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# Effectiveness and Safety of Oral Anticoagulants among NVAF Patients with Obesity: Insights from the ARISTOPHANES Study

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**Abstract:** This ARISTOPHANES analysis examined stroke/systemic embolism (SE) and major bleeding (MB) among a subgroup of nonvalvular atrial fibrillation (NVAF) patients with obesity prescribed warfarin or non-vitamin K antagonist oral anticoagulants (NOACs) in order to inform clinical decision making. A retrospective observational study was conducted among NVAF patients who were obese and initiated apixaban, dabigatran, rivaroxaban, or warfarin from 1 January 2013–30 September 2015, with data pooled from CMS Medicare and four US commercial claims databases. Propensity score matching was completed between NOACs and against warfarin in each database, and the results were pooled. Cox models were used to evaluate the risks of stroke/SE and MB. A total of 88,461 patients with obesity were included in the study. Apixaban and rivaroxaban were associated with a lower risk of stroke/SE vs. warfarin (HR: 0.63, 95% CI: 0.49–0.82 and HR: 0.84, 95% CI: 0.72–0.98). Dabigatran was associated with a similar risk of stroke/SE compared to warfarin. Compared with warfarin, apixaban and dabigatran had a lower risk of MB (HR: 0.54, 95% CI: 0.49–0.61 and HR: 0.75, 95% CI: 0.63–0.91). Rivaroxaban was associated with a similar risk of MB compared to warfarin. In this high-risk population with obesity, NOACs had a varying risk of stroke/SE and MB vs. warfarin.

**Keywords:** stroke; coagulation; outcomes; cardiovascular disease

## 1. Introduction

Atrial fibrillation (AF) is the most common type of arrhythmia in the USA and European countries, with a current estimated prevalence between 1% and 4% [1]. Its prevalence is of critical concern owing to its cardiovascular complications such as ischemic stroke, heart failure, and increasing mortality [2]. Obesity, another prevalent condition worldwide, was estimated to cause 3.4 million deaths in 2010. If current trends continue, forecasts estimate that 1 billion adults will be obese by the year 2030 [3]. Moreover, obesity has been linked with AF, due to its association with obstructive sleep apnea, diabetes mellitus, hypertension, left ventricular dysfunction, heart failure with preserved left ventricular function, and left atrial enlargement [4–6]. It has also been associated with hypofibrinolysis, inflammation, and a prothrombotic state, further bolstering the link with the thromboembolic effects of AF [4,5].

In the Atherosclerosis Risk in Communities (ARIC) study, obesity and overweight accounted for 17.9% of all AF cases [6]. Though AF risk appears to follow a linear relationship with an increase in BMI, the pathophysiological basis of the obesity–AF relationship is complex and multifactorial [7]. Exploring the risk of stroke in a subgroup of an AF population with obesity is paramount due to prevalence and the potential for high morbidity and mortality.

In the years since their approval, non-vitamin K oral anticoagulants (NOACs) have been increasingly preferred over warfarin due to the convenience of fewer routine monitoring visits, no requirements for dose adjustment, and limited dietary interactions. With the current fixed-dose NOAC prescriptions, the clinical impact of anticoagulation on non-valvular atrial fibrillation (NVAF) patients with obesity is expected to be similar, provided patients have optimum peak and trough levels of NOACs [8]. The International Society of Thrombosis and Hemostasis recommends the standard dosing of NOACs in patients with obesity and with a BMI ≤ 40 or weight ≤ 120 kg but suggests that NOACs should not be used among patients with a BMI > 40 or weight > 120 kg because there is limited clinical data for these patients [9,10]. The use of NOACs in patients with morbid obesity has not been as well-documented or established. Therefore, comparing the risk of stroke and major bleeding (MB) in a real-world population of NVAF patients with obesity and morbid obesity among oral anticoagulant (OAC) users is crucial.

The NOAC clinical trials RE-LY and ROCKET-AF suggested that there was no significant interaction between weight categories (≥100 kg vs. <100 kg) regarding the impact of dabigatran and rivaroxaban versus warfarin on the risk of stroke/systemic embolism (SE) [11,12]. A similar risk of major and clinically relevant non-MB was also seen among the subgroup with obesity for rivaroxaban vs. warfarin in the ROCKET-AF trial [12]. A post-hoc analysis using the patients in the ARISTOTLE trial showed evidence of significant interaction between BMI and MB, comparing apixaban vs. warfarin, with a larger reduction in MB with normal vs. higher BMI [13].

Additionally, several observational studies evaluating patients with morbid obesity (BMI ≥ 35 or BMI ≥ 40, depending on the source) showed that NOACs had a similar risk of stroke/SE and MB compared to warfarin [14–17]. While they add valuable knowledge regarding the clinical course of patients with obesity and morbid obesity, existing real-world studies have limitations (e.g., small sample size and no individual NOAC comparisons) that suggest the need for the further evaluation of NOAC treatment in these populations. Larger real-world studies may be warranted to further examine the use of NOACs in this high-risk population with obesity. Using several data sources, this subgroup analysis of ARISTOPHANES (Anticoagulants for Reduction In Stroke: Observational Pooled analysis on Health outcomes And Experience of Patients; NCT03087487) aimed to respectively compare the risk of stroke/SE and MB among the NVAF population with obesity newly prescribed apixaban, dabigatran, rivaroxaban, or warfarin.

## 2. Experimental Section

### 2.1. Data Sources

This study was a retrospective observational database analysis of a patient population of >180 million beneficiaries per year (~56% of the United States population), using fee-for-service (FFS) Medicare data from the US Centers for Medicare & Medicaid Services (CMS) and four US commercial claims databases: the IBM MarketScan® Commercial Claims and Encounter Database, the IQVIA PharMetrics Plus™ Database, the Optum Clinformatics™ Data Mart, and the Humana Research Database. The databases include patients with Medicare FFS, Medicare Advantage, and commercial insurance. Database records include comprehensive demographic and clinical information and International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes, Healthcare Common Procedure Coding System codes, and National Drug Codes. Previously published articles include detailed descriptions of the datasets, the rationale for the pooling process, and the approaches to minimizing potential patient record duplicates across data sources [18,19].

### 2.2. Patient Selection

NVAF patients diagnosed with obesity were selected if they had ≥1 pharmacy claim for apixaban, dabigatran, rivaroxaban, or warfarin between 01 January 2013 and 30 September 2015 (identification period). Edoxaban was excluded from the final sample due to small sample size. Obesity is typically defined as a BMI ≥ 30 kg/m$^2$ [20] and was defined here by the presence of a diagnosis code containing obesity or an obese BMI designation (Table A1). The first NOAC prescription date was designated as the index date if patients had a NOAC claim. The first warfarin prescription date was designated as the index date for patients without any NOAC claim. Patients were required to have an AF diagnosis before or on the index date and have continuous medical and pharmacy health plan enrollment for ≥12 months pre-index date (baseline period).

To evaluate new initiators, patients treated with an OAC within 12 months pre-index date were excluded. Patients were also excluded if they had claims indicating any of the following: valvular heart disease, venous thromboembolism, transient AF (pericarditis, hyperthyroidism, or thyrotoxicity), heart valve replacement/transplant, or cardiac surgery during the baseline period; pregnancy during the study period; or hip or knee replacement surgery within 6 weeks pre-index date. In addition, patients were excluded if they had >1 OAC on the index date or had no follow-up. Lastly, patients with claims containing ICD-10 codes were excluded to ensure accurate classification, as the ICD-10-CM coding system was not fully adopted in the United States until 1 October 2015, after the study period ended.

### 2.3. Outcome Measures

The outcome measures were time to first stroke/SE, including ischemic stroke, hemorrhagic stroke, and SE; and time to first MB, including gastrointestinal (GI) bleeding, intracranial hemorrhage, and bleeding at other key sites (e.g., the genitourinary tract, respiratory tract, or ocular area; Table A1) [21,22]. Outcomes were based on hospitalizations with stroke/SE or MB as the principal or first-listed diagnosis. The follow-up period ranged from one day post-index date to 30 days after discontinuation, the switch date, death (only inpatient death for the commercial databases and all-cause death for the Medicare database), the end of continuous medical or pharmacy plan enrollment, or the end of the study (30 September 2015), whichever came first.

### 2.4. Statistical Methods

Propensity score matching (PSM) was conducted between the NOAC and warfarin cohorts (apixaban vs. warfarin, dabigatran vs. warfarin, and rivaroxaban vs. warfarin) and between the NOAC cohorts (apixaban vs. dabigatran, apixaban vs. rivaroxaban, and dabigatran vs. rivaroxaban). Patients were matched 1:1 in each dataset based on the propensity scores generated by logistic

regression using demographics, Charlson comorbidity index scores [23], comorbidities, and baseline co-medications. Patients were matched by nearest neighbor matching without replacement (with a caliper of 0.01). Covariate balance was checked through standardized differences, with a threshold of 10% [24]. After ensuring the cohorts were balanced in each database, study patients from the five datasets were pooled for analysis.

The risks of stroke/SE and MB were evaluated using Cox proportional hazard models, with robust sandwich estimates [25]. $p$-values $< 0.05$ were considered statistically significant. OAC treatment was included as the independent variable; as the cohorts were balanced, no other covariates were included in the model.

### 2.5. Subgroup Analyses

Two subgroup analyses were conducted. First, PSM and Cox proportional hazard models were completed for patients prescribed standard dose NOACs (apixaban 5 mg twice a day (BID), dabigatran 150 mg BID, rivaroxaban 20 mg once a day (QD)). A second subgroup analysis was conducted among patients with morbid obesity. Patients with morbid obesity were defined using diagnosis codes indicating morbid obesity or a BMI $\geq 40$ and were re-matched (Table A1) [15]. For both subgroup analyses, the same methodology as that for the main analysis was used.

Institutional Review Board approval was not required because the study did not involve the collection, use, or transmittal of individual identifiable data. Both the datasets and the security of the offices where analysis was completed (and where the datasets are kept) met the requirements of the Health Insurance Portability and Accountability Act of 1996.

## 3. Results

After applying the selection criteria, a total of 88,461 (18.9%) NVAF patients with obesity were identified, including 21,242 apixaban (24.0%), 7171 dabigatran (8.1%), 29,146 rivaroxaban (32.9%), and 30,902 warfarin (34.9%) patients (Figure 1). Before PSM, the warfarin patients were the oldest and had the highest $CHA_2DS_2$-VASc and HAS-BLED scores, followed by apixaban, rivaroxaban, and dabigatran patients (Table A2).

The unadjusted incidence rates of stroke/SE were 2.0, 1.3, 1.5, and 1.3 for warfarin, apixaban, dabigatran, and rivaroxaban per 100 person-years, respectively. The unadjusted rates for MB were 7.6, 3.9, 4.0, and 6.0 per 100 person-years for warfarin, apixaban, dabigatran, and rivaroxaban, respectively (Table A3).

The PSM procedure resulted in 18,181 pairs for the apixaban-warfarin, 6646 pairs for the dabigatran-warfarin, and 22,053 pairs for the rivaroxaban-warfarin cohorts with obesity. Matching for NOAC comparisons included 6884 patient pairs for the apixaban-dabigatran, 20,431 pairs for the apixaban-rivaroxaban, and 7103 pairs for the dabigatran-rivaroxaban cohorts (Figure 1). The mean follow-up time for the six matched cohorts ranged from 6 to 8 months. Within NOAC vs. warfarin comparisons, patients prescribed standard doses of NOACs included 84.8% of apixaban (5 mg), 86.5% of dabigatran (150 mg) and 75.3% of rivaroxaban (20 mg) patients. Select baseline characteristics of the matched populations are shown in Table 1a,b. After matching, all demographic and clinical characteristics were well balanced between pairs (a complete list of baseline variables appears in Tables A4 and A5).

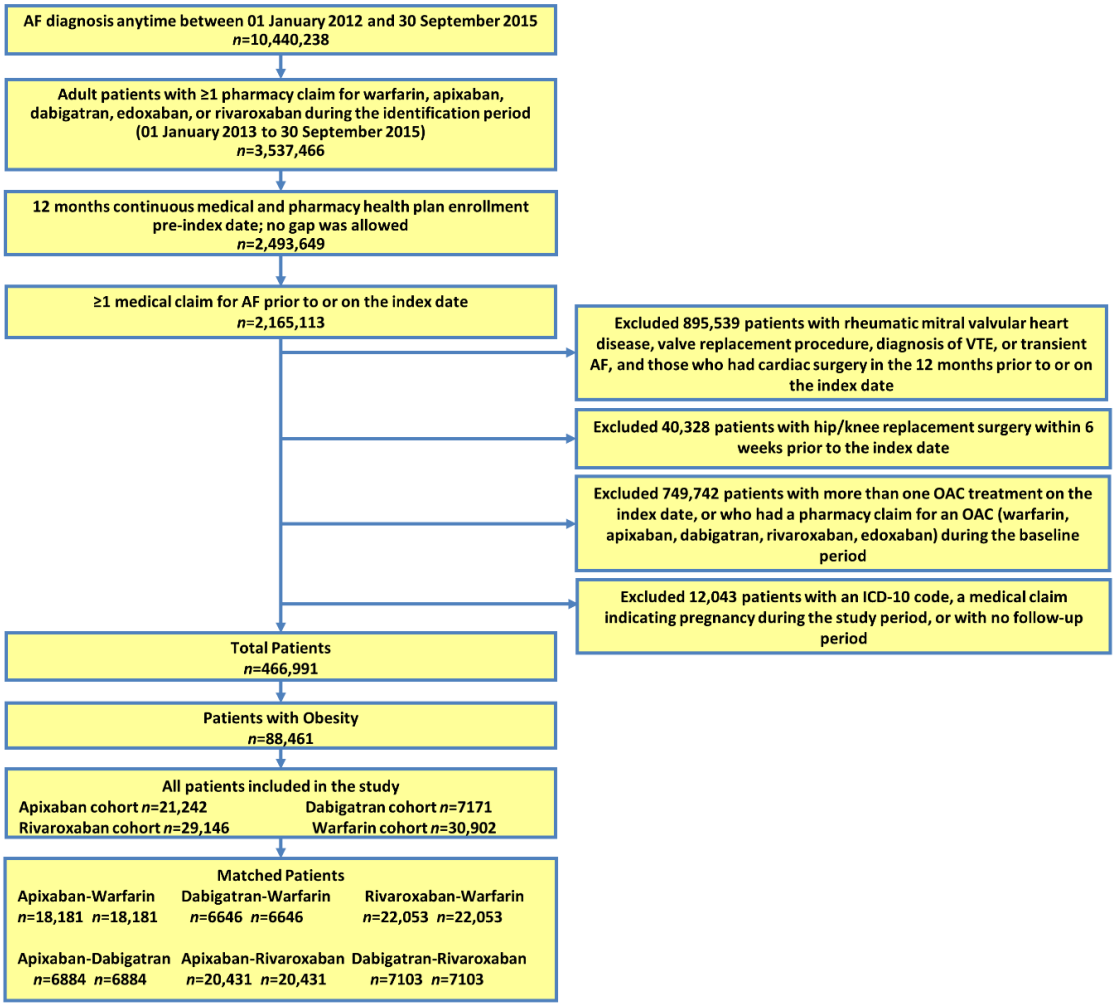



**Figure 1.** Patient selection figure. AF: atrial fibrillation; OAC: oral anticoagulant; VTE: venous thromboembolism. Edoxaban was excluded from the final population due to a small sample size.

**Table 1.** Baseline characteristics among NVAF patients with obesity after propensity score matching.

| (**A**) Baseline Characteristics among NVAF Patients with Obesity after Propensity Score Matching—NOACs vs. Warfarin. | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Apixaban Cohort** | | **Warfarin Cohort** | | **Dabigatran Cohort** | | **Warfarin Cohort** | | **Rivaroxaban Cohort** | | **Warfarin Cohort** | |
| | ***n*/Mean** | **%/SD** | ***n*/Mean** | **%/SD** | ***n*/Mean** | **%/SD** | ***n*/Mean** | **%/SD** | ***n*/Mean** | **%/SD** | ***n*/Mean** | **%/SD** |
| Sample Size | 18,181 | | 18,181 | | 6646 | | 6646 | | 22,053 | | 22,053 | |
| Age | 72.8 | 9.0 | 72.7 | 8.8 | 70.7 | 9.1 | 70.9 | 9.3 | 72.3 | 8.8 | 72.3 | 8.9 |
| Gender | | | | | | | | | | | | |
| Male | 9260 | 50.9% | 9268 | 51.0% | 3632 | 54.6% | 3633 | 54.7% | 11,313 | 51.3% | 11,372 | 51.6% |
| Female | 8921 | 49.1% | 8913 | 49.0% | 3014 | 45.4% | 3013 | 45.3% | 10,740 | 48.7% | 10,681 | 48.4% |
| Baseline Comorbidity | | | | | | | | | | | | |
| Deyo–Charlson Comorbidity Index | 3.9 | 2.9 | 4.0 | 2.9 | 3.5 | 2.8 | 3.5 | 2.9 | 3.9 | 2.9 | 3.9 | 2.9 |
| $CHA_2DS_2$-VASc Score | 4.1 | 1.6 | 4.2 | 1.6 | 3.8 | 1.7 | 3.9 | 1.6 | 4.1 | 1.6 | 4.1 | 1.6 |
| HAS-BLED Score [1] | 3.4 | 1.3 | 3.4 | 1.3 | 3.1 | 1.3 | 3.1 | 1.3 | 3.3 | 1.3 | 3.3 | 1.3 |
| Dose of the Index Prescription | | | | | | | | | | | | |
| Standard Dose [2] | 15,410 | 84.8% | | | 5747 | 86.5% | | | 16,599 | 75.3% | | |
| Low Dose [3] | 2771 | 15.2% | | | 899 | 13.5% | | | 5454 | 24.7% | | |
| Follow-Up Time (in Days) | 176.2 | 160.2 | 236.3 | 213.8 | 222.5 | 219.7 | 236.8 | 211.3 | 221.0 | 208.6 | 237.7 | 213.5 |
| Median | 120 | | 157 | | 128 | | 159 | | 142 | | 159 | |
| (**B**) Baseline Characteristics among NVAF Patients with Obesity after Propensity Score Matching among NOACs vs. NOACs. | | | | | | | | | | | | |
| | **Apixaban Cohort** | | **Dabigatran Cohort** | | **Apixaban Cohort** | | **Rivaroxaban Cohort** | | **Dabigatran Cohort** | | **Rivaroxaban Cohort** | |
| | ***n*/Mean** | **%/SD** | ***n*/Mean** | **%/SD** | ***n*/Mean** | **%/SD** | ***n*/Mean** | **%/SD** | ***n*/Mean** | **%/SD** | ***n*/Mean** | **%/SD** |
| Sample Size | 6884 | | 6884 | | 20,431 | | 20,431 | | 7103 | | 7103 | |
| Age | 70.5 | 10.0 | 70.0 | 9.8 | 71.5 | 9.8 | 71.5 | 9.7 | 69.7 | 10.0 | 69.5 | 9.9 |
| Gender | | | | | | | | | | | | |
| Male | 3776 | 54.9% | 3810 | 55.3% | 10,596 | 51.9% | 10,614 | 52.0% | 3982 | 56.1% | 4171 | 58.7% |
| Female | 3108 | 45.1% | 3074 | 44.7% | 9835 | 48.1% | 9817 | 48.0% | 3121 | 43.9% | 2932 | 41.3% |
| Baseline Comorbidity | | | | | | | | | | | | |
| Deyo–Charlson Comorbidity Index | 3.3 | 2.8 | 3.4 | 2.8 | 3.6 | 2.9 | 3.6 | 2.9 | 3.3 | 2.8 | 3.2 | 2.7 |
| $CHA_2DS_2$-VASc Score | 3.7 | 1.7 | 3.7 | 1.7 | 3.9 | 1.7 | 3.9 | 1.7 | 3.7 | 1.7 | 3.6 | 1.7 |
| HAS-BLED Score [1] | 3.1 | 1.4 | 3.1 | 1.3 | 3.2 | 1.4 | 3.2 | 1.4 | 3.0 | 1.4 | 3.0 | 1.3 |

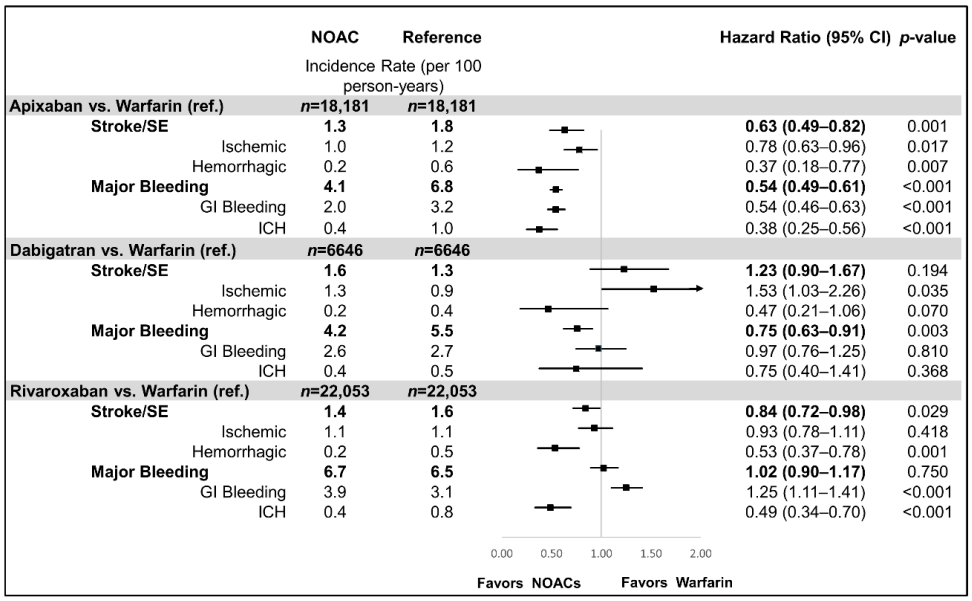
**Table 1.** *Cont.*

| Dose of the Index Prescription | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Standard Dose [2] | 6045 | 87.8% | 5979 | 86.9% | 17,634 | 86.3% | 15,514 | 75.9% | 6194 | 87.2% | 5698 | 80.2% |
| Low Dose [3] | 839 | 12.2% | 905 | 13.1% | 2797 | 13.7% | 4917 | 24.1% | 909 | 12.8% | 1405 | 19.8% |
| Follow-Up Time (in Days) | 176.2 | 158.3 | 221.5 | 218.3 | 176.1 | 159.6 | 220.4 | 208.6 | 220.7 | 218.1 | 217.4 | 206.4 |
| Median | 120 | | 127 | | 120 | | 141 | | 127 | | 140 | |

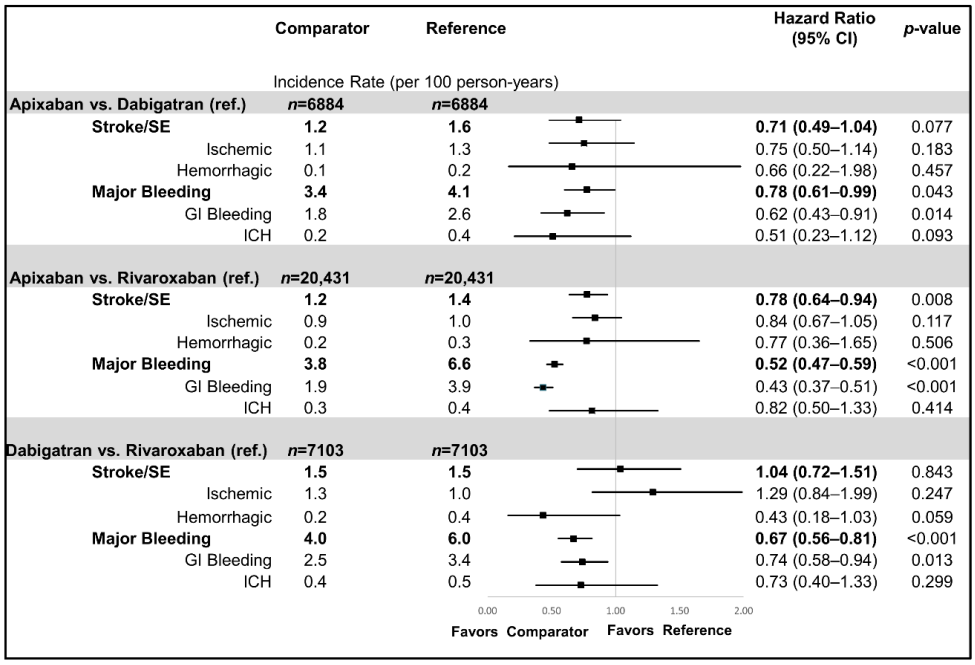
$CHA_2DS_2$-VASc: congestive heart failure, hypertension, aged ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, aged 65–74 years, sex category; HAS-BLED: hypertension, abnormal renal and liver function, stroke, bleeding, labile international normalized ratios, elderly, drugs and alcohol; NOACs: non-vitamin K oral anticoagulants; NVAF: non-valvular atrial fibrillation; SD: standard deviation. [1] As the INR value is not available in the databases, a modified HAS-BLED score was calculated with a range of 0 to 8. [2] Standard dose: 5 mg apixaban, 150 mg dabigatran, 20 mg rivaroxaban. [3] Lower dose: 2.5 mg apixaban, 75 mg dabigatran, 10 or 15 mg rivaroxaban; (**A**) 1053 patients treated with rivaroxaban were prescribed 10 mg rivaroxaban. (**B**) 950 and 310 patients were prescribed 10 mg of rivaroxaban in the apixaban-rivaroxaban and dabigatran-rivaroxaban cohorts, respectively.

### 3.1. NOAC vs. Warfarin Comparison

Patients prescribed apixaban and rivaroxaban had a lower risk of stroke/SE compared to warfarin patients (apixaban: hazard ratio (HR): 0.63, 95% confidence interval (CI): 0.49–0.82; rivaroxaban: HR: 0.84, 95% CI: 0.72–0.98), while dabigatran patients had a similar risk of stroke/SE compared to warfarin patients (HR: 1.23, 95% CI: 0.90–1.67). Compared with warfarin, apixaban and dabigatran (HR: 0.54, 95% CI: 0.49–0.61; HR: 0.75, 95% CI: 0.63–0.91, respectively) were associated with a lower risk of MB (Figure 2a). Rivaroxaban had a similar risk of MB (HR: 1.02, 95% CI: 0.90–1.17) compared to warfarin.




(**A**)




(**B**)

**Figure 2.** Incidence rates and hazard ratios for stroke/SE and major bleeding among NOACs vs. warfarin and NOACs vs. NOACs. (**A**) NOACs vs. warfarin. (**B**) NOACs vs. NOACs. CI: confidence interval; GI: gastrointestinal; ICH: intracranial hemorrhage; NOACs: non-vitamin K oral anticoagulants; ref: reference; SE: systemic embolism.

### 3.2. NOAC vs. NOAC Comparisons

Compared to rivaroxaban, apixaban was associated with a lower risk of stroke/SE (HR: 0.78, 95% CI: 0.64–0.94) and MB (HR: 0.52, 95% CI: 0.47–0.59). Compared to dabigatran, apixaban had a non-significant difference for the risk of stroke/SE (HR: 0.71, 95% CI: 0.49–1.04) and a lower risk of MB (HR: 0.78, 95% CI: 0.61–0.99). Dabigatran was associated with a lower risk of MB (HR: 0.67, 95% CI: 0.56–0.81) than rivaroxaban while having a similar risk of stroke/SE (HR: 1.04, 95% CI: 0.72–1.51) (Figure 2b). The Kaplan–Meier curves for the cumulative incidence rates of stroke/SE and MB in the matched populations have been included in Figure A1(a)–(l)

### 3.3. Subgroup Analyses

The results of the standard dose subgroup analysis were generally consistent with the main analysis. However, there was no significant difference between apixaban and dabigatran for major bleeding (HR: 0.77, 95% CI: 0.59–1.00) and between apixaban and rivaroxaban for stroke/SE (HR: 0.93, 95% CI: 0.74–1.17). (Table 2).

**Table 2.** Incidence and hazard ratios of outcomes for standard-dosed NOACs vs. warfarin and NOACs vs. NOACs.

| NOACs vs. Warfarin | | | | | NOACs vs. NOACs | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Incidence per 100 person-years | | Hazard Ratio (95% CI) | *p*-value | | Incidence per 100 person-years | | Hazard Ratio (95% CI) | *p*-value |
| | 5 mg Apixaban *n* = 15,364 | Warfarin *n* = 15,364 | | | | 5 mg Apixaban *n* = 5904 | 150 mg Dabigatran *n* = 5904 | | |
| Stroke/SE | 1.2 | 1.9 | 0.61 (0.46–0.81) | 0.001 | Stroke/SE | 1.3 | 1.3 | 0.92 (0.55–1.52) | 0.733 |
| MB | 4.0 | 6.3 | 0.57 (0.51–0.64) | <0.001 | MB | 3.0 | 3.7 | 0.77 (0.59–1.00) | 0.052 |
| | 150 mg Dabigatran *n* = 5756 | Warfarin *n* = 5756 | | | | 5 mg Apixaban *n* = 16,553 | 20 mg Rivaroxaban *n* = 16,553 | | |
| Stroke/SE | 1.3 | 1.2 | 1.04 (0.70–1.56) | 0.843 | Stroke/SE | 1.2 | 1.2 | 0.93 (0.74–1.17) | 0.524 |
| MB | 3.8 | 5.0 | 0.73 (0.56–0.96) | 0.024 | MB | 3.3 | 5.7 | 0.53 (0.47–0.60) | <0.001 |
| | 20 mg Rivaroxaban *n* = 17,123 | Warfarin *n* = 17,123 | | | | 150 mg Dabigatran *n* = 6169 | 20 mg Rivaroxaban *n* = 6169 | | |
| Stroke/SE | 1.2 | 1.6 | 0.75 (0.62–0.90) | 0.002 | Stroke/SE | 1.3 | 1.1 | 1.18 (0.85–1.65) | 0.322 |
| MB | 5.8 | 5.5 | 1.04 (0.92–1.17) | 0.550 | MB | 3.6 | 4.9 | 0.74 (0.61–0.89) | 0.002 |

CI: confidence interval; MB: major bleeding; NOAC: non-vitamin K oral anticoagulants; SE: systemic embolism.

Among all the patients with obesity in the pooled sample, 39.5% were identified as morbidly obese. PSM resulted in 6310 apixaban-warfarin, 2342 dabigatran-warfarin, 8055 rivaroxaban-warfarin, 2373 apixaban-dabigatran, 7180 apixaban-rivaroxaban, and 2617 dabigatran-rivaroxaban pairs of patients. There was no significant difference in the risk of stroke/SE between each NOAC versus warfarin or between NOACs. Apixaban had a lower risk of MB compared to warfarin, dabigatran, and rivaroxaban. Conversely, dabigatran and rivaroxaban were both associated with a similar risk of MB compared to warfarin in the population with morbid obesity (Table 3).

**Table 3.** Incidence rates and hazard ratios of NOACs vs. warfarin and NOACs vs. NOACs among patients with morbid obesity.

| NOACs vs. Warfarin | | | | | NOACs vs. NOACs | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Incidence per 100 person-years | | Hazard Ratio (95% CI) | *p*-value | | Incidence per 100 person-years | | Hazard Ratio (95% CI) | *p*-value |
| | Apixaban *n* = 6310 | Warfarin *n* = 6310 | | | | Apixaban *n* = 2373 | Dabigatran *n* = 2373 | | |
| Stroke/SE | 1.3 | 1.6 | 0.72 (0.48–1.08) | 0.113 | Stroke/SE | 0.7 | 1.3 | 0.51 (0.19–1.35) | 0.175 |
| MB | 4.6 | 7.8 | 0.53 (0.44–0.64) | <0.001 | MB | 3.9 | 5.6 | 0.63 (0.44–0.90) | 0.011 |
| | Dabigatran *n* = 2342 | Warfarin *n* = 2342 | | | | Apixaban *n* = 7180 | Rivaroxaban *n* = 7180 | | |
| Stroke/SE | 1.5 | 1.9 | 0.77 (0.47–1.27) | 0.304 | Stroke/SE | 1.3 | 1.3 | 0.93 (0.68–1.26) | 0.618 |
| MB | 5.7 | 7.4 | 0.76 (0.56–1.04) | 0.088 | MB | 4.0 | 7.9 | 0.47 (0.39–0.56) | <0.001 |
| | Rivaroxaban *n* = 8055 | Warfarin *n* = 8055 | | | | Dabigatran *n* = 2617 | Rivaroxaban *n* = 2617 | | |
| Stroke/SE | 1.3 | 1.8 | 0.72 (0.50–1.04) | 0.079 | Stroke/SE | 1.4 | 1.3 | 1.13 (0.68–1.89) | 0.629 |
| MB | 8.3 | 7.6 | 1.09 (0.92–1.28) | 0.317 | MB | 5.4 | 6.7 | 0.79 (0.61–1.03) | 0.086 |

CI: confidence interval; MB: major bleeding; NOAC: non-vitamin K oral anticoagulants; SE: systemic embolism.

## 4. Discussion

To date, this ARISTOPHANES obesity subgroup analysis is the largest retrospective observational study evaluating the risk of stroke/SE and MB among NVAF patients with obesity who initiated OAC treatment. Due to the increasing prevalence of obesity in the United States, the complexity of case management, and the limited data, we chose to examine the effectiveness and safety of NOACs within an NVAF sub-population with obesity [3,4]. With CMS Medicare and four large US national claims datasets, this study found that NOACs had a varying risk of stroke/SE and MB compared to warfarin and among each other in this population with obesity.

These results are largely consistent with subgroup analysis results from previous randomized controlled trials (RCT)s. Post-hoc obesity analyses from the ARISTOTLE trial demonstrated that BMI (18.5 to 25, 25 to 30, and ≥30) did not have significant interaction with treatment and stroke/SE, death, or MACE (composite of stroke/SE, myocardial infarction, and death) [13]. However, the BMI categories had a significant interaction with MB ($P_{interaction}$ = 0.006); for patients with a BMI ≥ 30, apixaban had a similar risk of MB to warfarin; for patients with normal and overweight BMIs, the risk of MB for apixaban was lower compared to that for warfarin. This trend was also seen in the other BMI categories with varying levels of magnitude. The reason for this is likely multifactorial—it is possible that differences in age and comorbidity levels may confound the risk of bleeding. Sub-analysis from the RE-LY trial examined the effect of dabigatran on the risk of stroke/SE by weight categories (<50 kg, 50–99 kg and ≥100 kg). The interaction of the weight of patients on dabigatran (110 mg and 150 mg) had no significant effect on the risk of stroke/SE ($p$ = 0.48 and $p$ = 0.42, respectively) [11]. Additionally, sub-analysis from the ROCKET-AF trial showed no significant interaction between the BMI categories and stroke/SE ($p$ = 0.537) and MB outcomes ($p$ = 0.310), comparing rivaroxaban and warfarin [12]. Therefore, based on weight or BMI, the referenced trials have demonstrated a similar efficacy and risk of safety outcomes between NOACs and warfarin in a population with obesity. Furthermore, in a meta-analysis of RCTs and observational studies among patients with obesity, NOACs showed a similar risk of stroke/SE (HR: 0.84, 95% CI: 0.70–1.03) and MB (HR: 1.03, 95% CI: 0.90–1.18) compared to warfarin [26].

Apart from RCTs, few real-world studies have compared the effectiveness and safety of OACs in an NVAF population with obesity. Additionally, very few studies have compared NOACs individually

rather than as a class. In the Dresden NOAC Registry, based in Germany, there was no indication that increased BMI was associated with a lack of NOAC effectiveness or safety [27]. Just as for obesity, very few studies have evaluated the effectiveness of NOACs in a population with morbid obesity. A retrospective cohort study of 64 patients with morbid obesity (BMI > 40) found that NOACs had a similar risk of ischemic stroke/transient ischemic attack and MB compared to warfarin [16]. In a recent real-world analysis, the electronic medical records from patients with morbid obesity (BMI > 40) at Montefiore Medical Center (NY, USA) suggested that apixaban had a similar risk of stroke and bleeding compared to warfarin [14]. Another study from the Montefiore Medical Center found that there was no significant difference in the incidence of stroke or major bleeding between apixaban, rivaroxaban, and warfarin patients [17]. A recent real-world analysis using US Truven MarketScan claims among NVAF patients with morbid obesity found that rivaroxaban showed a similar risk of stroke and MB compared to warfarin [15]. Our analysis on patients with morbid obesity found a similar risk of stroke/SE between NOACs and warfarin and suggested a lower risk of MB with apixaban vs. warfarin, apixaban vs. dabigatran, and apixaban vs. rivaroxaban.

Prior studies have not evaluated the effect of dose among patients with obesity. In our dose subgroup analysis, we found that standard dose apixaban and rivaroxaban were associated with a lower risk of stroke/SE compared to warfarin, and standard-dose apixaban and dabigatran were associated with a lower risk of MB compared to warfarin. In addition to this subgroup analysis, some real-world studies have evaluated the effectiveness of fixed-dose NOACs in patients with obesity [28]. While patients with obesity often require the dose adjustment of drugs due to altered pharmacokinetics, the current recommendations for NOAC therapy imply fixed-dose treatment. Furthermore, it has been found that while the plasma levels of NOACs varied by body weight, the variance was not significant [28]. Further studies are needed to evaluate the use of standard-dose NOACs among patients with obesity.

Compared to previous studies that evaluated the safety and effectiveness of NOACs among NVAF patients with obesity, the ARISTOPHANES pooled study provided a larger sample size with higher statistical power to compare outcomes for each OAC in the NVAF subgroup with obesity. The study findings showed that in this high-risk subgroup of NVAF patients, apixaban and rivaroxaban patients had a lower risk of stroke/SE compared to warfarin patients, and rivaroxaban had a similar risk of MB compared to warfarin. Compared with warfarin, apixaban and dabigatran were associated with a lower risk of MB, while dabigatran patients had a similar risk of stroke/SE. In addition, the study found that compared to dabigatran, apixaban had a non-significant difference for the risk of stroke/SE and had a lower risk of MB. Apixaban patients were also found to have a lower risk of stroke/SE and MB compared to rivaroxaban patients. Dabigatran was associated with a lower risk of MB and a similar risk of stroke/SE when compared to rivaroxaban. These results provide information complementary to the obesity post-hoc and sub-analyses from existing trials. While hypothesis-generating, this real-world evidence supports the fixed dose regimen of NOACs, which appears to maintain safety and effectiveness compared to traditional vitamin K antagonist therapy.

## 5. Limitations

This retrospective observational study has several limitations. First, only statistical associations could be concluded, not causal relationships. Although cohorts were matched through PSM, there were potential residual confounders. This limitation is especially important for interpreting the NOAC vs. NOAC comparison results, which are intended for hypothesis generation, given the lack of head-to-head trials. In addition, since the two drug cohorts were matched independently, conclusions can only be drawn between the matched cohorts, not across the comparisons. Second, due to the nature of the claims studies, outcome measures could only be based on ICD-9-CM codes without further adjustment with precise clinical criteria. More importantly, obesity indicators were ascertained based on ICD-9-CM coding (for ≥30 BMI or an indication of obesity). Body measurements such as weight or lean body mass were not available in the claims data. A separate analysis was conducted

to validate the diagnosis codes used to identify obesity and morbid obesity in this study by using one of the five databases linked with electronic medical records [29]. The results from that study showed the obesity diagnosis codes had high positive predictive value (PPV) (89.8%), high specificity (95.2%), and modest sensitivity (48.7%) among newly treated NVAF patients. The morbid obesity diagnosis codes also had high specificity (96.5%) but modest PPV (67.9%) and sensitivity (62.8%) [29]. The modest sensitivity suggests that we may fail to identify some of the patients with obesity and morbid obesity. The moderate PPV for the morbid obesity diagnosis codes indicates that there may be some misclassified patients in this group.

An additional study limitation is that laboratory values—such as international normalized ratio (INR) measurements—are not available in the dataset, so the time in the therapeutic range for the patients prescribed warfarin was indeterminable. Nonetheless, the inclusion of patients with potentially poorer quality control of warfarin therapy in everyday clinical practice may enable the study findings to better reflect real-world situations. Additionally, unobserved heterogeneity may exist across the five data sources. Finally, the results may not reflect 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.

## 6. Conclusions

This study, the largest observational study of NVAF patients with obesity, shows that NOACs were associated with a varying risk of stroke/SE and MB compared to warfarin and among each other. Apixaban was associated with a lower risk of stroke/SE and MB compared to warfarin. Additionally, compared with warfarin, dabigatran was associated with a lower risk of MB and a similar risk of stroke/SE; rivaroxaban was associated with a lower risk of stroke/SE and a similar risk of MB. Additional real-world studies are warranted in the population with obesity to understand the impact of NOACs on this high-risk group. These findings may help clinicians better understand the differentiated profile of OACs in an NVAF patient population with obesity.

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## Appendix A

**Table A1.** ICD-9-CM diagnosis and procedure codes for selection criteria and outcomes.

| Diagnosis | ICD-9-CM Diagnosis and Procedure Codes |
|---|---|
| **Selection Criteria** | |
| Atrial Fibrillation | 427.31 |
| Valvular Heart Disease | 394.0, 394.1, 394.2, 394.9, 396.0, 396.1, 396.8, 396.9, 424.0, 745.xx |
| Heart Valve Replacement | V42.2, V43.3, 35.05–35.09, 35.20–35.28, 35.97 |
| VTE | 451–453, 671.3, 671.4, 671.9, 415.1, 673.2, 673.8 |
| Transient AF (Heart Valve Replacement/Transplant, Pericarditis, Thyrotoxicity) | Pericarditis: 006.8, 017.9, 036.41, 074.21, 093.81, 098.83, 115.93, 390, 391, 392.0, 393, 411.0, 420.90, 420.91, 420.99, 423.0, 423.1, 423.2, 423.8, 423.9 |
| | Thyrotoxicity: 242.0, 242.1, 242.2, 242.3, 242.4, 242.8, 242.9 |
| Pregnancy | ICD-9-CM: 630–679, V22, V23, V24, V27, V28, V61.6, V61.7, 792.3, 796.5, 72–75.99 |
| | HCPCS: 59000–59350, 76801–76828, 83661–83664 |
| Obesity | 278.00 (obesity, unspecified), 278.01 (morbid obesity), 278.03 (obesity hypoventilation syndrome), V85.3 (BMI of 30–39), V85.4 (BMI 40 and over) |
| Morbid Obesity | 278.01 (morbid obesity), V85.4 (BMI 40 and over) |
| **Outcomes** | |
| Hemorrhagic Stroke | 430.xx–432.xx |
| | Cases were excluded if traumatic brain injury (ICD-9-CM: 800–804, 850–854) was present during hospitalization. |
| Ischemic Stroke | 433.x1, 434.x1, 436 |
| Systemic Embolism | 444.x, 445.x |
| Major Gastrointestinal Bleeding | 456.0, 456.20, 530.82, 531.0x, 531.2x, 531.4x, 531.6x, 532.0x, 532.2x, 532.4x, 532.6x, 533.0x, 533.2x, 533.4x, 533.6x, 534.0x, 534.2x, 534.4x, 534.6x, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 537.83, 562.02, 562.03, 562.12, 562.13, 568.81, 569.3, 569.85, 578.x |
| | Procedure code: 44.43 |
| Major Intracranial Hemorrhage | 430, 431, 432.0, 432.1, 432.9, 852.0x, 852.2x, 852.4x, 853.0x, |
| Major Other Hemorrhage | 285.1, 360.43, 362.43, 362.81, 363.61, 363.62, 363.72, 364.41, 372.72, 374.81, 376.32, 377.42, 379.23, 423.0x, 596.7x, 599.7x, 602.1x, 620.1, 621.4, 626.2, 626.5, 626.7, 626.8, 626.9, 719.1x, 782.7, 784.7, 784.8, 786.3x, 958.2, 997.02, 998.11 |
| | Procedure code: 99.04 |

AF: atrial fibrillation; BMI: body mass index; HCPCS: Healthcare Common Procedural Coding System; ICD-9: International Classifications of Diseases, Ninth Edition; VTE: venous thromboembolism.

**Table A2.** Baseline characteristics of NVAF patients with obesity before PSM.

| | Warfarin Cohort | | Apixaban Cohort | | Dabigatran Cohort | | Rivaroxaban Cohort | |
|---|---|---|---|---|---|---|---|---|
| | *n*/Mean | %/SD | *n*/Mean | %/SD | *n*/Mean | %/SD | *n*/Mean | %/SD |
| Sample Size | 30,902 | | 21,242 | | 7171 | | 29,146 | |
| Age | 72.8 | 8.8 | 71.5 | 9.9 | 69.6 | 10.0 | 70.0 | 10.3 |
| 18–54 | 1038 | 3.4% | 1285 | 6.0% | 606 | 8.5% | 2346 | 8.0% |
| 55–64 | 2895 | 9.4% | 2793 | 13.1% | 1112 | 15.5% | 4636 | 15.9% |
| 65–74 | 14,044 | 45.4% | 8977 | 42.3% | 3215 | 44.8% | 12,486 | 42.8% |
| ≥75 | 12,925 | 41.8% | 8187 | 38.5% | 2238 | 31.2% | 9678 | 33.2% |
| Gender | | | | | | | | |
| Male | 15,974 | 51.7% | 11,027 | 51.9% | 4033 | 56.2% | 15,647 | 53.7% |
| Female | 14,928 | 48.3% | 10,215 | 48.1% | 3138 | 43.8% | 13,499 | 46.3% |
| U.S. Geographic Region | | | | | | | | |
| Northeast | 5330 | 17.2% | 3405 | 16.0% | 1367 | 19.1% | 4944 | 17.0% |
| Midwest | 9934 | 32.1% | 4980 | 23.4% | 1701 | 23.7% | 7372 | 25.3% |
| South | 10,693 | 34.6% | 10,103 | 47.6% | 3017 | 42.1% | 12,705 | 43.6% |
| West | 4857 | 15.7% | 2676 | 12.6% | 1052 | 14.7% | 3988 | 13.7% |
| Other | 88 | 0.3% | 78 | 0.4% | 34 | 0.5% | 137 | 0.5% |
| Race (only for Humana and Medicare) | | | | | | | | |
| White | 21,856 | 88.2% | 14,231 | 89.1% | 4376 | 88.0% | 18,059 | 88.5% |
| Black | 1917 | 7.7% | 1031 | 6.5% | 328 | 6.6% | 1277 | 6.3% |
| Other | 1004 | 4.1% | 711 | 4.5% | 270 | 5.4% | 1075 | 5.3% |
| Baseline Comorbidity | | | | | | | | |
| Deyo–Charlson Comorbidity Index | 4.5 | 3.1 | 3.7 | 2.9 | 3.3 | 2.8 | 3.4 | 2.8 |
| $CHADS_2$ Score | 2.8 | 1.3 | 2.5 | 1.3 | 2.4 | 1.3 | 2.4 | 1.3 |
| 0 | 567 | 1.8% | 594 | 2.8% | 262 | 3.7% | 1031 | 3.5% |
| 1 | 3942 | 12.8% | 4185 | 19.7% | 1572 | 21.9% | 6374 | 21.9% |
| 2 | 8708 | 28.2% | 6475 | 30.5% | 2354 | 32.8% | 9320 | 32.0% |
| 3+ | 17,685 | 57.2% | 9988 | 47.0% | 2983 | 41.6% | 12,421 | 42.6% |
| $CHA_2DS_2$-VASc Score | 4.3 | 1.6 | 3.9 | 1.7 | 3.7 | 1.7 | 3.7 | 1.7 |
| 0 | 254 | 0.8% | 349 | 1.6% | 169 | 2.4% | 646 | 2.2% |
| 1 | 796 | 2.6% | 1045 | 4.9% | 506 | 7.1% | 1936 | 6.6% |
| 2 | 2669 | 8.6% | 2842 | 13.4% | 1112 | 15.5% | 4466 | 15.3% |
| 3 | 5836 | 18.9% | 4464 | 21.0% | 1610 | 22.5% | 6305 | 21.6% |
| 4+ | 21,347 | 69.1% | 12,542 | 59.0% | 3774 | 52.6% | 15,793 | 54.2% |
| HAS-BLED Score | 3.5 | 1.4 | 3.2 | 1.4 | 3.0 | 1.4 | 3.1 | 1.4 |
| 0 | 246 | 0.8% | 281 | 1.3% | 133 | 1.9% | 553 | 1.9% |
| 1 | 1501 | 4.9% | 1728 | 8.1% | 787 | 11.0% | 2993 | 10.3% |
| 2 | 5661 | 18.3% | 4657 | 21.9% | 1793 | 25.0% | 6992 | 24.0% |
| 3+ | 23,494 | 76.0% | 14,576 | 68.6% | 4458 | 62.2% | 18,608 | 63.8% |
| Bleeding History | 8496 | 27.5% | 4425 | 20.8% | 1329 | 18.5% | 5822 | 20.0% |
| Congestive Heart Failure | 14,722 | 47.6% | 8068 | 38.0% | 2487 | 34.7% | 10,246 | 35.2% |
| Diabetes Mellitus | 18,984 | 61.4% | 11,390 | 53.6% | 3778 | 52.7% | 15,164 | 52.0% |
| Hypertension | 29,379 | 95.1% | 20,022 | 94.3% | 6670 | 93.0% | 27,161 | 93.2% |
| Renal Disease | 12,934 | 41.9% | 6445 | 30.3% | 1720 | 24.0% | 7489 | 25.7% |
| Liver Disease | 2382 | 7.7% | 1471 | 6.9% | 472 | 6.6% | 2051 | 7.0% |
| Myocardial Infarction | 4905 | 15.9% | 2528 | 11.9% | 722 | 10.1% | 3235 | 11.1% |

**Table A2.** *Cont.*

| | Warfarin Cohort | | Apixaban Cohort | | Dabigatran Cohort | | Rivaroxaban Cohort | |
|---|---|---|---|---|---|---|---|---|
| | ***n*/Mean** | **%/SD** | ***n*/Mean** | **%/SD** | ***n*/Mean** | **%/SD** | ***n*/Mean** | **%/SD** |
| Dyspepsia or Stomach Discomfort | 7974 | 25.8% | 5014 | 23.6% | 1555 | 21.7% | 6711 | 23.0% |
| Non-Stroke/SE Peripheral Vascular Disease | 19,062 | 61.7% | 11,847 | 55.8% | 3745 | 52.2% | 15,274 | 52.4% |
| Stroke/SE | 4669 | 15.1% | 2307 | 10.9% | 723 | 10.1% | 2937 | 10.1% |
| Transient Ischemic Attack | 2295 | 7.4% | 1397 | 6.6% | 445 | 6.2% | 1787 | 6.1% |
| Anemia and Coagulation Defects | 12,178 | 39.4% | 6478 | 30.5% | 1845 | 25.7% | 7949 | 27.3% |
| Alcoholism | 788 | 2.5% | 517 | 2.4% | 203 | 2.8% | 874 | 3.0% |
| Peripheral Artery Disease | 8357 | 27.0% | 4563 | 21.5% | 1339 | 18.7% | 6000 | 20.6% |
| Coronary Artery Disease | 16,865 | 54.6% | 10,616 | 50.0% | 3315 | 46.2% | 13,513 | 46.4% |
| Dyslipidemia | 25,528 | 82.6% | 17,510 | 82.4% | 5775 | 80.5% | 23,533 | 80.7% |
| Morbid Obesity | 12,779 | 41.4% | 7962 | 37.5% | 2752 | 38.4% | 11,447 | 39.3% |
| Baseline Medication Use | | | | | | | | |
| ACEi/ARB | 21,240 | 68.7% | 14,912 | 70.2% | 4964 | 69.2% | 20,093 | 68.9% |
| Amiodarone | 4143 | 13.4% | 2839 | 13.4% | 859 | 12.0% | 3576 | 12.3% |
| Beta Blockers | 19,252 | 62.3% | 13,486 | 63.5% | 4347 | 60.6% | 18,192 | 62.4% |
| H2-Receptor Antagonist | 2663 | 8.6% | 1569 | 7.4% | 485 | 6.8% | 2081 | 7.1% |
| Proton Pump Inhibitor | 10,973 | 35.5% | 7530 | 35.4% | 2354 | 32.8% | 9922 | 34.0% |
| Statins | 20,288 | 65.7% | 13,579 | 63.9% | 4324 | 60.3% | 17,928 | 61.5% |
| Anti-Platelets | 6869 | 22.2% | 4597 | 21.6% | 1244 | 17.3% | 5488 | 18.8% |
| NSAIDS | 8019 | 25.9% | 6379 | 30.0% | 2194 | 30.6% | 9165 | 31.4% |
| Dose of the Index Prescription | | | | | | | | |
| Standard Dose [1] | | | 18,290 | 86.1% | 6254 | 87.2% | 22,908 | 78.6% |
| Lower Dose [2] | | | 2952 | 13.9% | 917 | 12.8% | 6238 | 21.4% |
| Follow-up Time (in Days) | 232.4 | 211.1 | 175.6 | 159.1 | 220.5 | 217.9 | 217.9 | 206.4 |
| Median | 154 | | 120 | | 126 | | 139 | |

ACEi/ARB: angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers; $CHA_2DS_2$-VASc: congestive heart failure, hypertension, aged ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, aged 65–74 years, sex category; HAS-BLED: hypertension, abnormal renal and liver function, stroke, bleeding, labile international normalized ratios, elderly, drugs and alcohol; NSAIDs: non-steroidal anti-inflammatory drugs; NVAF: nonvalvular atrial fibrillation; PSM: propensity score matching; SD: standard deviation; SE: systemic embolism. [1] Standard dose: 5 mg apixaban, 150 mg dabigatran, 20 mg rivaroxaban. [2] Lower dose: 2.5 mg apixaban, 75 mg dabigatran, 10 or 15 mg rivaroxaban; 1311 patients were prescribed 10 mg of rivaroxaban in the rivaroxaban cohort.

**Table A3.** Outcomes characteristics of NVAF patients before PSM.

| | Warfarin Cohort | | Apixaban Cohort | | Dabigatran Cohort | | Rivaroxaban Cohort | |
|---|---|---|---|---|---|---|---|---|
| | ***n*/Mean** | **%/SD** | ***n*/Mean** | **%/SD** | ***n*/Mean** | **%/SD** | ***n*/Mean** | **%/SD** |
| Sample Size | 30,902 | | 21,242 | | 7171 | | 29,146 | |
| Discontinuation | 17,553 | 56.8% | 8035 | 37.8% | 4100 | 57.2% | 14,575 | 50.0% |
| Time-to-Discontinuation | 165.3 | 163.8 | 114.9 | 117.0 | 141.4 | 152.7 | 143.6 | 153.1 |
| Switch | | | 787 | 3.7% | 748 | 10.4% | 1972 | 6.8% |
| Time-to-Switch | | | 94.8 | 103.0 | 116.2 | 136.2 | 122.7 | 142.4 |
| Stroke/SE [1] | 406 | 1.3% | 132 | 0.6% | 67 | 0.9% | 226 | 0.8% |
| Hemorrhagic Stroke | 115 | 0.4% | 23 | 0.1% | | | 41 | 0.1% |
| Ischemic Stroke | 276 | 0.9% | 107 | 0.5% | 56 | 0.8% | 170 | 0.6% |
| Systemic Embolism | 20 | 0.1% | | | | | 17 | 0.1% |
| Major Bleeding | 1491 | 4.8% | 399 | 1.9% | 174 | 2.4% | 1050 | 3.6% |
| Gastrointestinal Bleeding | 721 | 2.3% | 195 | 0.9% | 110 | 1.5% | 612 | 2.1% |
| Intracranial Hemorrhage | 190 | 0.6% | 38 | 0.2% | 17 | 0.2% | 67 | 0.2% |
| Other Sites | 676 | 2.2% | 187 | 0.9% | 55 | 0.8% | 447 | 1.5% |
| Stroke/SE Incidence Rate (per 100 person-years) | 2.0 | | 1.3 | | 1.5 | | 1.3 | |
| Major Bleeding Incidence Rate (per 100 person-years) | 7.6 | | 3.9 | | 4.0 | | 6.0 | |

NVAF: nonvalvular atrial fibrillation; PSM: propensity score matching; SD: standard deviation; SE: systemic embolism. [1] For some cohorts, the number of patients with a stroke event is <11, which cannot be presented per the data use agreement.

**Table A4.** Baseline characteristics among NVAF patients with obesity after propensity score matching—NOACs vs. warfarin.

| | Warfarin Cohort | | Apixaban Cohort | | | Warfarin Cohort | | Dabigatran Cohort | | | Warfarin Cohort | | Rivaroxaban Cohort | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *n*/Mean | %/SD | *n*/Mean | %/SD | STD [1] | *n*/Mean | %/SD | *n*/Mean | %/SD | STD [1] | *n*/Mean | %/SD | *n*/Mean | %/SD | STD [1] |
| Sample Size | 18,181 | | 18,181 | | | 6646 | | 6646 | | | 22,053 | | 22,053 | | |
| Age [2] | 72.7 | 8.8 | 72.8 | 9.0 | 1.52 | 70.9 | 9.3 | 70.7 | 9.1 | 1.51 | 72.3 | 8.9 | 72.3 | 8.8 | 0.21 |
| 18–54 | 655 | 3.6% | 659 | 3.6% | 0.12 | 370 | 5.6% | 391 | 5.9% | 1.36 | 865 | 3.9% | 828 | 3.8% | 0.87 |
| 55–64 | 1746 | 9.6% | 1709 | 9.4% | 0.69 | 901 | 13.6% | 879 | 13.2% | 0.97 | 2197 | 10.0% | 2210 | 10.0% | 0.20 |
| 65–74 | 8192 | 45.1% | 8184 | 45.0% | 0.09 | 3120 | 46.9% | 3147 | 47.4% | 0.81 | 10,347 | 46.9% | 10,360 | 47.0% | 0.12 |
| ≥75 | 7588 | 41.7% | 7629 | 42.0% | 0.46 | 2255 | 33.9% | 2229 | 33.5% | 0.83 | 8644 | 39.2% | 8655 | 39.2% | 0.10 |
| Gender [2] | | | | | | | | | | | | | | | |
| Male | 9268 | 51.0% | 9260 | 50.9% | 0.09 | 3633 | 54.7% | 3632 | 54.6% | 0.03 | 11,372 | 51.6% | 11,313 | 51.3% | 0.54 |
| Female | 8913 | 49.0% | 8921 | 49.1% | 0.09 | 3013 | 45.3% | 3014 | 45.4% | 0.03 | 10,681 | 48.4% | 10,740 | 48.7% | 0.54 |
| U.S. Geographic Region [2] | | | | | | | | | | | | | | | |
| Northeast | 3132 | 17.2% | 3137 | 17.3% | 0.07 | 1264 | 19.0% | 1244 | 18.7% | 0.77 | 3776 | 17.1% | 3828 | 17.4% | 0.62 |
| Midwest | 4588 | 25.2% | 4608 | 25.3% | 0.25 | 1640 | 24.7% | 1624 | 24.4% | 0.56 | 6275 | 28.5% | 6174 | 28.0% | 1.02 |
| South | 7908 | 43.5% | 7834 | 43.1% | 0.82 | 2643 | 39.8% | 2724 | 41.0% | 2.48 | 8560 | 38.8% | 8624 | 39.1% | 0.60 |
| West | 2501 | 13.8% | 2553 | 14.0% | 0.83 | 1073 | 16.1% | 1024 | 15.4% | 2.02 | 3377 | 15.3% | 3365 | 15.3% | 0.15 |
| Other | 52 | 0.3% | 49 | 0.3% | 0.31 | 26 | 0.4% | 30 | 0.5% | 0.93 | 65 | 0.3% | 62 | 0.3% | 0.25 |
| Race (Only for Humana and Medicare) [2] | | | | | | | | | | | | | | | |
| White | 13,165 | 89.0% | 13,190 | 89.2% | 0.54 | 4367 | 88.8% | 4338 | 88.2% | 1.85 | 15,805 | 88.9% | 15,796 | 88.9% | 0.16 |
| Black | 1010 | 6.8% | 981 | 6.6% | 0.78 | 298 | 6.1% | 324 | 6.6% | 2.17 | 1158 | 6.5% | 1178 | 6.6% | 0.45 |
| Other | 619 | 4.2% | 623 | 4.2% | 0.13 | 251 | 5.1% | 254 | 5.2% | 0.28 | 812 | 4.6% | 801 | 4.5% | 0.30 |
| Baseline Comorbidity | | | | | | | | | | | | | | | |
| Deyo–Charlson Comorbidity Index [2] | 4.0 | 2.9 | 3.9 | 2.9 | 0.92 | 3.5 | 2.9 | 3.5 | 2.8 | 3.05 | 3.9 | 2.9 | 3.9 | 2.9 | 0.27 |
| $CHA_2DS_2$-VASc Score | 4.2 | 1.6 | 4.1 | 1.6 | 0.61 | 3.9 | 1.6 | 3.8 | 1.7 | 1.99 | 4.1 | 1.6 | 4.1 | 1.6 | 0.12 |
| 0 | 198 | 1.1% | 165 | 0.9% | 1.83 | 96 | 1.4% | 107 | 1.6% | 1.35 | 229 | 1.0% | 222 | 1.0% | 0.32 |
| 1 | 544 | 3.0% | 565 | 3.1% | 0.67 | 313 | 4.7% | 324 | 4.9% | 0.77 | 731 | 3.3% | 751 | 3.4% | 0.50 |
| 2 | 1848 | 10.2% | 2029 | 11.2% | 3.23 | 880 | 13.2% | 951 | 14.3% | 3.10 | 2306 | 10.5% | 2540 | 11.5% | 3.39 |
| 3 | 3729 | 20.5% | 3718 | 20.4% | 0.15 | 1559 | 23.5% | 1534 | 23.1% | 0.89 | 4775 | 21.7% | 4596 | 20.8% | 1.98 |
| 4+ | 11,862 | 65.2% | 11,704 | 64.4% | 1.82 | 3798 | 57.1% | 3730 | 56.1% | 2.06 | 14,012 | 63.5% | 13,944 | 63.2% | 0.64 |
| HAS-BLED Score [3] | 3.4 | 1.3 | 3.4 | 1.3 | 0.54 | 3.1 | 1.3 | 3.1 | 1.3 | 1.47 | 3.3 | 1.3 | 3.3 | 1.3 | 0.39 |

**Table A4.** *Cont.*

| | Warfarin Cohort | | Apixaban Cohort | | | Warfarin Cohort | | Dabigatran Cohort | | | Warfarin Cohort | | Rivaroxaban Cohort | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *n*/Mean | %/SD | *n*/Mean | %/SD | STD [1] | *n*/Mean | %/SD | *n*/Mean | %/SD | STD [1] | *n*/Mean | %/SD | *n*/Mean | %/SD | STD [1] |
| 0 | 184 | 1.0% | 144 | 0.8% | 2.33 | 96 | 1.4% | 93 | 1.4% | 0.38 | 224 | 1.0% | 198 | 0.9% | 1.21 |
| 1 | 991 | 5.5% | 1063 | 5.8% | 1.72 | 567 | 8.5% | 565 | 8.5% | 0.11 | 1289 | 5.8% | 1402 | 6.4% | 2.14 |
| 2 | 3799 | 20.9% | 3696 | 20.3% | 1.40 | 1585 | 23.8% | 1631 | 24.5% | 1.62 | 4851 | 22.0% | 4738 | 21.5% | 1.24 |
| 3+ | 13,207 | 72.6% | 13,278 | 73.0% | 0.88 | 4398 | 66.2% | 4357 | 65.6% | 1.30 | 15,689 | 71.1% | 15,715 | 71.3% | 0.26 |
| Bleeding History [2] | 4171 | 22.9% | 4127 | 22.7% | 0.58 | 1346 | 20.3% | 1294 | 19.5% | 1.96 | 5015 | 22.7% | 5046 | 22.9% | 0.33 |
| Congestive Heart Failure [2] | 7553 | 41.5% | 7485 | 41.2% | 0.76 | 2436 | 36.7% | 2424 | 36.5% | 0.37 | 8926 | 40.5% | 8877 | 40.3% | 0.45 |
| Diabetes Mellitus [2] | 10,265 | 56.5% | 10,297 | 56.6% | 0.36 | 3716 | 55.9% | 3611 | 54.3% | 3.18 | 12,438 | 56.4% | 12,435 | 56.4% | 0.03 |
| Hypertension [2] | 17,276 | 95.0% | 17,273 | 95.0% | 0.08 | 6235 | 93.8% | 6223 | 93.6% | 0.74 | 20,842 | 94.5% | 20,833 | 94.5% | 0.18 |
| Renal Disease [2] | 6173 | 34.0% | 6166 | 33.9% | 0.08 | 1758 | 26.5% | 1697 | 25.5% | 2.09 | 6893 | 31.3% | 6891 | 31.2% | 0.02 |
| Liver Disease [2] | 1280 | 7.0% | 1271 | 7.0% | 0.19 | 472 | 7.1% | 453 | 6.8% | 1.12 | 1601 | 7.3% | 1620 | 7.3% | 0.33 |
| Myocardial Infarction [2] | 2369 | 13.0% | 2343 | 12.9% | 0.43 | 700 | 10.5% | 711 | 10.7% | 0.54 | 2771 | 12.6% | 2794 | 12.7% | 0.31 |
| Dyspepsia or Stomach Discomfort [2] | 4502 | 24.8% | 4430 | 24.4% | 0.92 | 1486 | 22.4% | 1488 | 22.4% | 0.07 | 5375 | 24.4% | 5390 | 24.4% | 0.16 |
| Non-Stroke/SE Peripheral Vascular Disease [2] | 10,753 | 59.1% | 10,676 | 58.7% | 0.86 | 3639 | 54.8% | 3624 | 54.5% | 0.45 | 12,750 | 57.8% | 12,759 | 57.9% | 0.08 |
| Stroke/SE [2] | 2273 | 12.5% | 2183 | 12.0% | 1.51 | 739 | 11.1% | 710 | 10.7% | 1.40 | 2699 | 12.2% | 2639 | 12.0% | 0.83 |
| Transient Ischemic Attack [2] | 1278 | 7.0% | 1257 | 6.9% | 0.45 | 456 | 6.9% | 432 | 6.5% | 1.45 | 1511 | 6.9% | 1510 | 6.8% | 0.02 |
| Anemia and Coagulation Defects [2] | 6164 | 33.9% | 6082 | 33.5% | 0.95 | 1874 | 28.2% | 1814 | 27.3% | 2.02 | 7167 | 32.5% | 7105 | 32.2% | 0.60 |
| Alcoholism [2] | 428 | 2.4% | 429 | 2.4% | 0.04 | 192 | 2.9% | 182 | 2.7% | 0.91 | 621 | 2.8% | 620 | 2.8% | 0.03 |
| Peripheral Artery Disease | 4513 | 24.8% | 4228 | 23.3% | 3.67 | 1464 | 22.0% | 1319 | 19.8% | 5.36 | 5287 | 24.0% | 5282 | 24.0% | 0.05 |
| Coronary Artery Disease | 9491 | 52.2% | 9544 | 52.5% | 0.58 | 3168 | 47.7% | 3197 | 48.1% | 0.87 | 11,153 | 50.6% | 11,261 | 51.1% | 0.98 |
| Dyslipidemia [2] | 15,199 | 83.6% | 15,191 | 83.6% | 0.12 | 5419 | 81.5% | 5402 | 81.3% | 0.66 | 18,168 | 82.4% | 18,237 | 82.7% | 0.82 |
| Morbid Obesity | 7207 | 39.6% | 6777 | 37.3% | 4.86 | 2619 | 39.4% | 2523 | 38.0% | 2.97 | 8782 | 39.8% | 8660 | 39.3% | 1.13 |
| Baseline Medication Use [2] | | | | | | | | | | | | | | | |
| ACEi/ARB | 12,771 | 70.2% | 12,788 | 70.3% | 0.20 | 4615 | 69.4% | 4651 | 70.0% | 1.18 | 15,371 | 69.7% | 15,345 | 69.6% | 0.26 |
| Amiodarone | 2429 | 13.4% | 2446 | 13.5% | 0.27 | 810 | 12.2% | 810 | 12.2% | 0.00 | 2793 | 12.7% | 2816 | 12.8% | 0.31 |
| Beta Blockers | 11,442 | 62.9% | 11,562 | 63.6% | 1.37 | 4051 | 61.0% | 4025 | 60.6% | 0.80 | 13,732 | 62.3% | 13,778 | 62.5% | 0.43 |
| H2-Receptor Antagonist | 1438 | 7.9% | 1419 | 7.8% | 0.39 | 500 | 7.5% | 464 | 7.0% | 2.09 | 1735 | 7.9% | 1760 | 8.0% | 0.42 |
| Proton Pump Inhibitor | 6477 | 35.6% | 6510 | 35.8% | 0.38 | 2259 | 34.0% | 2229 | 33.5% | 0.95 | 7725 | 35.0% | 7755 | 35.2% | 0.29 |
| Statins | 11,915 | 65.5% | 11,913 | 65.5% | 0.02 | 4213 | 63.4% | 4111 | 61.9% | 3.17 | 14,141 | 64.1% | 14,210 | 64.4% | 0.65 |
| Anti-Platelets | 4070 | 22.4% | 4066 | 22.4% | 0.05 | 1195 | 18.0% | 1215 | 18.3% | 0.78 | 4606 | 20.9% | 4585 | 20.8% | 0.23 |
| NSAIDS | 5211 | 28.7% | 5255 | 28.9% | 0.53 | 2025 | 30.5% | 2016 | 30.3% | 0.29 | 6384 | 28.9% | 6408 | 29.1% | 0.24 |

**Table A4.** *Cont.*

| | Warfarin Cohort | | Apixaban Cohort | | | Warfarin Cohort | | Dabigatran Cohort | | | Warfarin Cohort | | Rivaroxaban Cohort | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *n*/Mean | %/SD | *n*/Mean | %/SD | STD [1] | *n*/Mean | %/SD | *n*/Mean | %/SD | STD [1] | *n*/Mean | %/SD | *n*/Mean | %/SD | STD [1] |
| Dose of the Index Prescription | | | | | | | | | | | | | | | |
| Standard Dose [4] | | | 15,410 | 84.8% | | | | 5747 | 86.5% | | | | 16,599 | 75.3% | |
| Low Dose [5] | | | 2771 | 15.2% | | | | 899 | 13.5% | | | | 5454 | 24.7% | |
| Follow-Up Time (in Days) | 236.3 | 213.8 | 176.2 | 160.2 | 31.85 | 236.8 | 211.3 | 222.5 | 219.7 | 6.60 | 237.7 | 213.5 | 221.0 | 208.6 | 7.92 |
| Median | 157 | | 120 | | | 159 | | 128 | | | 159 | | 142 | | |

ACEi/ARB: angiotensin converting enzyme inhibitors/angiotensin-receptor blockers; $CHA_2D_{S2}$-VASc: congestive heart failure, hypertension, aged ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, aged 65–74 years, sex category; HAS-BLED: hypertension, abnormal renal and liver function, stroke, bleeding, labile international normalized ratios, elderly, drugs and alcohol; NOACs: non-vitamin K oral anticoagulants; NSAIDs: non-steroidal anti-inflammatory drugs; NVAF: non-valvular atrial fibrillation; SD: standard deviation; SE: systemic embolism; STD: standardized difference. [1] Std difference = 100 ×|actual std diff|. Std difference greater than 10 is considered significant. [2] Variables used in propensity score matching. [3] As the INR value is not available in the databases, a modified HAS-BLED score was calculated with a range of 0 to 8. [4] Standard dose: 5 mg apixaban, 150 mg dabigatran, 20 mg rivaroxaban. [5] Lower dose: 2.5 mg apixaban, 75 mg dabigatran, 10 or 15 mg rivaroxaban; 1053 patients treated with rivaroxaban were prescribed 10 mg rivaroxaban.

**Table A5.** Baseline characteristics among NVAF patients with obesity after propensity score matching among NOACs vs. NOACs.

| | Apixaban Cohort | | Dabigatran Cohort | | | Apixaban Cohort | | Rivaroxaban Cohort | | | Dabigatran Cohort | | Rivaroxaban Cohort | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *n*/Mean | %/SD | *n*/Mean | %/SD | STD [1] | *n*/Mean | %/SD | *n*/Mean | %/SD | STD [1] | *n*/Mean | %/SD | *n*/Mean | %/SD | STD [1] |
| Sample Size | 6884 | | 6884 | | | 20,431 | | 20,431 | | | 7103 | | 7103 | | |
| Age [2] | 70.5 | 10.0 | 70.0 | 9.8 | 4.23 | 71.5 | 9.8 | 71.5 | 9.7 | 0.85 | 69.7 | 10.0 | 69.5 | 9.9 | 1.40 |
| 18–54 | 510 | 7.4% | 521 | 7.6% | 0.61 | 1200 | 5.9% | 1215 | 5.9% | 0.31 | 590 | 8.3% | 581 | 8.2% | 0.46 |
| 55–64 | 980 | 14.2% | 988 | 14.4% | 0.33 | 2586 | 12.7% | 2599 | 12.7% | 0.19 | 1102 | 15.5% | 1102 | 15.5% | 0.00 |
| 65–74 | 3069 | 44.6% | 3159 | 45.9% | 2.63 | 8828 | 43.2% | 8689 | 42.5% | 1.37 | 3193 | 45.0% | 3366 | 47.4% | 4.89 |
| ≥75 | 2325 | 33.8% | 2216 | 32.2% | 3.37 | 7817 | 38.3% | 7928 | 38.8% | 1.12 | 2218 | 31.2% | 2054 | 28.9% | 5.04 |
| Gender [2] | | | | | | | | | | | | | | | |
| Male | 3776 | 54.9% | 3810 | 55.3% | 0.99 | 10,596 | 51.9% | 10,614 | 52.0% | 0.18 | 3982 | 56.1% | 4171 | 58.7% | 5.38 |
| Female | 3108 | 45.1% | 3074 | 44.7% | 0.99 | 9835 | 48.1% | 9817 | 48.0% | 0.18 | 3121 | 43.9% | 2932 | 41.3% | 5.38 |
| U.S. Geographic Region [2] | | | | | | | | | | | | | | | |
| Northeast | 1256 | 18.2% | 1255 | 18.2% | 0.04 | 3339 | 16.3% | 3356 | 16.4% | 0.22 | 1345 | 18.9% | 1445 | 20.3% | 3.54 |
| Midwest | 1624 | 23.6% | 1640 | 23.8% | 0.55 | 4850 | 23.7% | 4861 | 23.8% | 0.13 | 1688 | 23.8% | 1613 | 22.7% | 2.50 |
| South | 2966 | 43.1% | 2962 | 43.0% | 0.12 | 9563 | 46.8% | 9580 | 46.9% | 0.17 | 2999 | 42.2% | 2920 | 41.1% | 2.26 |

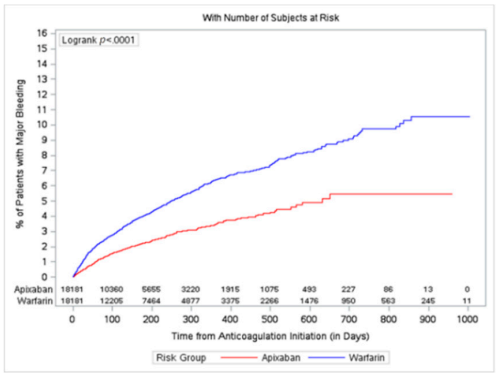
**Table A5.** *Cont.*

| | Apixaban Cohort | | Dabigatran Cohort | | | Apixaban Cohort | | Rivaroxaban Cohort | | | Dabigatran Cohort | | Rivaroxaban Cohort | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *n*/Mean | %/SD | *n*/Mean | %/SD | STD [1] | *n*/Mean | %/SD | *n*/Mean | %/SD | STD [1] | *n*/Mean | %/SD | *n*/Mean | %/SD | STD [1] |
| West | 1008 | 14.6% | 1000 | 14.5% | 0.33 | 2606 | 12.8% | 2561 | 12.5% | 0.66 | 1038 | 14.6% | 1098 | 15.5% | 2.36 |
| Other | 30 | 0.4% | 27 | 0.4% | 0.68 | 73 | 0.4% | 73 | 0.4% | 0.00 | 33 | 0.5% | 27 | 0.4% | 1.30 |
| Race (Only for Humana and Medicare) [2] | | | | | | | | | | | | | | | |
| White | 4361 | 88.2% | 4358 | 88.1% | 0.19 | 13,910 | 89.2% | 13,926 | 89.3% | 0.33 | 4368 | 88.1% | 4374 | 88.2% | 0.37 |
| Black | 321 | 6.5% | 322 | 6.5% | 0.08 | 994 | 6.4% | 1001 | 6.4% | 0.18 | 325 | 6.6% | 318 | 6.4% | 0.57 |
| Other | 265 | 5.4% | 267 | 5.4% | 0.18 | 692 | 4.4% | 669 | 4.3% | 0.72 | 266 | 5.4% | 267 | 5.4% | 0.09 |
| Baseline Comorbidity | | | | | | | | | | | | | | | |
| Deyo–Charlson Comorbidity Index [2] | 3.3 | 2.8 | 3.4 | 2.8 | 0.27 | 3.6 | 2.9 | 3.6 | 2.9 | 0.15 | 3.3 | 2.8 | 3.2 | 2.7 | 2.72 |
| $CHA_2DS_2$-VASc Score | 3.7 | 1.7 | 3.7 | 1.7 | 0.57 | 3.9 | 1.7 | 3.9 | 1.7 | 0.72 | 3.7 | 1.7 | 3.6 | 1.7 | 4.04 |
| 0 | 132 | 1.9% | 142 | 2.1% | 1.04 | 326 | 1.6% | 337 | 1.6% | 0.43 | 165 | 2.3% | 167 | 2.4% | 0.19 |
| 1 | 442 | 6.4% | 438 | 6.4% | 0.24 | 988 | 4.8% | 1025 | 5.0% | 0.84 | 498 | 7.0% | 516 | 7.3% | 0.98 |
| 2 | 1073 | 15.6% | 1032 | 15.0% | 1.65 | 2722 | 13.3% | 2642 | 12.9% | 1.16 | 1100 | 15.5% | 1173 | 16.5% | 2.80 |
| 3 | 1531 | 22.2% | 1547 | 22.5% | 0.56 | 4326 | 21.2% | 4221 | 20.7% | 1.26 | 1594 | 22.4% | 1612 | 22.7% | 0.61 |
| 4+ | 3706 | 53.8% | 3725 | 54.1% | 0.55 | 12,069 | 59.1% | 12,206 | 59.7% | 1.37 | 3746 | 52.7% | 3635 | 51.2% | 3.13 |
| HAS-BLED Score [3] | 3.1 | 1.4 | 3.1 | 1.3 | 2.06 | 3.2 | 1.4 | 3.2 | 1.4 | 0.10 | 3.0 | 1.4 | 3.0 | 1.3 | 4.61 |
| 0 | 96 | 1.4% | 112 | 1.6% | 1.91 | 266 | 1.3% | 288 | 1.4% | 0.93 | 130 | 1.8% | 145 | 2.0% | 1.53 |
| 1 | 695 | 10.1% | 680 | 9.9% | 0.73 | 1640 | 8.0% | 1662 | 8.1% | 0.40 | 773 | 10.9% | 821 | 11.6% | 2.14 |
| 2 | 1646 | 23.9% | 1708 | 24.8% | 2.10 | 4508 | 22.1% | 4555 | 22.3% | 0.55 | 1771 | 24.9% | 1807 | 25.4% | 1.17 |
| 3+ | 4447 | 64.6% | 4384 | 63.7% | 1.91 | 14,017 | 68.6% | 13,926 | 68.2% | 0.96 | 4429 | 62.4% | 4330 | 61.0% | 2.87 |
| Bleeding History [2] | 1290 | 18.7% | 1296 | 18.8% | 0.22 | 4268 | 20.9% | 4265 | 20.9% | 0.04 | 1317 | 18.5% | 1235 | 17.4% | 3.01 |
| Congestive Heart Failure [2] | 2459 | 35.7% | 2430 | 35.3% | 0.88 | 7737 | 37.9% | 7779 | 38.1% | 0.42 | 2471 | 34.8% | 2451 | 34.5% | 0.59 |
| Diabetes Mellitus [2] | 3553 | 51.6% | 3645 | 52.9% | 2.68 | 10,967 | 53.7% | 11,007 | 53.9% | 0.39 | 3740 | 52.7% | 3773 | 53.1% | 0.93 |
| Hypertension [2] | 6418 | 93.2% | 6435 | 93.5% | 0.99 | 19,262 | 94.3% | 19,266 | 94.3% | 0.08 | 6611 | 93.1% | 6569 | 92.5% | 2.28 |
| Renal Disease [2] | 1728 | 25.1% | 1690 | 24.5% | 1.28 | 6072 | 29.7% | 6109 | 29.9% | 0.40 | 1708 | 24.0% | 1580 | 22.2% | 4.27 |
| Liver Disease [2] | 448 | 6.5% | 466 | 6.8% | 1.05 | 1423 | 7.0% | 1379 | 6.7% | 0.85 | 471 | 6.6% | 474 | 6.7% | 0.17 |
| Myocardial Infarction [2] | 711 | 10.3% | 706 | 10.3% | 0.24 | 2400 | 11.7% | 2426 | 11.9% | 0.39 | 716 | 10.1% | 692 | 9.7% | 1.13 |
| Dyspepsia or Stomach Discomfort [2] | 1514 | 22.0% | 1505 | 21.9% | 0.32 | 4826 | 23.6% | 4768 | 23.3% | 0.67 | 1544 | 21.7% | 1478 | 20.8% | 2.27 |

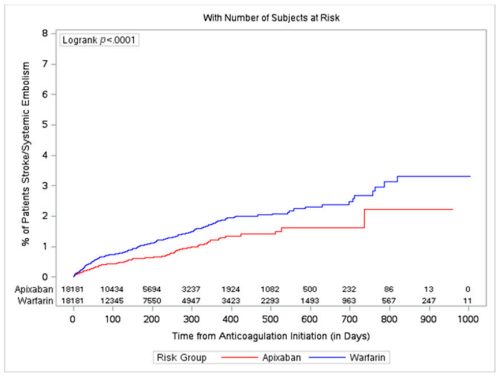
**Table A5.** *Cont.*

| | Apixaban Cohort | | Dabigatran Cohort | | | Apixaban Cohort | | Rivaroxaban Cohort | | | Dabigatran Cohort | | Rivaroxaban Cohort | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *n*/Mean | %/SD | *n*/Mean | %/SD | STD [1] | *n*/Mean | %/SD | *n*/Mean | %/SD | STD [1] | *n*/Mean | %/SD | *n*/Mean | %/SD | STD [1] |
| Non-Stroke/SE Peripheral Vascular Disease [2] | 3676 | 53.4% | 3648 | 53.0% | 0.82 | 11,365 | 55.6% | 11,484 | 56.2% | 1.17 | 3712 | 52.3% | 3710 | 52.2% | 0.06 |
| Stroke/SE [2] | 720 | 10.5% | 704 | 10.2% | 0.76 | 2194 | 10.7% | 2192 | 10.7% | 0.03 | 711 | 10.0% | 733 | 10.3% | 1.02 |
| Transient Ischemic Attack [2] | 414 | 6.0% | 427 | 6.2% | 0.79 | 1316 | 6.4% | 1339 | 6.6% | 0.46 | 442 | 6.2% | 444 | 6.3% | 0.12 |
| Anemia and Coagulation Defects [2] | 1873 | 27.2% | 1815 | 26.4% | 1.90 | 6197 | 30.3% | 6242 | 30.6% | 0.48 | 1838 | 25.9% | 1709 | 24.1% | 4.20 |
| Alcoholism [2] | 186 | 2.7% | 195 | 2.8% | 0.80 | 483 | 2.4% | 471 | 2.3% | 0.39 | 203 | 2.9% | 221 | 3.1% | 1.49 |
| Peripheral Artery Disease | 1350 | 19.6% | 1311 | 19.0% | 1.43 | 4364 | 21.4% | 4677 | 22.9% | 3.69 | 1327 | 18.7% | 1463 | 20.6% | 4.82 |
| Coronary Artery Disease | 3281 | 47.7% | 3230 | 46.9% | 1.48 | 10,183 | 49.8% | 10,138 | 49.6% | 0.44 | 3285 | 46.2% | 3222 | 45.4% | 1.78 |
| Dyslipidemia [2] | 5560 | 80.8% | 5568 | 80.9% | 0.30 | 16,857 | 82.5% | 16,842 | 82.4% | 0.19 | 5716 | 80.5% | 5688 | 80.1% | 0.99 |
| Morbid Obesity | 2601 | 37.8% | 2658 | 38.6% | 1.70 | 7660 | 37.5% | 7896 | 38.6% | 2.38 | 2726 | 38.4% | 2735 | 38.5% | 0.26 |
| Baseline Medication Use [2] | | | | | | | | | | | | | | | |
| ACEi/ARB | 4805 | 69.8% | 4799 | 69.7% | 0.19 | 14,341 | 70.2% | 14,312 | 70.1% | 0.31 | 4922 | 69.3% | 4929 | 69.4% | 0.21 |
| Amiodarone | 827 | 12.0% | 836 | 12.1% | 0.40 | 2671 | 13.1% | 2658 | 13.0% | 0.19 | 849 | 12.0% | 874 | 12.3% | 1.08 |
| Beta Blockers | 4287 | 62.3% | 4198 | 61.0% | 2.66 | 12,981 | 63.5% | 12,917 | 63.2% | 0.65 | 4311 | 60.7% | 4260 | 60.0% | 1.47 |
| H2-Receptor Antagonist | 493 | 7.2% | 477 | 6.9% | 0.91 | 1496 | 7.3% | 1473 | 7.2% | 0.43 | 482 | 6.8% | 460 | 6.5% | 1.24 |
| Proton Pump Inhibitor | 2301 | 33.4% | 2275 | 33.0% | 0.80 | 7222 | 35.3% | 7151 | 35.0% | 0.73 | 2342 | 33.0% | 2259 | 31.8% | 2.50 |
| Statins | 4212 | 61.2% | 4193 | 60.9% | 0.57 | 13,057 | 63.9% | 13,149 | 64.4% | 0.94 | 4285 | 60.3% | 4189 | 59.0% | 2.75 |
| Anti-Platelets | 1312 | 19.1% | 1221 | 17.7% | 3.41 | 4328 | 21.2% | 4392 | 21.5% | 0.76 | 1235 | 17.4% | 1150 | 16.2% | 3.20 |
| NSAIDS | 2119 | 30.8% | 2122 | 30.8% | 0.09 | 6191 | 30.3% | 6230 | 30.5% | 0.41 | 2183 | 30.7% | 2104 | 29.6% | 2.42 |
| Dose of the Index Prescription | | | | | | | | | | | | | | | |
| Standard Dose [4] | 6045 | 87.8% | 5979 | 86.9% | 2.88 | 17,634 | 86.3% | 15,514 | 75.9% | 26.75 | 6194 | 87.2% | 5698 | 80.2% | 18.99 |
| Low Dose [5] | 839 | 12.2% | 905 | 13.1% | 2.88 | 2797 | 13.7% | 4917 | 24.1% | 15.45 | 909 | 12.8% | 1405 | 19.8% | 7.53 |
| Follow-Up Time (in Days) | 176.2 | 158.3 | 221.5 | 218.3 | 23.72 | 176.1 | 159.6 | 220.4 | 208.6 | 23.89 | 220.7 | 218.1 | 217.4 | 206.4 | 1.54 |
| Median | 120 | | 127 | | | 120 | | 141 | | | 127 | | 140 | | |

ACEi/ARB: angiotensin converting enzyme inhibitors/angiotensin-receptor blockers; $CHA_2DS_2$-VASc: congestive heart failure, hypertension, aged ≥ 75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, aged 65–74 years, sex category; HAS-BLED: hypertension, abnormal renal and liver function, stroke, bleeding, labile international normalized ratios, elderly, drugs and alcohol; NOACs: non-vitamin K oral anticoagulants; NSAIDs: non-steroidal anti-inflammatory drugs; NVAF: non-valvular atrial fibrillation; PSM: propensity score matching; SD: standard deviation; SE: systemic embolism; STD: standardized difference. [1] Std difference = 100 ×|actual std diff|. Std difference greater than 10 is considered significant. [2] Variables used in propensity score matching. [3] As the INR value is not available in the databases, a modified HAS-BLED score was calculated with a range of 0 to 8. [4] Standard dose: 5 mg apixaban, 150 mg dabigatran, 20 mg rivaroxaban. [5] Lower dose: 2.5 mg apixaban, 75 mg dabigatran, 10 or 15 mg rivaroxaban; 950 and 310 patients were prescribed 10 mg of rivaroxaban in the apixaban-rivaroxaban and dabigatran-rivaroxaban cohorts, respectively.




(**A**)

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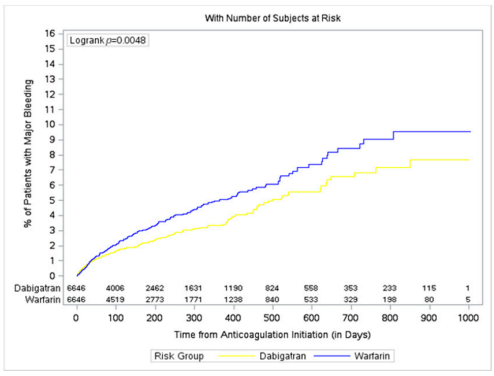


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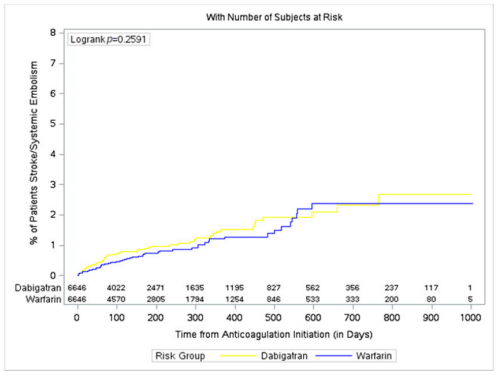


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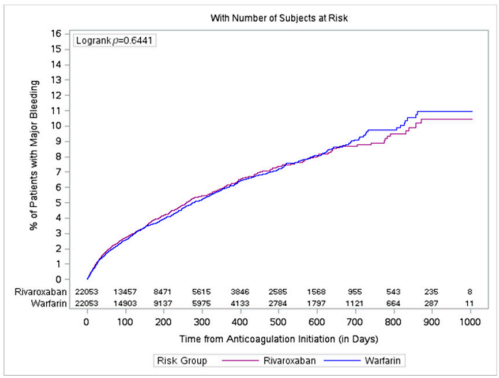
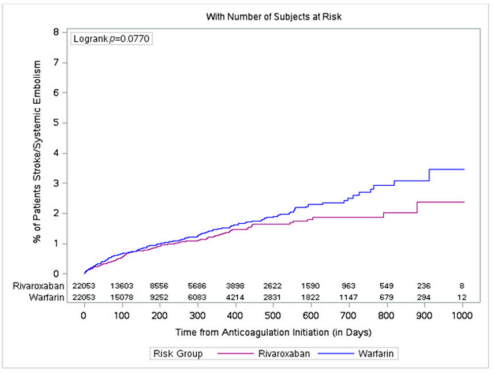
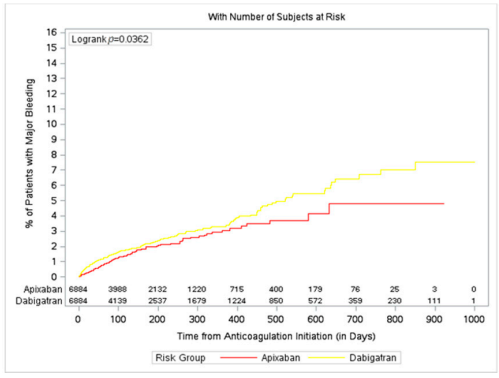


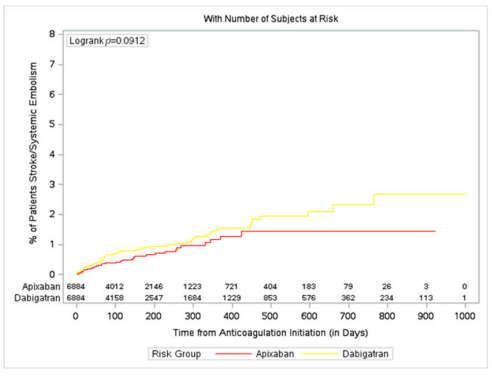

(**E**)




(**F**)




(**G**)




(**H**)

**Figure A1.** *Cont.*

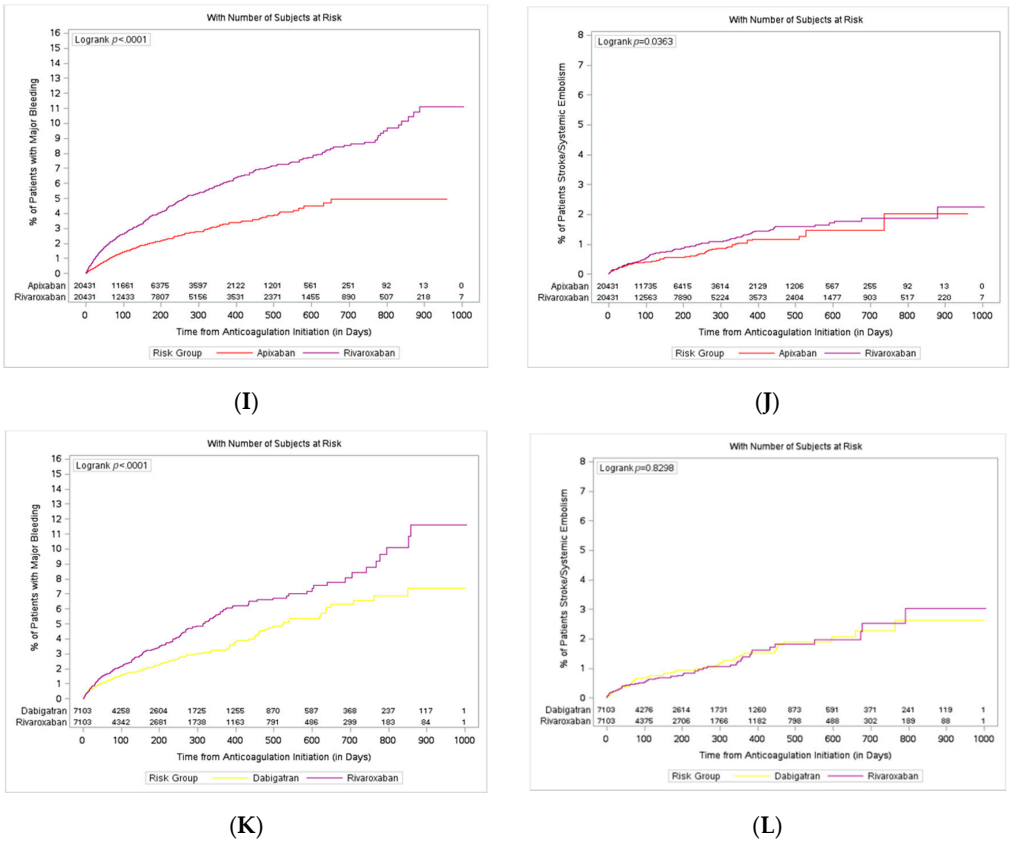



**Figure A1.** Cumulative incidence of major bleeding and stroke/systemic embolism. (**A**) Major bleeding for apixaban vs. warfarin; (**B**) Stroke/systemic embolism for apixaban vs. warfarin; (**C**) Major bleeding for dabigatran vs. warfarin; (**D**) Stroke/systemic embolism for dabigatran vs. warfarin; (**E**) Major bleeding for rivaroxaban vs. warfarin; (**F**) Stroke/systemic embolism for rivaroxaban vs. warfarin; (**G**) Major bleeding for apixaban vs. dabigatran; (**H**) Stroke/systemic embolism for apixaban vs. dabigatran; (**I**) Major bleeding for apixaban vs. rivaroxaban; (**J**) Stroke/systemic embolism for apixaban vs. rivaroxaban; (**K**) Major bleeding for dabigatran vs. rivaroxaban; (**L**) Stroke/systemic embolism for dabigatran vs. rivaroxaban.

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