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Effectiveness and Safety of Oral Anticoagulants Among Non-Valvular Atrial Fibrillation Patients with Polypharmacy

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Aims: Polypharmacy is prevalent among non-valvular atrial fibrillation (NVAF) patients and presents a potential issue for the effective management of NVAF. This study compared the risk of stroke/systemic embolism (SE) and major bleeding (MB) among NVAF patients with polypharmacy newly prescribed oral anticoagulants (OACs).

Methods and Results: A retrospective study of NVAF patients with polypharmacy who initiated OACs from 01JAN2013-30SEP2015 was conducted using US CMS Medicare and four commercial databases. Polypharmacy was defined as ≥6 concomitant medications on the index date. Propensity score matching was conducted to compare non-Vitamin K antagonists OACs (NOACs) to warfarin as well as between NOACs. Cox proportional hazard models were used to evaluate the risk of stroke/SE and MB. A total of 188,893 patients with polypharmacy were included, with an average of 8 concomitant medications (IQR 6-9). Compared to warfarin, apixaban (HR: 0.59, 95% CI: 0.52-0.68) and rivaroxaban (HR: 0.75, 95% CI: 0.69-0.83) were associated with a lower risk of stroke/SE. Apixaban (HR: 0.57, 95% CI: 0.54-0.61) and dabigatran (HR: 0.76, 95% CI: 0.66-0.88) were associated with a decreased risk of MB compared with warfarin. Compared with dabigatran and rivaroxaban, apixaban was associated with a lower risk of stroke/SE and MB. Dabigatran was associated with lower risk of MB compared with rivaroxaban.

Conclusions: In this observational study of anticoagulated NVAF patients with polypharmacy, effectiveness and safety profiles are more favorable for NOACs vs warfarin. Our observations are hypothesis generating and may help inform future clinical trials regarding appropriate OAC treatment selection in polypharmacy patients.

Key Words: anticoagulants; effectiveness; major bleeding; polypharmacy; stroke.

Introduction:

Atrial fibrillation (AF), the most commonly occurring arrhythmia, is an independent risk factor for stroke.[1,2] Non-valvular AF (NVAF), which constitutes approximately 70% of AF cases, increases the risk of stroke by almost fivefold.[3,4] The majority of patients affected by AF (70%) are between ages 65-85.[5] Among these elderly patients, multimorbidity and polypharmacy are common.[6]

Importantly, AF disease presentation and management often necessitates polypharmacy.[6,7,8,9,10,11] Indeed, the rate of polypharmacy in AF patients can be as high as 76.5%.[12] Polypharmacy is associated with negative clinical outcomes including potentially serious drug-drug interactions, adverse drug reactions, and related hospitalizations.[13,14] The consequences of polypharmacy – such as pill burden, drug-drug interactions, medication non-adherence, inappropriate drug use/medication errors, bleeding complications, increased morbidity and mortality, and increased length of hospital stay – should be considered and balanced against the possible benefits of using multiple drugs for treatment.[13]

As a significant portion of the NVAF population has polypharmacy, it is important to identify safe and effective oral anticoagulant (OAC) treatments for this group of patients. While two ad-hoc analyses of patients with polypharmacy have been conducted using data from the ARISTOTLE trial and the ROCKET AF trial, there has been a lack of real world evidence about the safety and effectiveness of oral OACs among patients with polypharmacy.[7,10] Using several data sources, this subgroup analysis of the ARISTOPHANES (Anticoagulants for Reduction In STroke: Observational Pooled analysis on Health outcomes ANd Experience of patientS; NCT03087487) study compared the risk of stroke/SE and major bleeding (MB) among NVAF patients newly prescribed apixaban, dabigatran, rivaroxaban, or warfarin with polypharmacy.

Methods

Data Sources

This retrospective observational database analysis of data pooled from the US Centers for Medicare & Medicaid Services (CMS) and four US commercial claims databases: the Truven MarketScan® Commercial Claims and Encounter and Medicare Supplemental and Coordination of Benefits Database, the IMS PharMetrics Plus™ Database, the Optum Clinformatics™ Data Mart, and the Humana Research Database. Data description, pooling procedures of the ARISTOPHANES study, as well as measures taken to minimize patient record duplicates across the data sources have been published previously.[15,16]

Patient Selection

Polypharmacy was defined as usage of 6 or more medications on index date, which was based on the distribution of non-OAC prescriptions on the index date and the ad-hoc ARISTOTLE analysis.[7] The ARISTOTLE trial observed that the median number of drugs patients used was 6 (IQR 5-9).[7] NVAF patients with polypharmacy were selected if they had ≥1 pharmacy claim for apixaban, dabigatran, rivaroxaban or warfarin between 01JAN2013-30SEP2015. The first non-Vitamin K antagonist OAC (NOAC) prescription date was designated as the index date if patients had NOAC claim(s). 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 the index date and have continuous medical and pharmacy health plan enrollment for ≥12 months pre-index date (baseline period).

Patients treated with an OAC within 12 months pre-index date were excluded. Patients were also excluded if they had evidence of valvular heart disease, venous thromboembolism, transient AF (eg. due to pericarditis, hyperthyroidism, thyrotoxicity), heart valve replacement/transplant during the baseline period, pregnancy during the study period, or hip or knee replacement surgery within 6 weeks pre-index date. Additional exclusion criteria are shown in Figure 1.

Outcome Measures

The primary outcomes measured were stroke/SE (including ischemic stroke, hemorrhagic stroke, and SE), and MB (including gastrointestinal bleeding, intracranial hemorrhage, and bleeding at other key sites; Supplemental Table 1).[17,18] 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 the first of 30 days after discontinuation, switch date, death, end of continuous medical or pharmacy plan enrollment, or end of study.

Statistical Methodology

Propensity score matching (PSM) was conducted between each NOAC and warfarin cohort and between the NOAC cohorts within each individual dataset. For each of the six comparisons, patients were matched 1:1 on propensity score generated by logistic regression using patient demographics, Charlson comorbidity index (CCI) scores, common comorbidities, and comedications.[19] Patients from each database were matched 1:1 by nearest neighbor matching without replacement (with a caliper of 0.01). The covariate balance was checked using standardized differences, with a threshold of 10%.[20] After ensuring the cohorts were balanced in each database, study patients from the five datasets were pooled for analysis.

Incidence rates were calculated per 100 person-years for stroke/SE and MB. Cox proportional hazard models with robust sandwich estimates were used to measure the risk of stroke/SE and MB.[21] As the cohorts were all balanced, no other variables were included in the model. Statistical significance was determined at $p<0.05$.

Subgroup and Sensitivity Analyses

Two subgroup analyses were conducted. The first studied the impact of standard dosage (apixaban 5 mg b.i.d.BD, dabigatran 150 mg b.i.d., rivaroxaban 20 mg QD), low dosage (apixaban 2.5 mg b.i.d., dabigatran 75 mg b.i.d., rivaroxaban 10 mg/15 mg QD) on stroke/SE and MB. PSM was conducted again in subgroup patients based on the index dose of the NOAC. Cox proportional hazard models were completed for the standard dose and lower dose subgroups separately. The second subgroup analysis addressed the impact of the number of non-OAC medications on outcomes. Number of medications were dichotomized as 6-8 versus ≥9 prescriptions. The interaction effect of OAC used and the number of prescriptions were evaluated. Cox proportional hazard models were computed to evaluate the associated risks. As a sensitivity analysis, inverse probability of treatment weighting (IPTW) was performed using the same list of covariates as the PSM. Cox proportional hazard models were completed in the weighted population. As a separate sensitivity analysis, as there are 6 possible treatment comparisons, we applied Bonferroni correction and adjusted the significance level to 0.008 ($p = 0.05/6$).

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

Results

There were a total of 466,991 patients included in the final analysis. Approximately 72% of the overall OAC-treated NVAF sample took at least twice daily non-OAC medications, and 93% took at least once daily non-OAC medications. The most common therapeutic classes of medication were beta blockers (62%), antihyperlipidemic drugs (50%), calcium channel medications (36%; Supplemental Table 2a).

40% of NVAF patients (n=188,893) with polypharmacy were identified, including 44,846 apixaban, 14,255 dabigatran, 58,668 rivaroxaban and 71,124 warfarin patients (Figure 1). Of those patients, over 90% were taking at least twice daily (BID or more) non-OAC medications and the average number of concomitant medications was approximately 8 (Supplemental Table 3). The therapeutic classes frequently used were similar between the overall pooled population and the polypharmacy population, with beta blockers, antihyperlipidemic drugs, calcium channel medications being the most commonly used (Supplemental Table 2b). Among patients with polypharmacy, >63% of patients had CHA_2DS_2-VASc of 4 or higher and >70% had HAS-BLED scores of 3 or higher. Prior to PSM, warfarin users had the highest scores for CHA_2DS_2-VASc and HAS-BLED (Supplemental Table 3).

The unadjusted incidence rates of stroke/SE were 2.5 (warfarin), 1.5 (apixaban), 1.8 (dabigatran), 1.7 (rivaroxaban) per 100 person-years. The unadjusted incidence rates of MB were 8.5 (warfarin, 5.1 (apixaban), 5.1 (dabigatran), 7.6 (rivaroxaban) 100 person-years (Supplemental Table 4).

After PSM, 41,662 apixaban-warfarin, 13,861 dabigatran-warfarin, and 50,192 rivaroxaban-warfarin patient pairs were identified. NOAC comparison matchings yielded 13,969 apixaban-dabigatran, 43,250 apixaban-rivaroxaban, and 14,205 dabigatran-rivaroxaban patient pairs. Mean

follow-up time ranged from 187-243 days in the matched cohorts. After matching, all demographic and clinical characteristics were well balanced. Further details regarding baseline characteristics can be found in Tables 1A and 1B.

NOAC-Warfarin Comparisons

Compared to warfarin, apixaban and rivaroxaban were associated with a significantly lower risk of stroke/SE (apixaban: hazard ratio [HR]: 0.59, 95% confidence interval [CI]: 0.52-0.68; rivaroxaban (HR: 0.75, 95% CI: 0.69-0.83). Dabigatran was associated with a non-significant difference in risk of stroke/SE (HR: 0.89, 95% CI: 0.75-1.06) compared to warfarin (Figure 2A).

Apixaban (HR: 0.57, 95% CI: 0.54-0.61) and dabigatran (HR: 0.76, 95% CI: 0.66-0.88) were associated with a significantly lower risk of MB in comparison to warfarin. (Figure 2A). Rivaroxaban was associated with a similar risk of MB (HR: 1.05, 95% CI: 0.99-1.11) compared to warfarin (Figure 2A).

NOAC-NOAC Comparisons

Compared to dabigatran, apixaban was associated with a significantly lower risk of stroke/SE (HR: 0.64, 95% CI: 0.51-0.82) and MB (HR: 0.78, 95% CI: 0.68-0.89). Apixaban was associated with a significantly lower risk of stroke/SE (HR: 0.80, 95% CI: 0.68-0.95) and MB (HR: 0.57, 95% CI: 0.53-0.61) when compared to rivaroxaban. Compared to rivaroxaban, dabigatran was associated with a significantly lower risk of MB (HR: 0.76, 95% CI: 0.68-0.85) and a similar risk of stroke/SE (HR: 1.17, 95% CI: 0.97-1.41; Figure 2B). The Kaplan-Meier curves for cumulative incidence rates of stroke/SE and MB in the matched population are presented in Supplemental Figures 1 and 2.

Subgroup and Sensitivity Analyses

Results of the dose subgroup analysis were generally consistent with the main analysis. (Supplemental Table 5 and 6). The comparative risks of stroke/SE and MB were consistent among patients with 6-8 and ≥9 non-OAC prescription drugs for the subgroup interaction analyses (Supplemental Table 7A and 7B). The sensitivity analysis using IPTW was also consistent with the main analysis (Supplemental Table 8). After using Bonferroni correction to use a more restrictive p-value ($p < 0.008$), the comparative risks of stroke/SE and MB showed similar trends other than the loss of significance for the stroke/SE apixaban versus rivaroxaban comparison (Supplemental Table 9).

Discussion

As far as we are aware, this ARISTOPHANES sub-analysis is the largest observational study to date addressing effectiveness and safety of OACs among NVAF patients with polypharmacy. NOACs were found to be associated with similar or lower risks of stroke/SE and MB compared to warfarin, and effectiveness and safety profiles may potentially differ across different NOACs. Further analyses in key subgroups, including NOAC low- and standard-dose populations and patients with moderate vs. high polypharmacy showed generally consistent findings. Our findings are important given that polypharmacy is common among patients with cardiovascular diseases and presents a critical treatment issue due to associated adverse events.[13,22]

In the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial, 76.5% of the patients had ≥5 concomitant medications at the baseline. A post-hoc analysis of the ARISTOTLE Trial indicated that the rates of stroke/SE, mortality and MB increased with the number of concomitant medications (0-5, 6-8, ≥9) taken.[7] There was a

consistent reduction in stroke/SE for apixaban versus warfarin, regardless of the number of concomitant drugs (interaction P=0.82). A smaller reduction in MB was observed for apixaban versus warfarin with increasing numbers of concomitant drugs (interaction P=0.017). For MB, absolute rate reductions per 100 patient years of 1.28, 0.82, and 0.66 for the three groups (0-5, 6-8, and ≥9 drugs, respectively) were noted for apixaban versus warfarin. In the current study, apixaban was associated with lower risk of stroke/SE and MB compared to warfarin among patients with ≥6 prescription drugs and further subgroup analysis showed similar results among patients with 6-8 and ≥9 prescription drugs.

Polypharmacy was associated with higher risks of composite outcomes (combined end point of stroke, non–central nervous system embolism, vascular death, or myocardial infarction and nonmajor clinically relevant or MB) in the post-hoc analysis of the ROCKET AF trial.[10] In all three groups stratifying by the number of concomitant medications (0-4, 5-9, ≥10), the efficacy end points (stroke or non-CNS embolism intracranial hemorrhage, or all cause death) were numerically higher in the warfarin arm than the rivaroxaban arm. Our current study found that rivaroxaban vs. warfarin was associated with a lower risk of stroke/SE among patients with ≥6 non-OAC prescription drugs and similar findings were observed among patients with 6-8 and ≥9 non-OAC prescription drugs. The post-hoc analysis of the ROCKET AF also indicated that the occurrence of both major and nonmajor clinically relevant bleeding were similar between the rivaroxaban and warfarin arms. Intracranial hemorrhage, however, was less frequent in the rivaroxaban arm across the three groups with different number of concurrent medications (0-4, 5-9, ≥10). Indeed, similar results were noted in the current study of patients with polypharmacy.

Studies using real-world data have also been conducted among NVAF patients with polypharmacy with results indicating an improved effectiveness for NOACs in comparison to warfarin.[23] In a

retrospective claims study of OAC-naïve patients with NVAF, PSM of rivaroxaban and warfarin patients taking ≥5 non-OAC chronic medications showed that rivaroxaban was associated with 34% and 40% hazard reductions in stroke/SE and ischemic stroke alone versus warfarin with no significant difference in MB.[23]

In comparison to previous studies, this subgroup analysis of the ARISTOPHANES study consisted of a substantially larger sample of NVAF patients with polypharmacy. Additionally, this study provided the first NOAC to NOAC comparisons among NVAF patients with polypharmacy in routine clinical practice, potentially giving additional insight into the performance of each therapy among patients with polypharmacy. Results of this study may help decision making when choosing appropriate treatments for patients with polypharmacy.

Study Limitations

This observational study had several limitations. Causal relationships cannot be inferred, as this study was designed to study associations between OAC treatments and clinical outcomes. Despite the use of PSM, there is the potential for residual confounding. This limitation must be noted when interpreting results of the NOAC to NOAC comparisons, in the absence of head to head trials. It should be noted that the NOAC to NOAC comparisons conducted in this study are for the purposes of hypotheses generation only. While the use of PSM ensured the characteristics were balanced in the medication cohorts in our analysis, there are also inherent associated limitations with the use of instrumental variables, an alternative methodology. One of the concerns with instrumental variables assumption violations is that providers who prefer one NOAC over another may also provide better care in other ways.[24,25] An additional violation is that patients who report to one

clinic may be different in unmeasured ways from patients who report to a different clinic.**Error! Bookmark not defined.**

Information related over-the-counter medication usage and laboratory values are not available in claims data and thus cannot be evaluated. Due to the use of claims data, outcome measures were based on ICD-9-CM codes and may lack clinical accuracy. Additionally, factors related to physician practice cannot be measured in claims data and could have impacted the results of this study. The INR measurements for warfarin patients were also unavailable, thus the time in therapeutic range for patients treated with warfarin cannot be determined.[26] Age is top-coded in several datasets, which may have led to an underestimation of mean age. The use of a more stringent definition could have underestimated the number patients with polypharmacy in this analysis. However, our definition was based on an analysis of prescription distribution and consistent with prior studies.[7,10] Lastly, the generalizability of our findings is limited to those patients with Medicare or commercial insurance, and findings may differ in uninsured patients.

Conclusion:

In this observational study of anticoagulated NVAF patients with polypharmacy, effectiveness and safety profiles are more favorable for NOACs vs warfarin. Our observations are hypothesis generating and may help inform future clinical trials regarding appropriate OAC treatment selection in polypharmacy patients.

Data Availability Statement: The raw data on which this study was based are from the US Centers for Medicare & Medicaid Services (CMS) and four US commercial claims databases: the Truven MarketScan® Commercial Claims and Encounter and Medicare Supplemental and Coordination of Benefits Database, the IMS PharMetrics Plus™ Database, the Optum Clinformatics™ Data Mart, and the Humana Research Database. These data are available from the aforementioned databases and organization upon requests.

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Table 1A. Baseline Characteristics Among Polypharmacy NVAF Patients after Propensity Score Matching Among 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	**41,662**		**41,662**			**13,861**		**13,861**			**50,192**		**50,192**	
Age*	76.9	8.9	76.9	8.8		74.8	8.9	74.9	9.0		76.2	8.7	76.2	8.7
18-54	496	1.2%	507	1.2%		288	2.1%	281	2.0%		647	1.3%	695	1.4%
55-64	2,228	5.3%	2,203	5.3%		1,145	8.3%	1,161	8.4%		2,908	5.8%	2,937	5.9%
65-74	13,956	33.5%	13,857	33.3%		5,297	38.2%	5,254	37.9%		17,983	35.8%	17,915	35.7%
75-79	8,654	20.8%	8,674	20.8%		2,998	21.6%	3,020	21.8%		10,828	21.6%	10,826	21.6%
≥80	16,328	39.2%	16,421	39.4%		4,133	29.8%	4,145	29.9%		17,826	35.5%	17,819	35.5%
Gender*														
Male	20,234	48.6%	20,207	48.5%		7,157	51.6%	7,113	51.3%		25,009	49.8%	25,082	50.0%
Female	21,428	51.4%	21,455	51.5%		6,704	48.4%	6,748	48.7%		25,183	50.2%	25,110	50.0%
US Geographic Region*														
Northeast	6,739	16.2%	6,711	16.1%		2,420	17.5%	2,444	17.6%		8,365	16.7%	8,349	16.6%
Midwest	9,638	23.1%	9,611	23.1%		3,284	23.7%	3,256	23.5%		12,997	25.9%	13,004	25.9%
South	18,927	45.4%	18,993	45.6%		5,793	41.8%	5,746	41.5%		20,286	40.4%	20,262	40.4%
West	6,271	15.1%	6,282	15.1%		2,321	16.7%	2,378	17.2%		8,414	16.8%	8,449	16.8%
Other	87	0.2%	65	0.2%		43	0.3%	37	0.3%		130	0.3%	128	0.3%
Baseline Comorbidity														
Deyo-Charlson Comorbidity Index*	3.9	2.8	3.9	2.8		3.5	2.7	3.5	2.7		3.7	2.8	3.8	2.8
CHA_2DS_2-VASc Score	4.4	1.6	4.4	1.5		4.1	1.6	4.1	1.5		4.3	1.6	4.3	1.5
0	134	0.3%	103	0.2%		75	0.5%	58	0.4%		170	0.3%	145	0.3%
1	888	2.1%	847	2.0%		424	3.1%	432	3.1%		1,169	2.3%	1,151	2.3%
2	3,543	8.5%	3,298	7.9%		1,437	10.4%	1,380	10.0%		4,522	9.0%	4,203	8.4%

	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
3	7,744	18.6%	7,762	18.6%		2,989	21.6%	2,929	21.1%		9,887	19.7%	9,821	19.6%
≥4	29,353	70.5%	29,652	71.2%		8,936	64.5%	9,062	65.4%		34,444	68.6%	34,872	69.5%
HAS-BLED Score[†]	3.5	1.3	3.5	1.3		3.3	1.3	3.3	1.3		3.4	1.3	3.4	1.3
0	95	0.2%	102	0.2%		83	0.6%	78	0.6%		162	0.3%	170	0.3%
1	1,932	4.6%	1,896	4.6%		812	5.9%	812	5.9%		2,535	5.1%	2,480	4.9%
2	7,880	18.9%	8,183	19.6%		3,145	22.7%	3,159	22.8%		10,075	20.1%	10,477	20.9%
≥3	31,755	76.2%	31,481	75.6%		9,821	70.9%	9,812	70.8%		37,420	74.6%	37,065	73.8%
Comorbidities														
Bleeding history*	9,149	22.0%	9,116	21.9%		2,720	19.6%	2,830	20.4%		10,957	21.8%	10,905	21.7%
Congestive heart failure*	16,769	40.3%	16,835	40.4%		4,974	35.9%	4,954	35.7%		19,597	39.0%	19,650	39.1%
Diabetes mellitus*	20,531	49.3%	20,472	49.1%		7,019	50.6%	7,024	50.7%		24,978	49.8%	25,035	49.9%
Hypertension*	38,372	92.1%	38,369	92.1%		12,795	92.3%	12,824	92.5%		46,034	91.7%	46,012	91.7%
Renal disease*	13,546	32.5%	13,571	32.6%		3,426	24.7%	3,459	25.0%		14,688	29.3%	14,659	29.2%
Liver disease*	2,375	5.7%	2,384	5.7%		728	5.3%	730	5.3%		2,901	5.8%	2,872	5.7%
Myocardial infarction*	5,414	13.0%	5,413	13.0%		1,501	10.8%	1,529	11.0%		6,510	13.0%	6,586	13.1%
Dyspepsia or stomach discomfort*	9,720	23.3%	9,707	23.3%		2,975	21.5%	3,003	21.7%		11,702	23.3%	11,657	23.2%
Non-stroke/SE peripheral vascular disease*	26,171	62.8%	26,267	63.0%		8,193	59.1%	8,230	59.4%		30,852	61.5%	30,917	61.6%
Stroke/SE*	5,790	13.9%	5,785	13.9%		1,699	12.3%	1,739	12.5%		6,698	13.3%	6,789	13.5%
Transient ischemic attack*	3,274	7.9%	3,285	7.9%		998	7.2%	1,009	7.3%		3,757	7.5%	3,747	7.5%

	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
Anemia and coagulation defects*	14,463	34.7%	14,470	34.7%		4,123	29.7%	4,094	29.5%		16,811	33.5%	16,766	33.4%
Alcoholism*	856	2.1%	845	2.0%		326	2.4%	306	2.2%		1,171	2.3%	1,179	2.3%
Peripheral artery disease	10,589	25.4%	11,019	26.4%		3,084	22.2%	3,291	23.7%		12,691	25.3%	12,708	25.3%
Coronary artery disease	23,443	56.3%	23,238	55.8%		7,337	52.9%	7,189	51.9%		27,445	54.7%	27,293	54.4%
Baseline Medication Use*														
ACE/ARB	31,204	74.9%	31,236	75.0%		10,624	76.6%	10,681	77.1%		37,702	75.1%	37,756	75.2%
Amiodarone	6,967	16.7%	6,932	16.6%		2,098	15.1%	2,064	14.9%		7,917	15.8%	7,943	15.8%
Beta blockers	27,931	67.0%	27,926	67.0%		9,177	66.2%	9,086	65.6%		33,418	66.6%	33,407	66.6%
H2-receptor antagonists	4,279	10.3%	4,289	10.3%		1,370	9.9%	1,342	9.7%		5,179	10.3%	5,172	10.3%
Proton pump inhibitors	18,742	45.0%	18,688	44.9%		5,892	42.5%	5,940	42.9%		22,075	44.0%	22,103	44.0%
Statins	31,482	75.6%	31,573	75.8%		10,223	73.8%	10,176	73.4%		37,372	74.5%	37,319	74.4%
Anti-platelets	12,291	29.5%	12,296	29.5%		3,506	25.3%	3,555	25.6%		13,964	27.8%	14,077	28.0%
NSAIDs	11,831	28.4%	11,789	28.3%		4,224	30.5%	4,233	30.5%		14,467	28.8%	14,510	28.9%
Distribution of Polypharmacy														
Mean	8.2	2.3	8.2	2.3		8.1	2.3	8.1	2.3		8.2	2.3	8.2	2.3
Min	6		6			6		6			6		6	
25%	6		6			6		6			6		6	
Median	8		8			7		8			8		8	
75%	9		9			9		9			9		9	
Max	32		34			32		25			32		34	

	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
Dose of the Index Prescription														
Standard Dose‡	29,878	71.7%				10,933	78.9%				32,636	65.0%		
Low Dose§	11,784	28.3%				2,928	21.1%				17,556	35.0%		
Follow-up Time (in days)	186.8	168.0	238.4	216.8		234.2	229.9	243.1	219.5		229.3	216.0	240.4	217.8
Median	127		158			136		160			146		158	

ACE: angiotensin-converting enzyme inhibitor; ARB: angiotensin-receptor blocker; CHA_2DS_2VASC: congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, age 65 – 74 years, sex category; HAS-BLED: hypertension, abnormal renal and liver function, stroke, bleeding, labile INRs (international normalized ratio), elderly, drugs and alcohol; NOACs: non-vitamin K antagonist oral anticoagulants; NSAIDs: non-steroidal anti-inflammatory drugs; NVAF: non-valvular atrial fibrillation; SD: standard deviation; SE: systemic embolism

* Variables controlled for in the propensity score matching.

† as the INR value is not available in the databases, a modified HAS-BLED score was calculated with a range of 0 to 8.

‡ Standard dose: 5 mg apixaban b.i.d. 150 mg dabigatran b.i.d., 20 mg rivaroxaban QD.

§ Lower dose: 2.5 mg apixaban b.i.d., 75 mg dabigatran b.i.d., 10/15 mg rivaroxaban QD. 14,474 and 3,082 patients received 15 mg and 10 mg rivaroxaban QD, respectively.

Table 1B. Baseline Characteristics Among Polypharmacy NVAF Patients 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	**13,969**	**100%**	**13,969**	**100%**		**43,250**	**100%**	**43,250**	**100%**		**14,205**	**100%**	**14,205**	**100%**
Age*	74.6	9.2	74.6	9.1		76.2	9.2	76.1	9.2		74.4	9.2	74.4	9.3
18-54	353	2.5%	343	2.5%		814	1.9%	800	1.8%		394	2.8%	402	2.8%
55-64	1,214	8.7%	1,248	8.9%		3,026	7.0%	3,081	7.1%		1,347	9.5%	1,344	9.5%
65-74	5,283	37.8%	5,274	37.8%		14,542	33.6%	14,556	33.7%		5,336	37.6%	5,299	37.3%
75-79	2,970	21.3%	2,980	21.3%		8,851	20.5%	8,838	20.4%		2,993	21.1%	3,021	21.3%
≥80	4,149	29.7%	4,124	29.5%		16,017	37.0%	15,975	36.9%		4,135	29.1%	4,139	29.1%
Gender*														
Male	7,174	51.4%	7,238	51.8%		21,148	48.9%	21,220	49.1%		7,424	52.3%	7,398	52.1%
Female	6,795	48.6%	6,731	48.2%		22,102	51.1%	22,030	50.9%		6,781	47.7%	6,807	47.9%
US Geographic Region*														
Northeast	2,374	17.0%	2,379	17.0%		6,678	15.4%	6,650	15.4%		2,469	17.4%	2,489	17.5%
Midwest	3,282	23.5%	3,277	23.5%		9,698	22.4%	9,656	22.3%		3,325	23.4%	3,342	23.5%
South	6,016	43.1%	6,012	43.0%		20,571	47.6%	20,616	47.7%		6,052	42.6%	6,032	42.5%
West	2,265	16.2%	2,260	16.2%		6,215	14.4%	6,246	14.4%		2,315	16.3%	2,292	16.1%
Other	32	0.2%	41	0.3%		88	0.2%	82	0.2%		44	0.3%	50	0.4%
Baseline Comorbidity														
Deyo-Charlson Comorbidity Index*	3.4	2.7	3.5	2.7		3.7	2.8	3.7	2.8		3.4	2.7	3.4	2.7
CHA_2DS_2-VASc Score	4.1	1.6	4.1	1.6		4.3	1.6	4.3	1.6		4.1	1.6	4.1	1.6
0	72	0.5%	72	0.5%		164	0.4%	154	0.4%		89	0.6%	74	0.5%
1	493	3.5%	505	3.6%		1,210	2.8%	1,217	2.8%		546	3.8%	551	3.9%
2	1,562	11.2%	1,514	10.8%		4,142	9.6%	4,139	9.6%		1,586	11.2%	1,637	11.5%

	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
3	2,964	21.2%	2,991	21.4%		8,322	19.2%	8,435	19.5%		3,042	21.4%	3,024	21.3%
≥4	8,878	63.6%	8,887	63.6%		29,412	68.0%	29,305	67.8%		8,942	62.9%	8,919	62.8%
HAS-BLED Score[†]	3.2	1.3	3.2	1.3		3.4	1.3	3.4	1.3		3.2	1.3	3.2	1.3
0	47	0.3%	72	0.5%		113	0.3%	105	0.2%		94	0.7%	74	0.5%
1	877	6.3%	844	6.0%		2,277	5.3%	2,355	5.4%		910	6.4%	961	6.8%
2	3,252	23.3%	3,245	23.2%		8,613	19.9%	8,627	19.9%		3,307	23.3%	3,171	22.3%
≥3	9,793	70.1%	9,808	70.2%		32,247	74.6%	32,163	74.4%		9,894	69.7%	9,999	70.4%
Comorbidities														
Bleeding history*	2,737	19.6%	2,707	19.4%		9,121	21.1%	9,068	21.0%		2,741	19.3%	2,769	19.5%
Congestive heart failure*	4,899	35.1%	4,936	35.3%		16,547	38.3%	16,557	38.3%		4,995	35.2%	4,937	34.8%
Diabetes Mellitus*	7,004	50.1%	7,020	50.3%		20,964	48.5%	21,074	48.7%		7,152	50.3%	7,182	50.6%
Hypertension*	12,937	92.6%	12,918	92.5%		39,911	92.3%	39,929	92.3%		13,112	92.3%	13,163	92.7%
Renal disease*	3,290	23.6%	3,407	24.4%		12,862	29.7%	12,906	29.8%		3,425	24.1%	3,419	24.1%
Liver disease*	685	4.9%	723	5.2%		2,459	5.7%	2,416	5.6%		733	5.2%	775	5.5%
Myocardial infarction*	1,463	10.5%	1,487	10.6%		5,331	12.3%	5,356	12.4%		1,507	10.6%	1,543	10.9%
Dyspepsia or stomach discomfort*	2,944	21.1%	2,977	21.3%		10,076	23.3%	10,074	23.3%		3,019	21.3%	3,066	21.6%
Non-stroke/ SE peripheral vascular disease*	8,188	58.6%	8,200	58.7%		26,743	61.8%	26,734	61.8%		8,291	58.4%	8,276	58.3%
Stroke/SE*	1,739	12.4%	1,695	12.1%		5,644	13.0%	5,648	13.1%		1,701	12.0%	1,700	12.0%

	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
Transient ischemic attack*	1,000	7.2%	994	7.1%		3,305	7.6%	3,281	7.6%		1,002	7.1%	992	7.0%
Anemia and coagulation defects*	4,031	28.9%	4,101	29.4%		14,206	32.8%	14,208	32.9%		4,130	29.1%	4,120	29.0%
Alcoholism*	302	2.2%	326	2.3%		893	2.1%	900	2.1%		339	2.4%	332	2.3%
Peripheral artery disease	3,069	22.0%	3,083	22.1%		10,562	24.4%	10,918	25.2%		3,100	21.8%	3,252	22.9%
Coronary artery disease	7,341	52.6%	7,332	52.5%		23,957	55.4%	23,801	55.0%		7,418	52.2%	7,330	51.6%
Baseline Medication Use*														
ACE/ARB	10,675	76.4%	10,715	76.7%		32,607	75.4%	32,688	75.6%		10,899	76.7%	10,871	76.5%
Amiodarone	2,010	14.4%	2,095	15.0%		7,076	16.4%	7,006	16.2%		2,119	14.9%	2,131	15.0%
Beta blockers	9,327	66.8%	9,267	66.3%		28,961	67.0%	29,011	67.1%		9,388	66.1%	9,414	66.3%
H2-receptor antagonists	1,412	10.1%	1,369	9.8%		4,306	10.0%	4,367	10.1%		1,381	9.7%	1,389	9.8%
Proton pump inhibitors	5,973	42.8%	5,948	42.6%		19,441	45.0%	19,420	44.9%		6,020	42.4%	6,029	42.4%
Statins	10,342	74.0%	10,286	73.6%		32,545	75.2%	32,602	75.4%		10,428	73.4%	10,415	73.3%
Anti-platelets	3,598	25.8%	3,521	25.2%		12,754	29.5%	12,768	29.5%		3,557	25.0%	3,525	24.8%
NSAIDs	4,315	30.9%	4,339	31.1%		12,951	29.9%	12,994	30.0%		4,414	31.1%	4,461	31.4%
Distribution of Polypharmacy														
Mean	8.1	2.2	8.1	2.3		8.2	2.3	8.2	2.3		8.1	2.3	8.1	2.3
Min	6		6			6		6			6		6	
25%	6		6			6		6			6		6	
Median	7		7			8		8			7		7	

	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
75%	9		9			9		9			9		9	
Max	32		32			32		28			32		32	
Dose of the Index Prescription														
Standard Dose‡	10,970	78.5%	11,055	79.1%		31,733	73.4%	27,972	64.7%		11,278	79.4%	9,877	69.5%
Low Dose§	2,999	21.5%	2,914	20.9%		11,517	26.6%	15,278	35.3%		2,927	20.6%	4,328	30.5%
Follow-up Time (in days)	191.0	170.6	233.6	229.2		187.7	168.3	229.9	216.7		233.3	229.0	234.0	218.5
Median	132		136			128		146			135		150	

ACE: angiotensin-converting enzyme inhibitor; ARB: angiotensin-receptor blocker; CHA_2DS_2VASC: congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, age 65 – 74 years, sex category; HAS-BLED: hypertension, abnormal renal and liver function, stroke, bleeding, labile INRs (international normalized ratio), elderly, drugs and alcohol; NOACs: non-vitamin K antagonist oral anticoagulants; NSAIDs: non-steroidal anti-inflammatory drugs; NVAF: non-valvular atrial fibrillation; SD: standard deviation; SE: systemic embolism

* Variables controlled for in the propensity score matching.

† as the INR value is not available in the databases, a modified HAS-BLED score was calculated with a range of 0 to 8.

‡ Standard dose: 5 mg apixaban b.i.d., 150 mg dabigatran b.i.d., 20 mg rivaroxaban QD.

§ Lower dose: 2.5 mg apixaban b.i.d., 75 mg dabigatran b.i.d., 10/15 mg rivaroxaban QD. 12,612 and 2,666 patients received 15 mg and 10 mg rivaroxaban QD, respectively, in the apixaban-rivaroxaban cohort. 3,495 and 833 patients received 10 mg rivaroxaban, respectively, QD in the dabigatran-rivaroxaban cohort.

Figure Legends

Figure 1. Patient Selection Criteria

***470 Edoxaban patients were excluded from the study**

AF: atrial fibrillation; ICD-9-CM: International Classification of Diseases – 9th Revision – Clinical Modification; OAC: oral anticoagulant; VTE: venous thromboembolism.

Figure 2A. Incidence and Hazard Ratios of Stroke/SE and Major Bleeding for NOACs vs Warfarin

GI: gastrointestinal; ICH: intracranial hemorrhage; SE: systemic embolism

Figure 2B. Incidence and Hazard Ratios of Stroke/SE and Major Bleeding for NOACs vs NOACs

GI: gastrointestinal; ICH: intracranial hemorrhage; SE: systemic embolism.

References

[1] Fohtung RB, Rich MW. Identification of patients at risk of stroke from atrial fibrillation. *US Cardiology Review*. 2016; 10(2):60-64.

[2] Lip G, Freedman B, De Caterina R, Potpara TS.Stroke prevention in atrial fibrillation: past, present, and future. Comparing the guidelines and practical decision-making. *Thromb Haemost*. 2017;117(7):1230–1239.

[3] Atrial Fibrillation Investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. *Arch Intern Med*. 1994;154(13):1449–57.

[4] Fitch K, Iwasaki K, Pyenson B. Non-Valvular Atrial Fibrillation & Anticoagulation Therapy: An Actuarial Study of the Medicare Population. Milliman, 2010.

[5] Amin A, Houmsse A, Ishola A, Houmsse M. The current approach of atrial fibrillation management. *Avicenna J Med*. 2016; 6(1):8-16.

[6] Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic review of definitions. *BMC Geriatrics*. 2017;17(1):230.

[7] Focks JJ, Brouwer MA, Wojdyla DM, Thomas L, Lopes RD, Washam JB, Lanas F, Xavier D, Husted S, Wallentin L, Alexander JH, Granger B, Verheugt FWA. Polypharmacy and effects of apixaban versus warfarin in patients with atrial fibrillation: post hoc analysis of the ARISTOTLE trial. *BMJ*. 2016;353:i2868.

[8] Abdel-Aziz MI, Ali MA, Hassan AK, Elfaham TH. Warfarin-drug interactions: an emphasis on influence of polypharmacy and high doses of amoxicillin/clavulanate. *J Clin Pharmacol*. 2016.56(1):39-46.

[9] LaMori JC, Mody SH, Gross HJ, DiBonaventura MD, Patel AA, Schein JR, Nelson WW. Burden of comorbidities among patients with atrial fibrillation. *Ther Adv Cardiovasc Dis*. 2013;7(2):53-62.

[10] Piccini JP, Hellkamp AS, Washam JB, Becker RC, Breithardt GB, Berkowitz SD, Halperin JL, Hankey GJ, Hacke W, Mahaffey KW, Nessel CC, Singer DE, Fox KAA, Patel MR. Polypharmacy and the efficacy and safety of rivaroxaban versus warfarin in the prevention of stroke in patients with nonvalvular atrial fibrillation. *Circulation*. 2016;133(4):352-360.

[11] Wang Y, Singh S, Bajorek B. Old age, high risk medication, polypharmacy: a 'trilogy' of risks in older patients with atrial fibrillation. *Pharmacy Practice (Granada)*. 2016;14(2):706.

[12] Shaikh F, Pasch LB, Newton PJ, Bajorek BV, Ferguson C. Addressing multimorbidity and polypharmacy in individuals with atrial fibrillation. *Curr Cardiol Report*. 2018;20(5):32.

[13] Guthrie B, Makubate B, Hernandez-Santiago V, Dreischulte T. The rising tide of polypharmacy and drug-drug interactions: population database analysis 1995–2010. *BMC medicine*. 2015;13(1):74.

[14] Onder G, Pedone C, Landi F, Cesari M, Vedova CD, Bernabei R, Gambassi G. Adverse drug reactions as cause of hospital admissions: results from the Italian Group of Pharmacoepidemiology in the Elderly (GIFA). *J Am Geriatr Soc*. 2002;50(12):1962-1968.

[15] Li X, Deitelzweig S, Keshishian A, Hamilton M, Horblyuk R, Gupta K, Luo X, Mardekian J, Friend K, Nadkarni A, Pan X, Lip GYH. Effectiveness and safety of apixaban versus warfarin in non-valvular atrial fibrillation patients in “real-world” clinical practice. A propensity-matched analysis of 76,940 patients. *Thromb Haemost.* 2017;117(6):1072–1082.

[16] Lip GYH, Keshishian A, Li X, Hamilton M, Masseria C, Gupta K, Luo X, Mardekian J, Friend K, Nadkarni A, Pan X, Baser O, Deitelzweig S. Effectiveness and safety of oral anticoagulants among non-valvular atrial fibrillation patients. *Stroke.* 2018;49(12):2933–2944.

[17] Thigpen JL, Dillon C, Forster KB, Henault L, Quinn EK, Tripodis Y, Berger PB, Hylek EM, Limdi NA. Validity of international classification of disease codes to identify ischemic stroke and intracranial

hemorrhage among individuals with associated diagnosis of atrial fibrillation. *Circ Cardiovasc Qual Outcomes*. 2015;8(1):8-14.

[18] Cunningham A, Stein CM, Chung CP, Daugherty JR, Smalley WE, Ray WA. An automated database case definition for serious bleeding related to oral anticoagulant use. *Pharmacoepidemiol Drug Saf*. 2011;20(6):560-566.

[19] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbiditiy in longitudinal studies: Development and validation. *J Chronic Dis*. 1987;40(5):373-383.

[20] Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med*. 2009;28(25):3083-3107.

[21] Austin PC. The use of propensity score methods with survival or time- to- event outcomes: reporting measures of effect similar to those used in randomized experiments. *Stat Med*. 2014;33(7):1242-1258.

[22] Bjerrum L, Søgaard J, Hallas J, Kragstrup J. Polypharmacy: correlations with sex, age and drug regimen a prescription database study. *Eur J Clin Pharmacol*. 1998;54(3):197-202.

[23] Martinez BK, Baker WL, Sood NA, Bunz TJ, Meinecke AK, Eriksson D, Coleman CI. Influence of Polypharmacy on the effectiveness and safety of rivaroxaban versus warfarin in patients with nonvalvular atrial fibrillation. *Pharmacother: J Human Pharmacol and Drug Ther*. 2019;39(2):196-203.

[24] Bonde AN, Martinussen T, Lee C JY, Lip GYH, Staerk L, Bang CN, Bhattacharya J, Gislason G, Torp-Pedersen C, Olesen JB, Hlatky MA. Rivaroxaban versus apixaban for stroke prevention in atrial fibrillation: an instrumental variable analysis of a nationwide cohort. *Circulation: Cardiovascular Quality and Outcomes.* 2020;13(4): e006058.

[25] Yao X,. Noseworthy P. Finding order in chaos: can instrumental variables help us understand observed treatment effects? *Circ Cardiovasc Qual Outcomes*. 2020: e006650.

[26] Huybrechts KF, Gopalakrishnan C, Franklin JM, Zint K, Franca LR, Bartels DB, Landon J, Schneeweiss S. Claims data studies of direct oral anticoagulants can achieve balance in important clinical parameters only observable in electronic health records. *Clin Pharmacol Ther*. 2019;105(4):979-993.

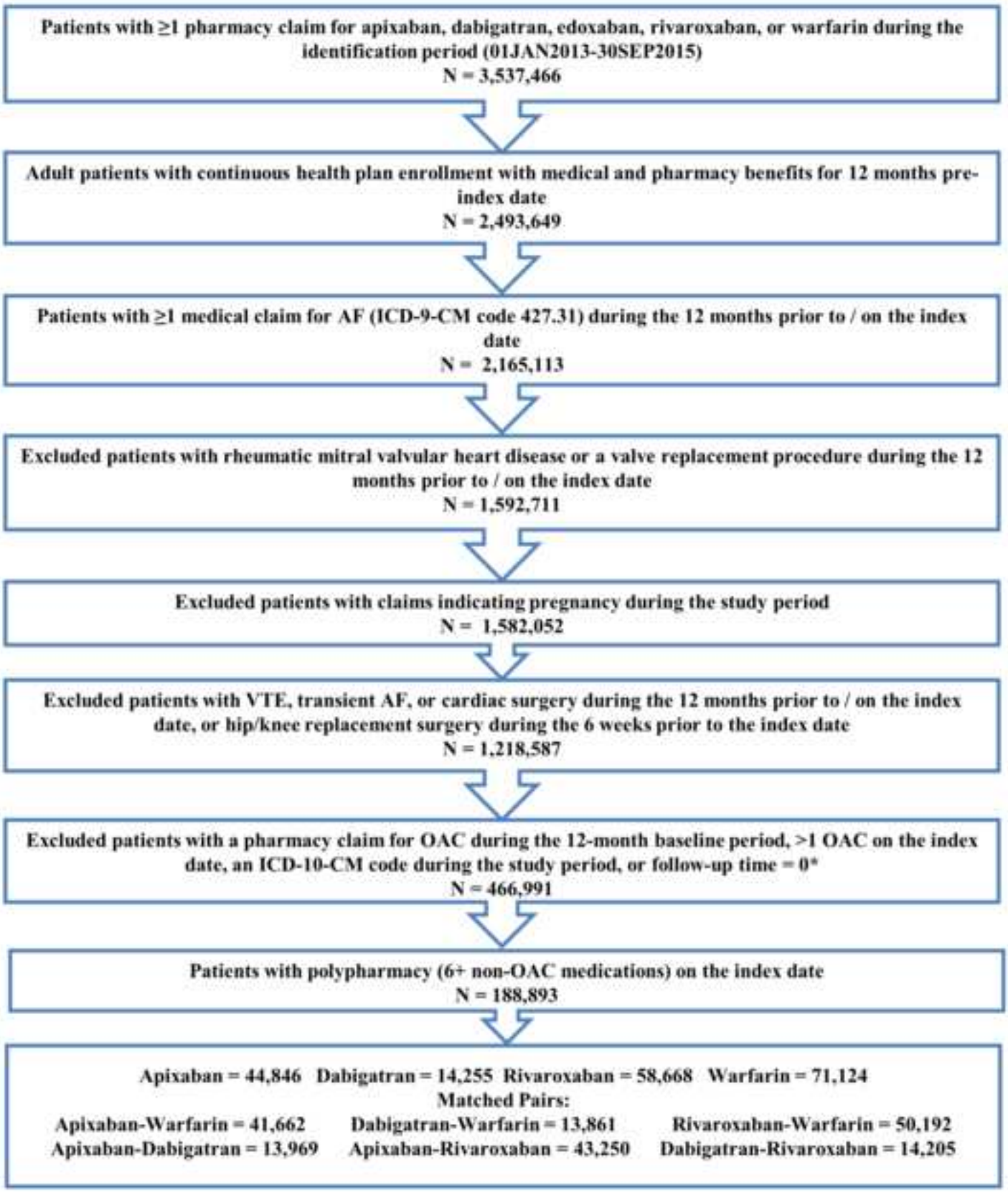

Figure 2

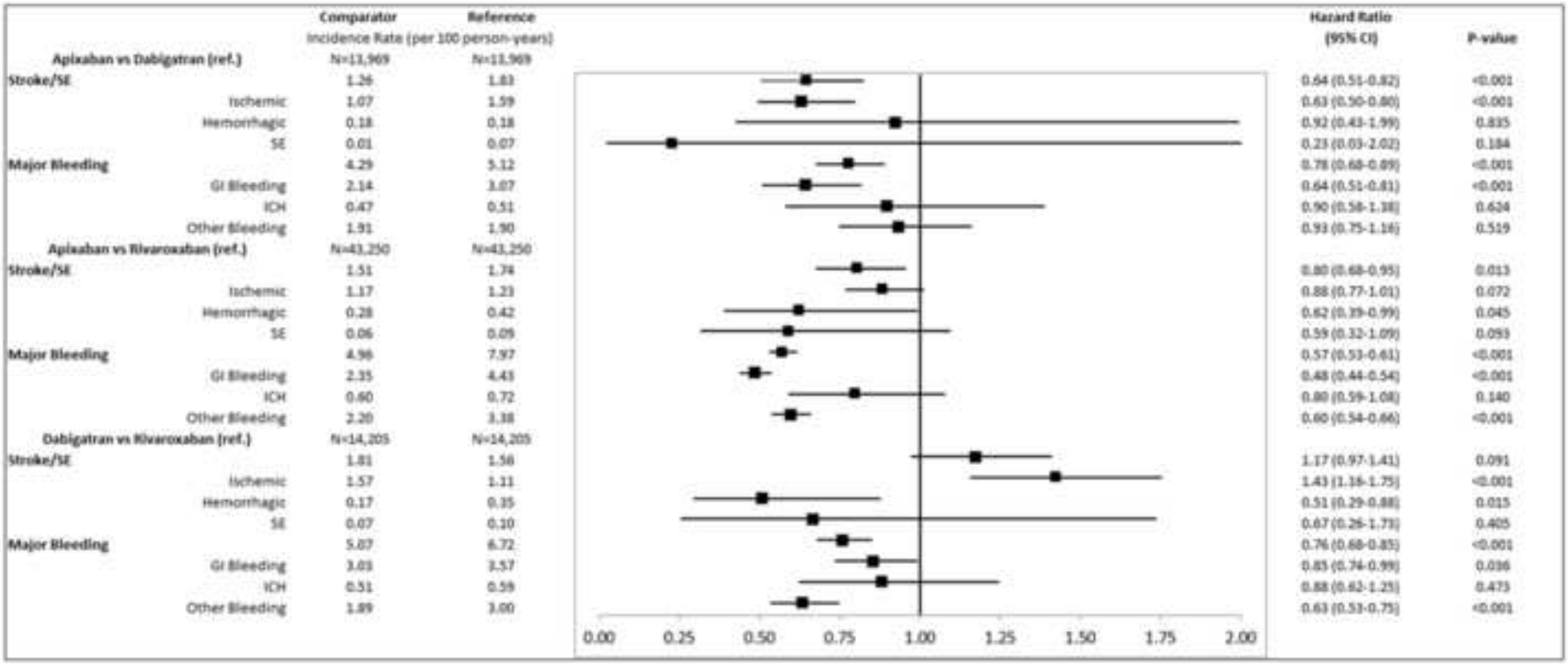

Figure 2

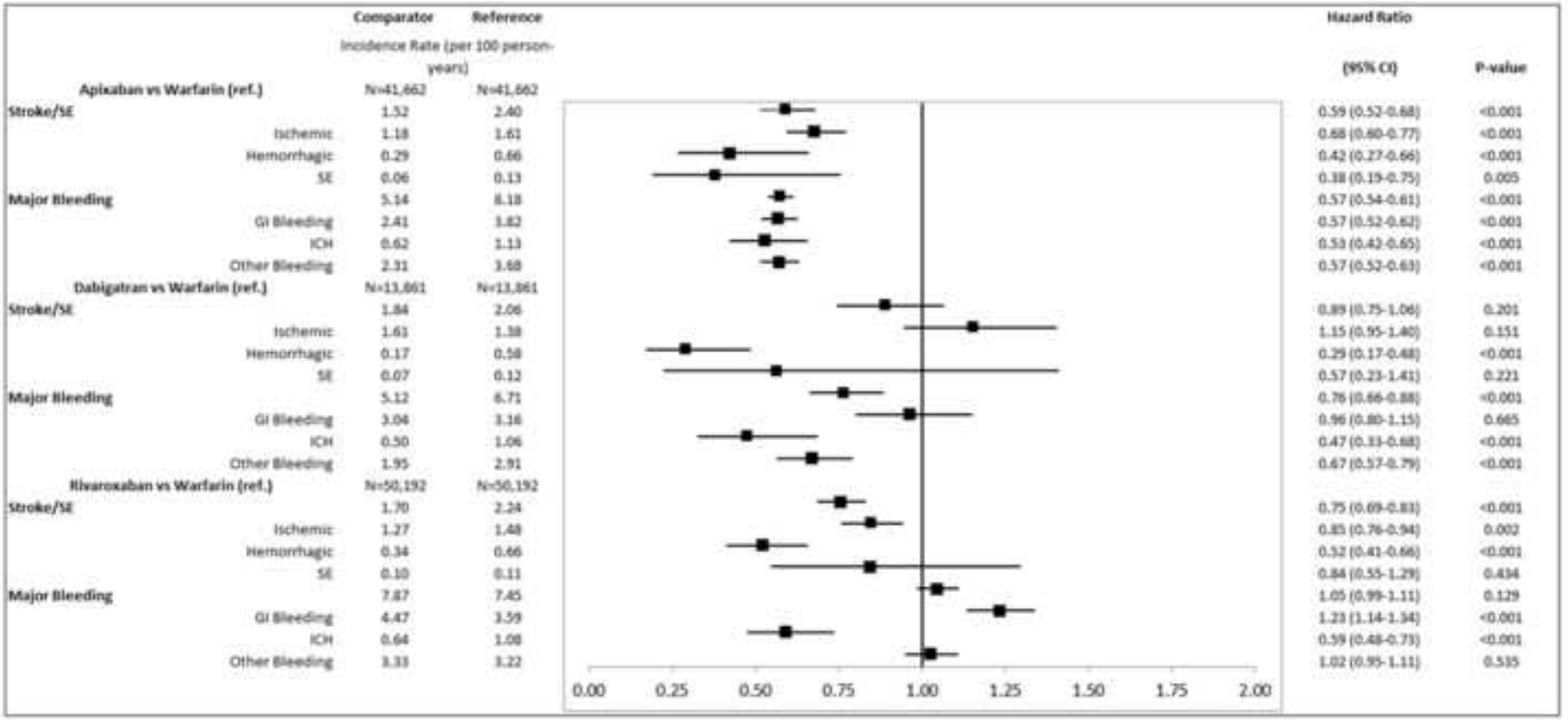

Figure 1