



Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original article

Delaying clinical events among patients with non-valvular atrial fibrillation treated with oral anticoagulants: Insights from the ARISTOPHANES study

Steven Deitelzweig^{a,*}, Allison Keshishian^b, Amiee Kang^c, Aaron Jenkins^d, Nipun Atreja^c, Patricia Schuler^c, Jenny Jiang^c, Huseyin Yuce^e, Xiaoxi Sun^b, Gregory Y.H. Lip^f

^a Ochsner Clinic Foundation, Department of Hospital Medicine, New Orleans, LA, USA and The University of Queensland School of Medicine, Ochsner Clinical School, New Orleans, LA, USA

^b STATinMED, LLC, Ann Arbor, MI, USA

^c Bristol-Myers Squibb Company, Lawrenceville, NJ, USA

^d Pfizer Ltd, Tadworth, UK

^e New York City College of Technology, City University of New York, New York, NY, USA

^f Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, United Kingdom; and Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

ARTICLE INFO

Keywords:

Oral anticoagulant therapy

Atrial fibrillation

Non-vitamin K antagonist oral anticoagulant

Direct oral anticoagulant

Non-valvular atrial fibrillation

NVAF

ABSTRACT

Background: Oral anticoagulants (OACs) mitigate stroke and systemic embolism (SE) risk in non-valvular atrial fibrillation (AF) patients but can increase the risk of major bleeding (MB). This study analyzed the gains in event-free time for these outcomes among OAC treatment options represented in the ARISTOPHANES study.

Methods: This sub-analysis consisted of NVAF patients who initiated warfarin, apixaban, dabigatran, or rivaroxaban from 01JAN2013-30SEP2015, with data pooled from Medicare and 4 US commercial claims databases. Propensity score matching was conducted between non-vitamin K antagonist OAC (NOAC) and warfarin cohorts in each database and results were pooled. Laplace regression was used to evaluate the delay in time to stroke/SE and MB events between NOACs and warfarin and between NOACs after the first 12-months of follow-up.

Results: The population included 466,991 patients (167,413 warfarin; 108,852 apixaban; 37,724 dabigatran; and 153,002 rivaroxaban). Event-free time gain (95% confidence interval) for apixaban versus warfarin was 101 days (78- 124) for stroke/SE and 116 (103- 130) days for MB. The gain in event-free time for dabigatran versus warfarin was 45 days (3- 87) for stroke/SE and 92 (68- 116) days for MB. The gain in event-free time for rivaroxaban versus warfarin was 63 days (42- 84) for stroke/SE but event-free time decreased by 18 (-31-6) days for MB.

Conclusions: Over 12 months after initiation, apixaban and dabigatran conferred progressive increases in event free time for stroke/SE and MB vs warfarin, whereas rivaroxaban conferred an increase in stroke/SE-free time but a loss in MB-free time vs warfarin.

1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia in the United States, with prevalence currently estimated at 6 million which is projected to increase to 12 million by 2030, in line with the aging population [1,2]. AF is associated with a 5-fold increased risk of stroke [3], a 3 to 11-fold risk of heart failure (for men and women, respectively) [4], and a higher risk of premature mortality and increasing healthcare costs [5].

Clinical guidelines for the management of patients with non-valvular

AF (NVAF) recommend oral anticoagulants (OACs) as thromboprophylaxis [6] as part of a holistic and integrated care approach to AF care that is associated with better outcomes [7,8]. Non-vitamin K antagonist oral anticoagulants (NOACs) are now recommended (and increasingly used) as first line OAC treatment choice among eligible patients given their favorable safety and efficacy as compared with warfarin [9,10].

While OAC utilization has increased in recent years, especially following FDA approval of NOACs beginning in 2010, underutilization remains an issue in routine practice [11–14]. Physician reluctance to prescribe OACs to eligible elderly patients due to concerns over bleeding

* Corresponding author at: 1514 Jefferson Highway, 11th floor – Hospital Medicine Oschner Health System, New Orleans, LA 70121, USA.

E-mail address: sdeitelzweig@ochsner.org (S. Deitelzweig).

<https://doi.org/10.1016/j.ejim.2022.10.021>

Received 26 May 2022; Received in revised form 30 September 2022; Accepted 24 October 2022

0953-6205/© 2022 The Authors. Published by Elsevier B.V. on behalf of European Federation of Internal Medicine. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

may contribute to persistent underutilization or unnecessarily limit treatment options, even though such patients do well on NOACs [15]. Thus, it is important for clinicians and patients to comprehensively consider the risks and benefits of OAC treatment overall, as well as the advantages of specific treatments for individual patients. Traditionally, the treatment effects of OACs have been calculated through proportional hazards regression modeling and expressed as hazard ratios, but this presentation of data can impede lay comprehension of risks and benefits, as it shows only the absolute risk of patients developing a clinical event [16]. In contrast to time-to-event analyses that are typically the basis for calculating the hazard ratio, delay-of-event analyses illustrate differences between treatments in the delay of an event at a specific timepoint among only patients who experience the event, on a clinically-relevant time scale [16]. Such measures have been proposed as an adjunct to hazard ratios to aid patient understanding and clinical decision making [16–23].

To our best knowledge, only one previous study has employed this measure to provide supplemental data presentation on safety and effectiveness outcomes among OAC-treated patients with AF [16]. However, this study was a post hoc analysis of the ARISTOTLE randomized controlled trial population, which compared only warfarin and apixaban initiators [24].

To add to the evidence on effectiveness and safety outcomes in routine contemporary practice, we conducted an observational cohort study among a large, nationally-representative sample of combined commercial and federal health plan enrollees from the ARISTOPHANES study [25]. Our new analysis compared the delay of stroke/SE and MB events among comprehensive treatment cohorts of newly-anticoagulated patients with AF, at different follow-up time points.

2. Methods

Details of the ARISTOPHANES study have been previously published [25]. ARISTOPHANES was a retrospective cohort study that used a large, nationally representative pooled commercial and federal health plan dataset from January 1, 2013, through September 30, 2015. The data sources included the MarketScan® Commercial Claims and Encounter and Medicare Supplemental and Coordination of Benefits Database, the IQVIA PharMetrics Plus™ Database, the Optum Clinformatics™ Data Mart, the Humana Research Database, and fee-for-service (FFS) Medicare data from the US Centers for Medicare & Medicaid Services (CMS). Database records included comprehensive demographic and clinical information and International Classification of Diseases, Ninth Revisions, Clinical Modification (ICD-9-CM) codes, Healthcare Common Procedure Coding System codes, and National Drug Codes. The original study has detailed descriptions of the datasets, the rationale for the pooling process, and the approaches to minimizing potential patient record duplicates across data sources [25].

2.1. Patient selection

The study included adult patients with ≥ 1 AF diagnosis and ≥ 1 pharmacy claim for an OAC (apixaban, dabigatran, rivaroxaban, or warfarin) between January 1, 2013, and September 30, 2015. Edoxaban was excluded because of the small sample size ($N=223$, 0.1% of sample). 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 further required to have continuous medical and pharmacy health plan enrollment for ≥ 12 months before the index date (baseline period). Patients were excluded if treated with any OAC during baseline or had evidence of valvular heart disease, venous thromboembolism, transient AF (pericarditis, hyperthyroidism, thyrotoxicity), or heart valve replacement/transplant during the baseline period. Additional exclusion criteria appear in Supplemental Fig. 1.

2.2. Baseline variables

Patient demographics and clinical characteristics from the original study population were assessed during the 12-month baseline period; age, sex, and clinical scores were measured on the index date, while comorbidities and event history were assessed during the 12-month pre-index baseline period. Deyo-Charlson comorbidity index, CHA₂DS₂-VASc, and modified HAS-BLED scores (without international normalized ratio [INR], lab values, and self-reported alcohol consumption) and evidence of bleeding and stroke were recorded.

2.3. Outcome measures

We compared the delay of the first event in each cohort for: stroke/SE, including ischemic stroke, hemorrhagic stroke, and systemic embolism (SE); major bleeding (MB), including gastrointestinal (GI) bleeding, intracranial hemorrhage, and bleeding at other key sites (e.g., the genitourinary tract, respiratory tract, or ocular area) [11,16,26]. We assessed outcomes at 3, 6, 12, and 18 months after initiation (index date). We defined outcomes by hospitalizations with stroke/SE or MB as the principal or first-listed diagnosis. Follow-up ranged from 1 day post-index date through the earliest of 30 days after discontinuation, a 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 study end.

2.4. Statistical analysis

We conducted PSM between the warfarin and NOAC cohorts (warfarin [reference] vs: apixaban; dabigatran; and rivaroxaban) and between the NOAC cohorts (apixaban vs dabigatran; apixaban vs rivaroxaban; and dabigatran vs rivaroxaban). We matched patients 1:1 in each dataset based on logistic regression using demographics, Deyo-Charlson comorbidity index scores, clinically relevant comorbidities, and baseline concomitant medications. We matched patients with the nearest neighbor method without replacement (with a caliper of 0.01) and checked covariate balance through standardized differences, with a threshold of 10%. We estimated delay of events and corresponding 95% confidence intervals (CIs) in days with Laplace regression models, which is a type of quantile regression for censored data [22,27]. The delay of the event was calculated at four time points (3, 6, 12, and 18 months) where the differences in time-to-stroke/SE or MB between the two cohorts at equal proportions of events (percentiles) were calculated. We calculated the risk of stroke/SE and MB using Cox proportional hazard models, with robust sandwich estimates, with the threshold of statistical significance set at $P < 0.05$.

2.5. Institutional review board approval

Since this study did not involve the collection, use, or transmittal of individually identifiable data, it was exempt from Institutional Review Board review. Both the datasets and the security of the offices where analysis was completed (and where the datasets are kept) meet the requirements of the Health Insurance Portability and Accountability Act of 1996.

3. Results

3.1. Baseline characteristics

The 466,991 selected patients in the ARISTOPHANES study included: 167,413 prescribed warfarin; 108,852 prescribed apixaban; 37,724 prescribed dabigatran; and 153,002 prescribed rivaroxaban. The population was predominantly male (>50% for all), with mean ages ranging from 73 to 77. Deyo-CCI scores ranged from 2.5 to 3.3, CHA₂DS₂-VASc scores from 3.5 to 4.0, and HAS-BLED scores from 2.7 to

3.1. The most prevalent baseline comorbidity across cohorts was hypertension (83-85%), followed by peripheral vascular disease (46-53%).

After PSM, the following cohorts were created: apixaban-warfarin (n=100,977 per arm), dabigatran-warfarin (n=36,990 per arm), rivaroxaban-warfarin (n=125,068 per arm), apixaban-dabigatran (n=37,314 per arm), apixaban-rivaroxaban (n=107,236 per arm), and dabigatran-rivaroxaban (n= 37,693 per arm). Baseline characteristics are shown in Tables 1 and 2.

3.2. Warfarin vs NOAC

At 12 months post-initiation, 0.65% of apixaban patients had a hospitalization with a stroke/SE diagnosis; apixaban delayed the events by 101 days (95% CI: 78-124) as compared with warfarin. Delays were directionally consistent across time points and tended to increase with a longer time from the index date. A total of 1.75% of the apixaban patients in the same matched cohorts had a hospitalization with an MB diagnosis at 12 months; apixaban delayed the events by 116 days (95% CI: 103-130) as compared with warfarin. Delays across timepoints followed trends similar to stroke/SE (Table 3). Overall, the apixaban cohort was 36% less likely to experience stroke/SE (HR: 0.64; 95% CI: 0.58-0.70) and 40% less likely to experience MB (HR:0.60; 95% CI: 0.56-0.63) as compared with warfarin (Table 3).

At 12 months, 0.81% of the dabigatran patients in the matched dabigatran-warfarin cohorts had a hospitalization with a stroke/SE diagnosis; dabigatran delayed the events by 45 days (95% CI: 3-87) as compared with warfarin. A total of 1.92% of the dabigatran patients in the same matched cohort had a hospitalization with an MB diagnosis; dabigatran delayed the events by 92 days (95% CI: 68-116) as compared with warfarin. For both stroke/SE and MB, delays were directionally consistent across time points and tended to increase with longer time from the index date (Table 3). Overall, the dabigatran cohort was 18% less likely to experience stroke/SE (HR:0.82; 95% CI: 0.71-0.95) and 29% less likely to experience MB (HR:0.71; 95% CI: 0.65-0.78) as compared with warfarin (Table 3).

Table 1

Baseline characteristics of patients prescribed warfarin and NOACs after propensity score matching.

	Apixaban (N = 100,977) Mean/%	Warfarin (N = 100,977) Mean/%	Dabigatran (N = 36,990) Mean/%	Warfarin (N = 36,990) Mean/%	Rivaroxaban (N = 125,068) Mean/%	Warfarin (N = 125,068) Mean/%
Age	76.1	76.0	73.2	73.3	75.6	75.7
<65	10,115 (10.0%)	10,174 (10.1%)	6,329 (17.1%)	6,337 (17.1%)	12,394 (9.9%)	12,538 (10.0%)
65-74	32,675 (32.4%)	32,895 (32.6%)	13,307 (36.0%)	13,526 (36.6%)	42,870 (34.3%)	42,983 (34.4%)
75-79	20,172 (20.0%)	20,048 (19.9%)	7,256 (19.6%)	7,392 (20.0%)	26,191 (20.9%)	26,074 (20.8%)
≥80	38,015 (37.7%)	37,860 (37.5%)	10,098 (27.3%)	9,735 (26.3%)	43,613 (34.9%)	43,473 (34.8%)
Sex						
Male	51,880 (51.4%)	51,811 (51.3%)	20,933 (56.6%)	21,078 (57.0%)	66,267 (53.0%)	66,563 (53.2%)
Female	49,097 (48.6%)	49,166 (48.7%)	16,057 (43.4%)	15,912 (43.0%)	58,800 (47.0%)	58,505 (46.8%)
Baseline Comorbidity						
Deyo-Charlson Comorbidity Index Score	2.9	3.0	2.5	2.6	2.8	2.8
CHA ₂ DS ₂ -VAsc Score	3.9	3.9	3.5	3.5	3.8	3.8
HAS-BLED Score*	3.1	3.0	2.8	2.8	3.0	3.0
Congestive heart failure	28,695 (28.4%)	29,008 (28.7%)	8,999 (24.3%)	9,423 (25.5%)	34,432 (27.5%)	34,614 (27.7%)
Diabetes mellitus	35,866 (35.5%)	35,974 (35.6%)	13,017 (35.2%)	13,326 (36.0%)	44,855 (35.9%)	44,753 (35.8%)
Renal disease	23,908 (23.7%)	24,085 (23.9%)	6,133 (16.6%)	6,348 (17.2%)	26,303 (21.0%)	26,509 (21.2%)
Stroke/SE	12,200 (12.1%)	12,257 (12.1%)	3,737 (10.1%)	3,938 (10.6%)	14,463 (11.6%)	14,564 (11.6%)
Peripheral artery disease	19,800 (19.6%)	20,738 (20.5%)	5,985 (16.2%)	6,570 (17.8%)	24,080 (19.3%)	24,471 (19.6%)
Coronary artery disease	45,367 (44.9%)	44,886 (44.5%)	14,964 (40.5%)	15,057 (40.7%)	53,954 (43.1%)	53,839 (43.0%)
Dose of the Index Prescription						
Standard Dose [†]	76,107 (75.4%)		30,997 (83.8%)		88,157 (70.5%)	
Lower Dose [‡]	24,870 (24.6%)		5,993 (16.2%)		36,911 (29.5%)	
Follow-up time, days	187.6	242.3	226.8	240.4	230.3	243.2
Median	126	158	124	156	146	159

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

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

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

[‡] Lower dose: 2.5mg Apixaban, 75mg Dabigatran, 10 or 15mg Rivaroxaban. 6,800 patients in the rivaroxaban-warfarin cohort received 10mg rivaroxaban.

At 12 months, 0.85% of the rivaroxaban patients in the matched rivaroxaban-warfarin cohort had a hospitalization with a stroke/SE diagnosis; rivaroxaban delayed the events by 63 days (95% CI: 42-84) as compared with warfarin. A total of 3.19% of the warfarin patients in the same matched cohorts had a hospitalization with an MB diagnosis. In contrast to the other matched cohorts, rivaroxaban *accelerated* the events by 18 days (95% CI: -31 to -6) as compared with warfarin. Increasing event rates and frequency was directionally consistent across time points and increased progressively (Table 3). Overall, the rivaroxaban cohort was 21% less likely to experience stroke/SE (HR:0.79; 95% CI: 0.73-0.85) but 6% more likely to experience MB (HR:1.06; 95% CI: 1.02-1.10) (Table 3).

3.3. NOAC vs NOAC

At 12 months, 0.55% and 0.62% of the apixaban patients in the matched apixaban-dabigatran and apixaban-rivaroxaban cohorts, respectively, had a hospitalization with a stroke/SE diagnosis. Apixaban delayed the events by 72 days (95% CI: 24-120) and 51 days (95% CI: 25-77), as compared with dabigatran and rivaroxaban, respectively. Delays were directionally consistent across time points and increased progressively among both cohort pairs. A total of 1.43% and 1.69% of the apixaban patients in the apixaban-dabigatran and apixaban-rivaroxaban cohorts, respectively, had a hospitalization with an MB diagnosis at twelve months. Apixaban delayed the events by 55 days (95% CI: 28-83) and 130 days (95% CI: 117-143), as compared with dabigatran and rivaroxaban, respectively (Table 4). Overall, the apixaban cohort was 38% (HR:0.72; 95% CI: 0.60-0.85) and 20% (HR:0.80; 95% CI: 0.73-0.89) less likely to experience stroke/SE as compared with dabigatran and rivaroxaban, respectively, and 22% (HR:0.78; 95% CI: 0.70-0.87) and 45% (HR:0.55; 95% CI: 0.53-0.59) less likely to experience MB (Table 4). Cumulative incidence of stroke/SE and MB followed similar trends (Supplemental Figs. 2 and Figure 3).

At 12 months, 0.73% of the rivaroxaban patients in the matched dabigatran-rivaroxaban cohorts had a hospitalization with a stroke/SE

Table 2
Baseline characteristics of patients prescribed NOACs and NOACs after propensity score matching.

	Apixaban (N = 37,314) Mean/%	Dabigatran (N = 37,314) Mean/%	Apixaban (N = 107,236) Mean/%	Rivaroxaban (N = 107,236) Mean/%	Dabigatran (N = 37,693) Mean/%	Rivaroxaban (N = 37,693) Mean/%
Age	73.2	73.0	75.2	75.1	72.8	73.0
<65	6,755 (18.1%)	6,727 (18.0%)	13,990 (13.1%)	13,930 (13.0%)	7,006 (18.6%)	7,026 (18.6%)
65-74	13,219 (35.4%)	13,259 (35.5%)	34,552 (32.2%)	34,523 (32.2%)	13,338 (35.4%)	13,243 (35.1%)
75-79	7,199 (19.3%)	7,243 (19.4%)	20,751 (19.4%)	20,850 (19.4%)	7,254 (19.2%)	7,526 (20.0%)
≥80	10,141 (27.2%)	10,085 (27.0%)	37,943 (35.4%)	37,933 (35.4%)	10,095 (26.8%)	9,898 (26.3%)
Sex						
Male	21,435 (57.4%)	21,200 (56.8%)	55,729 (52.0%)	55,267 (51.5%)	21,540 (57.1%)	21,435 (56.9%)
Female	15,879 (42.6%)	16,114 (43.2%)	51,507 (48.0%)	51,969 (48.5%)	16,153 (42.9%)	16,258 (43.1%)
Baseline Comorbidity						
Deyo-Charlson Comorbidity Index Score	2.5	2.5	2.8	2.8	2.5	2.5
CHA ₂ DS ₂ -VAsc Score	3.5	3.5	3.8	3.7	3.5	3.5
HAS-BLED Score*	2.8	2.8	3.0	3.0	2.7	2.8
Congestive heart failure	8,972 (24.0%)	8,963 (24.0%)	28,704 (26.8%)	28,294 (26.4%)	9,015 (23.9%)	9,298 (24.7%)
Diabetes mellitus	12,811 (34.3%)	12,968 (34.8%)	36,891 (34.4%)	36,637 (34.2%)	13,108 (34.8%)	13,487 (35.8%)
Renal disease	6,178 (16.6%)	6,125 (16.4%)	23,270 (21.7%)	23,092 (21.5%)	6,136 (16.3%)	6,390 (17.0%)
Stroke/SE	3,708 (9.9%)	3,726 (10.0%)	12,077 (11.3%)	11,904 (11.1%)	3,734 (9.9%)	3,924 (10.4%)
Peripheral artery disease	6,148 (16.5%)	5,986 (16.0%)	20,119 (18.8%)	20,431 (19.1%)	6,003 (15.9%)	6,472 (17.2%)
Coronary artery disease	15,037 (40.3%)	14,986 (40.2%)	47,207 (44.0%)	46,429 (43.3%)	15,058 (39.9%)	15,169 (40.2%)
Dose of the Index Prescription						
Standard Dose [†]	30,584 (82.0%)	31,326 (84.0%)	82,369 (76.8%)	75,550 (70.5%)	31,689 (84.1%)	28,390 (75.3%)
Lower Dose [‡]	6,730 (18.0%)	5,988 (16.0%)	24,867 (23.2%)	31,686 (29.5%)	6,004 (15.9%)	9,303 (24.7%)
Follow-up time, days	186.0	226.3	187.2	230.3	225.7	228.7
Median	124	123	125	145	123	143

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

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

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

[‡] Lower dose: 2.5mg Apixaban, 75mg Dabigatran, 10 or 15mg Rivaroxaban. 5,679 and 1,824 patients in the apixaban-rivaroxaban, and dabigatran-rivaroxaban cohorts received 10mg rivaroxaban, respectively.

Table 3
Overall outcome and delay of events associated with NOAC vs Warfarin

			3 Months		6 Months		12 Months		18 Months		
			HR (95% CI)	E (%)	DoE* (days) (95% CI)	E (%)	DoE* (days) (95% CI)	E (%)	DoE* (days) (95% CI)	E (%)	DoE* (days) (95% CI)
Stroke/SE	Apixaban ^a	Warfarin ^a	0.64 (0.58-0.70)	0.39 ^b	36 (27-45)	0.53 ^b	75 (50-100)	0.65 ^b	101 (78-124)	0.68 ^b	113 (86-140)
	Major Bleeding		0.60 (0.56-0.63)	1.06 ^b	51 (44-58)	1.45 ^b	88 (81-95)	1.75 ^b	116 (103-130)	1.85 ^b	131 (116-146)
Stroke/SE	Dabigatran ^a	Warfarin ^a	0.82 (0.71-0.95)	0.51 ^c	10 (-17-36)	0.66 ^c	21 (-12-55)	0.81 ^c	45 (3-87)	0.85 ^c	49 (5-94)
	Major Bleeding		0.71 (0.65-0.78)	1.13 ^c	41 (28-54)	1.54 ^c	58 (37-79)	1.92 ^c	92 (68-116)	2.12 ^c	108 (79-136)
Stroke/SE	Rivaroxaban ^a	Warfarin ^a	0.79 (0.73-0.85)	0.47 ^d	35 (25-45)	0.67 ^d	45 (28-62)	0.85 ^d	63 (42-84)	0.93 ^d	76 (52-100)
	Major Bleeding		1.06 (1.02-1.10)	1.88 ^e	-2 (-8-3)	2.57 ^e	-12 (-22--2)	3.19 ^e	-18 (-31--6)	3.46 ^e	-16 (-30--3)

CI: confidence interval; DoE: delay of events; HR: Hazard Ratio; SE: systemic embolism

^a Incidence rate per 100 person-years

^b Event in percent (percentile) reached in the apixaban group at the time point and measuring point for presented DoE in days.

^c Event in percent (percentile) reached in the dabigatran group at the time point and measuring point for presented DoE in days.

^d Event in percent (percentile) reached in the rivaroxaban group at the time point and measuring point for presented DoE in days.

^e Event in percent (percentile) reached in the warfarin group at the time point and measuring point for presented DoE in days.

* DoE = the average days for DOAC group to reach to E(%) - the average days for Warfarin group(reference) to reach to E(%)

diagnosis. There was no significant difference between the event rates at 12 months (DoE: 23 days; 95% CI: -25 to +71). A total of 1.89% of the dabigatran patients in the same matched cohorts had a hospitalization with an MB diagnosis at 12 months; dabigatran delayed the events by 95 days (95% CI: 71-119) as compared with rivaroxaban (Table 4). Overall, there was no statistically significant difference between the dabigatran

and rivaroxaban cohorts for stroke/SE (HR:1.10; 95% CI: 0.95-1.23) but dabigatran patients were 29% less likely to experience MB (HR:0.71; 95% CI: 0.65-0.78) as compared with rivaroxaban (Table 4). Cumulative incidences of stroke/SE and MB are shown in Supplemental Figs. 2 and 3.

Table 4
Overall outcome and delay of events associated with NOACs vs NOACs

			3 Months			6 Months		12 Months		18 Months	
	Apixaban ^a	§Dabigatran ^a	HR (95% CI)	E (%)	DoE (days) (95% CI)	E (%)	*DoE (days) (95% CI)	E (%)	*DoE (days) (95% CI)	E (%)	*DoE (days) (95% CI)
Stroke/SE	1.12	1.43	0.72 (0.60-0.85)	0.33 ^b	40 (13-68)	0.45 ^b	64 (32-96)	0.55 ^b	72 (24-120)	0.57 ^b	76 (25-127)
Major Bleeding	2.98	3.58	0.78 (0.70-0.87)	0.84 ^b	28 (11-45)	1.16 ^b	40 (17-63)	1.43 ^b	55 (28-83)	1.51 ^b	55 (24-87)
	Apixaban ^a	§Rivaroxaban ^a	HR (95% CI)	E (%)	*DoE (days) (95% CI)	E (%)	*DoE (days) (95% CI)	E (%)	*DoE (days) (95% CI)	E (%)	*DoE (days) (95% CI)
Stroke/SE	1.28	1.47	0.8 (0.73-0.89)	0.37 ^b	20 (5-35)	0.51 ^b	41 (21-61)	0.62 ^b	51 (25-77)	0.65 ^b	51 (23-79)
Major Bleeding	3.52	5.88	0.55 (0.53-0.59)	1.02 ^b	53 (47-59)	1.40 ^b	91 (80-101)	1.69 ^b	130 (117-143)	1.79 ^b	145 (130-160)
	Rivaroxaban ^a	§Dabigatran ^a	HR (95% CI)	E (%)	◇DoE (days) (95% CI)	E (%)	◇DoE (days) (95% CI)	E (%)	◇DoE (days) (95% CI)	E (%)	◇DoE (days) (95% CI)
Stroke/SE	1.29	1.42	0.91 (0.81-1.05)	0.37 ^c	31 (9-53)	0.57 ^c	33 (-1-67)	0.73 ^c	23 (-25-71)	0.80 ^c	36 (-14-86)
Major Bleeding	5.02	3.57	1.41 (1.28-1.54)	1.11 ^d	-39 (-51 - -26)	1.51 ^d	-68 (-88 - -47)	1.89 ^d	-95 (-119 - -71)	2.09 ^d	-114 (-142 - -86)

CI: confidence interval; DoE: delay of events; HR: Hazard Ratio; SE: systemic embolism

^a Incidence rate per 100 person-years

^b Event in percent (percentile) reached in the apixaban group at the time point and measuring point for presented DoE in days.

^c Event in percent (percentile) reached in the rivaroxaban group at the time point and measuring point for presented DoE in days.

^d Event in percent (percentile) reached in the dabigatran group at the time point and measuring point for presented DoE in days.

§ Indicates referent group

* DoE = the average days for apixaban group to reach to E(%) - the average days for other NOAC group(reference) to reach to E(%)

◇ DoE = the average days for rivaroxaban group to reach to E(%) - the average days for dabigatran group(reference) to reach to E(%)

4. Discussion

This sub-analysis of the large real-world sample of patients with NVAF in the ARISTOPHANES study population evaluated gains in event-free time to add nuance to the evidence on the safety and effectiveness profiles of OACs in routine practice. Overall, apixaban and dabigatran treatment was associated with generally consistent delayed clinical events as compared with warfarin, i.e., gains in stroke/SE and MB event-free time. Second, apixaban was associated with the largest gains in event-free time compared with warfarin and greater gains compared with both dabigatran and rivaroxaban; also, the gains generally progressed with time on treatment. Third, rivaroxaban was associated with a loss of MB event-free time rather than a gain, as compared with warfarin, and these losses compounded over time. Studies have found substantially greater peak-trough variation in rivaroxaban concentrations, which raised concern that rivaroxaban may have less favorable efficacy/effectiveness and safety. Additionally, rivaroxaban needs to be taken with food together to increase bioavailability. However, a RWD study by Packard et al. found that about one third of rivaroxaban patients did not take with an adequate meal, which may also impact the efficacy/effectiveness of rivaroxaban.

To the best of our knowledge, our delay of clinical event findings for warfarin-NOAC and NOAC vs NOAC pairs is novel. These results are consistent with event risk findings in ARISTOPHANES and subsequent clinical subgroup analyses [25,28,29]. Moreover, the findings for apixaban vs warfarin generally align with a similar delay-of-event analysis of the ARISTOTLE trial population which used the time points of 3, 6, 12, and 18 months after initiation [16].

The specific trends we observed across timepoints are largely consistent with the delay-of-event analysis of the ARISTOTLE trial, given the differences between a randomized controlled trial vs a real-world study population [16]. Of note, Berglund et al. found that with a median of 22 months of follow-up, patients prescribed apixaban had slower initial gains in event-free time for stroke/SE over the warfarin cohort, but progresses at greater magnitude, with 53, 116, and 149-day delays at 6, 12, and 18 months, respectively, as compared with 75, 101, and 113-day delays at 6, 12, and 18 months in our study.

Apixaban-associated time gains for MB followed a similar trend of a slower start but greater gains over time, with delays of 79, 141, and 199 days at 6, 12, and 18 months, respectively, vs 88, 116, and 131 days in our study. Differences in patient characteristics between the study populations may account for this discrepancy; specifically, the ARISTOTLE study included patients from 39 countries who met stricter inclusion criteria, whereas ARISTOPHANES included a larger, real-world US sample of older patients with higher baseline comorbidity. Due to the lack of comprehensive death information in the commercial data sources, the number of subjects at risk for both apixaban and warfarin group may be inflated. This is especially a problem if there are more deaths in warfarin group compared to apixaban group. The event free effect of apixaban vs. warfarin maybe underestimated in our study because mortality risk was lower in apixaban cohort. Regardless, the difference in trends warrants future investigation of the roles of age, comorbidity, and adherence in the delay of clinical events.

Given the general consistency with previous findings, our results may be helpful to augment traditional risk assessment measures with more granular information on the magnitude of treatment effects and thereby convey a more comprehensive assessment of treatment options to clinicians as well as patients [17–23]. Our results add to the growing body of evidence suggesting utility in time-to-event measures presented alongside traditional risk measures in future real-world studies on anticoagulation among patients with AF.

4.1. Strengths and limitations

The primary strengths of this study are the large, nationally representative sample and novel event time measures. However, results should be interpreted in the context of certain limitations. As with all retrospective observational studies, interpretation is limited to the observation of associations rather than the inference of causality. Coding errors and lack of specific clinical information may have introduced bias in the study. The databases do not include laboratory values or self-reported data; thus outcomes and risk assessment (such as the modified HAS-BLED score) should be interpreted cautiously. The presence of prescription claims does not denote that the medication was taken as

prescribed or at all, and concomitant use of over-the-counter medications was not observable in the dataset. In addition, adherence was unable to be determined given the tailored aspect of anticoagulant dosing. Interpretations of results should take into consideration that adherence may differ across treatments. Finally, the pharmacologic differences between warfarin and NOACs (i.e. half-life and interaction with food and other medications) are unable to be accounted for in this particular dataset and results should be interpreted with these in mind [25,30].

5. Conclusion

This analysis of the ARISTOPHANES population of NVAf patients newly treated with an anticoagulant found that over the course of 12 months of treatment after drug initiation, all NOACs increased stroke-free time when compared to warfarin, but MB-free time results differ by NOACs.

Funding

This study was funded by Pfizer Inc. and Bristol-Myers Squibb. SD and GYHL received research support from Pfizer and Bristol Myers Squibb. AK and XS were employed by STATinMED, LLC at the time of the study., a paid consultant to Pfizer and Bristol Myers Squibb, in connection with the development of the manuscript. AK, NA, PS, and JJ are employees of Bristol Myers Squibb, a study sponsor. AJ is an employee of Pfizer, a study sponsor.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.ejim.2022.10.021](https://doi.org/10.1016/j.ejim.2022.10.021).

References

- Colilla S, Crow A, Petkun W, Singer DE, Simon T, Liu X. Estimates of current and future incidence and prevalence of atrial fibrillation in the U.S. adult population. *Am J Cardiol* 2013;112(8):1142–7.
- Kornej J, Borschel CS, Benjamin EJ, Schnabel RB. Epidemiology of atrial fibrillation in the 21st century: novel methods and new insights. *Circ Res* 2020;127(1):4–20.
- Fohtung RB RM. Identification of patients at risk of stroke from atrial fibrillation. *US Cardiol Rev* 2016;10(2):60–4.
- McManus DD, Shaikh AY, Abhishek F, Vasan RS. Atrial fibrillation and heart failure parallels: lessons for atrial fibrillation prevention. *Crit Pathw Cardiol* 2011;10(1):46–51.
- Burdett P, Lip GYH. Atrial fibrillation in the United Kingdom: predicting costs of an emerging epidemic recognising and forecasting the cost drivers of atrial fibrillation-related costs. *Eur Heart J Qual Care Clin Outcomes* 2020.
- Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European association for cardio-thoracic surgery (EACTS): the task force for the diagnosis and management of atrial fibrillation of the European society of cardiology (ESC) developed with the special contribution of the European heart rhythm association (EHRA) of the ESC. *Eur Heart J* 2021;42(5):373–498.
- Romiti GF, Pastori D, Rivera-Caravaca JM, Ding WY, Gue YX, Menichelli D, et al. Adherence to the 'Atrial Fibrillation Better Care' Pathway in Patients with Atrial Fibrillation: Impact on Clinical Outcomes-A Systematic Review and Meta-Analysis of 285,000 Patients. *Thromb Haemost* 2021.
- Yoon M, Yang PS, Jang E, Yu HT, Kim TH, Uhm JS, et al. Improved Population-Based Clinical Outcomes of Patients with Atrial Fibrillation by Compliance with the Simple ABC (Atrial Fibrillation Better Care) Pathway for Integrated Care Management: A Nationwide Cohort Study. *Thromb Haemost* 2019;119(10):1695–703.
- Hohmann C, Hohnloser SH, Jacob J, Walker J, Baldus S, Pfister R. Non-Vitamin K Oral Anticoagulants in Comparison to Phenprocoumon in Geriatric and Non-Geriatric Patients with Non-Valvular Atrial Fibrillation. *Thromb Haemost* 2019;119(6):971–80.
- Hohnloser SH, Basic E, Nabauer M. Changes in Oral Anticoagulation Therapy over One Year in 51,000 Atrial Fibrillation Patients at Risk for Stroke: A Practice-Derived Study. *Thromb Haemost* 2019;119(6):882–93.
- Generalova D, Cunningham S, Leslie SJ, Rushworth GF, McIver L, Stewart D. A systematic review of clinicians' views and experiences of direct-acting oral anticoagulants in the management of nonvalvular atrial fibrillation. *Br J Clin Pharmacol* 2018;84(12):2692–703.
- Al-Khatib SM, Pokorney SD, HR Al-Khalidi, Haynes K, Garcia C, Martin D, et al. Underuse of oral anticoagulants in privately insured patients with atrial fibrillation: A population being targeted by the Implementation of a randomized controlled trial to improve treatment with oral Anticoagulants in patients with Atrial Fibrillation (IMPACT-AFib). *Am Heart J* 2020;229:110–7.
- Hsu JC, Maddox TM, Kennedy KF, Katz DF, Marzec LN, Lubitz SA, et al. Oral Anticoagulant Therapy Prescription in Patients With Atrial Fibrillation Across the Spectrum of Stroke Risk: Insights From the NCDR PINNACLE Registry. *JAMA cardiology* 2016;1(1):55–62.
- Lubitz SA, Khurshid S, Weng LC, Doros G, Keach JW, Gao Q, et al. Predictors of oral anticoagulant non-prescription in patients with atrial fibrillation and elevated stroke risk. *Am Heart J* 2018;200:24–31.
- Chao TF, Chiang CE, Chan YH, Liao JN, Chen TJ, Lip GYH, et al. Oral anticoagulants in extremely-high-risk, very elderly (>90 years) patients with atrial fibrillation. *Heart Rhythm* 2021;18(6):871–7.
- Berglund E, Wallentin L, Oldgren J, Renlund H, Alexander JH, Granger CB, et al. Effects of apixaban compared with warfarin as gain in event-free time - a novel assessment of the results of the ARISTOTLE trial. *Eur J Prev Cardiol* 2020;27(12):1311–9.
- Uno H, Wittes J, Fu H, Solomon SD, Claggett B, Tian L, et al. Alternatives to Hazard Ratios for Comparing the Efficacy or Safety of Therapies in Noninferiority Studies. *Ann Intern Med* 2015;163(2):127–34.
- Lytsy P, Berglund L, Sundström J. A proposal for an additional clinical trial outcome measure assessing preventive effect as delay of events. *Eur J Epidemiol* 2012;27(12):903–9.
- Bellavia A, Wallentin L, Orsini N, James SK, Cannon CP, Himmelmann A, et al. Time-based measures of treatment effect: reassessment of ticagrelor and clopidogrel from the PLATO trial. *Open Heart* 2017;4(2):e000557.
- Halvorsen PA, Wisløff TF, Støvring H, Aasland O, Kristiansen IS. Therapeutic decisions by number needed to treat and survival gains: a cross-sectional survey of lipid-lowering drug recommendations. *Br J Gen Pract* 2011;61(589):e477–83.
- Christensen PM, Brosen K, Brixen K, Andersen M, Kristiansen IS. A randomized trial of laypersons' perception of the benefit of osteoporosis therapy: number needed to treat versus postponement of hip fracture. *Clin Ther* 2003;25(10):2575–85.
- Berglund E, Westerling R, Sundström J, Lytsy P. Treatment effect expressed as the novel Delay of Event measure is associated with high willingness to initiate preventive treatment - A randomized survey experiment comparing effect measures. *Patient Educ Couns* 2016;99(12):2005–11.
- Berglund E, Westerling R, Sundström J, Lytsy P. Length of time periods in treatment effect descriptions and willingness to initiate preventive therapy: a randomised survey experiment. *BMC Med Inform Decis Mak* 2018;18(1):106.
- Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. *New Engl J Med* 2011;365(11):981–92.
- Lip GYH, Keshishian A, Li X, Hamilton M, Masseria C, Gupta K, et al. Effectiveness and Safety of Oral Anticoagulants Among Nonvalvular Atrial Fibrillation Patients. *Stroke* 2018;49(12):2933–44.
- Thigpen JL, Dillon C, Forster KB, Henault L, Quinn EK, Tripodis Y, et al. 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.
- Bottai M, Zhang J. Laplace regression with censored data. *Biom J* 2010;52(4):487–503.
- Deitelzweig S, Keshishian A, Kang A, Dhamane AD, Luo X, Li X, et al. Effectiveness and Safety of Oral Anticoagulants among NVAf Patients with Obesity: Insights from the ARISTOPHANES Study. *J Clin Med* 2020;9(6).
- Lip GYH, Keshishian AV, Kang AL, Dhamane AD, Luo X, Li X, et al. Oral anticoagulants for nonvalvular atrial fibrillation in frail elderly patients: insights from the ARISTOPHANES study. *J Intern Med* 2021;289(1):42–52.
- Mueck W, Schwerts S, Stampfuss J. Rivaroxaban and other novel oral anticoagulants: pharmacokinetics in healthy subjects, specific patient populations and relevance of coagulation monitoring. *Thromb J* 2013;11(1):10.