# Effectiveness and Safety of Oral Anticoagulants Among Nonvalvular Atrial Fibrillation Patients

## The ARISTOPHANES Study

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***Background and Purpose***—This ARISTOPHANES study (Anticoagulants for Reduction in Stroke: Observational Pooled Analysis on Health Outcomes and Experience of Patients) used multiple data sources to compare stroke/systemic embolism (SE) and major bleeding (MB) among a large number of nonvalvular atrial fibrillation patients on non–vitamin K antagonist oral anticoagulants (NOACs) or warfarin.

***Methods***—A retrospective observational study of nonvalvular atrial fibrillation patients initiating apixaban, dabigatran, rivaroxaban, or warfarin from January 1, 2013, to September 30, 2015, was conducted pooling Centers for Medicare and Medicaid Services Medicare data and 4 US commercial claims databases. After 1:1 NOAC-warfarin and NOAC-NOAC propensity score matching in each database, the resulting patient records were pooled. Cox models were used to evaluate the risk of stroke/SE and MB across matched cohorts.

***Results***—A total of 285 292 patients were included in the 6 matched cohorts: 57 929 apixaban-warfarin, 26 838 dabigatran-warfarin, 83 007 rivaroxaban-warfarin, 27 096 apixaban-dabigatran, 62 619 apixaban-rivaroxaban, and 27 538 dabigatran-rivaroxaban patient pairs. Apixaban (hazard ratio [HR], 0.61; 95% CI, 0.54–0.69), dabigatran (HR, 0.80; 95% CI, 0.68–0.94), and rivaroxaban (HR, 0.75; 95% CI, 0.69–0.82) were associated with lower rates of stroke/SE compared with warfarin. Apixaban (HR, 0.58; 95% CI, 0.54–0.62) and dabigatran (HR, 0.73; 95% CI, 0.66–0.81) had lower rates of MB, and rivaroxaban (HR, 1.07; 95% CI, 1.02–1.13) had a higher rate of MB compared with warfarin. Differences exist in rates of stroke/SE and MB across NOACs.

***Conclusions***—In this largest observational study to date on NOACs and warfarin, the NOACs had lower rates of stroke/SE and variable comparative rates of MB versus warfarin. The findings from this study may help inform the discussion on benefit and risk in the shared decision-making process for stroke prevention between healthcare providers and nonvalvular atrial fibrillation patients.

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**Key Words:** anticoagulants ■ apixaban ■ dabigatran ■ hemorrhage ■ rivaroxaban ■ stroke ■ warfarin

Stroke prevention is the principal priority in the management of atrial fibrillation (AF); in the presence of stroke risk factors, oral anticoagulants (OACs) are recommended to reduce this risk, as well as all-cause mortality.[1] Vitamin K antagonists (VKAs), such as warfarin, have been the standard OAC for several decades; however, an increased rate of major bleeding (MB) was observed in AF patients when compared with no anticoagulant treatment or placebo.[2] In addition, warfarin treatment has a narrow therapeutic range, drug and food interactions, the requirement of regular blood test monitoring

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of the international normalized ratio, and frequent need for dose adjustment.[3]

In recent years, 4 non-VKA OACs (NOACs), dabigatran, rivaroxaban, apixaban, and edoxaban, have been approved for stroke prevention in AF based on their noninferiority in efficacy and safety compared with warfarin in randomized controlled trials (RCTs).[4] In addition, no anticoagulation monitoring is required, and fewer drug and food interactions are evident.[5] NOACs have changed the landscape of OAC use for stroke prevention in AF,[6] but there are some pharmacological differences among different NOACs, such as the mechanism of action, food effect, and renal clearance.[5]

There are no head-to-head clinical trials comparing the efficacy of NOACs versus other NOACs. However, indirect comparisons and network meta-analyses based on RCTs have demonstrated that NOACs have generally similar efficacy but varied safety profiles.[7,8] Emerging observational studies have evaluated the effectiveness and safety among different NOACs in US clinical practice using single data sources, providing some evidence of the comparative effectiveness and safety between NOACs but with limited generalizability and a lack of a comprehensive evaluation on outcomes across various subgroups within nonvalvular AF (NVAF) patients.[9,10]

Using multiple data sources, this ARISTOPHANES study (Anticoagulants for Reduction in Stroke: Observational Pooled Analysis on Health Outcomes and Experience of Patients) compared the rates of stroke/SE and MB and evaluated comparative rates across various subgroups among NVAF patients newly prescribed apixaban, dabigatran, rivaroxaban, or warfarin.

# Methods

## Data Sources

Authors will not be able to make their data available to other researchers because of restrictions specified in data licenses and data use agreements. However, the corresponding author is willing to share any nonproprietary information about analytical methods with any other researchers who want to reproduce the results or replicate the procedure if they have specific questions about the manuscript. This study was registered at URL: https://www.clincialtrials.gov (Unique identifier: NCT03087487).

Data in this study were pooled from the US Centers for Medicare and Medicaid Services Medicare data and 4 commercial claims databases in the United States: the Truven MarketScan Commercial Claims and Encounter and Medicare Supplemental and Coordination of Benefits Database (MarketScan), the IMS PharMetrics Plus Database (PharMetrics), the Optum Clinformatics Data Mart (Optum), and the Humana Research Database (Humana)—which cover >180 million beneficiaries annually (≈56% of the US population).

Centers for Medicare and Medicaid Services Medicare data contain medical and pharmacy claims from the 100% Medicare population enrolled in Part A, Part B, and Part D programs (medical and pharmacy coverage). Detailed descriptions for the 5 data sets, rationale for the pooling process, and our approaches to minimize potential patient record duplicates across data sources can be found in a previously published article and Document I in the online-only Data Supplement.[11]

## Patient Selection

Patients with ≥1 pharmacy claim for apixaban, dabigatran, rivaroxaban, or warfarin between January 1, 2013, and September 30, 2015, (identification period) were selected. The first NOAC pharmacy claim date during the identification period was designated as the index date for patients with any NOAC claim(s). For those without a NOAC claim, the first warfarin prescription date was designated as the index date. Patients were required to have an AF diagnosis on or before the index date and have continuous medical and pharmacy health plan enrollment for ≥12 months before the index date (baseline period).

Patients treated with any OAC within 12 months before the index date, with evidence of valvular heart disease, venous thromboembolism, transient AF (pericarditis, hyperthyroidism, thyrotoxicity), or heart valve replacement/transplant during the baseline period, with pregnancy during the study period, or with hip or knee replacement surgery within 6 weeks before the index date, were excluded. Additional exclusion criteria can be found in Figure I in the online-only Data Supplement.

## Outcome Measures

Outcome measures were time to first stroke/SE, including ischemic stroke, hemorrhagic stroke, and SE, and time to first MB, including gastrointestinal bleeding, intracranial hemorrhage, and MB at other key sites (Table I in the online-only Data Supplement).[12,13] Outcomes were based on hospitalizations with stroke/SE or MB as the principal or first-listed diagnosis. The follow-up period was from the day after the index date to 30 days after the discontinuation date, switch date, death (only inpatient death for the commercial databases and all-cause death for Medicare database), end of continuous medical or pharmacy plan enrollment, or the end of study period (September 30, 2015), whichever occurred first. Additional details about patient selection and outcome measures can be found in Document I in the online-only Data Supplement.

## Statistical Methods

One-to-one propensity score matching (PSM) was conducted between NOACs and warfarin (apixaban versus warfarin, dabigatran versus warfarin, and rivaroxaban versus warfarin) and between the NOACs (apixaban versus dabigatran, apixaban versus rivaroxaban, and dabigatran versus rivaroxaban). Patients were matched 1:1 in each data set based on the propensity scores generated by logistic regression based on demographics, Charlson Comorbidity Index score,[14] baseline bleeding and stroke/SE history, comorbidities, and baseline comedications (complete list of covariates in Table II in the online-only Data Supplement). Nearest neighbor matching method without replacement with a caliper of 0.01 was used to match the patients.[15] The balance of covariates was checked based on standardized differences with a threshold of 10%.[16] Study patients from the 5 datasets were pooled for analysis after ensuring cohorts were balanced.

After PSM, the rate of stroke/SE and MB in each PSM cohort was evaluated with Cox proportional hazard models with robust sandwich estimates.[15] OAC treatment was included as the independent variable, and no other covariates were included in the model because the cohorts were balanced.

## Subgroup Analyses

Subgroup analyses were conducted for the following subgroups within the matched cohorts: age strata (<65, 65–74, 75–79, and ≥80 years), sex, baseline $CHA_2DS_2$-VASc score (0–1, 2–3, and ≥4), baseline HAS-BLED score (<3 and ≥3), congestive heart failure, coronary artery disease, peripheral arterial disease, diabetes mellitus, renal disease, and prior stroke/SE. For the baseline $CHA_2DS_2$-VASc score subgroup, female patients without other stroke risk factors (ie, low risk) were assigned with a score of 0.[17] In each subgroup, the balance of baseline characteristics between the treatment cohorts was evaluated. When the standardized difference was >10%, the covariate was included in the Cox proportional hazards model. In each subgroup analysis, the statistical significance ($P$<0.10) of the interaction between treatment and the specific subgroup(s) was evaluated.

As another set of subgroup analysis, PSM and Cox models were reconducted to separately evaluate outcomes associated with each standard-dose NOAC (apixaban 5 mg, dabigatran 150 mg, rivaroxaban 20 mg) and lower-dose NOAC (apixaban 2.5 mg, dabigatran 75 mg, rivaroxaban 15 mg/10 mg) based on the index prescription dosage. Rematched cohorts included standard-dose NOAC versus

warfarin, lower-dose NOAC versus warfarin, standard-dose NOAC versus standard-dose NOAC, and lower-dose NOAC versus lower-dose NOAC.

### Sensitivity Analysis

Three sensitivity analyses were conducted. First, a sensitivity analysis was conducted by restricting the follow-up period to 1 year to help balance the follow-up period between the cohorts. Second, multivariate Cox proportional hazard models were conducted on all patients meeting the eligibility criteria (without PSM but with all covariates previously used for propensity score estimation alternatively adjusted for in the Cox models). Third, we evaluated the rate of all-cause death for Medicare patients. In the Medicare data, death was obtained by validated Social Security records that include the date of death. The other databases do not include complete death information, so mortality was only evaluated using the Centers for Medicare and Medicaid Services Medicare data.

Because the core study herein does not involve the collection, use, or transmittal of individual identifiable data, institutional review board approval is not required. Both the data sets and the security of the offices where analysis was completed (and where the data sets are kept) meet the requirements of the Health Insurance Portability and Accountability Act of 1996.

## Results

After applying the selection criteria, a total of 321 182 NVAF patients were identified, including 63 484 apixaban, 27 571 dabigatran, 103 477 rivaroxaban, and 126 650 warfarin patients (Figure I in the online-only Data Supplement). Before PSM, warfarin patients were the oldest and had the highest baseline $CHA_2DS_2$-VASc and HAS-BLED scores, followed by apixaban, rivaroxaban, and dabigatran patients. For apixaban, dabigatran, and rivaroxaban patients, 21% (2.5 mg), 15% (75 mg), and 24% (19% on 15 mg and 5% on 10 mg) had lower dosage regimens, respectively.

The unadjusted incidence rate of stroke/SE—including ischemic stroke, hemorrhagic stroke, and systemic embolism—was 1.3 (apixaban), 1.5 (dabigatran), 1.4 (rivaroxaban), and 2.2 (warfarin) per 100 person-years. The unadjusted incidence rate of MB was 3.5 (apixaban), 3.5 (dabigatran), 5.3 (rivaroxaban), and 6.3 (warfarin) per 100 person-years (Table II in the online-only Data Supplement).

After PSM, a total of 285 292 unique patients were included in the 6 matched cohorts: 57 929 apixaban-warfarin, 26 838 dabigatran-warfarin, 83 007 rivaroxaban-warfarin, 27 096 apixaban-dabigatran, 62 619 apixaban-rivaroxaban, and 27 538 dabigatran-rivaroxaban PSM pairs. Each cohort was matched separately; therefore, it is not appropriate to compare across the cohorts. The baseline characteristics of the matched populations are shown in Table 1 and Tables III and IV in the online-only Data Supplement.

### NOAC-Warfarin and NOAC-NOAC Comparisons

The Kaplan-Meier curves for cumulative incidence rates of stroke/SE and MB in the matched populations are shown in Figure 1A and 1B.

Compared with warfarin, apixaban (hazard ratio [HR], 0.61; 95% CI, 0.54–0.69), dabigatran (HR, 0.80; 95% CI, 0.68–0.94), and rivaroxaban (HR, 0.75; 95% CI, 0.69–0.82) were all associated with lower rates of stroke/SE (Figure 2A). All NOACs were associated with lower rates of hemorrhagic stroke, whereas apixaban and rivaroxaban patients were associated with lower rates of ischemic stroke compared with warfarin.

Apixaban (HR, 0.58; 95% CI, 0.54–0.62) and dabigatran (HR, 0.73; 95% CI, 0.66–0.81) were associated with lower rates of MB compared with warfarin. Rivaroxaban (HR, 1.07; 95% CI, 1.02–1.13) was associated with a higher rate of MB compared with warfarin. All 3 NOACs were associated with a lower rate of intracranial hemorrhage compared with warfarin. Apixaban was associated with a lower rate (HR, 0.59; 95% CI, 0.54–0.66), and rivaroxaban was associated with a higher rate (HR, 1.25; 95% CI, 1.16–1.34) of gastrointestinal bleeding compared with warfarin.

Apixaban was associated with a lower rate of stroke/SE and MB compared with dabigatran (stroke/SE—HR, 0.69; 95% CI, 0.56–0.84; MB—HR, 0.77; 95% CI, 0.68–0.87) and rivaroxaban (stroke/SE—HR, 0.80; 95% CI, 0.71–0.91; MB—HR, 0.55; 95% CI, 0.51–0.59; Figure 2B). Dabigatran was associated with a lower rate of MB (HR, 0.70; 95% CI, 0.63–0.77) compared with rivaroxaban, with similar rates of stroke/SE (HR, 1.15; 95% CI, 0.96–1.37).

### Subgroup Analyses

The results of the subgroup analyses on age strata, sex, and baseline $CHA_2DS_2$-VASc score, HAS-BLED score, congestive heart failure, coronary artery disease, peripheral arterial disease, diabetes mellitus, renal disease, and prior stroke/SE were generally consistent with the main results. A few significant interactions were evident.

The magnitude of stroke/SE risk reduction for apixaban versus warfarin was greater in patients aged 75+ than those with aged <75 ($P_{int}$=0.049). Significant interaction was also found when evaluating the comparisons in MB for dabigatran and rivaroxaban versus warfarin across age/sex/$CHA_2DS_2$-VASc score, with lower HRs observed in patients who were younger, male, and with lower baseline $CHA_2DS_2$-VASc scores (Figure 3A and 3B).

In the dose subgroup analysis, patients with lower- and standard-dose NOACs had very different baseline characteristics (Tables V through X in the online-only Data Supplement). After PSM, both lower- and standard-dose patients showed broadly consistent results to the main analysis (Figure 3).

In the 2 sensitivity analyses, the results were generally consistent with the main analysis. When evaluating mortality in the Medicare population, all NOACs were associated with a lower rate of mortality compared with warfarin, and apixaban was associated with a lower rate of mortality compared with dabigatran and rivaroxaban (Tables XI through XIII in the online-only Data Supplement).

## Discussion

To our best knowledge, the ARISTOPHANES study is the largest retrospective observational study to date examining the risk of stroke/SE and MB among NVAF patients who initiated NOAC treatment. By pooling the Centers for Medicare and Medicaid Services Medicare and 4 large US national claims data sets, this study demonstrated that apixaban, dabigatran, and rivaroxaban were associated with lower rates of stroke/SE compared with warfarin, and the safety results varied across NOACs.

**Table 1. Baseline Characteristics of Patients Prescribed Warfarin and NOACs After Propensity Score Matching**

| | Apixaban (N=57 929) | Warfarin (N=57 929) | Dabigatran (N=26 838) | Warfarin (N=26 838) | Rivaroxaban (N=83 007) |
|---|---|---|---|---|---|
| | Mean/% | Mean/% | Mean/% | Mean/% | Mean/% |
| Age | 74.3 | 74.2 | 71.9 | 72.0 | 74.4 |
| <65 | 17.5% | 17.6% | 23.6% | 23.6% | 14.9% |
| 65–74 | 30.9% | 31.0% | 33.4% | 34.0% | 33.7% |
| 75–79 | 18.1% | 18.1% | 17.9% | 18.0% | 19.4% |
| ≥80 | 33.5% | 33.3% | 25.1% | 24.4% | 32.0% |
| Sex | | | | | |
| Male | 54.1% | 53.8% | 58.8% | 58.6% | 55.1% |
| Female | 45.9% | 46.2% | 41.2% | 41.4% | 44.9% |
| Baseline comorbidity | | | | | |
| $CHA_2DS_2$-VASc Score | 3.7 | 3.7 | 3.4 | 3.4 | 3.7 |
| 0 | 3.6% | 3.4% | 5.4% | 5.3% | 2.9% |
| 1 | 6.2% | 6.1% | 8.8% | 8.8% | 6.1% |
| 2 | 14.5% | 13.8% | 16.9% | 16.6% | 14.6% |
| 3 | 21.5% | 22.0% | 22.5% | 22.8% | 22.6% |
| 4+ | 54.2% | 54.7% | 46.3% | 46.5% | 53.8% |
| HAS-BLED score* | 3.0 | 3.0 | 2.7 | 2.7 | 2.9 |
| 0 | 2.9% | 2.9% | 4.5% | 4.6% | 2.5% |
| 1 | 10.5% | 10.6% | 14.0% | 14.0% | 10.5% |
| 2 | 25.3% | 25.5% | 29.1% | 28.6% | 26.7% |
| 3+ | 61.4% | 61.0% | 52.3% | 52.7% | 60.3% |
| Congestive heart failure | 28.5% | 28.9% | 24.5% | 24.8% | 27.8% |
| Diabetes mellitus | 34.8% | 34.7% | 35.0% | 35.1% | 35.8% |
| Renal disease | 23.0% | 23.3% | 16.2% | 16.6% | 20.4% |
| Stroke/SE | 12.1% | 12.3% | 10.1% | 10.3% | 11.7% |
| Peripheral artery disease | 19.3% | 20.3% | 15.6% | 16.9% | 19.0% |
| Coronary artery disease | 46.2% | 45.5% | 40.5% | 39.7% | 44.3% |
| Dose of the index prescription | | | | | |
| Standard dose† | 77.5% | | 84.6% | | 72.1% |
| Lower dose‡ | 22.5% | | 15.4% | | 27.9% |
| Follow-up time, d | 200.4 | 246.9 | 236.4 | 246.1 | 246.9 |
| Median | 135 | 158 | 130 | 156 | 153 |

(*Continued*)

The results of this study add evidence to supplement results from clinical trials, where all the NOACs had noninferior rates of stroke/SE and MB compared with warfarin.[4,18–20] The results for apixaban versus warfarin were similar to the results of the ARISTOTLE trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation), wherein apixaban was superior to warfarin in preventing stroke/SE and in reducing the risk of MB.[20] In the RE-LY trial (Randomized Evaluation of Long-Term Anticoagulation Therapy), dabigatran 150 mg was associated with a lower risk of stroke/SE and a similar risk of MB; in our study, we found that dabigatran was associated with a lower risk of both stroke/SE and MB.[18] In the ROCKET-AF trial (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation), rivaroxaban was noninferior for both stroke/SE and MB compared with warfarin; a significantly lower risk of stroke/SE was found for rivaroxaban versus warfarin in our study, and the difference in MB between rivaroxaban and warfarin reached statistical significance (with higher bleeding risk associated with rivaroxaban).[19] The findings from this study may help inform the discussion of benefit and risk in the shared decision-making process for stroke prevention between healthcare providers and individual NVAF patients, when considering the balance between thromboembolic and bleeding risks.[21]

**Table 1. Continued**

| Warfarin (N=83007) | Apixaban (N=27096) | Dabigatran (N=27096) | Apixaban (N=62619) | Rivaroxaban (N=62619) | Dabigatran (N=27538) | Rivaroxaban (N=27538) |
|---|---|---|---|---|---|---|
| Mean/% | Mean/% | Mean/% | Mean/% | Mean/% | Mean/% | Mean/% |
| 74.4 | 71.7 | 71.6 | 73.1 | 72.9 | 71.4 | 71.4 |
| 15.1% | 24.9% | 24.8% | 22.3% | 22.3% | 25.4% | 25.5% |
| 33.6% | 32.8% | 32.8% | 29.8% | 30.3% | 32.7% | 32.3% |
| 19.4% | 17.4% | 17.6% | 17.1% | 16.8% | 17.4% | 17.8% |
| 31.9% | 24.9% | 24.8% | 30.7% | 30.6% | 24.5% | 24.4% |
| | | | | | | |
| 55.1% | 59.3% | 59.1% | 55.2% | 54.8% | 59.5% | 59.8% |
| 44.9% | 40.7% | 40.9% | 44.8% | 45.2% | 40.5% | 40.2% |
| | | | | | | |
| 3.7 | 3.3 | 3.3 | 3.5 | 3.5 | 3.3 | 3.3 |
| 2.8% | 5.9% | 5.8% | 4.5% | 4.6% | 6.0% | 5.9% |
| 5.6% | 9.7% | 9.6% | 8.0% | 8.5% | 9.8% | 10.1% |
| 13.9% | 17.3% | 16.8% | 15.8% | 15.8% | 17.0% | 17.2% |
| 23.5% | 22.1% | 22.2% | 21.3% | 21.2% | 22.1% | 21.7% |
| 54.1% | 45.0% | 45.6% | 50.5% | 50.0% | 45.1% | 45.1% |
| 2.9 | 2.6 | 2.7 | 2.9 | 2.8 | 2.6 | 2.6 |
| 2.5% | 4.7% | 4.6% | 3.4% | 3.5% | 4.9% | 4.9% |
| 10.4% | 14.6% | 14.4% | 12.4% | 12.7% | 14.7% | 14.8% |
| 27.3% | 29.3% | 29.2% | 26.0% | 26.3% | 29.2% | 27.9% |
| 59.8% | 51.4% | 51.7% | 58.2% | 57.5% | 51.2% | 52.4% |
| 27.9% | 23.6% | 24.1% | 26.6% | 26.1% | 23.9% | 23.9% |
| 35.7% | 33.6% | 34.2% | 33.5% | 32.9% | 34.4% | 34.7% |
| 20.6% | 16.1% | 16.0% | 20.9% | 20.8% | 15.8% | 15.9% |
| 11.9% | 9.7% | 9.9% | 11.2% | 11.0% | 9.8% | 10.0% |
| 19.5% | 15.6% | 15.5% | 18.1% | 18.4% | 15.3% | 16.2% |
| 44.1% | 39.7% | 40.1% | 44.6% | 43.5% | 39.8% | 39.8% |
| | | | | | | |
| | 83.2% | 84.8% | 79.3% | 73.3% | 85.0% | 76.7% |
| | 16.8% | 15.2% | 20.7% | 26.7% | 15.0% | 23.3% |
| 250.5 | 198.9 | 235.5 | 198.6 | 240.1 | 234.6 | 241.2 |
| 160 | 133 | 130 | 133 | 149 | 128 | 149 |

HAS-BLED indicates hypertension, abnormal renal and liver function, stroke, bleeding, labile international normalized ratio, elderly, drugs and alcohol; INR, international normalized ratio; and NOAC, non–vitamin K antagonists oral anticoagulants.

*As the INR value is not available in the databases, a modified HAS-BLED score was calculated with a range of 0–8.

†Standard dose: 5 mg Apixaban, 150 mg Dabigatran, 20 mg Rivaroxaban.

‡Lower dose: 2.5 mg Apixaban, 75 mg Dabigatran, 10 or 15 mg Rivaroxaban. 4510; 3239; and 1350 patients in rivaroxaban-warfarin, apixaban-rivaroxaban, and dabigatran-rivaroxaban cohorts received 10 mg rivaroxaban, respectively.

Other retrospective observational studies comparing NOACs to warfarin have also been conducted using various US data sources.[11,22–28] Systematic reviews and meta-analyses concluded that the comparative effectiveness and safety results in the real-world studies are generally consistent with those in the RCTs: all the NOACs were associated with similar or lower rates of stroke/SE and lower intracranial hemorrhage; apixaban was associated with lower rates of MB and gastrointestinal bleeding; dabigatran was associated with similar or lower rates of MB but similar or higher rates of gastrointestinal bleeding; and rivaroxaban was associated with similar rates of MB and similar or higher gastrointestinal bleeding compared with warfarin.[29–33] Our findings are generally consistent with these results.

Using the large pooled ARISTOPHANES data set with more statistical power and improved generalizability compared with previous literature, most of which used a single data source, this study showed consistent comparative effectiveness and safety results between NOACs and warfarin with

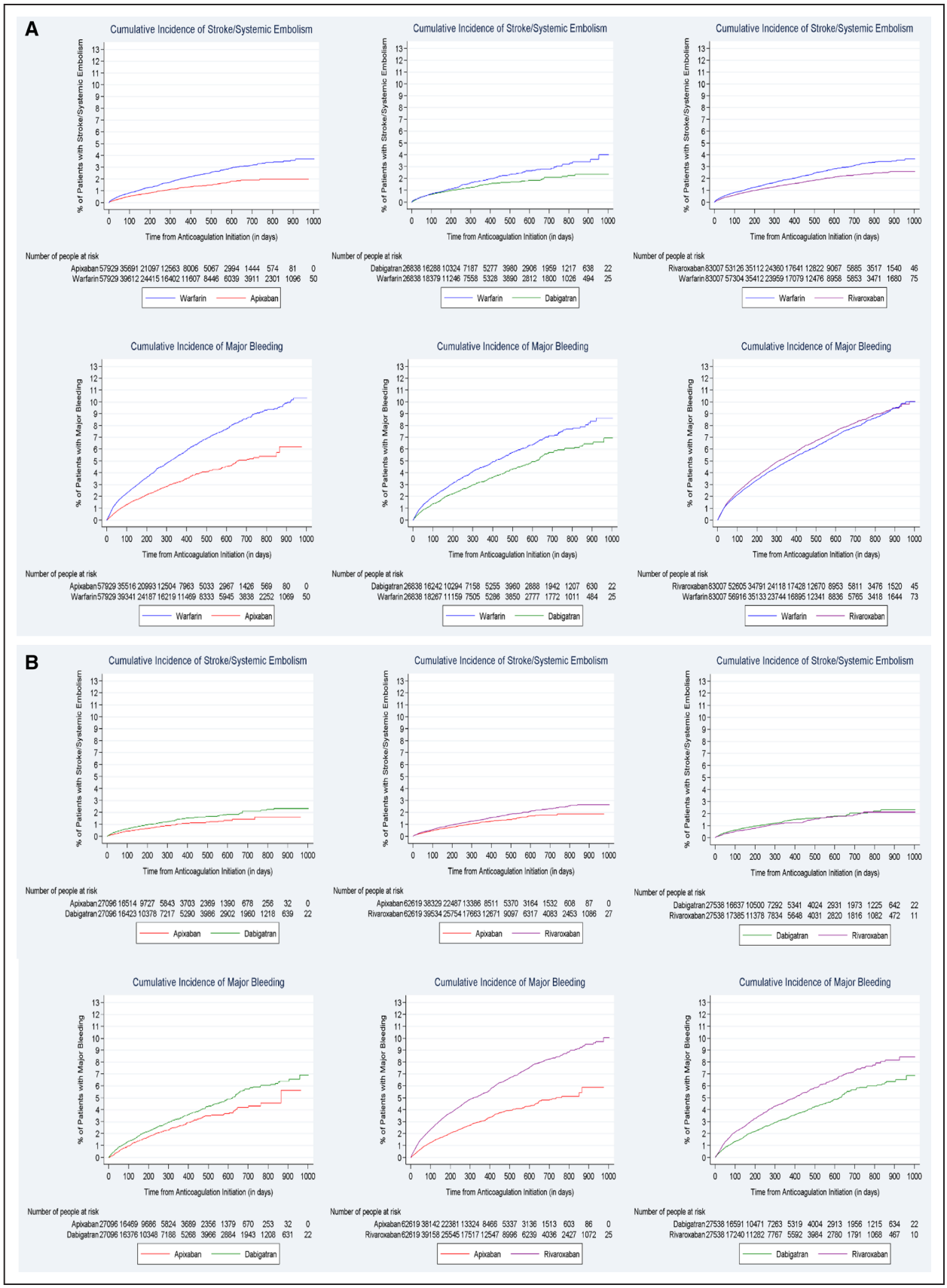



**Figure 1.** Kaplan-Meier curves for stroke/SE and major bleeding. **A**, Cumulative incidence of stroke/systemic embolism (SE) and major bleeding in non–vitamin K antagonist oral anticoagulant (NOAC)-warfarin propensity score–matched cohorts. **B**, Cumulative incidence of Stroke/SE and major bleeding in NOAC-NOAC propensity score–matched cohorts.

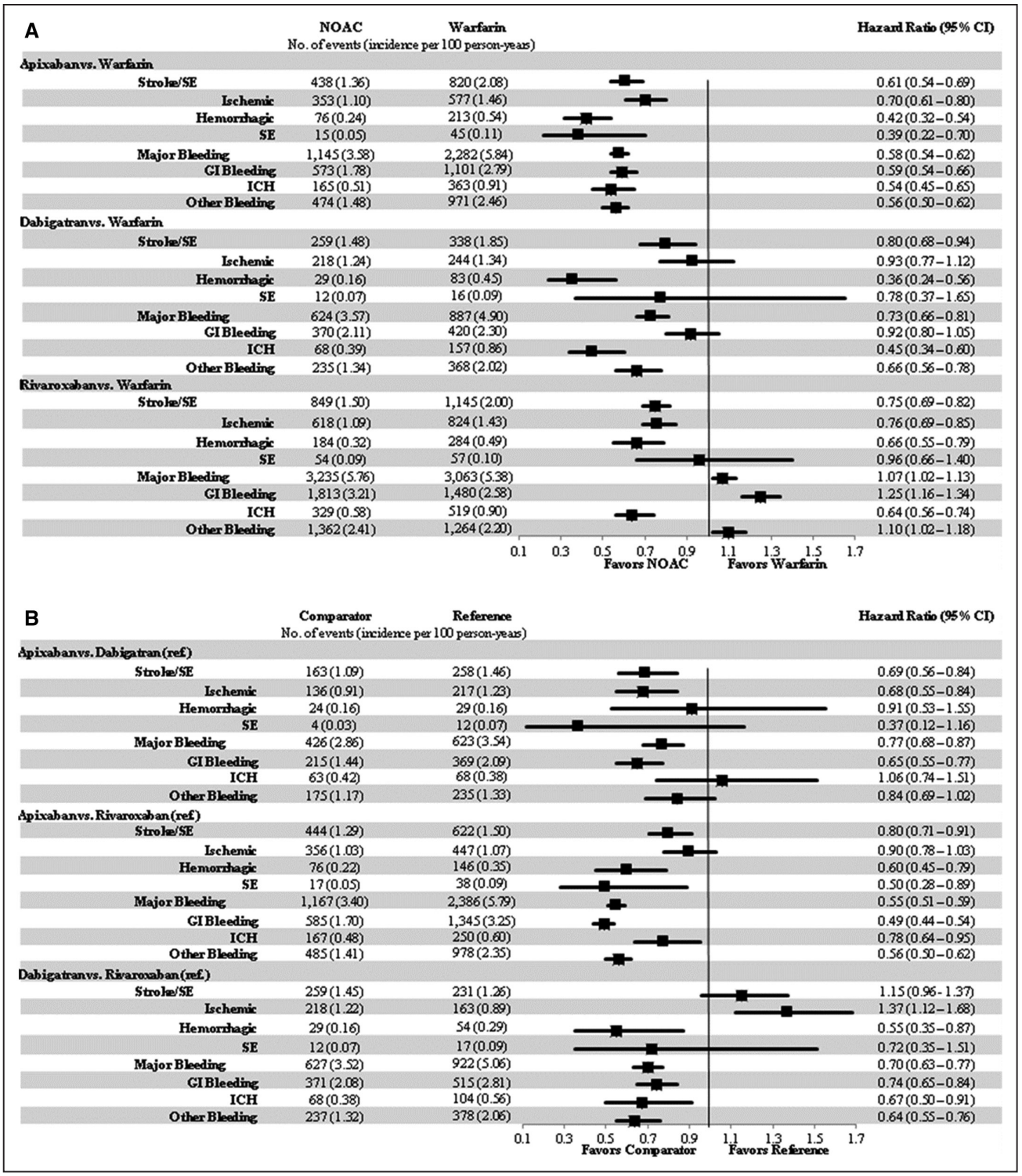
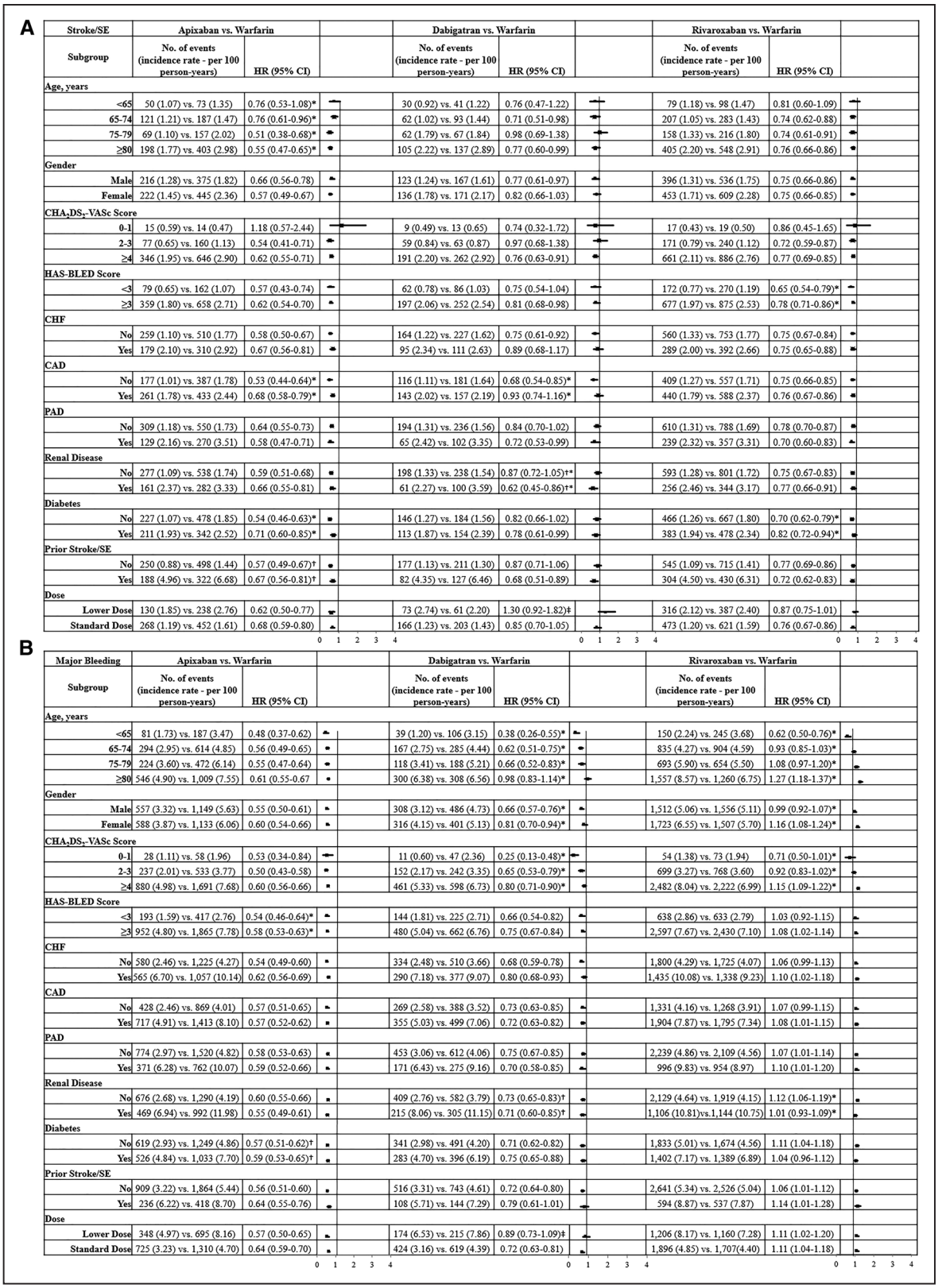



**Figure 2.** Comparison of stroke/SE and major bleeding between OACs. **A**, Incidence rates and hazard ratios of stroke/systemic embolism (SE) and major bleeding for non–vitamin K antagonist oral anticoagulants (NOACs) vs warfarin propensity score–matched cohorts. **B**, Incidence rates and hazard ratios of stroke/SE and major bleeding for NOACs vs NOACs propensity score–matched cohorts. GI indicates gastrointestinal; and ICH, intracranial hemorrhage.

previous studies. For example, this analysis had more statistical power in evaluating less frequent events (eg, intracranial hemorrhage) and subgroups with limited sample size in RCTs (eg, peripheral arterial disease). Indeed, our subgroup analyses provide supplemental information of the comparative effectiveness and safety among OACs stratifying by patient's demographics, risk scores, and comorbidities, which showed generally consistent results with the main analysis.

## Limitations

This retrospective observational study has several limitations. First, our study is subject to the inherent limitations



**A**

| Stroke/SE | Apixaban vs. Warfarin | | Dabigatran vs. Warfarin | | Rivaroxaban vs. Warfarin | |
|---|---|---|---|---|---|---|
| Subgroup | No. of events (incidence rate - per 100 person-years) | HR (95% CI) | No. of events (incidence rate - per 100 person-years) | HR (95% CI) | No. of events (incidence rate - per 100 person-years) | HR (95% CI) |
| **Age, years** | | | | | | |
| <65 | 50 (1.07) vs. 73 (1.35) | 0.76 (0.53-1.08)* | 30 (0.92) vs. 41 (1.22) | 0.76 (0.47-1.22) | 79 (1.18) vs. 98 (1.47) | 0.81 (0.60-1.09) |
| 65-74 | 121 (1.21) vs. 187 (1.47) | 0.76 (0.61-0.96)* | 62 (1.02) vs. 93 (1.44) | 0.71 (0.51-0.98) | 207 (1.05) vs. 283 (1.43) | 0.74 (0.62-0.88) |
| 75-79 | 69 (1.10) vs. 157 (2.02) | 0.51 (0.38-0.68)* | 62 (1.79) vs. 67 (1.84) | 0.98 (0.69-1.38) | 158 (1.33) vs. 216 (1.80) | 0.74 (0.61-0.91) |
| ≥80 | 198 (1.77) vs. 403 (2.98) | 0.55 (0.47-0.65)* | 105 (2.22) vs. 137 (2.89) | 0.77 (0.60-0.99) | 405 (2.20) vs. 548 (2.91) | 0.76 (0.66-0.86) |
| **Gender** | | | | | | |
| Male | 216 (1.28) vs. 375 (1.82) | 0.66 (0.56-0.78) | 123 (1.24) vs. 167 (1.61) | 0.77 (0.61-0.97) | 396 (1.31) vs. 536 (1.75) | 0.75 (0.66-0.86) |
| Female | 222 (1.45) vs. 445 (2.36) | 0.57 (0.49-0.67) | 136 (1.78) vs. 171 (2.17) | 0.82 (0.66-1.03) | 453 (1.71) vs. 609 (2.28) | 0.75 (0.66-0.85) |
| **$CHA_2DS_2$-VASc Score** | | | | | | |
| 0-1 | 15 (0.59) vs. 14 (0.47) | 1.18 (0.57-2.44) | 9 (0.49) vs. 13 (0.65) | 0.74 (0.32-1.72) | 17 (0.43) vs. 19 (0.50) | 0.86 (0.45-1.65) |
| 2-3 | 77 (0.65) vs. 160 (1.13) | 0.54 (0.41-0.71) | 59 (0.84) vs. 63 (0.87) | 0.97 (0.68-1.38) | 171 (0.79) vs. 240 (1.12) | 0.72 (0.59-0.87) |
| ≥4 | 346 (1.95) vs. 646 (2.90) | 0.62 (0.55-0.71) | 191 (2.20) vs. 262 (2.92) | 0.76 (0.63-0.91) | 661 (2.11) vs. 886 (2.76) | 0.77 (0.69-0.85) |
| **HAS-BLED Score** | | | | | | |
| <3 | 79 (0.65) vs. 162 (1.07) | 0.57 (0.43-0.74) | 62 (0.78) vs. 86 (1.03) | 0.75 (0.54-1.04) | 172 (0.77) vs. 270 (1.19) | 0.65 (0.54-0.79)* |
| ≥3 | 359 (1.80) vs. 658 (2.71) | 0.62 (0.54-0.70) | 197 (2.06) vs. 252 (2.54) | 0.81 (0.68-0.98) | 677 (1.97) vs. 875 (2.53) | 0.78 (0.71-0.86)* |
| **CHF** | | | | | | |
| No | 259 (1.10) vs. 510 (1.77) | 0.58 (0.50-0.67) | 164 (1.22) vs. 227 (1.62) | 0.75 (0.61-0.92) | 560 (1.33) vs. 753 (1.77) | 0.75 (0.67-0.84) |
| Yes | 179 (2.10) vs. 310 (2.92) | 0.67 (0.56-0.81) | 95 (2.34) vs. 111 (2.63) | 0.89 (0.68-1.17) | 289 (2.00) vs. 392 (2.66) | 0.75 (0.65-0.88) |
| **CAD** | | | | | | |
| No | 177 (1.01) vs. 387 (1.78) | 0.53 (0.44-0.64)* | 116 (1.11) vs. 181 (1.64) | 0.68 (0.54-0.85)* | 409 (1.27) vs. 557 (1.71) | 0.75 (0.66-0.85) |
| Yes | 261 (1.78) vs. 433 (2.44) | 0.68 (0.58-0.79)* | 143 (2.02) vs. 157 (2.19) | 0.93 (0.74-1.16)* | 440 (1.79) vs. 588 (2.37) | 0.76 (0.67-0.86) |
| **PAD** | | | | | | |
| No | 309 (1.18) vs. 550 (1.73) | 0.64 (0.55-0.73) | 194 (1.31) vs. 236 (1.56) | 0.84 (0.70-1.02) | 610 (1.31) vs. 788 (1.69) | 0.78 (0.70-0.87) |
| Yes | 129 (2.16) vs. 270 (3.51) | 0.58 (0.47-0.71) | 65 (2.42) vs. 102 (3.35) | 0.72 (0.53-0.99) | 239 (2.32) vs. 357 (3.31) | 0.70 (0.60-0.83) |
| **Renal Disease** | | | | | | |
| No | 277 (1.09) vs. 538 (1.74) | 0.59 (0.51-0.68) | 198 (1.33) vs. 238 (1.54) | 0.87 (0.72-1.05)†* | 593 (1.28) vs. 801 (1.72) | 0.75 (0.67-0.83) |
| Yes | 161 (2.37) vs. 282 (3.33) | 0.66 (0.55-0.81) | 61 (2.27) vs. 100 (3.59) | 0.62 (0.45-0.86)†* | 256 (2.46) vs. 344 (3.17) | 0.77 (0.66-0.91) |
| **Diabetes** | | | | | | |
| No | 227 (1.07) vs. 478 (1.85) | 0.54 (0.46-0.63)* | 146 (1.27) vs. 184 (1.56) | 0.82 (0.66-1.02) | 466 (1.26) vs. 667 (1.80) | 0.70 (0.62-0.79)* |
| Yes | 211 (1.93) vs. 342 (2.52) | 0.71 (0.60-0.85)* | 113 (1.87) vs. 154 (2.39) | 0.78 (0.61-0.99) | 383 (1.94) vs. 478 (2.34) | 0.82 (0.72-0.94)* |
| **Prior Stroke/SE** | | | | | | |
| No | 250 (0.88) vs. 498 (1.44) | 0.57 (0.49-0.67)† | 177 (1.13) vs. 211 (1.30) | 0.87 (0.71-1.06) | 545 (1.09) vs. 715 (1.41) | 0.77 (0.69-0.86) |
| Yes | 188 (4.96) vs. 322 (6.68) | 0.67 (0.56-0.81)† | 82 (4.35) vs. 127 (6.46) | 0.68 (0.51-0.89) | 304 (4.50) vs. 430 (6.31) | 0.72 (0.62-0.83) |
| **Dose** | | | | | | |
| Lower Dose | 130 (1.85) vs. 238 (2.76) | 0.62 (0.50-0.77) | 73 (2.74) vs. 61 (2.20) | 1.30 (0.92-1.82)‡ | 316 (2.12) vs. 387 (2.40) | 0.87 (0.75-1.01) |
| Standard Dose | 268 (1.19) vs. 452 (1.61) | 0.68 (0.59-0.80) | 166 (1.23) vs. 203 (1.43) | 0.85 (0.70-1.05) | 473 (1.20) vs. 621 (1.59) | 0.76 (0.67-0.86) |

0 1 2 3 4 0 1 2 3 4 0 1 2 3 4

**B**

| Major Bleeding | Apixaban vs. Warfarin | | Dabigatran vs. Warfarin | | Rivaroxaban vs. Warfarin | |
|---|---|---|---|---|---|---|
| Subgroup | No. of events (incidence rate - per 100 person-years) | HR (95% CI) | No. of events (incidence rate - per 100 person-years) | HR (95% CI) | No. of events (incidence rate - per 100 person-years) | HR (95% CI) |
| **Age, years** | | | | | | |
| <65 | 81 (1.73) vs. 187 (3.47) | 0.48 (0.37-0.62) | 39 (1.20) vs. 106 (3.15) | 0.38 (0.26-0.55)* | 150 (2.24) vs. 245 (3.68) | 0.62 (0.50-0.76)* |
| 65-74 | 294 (2.95) vs. 614 (4.85) | 0.56 (0.49-0.65) | 167 (2.75) vs. 285 (4.44) | 0.62 (0.51-0.75)* | 835 (4.27) vs. 904 (4.59) | 0.93 (0.85-1.03)* |
| 75-79 | 224 (3.60) vs. 472 (6.14) | 0.55 (0.47-0.64) | 118 (3.41) vs. 188 (5.21) | 0.66 (0.52-0.83)* | 693 (5.90) vs. 654 (5.50) | 1.08 (0.97-1.20)* |
| ≥80 | 546 (4.90) vs. 1,009 (7.55) | 0.61 (0.55-0.67 | 300 (6.38) vs. 308 (6.56) | 0.98 (0.83-1.14)* | 1,557 (8.57) vs. 1,260 (6.75) | 1.27 (1.18-1.37)* |
| **Gender** | | | | | | |
| Male | 557 (3.32) vs. 1,149 (5.63) | 0.55 (0.50-0.61) | 308 (3.12) vs. 486 (4.73) | 0.66 (0.57-0.76)* | 1,512 (5.06) vs. 1,556 (5.11) | 0.99 (0.92-1.07)* |
| Female | 588 (3.87) vs. 1,133 (6.06) | 0.60 (0.54-0.66) | 316 (4.15) vs. 401 (5.13) | 0.81 (0.70-0.94)* | 1,723 (6.55) vs. 1,507 (5.70) | 1.16 (1.08-1.24)* |
| **$CHA_2DS_2$-VASc Score** | | | | | | |
| 0-1 | 28 (1.11) vs. 58 (1.96) | 0.53 (0.34-0.84) | 11 (0.60) vs. 47 (2.36) | 0.25 (0.13-0.48)* | 54 (1.38) vs. 73 (1.94) | 0.71 (0.50-1.01)* |
| 2-3 | 237 (2.01) vs. 533 (3.77) | 0.50 (0.43-0.58) | 152 (2.17) vs. 242 (3.35) | 0.65 (0.53-0.79)* | 699 (3.27) vs. 768 (3.60) | 0.92 (0.83-1.02)* |
| ≥4 | 880 (4.98) vs. 1,691 (7.68) | 0.60 (0.56-0.66) | 461 (5.33) vs. 598 (6.73) | 0.80 (0.71-0.90)* | 2,482 (8.04) vs. 2,222 (6.99) | 1.15 (1.09-1.22)* |
| **HAS-BLED Score** | | | | | | |
| <3 | 193 (1.59) vs. 417 (2.76) | 0.54 (0.46-0.64)* | 144 (1.81) vs. 225 (2.71) | 0.66 (0.54-0.82) | 638 (2.86) vs. 633 (2.79) | 1.03 (0.92-1.15) |
| ≥3 | 952 (4.80) vs. 1,865 (7.78) | 0.58 (0.53-0.63)* | 480 (5.04) vs. 662 (6.76) | 0.75 (0.67-0.84) | 2,597 (7.67) vs. 2,430 (7.10) | 1.08 (1.02-1.14) |
| **CHF** | | | | | | |
| No | 580 (2.46) vs. 1,225 (4.27) | 0.54 (0.49-0.60) | 334 (2.48) vs. 510 (3.66) | 0.68 (0.59-0.78) | 1,800 (4.29) vs. 1,725 (4.07) | 1.06 (0.99-1.13) |
| Yes | 565 (6.70) vs. 1,057 (10.14) | 0.62 (0.56-0.69) | 290 (7.18) vs. 377 (9.07) | 0.80 (0.68-0.93) | 1,435 (10.08) vs. 1,338 (9.23) | 1.10 (1.02-1.18) |
| **CAD** | | | | | | |
| No | 428 (2.46) vs. 869 (4.01) | 0.57 (0.51-0.65) | 269 (2.58) vs. 388 (3.52) | 0.73 (0.63-0.85) | 1,331 (4.16) vs. 1,268 (3.91) | 1.07 (0.99-1.15) |
| Yes | 717 (4.91) vs. 1,413 (8.10) | 0.57 (0.52-0.62) | 355 (5.03) vs. 499 (7.06) | 0.72 (0.63-0.82) | 1,904 (7.87) vs. 1,795 (7.34) | 1.08 (1.01-1.15) |
| **PAD** | | | | | | |
| No | 774 (2.97) vs. 1,520 (4.82) | 0.58 (0.53-0.63) | 453 (3.06) vs. 612 (4.06) | 0.75 (0.67-0.85) | 2,239 (4.86) vs. 2,109 (4.56) | 1.07 (1.01-1.14) |
| Yes | 371 (6.28) vs. 762 (10.07) | 0.59 (0.52-0.66) | 171 (6.43) vs. 275 (9.16) | 0.70 (0.58-0.85) | 996 (9.83) vs. 954 (8.97) | 1.10 (1.01-1.20) |
| **Renal Disease** | | | | | | |
| No | 676 (2.68) vs. 1,290 (4.19) | 0.60 (0.55-0.66) | 409 (2.76) vs. 582 (3.79) | 0.73 (0.65-0.83)† | 2,129 (4.64) vs. 1,919 (4.15) | 1.12 (1.06-1.19)* |
| Yes | 469 (6.94) vs. 992 (11.98) | 0.55 (0.49-0.61) | 215 (8.06) vs. 305 (11.15) | 0.71 (0.60-0.85)† | 1,106 (10.81)vs.1,144 (10.75) | 1.01 (0.93-1.09)* |
| **Diabetes** | | | | | | |
| No | 619 (2.93) vs. 1,249 (4.86) | 0.57 (0.51-0.62)† | 341 (2.98) vs. 491 (4.20) | 0.71 (0.62-0.82) | 1,833 (5.01) vs. 1,674 (4.56) | 1.11 (1.04-1.18) |
| Yes | 526 (4.84) vs. 1,033 (7.70) | 0.59 (0.53-0.65)† | 283 (4.70) vs. 396 (6.19) | 0.75 (0.65-0.88) | 1,402 (7.17) vs. 1,389 (6.89) | 1.04 (0.96-1.12) |
| **Prior Stroke/SE** | | | | | | |
| No | 909 (3.22) vs. 1,864 (5.44) | 0.56 (0.51-0.60) | 516 (3.31) vs. 743 (4.61) | 0.72 (0.64-0.80) | 2,641 (5.34) vs. 2,526 (5.04) | 1.06 (1.01-1.12) |
| Yes | 236 (6.22) vs. 418 (8.70) | 0.64 (0.55-0.76) | 108 (5.71) vs. 144 (7.29) | 0.79 (0.61-1.01) | 594 (8.87) vs. 537 (7.87) | 1.14 (1.01-1.28) |
| **Dose** | | | | | | |
| Lower Dose | 348 (4.97) vs. 695 (8.16) | 0.57 (0.50-0.65) | 174 (6.53) vs. 215 (7.86) | 0.89 (0.73-1.09)‡ | 1,206 (8.17) vs. 1,160 (7.28) | 1.11 (1.02-1.20) |
| Standard Dose | 725 (3.23) vs. 1,310 (4.70) | 0.64 (0.59-0.70) | 424 (3.16) vs. 619 (4.39) | 0.72 (0.63-0.81) | 1,896 (4.85) vs. 1,707(4.40) | 1.11 (1.04-1.18) |

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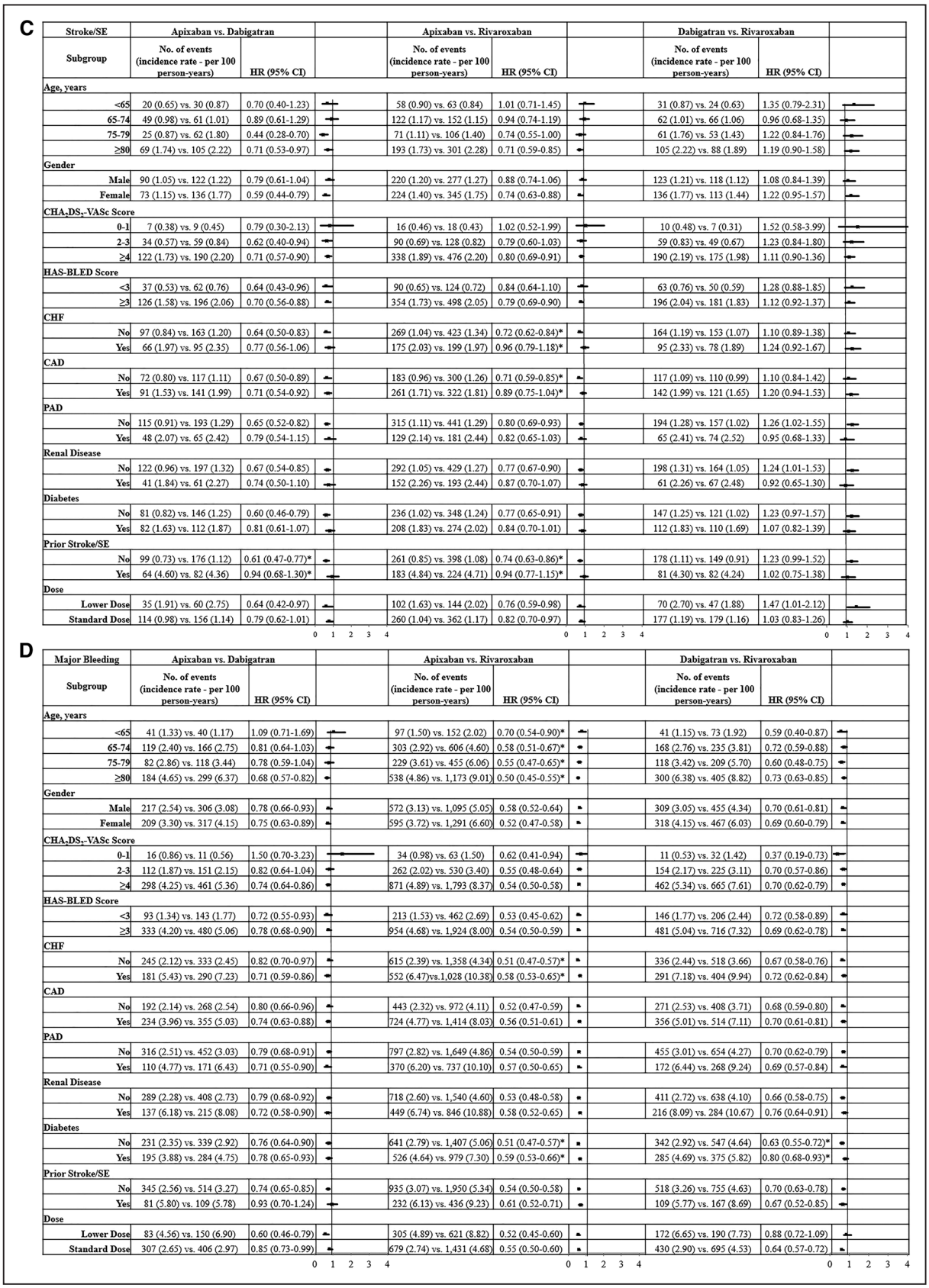
**Figure 3.** Subgroup analysis. **A**, Propensity score–matched hazard ratios of stroke/systemic embolism (SE) for non–vitamin K antagonist oral anticoagulant (NOAC)-warfarin comparisons. †Age was included in the model because it was not balanced after propensity score matching (PSM) for apixaban and warfarin patients with prior stroke and for dabigatran and warfarin patients with renal disease. ‡Charlson Comorbidity Index (CCI) and anemia and coagulation defects were included in the model because they were not balanced after PSM between 75 mg dabigatran and warfarin patients. **B**, Propensity score–matched hazard ratios of major bleeding for NOAC-warfarin comparisons. †Age was included in the model because it was not balanced after PSM for apixaban and warfarin patients with prior stroke and for dabigatran and warfarin patients with renal disease. ‡CCI and anemia and coagulation defects were included in the model because they were not balanced after PSM between 75 mg dabigatran and warfarin patients. (*Continued*)



**C**

| Stroke/SE | Apixaban vs. Dabigatran | | Apixaban vs. Rivaroxaban | | Dabigatran vs. Rivaroxaban | |
|---|---|---|---|---|---|---|
| Subgroup | No. of events (incidence rate - per 100 person-years) | HR (95% CI) | No. of events (incidence rate - per 100 person-years) | HR (95% CI) | No. of events (incidence rate - per 100 person-years) | HR (95% CI) |
| **Age, years** | | | | | | |
| <65 | 20 (0.65) vs. 30 (0.87) | 0.70 (0.40-1.23) | 58 (0.90) vs. 63 (0.84) | 1.01 (0.71-1.45) | 31 (0.87) vs. 24 (0.63) | 1.35 (0.79-2.31) |
| 65-74 | 49 (0.98) vs. 61 (1.01) | 0.89 (0.61-1.29) | 122 (1.17) vs. 152 (1.15) | 0.94 (0.74-1.19) | 62 (1.01) vs. 66 (1.06) | 0.96 (0.68-1.35) |
| 75-79 | 25 (0.87) vs. 62 (1.80) | 0.44 (0.28-0.70) | 71 (1.11) vs. 106 (1.40) | 0.74 (0.55-1.00) | 61 (1.76) vs. 53 (1.43) | 1.22 (0.84-1.76) |
| ≥80 | 69 (1.74) vs. 105 (2.22) | 0.71 (0.53-0.97) | 193 (1.73) vs. 301 (2.28) | 0.71 (0.59-0.85) | 105 (2.22) vs. 88 (1.89) | 1.19 (0.90-1.58) |
| **Gender** | | | | | | |
| Male | 90 (1.05) vs. 122 (1.22) | 0.79 (0.61-1.04) | 220 (1.20) vs. 277 (1.27) | 0.88 (0.74-1.06) | 123 (1.21) vs. 118 (1.12) | 1.08 (0.84-1.39) |
| Female | 73 (1.15) vs. 136 (1.77) | 0.59 (0.44-0.79) | 224 (1.40) vs. 345 (1.75) | 0.74 (0.63-0.88) | 136 (1.77) vs. 113 (1.44) | 1.22 (0.95-1.57) |
| **$CHA_2DS_2$-VASc Score** | | | | | | |
| 0-1 | 7 (0.38) vs. 9 (0.45) | 0.79 (0.30-2.13) | 16 (0.46) vs. 18 (0.43) | 1.02 (0.52-1.99) | 10 (0.48) vs. 7 (0.31) | 1.52 (0.58-3.99) |
| 2-3 | 34 (0.57) vs. 59 (0.84) | 0.62 (0.40-0.94) | 90 (0.69) vs. 128 (0.82) | 0.79 (0.60-1.03) | 59 (0.83) vs. 49 (0.67) | 1.23 (0.84-1.80) |
| ≥4 | 122 (1.73) vs. 190 (2.20) | 0.71 (0.57-0.90) | 338 (1.89) vs. 476 (2.20) | 0.80 (0.69-0.91) | 190 (2.19) vs. 175 (1.98) | 1.11 (0.90-1.36) |
| **HAS-BLED Score** | | | | | | |
| <3 | 37 (0.53) vs. 62 (0.76) | 0.64 (0.43-0.96) | 90 (0.65) vs. 124 (0.72) | 0.84 (0.64-1.10) | 63 (0.76) vs. 50 (0.59) | 1.28 (0.88-1.85) |
| ≥3 | 126 (1.58) vs. 196 (2.06) | 0.70 (0.56-0.88) | 354 (1.73) vs. 498 (2.05) | 0.79 (0.69-0.90) | 196 (2.04) vs. 181 (1.83) | 1.12 (0.92-1.37) |
| **CHF** | | | | | | |
| No | 97 (0.84) vs. 163 (1.20) | 0.64 (0.50-0.83) | 269 (1.04) vs. 423 (1.34) | 0.72 (0.62-0.84)* | 164 (1.19) vs. 153 (1.07) | 1.10 (0.89-1.38) |
| Yes | 66 (1.97) vs. 95 (2.35) | 0.77 (0.56-1.06) | 175 (2.03) vs. 199 (1.97) | 0.96 (0.79-1.18)* | 95 (2.33) vs. 78 (1.89) | 1.24 (0.92-1.67) |
| **CAD** | | | | | | |
| No | 72 (0.80) vs. 117 (1.11) | 0.67 (0.50-0.89) | 183 (0.96) vs. 300 (1.26) | 0.71 (0.59-0.85)* | 117 (1.09) vs. 110 (0.99) | 1.10 (0.84-1.42) |
| Yes | 91 (1.53) vs. 141 (1.99) | 0.71 (0.54-0.92) | 261 (1.71) vs. 322 (1.81) | 0.89 (0.75-1.04)* | 142 (1.99) vs. 121 (1.65) | 1.20 (0.94-1.53) |
| **PAD** | | | | | | |
| No | 115 (0.91) vs. 193 (1.29) | 0.65 (0.52-0.82) | 315 (1.11) vs. 441 (1.29) | 0.80 (0.69-0.93) | 194 (1.28) vs. 157 (1.02) | 1.26 (1.02-1.55) |
| Yes | 48 (2.07) vs. 65 (2.42) | 0.79 (0.54-1.15) | 129 (2.14) vs. 181 (2.44) | 0.82 (0.65-1.03) | 65 (2.41) vs. 74 (2.52) | 0.95 (0.68-1.33) |
| **Renal Disease** | | | | | | |
| No | 122 (0.96) vs. 197 (1.32) | 0.67 (0.54-0.85) | 292 (1.05) vs. 429 (1.27) | 0.77 (0.67-0.90) | 198 (1.31) vs. 164 (1.05) | 1.24 (1.01-1.53) |
| Yes | 41 (1.84) vs. 61 (2.27) | 0.74 (0.50-1.10) | 152 (2.26) vs. 193 (2.44) | 0.87 (0.70-1.07) | 61 (2.26) vs. 67 (2.48) | 0.92 (0.65-1.30) |
| **Diabetes** | | | | | | |
| No | 81 (0.82) vs. 146 (1.25) | 0.60 (0.46-0.79) | 236 (1.02) vs. 348 (1.24) | 0.77 (0.65-0.91) | 147 (1.25) vs. 121 (1.02) | 1.23 (0.97-1.57) |
| Yes | 82 (1.63) vs. 112 (1.87) | 0.81 (0.61-1.07) | 208 (1.83) vs. 274 (2.02) | 0.84 (0.70-1.01) | 112 (1.83) vs. 110 (1.69) | 1.07 (0.82-1.39) |
| **Prior Stroke/SE** | | | | | | |
| No | 99 (0.73) vs. 176 (1.12) | 0.61 (0.47-0.77)* | 261 (0.85) vs. 398 (1.08) | 0.74 (0.63-0.86)* | 178 (1.11) vs. 149 (0.91) | 1.23 (0.99-1.52) |
| Yes | 64 (4.60) vs. 82 (4.36) | 0.94 (0.68-1.30)* | 183 (4.84) vs. 224 (4.71) | 0.94 (0.77-1.15)* | 81 (4.30) vs. 82 (4.24) | 1.02 (0.75-1.38) |
| **Dose** | | | | | | |
| Lower Dose | 35 (1.91) vs. 60 (2.75) | 0.64 (0.42-0.97) | 102 (1.63) vs. 144 (2.02) | 0.76 (0.59-0.98) | 70 (2.70) vs. 47 (1.88) | 1.47 (1.01-2.12) |
| Standard Dose | 114 (0.98) vs. 156 (1.14) | 0.79 (0.62-1.01) | 260 (1.04) vs. 362 (1.17) | 0.82 (0.70-0.97) | 177 (1.19) vs. 179 (1.16) | 1.03 (0.83-1.26) |

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**D**

| Major Bleeding | Apixaban vs. Dabigatran | | Apixaban vs. Rivaroxaban | | Dabigatran vs. Rivaroxaban | |
|---|---|---|---|---|---|---|
| Subgroup | No. of events (incidence rate - per 100 person-years) | HR (95% CI) | No. of events (incidence rate - per 100 person-years) | HR (95% CI) | No. of events (incidence rate - per 100 person-years) | HR (95% CI) |
| **Age, years** | | | | | | |
| <65 | 41 (1.33) vs. 40 (1.17) | 1.09 (0.71-1.69) | 97 (1.50) vs. 152 (2.02) | 0.70 (0.54-0.90)* | 41 (1.15) vs. 73 (1.92) | 0.59 (0.40-0.87) |
| 65-74 | 119 (2.40) vs. 166 (2.75) | 0.81 (0.64-1.03) | 303 (2.92) vs. 606 (4.60) | 0.58 (0.51-0.67)* | 168 (2.76) vs. 235 (3.81) | 0.72 (0.59-0.88) |
| 75-79 | 82 (2.86) vs. 118 (3.44) | 0.78 (0.59-1.04) | 229 (3.61) vs. 455 (6.06) | 0.55 (0.47-0.65)* | 118 (3.42) vs. 209 (5.70) | 0.60 (0.48-0.75) |
| ≥80 | 184 (4.65) vs. 299 (6.37) | 0.68 (0.57-0.82) | 538 (4.86) vs. 1,173 (9.01) | 0.50 (0.45-0.55)* | 300 (6.38) vs. 405 (8.82) | 0.73 (0.63-0.85) |
| **Gender** | | | | | | |
| Male | 217 (2.54) vs. 306 (3.08) | 0.78 (0.66-0.93) | 572 (3.13) vs. 1,095 (5.05) | 0.58 (0.52-0.64) | 309 (3.05) vs. 455 (4.34) | 0.70 (0.61-0.81) |
| Female | 209 (3.30) vs. 317 (4.15) | 0.75 (0.63-0.89) | 595 (3.72) vs. 1,291 (6.60) | 0.52 (0.47-0.58) | 318 (4.15) vs. 467 (6.03) | 0.69 (0.60-0.79) |
| **$CHA_2DS_2$-VASc Score** | | | | | | |
| 0-1 | 16 (0.86) vs. 11 (0.56) | 1.50 (0.70-3.23) | 34 (0.98) vs. 63 (1.50) | 0.62 (0.41-0.94) | 11 (0.53) vs. 32 (1.42) | 0.37 (0.19-0.73) |
| 2-3 | 112 (1.87) vs. 151 (2.15) | 0.82 (0.64-1.04) | 262 (2.02) vs. 530 (3.40) | 0.55 (0.48-0.64) | 154 (2.17) vs. 225 (3.11) | 0.70 (0.57-0.86) |
| ≥4 | 298 (4.25) vs. 461 (5.36) | 0.74 (0.64-0.86) | 871 (4.89) vs. 1,793 (8.37) | 0.54 (0.50-0.58) | 462 (5.34) vs. 665 (7.61) | 0.70 (0.62-0.79) |
| **HAS-BLED Score** | | | | | | |
| <3 | 93 (1.34) vs. 143 (1.77) | 0.72 (0.55-0.93) | 213 (1.53) vs. 462 (2.69) | 0.53 (0.45-0.62) | 146 (1.77) vs. 206 (2.44) | 0.72 (0.58-0.89) |
| ≥3 | 333 (4.20) vs. 480 (5.06) | 0.78 (0.68-0.90) | 954 (4.68) vs. 1,924 (8.00) | 0.54 (0.50-0.59) | 481 (5.04) vs. 716 (7.32) | 0.69 (0.62-0.78) |
| **CHF** | | | | | | |
| No | 245 (2.12) vs. 333 (2.45) | 0.82 (0.70-0.97) | 615 (2.39) vs. 1,358 (4.34) | 0.51 (0.47-0.57)* | 336 (2.44) vs. 518 (3.66) | 0.67 (0.58-0.76) |
| Yes | 181 (5.43) vs. 290 (7.23) | 0.71 (0.59-0.86) | 552 (6.47)vs.1,028 (10.38) | 0.58 (0.53-0.65)* | 291 (7.18) vs. 404 (9.94) | 0.72 (0.62-0.84) |
| **CAD** | | | | | | |
| No | 192 (2.14) vs. 268 (2.54) | 0.80 (0.66-0.96) | 443 (2.32) vs. 972 (4.11) | 0.52 (0.47-0.59) | 271 (2.53) vs. 408 (3.71) | 0.68 (0.59-0.80) |
| Yes | 234 (3.96) vs. 355 (5.03) | 0.74 (0.63-0.88) | 724 (4.77) vs. 1,414 (8.03) | 0.56 (0.51-0.61) | 356 (5.01) vs. 514 (7.11) | 0.70 (0.61-0.81) |
| **PAD** | | | | | | |
| No | 316 (2.51) vs. 452 (3.03) | 0.79 (0.68-0.91) | 797 (2.82) vs. 1,649 (4.86) | 0.54 (0.50-0.59) | 455 (3.01) vs. 654 (4.27) | 0.70 (0.62-0.79) |
| Yes | 110 (4.77) vs. 171 (6.43) | 0.71 (0.55-0.90) | 370 (6.20) vs. 737 (10.10) | 0.57 (0.50-0.65) | 172 (6.44) vs. 268 (9.24) | 0.69 (0.57-0.84) |
| **Renal Disease** | | | | | | |
| No | 289 (2.28) vs. 408 (2.73) | 0.79 (0.68-0.92) | 718 (2.60) vs. 1,540 (4.60) | 0.53 (0.48-0.58) | 411 (2.72) vs. 638 (4.10) | 0.66 (0.58-0.75) |
| Yes | 137 (6.18) vs. 215 (8.08) | 0.72 (0.58-0.90) | 449 (6.74) vs. 846 (10.88) | 0.58 (0.52-0.65) | 216 (8.09) vs. 284 (10.67) | 0.76 (0.64-0.91) |
| **Diabetes** | | | | | | |
| No | 231 (2.35) vs. 339 (2.92) | 0.76 (0.64-0.90) | 641 (2.79) vs. 1,407 (5.06) | 0.51 (0.47-0.57)* | 342 (2.92) vs. 547 (4.64) | 0.63 (0.55-0.72)* |
| Yes | 195 (3.88) vs. 284 (4.75) | 0.78 (0.65-0.93) | 526 (4.64) vs. 979 (7.30) | 0.59 (0.53-0.66)* | 285 (4.69) vs. 375 (5.82) | 0.80 (0.68-0.93)* |
| **Prior Stroke/SE** | | | | | | |
| No | 345 (2.56) vs. 514 (3.27) | 0.74 (0.65-0.85) | 935 (3.07) vs. 1,950 (5.34) | 0.54 (0.50-0.58) | 518 (3.26) vs. 755 (4.63) | 0.70 (0.63-0.78) |
| Yes | 81 (5.80) vs. 109 (5.78) | 0.93 (0.70-1.24) | 232 (6.13) vs. 436 (9.23) | 0.61 (0.52-0.71) | 109 (5.77) vs. 167 (8.69) | 0.67 (0.52-0.85) |
| **Dose** | | | | | | |
| Lower Dose | 83 (4.56) vs. 150 (6.90) | 0.60 (0.46-0.79) | 305 (4.89) vs. 621 (8.82) | 0.52 (0.45-0.60) | 172 (6.65) vs. 190 (7.73) | 0.88 (0.72-1.09) |
| Standard Dose | 307 (2.65) vs. 406 (2.97) | 0.85 (0.73-0.99) | 679 (2.74) vs. 1,431 (4.68) | 0.55 (0.50-0.60) | 430 (2.90) vs. 695 (4.53) | 0.64 (0.57-0.72) |

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**Figure 3 Continued.** **C**, Propensity score–matched hazard ratios of stroke/SE for NOAC-NOAC comparisons. **D**, Propensity score–matched hazard ratios of major bleeding for NOAC-NOAC comparisons. *Significant interactions were found (whether treatment effect was statistically different across subgroups). CAD indicates coronary artery disease; CHF, congestive heart failure; HAS-BLED, hypertension, abnormal renal and liver function, stroke, bleeding, labile international normalized ratio, elderly, drugs and alcohol; and PAD, peripheral artery disease.

of retrospective evaluations using healthcare claims data. Only statistical association rather than causal relationships could be concluded. Although cohorts were matched through PSM, potential residual confounders exist. In clinical practice, patients who receive different OACs may be systematically different, and to the extent that such differences are unobserved, study results may be biased. Other unmeasurable factors including differences in physician-level, practice-level, and health plan-level characteristics may also confound the estimated association between medication exposure (individual OAC) and outcomes (stroke/SE and MB). This limitation is especially important for interpreting NOAC versus NOAC comparison results, which are for hypothesis generation given the lack of head-to-head trials. From an exploratory power calculation conducted by authors based on indirect treatment comparison of pivotal RCTs, nearly 27 000 patients would be needed to evaluate stroke/SE and MB outcomes across the 3 NOACs in a hypothetical head-to-head trial (assuming a 90% power). Second, because of the nature of claims studies, outcome measures were based on *International Classification of Diseases, Ninth Revision, Clinical Modification* codes without further adjudication using precise clinical criteria or further validation against healthcare providers' medical records. No evaluation of the dose reduction criteria for NOACs was allowed without comprehensive data on body weight or serum creatinine/creatinine clearance. In addition, laboratory values, such as international normalized ratio measurements, are not available in the data set so we are unable to determine time in therapeutic range for patients prescribed warfarin. Nonetheless, by including patients with potentially poorer quality control of warfarin in everyday clinical practice, the findings of this study may better reflect real-world situations. Many clinically important outcomes (eg, mild to moderate bleeding) associated with OAC use were not evaluated in the study because they cannot be reliably measured in claims databases. We relied on prescription dispense records to characterize OAC drug exposure, but patients' actual drug taking behaviors cannot be measured. Observed and unobserved heterogeneity may exist across the 5 data sources. However, published NOAC studies using those data sources have reported generally consistent findings.[11,24,27,28] Finally, the results may not be generalizable to the overall NVAF population in the United States because the study did not include uninsured patients and patients solely covered by other public health insurance plans.

Some literature has proposed hypotheses on potential differences in clinical outcomes between patients with different NOAC treatment based on existing pharmacological differences across NOACs (Table 2). A pharmacokinetics and pharmacodynamics study suggested that once-daily dosing may potentially increase absolute patient adherence, but twice-daily dosing regimens may be more forgiving among patients with suboptimal adherence because of lower peak level and higher trough level of drug concentration.[34] Rivaroxaban should be taken together with an evening meal, as this increases bioavailability.[35,36] In a recent US real-world study, about one-third of rivaroxaban users did not take rivaroxaban with an adequate meal.[37] Apixaban and dabigatran do not demonstrate the same degree of food effect. However, no study has formally tested the causal relationship between pharmacological difference and clinical outcomes.

Please note that our NOAC versus NOAC comparisons are for hypotheses generating only. Those results should be interpreted with caution and need to be confirmed by findings from NOAC versus NOAC RCTs which are expected to be released in the upcoming years (eg, DARING-AF trial [Comparison of Efficacy and Safety Among Dabigatran, Rivaroxaban, and Apixaban in Non-Valvular Atrial Fibrillation; URL: https://www.clinicaltrials.gov. Unique identifier: NCT02666157] in Taiwan and DANNOAC-AF trial [The Danish Non-Vitamin K Antagonist Oral Anticoagulation Study: A Cluster Randomized Study Comparing Safety and Efficacy of Edoxaban, Apixaban, Rivaroxaban and Dabigatran for

**Table 2. Clinical Pharmacology of Oral Anticoagulants**

| | Warfarin | Dabigatran | Rivaroxaban | Apixaban | Edoxaban |
|---|---|---|---|---|---|
| Mechanism of action | Inhibitor of vitamin K–dependent factors | Direct thrombin inhibitor | Direct factor Xa inhibitor | Direct factor Xa inhibitor | Direct factor Xa inhibitor |
| Oral bioavailability | >95% | ≈6.5% | 80%–100% | ≈50% | ≈62% |
| Pro-drug | No | Yes | No | No | No |
| Food effect | Yes (foods high in vitamin K) | No | Yes (20 mg and 15 mg doses need to be taken with food) | No | No |
| Renal clearance | Metabolized in liver, and excreted in urine mainly as metabolites | 85% | ≈33%* | ≈27% | 50% |
| Mean half-life ($t_{1/2}$) | 40 h | 14–18 h† | 5–9 h (young)<br>11–13 h (elderly) | 12 h | 10–14 h |
| $T_{max}$ | 72–96 h | 0.5–2 h | 2–4 h | 3–4 h | 1–2 h |

OACs indicates oral anticoagulants; PI, prescribing information; and $T_{max}$, time to reach peak plasma concentration.
*Direct renal excretion as unchanged active substance.
†Prolonged in patients with impaired renal function, licensed for patients up to moderate renal impairment.

Oral Anticoagulation in Atrial Fibrillation; URL: https://www.clinicaltrials.gov. Unique identifier: NCT03129490] in Denmark).[38,39]

## Conclusions

In the largest observational study of NOAC use to date, we show that NOACs had lower rates of stroke/SE and variable comparative rates of MB versus warfarin. A comprehensive set of subgroup analyses in this study provide further evidence in the important subgroups of NVAF patients.

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A. Keshishian is a paid employee of STATinMED Research which is a paid consultant to Pfizer and Bristol-Myers Squibb. Dr Li, M. Hamilton, Dr Gupta, K. Friend, X. Pan, and Dr Nadkarni are paid employees of Bristol-Myers Squibb with ownership of stocks in Bristol-Myers Squibb. Drs Masseria, Luo, and Mardekian are paid employees of Pfizer Inc with ownership of stocks in Pfizer Inc. Dr Lip is a consultant for Bayer/Janssen, Merck, Sanofi, Bristol-Myers Squibb Company/Pfizer Inc, Daiichi-Sankyo, Biotronik, Medtronic, Portola, Novartis, Verseon, and Boehringer Ingelheim and has been on the speakers' bureau for Bayer, Bristol-Myers Squibb Company/Pfizer Inc, Boehringer Ingelheim, Daiichi-Sankyo, and Medtronic. Dr Deitelzweig is a consultant for Bayer/Janssen, Bristol-Myers Squibb Company/Pfizer Inc, Daiichi-Sankyo, Portola, and Boehringer Ingelheim and has been on the speakers' bureau for Janssen, Bristol-Myers Squibb Company/Pfizer Inc, and Boehringer Ingelheim. Dr Lip, A. Keshishian, Dr Li, M. Hamilton, Dr Masseria, Dr Gupta, Dr Luo, Dr Friend, Dr Nadkarni, and Dr Deitelzweig contributed to conceptualize or design the work. A. Keshishian, Dr Li, X. Pan, and Dr Baser contributed to acquire the data for the work. A. Keshishian, Dr Mardekian, and X. Pan contributed to analyze the data for the work. All authors contributed to interpret the data for the work. A. Keshishian, Dr Li, Dr Luo, and Dr Friend drafted the work. All authors critically revised for important intellectual content. All authors finally approved the version to be published. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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