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Major bleeding risk among non-valvular atrial fibrillation patients initiated on apixaban, dabigatran, rivaroxaban or warfarin: a "real-world" observational study in the United States

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Summary

Background: Limited data are available about the real-world safety of non-vitamin K antagonist oral anticoagulants (NOACs).

Objectives: To compare the major bleeding risk among newly anticoagulated non-valvular atrial fibrillation (NVAF) patients initiating apixaban, warfarin, dabigatran or rivaroxaban in the United States.

Methods and results: A retrospective cohort study was conducted to compare the major bleeding risk among newly anticoagulated NVAF patients initiating warfarin, apixaban, dabigatran or rivaroxaban. The study used the Truven MarketScan® Commercial & Medicare supplemental US database from 1 January 2013 through 31 December 2013. Major bleeding was defined as bleeding requiring hospitalisation. Cox model estimated hazard ratios (HRs) of major bleeding were adjusted for age, gender, baseline comorbidities and co-medications. Among 29 338 newly anticoagulated NVAF patients, 2402 (8.19%) were on apixaban; 4173 (14.22%) on dabigatran; 10 050 (34.26%) on rivaroxaban; and 12 713 (43.33%) on warfarin. After adjusting for baseline characteristics, initiation on warfarin [adjusted HR (aHR): 1.93, 95% confidence interval (CI): 1.12–3.33, *P*=.018] or rivaroxaban (aHR: 2.19, 95% CI: 1.26–3.79, *P*=.005) had significantly greater risk of major bleeding vs *apixaban*. Dabigatran initiation (aHR: 1.71, 95% CI: 0.94–3.10, *P*=.079) had a non-significant major bleeding risk vs apixaban. *When compared with warfarin*, apixaban (aHR: 0.52, 95% CI: 0.30–0.89, *P*=.018) had significantly lower major bleeding risk. Patients initiating rivaroxaban (aHR: 1.13, 95% CI: 0.91–1.41, *P*=.262) or dabigatran (aHR: 0.88, 95% CI: 0.64–1.21, *P*=.446) had a non-significant major bleeding risk vs warfarin.

Conclusion: Among newly anticoagulated NVAF patients in the real-world setting, initiation with rivaroxaban or warfarin was associated with a significantly greater risk of major bleeding compared with initiation on apixaban. When compared with warfarin, initiation with apixaban was associated with significantly lower risk of major bleeding. Additional observational studies are required to confirm these findings.

H. Phatak and A. Bruno were employees of Bristol-Myers Squibb at the time of this research.

1 | INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia seen in clinical practice, with an estimated 70% of cases classifiable as non-valvular atrial fibrillation (NVAF). An estimated 33 million individuals are affected by AF worldwide, including 1%–4% of adults in Australia, Europe and the United States.[1] The incidence of stroke in patients with AF is nearly fivefold higher than that of the general population, resulting in significant morbidity and mortality. Also, AF-related strokes have higher mortality, greater disability, costs, and increased incidence of recurrent stroke compared with non-AF-related strokes.[2–4] For several decades, Vitamin K Antagonists (VKA, e.g. warfarin) were the primary oral anticoagulant used for stroke prevention in AF, being highly effective for preventing stroke and reducing all-cause mortality in patients with AF. However, managing the proper dose of warfarin to achieve the international normalisation range (INR) of 2–3 is difficult and lack of control is associated with a significant rate of major bleeding.[5] As a result, approximately 30%–50% of AF patients were undertreated with either suboptimal warfarin treatment, or given aspirin or no anticoagulation.[6] In recent years, four non-VKA oral anticoagulants (NOACs) have been approved for stroke prevention in AF. In clinical trials, all NOACs have all been shown to be at least as safe and effective as warfarin.[7] These new agents do not require regular INR monitoring and have few major drug and food interactions, as compared with warfarin.[7,8] The four NOACs were approved in the United States over a period of 6 years: Dabigatran 150 mg b.i.d. was the first NOAC approved in 2010, followed by rivaroxaban 20 mg q.i.d. in 2011, apixaban 5 mg b.i.d. in 2012, and edoxaban 60 mg q.i.d. in 2015. After approval in the United States, marketing authorisation for each of the NOACs expanded globally. By 2015, when edoxaban was approved in the United States, the first three NOACs were approved for marketing in the United Kingdom, Europe and Asia. For this study, we focused on apixaban, dabigatran and rivaroxaban, as there are no real-world data available for edoxaban in the United States. Despite evidence on the efficacy and safety of these NOACs from randomised controlled trials, little is known about the bleeding events associated with the use of NOACs among NVAF patients in real-world settings.[9] The key objectives of this study were to (i) describe the clinical and demographic patient characteristics of newly anticoagulated NVAF patients who initiated apixaban, dabigatran, rivaroxaban, and warfarin in the United States; (ii) assess unadjusted rates of first major bleeding; and (iii) compare the risk of major bleeding among newly anticoagulated NVAF patients initiating apixaban vs warfarin, dabigatran or rivaroxaban, adjusting for demographic and clinical characteristics. Further, we also assessed the risk of major bleeding among newly anticoagulated NVAF patients initiating warfarin vs apixaban, dabigatran or rivaroxaban, adjusting for demographic and clinical characteristics.

What's known

Apart from warfarin, non-vitamin K antagonist oral anticoagulants are licensed for stroke prevention in atrial fibrillation based on large randomised clinical trials, but real-world comparative safety data are limited.

What's new

- Major bleeding risk was evaluated for oral anticoagulant initiators using US claims database.
- Rivaroxaban or warfarin had significantly higher major bleeding risk vs apixaban initiation.
- Only apixaban initiation had significantly lower major bleeding risk vs warfarin initiation.
- Dabigatran initiation had a non-significant major bleeding risk vs apixaban.

2 | METHODS

A retrospective cohort study was conducted using Truven MarketScan® Commercial and Medicare supplemental data to compare the risk of major bleeding in NVAF patients newly initiated on apixaban compared with warfarin, dabigatran or rivaroxaban and patients newly initiated on warfarin compared with apixaban, dabigatran or rivaroxaban.

The Truven MarketScan® (Truven Health Analytics, Ann Arbor, MI, USA) database consists of administrative healthcare claims for employees of large self-insured companies and members of private healthcare plans in the United States. Each claim contains a unique encrypted patient identifier that is used to construct a longitudinal record of medical and pharmacy services for these people. Membership information is used to ensure that these patients are eligible for benefits during the period of the study. Medical information is obtained from the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes contained in the claims. Pharmacy claims include the drug dispensed using the National Drug Code coding system. Every claim contains the dates of service, provider of the service, and information about units for physician services or date medications were dispensed.

The "commercial" population of this database represents those patients who were <65 years and were not covered by Medicare (the US government program for those ≥65 years). The "Medicare Supplemental" population of the database represented those patients who were ≥65 and either participated in the Medicare program or continued to be covered by their employer's health plan. For this study, we included unique patient identifiers from both the commercial and Medical supplemental population.

NVAF (ICD-9-CM codes: 427.31, 472.32 for primary or secondary diagnosis) patients ≥18 years with 1 year of baseline period with continuous enrolment were included if they were newly prescribed oral anticoagulants from 1 January 2013 to 31 December 2013. Patients included in this study were new initiators without anticoagulant treatment within 1 year prior to the initiation. Patients with evidence of valvular heart disease, thyrotoxicosis, pericarditis, mitral stenosis, VTE, heart surgery and endocarditis during the baseline period (any

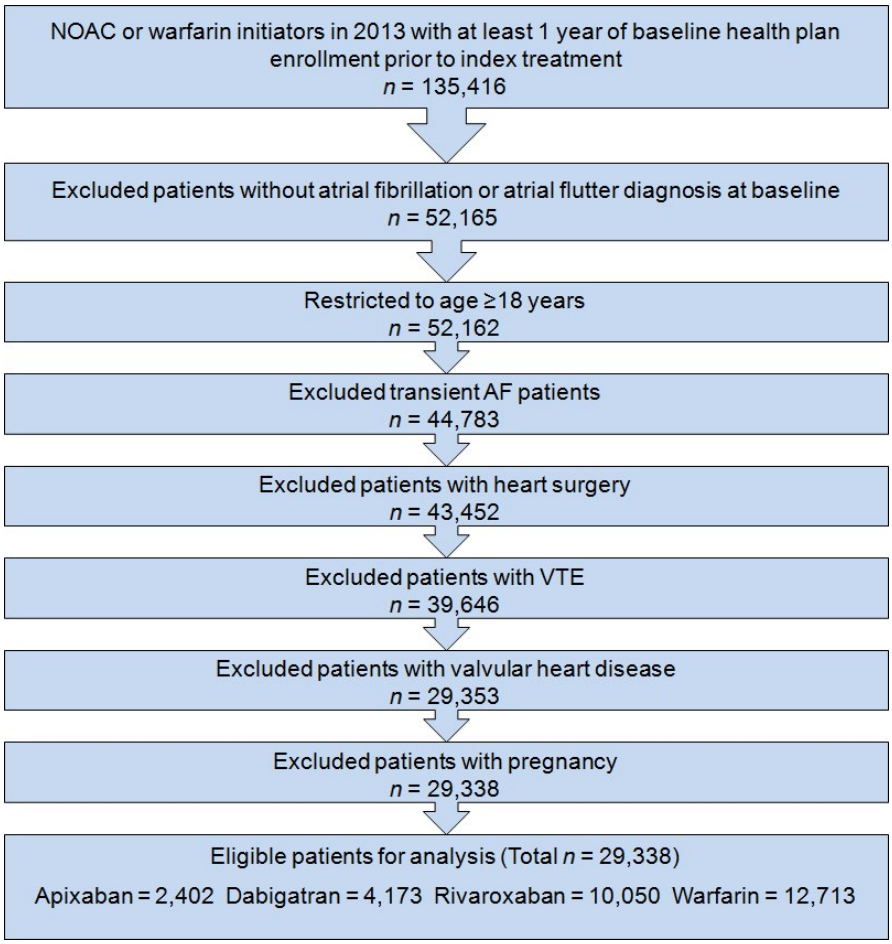


FIGURE 1 Patient selection criteria

time prior to or on index date) were excluded. Patients with any evidence of pregnancy at any time during the baseline were excluded (Fig. 1).

A new initiator (i.e. new user) was required to have at least one claim with a diagnosis of AF and at least one prescription claim for oral anticoagulant (OAC), either warfarin, apixaban, dabigatran or rivaroxaban with no prior use of anticoagulant in the baseline. Index date was defined as the date of first prescription after the NVAF diagnosis. Index drug was defined as the first anticoagulation treatment prescribed to patients included in the study.

Major bleeding on an anticoagulant was defined as bleeding requiring hospitalisation (i.e. inpatient bleeding) any time during the period of drug use or within 30 days from the last day of supply of treatment prescription. Major bleeding was identified using hospital claims, which had a bleeding diagnosis code as the first listed ICD-9-CM diagnosis code. ICD-9-CM codes are provided in Table S1. The definition of major bleeding was modified from a published administrative claims-based algorithm[10] and captures major bleeding at key sites, including but not limited to intracranial, gastrointestinal, liver, splenic and ocular haemorrhage requiring hospitalisation with a diagnosis for bleeding.

Patients were followed from the index date to the first major bleeding event, date of discontinuation from index medication, date of a switch, end of study period or interruption in continuous enrolment, whichever occurred earlier.

In the eligible population, baseline demographic and clinical categorical and continuous variables were compared across treatments using Pearson's chi-square test and Kruskal-Wallis test, respectively. Unadjusted rates of first major bleeding event were described as the number of bleeding events per 100 person-years and compared using Poisson distribution using both warfarin and apixaban as the reference category. The rate of major bleeding was calculated as the number of first major bleeding events divided by the total time at risk for major bleeding within the study period. Kaplan-Meier curves were used to present the cumulative incidence of a first major bleeding event. A Cox proportional hazards model was used to estimate the hazard ratios (HR) of major bleeding adjusted for a prespecified set of baseline demographic and clinical factors, including age, sex, region, embolic or primary ischaemic stroke, dyspepsia or stomach discomfort, congestive heart failure, coronary artery disease, diabetes, hypertension, renal disease, myocardial infarction, history of stroke or transient ischaemic attack, history of bleeding, Charlson Comorbidity Index (CCI)

and baseline medications including angiotensin converting enzyme inhibitor, amiodarone, angiotensin receptor blocker, beta blocker, H2-receptor antagonist, proton pump inhibitor and statins. We selected these baseline variables for the Cox model whose $P<.2$ or considered clinically important. These baseline variables were similar to baseline factors used in other recent work.[11–13] All analyses were performed with SAS system, version 9.2. A $P<0.05$ was considered statistically significant.

To assess robustness of the main study results, we conducted the following sensitivity analysis:

- We defined first major bleeding on an anticoagulant as a major critical site bleeding in an inpatient or outpatient setting, occurring anytime during the period of drug use or within 30 days from the last day of supply of treatment prescription. Major critical site bleeding was identified using inpatient as well as outpatient claims, which had a bleeding diagnosis code across primary and secondary ICD-9-CM diagnosis codes. ICD-9-CM codes for major critical site bleeding are provided in Table S2. This definition of major bleeding was assessed as a sensitivity analysis of the study for robustness of the main results.
- While no dose-based interaction effect was observed with bleeding in clinical trials, one may hypothesise that such an interaction may exist. Thus, we evaluated the risk of major bleeding requiring hospitalisation, among NVAF patients newly initiated on dose-adjusted warfarin, and standard dose of apixaban 5 mg b.i.d., rivaroxaban 20 mg q.i.d. or dabigatran 150 mg b.i.d. to assess the robustness of the main study results.
- Apixaban users have a shorter follow-up because apixaban was approved in the United States in December 2012. In order to account for the differences in follow-up, we censored patients at 90 and 180 days to create a more similar follow-up between the treatment cohorts.

TABLE 1 Baseline Demographic Characteristics by Index Anticoagulant Initiation

	Apixaban (N=2402)		Dabigatran (N=4173)		Rivaroxaban (N=10 050)		Warfarin (N=12 713)		
Demographics	**N/Mean**	**%/SD**	**N/Mean**	**%/SD**	**N/Mean**	**%/SD**	**N/Mean**	**%/SD**	***P*-value[a]**
Age	69.34	12.33	66.83	12.17	67.33	12.25	72.53	11.88	<.001
18–40	22	0.92	56	1.34	143	1.42	58	0.46	<.001
40–49	101	4.20	217	5.20	490	4.88	313	2.46	
50–59	404	16.82	880	21.09	2052	20.42	1500	11.80	
60–69	675	28.1	1320	31.63	3072	30.57	3109	24.46	
70–79	605	25.19	961	23.03	2358	23.46	3556	27.97	
80+	595	24.77	739	17.71	1935	19.25	4177	32.86	
Sex									
Male	1518	63.20	2747	65.83	6340	63.08	7734	60.84	<.001
Female	884	36.80	1426	34.17	3710	36.92	4979	39.16	
Region									
Northeast	334	13.91	935	22.41	1693	16.85	2199	17.30	<.001
North Central	727	30.27	1077	25.81	2705	26.92	3719	29.25	
South	851	35.43	1112	26.65	3452	34.35	2887	22.71	
West	447	18.61	895	21.45	1996	19.86	3638	28.62	
Unknown	43	1.79	154	3.69	204	2.03	270	2.12	
Health plan									
Commercial	941	39.18	2025	48.53	4737	47.13	3715	29.22	<.001
Medicare	1461	60.82	2148	51.47	5313	52.87	8998	70.78	
Plan type									
Comprehensive	783	32.60	1032	24.73	2866	28.52	3974	31.26	<.001
Exclusive provider organization	10	0.42	44	1.05	50	0.50	76	0.60	
Health maintenance organization	237	9.87	470	11.26	988	9.83	2435	19.15	
Point of service	146	6.08	280	6.71	621	6.18	675	5.31	
Preferred provider organization	1033	43.01	1914	45.87	4447	44.25	4593	36.13	
POS with capitation	1	0.04	7	0.17	36	0.36	22	0.17	
Consumer driven health plan	67	2.79	127	3.04	354	3.52	269	2.12	
High-deductible health plan	50	2.08	66	1.58	170	1.69	152	1.20	
Unknown	75	3.12	233	5.58	518	5.15	517	4.07	

POS, point of service.

[a]*P*-value was obtained using the Kruskal-Wallis test and the chi-squared test.

3 | RESULTS

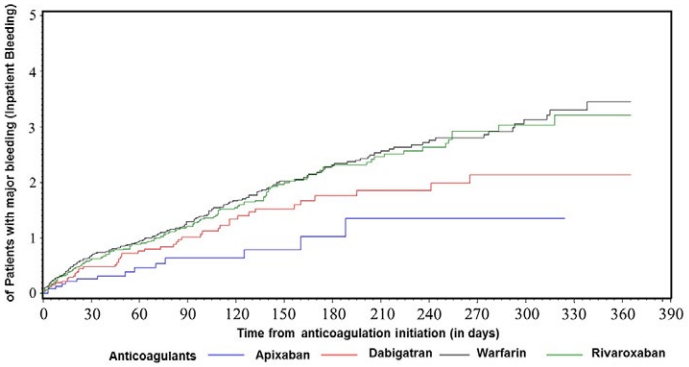
Among 29 338 eligible patients, 2402 (8.19%) were initiated on apixaban with a mean ± SD follow-up of 90.37±72.06 days; 4173 (14.22%) on dabigatran with a mean follow-up of 126.74±102.54 days; 10 050 (34.26%) on rivaroxaban with a mean follow-up of 117.71±97.17 days; and 12 713 (43.33%) on warfarin with a mean follow-up of 127.55±102.09 days. The mean age of apixaban, dabigatran, rivaroxaban and warfarin patients was 69.3±12.3, 66.8±12.2, 67.3±12.3, and 72.5±11.9 years, respectively. Patients initiating warfarin were older and at a higher stroke risk based on the CHA_2DS_2–VASc score (3.22±1.65) and had a higher CCI score of 2.37±2.33 followed by apixaban, rivaroxaban and dabigatran (*P*<.001 across all treatments). Compared with patients initiating rivaroxaban or dabigatran, patients initiating apixaban were older and had higher mean CHA_2DS_2–VASc and CCI scores. Compared with patients initiating rivaroxaban or dabigatran, apixaban patients had greater use of ACE inhibitors, amiodarone, beta blockers, statins and H2-receptor antagonists (Tables 1 and 2).

The unadjusted incidence rate (per 100 person-years) for major bleeding requiring hospitalisation was 4.66 for warfarin, 4.57 for rivaroxaban, 3.38 for dabigatran and 2.35 for apixaban patients (Table S3). The cumulative incidence of major bleeding for new initiations on anticoagulants is represented in Fig. 2.

TABLE 2 Baseline comorbidities and co-medications by index anticoagulant initiation

	Apixaban (N=2402) (Ref)		Dabigatran (N=4173)		Rivaroxaban (N=10 050)		Warfarin (N=12 713)		
	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD	*P*-value[a]
Comorbidities									
Congestive heart failure	486	20.23	845	20.25	1955	19.45	3476	27.34	<.001
Diabetes	643	26.77	1153	27.63	2687	26.74	4043	31.80	<.001
Hypertension	1746	72.69	2941	70.48	7112	70.77	9287	73.05	<.001
Renal disease	182	7.58	306	7.33	809	8.05	1860	14.63	<.001
Myocardial infarction	146	6.08	213	5.10	531	5.28	805	6.33	.001
Dyspepsia or stomach discomfort	326	13.57	513	12.29	1469	14.62	1906	14.99	<.001
Peripheral vascular disease	919	38.26	1314	31.49	3330	33.13	5075	39.92	<.001
Stroke or transient ischemic attack	255	10.62	384	9.20	904	9	1555	12.23	<.001
Coronary artery disease	831	34.60	1200	28.76	2980	29.65	4333	34.08	<.001
Prior bleeding history	275	11.45	457	10.95	1285	12.79	2046	16.09	<.001
$CHADS_2$ score	1.78	1.21	1.66	1.19	1.66	1.20	2.05	1.26	<.001
0	319	13.28	688	16.49	1607	15.99	1195	9.40	<.001
1	755	31.43	1326	31.78	3363	33.46	3237	25.46	–
2	742	30.89	1290	30.91	2968	29.53	4223	33.22	–
3+	586	24.40	869	20.82	2112	21.01	4058	31.92	–
Charlson Comorbidity Index	1.85	1.98	1.74	1.97	1.79	2.04	2.37	2.33	<.001
0	698	29.06	1358	32.54	3292	32.76	3025	23.79	<.001
1	636	26.48	1054	25.26	2520	25.07	2797	22.00	–
2	382	15.90	667	15.98	1489	14.82	2006	15.78	–
3+	686	28.56	1094	26.22	2749	27.35	4885	38.43	–
CHA_2DS_2–VASc Score	2.83	1.64	2.58	1.65	2.62	1.65	3.22	1.65	<.001
0	160	6.66	396	9.49	878	8.74	565	4.44	<.001
1	378	15.74	808	19.36	1956	19.46	1397	10.99	–
2	533	22.19	917	21.97	2173	21.62	2327	18.30	–
3+	1331	55.41	2052	49.17	5043	50.18	8424	66.26	–
Co-medications									
Angiotensin converting enzyme inhibitor	815	33.93	1205	28.88	3049	30.34	3930	30.91	<.001
Amiodarone	170	7.08	185	4.43	472	4.70	555	4.37	<.001
Angiotensin receptor blocker	553	23.02	795	19.05	2207	21.96	2389	18.79	<.001
Beta blockers	1402	58.37	2016	48.31	5010	49.85	6177	48.59	<.001
H_2-receptor antagonist	104	4.33	123	2.95	341	3.39	498	3.92	.004
Proton pump inhibitor	469	19.53	712	17.06	1990	19.80	2246	17.67	<.001
Statins	1330	55.37	1922	46.06	5088	50.63	6395	50.30	<.001

[a]*P*-value was obtained using the Kruskal-Wallis test and the chi-squared test.



N of Patients at Risk	Day 0	Day 30	Day 60	Day 90	Day 120	Day 150	Day 180	Day 210	Day 240	Day 270	Day 300	Day 330	Day 360
Apixaban	2402	1969	1283	963	660	472	334	221	120	61	13	0	0
Dabigatran	4173	3745	2610	2151	1641	1366	1124	907	754	593	416	266	48
Warfarin	12713	10979	8118	6798	5041	4192	3418	2786	2266	1756	1309	776	128
Rivaroxaban	10050	8542	6072	4897	3823	3065	2461	1905	1483	1110	749	397	48

FIGURE 2 Cumulative incidence of major bleeding requiring hospitalisation for anticoagulant initiation

After adjusting for baseline characteristics, *as compared with patients newly initiated on apixaban*, patients newly initiated on warfarin (HR: 1.93, 95% CI: 1.12–3.33, *P*=.018) or rivaroxaban (HR: 2.19, 95% CI: 1.26–3.79, *P*=.005) were more likely to experience a major bleeding event. Patients newly initiated on dabigatran (HR: 1.71, 95% CI: 0.94–3.10, *P*=.079) had a non-significant trend for more major bleeding compared with those initiated on apixaban (Table 3).

After adjusting for baseline characteristics, *as compared with patients newly initiated on warfarin*, patients newly initiating apixaban (HR: 0.52, 95% CI: 0.30–0.89, *P*=.018) were less likely to experience a major bleeding event. There was no significant differences in major bleeding between *patients newly initiated on warfarin* and those initiated on rivaroxaban (HR: 1.13, 95% CI: 0.91–1.41, *P*=.262) or dabigatran (HR: 0.88, 95% CI: 0.64–1.21, *P*=.446) (Table 3 and Fig. 3). Besides OAC treatment, the factors associated with major bleeding requiring hospitalisation included the following: history of prior bleeding and comorbidities, including congestive heart failure, renal disease and dyspepsia or stomach discomfort (Table 3).

3.1 | Major critical site bleeding in inpatient or outpatient setting

The unadjusted incidence rate (per 100 person-years) for major critical site bleeding in an inpatient or outpatient setting was 13.01 for warfarin compared with 8.15 for apixaban, 12.41 for rivaroxaban and 9.01 for dabigatran. These unadjusted incidence rates showed a similar pattern to the unadjusted incidence rates obtained for major bleeding requiring hospitalisation in the main analysis. After adjusting for baseline characteristics, as compared with *patients newly initiated on apixaban*, patients newly initiated on warfarin (HR: 1.62, 95% CI: 1.20–2.18, *P*=.002) or rivaroxaban (HR: 1.70, 95% CI: 1.26–2.29, *P*<.001) were more likely to experience a major critical site bleeding event. Patients newly initiated on dabigatran (HR: 1.28, 95% CI: 0.92–1.79, *P*=.144) had a numerically greater but non-significant risk of major bleeding compared with those initiated on apixaban (Table 4). As compared with *patients newly initiated on warfarin*, patients newly initiated on dabigatran (HR: 0.79, 95% CI: 0.65–0.96, *P*=.018) or apixaban (HR: 0.62, 95% CI: 0.46–0.83, *P*=.002) were less likely to experience a major critical site bleeding event.

3.2 | Risk of first major bleeding event among NVAF patients newly initiated with dose-adjusted warfarin, apixaban 5 mg b.i.d., rivaroxaban 20 mg q.i.d. or dabigatran 150 mg b.i.d

The unadjusted incidence rate (per 100 person-years) for major bleeding requiring hospitalisation was 4.66 for dose-adjusted warfarin compared with 2.17 for apixaban 5 mg b.i.d., 3.99 for rivaroxaban 20 mg q.i.d. and 2.98 for dabigatran 150 mg b.i.d. These unadjusted incidence rates for standard doses showed a similar pattern to the unadjusted incidence rates obtained for major bleeding requiring hospitalisation in the main analysis.

After adjusting for baseline characteristics, *as compared with patients newly initiated on apixaban* 5 mg b.i.d., those patients newly initiated on dose-adjusted warfarin (HR: 1.90, 95% CI: 1.03–3.51, *P*=.040) or rivaroxaban 20 mg q.i.d. (HR: 2.06, 95% CI: 1.11–3.84, *P*=.023) were more likely to experience a major bleeding event. Patients newly initiated on dabigatran, 150 mg b.i.d. (HR: 1.56, 95% CI: 0.79–3.04, *P*=.198), had a numerically greater but non-significant risk of major bleeding compared with those initiated on apixaban 5 mg b.i.d. (Table 5). As compared with patients newly initiated on dose-adjusted warfarin, those patients newly initiated on apixaban, 5 mg b.i.d. (HR: 0.53, 95% CI: 0.29–0.97, *P*=.040), were less likely to experience a major bleeding event. Patients newly initiated on dabigatran, 150 mg b.i.d. (HR: 0.82, 95% CI: 0.58–1.16, *P*=.262) or rivaroxaban, 20 mg q.i.d. (HR: 1.08, 95% CI: 0.85–1.39, *P*=.525) had a non-significant risk of major bleeding compared with those initiated on dose-adjusted warfarin. The third sensitivity analysis where patients were censored at 90 and 180 days showed similar results to the main analysis (Tables S3, S4 and Figs S1, S2).

TABLE 3 Risk of major bleeding requiring hospitalization among patients initiating anticoagulants after adjusting for clinical and demographic characteristics

	Hazard ratio	95% HR confidence limits	*P*-Value	Hazard ratio	95% HR confidence limits	*P*-Value
Warfarin	1.93	1.12–3.33	0.018	1.00 Ref		
Rivaroxaban	2.19	1.26–3.79	0.005	1.13	0.91–1.41	.262
Dabigatran	1.71	0.94–3.1	0.079	0.88	0.64–1.21	.446
Apixaban	1.00 Ref			0.52	0.30–0.89	.018
Covariates included in both models have the same estimates as shown below						
	Hazard ratio			**95% HR confidence limits**		***P*-value**
Age (80+ as a reference category)						
18–39	0.72			0.18–2.96		.653
40–49	0.58			0.29–1.14		.114
50–59	0.48			0.33–0.70		<.001
60–69	0.69			0.53–0.90		.006
70–79	0.69			0.54–0.89		.004
Male	0.95			0.77–1.16		.584
Region (North central as a reference category)						
Northeast	1.29			0.97–1.70		.076
South	1.30			1.01–1.67		.043
Unknown	1.24			0.62–2.46		.541
West	0.74			0.55–0.99		.042
Embolic or primary ischemic stroke	1.06			0.62–1.81		.836
Dyspepsia or stomach discomfort	1.33			1.04–1.70		.021
Congestive heart failure	1.47			1.17–1.84		<.001
Coronary artery disease	1.01			0.79–1.28		.970
Diabetes	1.25			1.00–1.58		.051
Hypertension	1.00			0.78–1.27		.991
Renal disease	1.41			1.07–1.84		.014
Myocardial infarction	1.30			0.91–1.84		.149
Stroke or transient ischemic attack	1.03			0.64–1.65		.916
Bleeding at baseline	1.72			1.37–2.16		<.001
Charlson Comorbidity Index (CCI 0 as a reference category)						
CCI 1	1.08			0.76–1.53		.679
CCI 2	1.19			0.81–1.76		.369
CCI 3+	1.37			0.92–2.06		.123
Angiotensin converting enzyme inhibitor	0.86			0.69–1.09		.206
Amiodarone	1.14			0.76–1.72		.531
Angiotensin receptor blocker	1.08			0.85–1.38		.526
Beta blockers	1.06			0.86–1.30		.585
H2-receptor antagonist	0.86			0.51–1.44		.567
Proton pump inhibitor	0.95			0.74–1.22		.700
Statins	0.98			0.79–1.21		.838

4 | DISCUSSION

In this study, we show that among newly anticoagulated NVAF patients in the real-world US setting, initiation with rivaroxaban or warfarin was associated with a significantly greater risk of major bleeding as compared with initiation on apixaban. No prior observational study has evaluated risk of major bleeding as a comparative safety between various oral anticoagulants, apixaban and other NOACs or warfarin. The results of this study corroborates indirect treatment and network meta-analysis findings, based on clinical trials data, that apixaban was associated with a significantly lower hazard of major bleeding compared with warfarin and rivaroxaban.[14–16] Previous studies have presented the incidence and HRs of risk of major bleeding for rivaroxaban vs warfarin and dabigatran vs warfarin in real-world settings. The findings of this study are qualitatively comparable to other real-world studies focused on rivaroxaban vs warfarin[17] and dabigatran vs warfarin.[18,19]

This study used real-world claims data from the US population to demonstrate comparative safety in an adult NVAF population newly initiated on warfarin, rivaroxaban, dabigatran or apixaban therapy. Apixaban has been available in the United States since 2013; thus,

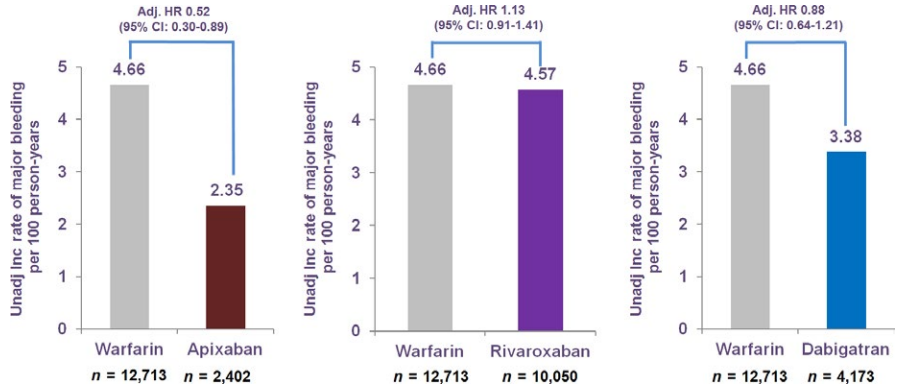


FIGURE 3 Unadjusted incidence rates of major bleeding requiring hospitalisation (per 100 person-year) and adjusted hazard ratios for anticoagulant initiation – apixaban, rivaroxaban, and dabigatran compared with warfarin. Hazard ratios (HRs) are adjusted based on the Cox proportional hazards model adjusted for: age, sex, region, embolic or primary ischaemic stroke, dyspepsia or stomach discomfort, congestive heart failure, coronary artery disease, diabetes, hypertension, renal disease, myocardial infarction, history of stroke or transient ischaemic attack, history of bleeding, Charlson comorbidity Index score and baseline medications, including angiotensin converting enzyme inhibitor, amiodarone, angiotensin receptor blocker, beta blocker, H2-receptor antagonist, proton pump inhibitor and statins.

the follow-up period on apixaban was relatively shorter compared with warfarin, rivaroxaban and dabigatran in this study. Despite major bleeding being a relatively rare event, the risk differences between the treatments groups were detected and the study was focused on newly initiated and previously anticoagulation-naïve patients. Given that warfarin requires more time than NOACs to reach peak anticoagulant effect,[20] the rate of clinical events during the initial months may reflect warfarin's lower effectiveness in preventing thrombosis events,[21] and its lower likelihood of bleeding events.

Nevertheless, in this study, rivaroxaban and warfarin have demonstrated a significantly higher likelihood of bleeding risk compared with apixaban. Further, the sensitivity analyses focused on assessing major critical site bleeding in an inpatient or outpatient setting, identified based on primary or secondary ICD-9-CM codes. The trends remained the same except that dabigatran initiators, in addition to apixaban initiators, showed a significantly lower risk of major critical site bleeding compared with warfarin initiators. In addition, the sensitivity analysis evaluated the risk of major bleeding requiring hospitalisation, among patients newly initiated on dose-adjusted warfarin, rivaroxaban 20 mg q.i.d., dabigatran 150 mg b.i.d., or apixaban 5 mg b.i.d., to assess the standard dose treatment effect on the risk of major bleeding requiring hospitalisation, revealed similar trends and thus, confirmed the robustness of main study findings.

Besides OACs, factors associated with the risk of major bleeding requiring hospitalisation were a history of prior bleeding and comorbidities, including congestive heart failure, renal disease and dyspepsia or stomach discomfort. Besides OACs, factors associated with the risk of major critical site bleeding in an inpatient or outpatient setting, were history of prior bleeding, higher categories of CCI, and comorbidities, including congestive heart failure, dyspepsia or stomach discomfort, myocardial infarction, renal disease and male gender (as a protective factor). These risk factors associated with major bleeding were consistent with the findings from the ARISTOTLE trial, where older age, prior haemorrhage, prior stroke or TIA, diabetes, lower creatinine clearance and decreased haematocrit level were shown to be independently associated with an increased risk of major bleeding.[22] Furthermore, warfarin was preferentially initiated among older and sicker patients among newly anticoagulated NVAF patients. Among those initiating NOACs, however, apixaban patients were older and had a greater baseline clinical risk compared with those initiating dabigatran or rivaroxaban. Thus, randomised controlled trial findings are robust to variation in patient characteristics including age, baseline clinical risk and comorbid conditions.

When assessed using the standard of care warfarin as a reference comparison, we observed that the real-world major bleeding results were in concordance with results observed in clinical trials. For patients newly initiated on dabigatran, as compared with warfarin, the risk of major bleeding was shown to be lowered by 12%–21%.[18,23] These results are generally consistent with the lower risk of major bleeding for dabigatran compared with warfarin, as demonstrated in the RE-LY trial.[24]

Patients newly initiating rivaroxaban, as compared with warfarin, were numerically more likely to experience a major bleeding event but the adjusted differences in major bleeding between rivaroxaban and warfarin did not reach statistical significance. This is consistent with numerically higher adjusted risk of major bleeding with rivaroxaban compared with warfarin as demonstrated in the ROCKET-AF trial.[25] In the real-world studies conducted using the healthcare claims database,[17] a numerically higher but non-significant risk of major bleeding was observed for rivaroxaban as compared with warfarin which is consistent with our study. Interestingly, our study showed similar crude incidence rates of major bleeding among rivaroxaban and warfarin patients (around 4.6 per 100 person-years) although studies have shown that the mean time in therapeutic range (TTR) is relatively low in real-world settings, usually below or around 60%.[26,27] In addition, the incidence rate of major bleeding (per 100 person-years) was higher than previously reported in the XANTUS study (2.1; 95% CI: 1.8–2.5), Dresden NOAC registry (3.1; 95% CI: 2.2–4.3), and a retrospective claims study using the US Department of Defense health records (2.9; 95% CI: 2.61–3.13).[28–30] These differences in incidence rates may be because of the difference in study design, patient selection criteria, and the definition of major bleeding.

TABLE 4 Risk of major critical site bleeding (inpatient or outpatient setting) among patients initiating anticoagulants after adjusting for clinical and demographic characteristics

	Hazard ratio	95% HR confidence limits	*P*-Value	Hazard ratio	95% HR confidence limits	*P*-Value
Warfarin	1.62	1.20–2.18	0.002	1.00 Ref		
Rivaroxaban	1.70	1.26–2.29	<0.001	1.05	0.92–1.20	.511
Dabigatran	1.28	0.92–1.79	0.144	0.79	0.65–0.96	.018
Apixaban	1.00 Ref			0.62	0.46–0.83	.002
Covariates included in both models have the same estimates as shown below						
	Hazard ratio		**95% HR confidence limits**			***P*-Value**
Age (80+ as a reference category)						
18–39	1.06		0.47–2.39			.89
40–49	1.02		0.70–1.48			.94
50–59	0.84		0.68–1.03			.10
60–69	1.03		0.88–1.21			.72
70–79	0.87		0.74–1.02			.08
Male	0.84		0.74–0.94			.00
Region (North central as a reference category)						
Northeast	1.07		0.90–1.27			.42
South	1.03		0.88–1.20			.73
Unknown	0.78		0.49–1.25			.30
West	0.86		0.73–1.01			.07
Embolic or primary ischemic stroke	1.11		0.79–1.54			.55
Dyspepsia or stomach discomfort	1.24		1.07–1.45			.00
Congestive heart failure	1.21		1.05–1.40			.01
Coronary artery disease	1.02		0.88–1.18			.83
Diabetes	1.02		0.89–1.17			.79
Hypertension	1.16		1.00–1.35			.055
Renal disease	1.20		1.01–1.43			.038
Myocardial infarction	1.28		1.03–1.60			.026
Stroke or transient ischemic attack	1.00		0.74–1.33			.974
Bleeding at baseline	2.30		2.01–2.62			<.001
Charlson Comorbidity Index (CCI 0 as a reference category)						
CCI 1	1.21		0.99–1.48			.065
CCI 2	1.28		1.02–1.61			.034
CCI 3+	1.52		1.19–1.93			.001
Angiotensin converting enzyme inhibitor	0.95		0.83–1.10			.504
Amiodarone	1.02		0.78–1.33			.891
Angiotensin receptor blocker	1.09		0.94–1.26			.267
Beta blockers	1.00		0.89–1.13			.970
H2-receptor antagonist	0.98		0.73–1.32			.902
Proton pump inhibitor	0.97		0.84–1.13			.711
Statins	0.95		0.83–1.08			.405

For patients newly initiated on apixaban, compared with warfarin, there was a statistically significant reduction by 38%–48% in the risk of major bleeding. These results are consistent with the statistically significant 31% relative reduction in the risk of major bleeding for apixaban compared with warfarin, as demonstrated in the ARISTOTLE trial.[31] Indeed, our study supports that the benefits of apixaban demonstrated in randomised clinical trial may also be achieved in a broad population receiving clinical care in routine practice.

A limitation of this study is that as with any retrospective observational study and common to database analysis, we can only study association between variables. As with any retrospective observational database study, there is a potential for selection bias. We conducted rigorous and thorough multivariate analyses along with sensitivity analyses for bleeding definition to ensure robustness of our findings. Comorbidities at baseline (e.g. presence of renal impairment) are determined by presence of diagnosis code in the baseline period and not based on actual lab values or clinical assessment. As is the case with any claims database, there is a potential for coding errors and missing data. Similar to any pharmacy claims data in the United States, the Truven MarketScan pharmacy claims data does not routinely capture aspirin utilisation given that aspirin is typically

TABLE 5 Risk of major bleeding requiring hospitalization among patients initiating apixaban 5 mg b.i.d. compared to other anticoagulants after adjusting for clinical and demographic characteristics

	Hazard ratio	95% HR confidence limits	*P*-value	Hazard ratio	95% HR confidence limits	*P*-Value
Warfarin	1.90	1.03–3.51	0.040	1.00 Ref		
Rivaroxaban 20 mg q.i.d.	2.06	1.11–3.84	0.023	1.08	0.85–1.39	.525
Dabigatran 150 mg b.i.d.	1.50	0.79–3.04	0.198	0.82	0.58–1.16	.262
Apixaban 5 mg b.i.d.	1.00 Ref			0.53	0.29–0.97	.040
Covariates included in both models have the same estimates as shown below						
	Hazard ratio			**95% HR confidence limits**		***P*-Value**
Age (80+ as a reference category)						
18–39	0.76			0.19–3.13		.707
40–49	0.62			0.31–1.24		.173
50–59	0.52			0.35–0.76		.001
60–69	0.70			0.53–0.93		.015
70–79	0.70			0.53–0.91		.009
Male	0.98			0.79–1.23		.883
Region (North central as a reference category)						
Northeast	1.36			1.01–1.83		.042
South	1.26			0.95–1.66		.104
Unknown	1.33			0.67–2.66		.418
West	0.80			0.59–1.10		.167
Embolic or primary ischemic stroke	1.08			0.61–1.93		.793
Dyspepsia or stomach discomfort	1.46			1.13–1.90		.004
Congestive heart failure	1.33			1.04–1.70		.022
Coronary artery disease	1.01			0.78–1.31		.954
Diabetes	1.26			0.99–1.61		.066
Hypertension	0.97			0.75–1.26		.814
Renal disease	1.44			1.07–1.94		.016
Myocardial infarction	1.47			1.02–2.12		.040
Stroke or transient ischemic attack	1.06			0.63–1.77		.839
Bleeding at baseline	1.63			1.27–2.10		<.001
Charlson Comorbidity Index (CCI 0 as a reference category)						
CCI 1	1.05			0.73–1.52		.802
CCI 2	1.18			0.78–1.78		.437
CCI 3+	1.37			0.89–2.10		.151
Angiotensin converting enzyme inhibitor	0.95			0.75–1.21		.680
Amiodarone	1.04			0.65–1.65		.884
Angiotensin receptor blocker	1.07			0.82–1.40		.607
Beta blockers	1.02			0.82–1.28		.830
H2-receptor antagonist	0.83			0.46–1.47		.515
Proton pump inhibitor	0.90			0.68–1.18		.430
Statins	0.95			0.76–1.10		.683

obtained over-the-counter. Thus, aspirin use was not accounted in the analyses.

Oral anticoagulant initiation criterion was based on lack of anticoagulation prescription during 1 year baseline period. It was possible that patients may have used anticoagulation or aspirin concurrently prior to the baseline period. This design limitation is consistent across all OACs studied and hence is unlikely to change results. In addition, we do not have data on quality of anticoagulation control, as reflected by TTR which can influence efficacy and safety of VKA therapy.[23,32,33]

In addition, only inpatient deaths are observed and information about mortality was not available in the database, which may have biased the survival analysis. The mean length of follow-up for apixaban-treated patients was approximately 1 month shorter than for the other OACs. We used survival methods to account for varying lengths of follow-up. However, if bleeding events tend to occur later on apixaban than the other OACs, the difference in follow-up period may have affected the results. Because of the difference in follow-up, we conducted sensitivity analyses by limiting the follow-up to 90 and 180 days and found the results to be generally consistent. However, larger sample size and longer follow-up is needed to compare adequately powered events among the NOACs and warfarin.

It was also not possible to apply dose-adjustment in this analysis for following reasons: (i) Renal function and weights are not available in claims analyses and (ii) warfarin treatment is continuously dose-adjusted so there is no low- or high-dose strategy which can be defined in a manner similar to NOACs in the study. Further, it is unclear if adjusted study results would be any different from a clinical study conducted with above variables in consideration.

The strengths of our study are that we assessed a real-world comparative safety of newly initiating warfarin, apixaban, rivaroxaban, and dabigatran using the comprehensive Truven MarketScan® claims database which incorporates all medical and pharmacy claims of patients in the United States and allows for longitudinal analysis of a nationally representative sample for the study. Medications being studied are relatively new to market and this database encompassing both commercial and Medicare lives allows for selection of the best sample size for this study. Our results are based on real-world data and incorporate observed treatment patterns as recorded in the Marketscan database. Although Truven MarketScan® database allows for selection of the nationally representative sample for this study, the results may not be necessarily generalisable to the entire NVAF population in the United States or extrapolated to other parts of the world.

In conclusion, this study demonstrates that initiation with apixaban was associated with a significantly lower risk of major bleeding as compared with initiation on warfarin among newly anticoagulated NVAF patients in the real-world setting. Furthermore, patients initiating on rivaroxaban or warfarin had a significantly greater risk of major bleeding compared with those initiating apixaban. There was no significant difference in the risk of major bleeding among patients newly initiated on dabigatran compared with apixaban or warfarin initiators. Future analyses using a large propensity matched cohort comparing the treatment effect on the risk of major bleeding is needed to confirm the current study findings.

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AUTHOR CONTRIBUTIONS

G.Y.H. Lip, S. Kamble, and H. Phatak conceptualised and designed the study. X. Pan and H. Kawabata collected and analysed the data. G.Y.H. Lip, S. Kamble, H. Phatak, J. Mardekian, C. Masseria and A. Bruno substantially contributed to interpretation of the data. S. Kamble, H. Phatak, G.Y.H. Lip, X. Pan, H. Kawabata, C. Masseria, A. Bruno and J. Mardekian wrote the manuscript and/or substantially contributed to critical revisions of the intellectual content. All authors agreed to the final version.

DISCLOSURE

This study was sponsored by Bristol-Myers Squibb and Pfizer. Professor Lip has served as a consultant for Bayer, Merck, Sanofi, BMS/Pfizer, Daiichi-Sankyo, Biotronik, Medtronic, Portola and Boehringer Ingelheim and has been on the speaker's Bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, Medtronic. Ms Pan is an employee of Bristol-Myers Squibb with ownership of stocks in Bristol-Myers Squibb. Drs Kamble and Kawabata are employees of Bristol-Myers Squibb with ownership of stocks in Bristol-Myers Squibb. Drs Mardekian and Masseria are employees of Pfizer Inc. with ownership of stocks in Pfizer Inc. Drs Bruno and Phatak were employees of Bristol-Myers Squibb, at the time of research, with ownership of stocks in Bristol-Myers Squibb. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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SUPPORTING INFORMATION

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