Comparative Effectiveness and Safety of Non-VKA Oral Anticoagulants versus Warfarin in Non-valvular Atrial Fibrillation Patients with Differential Duration of Treatment: An Analysis of the ARISTOPHANES Study

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INTRODUCTION

- Atrial fibrillation (AF) is the most common arrhythmia in the elderly and an independent risk factor for stroke.[1] Oral anticoagulants (OACs) are recommended for stroke prevention among AF patients.[2]
- Warfarin, an oral vitamin K antagonist (VKA), has been found to reduce stroke by 60% when compared to controls, such as aspirin and placebo, and was the traditional treatment for stroke prevention among non-valvular AF (NVAF) patients.[3]
- In recent years, four non-VKA OACs (NOACs; apixaban, dabigatran, edoxaban, and rivaroxaban) have been approved for stroke prevention in AF based on their non-inferiority in efficacy and safety compared to warfarin in randomized controlled trials (RCTs).[4] Additionally, no anticoagulation monitoring is required and fewer drug and food interactions are evident.[5]
- The ARISTOPHANES (Anticoagulants for Reduction In STroke: Observational Pooled analysis on Health outcomes ANd Experience of patientS; ClinicalTrials.gov ID: NCT03087487) study showed that NOACs were associated with lower risks of stroke/systemic embolism (SE) and variable comparative risks of major bleeding (MB) versus warfarin.[6]
- There is evidence of short NOAC treatment durations having a different clinical effect than long NOAC treatment durations.[7] However, limited real-world evidence exists on comparative effectiveness and safety of NOACs versus warfarin by duration of treatment, especially after a long term treatment.[8,9]

OBJECTIVES

This subgroup analysis of the ARISTOPHANES study aimed to assess long-term use of NOACs vs. warfarin by evaluating the risk of stroke/SE and MB among NVAF patients by duration of treatment (<1 and ≥1 year).

METHODS

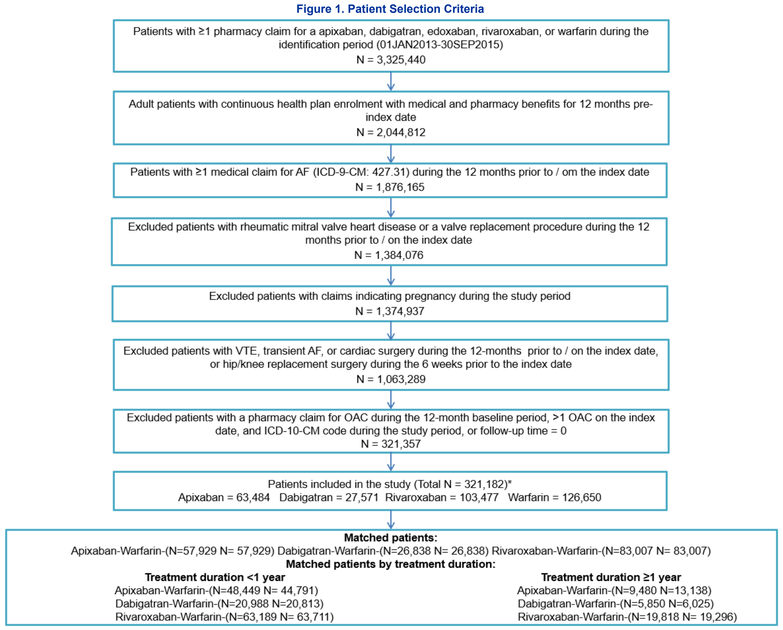
Data Source

This was a retrospective observational study using US Centers for Medicare and Medicaid Services (CMS), Truven MarketScan® Commercial Claims and Encounter and Medicare Supplemental and Coordination of Benefits Database (“MarketScan”), IMS PharMetrics Plus™ Database (“PharMetrics”), Optum Clinformatics™ Data Mart (“Optum”), and the Humana Research Database (“Humana”), covering >180 million beneficiaries annually (~56% of the US population).

Study Sample

- AF patients (International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] code 427.31) aged ≥18 years with ≥1 pharmacy claim for apixaban, dabigatran, edoxaban, rivaroxaban, or warfarin from January 1, 2013 - September 30, 2015 were included in the study.
- The first NOAC prescription date was designated as the index date for patients with NOAC claim(s); the first warfarin prescription date was designated as the index date for those without a NOAC claim.
- Patients were required to have continuous medical and pharmacy health plan enrollment for ≥12 months prior to the index date (baseline period).
- Inclusion and exclusion criteria are shown in Figure 1.
- The follow-up period was from the day after the index date to 30 days post discontinuation date, switch date, death (only inpatient death for the commercial databases and all-cause death for the Medicare database), end of continuous health plan enrollment, or the end of the study period, whichever occurred first.

Figure 1. Patient Selection Criteria



*Edoxaban was not included in the final analysis given the recent US Food and Drug Administration approval in 2015 and hence small sample size (N = 175).
AF: atrial fibrillation; ICD-9-CM: International Classification of Diseases, 9th revision, Clinical Modification; 10-CM: 10th revision; OAC: oral anticoagulant; VTE: venous thromboembolism.

METHODS - cont’d

Outcomes

- Outcome measures were time to first stroke/SE and MB events based on the principal or first-listed ICD-9-CM diagnosis on an inpatient claim. The diagnosis codes used for stroke/SE and MB were based on validated administrative claims-based algorithms and the International Society on Thrombosis and Haemostasis’ definition of MB.[10,11]
- Stroke/SE was further categorized into ischemic stroke, hemorrhagic stroke, and SE; MB was further categorized into gastrointestinal (GI) bleeding, intracranial hemorrhage (ICH), and other MB.

Statistical Analysis

- Patients were 1:1 matched based on the propensity scores generated by logistic regression using the nearest neighbor matching method without replacement with a caliper of 0.01.[12] Demographics, Charlson Comorbidity Index (CCI) scores, baseline bleeding and stroke/SE history, comorbidities, and baseline co-medications were included in the models.
- After 1:1 propensity score matching (PSM) in each database between NOACs and warfarin (apixaban-warfarin, dabigatran-warfarin, and rivaroxaban-warfarin), the resulting patient records were pooled.
- Within the matched NOAC-warfarin cohorts, patients were analyzed separately by the length of treatment duration (<1 & ≥1 year). The balance of matched covariates was checked (Tables 1&2).
- Incidence of stroke/SE and MB in the PSM-adjusted cohorts were calculated as the number of stroke/SE and MB events, respectively, per 100 person-years.
- Cox proportional hazards models with robust sandwich estimates were used to estimate hazard ratios of stroke/SE and MB during the observed treatment duration.

RESULTS

- After applying the selection criteria, a total of 321,182 NVAF patients were identified – including 63,484 apixaban, 27,571 dabigatran, 103,477 rivaroxaban, and 126,650 warfarin patients. Edoxaban was not included in the final patient population given the small sample size (N =175). After PSM, a total of 285,292 unique patients were included in the three matched cohorts: 57,929 apixaban-warfarin, 26,838 dabigatran-warfarin, and 83,007 rivaroxaban-warfarin PSM pairs.
- Given the variety of time for market entry, around 16%, 22%, and 24% of apixaban, dabigatran, and rivaroxaban patients, respectively, had treatment duration ≥1 year.
- After separating the matched drug cohorts by treatment duration, baseline characteristics remained balanced. The mean treatment duration for patients with shorter (<1 year) vs longer (≥1 year) duration was 4-5 months vs 18-21 months, respectively, across the three matched cohorts.
- The mean ages for the <1 year treatment duration cohorts were 71-74 years with mean CHA_2DS_2-VASc scores of 3.3-3.7 and HAS-BLED scores ranging from 2.6-3.0 (Table 1).
- The mean ages for the ≥1 year treatment duration cohorts were 74-76 years with mean CHA_2DS_2-VASc scores of 3.6-3.8 and HAS-BLED scores of 2.8-3.0 (Table 2).

Table 1. PSM Baseline Characteristics of Patients Prescribed Warfarin, Apixaban, Dabigatran, or Rivaroxaban (Treatment Duration <1 year)

	Apixaban Cohort (N = 48,449)		Warfarin Cohort (N = 44,791)		Dabigatran Cohort (N = 20,988)		Warfarin Cohort (N = 20,813)		Rivaroxaban Cohort (N = 63,189)		Warfarin Cohort (N = 63,711)	
	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD
Age	74.0	11.1	73.8	11.2	71.3	11.4	71.5	11.4	74.1	10.6	74.1	10.6
<65	8,961	18.5%	8,697	19.4%	5,411	25.8%	5,408	26.0%	10,413	16.5%	10,713	16.8%
65-74	14,955	30.9%	13,633	30.4%	6,928	33.0%	6,936	33.3%	21,011	33.3%	21,143	33.2%
75-79	8,532	17.6%	7,783	17.4%	3,573	17.0%	3,562	17.1%	11,797	18.7%	11,895	18.7%
≥80	16,001	33.0%	14,678	32.8%	5,076	24.2%	4,907	23.6%	19,968	31.6%	19,960	31.3%
Gender												
Male	26,536	54.8%	24,455	54.6%	12,579	59.9%	12,387	59.5%	35,481	56.2%	35,631	55.9%
Female	21,913	45.2%	20,336	45.4%	8,409	40.1%	8,426	40.5%	27,707	43.8%	28,080	44.1%
U.S. Geographic Region												
Northeast	7,362	15.2%	6,882	15.4%	3,767	17.9%	3,923	18.8%	10,429	16.5%	10,813	17.0%
North Central	11,092	22.9%	10,145	22.6%	5,035	24.0%	4,939	23.7%	15,663	24.8%	15,425	24.2%
South	21,536	44.5%	19,807	44.2%	8,430	40.2%	8,299	39.9%	24,941	39.5%	25,253	39.6%
West	8,277	17.1%	7,775	17.4%	3,633	17.3%	3,526	16.9%	11,894	18.8%	11,947	18.8%
Other	182	0.4%	182	0.4%	123	0.6%	126	0.6%	262	0.4%	273	0.4%
Baseline Comorbidity												
Deyo-Charlson Comorbidity Index	3.0	2.7	3.0	2.7	2.5	2.5	2.5	2.6	2.9	2.7	2.9	2.7
$CHADS_2$ Score	2.3	1.4	2.3	1.3	2.1	1.3	2.1	1.3	2.3	1.4	2.3	1.3
CHA_2DS_2-VASc Score	3.7	1.8	3.7	1.7	3.3	1.8	3.3	1.8	3.7	1.7	3.7	1.7
HAS-BLED Score[a]	3.0	1.4	3.0	1.4	2.6	1.4	2.6	1.4	2.9	1.4	2.9	1.4
Bleeding history	9,627	19.9%	9,043	20.2%	3,455	16.5%	3,485	16.7%	12,667	20.0%	12,570	19.7%
Non-stroke/ SE Peripheral vascular disease	25,487	52.6%	23,616	52.7%	9,675	46.1%	9,647	46.4%	32,464	51.4%	32,658	51.3%
Stroke	5,874	12.1%	5,485	12.2%	2,033	9.7%	2,057	9.9%	7,243	11.5%	7,521	11.8%
Transient ischemic attack (TIA)	3,555	7.3%	3,245	7.2%	1,250	6.0%	1,266	6.1%	4,261	6.7%	4,378	6.9%
Anemia and coagulation defects	12,854	26.5%	12,256	27.4%	4,491	21.4%	4,663	22.4%	16,985	26.9%	17,062	26.8%

[a]As the INR value was not available in the data, a modified HAS-BLED score was calculated using a range of 0 to 8.
CHA_2DS_2-VASc: 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, elderly, drugs, and alcohol; PSM: propensity score matching; SD: standard deviation; SE: systemic embolism

Table 2. PSM Baseline Characteristics of Patients Prescribed Warfarin, Apixaban, Dabigatran, or Rivaroxaban (Treatment Duration ≥1 year)

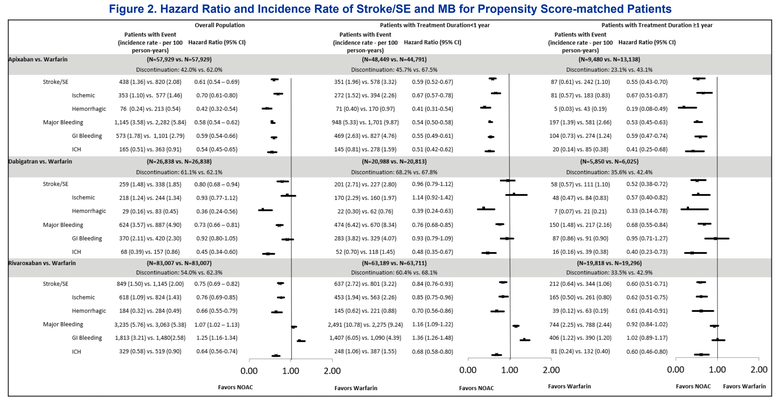
	Apixaban Cohort (N = 9,480)		Warfarin Cohort (N = 13,138)		Dabigatran Cohort (N = 5,850)		Warfarin Cohort (N = 6,025)		Rivaroxaban Cohort (N = 19,818)		Warfarin Cohort (N = 19,296)	
	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD
Age	75.7	9.8	75.5	9.6	73.9	9.6	73.8	9.7	75.4	9.0	75.6	9.1
<65	1,154	12.2%	1,477	11.2%	918	15.7%	929	15.4%	1,981	10.0%	1,825	9.5%
65-74	2,939	31.0%	4,339	33.0%	2,043	34.9%	2,184	36.2%	6,955	35.1%	6,773	35.1%
75-79	1,968	20.8%	2,730	20.8%	1,224	20.9%	1,277	21.2%	4,307	21.7%	4,218	21.9%
≥80	3,419	36.1%	4,592	35.0%	1,665	28.5%	1,635	27.1%	6,575	33.2%	6,480	33.6%
Gender												
Male	4,808	50.7%	6,707	51.1%	3,208	54.8%	3,349	55.6%	10,224	51.6%	10,114	52.4%
Female	4,672	49.3%	6,431	48.9%	2,642	45.2%	2,676	44.4%	9,594	48.4%	9,182	47.6%
U.S. Geographic Region												
Northeast	1,633	17.2%	2,077	15.8%	1,211	20.7%	1,126	18.7%	3,761	19.0%	3,307	17.1%
North Central	2,133	22.5%	3,149	24.0%	1,484	25.4%	1,572	26.1%	4,921	24.8%	5,096	26.4%
South	4,038	42.6%	5,668	43.1%	2,105	36.0%	2,303	38.2%	7,560	38.1%	7,309	37.9%
West	1,660	17.5%	2,220	16.9%	1,034	17.7%	1,008	16.7%	3,533	17.8%	3,549	18.4%
Other	16	0.2%	24	0.2%	16	0.3%	16	0.3%	43	0.2%	35	0.2%
Baseline Comorbidity												
Deyo-Charlson Comorbidity Index	2.6	2.4	2.7	2.5	2.4	2.3	2.5	2.3	2.6	2.4	2.7	2.4
$CHADS_2$ Score	2.4	1.3	2.4	1.3	2.3	1.2	2.3	1.3	2.3	1.3	2.4	1.2
CHA_2DS_2-VASc Score	3.8	1.6	3.8	1.6	3.6	1.6	3.6	1.6	3.8	1.6	3.8	1.5
HAS-BLED Score[a]	3.0	1.3	3.0	1.3	2.8	1.2	2.8	1.3	2.9	1.2	3.0	1.2
Bleeding history	1,773	18.7%	2,354	17.9%	929	15.9%	962	16.0%	3,432	17.3%	3,493	18.1%
Non-stroke/ SE Peripheral vascular disease	4,904	51.7%	6,875	52.3%	2,714	46.4%	2,793	46.4%	9,847	49.7%	9,787	50.7%
Stroke	1,158	12.2%	1,639	12.5%	671	11.5%	717	11.9%	2,471	12.5%	2,347	12.2%
Transient ischemic attack (TIA)	775	8.2%	1,104	8.4%	465	7.9%	420	7.0%	1,557	7.9%	1,513	7.8%
Anemia and coagulation defects	2,401	25.3%	3,163	24.1%	1,252	21.4%	1,227	20.4%	4,670	23.6%	4,561	23.6%

[a]As the INR value was not available in the data, a modified HAS-BLED score was calculated using a range of 0 to 8.
CHA_2DS_2-VASc: 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, elderly, drugs, and alcohol; PSM: propensity score matching; SD: standard deviation; SE: systemic embolism

RESULTS (cont’d)

- For patients with <1 year duration of treatment, apixaban patients had a lower risk of stroke/SE and MB versus warfarin; dabigatran patients had a lower risk of MB and similar risk of stroke/SE versus warfarin; and rivaroxaban patients had a lower risk of stroke/SE and higher risk of MB versus warfarin (Figure 2).
- For patients with ≥1 year duration of treatment, apixaban and dabigatran patients had a lower risk of stroke/SE and MB versus warfarin and rivaroxaban patients had a lower risk of stroke/SE and similar risk of MB versus warfarin (Figure 2).
- Apixaban is the only NOAC that was associated with a lower risk of stroke/SE and MB versus warfarin regardless of treatment duration.

Figure 2. Hazard Ratio and Incidence Rate of Stroke/SE and MB for Propensity Score-matched Patients



GI: gastrointestinal; ICH: intracranial hemorrhage; MB: major bleeding; NOAC: non-vitamin K antagonist oral anticoagulant; SE: systemic embolism

LIMITATIONS

- PSM was conducted between each cohort pair, thus the results are not comparable across the matched populations.
- Only associations could be concluded from this retrospective observational study. Although cohorts were matched through PSM, potential residual confounders exist such as over-the-counter use of aspirin and dose changes in OAC treatment.
- Given the nature of claims data, laboratory test results and biomarkers were not available. Diagnoses and drug prescriptions were identified claims. Missing values, coding errors, and lack of clinical accuracy may have introduced bias into the study.
- Although some of the datasets contain information from different insurance plans that do not overlap at the plan level, others are employer-based claims datasets which may contain duplicate patient records when pooled together; however, the number of such duplicates is likely to be low – based on a published estimate of 0.5% – and therefore are unlikely to have a significant impact on the result.[13]

CONCLUSIONS

- **Among NVAF patients with duration of treatment <1 and ≥1 year in the ARISTOPHANES study, apixaban is the only drug that was associated with a lower risk of stroke/SE and MB regardless of studied treatment duration.**
- **These findings indicate varying long-term effectiveness and safety outcomes between NOACs and warfarin.**

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DISCLOSURES

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