Comparative Effectiveness and Safety between Apixaban, Dabigatran, Edoxaban, and Rivaroxaban among Patients with Atrial Fibrillation: A Multinational Population-Based Cohort Study

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Abstract

Background: Current guidelines recommend using direct oral anticoagulants (DOACs) over warfarin in patients with atrial fibrillation (AF), but head-to-head trial data do not exist to guide the choice of DOACs.

Objective: To conduct a large-scale comparison between all DOACs (apixaban, dabigatran, edoxaban, or rivaroxaban) in routine clinical practice.

Design: Multinational population-based cohort study.

Setting: Five standardised electronic healthcare databases, which covered 221 million people in France, Germany, the UK, and the US.

Participants: Patients newly diagnosed with AF from 2010 through 2019 and who received a new DOAC prescription.

Measurements: Database-specific hazard ratios (HR) of ischemic stroke/systemic embolism (SE), intracranial hemorrhage (ICH), gastrointestinal bleeding (GIB), and all-cause mortality between DOACs were estimated using propensity-score stratified Cox regression model and pooled using a random-effects model.

Results: There were 527,226 new DOAC users who met the inclusion criteria (apixaban n=281,320, dabigatran n=61,008, edoxaban n=12,722, rivaroxaban n=172,176). Apixaban use was associated with a lower risk of GIB compared to dabigatran (HR=0.81, 95% confidence interval [CI]=0.70-0.94), edoxaban (HR=0.77, 95%CI=0.66-0.91), and rivaroxaban (HR=0.72, 95%CI=0.66-0.79). No substantial differences were observed for other outcomes or DOAC-DOAC comparisons. The results were consistent for patients aged≥80 years. Consistent associations between a lower GIB risk and apixaban vs rivaroxaban were observed among patients taking standard-dose (HR=0.72, 95%CI=0.64-

0.82), reduced-dose (HR=0.68, 95%CI=0.61-0.77), or with chronic kidney disease (CKD) (HR=0.68, 95%CI=0.59-0.77).

Limitation: Residual confounding is possible.

Conclusions: Among patients with AF, apixaban use was associated with a lower risk of GIB and comparable rates of ischemic stroke/SE, ICH, and all-cause mortality when compared to dabigatran, edoxaban, and rivaroxaban. This finding was consistent for patients aged≥80 years and those with CKD, who are often under-represented in clinical trials.

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Introduction

Direct oral anticoagulants (DOACs) are used for stroke prevention in patients with atrial fibrillation (AF), the most common sustained arrhythmia affecting over 33 million people worldwide.(1) Warfarin, a vitamin K antagonist, has been the mainstay of anticoagulation therapy before the introduction of DOACs (apixaban, dabigatran, edoxaban, and rivaroxaban). Unlike warfarin, DOACs can be administered in fixed doses without frequent coagulation monitoring. Data from randomized controlled trials (RCTs) and post-marketing observational studies have shown that DOACs are non-inferior to warfarin in preventing stroke and have lower risks of bleeding and osteoporotic bone fractures.(2-4) Given their ease of use and superior safety, current guidelines recommend DOACs in preference to warfarin in patients with AF.(5, 6) More recently, many countries advise switching patients from warfarin to DOAC to negate the need for frequent monitoring during the coronavirus disease 2019 (COVID-19) pandemic.(7) Despite this, there is no clear guidance on how to choose between the four DOACs, because head-to-head clinical trial data are not available. A few small, single-site, observational studies comparing all the four DOACs have yielded mixed results.(8-10) Due to the lack of robust evidence, the choice between DOACs is often based on anecdotal experience.(11) As DOACs are now being offered to more patients worldwide, a comprehensive comparative assessment of the DOACs is urgently needed.

The objective of this study was to directly compare the effectiveness and safety outcomes between apixaban, dabigatran, edoxaban, and rivaroxaban among patients with AF. We used a standardized database network that covers 221 million patients from four different countries. We also conducted pre-specified subgroup analyses to compared DOAC use among older patients (aged ≥80 years) and those with chronic kidney diseases, who are often under-represented in RCTs.

Methods

Data sources

This study used the anonymized patient records from five electronic health databases in the Observational Health Data Science and Informatics (OHDSI) distributed data network.(12) OHDSI is an open-science, international, and interdisciplinary collaborative.(12) All community members within OHDSI were invited to run the analyses and returned the results for this study.(13) In the end, IQVIA provided five electronic health databases from four countries: France (LPD France), Germany (DA Germany), the United Kingdom (UK IMRD), and the United States (US Ambulatory EMR and US Hospital Charge Master), comprising 221 million people across primary care, outpatient, and hospital settings. Information including demographics, drug prescriptions, and diagnoses records are prospectively recorded in the databases as part of the routine clinical care of patients. All databases are standardized to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (version 5).(14) The databases are quality-controlled for research purpose(15) and they have been extensively used for conducting high-quality and large-scale multinational drug surveillance studies.(16-20) The details of the databases are described in **Appendix 1** and previous publications (16-20). The data partner has obtained institutional review board approval (for UK IMRD) or exemption (for all other databases) for their participation in this study.

Study design

This study used a new-user, active-comparator cohort design. We specified head-to-head target trials for each pairwise comparisons of DOACs: 1) apixaban vs dabigatran, 2) apixaban vs rivaroxaban, 3) apixaban vs edoxaban, 4) dabigatran vs rivaroxaban, 5) dabigtran vs edoxaban, and 6) rivaroxaban vs edoxaban, with the following protocol components (**Appendix 2**):

Eligibility criteria

Patients with AF who were aged ≥18 years and had never use the DOAC pairs of interest. Patients were required to have at least one year of observation period prior to the index date in the database to measure medical history. To identify patients with AF, patients were required to have a diagnosis of AF anytime on or before the index date, or within 90 days after the index date to account for any delay in recording the AF diagnosis. Patients with a history of mitral stenosis, hyperthyroidism, or mechanical heart valve replacement among whom DOACs might be contraindicated, or transient AF i.e., who had undergone cardiac surgery, or who were diagnosed with myocarditis, pericarditis, or pulmonary embolism, were excluded. Other exclusion criteria included a prescription of warfarin or other DOACs within 180 days on or before the index date; a prescription of another oral anticoagulant (other than the index anticoagulant) on the index date; and a history of the outcomes of interest to avoid its residual effects on future outcome events, which are difficult to control for in observational studies (**Figure 1**). The phenotype codes for clinical conditions, procedures, and drugs used in the study were compiled using a sequence of quality-control procedures in the databases (**Appendix 3**) and are listed in the study protocol and repository.(21)

Treatment Groups and Follow-up

For each head-to-head comparison, patients were classified into a DOAC group based on their first prescription of DOAC between 1 January 2010 (2012 for LPD France) and 31 December 2019. “Time zero” (index date) was defined as the date of the first prescription. Patients were followed from the index date until the occurrence of the study outcome, treatment discontinuation (allowing for 90-day gaps between consecutive prescriptions, with the date of treatment discontinuation being the end date of the last prescription [the “on-treatment” approach]), switching from the index medication to another oral anticoagulant

(apixaban, dabigatran, edoxaban, rivaroxaban, or warfarin), death, or the end of the study period (31 December 2019), whichever came first. For the databases with no death date available (LPD France and US Ambulatory EMR), the date of last consultation, instead of the date of death, was used for censoring.

Outcomes

The outcomes of interest included 1) a composite of ischaemic stroke and systemic embolism, 2) intracranial haemorrhage (ICH), 3) gastrointestinal bleeding (GIB), and 4) all-cause mortality (available in DA Germany, UK IMRD, and US Hospital Charge Master). The outcomes were identified based on published code lists (**Appendix 3**).

Statistical analysis

To address any potential bias due to nonrandomized treatment allocation, propensity score modelling was used to compare patients who differed with respect to treatment with anticoagulants but were similar with respect to other measured characteristics.(22) The propensity score is defined as the probability of receiving the targeted treatment, given the observed patient characteristics. We developed large-scale propensity score models for each comparison and database using a consistent data-driven process through regularized logistic regression, which used a large set (>90,000) of predefined baseline patient characteristics (including age, sex, and other demographics), care site (practice, hospital, etc) unique identifier, and previous medical conditions, drug exposures, procedures, and health service use behaviours to provide the most accurate prediction of treatment and balance the patient cohorts across many characteristics.(17, 23) All covariates were identified within the 365 days before and on the index date. The regularization propensity score method has been widely used for variable selection and confounding adjustment,(16, 18, 20) and has

consistently demonstrated equal or superior performance to traditional investigator-specified or high-dimensional propensity score approaches in both actual and simulation studies.(23, 24)

Patients were stratified into five strata based on their propensity score to estimate the average treatment effect. Standardized differences were used to assess the differences in patient characteristics between treatment groups before and after propensity score stratification. Proposed cut-offs for acceptable standardized differences range from 0.1 to 0.25.(3) Cox proportional hazard regression conditioned on the propensity score strata was applied to estimate the hazard ratio (HR) of the risk of outcomes in every pairwise DOAC comparison in each database. The HRs were pooled across the databases in a meta-analysis using a random-effects model.

In observational studies, residual bias could remain despite controlling for measured confounding through propensity score. Therefore, to further reduce bias from unmeasured and systematic sources, we conducted empirical calibration of confidence intervals (CIs).(25, 26) For this we used a data-rich algorithm (27) to identify 49 negative control outcomes (i.e. events that are not known to be associated with DOACs use and thus have a null effect size) to construct an empirical null distribution and quantify systematic error.(25, 26) (**Supplemental Figures 1-3**) We then incorporated the error observed for negative controls into our results to take into account both systematic and random errors in the study. The full list of negative control outcomes is presented in **Supplemental Table 1**.

In subgroup analyses, we restricted the analyses into those who initiated a standard dose regimen of DOACs (i.e., apixaban 5mg twice daily, dabigatran 150mg twice daily, edoxaban

60mg twice daily, and rivaroxaban 20mg once daily) and into those who initiated a reduced-dose DOAC (i.e., apixaban 2.5mg twice daily, dabigatran 110mg twice daily in Europe/dabigatran 75mg twice daily in the United States, edoxaban 30mg twice daily, and rivaroxaban 15mg once daily). Additional analyses were conducted for two important patient subgroups that are often under-represented in clinical trials: 1) patients who were aged ≥80 years at cohort entry; 2) patients with chronic kidney disease at cohort entry. Chronic kidney disease was defined as having a diagnosis of chronic kidney disease or a dialysis procedure, an algorithm used in the previous study in OHDSI.(16) All statistical analyses details are presented in **Appendix 4**.

We conducted additional sensitivity analyses in which the time-at-risk was not censored if the patients discontinued the index medication or switched to another anticoagulant (analogue to the "intention-to-treat" approach). We also repeated our analyses using propensity-score matching at a variable-matching ratio as sensitivity analyses to estimate the average treatment effect on the treated.(28) Overall, we specified 480 analyses per database (6 DOACs comparisons x 4 outcomes x 5 groups x 2 propensity score approaches x 2 time-at-risk definitions). For clarity, the result estimates from the on-treatment, propensity score stratification analyses are presented here. The complete set of results are presented in Supplementary materials and an interactive website (https://data.ohdsi.org/corazon) (**Appendix 5**).

All analyses were performed using the R programming language version 3.5.1. The analysis packages were built on the open-source OHDSI CohortMethod R package and the Cyclops R package.(21) The study protocol and all statistical analysis packages were pre-specified prior to analysis execution. The study protocol and analysis codes are publicly available to enhance

the transparency and reproducibility of the results.(21) This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Role of the Funding source

None.

Results

Patient characteristics

There were 527,226 new DOAC users meeting the inclusion criteria across the five databases (apixaban n=281,320, dabigatran n=61,008, edoxaban n=12,722, rivaroxaban n=172,176). The follow-up time varied by DOAC groups and databases, with the median overall follow-up ranging from 534 to 1612 days for each DOAC group per database (**Table 1**).

Across the five databases, the proportion of patients aged≥65 ranged from 77%-87% for apixaban, 75%-83% for dabigatran, 79%-86% for edoxaban, and 73%-83% for rivaroxaban. The age distributions are similar in the European databases. Apixaban users tended to be older than other DOAC users in the US Ambulatory EMR (prevalence of aged 80-84y=21.1% in apixaban vs 4%-11% in other DOACs, SMD>0.25) and older than dabigatran in the US Hospital CDM (21% vs 4% were aged 80-84y). The proportions of females were 42%-50% for apixaban, 40%-47% for dabigatran, 43%-48% for edoxaban, and 38%-47% for rivaroxaban. The mean CHA_2DS_2-VASc ranged from 2.8-3.9 for apixaban, 2.6-3.7 for dabigatran, 2.5-3.6 for rivaroxaban, and 2.9-3.8 for edoxaban across the five databases. Most baseline characteristics of DOAC users were similar before propensity score stratification with standardized differences<0.10 and remained well-balanced after stratification (Supplemental Figures 4-15). The baseline characteristics of all pairwise DOAC comparisons

are presented in **Supplemental Tables 2-25**.

DOAC-DOAC comparisons

In total, there were 9,530 ischaemic stroke/systemic embolism events, 841 ICH events, 8,319 GIB events, and 1,476 deaths identified over the study follow-up. After propensity-score stratification, there were no precise differences in ischaemic stroke/systemic embolism, ICH, and all-cause mortality between the DOACs (**Figure 2**). Apixaban use was associated with a lower risk of GIB compared to dabigatran (HR=0.81, 95%CI=0.70-0.94), rivaroxaban (HR=0.72, 95%CI=0.66-0.79), and edoxaban (HR=0.77, 95%CI=0.66-0.91) (**Table 2**). The results were consistent when the intention-to-treat approach or propensity-score matching method was used **(Supplemental Tables 26-28)**.

Standard-dose and reduced-dose DOACs

Of the 505,566 patients (96%) with identifiable dosing information, 382,265 patients (76%) initiated standard-dose DOACs (apixaban n=211,258, dabigatran n=45,228, edoxaban n=9,160, rivaroxaban n=116,619) and 123,301 patients (24%) initiated reduced-dose DOACs (apixaban n=67,416, dabigatran n=16,266, edoxaban n=2536, rivaroxaban n=37,083). Among patients who received a reduced-dose of DOAC, an association of lower ischaemic stroke/systemic embolism was observed for apixaban vs rivaroxaban (HR=0.68, 95%CI=0.46-1.01) and dabigatran vs rivaroxaban (HR=0.67, 95%CI=0.49-0.94) (**Supplemental Figure 16, Supplemental Tables 29-32**). These associations were not found among those prescribed standard-dose DOACs (**Supplemental Figure 17, Supplemental Tables 33-36**). Post-hoc analyses using leave-one-database-out approach showed that the results did not materially change after excluding one database at each analysis (**Supplemental Table 37**). For GIB, apixaban use was associated with a lower risk of GIB

when compared to rivaroxaban in both analyses of reduced-dose (HR=0.68, 95%CI=0.61-0.77) and standard-dose (HR=0.72, 95%CI=0.64-0.82). No precise differences in ICH and all-cause mortality were found in any of the standard-dose or reduced-dose DOAC comparisons (**Supplemental Tables 29-36**).

Chronic kidney disease

When restricting the patient cohort into those with chronic kidney disease (n=71,430, in which apixaban n=47,046, dabigatran n=4627, edoxaban n=1180, rivaroxaban n=18,577), the risks of ischaemic stroke/systemic embolism, ICH, and all-cause mortality were similar between the DOACs (**Supplemental Figure 18**). An association with a lower GIB risk was observed for apixaban vs dabigatran (HR=0.71, 95%CI=0.54-0.94) and apixaban vs rivaroxaban (HR=0.68, 95%CI=0.59-0.77) in the propensity-score stratified cohorts, while in the propensity-score matched cohorts in which the cohort size was reduced after matching, the HRs point to the same protective directions but the CIs are wider and include the null (**Supplemental Tables 38-41**).

Aged ≥ 80 years

Among patients aged ≥ 80 years (n=101,397, where apixaban n=67,734, dabigatran n=3609, edoxaban n=4292, rivaroxaban n=25,762), apixaban use was associated with a lower risk of GIB compared to dabigatran (HR=0.65, 95%CI=0.44-0.95), rivaroxaban (HR=0.64, 95%CI=0.57-0.72), and edoxaban (HR=0.64, 95%CI=0.50-0.82). No precise differences in ischaemic stroke/systemic embolism, ICH, and all-cause mortality were observed between DOACs (**Supplemental Figure 19**). The results were robust in all other analyses **(Supplemental Tables 42-45)**. Individual database results are shown in **Supplemental Tables 46-199**.

Discussion

Using longitudinal records of over half a million patients initiating DOACs, this study found that apixaban was associated with a lower risk of GIB when compared to dabigatran, edoxaban, and rivaroxaban, with a similar risk of ischaemic stroke/systemic embolism and ICH. These results were generally consistent with those obtained from patients with chronic kidney disease and those aged ≥80 years. To our knowledge, this is the largest and most comprehensive study that examined every pairwise comparison of DOACs in patients with AF, including comparisons of DOACs among important patient subgroups.

Comparison with other studies

We found that apixaban and rivaroxaban were the two most commonly prescribed DOACs, which is consistent with previous studies.(29) The outcomes of apixaban and rivaroxaban have been compared in several large observational studies in the US (Ray et al [n= 581,451],(30) Fralick et al [n=78,702],(31) Graham et al [n=179,428])(32) and a recent meta-analysis of 21 observational studies (n=605,711) across the US, Europe, and Asia (Menichelli et al).(33) Our HR estimate for ischemic stroke/systemic embolism (HR=0.89, 95%CI=0.78-1.02) are consistent with all 3 studies (HRs ranged from 0.82 to 0.98) and the meta-analysis (HR=0.71, 95%CI=0.56-1.00). All studies consistently suggested apixaban vs rivaroxaban was associated with a lower risk of GIB, with effect sizes ranging from 0.35 (95%CI=0.31-0.40) in DJ Graham et al to 0.72 (95%CI=0.66-0.79) in our study. Our study did not detect a substantial difference in ICH and all-cause mortality between apixaban and rivaroxaban, similar to Fralick et al and Menichelli et al respectively. In contrast, Ray et al, with a large sample size available, provided more precise estimates for both ICH (HR=0.68, 95%CI=0.59-0.77) and all-cause mortality (HR=0.94, 95%CI=0.92-0.98).

While head-to-head clinical trial data between DOACs do not exist, many network meta-analyses have conducted indirect comparisons among DOACs versus warfarin trials.(34) A systematic review of 22 network meta-analyses of RCTs concluded that apixaban generally has similar stroke risks and a lower risk of bleeding compared to other DOACs.(34) However, the differences between trials, such as those in blinding strategies and quality of anticoagulation control among warfarin patients, have limited the transitivity of the DOAC vs warfarin results used in network meta-analyses.(35) Therefore, direct head-to-head comparison using individual-level data is required to fully elucidate the comparative effects of DOACs.

Two single-site, observational studies have directly compared the four DOACs, but they have shown conflicting findings.(8, 9) A claims database study in Taiwan (Chan et al., n=69,922) reported that the four DOACs had comparable risks of ischaemic stroke, consistent with our findings in the Western population.(8) In contrast, a Korean claims database study (Lee et al., n=91,383) reported that dabigatran and rivaroxaban were associated with a higher risk of ischaemic stroke compared to apixaban and edoxaban;(9) but when those who prescribed reduced-dose DOACs were excluded, no association was found. This might suggest possible underdosing of dabigatran and rivaroxaban due to fear of excessive bleeding risk, a common phenomenon previously reported in the Korean population.(36)

In our subgroup analyses for DOAC doses, rivaroxaban use was associated with a higher risk of ischaemic stroke/systemic embolism compared to apixaban and dabigatran when prescribed at reduced dose, but not at standard dose. Evidence from current literature on reduced-dose DOAC is limited and inconclusive, with some studies also found a higher risk of stroke associated with rivaroxaban compared to dabigatran,(37, 38) while some studies did

not identify any differences between rivaroxaban, dabigatran, and apixaban.(39, 40) Our findings might be explained by chance or residual bias; however, we applied negative control analyses to reduce residual bias, and the results were consistent across all the databases from different country settings. Indeed, many patients with high-risk clinical features (e.g., older age and multimorbidity) commonly seen in daily practice were excluded from the clinical trials that evaluated the effects of reduced-dose DOACs. Our findings might raise the question of whether the reduced dose of rivaroxaban is appropriate to maintain effective stroke prevention outside restrictive trial settings. While we are waiting for the confirmation studies, we cautiously recommend monitoring patients carefully if a reduced dose of rivaroxaban is prescribed.

Our findings are broadly consistent with previous studies that suggest apixaban has a lower rate of GIB than dabigatran and rivaroxaban,(41) but we further established for the first time that apixaban also carries a lower risk of GIB than edoxaban. Both Lee et al. and Chan et al. did not find a difference in GIB rates between apixaban and edoxaban in the Korean and Taiwanese population respectively; however, only 302(9) and 44(8) GIB cases were included in their studies, compared to 2746 GIB cases in our study. To date, only one small observational study (n=1443) directly compared all four DOACs in a Western population (Spain).(10) The Spanish study suggested that all DOACs had similar rates of ischaemic stroke, and the rates of major bleeding were higher with dabigatran and apixaban than rivaroxaban and edoxaban. However, the analysis did not adjust for confounding factors, and so the results may be attributable to the differences between people.(10) No existing studies have compared all four DOACs at reduced-dose regimens, or among patient subgroups aged ≥80 years and chronic kidney disease. In these settings, we found general evidence of a lower

risk of GIB with apixaban compared to other DOACs, and a similar or lower risk of ischaemic stroke/systemic embolism and ICH.

Implications of findings

The preferential use of DOACs over warfarin has increased rapidly due to the recent treatment guidelines updates and the minimized monitoring during the COVID-19 pandemic.(11) The comparative effects of DOACs merits evaluation in head-to-head RCTs. However, measuring all outcomes with adequate power would require a very large trial, which could be difficult and costly to conduct. At present, both evidence from head-to-head trials and large real-world studies are lacking clear aid to clinicians on the choice of DOACs. Our results indicate that apixaban might be preferable to other DOACs because of the lower rate of GIB and comparable rates of stroke and ICH, although as with all treatment choices, a wider consideration of all potential risks and benefits would be needed, such as the use of gastroprotective agents in patients with a high risk of GIB.(42)

Strengths and Limitations

This study has considerable strengths. With over half a million patients across four countries, we examined all four DOACs with unprecedented precision and power. The standardization of databases allowed us to apply the same methodological approach to study DOACs in a large population. We used publicly available analysis packages to enhance transparency and reproducibility of the results;(21) and all results were reported to avoid publication bias and p-hacking in observational studies.

This study has limitations. We did not assess whether patients received DOAC doses consistent with labelling, but since 75% of the patients in our cohort received a standard dose,

off-label underdosing is unlikely to have had substantial effects. Previous studies suggested off-label overdose of DOACs is uncommon.(43) We identified bleeding events using diagnosis records, which had no information about the severity of bleeding and the role of reversal agents in treating the bleeding patients, if any. However, we have no prior reasons to believe the severity of bleeding differs substantially between DOACs. The on-treatment follow-up of the US databases are relatively short in our study. However, our meta-analytic estimates are largely consistent with the previous studies, and sensitivity analyses using intention-to-treat approach also yielded similar results.

In addition, as with all observational studies, we cannot rule out the possibility of potential residual confounding. However, because current guidelines do not express a preference on any DOACs, confounding by indication is less likely. Previous studies have consistently found that the differences between DOAC groups were small, or older patients who have multiple comorbidities and a higher risk of bleeding were more likely to receive apixaban.(44) This suggests any residual confounding could have biased our results towards higher bleeding rates in the apixaban group compared to other DOACs, and thus will not affect our study conclusion. To reduce confounding, we used rigorous statistical adjustment methods and conducted several sensitivity analyses, and the results were robust. Previous systematic reviews reported that many large, well-designed observational studies of DOACs versus warfarin in routine clinical settings have produced results consistent with those obtained from RCTs,(45, 46) supporting the advance in reducing the inherent bias in observational studies and their critical roles in extending the findings from RCTs.(2, 46)

Conclusion

DOACs are increasingly prescribed worldwide but there are limited comprehensive comparative assessments to guide the choice of DOACs. In this large multinational analysis

414 of patients with AF, the use of apixaban was associated with a lower risk of GIB and
415 comparable rates of ischaemic stroke/systemic embolism and ICH when compared with
416 dabigatran, edoxaban, and rivaroxaban. This finding was generally consistent for patients
417 aged ≥ 80 years and those with chronic kidney disease.

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Data sharing statements: Data presented in this manuscript are made publicly available at https://data.ohdsi.org/corazon and https://github.com/OHDSI/ShinyDeploy/tree/master/corazon/data. The study protocol, phenotype code list, and programming codes are publicly available in the GitHub repository: https://github.com/ohdsi-studies/Corazon.

Ethics committee approval: The data partner has obtained institutional review board approval from IQVIA (for UK IMRD) or exemption (for all other databases) for conducting this study.

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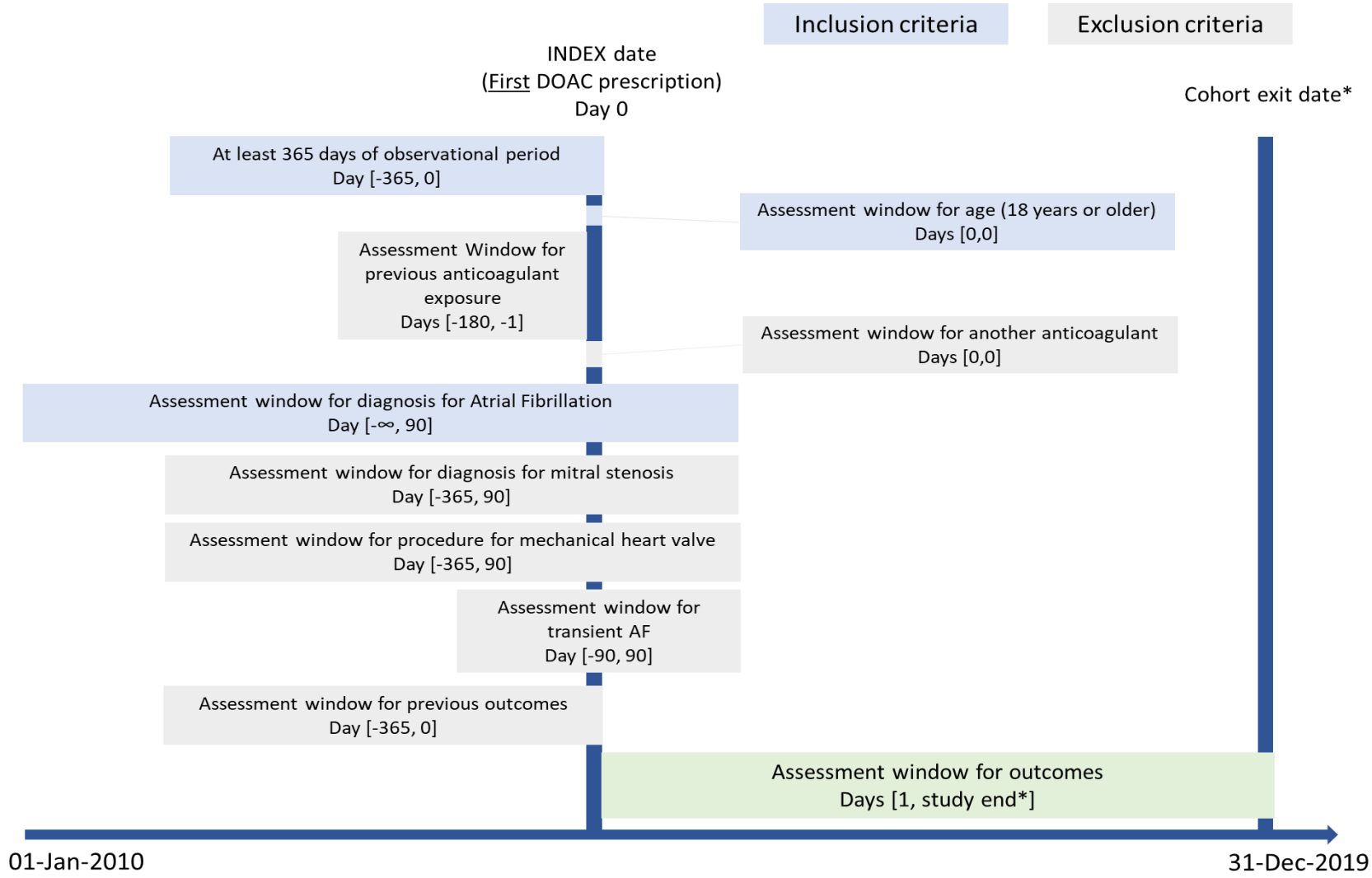

*The earliest of 31-Dec-2019 (study end), date of death, discontinuation of index DOAC (90 days gap), prescription of another anticoagulant

Figure 1. Study design

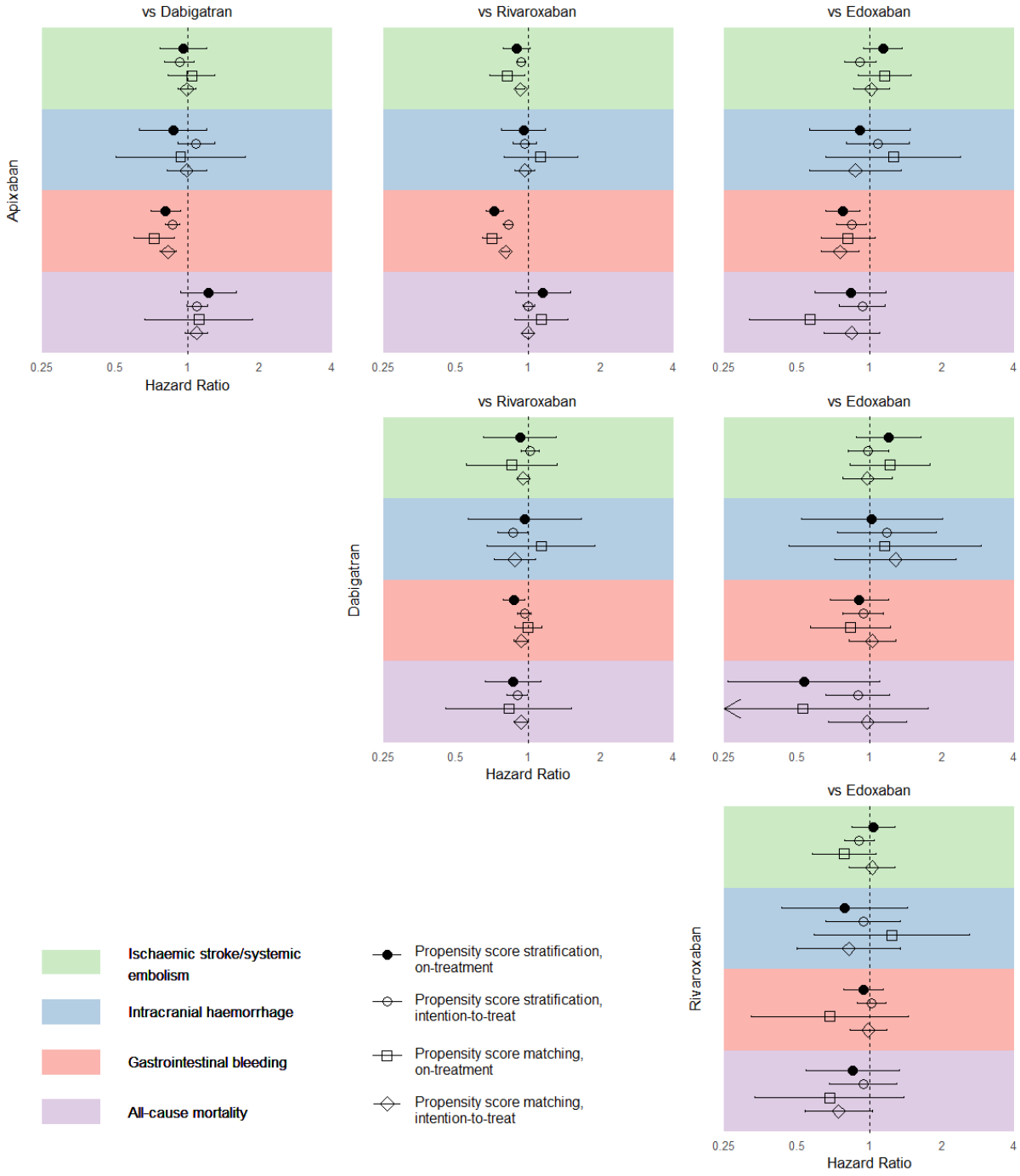

Figure 2. Comparative meta-analytic hazard ratios of apixaban, dabigatran, rivaroxaban, and edoxaban.

Table 1. Patient follow-up by drug groups and databases.

DOAC	Number of patients	On-treatment follow-up, median (IQR) in days[a]	Total follow-up, median (IQR) in days[b]
Apixaban			
LPD France	2949	177 (78-893)	1000 (510-1782)
DA Germany	18441	388 (99-1398)	1136 (689-1975)
UK IMRD	19517	595 (243-1345)	803 (451-1546)
US AMBEMR	168100	51 (29-173)	914 (507-1653)
US Hospital	72313	5 (3-51)	534 (109-1270)
Dabigatran			
LPD France	779	126 (59-700)	1220 (600-2353)
DA Germany	4237	224 (59-1447)	1612 (857-2991)
UK IMRD	2863	418 (108-1519)	1048 (475-2246)
US AMBEMR	37380	34 (29-134)	1482 (807-2827)
US Hospital	15749	4 (2-38)	726 (186-2079)
Edoxaban[c]			
DA Germany	8477	369 (97-1274)	1077 (688-1674)
UK IMRD	2842	440 (174-800)	592 (421-934)
US AMBEMR	1403	29 (29-126)	1283 (637-2043)
Rivaroxaban			
LPD France	3521	125 (55-741)	1071 (515-2094)
DA Germany	17731	277 (97-1448)	1400 (802-2551)
UK IMRD	15153	506 (157-1402)	860 (428-1735)
US AMBEMR	98732	43 (29-153)	1081 (573-2026)
US Hospital	37039	5 (2-48)	613 (142-1632)

Abbreviations: DOACs, direct oral anticoagulants; LPD France, Longitudinal Patients Database France; DA Germany, Disease Analyzer Germany; UK IMRD, United Kingdom IQVIA Medical Research Data; US AMBEMR, United States Ambulatory Electronic Medical Records; US Hospital, United States Hospital Charge Data Master; IQR, interquartile range.

[a]On-treatment follow-up was defined as the time between the index date and the earliest of: treatment discontinuation (90-day gaps between consecutive prescriptions), switching from the index medication to another oral anticoagulant, death, or the end of the study period.

[b]Total follow-up was defined as the time between the index date and the earliest of: death, or the end of study period.

[c]LPD France and US Hospital have a low number of edoxaban patients (n<1000) and were not included in the analyses for edoxaban.

Table 2. Patient cohort size, number of outcome events, and meta-analytic hazard ratios for the comparisons between direct oral anticoagulants (propensity score-stratified, on-treatment approach).

	Target		Comparator		
Target vs Comparator	**Patients**	**Outcome events/patient-years**	**Patients**	**Outcome events/patient-years**	**HR (95% CI)**
Ischaemic stroke/systemic embolism					
Apixaban vs Dabigatran	281320	5486/123829	61008	906/21910	0.96 (0.77 - 1.21)
Apixaban vs Rivaroxaban	281320	5486/123829	172176	2920/88347	0.89 (0.78 - 1.02)
Apixaban vs Edoxaban	206058	2206/116527	12722	218/17309	1.14 (0.95 - 1.37)
Dabigatran vs Rivaroxaban	61008	906/21910	172176	2920/88347	0.92 (0.65 - 1.31)
Dabigatran vs Edoxaban	44480	494/20419	12722	218/17309	1.20 (0.88 - 1.64)
Rivaroxaban vs Edoxaban	131616	1490/83055	12722	218/17309	1.04 (0.84 - 1.28)
Intracranial haemorrhage					
Apixaban vs Dabigatran	281320	465/125561	61008	68/22309	0.87 (0.63 - 1.21)
Apixaban vs Rivaroxaban	281320	465/125561	172176	262/89617	0.95 (0.77 - 1.18)
Apixaban vs Edoxaban	206058	318/118068	12722	46/17561	0.91 (0.56 - 1.47)
Dabigatran vs Rivaroxaban	61008	68/22309	172176	262/89617	0.96 (0.56 - 1.65)
Dabigatran vs Edoxaban	44480	50/20802	12722	46/17561	1.02 (0.52 - 2.00)
Rivaroxaban vs Edoxaban	131616	215/84227	12722	46/17561	0.79 (0.43 - 1.44)
Gastrointestinal bleeding					
Apixaban vs Dabigatran	281320	4188/123669	61008	813/21889	0.81 (0.70 - 0.94)
Apixaban vs Rivaroxaban	281320	4188/123669	172176	3011/87860	0.72 (0.66 - 0.79)
Apixaban vs Edoxaban	206058	2797/116302	12722	307/17232	0.77 (0.66 - 0.91)
Dabigatran vs Rivaroxaban	61008	813/21889	172176	3011/87860	0.87 (0.78 - 0.96)
Dabigatran vs Edoxaban	44480	628/20406	12722	307/17232	0.90 (0.68 - 1.20)
Rivaroxaban vs Edoxaban	131616	2456/82581	12722	307/17232	0.94 (0.78 - 1.14)
All-cause mortality					
Apixaban vs Dabigatran	110271	844/75180	22849	92/13336	1.22 (0.94 - 1.60)
Apixaban vs Rivaroxaban	110271	844/75180	69923	480/61184	1.15 (0.88 - 1.50)
Apixaban vs Edoxaban	37958	498/70801	11319	60/17321	0.83 (0.59 - 1.17)
Dabigatran vs Rivaroxaban	22849	92/13336	69923	480/61184	0.86 (0.66 - 1.12)
Dabigatran vs Edoxaban	7100	60/12587	11319	60/17321	0.53 (0.26 - 1.10)
Rivaroxaban vs Edoxaban	32884	393/59092	11319	60/17321	0.85 (0.55 - 1.33)

Abbreviations: HR, hazard ratio, CI, confidence interval. The numbers of patients, outcome events and patient-years were calculated by summing up the numbers from all databases before propensity-score stratification. The complete set of results for each database are available at https://data.ohdsi.org/corazon, https://github.com/OHDSI/ShinyDeploy/tree/master/corazon/data, and the Appendix.