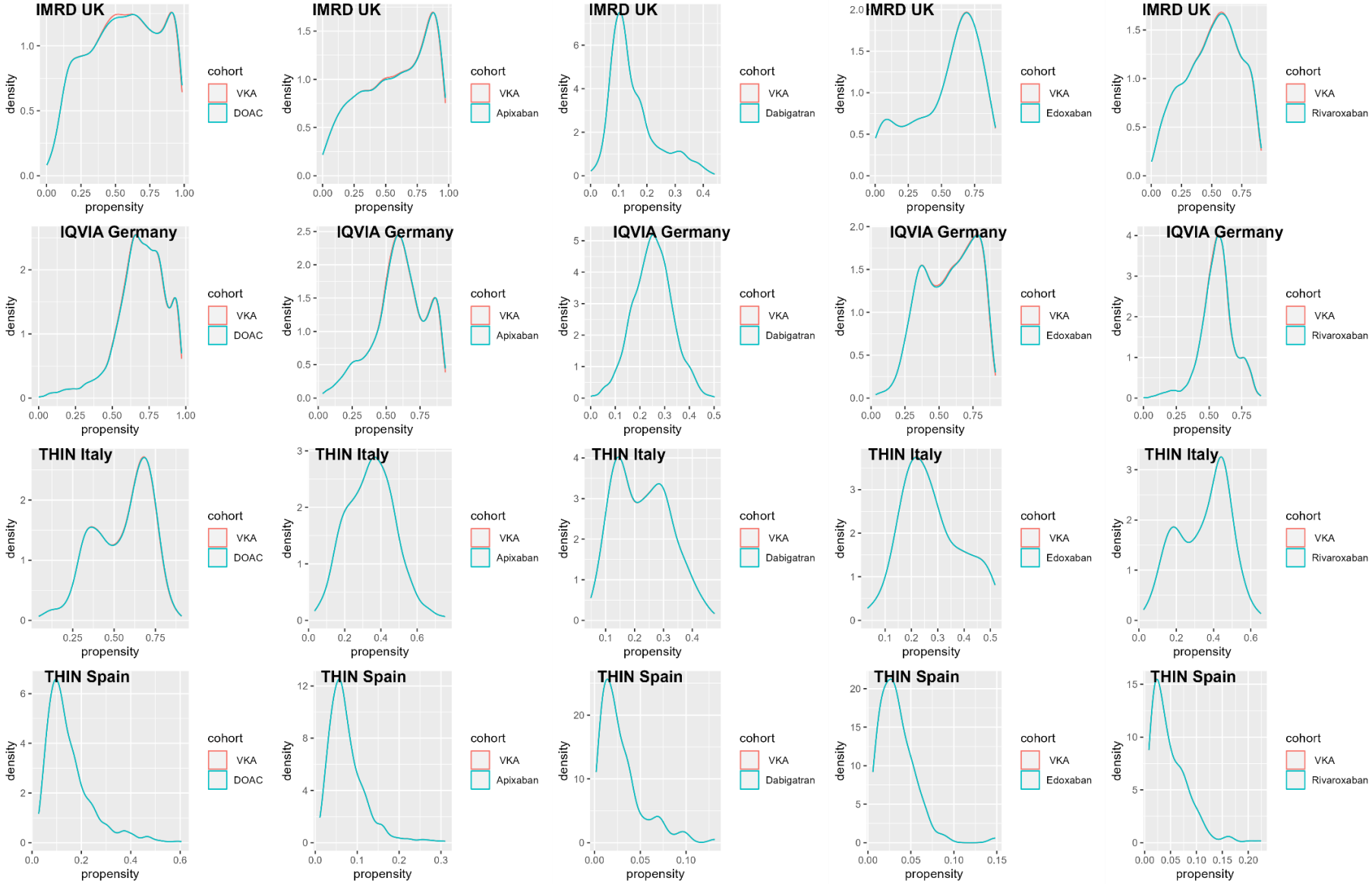


Table S9. Hazard ratios for incident ILD in new DOAC users vs new VKA users according to indication and treatment strategy with maximum 365 days follow-up.

	ITT				OT			
Database	**HR**	**95% CI lower**	**95% CI upper**	**p-value**	**HR**	**95% CI lower**	**95% CI upper**	**p-value**
AF cohorts								
IMRD UK	0.78	0.27	2.15	0.627	0.95	0.31	2.88	0.920
IQVIA Germany	0.74	0.23	2.20	0.584	2.33	0.38	24.06	0.365
THIN Spain	0.60	0.06	4.53	0.618	-	-	-	-
Meta-analysis	0.74	0.59	0.93	0.030	n/a			
VT cohorts								
IMRD UK	0.80	0.18	3.29	0.755	2.23	0.12	325.35	0.603
IQVIA Germany	0.48	0.14	1.40	0.183	0.78	0.12	5.21	0.782
Meta-analysis	n/a				n/a			

HR=hazard ratio. CI=confidence interval. AF=atrial fibrillation. VT=venous thromboembolism.
ITT=intention to treat. OT=on treatment. n/a=not applicable.
Meta-analysis=random effects. No meta-analysis performed when only 2 estimates are available.
Hypher= hazard ratio inestimable due to 0 count in the target, comparator cohorts or both.
Only cohorts with estimable hazard ratios shown.

Table S10. Number of person years of follow-up, events and incidence rates for ILD in individual DOAC and VKA matched cohorts using the ITT treatment strategy.

Target	Database	N VKA	N target	Py VKA	Py target	Events VKA	Events target	IR VKA	IR target
AF cohorts									
Apixaban	IMRD UK	1760	1760	5121.81	4894.66	13	8	25.38	16.34
Apixaban	IQVIA Germany	3812	3812	10995.27	10780.51	14	17	12.73	15.77
Apixaban	THIN Spain	456	456	1000*	1132.83	<5	0	8.90	0
Apixaban	THIN Italy	377	377	777.32	787.09	0	0	0	0
Dabigatran	IMRD UK	916	916	3606.88	3489.79	8	8	22.18	22.92
Dabigatran	IQVIA Germany	1964	1964	7462.41	7000*	5	<5	6.70	5.37
Dabigatran	THIN Spain	127	127	500*	314.13	<5	0	33.32	0
Dabigatran	THIN Italy	240	240	616.42	605.46	0	0	0	0
Edoxaban	IMRD UK	322	322	500*	500*	<5	<5	20.54	61.04
Edoxaban	IQVIA Germany	1866	1866	3772.20	3723.63	5	8	13.25	21.48
Edoxaban	THIN Spain	96	96	126.28	123.43	0	0	0	0
Edoxaban	THIN Italy	143	143	176.41	176.39	0	0	0	0
Rivaroxaban	IMRD UK	2775	2775	9437.18	9108.07	26	16	27.55	17.57
Rivaroxaban	IQVIA Germany	5505	5505	19545.75	19178.71	27	27	13.81	14.08
Rivaroxaban	THIN Spain	234	234	500*	500*	<5	<5	15.84	16.19
Rivaroxaban	THIN Italy	400	400	855.07	823.16	0	0	0	0
VT cohorts									
Apixaban	IMRD UK	651	651	1000*	1000*	<5	<5	30.27	23.31
Apixaban	IQVIA Germany	1870	1870	4520.14	4000*	7	<5	15.49	6.88
Apixaban	THIN Italy	5	5	6.24	7.20	0	0	0	0
Dabigatran	IMRD UK	26	26	81.03	66.06	0	0	0	0
Dabigatran	IQVIA Germany	377	377	1000*	1000*	<5	<5	8.46	26.93
Dabigatran	THIN Italy	<5	<5	1.28	1.94	0	0	0	0
Edoxaban	IMRD UK	102	102	500*	146.29	<5	0	62.43	0
Edoxaban	IQVIA Germany	940	940	1641.69	1500*	5	<5	30.46	6.23
Edoxaban	THIN Italy	<5	<5	2.74	2.51	0	0	0	0
Rivaroxaban	IMRD UK	1545	1545	4870.45	4653.35	7	12	14.37	25.79
Rivaroxaban	IQVIA Germany	4206	4206	15540.77	15123.39	22	15	14.16	9.92
Rivaroxaban	THIN Italy	9	9	25.38	18.11	0	0	0	0

DOAC=direct oral anticoagulant. VKA=Vitamin K antagonist anticoagulant.
N=number. Py=person years. IR=incidence rate per 10,000pys.
AF=atrial fibrillation. VT=venous thromboembolism.
ITT=intention to treat. OT=on treatment.
No matched VT cohort from THIN Spain.

Table S11. Distribution of cohorts that passed propensity score diagnostics prior to the generation of treatment effect hazard ratios.

	Database	Balanced covariate distribution	Variable failing PS SMD threshold (SMD)
AF cohorts			
DOACs	IMRD UK	Yes	
DOACs	IQVIA Germany	Yes	
DOACs	THIN Italy	Yes	
DOACs	THIN Spain	Yes	
Apixaban	IMRD UK	Yes	
Apixaban	IQVIA Germany	Yes	
Apixaban	THIN Italy	No	Cancer (-0.15), kidney disease (-0.15)
Apixaban	THIN Spain	No	Nitrofurantoin (-0.126)
Dabigatran	IMRD UK	Yes	
Dabigatran	IQVIA Germany	Yes	
Dabigatran	THIN Italy	No	Statins (0.11), Thiazide diuretics (0.15)
Dabigatran	THIN Spain	No	Smoker (-0.103), ACEi (-0.17), Amiodarone (0.15), fluoroquinolone (-.14), nitrofurantoin (-0.1), pneumonia (0.11), statins (-0.22)
Edoxaban	IMRD UK	No	Radiotherapy (0.123)
Edoxaban	IQVIA Germany	Yes	
Edoxaban	THIN Italy	No	Smoker (0.102), ACEi (0.14), age (0.12), COPD (0.1), Hep C (-0.1), methotrexate (0.1), sex (-0.14), sulfonamide (0.13)
Edoxaban	THIN Spain	No	Amiodarone or Dronedarone (-0.18), Antiplatelets (0.10), Autoimmune Disease (-0.11), Fluoroquinolones (0.15), Hepatitis C (-0.23), Pneumonia (-0.19), Sex (0.13), Sulfonamides (0.20), Thiazide Diuretics (-0.12).
Rivaroxaban	IMRD UK	Yes	
Rivaroxaban	IQVIA Germany	Yes	
Rivaroxaban	THIN Italy	Yes	
Rivaroxaban	THIN Spain	No	ACEIs (-0.12), Antiplatelets (-0.12).
VT cohorts			
DOACs	IMRD UK	Yes	
DOACs	IQVIA Germany	Yes	
DOACs	THIN Italy	No	Amiodarone or Dronedarone (0.14), Fluoroquinolones (0.26), Sex (0.21), SSRI or SNRI (-0.18), Statins (-0.22), Sulfonamides (0.12), Thiazide Diuretics (-0.17).
DOACs	THIN Spain	No	<20 individuals in cohort arms and many covariate SMRD >0.1
Apixaban	IMRD UK	Yes	
Apixaban	IQVIA Germany	Yes	
Apixaban	THIN Italy	No	<20 individuals in cohort arms and many covariate SMRD >0.1
Dabigatran	IMRD UK	No	ACEIs (0.17), Age (-0.13), Antiplatelets (0.19), ARBs (0.25), Autoimmune Disease (0.31), COPD (-0.58), Fluoroquinolones (0.20), Sex (-0.39), Smoker (-0.35), SSRI or SNRI (0.39), Statins (0.32). Anticonvulsants (-0.11)
Dabigatran	IQVIA Germany	No	
Dabigatran	THIN Italy	No	<20 individuals in cohort arms and many covariate SMRD >0.1
Edoxaban	IMRD UK	No	ACEIs (-0.10), Amiodarone or Dronedarone (0.15), Anticonvulsants (-0.11), Sex (0.27), Smoker (-0.13), Tuberculosis (-0.11).
Edoxaban	IQVIA Germany	Yes	
Edoxaban	THIN Italy	No	<20 individuals in cohort arms and many covariate SMRD >0.1
Rivaroxaban	IMRD UK	Yes	
Rivaroxaban	IQVIA Germany	Yes	
Rivaroxaban	THIN Italy	No	<20 individuals in cohort arms and many covariate SMRD >0.1

AF=atrial fibrillation. VT=venous thromboembolism. PS=propensity score. Shaded=failed PS diagnostics.
Yes=SMD<0.1 after matching. No=SMD >=0.1 after matching.
Matched VT cohorts from THIN Italy contain <20 individuals and most covariate SMRD >0.1.
No matched VT cohorts from THIN Spain.

Table S12. Hazard ratios for incident ILD in DOAC users according to drug substance, indication and treatment strategy in the matched cohorts.

		ITT				OT			
Target	Database	HR	95% CI lower	95% CI upper	p-value	HR	95% CI lower	95% CI upper	p-value
AF cohorts									
Apixaban	IMRD UK	0.66	0.27	1.54	0.340	0.66	0.22	1.91	0.436
Apixaban	IQVIA Germany	1.24	0.62	2.51	0.551	1.17	0.14	13.60	0.886
Apixaban	Meta-analysis	n/a				n/a			
Dabigatran	IMRD UK	1.03	0.39	2.71	0.956	1.76	0.39	10.08	0.466
Dabigatran	IQVIA Germany	0.81	0.22	2.86	0.743	XX			
Dabigatran	Meta-analysis	n/a				n/a			
Edoxaban	IMRD UK	2.33	0.38	24.01	0.366	1.43	0.19	15.70	0.725
Edoxaban	IQVIA Germany	1.57	0.54	4.91	0.406	0.21	0.01	5.68	0.394
Edoxaban	Meta-analysis	n/a				n/a			
Rivaroxaban	IMRD UK	0.65	0.34	1.19	0.160	0.87	0.40	1.91	0.730
Rivaroxaban	IQVIA Germany	1.02	0.60	1.73	0.951	3.11	0.64	30.32	0.174
Rivaroxaban	THIN Spain	1.01	0.08	12.46	0.992	3	0.16	437.76	0.469
Rivaroxaban	Meta-analysis	n/a				n/a			
VT cohorts									
Apixaban	IMRD UK	0.79	0.18	3.24	0.738	0.61	0.05	7.52	0.669
Apixaban	IQVIA Germany	0.48	0.12	1.62	0.243	0.40	0.02	6.57	0.507
Apixaban	Meta-analysis	n/a				n/a			
Edoxaban	IQVIA Germany	0.28	0.03	1.42	0.131	-	-	-	-
Edoxaban	Meta-analysis	n/a				n/a			
Rivaroxaban	IMRD UK	1.77	0.73	4.62	0.207	2.61	0.48	26.12	0.278
Rivaroxaban	IQVIA Germany	0.71	0.36	1.34	0.291	1.67	0.22	18.20	0.616
Rivaroxaban	Meta-analysis	n/a				n/a			

Comparison DOAC users (target treatment) vs VKA users (comparator treatment).
HR=hazard ratio. CI=confidence interval. AF=atrial fibrillation. VT=venous thromboembolism.
ITT=intention to treat. OT=on treatment. No estimates available for VT cohorts in THIN Spain and THIN Italy.
Meta-analysis=random effects only performed when ≥3 effect estimates are available.
Databases without estimates not shown.
Shaded row = did not pass PS diagnostics.

Table S13. Hazard ratios for incident ILD in DOAC users according to drug substance, indication and treatment strategy with maximum 365 days follow-up in the matched cohorts.

		ITT				OT			
Target	Database	HR	95% CI lower	95% CI upper	p-value	HR	95% CI lower	95% CI upper	p-value
AF cohorts									
Apixaban	IMRD UK	1.27	0.36	4.74	0.703	0.69	0.15	2.82	0.596
Apixaban	IQVIA Germany	0.70	0.19	2.30	0.552	1.14	0.13	13.37	0.905
Apixaban	Meta-analysis	n/a				n/a			
Dabigatran	IQVIA Germany	0.43	0.04	2.59	0.362	-	-	-	-
Dabigatran	Meta-analysis	n/a				n/a			
Edoxaban	IMRD UK	1.67	0.22	18.24	0.614	0.92	0.07	11.30	0.939
Edoxaban	IQVIA Germany	1.00	0.21	4.73	0.995	0.22	0.01	5.78	0.405
Edoxaban	Meta-analysis	n/a				n/a			
Rivaroxaban	IMRD UK	0.66	0.21	1.90	0.444	0.67	0.18	2.20	0.503
Rivaroxaban	IQVIA Germany	1.13	0.44	2.91	0.803	3.08	0.63	30.1	0.179
Rivaroxaban	THIN Spain	1.01	0.08	12.46	0.992	3	0.16	437.76	0.469
Rivaroxaban	Meta-analysis	n/a				n/a			
VT cohorts									
Apixaban	IMRD UK	1.01	0.16	6.51	0.994	-	-	-	-
Apixaban	IQVIA Germany	1.02	0.16	6.60	0.982	0.78	0.12	5.21	0.782
Apixaban	Meta-analysis	n/a				n/a			
Edoxaban	IQVIA Germany	1.00	0.08	12.33	0.999	0.33	0	6.26	0.470
Edoxaban	Meta-analysis	n/a				n/a			
Rivaroxaban	IMRD UK	2.25	0.54	12.52	0.269	4.84	0.39	669.35	0.241
Rivaroxaban	IQVIA Germany	0.82	0.22	2.90	0.760	1.67	0.22	18.20	0.616
Rivaroxaban	Meta-analysis	n/a				n/a			

Comparison DOAC users (target treatment) vs VKA users (comparator treatment).
HR=hazard ratio. CI=confidence interval. AF=atrial fibrillation. VT=venous thromboembolism.
ITT=intention to treat. OT=on treatment. No estimates available for VT cohorts in THIN Spain and THIN Italy.
Meta-analysis=random-effects. No meta-analysis performed for VT cohorts as only 2 estimates available.
Grey shaded rows=did not pass propensity score diagnostics.

Table S14. Characteristics of new DOAC and VKA users with VT before and after propensity score matching in IMRD UK.

	Before PS matching			After PS matching		
	VKA	DOAC	SMD	VKA	DOAC	SMD
n	7295	5289		1606	1606	
ACEIs = 1 (%)	2537 (34.8)	1726 (32.6)	-0.0457	540 (33.6)	553 (34.4)	0.0173
Age (median [IQR])	66.00 [52.00, 77.00]	66.00 [52.00, 77.00]	0.0023	66.00 [51.00, 77.00]	66.00 [52.00, 77.00]	0.027
AmiodaroneOrDronedarone = 1 (%)	74 (1.0)	19 (0.4)	-0.1095	11 (0.7)	10 (0.6)	-0.0104
Anticonvulsants = 1 (%)	1009 (13.8)	1040 (19.7)	0.1467	284 (17.7)	314 (19.6)	0.047
Antiplatelets = 1 (%)	581 (8.0)	516 (9.8)	0.0604	142 (8.8)	151 (9.4)	0.0189
ARBs = 1 (%)	914 (12.5)	643 (12.2)	-0.0114	227 (14.1)	205 (12.8)	-0.0419
AutoimmuneDisease = 1 (%)	313 (4.3)	241 (4.6)	0.0128	67 (4.2)	62 (3.9)	-0.0149
CalendarDays (median [IQR])	-1333.00 [-1954.50, -675.50]	629.00 [136.00, 1046.00]	2.9492	-53.00 [-395.00, 405.75]	-52.00 [-392.75, 423.75]	0.0051
Cancer = 1 (%)	1356 (18.6)	1110 (21.0)	0.0589	319 (19.9)	300 (18.7)	-0.0291
Chemotherapy = 1 (%)	186 (2.5)	171 (3.2)	0.0386	50 (3.1)	46 (2.9)	-0.0141
ConnectiveTissueDisease = 1 (%)	5 (0.1)	12 (0.2)	0.0333	<5	7 (0.4)	0.0393
COPD = 1 (%)	583 (8.0)	462 (8.7)	0.0263	124 (7.7)	141 (8.8)	0.0375
Cyclophosphamide = 1 (%)	<5	<5	0.0123	0 (0.0%)	0 (0.0%)	0
Fluoroquinolones = 1 (%)	1350 (18.5)	892 (16.9)	-0.0438	294 (18.3)	301 (18.7)	0.0116
HepatitisC = 1 (%)	27 (0.4)	54 (1.0)	0.0647	10 (0.6)	10 (0.6)	0
KidneyDisease = 1 (%)	1408 (19.3)	874 (16.5)	-0.0747	302 (18.8)	304 (18.9)	0.0034
Methotrexate = 1 (%)	177 (2.4)	120 (2.3)	-0.0106	38 (2.4)	36 (2.2)	-0.0084
Nitrofurantoin = 1 (%)	886 (12.1)	1020 (19.3)	0.181	275 (17.1)	282 (17.6)	0.011
Pneumonia = 1 (%)	464 (6.4)	484 (9.2)	0.0968	126 (7.8)	126 (7.8)	0
Radiotherapy = 1 (%)	113 (1.5)	136 (2.6)	0.0646	35 (2.2)	34 (2.1)	-0.0039
Sarcoidosis = 1 (%)	21 (0.3)	23 (0.4)	0.0223	7 (0.4)	8 (0.5)	0.0095
Sex = MALE (%)	3624 (49.7)	2663 (50.3)	0.0134	789 (49.1)	785 (48.9)	-0.005
Smoker = 1 (%)	884 (12.1)	645 (12.2)	0.0024	174 (10.8)	196 (12.2)	0.0419
SSRIOrSNRI = 1 (%)	3056 (41.9)	2541 (48.0)	0.1231	751 (46.8)	789 (49.1)	0.0474
Statins = 1 (%)	2687 (36.8)	1996 (37.7)	0.0187	598 (37.2)	594 (37.0)	-0.0051
Sulfonamides = 1 (%)	104 (1.4)	68 (1.3)	-0.0124	22 (1.4)	23 (1.4)	0.0055
ThiazideDiuretics = 1 (%)	1815 (24.9)	1034 (19.6)	-0.1344	345 (21.5)	351 (21.9)	0.0094
Tuberculosis = 1 (%)	37 (0.5)	26 (0.5)	-0.0022	6 (0.4)	10 (0.6)	0.0356
yearOfIndexDate (median [IQR])	2012.00 [2010.00, 2014.00]	2017.00 [2016.00, 2018.00]	2.9088	2015.00 [2014.00, 2017.00]	2015.00 [2014.00, 2017.00]	0
Propensity score			3.1456			0.0114

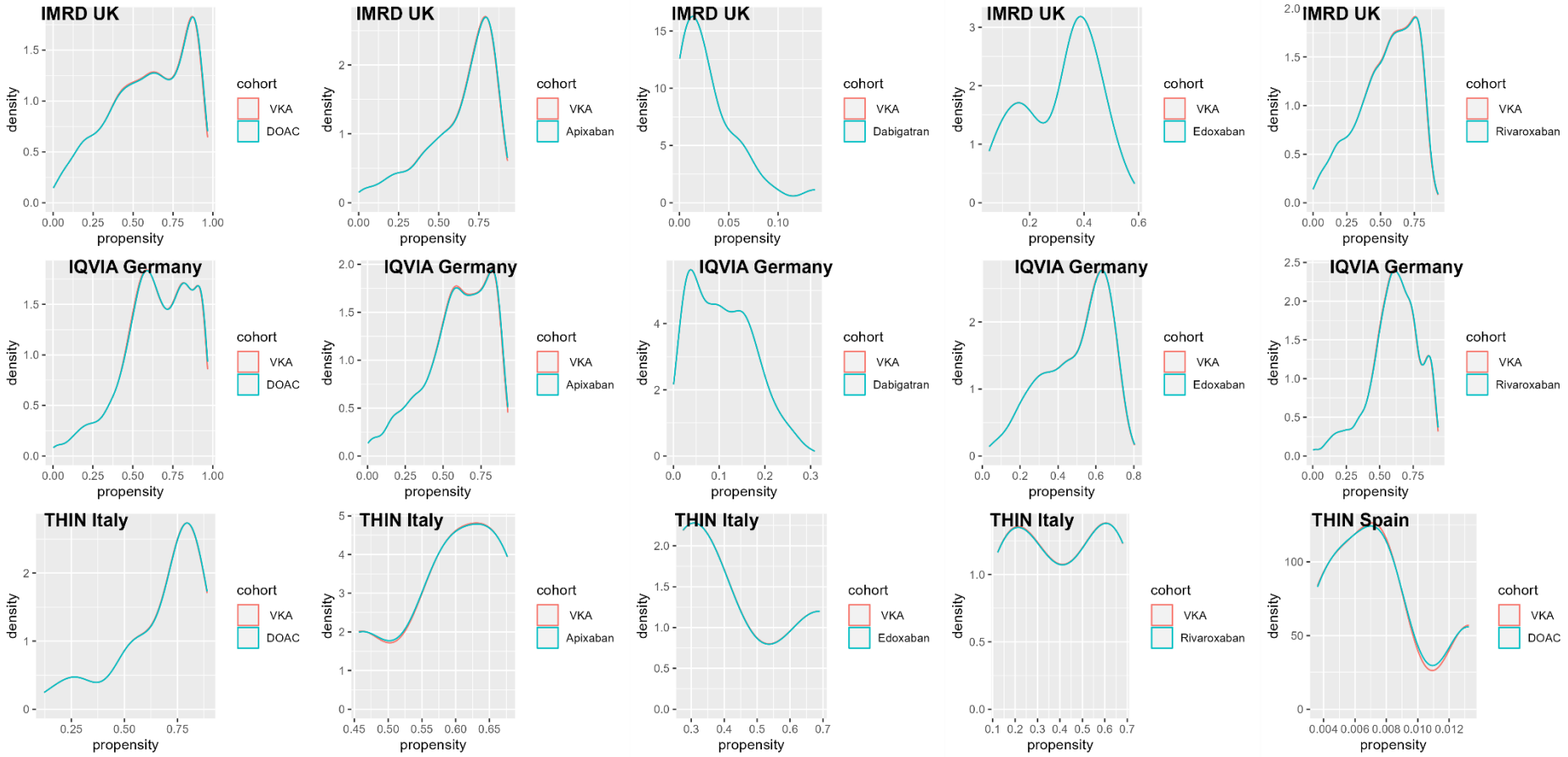
DOAC=direct oral anticoagulants. VKA=vitamin-K antagonists.
AF=atrial fibrillation. VT=venous thromboembolism.

Table S15. Characteristics of new DOAC and VKA users with VT before and after propensity score matching in IQVIA Germany.

	Before PS matching			After PS matching		
	VKA	DOAC	SMD	VKA	DOAC	SMD
n	9385	17083		4334	4334	
ACEIs = 1 (%)	3720 (39.6)	5652 (33.1)	-0.1393	1558 (35.9)	1501 (34.6)	-0.028
Age (median [IQR])	69.00 [55.00, 77.00]	67.00 [54.00, 77.00]	-0.0032	69.00 [55.00, 77.00]	68.00 [55.00, 77.00]	-0.0056
AmiodaroneOrDronedarone = 1 (%)	115 (1.2)	93 (0.5)	-0.0925	40 (0.9)	44 (1.0)	0.0125
Anticonvulsants = 1 (%)	733 (7.8)	1487 (8.7)	0.0317	343 (7.9)	352 (8.1)	0.0074
Antiplatelets = 1 (%)	526 (5.6)	847 (5.0)	-0.0298	243 (5.6)	246 (5.7)	0.0032
ARBs = 1 (%)	1954 (20.8)	3775 (22.1)	0.0308	960 (22.2)	957 (22.1)	-0.0017
AutoimmuneDisease = 1 (%)	838 (8.9)	1552 (9.1)	0.0054	410 (9.5)	428 (9.9)	0.0145
CalendarDays (median [IQR])	-1271.00 [-1933.00, -414.00]	599.00 [-14.50, 1047.00]	2.1311	-339.50 [-819.00, 297.00]	-336.50 [-826.00, 297.00]	0.011
Cancer = 1 (%)	1878 (20.0)	3635 (21.3)	0.031	885 (20.4)	889 (20.5)	0.0023
Chemotherapy = 1 (%)	235 (2.5)	436 (2.6)	0.0031	107 (2.5)	106 (2.4)	-0.0015
ConnectiveTissueDisease = 1 (%)	5 (0.1)	11 (0.1)	0.0044	<5	<5	-0.0091
COPD = 1 (%)	1531 (16.3)	2561 (15.0)	-0.037	689 (15.9)	696 (16.1)	0.0045
Cyclophosphamide = 1 (%)	<5	<5	-0.0341	0 (0.0%)	0 (0.0%)	0
Fluoroquinolones = 1 (%)	2577 (27.5)	4616 (27.0)	-0.0099	1162 (26.8)	1193 (27.5)	0.0161
HepatitisC = 1 (%)	63 (0.7)	113 (0.7)	-0.0012	33 (0.8)	29 (0.7)	-0.0114
KidneyDisease = 1 (%)	1842 (19.6)	3123 (18.3)	-0.0348	866 (20.0)	840 (19.4)	-0.0155
Methotrexate = 1 (%)	136 (1.4)	185 (1.1)	-0.0354	55 (1.3)	57 (1.3)	0.0045
Nitrofurantoin = 1 (%)	154 (1.6)	293 (1.7)	0.0057	82 (1.9)	77 (1.8)	-0.0089
Pneumonia = 1 (%)	930 (9.9)	1739 (10.2)	0.0089	428 (9.9)	422 (9.7)	-0.0046
Radiotherapy = 1 (%)	41 (0.4)	73 (0.4)	-0.0015	17 (0.4)	21 (0.5)	0.0141
Sarcoidosis = 1 (%)	45 (0.5)	73 (0.4)	-0.008	20 (0.5)	19 (0.4)	-0.0035
Sex = MALE (%)	4468 (47.6)	7961 (46.6)	-0.0202	2016 (46.5)	1986 (45.8)	-0.0139
Smoker = 1(%)	0 (0.0)	0 (0.0)	0	0 (0.0)	0 (0.0)	0
SSRIOrSNRI = 1 (%)	1499 (16.0)	2626 (15.4)	-0.0166	665 (15.3)	667 (15.4)	0.0013
Statins = 1 (%)	2401 (25.6)	3791 (22.2)	-0.0816	999 (23.1)	969 (22.4)	-0.0167
Sulfonamides = 1 (%)	1012 (10.8)	1460 (8.5)	-0.08	411 (9.5)	395 (9.1)	-0.0132
ThiazideDiuretics = 1 (%)	1293 (13.8)	1768 (10.3)	-0.1125	517 (11.9)	486 (11.2)	-0.0235
Tuberculosis = 1 (%)	57 (0.6)	84 (0.5)	-0.0165	21 (0.5)	21 (0.5)	0
yearOfIndexDate (median [IQR])	2012.00 [2010.00, 2014.00]	2017.00 [2015.00, 2018.00]	2.101	2015.00 [2013.00, 2016.00]	2015.00 [2013.00, 2016.00]	0
Propensity score			2.9297			0.0148

DOAC=direct oral anticoagulants. VKA=vitamin-K antagonists.
AF=atrial fibrillation. VT=venous thromboembolism.

Figure S2. Propensity score distributions for matched VT cohorts.



Appendix File 1

Events, person time and incidence for each negative control outcome.

Appendix File 1.xlsx