Annals of Internal Medicine ORIGINAL RESEARCH

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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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 DOAC.

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

Design: Multinational population-based cohort study.

Setting: Five standardized electronic health care databases, which covered 221 million people in France, Germany, the United Kingdom, and the United States.

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

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

Results: A total of 527 226 new DOAC users met the inclusion criteria (apixaban, n = 281 320; dabigatran, n = 61 008; edoxaban, n = 12 722; and rivaroxaban, n = 172 176). Apixaban use was associated with lower risk for GIB than use of dabigatran (HR, 0.81 [95% CI, 0.70 to 0.94]), edoxaban (HR, 0.77 [CI, 0.66 to 0.91]), or rivaroxaban (HR, 0.72 [CI, 0.66 to 0.79]). No substantial differences were observed for other outcomes or DOAC–DOAC comparisons. The results were consistent for patients aged 80 years or older. Consistent associations between lower GIB risk and apixaban versus rivaroxaban were observed among patients receiving the standard dose (HR, 0.72 [CI, 0.64 to 0.82]), those receiving a reduced dose (HR, 0.68 [CI, 0.61 to 0.77]), and those with chronic kidney disease (HR, 0.68 [CI, 0.59 to 0.77]).

Limitation: Residual confounding is possible.

Conclusion: Among patients with AF, apixaban use was associated with lower risk for GIB and similar rates of ischemic stroke or systemic embolism, ICH, and all-cause mortality compared with dabigatran, edoxaban, and rivaroxaban. This finding was consistent for patients aged 80 years or older and those with chronic kidney disease, who are often underrepresented in clinical trials.

Primary Funding Source: None.

Ann Intern Med. 2022;175:1515-1524. doi:10.7326/M22-0511 **Annals.org**
For author, article, and disclosure information, see end of text.
This article was published at Annals.org on 1 November 2022.
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Direct oral anticoagulants (DOACs) are used for stroke prevention in patients with atrial fibrillation (AF), the most common sustained arrhythmia, which affects more than 33 million people worldwide (1). The vitamin K antagonist warfarin was the mainstay of anticoagulation 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 postmarketing observational studies have shown that DOACs are noninferior to warfarin in preventing stroke and have lower risks for 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 have advised switching patients from warfarin to a DOAC to negate the need for frequent monitoring during the COVID-19 pandemic (7). Despite this, no clear guidance exists on how to choose among the 4 DOACs because head-to-head clinical trial data are not available. A few small, single-site, observational studies comparing all 4 DOACs have yielded mixed results (8–10). The lack of robust evidence means that the choice of DOAC is often based on anecdotal experience (11). Because 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 4 countries. We also did prespecified subgroup analyses to compare DOAC use among older patients (aged ≥80 years) and

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Supplement

those with chronic kidney disease, who are often underrepresented in RCTs.

METHODS

Data Sources

This study used anonymized patient records from 5 electronic health databases in the distributed data network of the Observational Health Data Science and Informatics (OHDSI) program (12), an open-science, international, and interdisciplinary collaborative (12). All community members in OHDSI were invited to run the analyses and return the results for this study (13). In the end, IQVIA provided 5 electronic health databases from 4 countries: France (Longitudinal Patients Database France), Germany (Disease Analyzer Germany), the United Kingdom (U.K. IQVIA Medical Research Data), and the United States (U.S. Ambulatory Electronic Medical Records and U.S. Hospital Charge Data Master). The databases comprised 221 million people across primary care, outpatient, and hospital settings. Information, including demographics, drug prescriptions, and diagnosis records, is prospectively recorded in the databases as part of the routine clinical care of patients. All databases are standardized to the Observational Medical Outcomes Partnership Common Data Model (version 5) (14). The databases are quality-controlled for research purposes (15) and have been extensively used for high-quality and large-scale multinational drug surveillance studies (16–20). Details about the databases are given in Part 1 of the Supplement (available at Annals.org) and previous publications (16–20). The data partner has obtained institutional review board approval (for U.K. IQVIA Medical Research Data) 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 comparison of DOACs: apixaban versus dabigatran, apixaban versus rivaroxaban, apixaban versus edoxaban, dabigatran versus rivaroxaban, dabigatran versus edoxaban, and rivaroxaban versus edoxaban. The following sections and Part 2 of the Supplement describe the protocol components.

Eligibility Criteria

Eligible patients had AF, were aged 18 years or older, and had never used the DOAC pairs of interest. Patients were required to have at least 1 year of observation before the index date in the database to record medical history. To identify those with AF, we required patients to have a diagnosis of AF any time on or before the index date or within 90 days after the index date to account for any delay in recording the AF diagnosis. We excluded patients with a history of mitral stenosis, hyperthyroidism, or mechanical heart valve replacement (among whom DOACs might be contraindicated) or transient AF (that is, those who had undergone cardiac surgery or were diagnosed with myocarditis, pericarditis, or pulmonary embolism). Other exclusion criteria included a prescription of warfarin or other DOACs on or within 180 days before the index date; a prescription of another oral anticoagulant (other than the index anticoagulant) on the index date; and a history of an outcome 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 (Part 3 of the Supplement) 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 a DOAC between 1 January 2010 (2012 for Longitudinal Patients Database France) and 31 December 2019. The 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 (Longitudinal Patients Database France and U.S. Ambulatory Electronic Medical Records), we used the date of last consultation instead of the date of death for censoring.

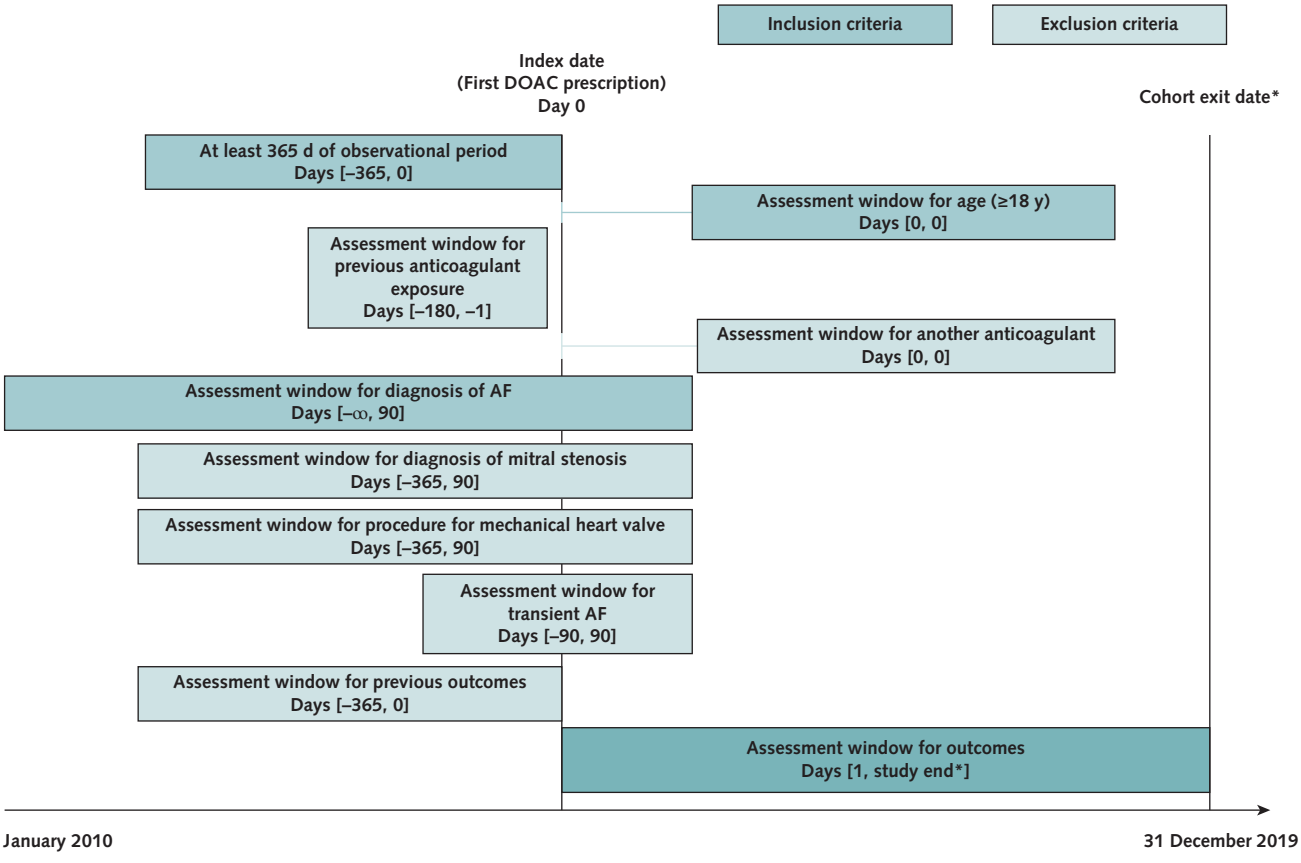
Outcomes

The following 4 outcomes were of interest: a composite of ischemic stroke and systemic embolism, intracranial hemorrhage (ICH), gastrointestinal bleeding (GIB), and all-cause mortality (available in Disease Analyzer Germany, U.K. IQVIA Medical Research Data, and U.S. Hospital Charge Data Master). The outcomes were identified on the basis of published code lists (Part 3 of the Supplement).

Statistical Analysis

To address any potential bias due to nonrandomized treatment allocation, we used propensity score modeling to compare patients who differed in anticoagulant treatment but were similar in 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); a unique identifier for care site (such as practice or hospital); and previous medical conditions, drug exposures, procedures, and health service use behaviors 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 including the index date. The regularization propensity

Figure 1. Study design.



AF = atrial fibrillation; DOAC = direct oral anticoagulant.
* The earliest of 31 December 2019 (study end), death, discontinuation of index DOAC therapy, or prescription of another anticoagulant.

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 5 strata based on 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 cutoffs for acceptable standardized differences range from 0.1 to 0.25 (3). Cox proportional hazards regression conditioned on the propensity score strata was applied to estimate the hazard ratio (HR) of the risk for 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 control for measured confounding through propensity scores. Therefore, to further reduce bias from unmeasured and systematic sources, we did empirical calibration of CIs (25, 26). For this, we used a data-rich algorithm (27) to identify 49 negative control outcomes (that is, events that are not known to be associated with DOAC use and thus have a null effect size) to construct an empirical null distribution and quantify systematic error (25, 26) (**Supplement Figures 1** to **3**, available at Annals.org). 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 in **Supplement Table 1** (available at Annals.org).

In subgroup analyses, we restricted the analyses to patients who initiated a standard-dose regimen of DOACs (that is, apixaban, 5 mg twice daily; dabigatran, 150 mg twice daily; edoxaban, 60 mg once daily; or rivaroxaban, 20 mg once daily) and to those who initiated a reduced-dose DOAC regimen (that is, apixaban, 2.5 mg twice daily; dabigatran, 110 mg twice daily in Europe or 75 mg twice daily in the United States; edoxaban, 30 mg once daily; or rivaroxaban, 15 mg once daily). Additional analyses were done for the following 2 important subgroups that are often underrepresented in clinical trials: patients who were aged 80 years or older at cohort entry and 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). Part 4 of the **Supplement** presents all statistical analysis details.

Table 1. Patient Follow-up, by Drug Group and Database

DOAC	Patients, *n*	Median On-Treatment Follow-up (IQR), *d**	Median Total Follow-up (IQR), *d*†
Apixaban			
LPD France	2949	177 (78–893)	1000 (510–1782)
DA Germany	18 441	388 (99–1398)	1136 (689–1975)
U.K. IMRD	19 517	595 (243–1345)	803 (451–1546)
U.S. AMBEMR	168 100	51 (29–173)	914 (507–1653)
U.S. Hospital Charge Data Master	72 313	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)
U.K. IMRD	2863	418 (108–1519)	1048 (475–2246)
U.S. AMBEMR	37 380	34 (29–134)	1482 (807–2827)
U.S. Hospital Charge Data Master	15 749	4 (2–38)	726 (186–2079)
Edoxaban‡			
DA Germany	8477	369 (97–1274)	1077 (688–1674)
U.K. IMRD	2842	440 (174–800)	592 (421–934)
U.S. AMBEMR	1403	29 (29–126)	1283 (637–2043)
Rivaroxaban			
LPD France	3521	125 (55–741)	1071 (515–2094)
DA Germany	17 731	277 (97–1448)	1400 (802–2551)
U.K. IMRD	15 153	506 (157–1402)	860 (428–1735)
U.S. AMBEMR	98 732	43 (29–153)	1081 (573–2026)
U.S. Hospital Charge Data Master	37 039	5 (2–48)	613 (142–1632)

AMBEMR = Ambulatory Electronic Medical Records; DA = Disease Analyzer; DOAC = direct oral anticoagulant; IMRD = IQVIA Medical Research Data; LPD = Longitudinal Patients Database.
* Defined as the time between the index date and the earliest of treatment discontinuation (90-d gaps between consecutive prescriptions), switching from the index medication to another oral anticoagulant, death, or the end of the study period.
† Defined as the time between the index date and the earliest of death or the end of the study period.
‡ LPD France and U.S. Hospital Charge Data Master have few patients receiving edoxaban ($n < 1000$) and were not included in the analyses for edoxaban.

We did additional sensitivity analyses in which the time at risk was not censored if a patient discontinued the index medication therapy 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 treated patients (28). Overall, we specified 480 analyses per database (6 DOAC comparisons × 4 outcomes × 5 groups × 2 propensity score approaches × 2 time-at-risk definitions). For clarity, we present the result estimates from the on-treatment, propensity score stratification analyses here. The complete set of results is in the **Supplement** and an interactive website (https://data.ohdsi.org/corazon) (Part 5 of the **Supplement**).

All analyses were done using the R programming language, version 3.5.1 (R Foundation). 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 prespecified before 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 STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guideline.

Role of the Funding Source

This study received no funding.

RESULTS

Patient Characteristics

A total of 527 226 new DOAC users met the inclusion criteria across the 5 databases (apixaban, $n = 281\,320$; dabigatran, $n = 61\,008$; edoxaban, $n = 12\,722$; and rivaroxaban, $n = 172\,176$). The follow-up time varied by DOAC group and database, and the median overall follow-up for a particular DOAC group in a particular database ranged from 534 to 1612 days (**Table 1**).

Across the 5 databases, the proportion of patients aged 65 years or older ranged from 77% to 87% for apixaban, 75% to 83% for dabigatran, 79% to 86% for edoxaban, and 73% to 83% for rivaroxaban. The age distributions are similar in the European databases. Apixaban users tended to be older than other DOAC users in the U.S. Ambulatory Electronic Medical Records (prevalence of age 80 to 84 years, 21.1% for apixaban vs. 4% to 11% for other DOACs; standardized mean difference > 0.25) and older than dabigatran users in the U.S. Hospital Charge Data Master (21% vs. 4% were aged 80 to 84 years). The proportions of women were 42% to 50% for apixaban, 40% to 47% for dabigatran, 43% to 48% for edoxaban, and 38% to 47% for rivaroxaban. The mean CHA_2DS_2-VASc score ranged from 2.8 to 3.9 for apixaban, 2.6 to 3.7 for dabigatran, 2.5 to 3.6 for rivaroxaban, and 2.9 to 3.8 for edoxaban across the 5 databases. Most baseline characteristics of DOAC users were similar before propensity score stratification, with standardized

differences less than 0.10, and remained well balanced after stratification (**Supplement Figures 4** to **15**, available at Annals.org). **Supplement Tables 2** to **25** (available at Annals.org) show the baseline characteristics of all pairwise DOAC comparisons.

DOAC–DOAC Comparisons

In total, 9530 ischemic stroke or systemic embolism events, 841 ICH events, 8319 GIB events, and 1476 deaths were identified over the study follow-up. After propensity score stratification, we found no precise differences between DOACs in ischemic stroke or systemic embolism, ICH, or all-cause mortality (**Figure 2**). Apixaban use was associated with lower risk for GIB than use of dabigatran (HR, 0.81 [95% CI, 0.70 to 0.94]), rivaroxaban (HR, 0.72 [CI, 0.66 to 0.79]), or edoxaban (HR, 0.77 [CI, 0.66 to 0.91]) (**Table 2**). The results were consistent when the intention-to-treat approach or propensity score matching method was used (**Supplement Tables 26** to **28**, available at Annals.org).

Standard-Dose and Reduced-Dose DOACs

Of the 505 566 patients (96%) with identifiable dosing information, 382 265 (76%) initiated standard-dose DOAC therapy (apixaban, $n = 211\,258$; dabigatran, $n = 45\,228$; edoxaban, $n = 9160$; and rivaroxaban, $n = 116\,619$) and 123 301 (24%) initiated reduced-dose DOAC therapy (apixaban, $n = 67\,416$; dabigatran, $n = 16\,266$; edoxaban, $n = 2536$; and rivaroxaban, $n = 37\,083$). Among patients who received a reduced dose of a DOAC, rates of ischemic stroke or systemic embolism were lower with apixaban than rivaroxaban (HR, 0.68 [CI, 0.46 to 1.01]) and lower with dabigatran than rivaroxaban (HR, 0.67 [CI, 0.49 to 0.94]) (**Supplement Figure 16** and **Supplement Tables 29** to **32**, available at Annals.org). These associations were not found among patients prescribed standard-dose DOACs (**Supplement Figure 17** and **Supplement Tables 33** to **36**, available at Annals.org). Post hoc analyses showed that the results did not materially change when 1 database at a time was excluded (**Supplement Table 37**, available at Annals.org). Apixaban use was associated with lower risk for GIB than rivaroxaban use in analyses of both the reduced dose (HR, 0.68 [CI, 0.61 to 0.77]) and the standard dose (HR, 0.72 [CI, 0.64 to 0.82]). We found no precise differences in ICH or all-cause mortality in any of the standard-dose or reduced-dose DOAC comparisons (**Supplement Tables 29** to **36**).

Chronic Kidney Disease

When we restricted the patient cohort to those with chronic kidney disease ($n = 71\,430$, of whom 47 046 received apixaban, 4627 dabigatran, 1180 edoxaban, and 18 577 rivaroxaban), the risks for ischemic stroke or systemic embolism, ICH, and all-cause mortality were similar between the DOACs (**Supplement Figure 18**, available at Annals.org). Risk for GIB was lower with apixaban than dabigatran (HR, 0.71 [CI, 0.54 to 0.94]) and lower with apixaban than rivaroxaban (HR, 0.68 [CI, 0.59 to 0.77]) in the propensity score–stratified cohorts. 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 (**Supplement Tables 38** to **41**, available at Annals.org).

Patients Aged 80 Years or Older

Among patients aged 80 years or older ($n = 101\,397$, of whom 67 734 received apixaban, 3609 dabigatran, 4292 edoxaban, and 25 762 rivaroxaban), apixaban use was associated with lower risk for GIB than use of dabigatran (HR, 0.65 [CI, 0.44 to 0.95]), rivaroxaban (HR, 0.64 [CI, 0.57 to 0.72]), or edoxaban (HR, 0.64 [CI, 0.50 to 0.82]). We found no precise differences between DOACs in ischemic stroke or systemic embolism, ICH, or all-cause mortality (**Supplement Figure 19**, available at Annals.org). The results were robust in all other analyses (**Supplement Tables 42** to **45**, available at Annals.org). Individual database results are shown in **Supplement Tables 46** to **199** (available at Annals.org).

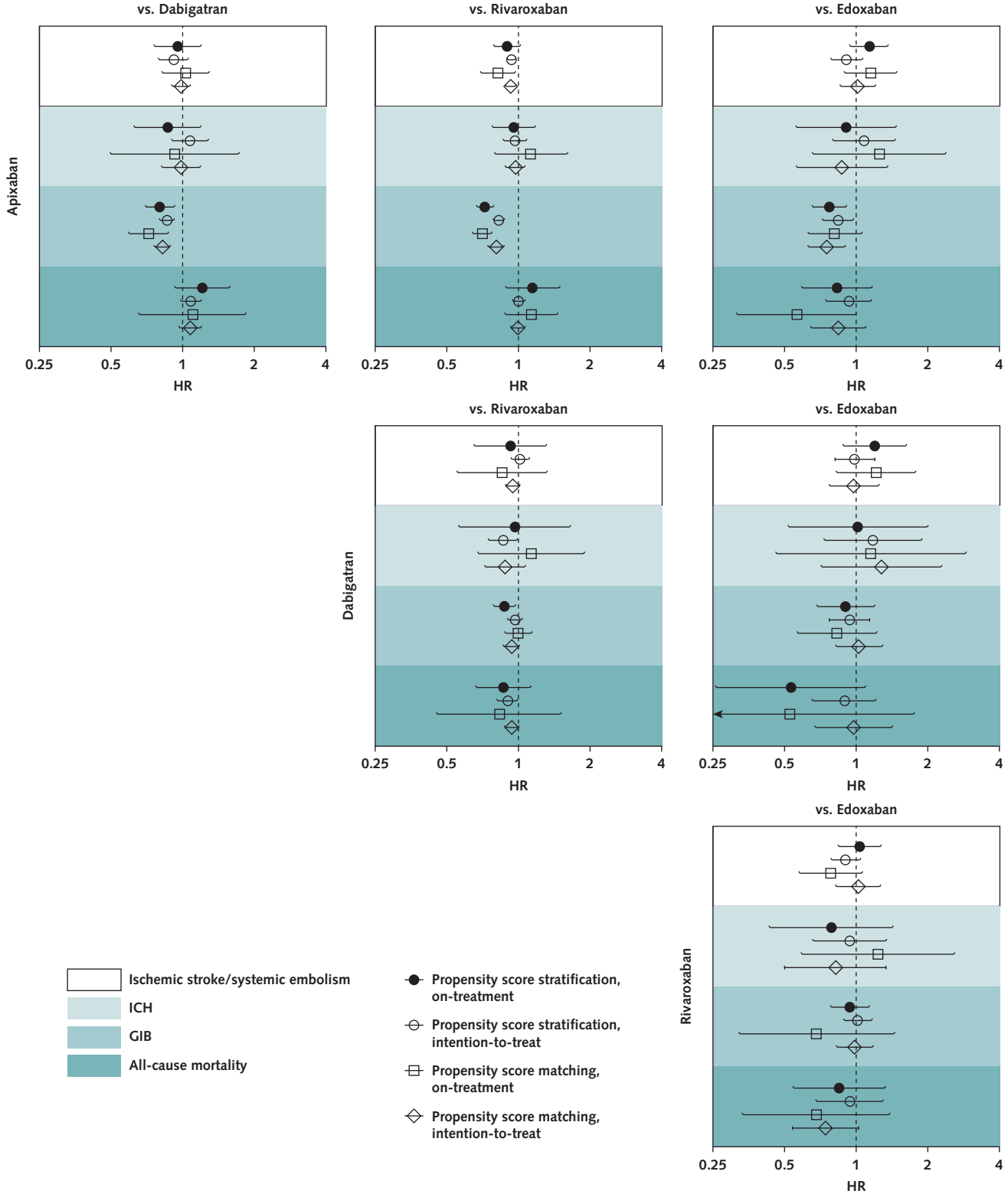
Discussion

Using longitudinal records of more than half a million patients initiating DOAC therapy, this study found that apixaban was associated with lower risk for GIB than dabigatran, edoxaban, and rivaroxaban, with similar risks for ischemic stroke or systemic embolism and ICH. These results were generally consistent with those obtained from patients with chronic kidney disease and those aged 80 years or older. To our knowledge, this is the largest and most comprehensive study to examine every pairwise comparison of DOACs in patients with AF, including among important patient subgroups.

We found that apixaban and rivaroxaban were the 2 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 United States (Ray and colleagues [30] [$n = 581\,451$], Fralick and colleagues [31] [$n = 78\,702$], and Graham and colleagues [32] [$n = 179\,428$]) and a recent meta-analysis of 21 observational studies across the United States, Europe, and Asia (Menichelli and colleagues [33] [$n = 605\,711$]). Our HR estimates for ischemic stroke or systemic embolism (HR, 0.89 [CI, 0.78 to 1.02]) are consistent with those of all 3 studies (HRs ranged from 0.82 to 0.98) and the meta-analysis (HR, 0.71 [CI, 0.56 to 1.00]). All studies consistently suggested that apixaban was associated with lower risk for GIB than rivaroxaban, with effect sizes ranging from 0.35 (CI, 0.31 to 0.40) in Graham and colleagues' study to 0.72 (CI, 0.66 to 0.79) in our study. We did not detect a substantial difference in ICH and all-cause mortality for apixaban versus rivaroxaban, similar to Fralick and colleagues and Menichelli and colleagues, respectively. In contrast, Ray and colleagues, with a large sample size available, provided more precise estimates for both ICH (HR, 0.68 [CI, 0.59 to 0.77]) and all-cause mortality (HR, 0.94 [CI, 0.92 to 0.98]).

Although head-to-head clinical trial data comparing DOACs do not exist, many network meta-analyses have done indirect comparisons among trials of DOACs versus warfarin (34). A systematic review of 22 network

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



GIB = gastrointestinal bleeding; HR = hazard ratio; ICH = intracranial hemorrhage.

Table 2. Patient Cohort Size, Number of Outcome Events, and Meta-analytic HRs for the Comparisons Between DOACs (Propensity Score–Stratified, On-Treatment Approach)*

Target vs. Comparator	Target		Comparator		HR (95% CI)
	Patients, *n*	Outcome Events/ Patient-Years, *n/N*	Patients, *n*	Outcome Events/ Patient-Years, *n/N*	
Ischaemic stroke/systemic embolism					
Apixaban vs. dabigatran	281 320	5486/123 829	61 008	906/21 910	0.96 (0.77–1.21)
Apixaban vs. rivaroxaban	281 320	5486/123 829	172 176	2920/88 347	0.89 (0.78–1.02)
Apixaban vs. edoxaban	206 058	2206/116 527	12 722	218/17 309	1.14 (0.95–1.37)
Dabigatran vs. rivaroxaban	61 008	906/21 910	172 176	2920/88 347	0.92 (0.65–1.31)
Dabigatran vs. edoxaban	44 480	494/20 419	12 722	218/17 309	1.20 (0.88–1.64)
Rivaroxaban vs. edoxaban	131 616	1490/83 055	12 722	218/17 309	1.04 (0.84–1.28)
ICH					
Apixaban vs. dabigatran	281 320	465/125 561	61 008	68/22 309	0.87 (0.63–1.21)
Apixaban vs. rivaroxaban	281 320	465/125 561	172 176	262/89 617	0.95 (0.77–1.18)
Apixaban vs. edoxaban	206 058	318/118 068	12 722	46/17 561	0.91 (0.56–1.47)
Dabigatran vs. rivaroxaban	61 008	68/22 309	172 176	262/89 617	0.96 (0.56–1.65)
Dabigatran vs. edoxaban	44 480	50/20 802	12 722	46/17 561	1.02 (0.52–2.00)
Rivaroxaban vs. edoxaban	131 616	215/84 227	12 722	46/17 561	0.79 (0.43–1.44)
GIB					
Apixaban vs. dabigatran	281 320	4188/123 669	61 008	813/21 889	0.81 (0.70–0.94)
Apixaban vs. rivaroxaban	281 320	4188/123 669	172 176	3011/87 860	0.72 (0.66–0.79)
Apixaban vs. edoxaban	206 058	2797/116 302	12 722	307/17 232	0.77 (0.66–0.91)
Dabigatran vs. rivaroxaban	61 008	813/21 889	172 176	3011/87 860	0.87 (0.78–0.96)
Dabigatran vs. edoxaban	44 480	628/20 406	12 722	307/17 232	0.90 (0.68–1.20)
Rivaroxaban vs. edoxaban	131 616	2456/82 581	12 722	307/17 232	0.94 (0.78–1.14)
All-cause mortality					
Apixaban vs. dabigatran	110 271	844/75 180	22 849	92/13 336	1.22 (0.94–1.60)
Apixaban vs. rivaroxaban	110 271	844/75 180	69 923	480/61 184	1.15 (0.88–1.50)
Apixaban vs. edoxaban	37 958	498/70 801	11 319	60/17 321	0.83 (0.59–1.17)
Dabigatran vs. rivaroxaban	22 849	92/13 336	69 923	480/61 184	0.86 (0.66–1.12)
Dabigatran vs. edoxaban	7100	60/12 587	11 319	60/17 321	0.53 (0.26–1.10)
Rivaroxaban vs. edoxaban	32 884	393/59 092	11 319	60/17 321	0.85 (0.55–1.33)

DOAC = direct oral anticoagulant; GIB = gastrointestinal bleeding; HR = hazard ratio; ICH = intracranial hemorrhage.
* The numbers of patients, outcome events, and patient-years were calculated by summing the numbers from all databases before propensity score stratification. The complete set of results for each database is available at https://data.ohdsi.org/corazon, at https://github.com/OHDSI/ShinyDeploy/tree/master/corazon/data, and in the Supplement (available at Annals.org).

meta-analyses of RCTs concluded that apixaban generally has similar stroke risks to and a lower risk for bleeding than other DOACs (34). However, the differences between trials, such as those in blinding strategies and quality of anticoagulation control among patients receiving warfarin, have limited the transitivity of the DOAC-versus-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 4 DOACs, but they have shown conflicting findings (8, 9). A claims database study in Taiwan (Chan and colleagues [8] [*n* = 69 922]) reported that the 4 DOACs had similar risks for ischemic stroke, consistent with our findings in the Western population. In contrast, a Korean claims database study (Lee and colleagues [9] [*n* = 91 383]) reported that dabigatran and rivaroxaban were associated with higher risk for ischemic stroke than apixaban and edoxaban, but when those 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 was associated with higher risk for ischemic stroke or systemic embolism than apixaban and dabigatran when prescribed at a reduced dose, but not at the standard dose. Evidence from current literature on reduced-dose DOACs is limited and inconclusive; some studies also found a higher risk for stroke associated with rivaroxaban than dabigatran (37, 38), whereas others 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 of the databases from different country settings. Indeed, many patients with high-risk clinical features (such as 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 await the confirmation studies, we cautiously recommend monitoring patients carefully if a reduced dose of rivaroxaban is prescribed.

Our findings are broadly consistent with those of previous studies that suggest a lower rate of GIB with apixaban than dabigatran and rivaroxaban (41), but we further established for the first time that apixaban also carries lower risk for GIB than edoxaban. Lee and colleagues (9) and Chan and colleagues (8) did not find a difference in GIB rates between apixaban and edoxaban in the Korean and Taiwanese populations, respectively; however, only 302 (9) and 44 (8) GIB cases were included in their studies, compared with 2746 cases in our study. To date, only 1 small observational study (n = 1443) has directly compared all 4 DOACs in a Western population (Spain) (10). The Spanish study suggested that all DOACs had similar rates of ischemic 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, so the results may be attributable to the differences between people (10). No existing studies have compared all 4 DOACs at reduced-dose regimens or among patient subgroups aged 80 years or older or with chronic kidney disease. In these settings, we found general evidence of lower risk for GIB with apixaban than other DOACs, as well as similar or lower risk for ischemic stroke or systemic embolism and ICH.

Our study's findings have some notable implications. The preferential use of DOACs over warfarin has increased rapidly because of the recent treatment guideline updates and the minimized monitoring during the COVID-19 pandemic (11). The comparative effects of DOACs merit 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, evidence from both head-to-head trials and large real-world studies is lacking, leaving clinicians without clear aid on the choice of DOAC. Our results indicate that apixaban might be preferable to other DOACs because of the lower rate of GIB and similar rates of stroke and ICH; however, 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 high risk for GIB (42).

This study has considerable strengths. With more than half a million patients across 4 countries, we examined all 4 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 the transparency and reproducibility of the results (21), and all results were reported to avoid publication bias and "p-hacking" (selective reporting) in observational studies.

This study has limitations. We did not assess whether patients received DOAC doses consistent with labeling, but because 75% of the patients in our cohort received a standard dose, off-label underdosing is unlikely to have had substantial effects. Previous studies have suggested that off-label overdosing of DOACs is uncommon (43). We identified bleeding events using diagnosis records, which had no information about the severity of bleeding or the role of reversal agents, if any, in treating the bleeding patients. However, we have no prior reasons to believe that the severity of bleeding differs substantially between DOACs. The on-treatment follow-up periods of the U.S. databases are relatively short in our study. However, our meta-analytic estimates are largely consistent with those of previous studies, and sensitivity analyses using the intention-to-treat approach also yielded similar results.

In addition, as with all observational studies, we cannot rule out the possibility of 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 that older patients who have multiple comorbid conditions and higher risk for bleeding were more likely to receive apixaban (44). This suggests that any residual confounding could have biased our results toward higher bleeding rates in the apixaban group than other DOAC groups and thus will not affect our study conclusion. To reduce confounding, we used rigorous statistical adjustment methods and did 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).

In conclusion, DOACs are increasingly prescribed worldwide, but comprehensive comparative assessments to guide the choice of DOAC are limited. In this large, multinational analysis of patients with AF, the use of apixaban compared with dabigatran, edoxaban, and rivaroxaban was associated with lower risk for GIB and similar rates of ischemic stroke or systemic embolism and ICH. This finding was generally consistent for patients aged 80 years or older and those with chronic kidney disease.

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Disclosures: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M22-0511.

Reproducible Research Statement: *Study protocol and statistical code:* The study protocol, phenotype code list, and programming codes are publicly available in the GitHub repository at https://github.com/ohdsi-studies/Corazon. *Data set:* Publicly available at https://data.ohdsi.org/corazon and https://github.com/OHDSI/ShinyDeploy/tree/master/corazon/data.

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Correction: This article was amended on 6 December 2022 to correct an error in the Statistical Analysis section in the description of dosing of edoxaban. A correction has been published (doi:10.7326/L22-0482).

Author contributions are available at Annals.org.

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