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Published in:
Advances in Therapy

DOI (link to publication from Publisher):
10.1007/s12325-021-01724-8

Publication date:
2021

Document Version
Publisher's PDF, also known as Version of record

Adv Ther (2021) 38:3166–3184
https://doi.org/10.1007/s12325-021-01724-8

ORIGINAL RESEARCH

Use of Non-Vitamin K Antagonist Oral Anticoagulants Among Patients with Nonvalvular Atrial Fibrillation and Multimorbidity

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Received: January 28, 2021 / Accepted: March 24, 2021 / Published online: May 7, 2021

ABSTRACT

Introduction: Non-valvular atrial fibrillation (NVAF) is often accompanied by multiple comorbid conditions, which increase the associated risks and complexity of patient management. This study evaluated the risk of stroke/systemic embolism (SE) and major bleeding (MB) among multimorbid patients with NVAF who were prescribed non-vitamin K antagonist oral anticoagulants (NOACs) or warfarin.

Methods: A retrospective study of patients with NVAF and high multimorbidity who initiated apixaban, dabigatran, rivaroxaban, or warfarin from 1 January 2013 to 30 September 2015 was conducted using five insurance claims databases. Multimorbidity was defined as six or more comorbid conditions, and 1:1 propensity score matching (PSM) was conducted between the NOAC-warfarin and NOAC-NOAC cohorts. Cox proportional hazard models were used to evaluate the hazard ratios of stroke/SE and MB.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12325-021-01724-8.

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Results: Of the NVAF population (n = 466,991), 33.4% (n = 155,959) had multimorbidity, including 36,921 apixaban, 10,248 dabigatran, 45,509 rivaroxaban, and 63,281 warfarin patients. Compared to warfarin, apixaban and rivaroxaban were associated with a lower risk of stroke/SE (hazard ratio [HR] 0.63, 95% CI 0.54–0.74; HR 0.70, 95% CI 0.64–0.77, respectively). Apixaban and dabigatran were associated with a lower risk of MB (HR 0.61, 95% CI 0.56–0.67; HR 0.75, 95% CI 0.66–0.86, respectively) and rivaroxaban was associated with a higher risk of MB (HR 1.06, 95% CI 1.01–1.12) compared to warfarin.

Conclusions: Among patients with NVAF and six or more comorbid conditions, NOACs were associated with varying risk of stroke/SE and MB compared to warfarin and to each other. Rather than a "one drug fits all" approach, our results may be useful for appropriate OAC treatment for multimorbid patients.

Keywords: Anticoagulation; Bleeding; Multimorbidity; Outcomes; Stroke

Key Summary Points
Why carry out this study?
The presence of multiple comorbid conditions increases the risk of adverse clinical outcomes in patients with AF.
This study evaluates the safety and effectiveness of non-vitamin K antagonist oral anticoagulants (NOACs) versus warfarin among patients with AF and multiple comorbid conditions.
What was learned from the study?
In this multimorbid subgroup of patients with AF, NOACs were associated with varying risks of stroke/SE and major bleeding compared to warfarin.
These results may help inform treatment selection in this high-risk subgroup of patients with AF by allowing clinicians to choose the safest and most effective treatment according to the patient comorbidity burden.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.14261612.

INTRODUCTION

Atrial fibrillation (AF) is the most common serious cardiac arrhythmia, affecting 2–3% of the population in North America [1]. Previously, vitamin K antagonists, such as warfarin, were the most commonly prescribed therapeutic agents for AF. However, the needs for periodic patient monitoring and frequent dose adjustment increase the patient burden of treatment [2]. Non-vitamin K antagonist oral anticoagulants (NOACs: apixaban, dabigatran, edoxaban, and rivaroxaban) offer a non-inferior, safe, effective treatment choice for stroke prevention in patients with non-valvular atrial fibrillation (NVAF) without the restrictions of conventional therapy [3, 4].

Multimorbidity, often defined as the coexistence of two or more comorbid conditions, may provide a proxy for identifying chronic disease burden and functional status and may influence treatment selection [5]. More than two-thirds of Medicare patients have two or more comorbidities; the median number is six, with AF being the 11th most common [6]. Multimorbidity is associated with an increased risk of AF, cerebrovascular events, and mortality, with the risk increasing in accordance with the number of long-term conditions [7, 8]. Furthermore, patients with multimorbidity receiving oral anticoagulation therapy are associated with an increased risk of stroke relative to patients without multimorbidity who receive anticoagulation therapy [6]. Indeed, ad hoc results from the ARISTOTLE trial found that the risk of major bleeding (MB) rises by approximately 15% for each singular comorbidity [9]. However, despite the need for a safe treatment in this patient population, anticoagulants are generally underused—fewer than half of older adults with AF, who are generally multimorbid, receive

anticoagulants even without contraindications [6].

There have been very few observational studies comparing NOACs and warfarin among patients with NVAF and multimorbidity. This ARISTOPHANES (Anticoagulants for Reduction In Stroke: Observational Pooled Analysis on Health Outcomes and Experience of Patients; NCT03087487) sub-study compared the risk of stroke/SE and MB among multimorbid patients with NVAF who were newly prescribed apixaban, dabigatran, rivaroxaban, or warfarin.

METHODS

Data Sources

This retrospective observational analysis utilized Medicare fee-for-service data from the US Centers for Medicare & Medicaid Services (CMS) and data from four US commercial claims databases: the IBM MarketScan® Commercial Claims and Encounter Database, the IQVIA PharMetrics Plus™ Database, the Optum Clinformatics™ Data Mart, and the Humana Research Database. Previously published articles include detailed descriptions of the datasets, the rationale for the pooling process, and the approaches to minimizing potential patient record duplicates across data sources [10, 11]. To avoid potential duplicates, patients with Medicare supplemental plans in MarketScan and PharMetrics data were excluded from the study because those patients may also have Medicare Part A and Part B coverage. For Optum and Humana, beneficiaries aged 65 years or more are enrolled in Medicare Advantage plans but are not covered in Medicare data. There is a possibility that employer-based commercial claims datasets may contain duplicate patient records when pooled together; however, the number of duplicates is likely to be small at an estimated 0.5%.

Patient Selection

For this study, multimorbidity was defined as the presence of six or more comorbid conditions, not including AF, among the 17 conditions listed in Tables 1 and 2 [9], based on both the distribution of comorbidities as well as the ARISTOTLE multimorbidity subgroup analysis, the only prior published analysis based on a phase 3 randomized controlled trial (RCT) for NOACs in a multimorbid population [9]. The present study utilized the same count for high multimorbidity as seen in the ARISTOTLE subgroup analysis. Patients with NVAF and multimorbidity were selected if they had at least one pharmacy claim for apixaban, dabigatran, rivaroxaban, or warfarin between 1 January 2013 to 30 September 2015 (identification period). Edoxaban was not included in the final analysis because of the small sample size. For patients with a NOAC claim during the identification period, the first NOAC prescription date was designated as the index date; for patients with no NOAC claim during the identification period, the first warfarin prescription date was designated as the index date. Patients were required to have an AF diagnosis before the index date and have continuous medical and pharmacy health plan enrollment for at least 12 months pre-index date.

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

Outcome Measures

The primary outcomes measured were time to first stroke/SE and time to first MB. Stroke/SE was stratified by ischemic stroke, hemorrhagic stroke, and systemic embolism (SE). MB was stratified by gastrointestinal (GI) bleeding, intracranial hemorrhage, and bleeding at other key sites (Supplementary Table S1) [12, 13]. Outcomes were based on hospitalizations with stroke/SE or MB as the principal or first-listed diagnosis. The follow-up period ranged from

Table 1 Baseline characteristics among multimorbid patients with NVAF after propensity score matching among NOACs vs warfarin

	Apixaban cohort		Warfarin cohort		Dabigatran cohort		Warfarin cohort		Rivaroxaban cohort		Warfarin cohort	
	N/mean	%/SD	*N*/mean	%/SD	*N*/mean	%/SD	*N*/mean	%/SD	*N*/mean	%/SD	*N*/mean	%/SD
Sample size	34,658	100%	34,658	100%	10,027	100%	10,027	100%	40,601	100%	40,601	100%
Age	78.68	8.50	78.57	8.45	77.07	8.31	77.20	8.51	77.89	8.45	77.99	8.53
18–54	205	0.59%	201	0.58%	76	0.76%	80	0.80%	275	0.68%	289	0.71%
55–64	974	2.81%	956	2.76%	408	4.07%	407	4.06%	1342	3.31%	1329	3.27%
65–74	10,055	29.01%	10,113	29.18%	3435	34.26%	3462	34.53%	12,866	31.69%	12,703	31.29%
≥ 75	23,424	67.59%	23,388	67.48%	6108	60.92%	6078	60.62%	26,118	64.33%	26,280	64.73%
Gender												
Male	16,281	46.98%	16,303	47.04%	4918	49.05%	4899	48.86%	19,479	47.98%	19,493	48.01%
Female	18,377	53.02%	18,355	52.96%	5109	50.95%	5128	51.14%	21,122	52.02%	21,108	51.99%
Baseline comorbidity												
Deyo-Charlson Comorbidity Index	5.21	2.65	5.22	2.64	4.94	2.58	4.95	2.56	5.13	2.62	5.12	2.61
CHA_2DS_2-VASc Score[a]	5.00	1.45	5.00	1.42	4.87	1.45	4.87	1.43	4.93	1.44	4.93	1.42
0												
1	75	0.22%	76	0.22%	39	0.39%	26	0.26%	114	0.28%	105	0.26%
2	968	2.79%	805	2.32%	330	3.29%	327	3.26%	1214	2.99%	1098	2.70%
3	3964	11.44%	3878	11.19%	1345	13.41%	1311	13.07%	5031	12.39%	4825	11.88%
4+	29,647	85.54%	29,894	86.25%	8312	82.90%	8361	83.38%	34,235	84.32%	34,563	85.13%
HAS-BLED Score[a]	4.05	1.14	4.04	1.15	3.91	1.15	3.90	1.14	4.00	1.14	3.99	1.15
0												
1	190	0.55%	181	0.52%	84	0.84%	71	0.71%	250	0.62%	263	0.65%

Table 1 continued

	Apixaban cohort		Warfarin cohort		Dabigatran cohort		Warfarin cohort		Rivaroxaban cohort		Warfarin cohort	
	N/mean	%/SD	*N*/mean	%/SD	*N*/mean	%/SD	*N*/mean	%/SD	*N*/mean	%/SD	*N*/mean	%/SD
2	2728	7.87%	2802	8.08%	974	9.71%	1015	10.12%	3437	8.47%	3631	8.94%
3+	31,739	91.58%	31,670	91.38%	8968	89.44%	8941	89.17%	36,909	90.91%	36,701	90.39%
Bleeding history	10,857	31.33%	10,844	31.29%	2966	29.58%	2979	29.71%	13,076	32.21%	13,087	32.23%
Stroke/SE	7683	22.17%	7687	22.18%	2117	21.11%	2146	21.40%	8781	21.63%	8819	21.72%
Comorbidities for multimorbidity definition												
CAD (CAD, prior MI, PCI/CABG)	24,926	71.92%	24,786	71.52%	7181	71.62%	7028	70.09%	28,723	70.74%	28,752	70.82%
Congestive heart failure	18,813	54.28%	18721	54.02%	5278	52.64%	5296	52.82%	21,662	53.35%	21,656	53.34%
Valvular disease	10,306	29.74%	10,044	28.98%	2682	26.75%	2820	28.12%	11,028	27.16%	11,445	28.19%
Hypertension	34,038	98.21%	34,051	98.25%	9822	97.96%	9835	98.09%	39,783	97.99%	39,736	97.87%
PVD (PAD or aortic aneurysm)	15,136	43.67%	15,695	45.29%	4218	42.07%	4486	44.74%	17,859	43.99%	18,237	44.92%
CVD (carotid stenosis, TIA, stroke)	13,555	39.11%	13,374	38.59%	3745	37.35%	3704	36.94%	15,474	38.11%	15,378	37.88%
Depression or dementia	17,870	51.56%	18,040	52.05%	5237	52.23%	5159	51.45%	21,432	52.79%	21,150	52.09%
Pulmonary (COPD, asthma)	12,090	34.88%	12,136	35.02%	3608	35.98%	3591	35.81%	14,972	36.88%	14,450	35.59%
Sleep apnea	8462	24.42%	7769	22.42%	2602	25.95%	2433	24.26%	9507	23.42%	9359	23.05%
GI disorder (dyspepsia, GERD, PUD)	21,461	61.92%	21,401	61.75%	6116	61.00%	6126	61.10%	25,176	62.01%	24,899	61.33%
Chronic liver disease	1687	4.87%	1652	4.77%	539	5.38%	491	4.90%	2180	5.37%	2073	5.11%
Hypo- or hyperthyroidism	13,889	40.07%	13017	37.56%	3925	39.14%	3790	37.80%	15,870	39.09%	15,161	37.34%
Diabetes	19,763	57.02%	19,868	57.33%	5953	59.37%	5985	59.69%	23,569	58.05%	23,456	57.77%
Musculoskeletal (falls, osteoporosis)	9206	26.56%	9023	26.03%	2489	24.82%	2465	24.58%	10,957	26.99%	10,497	25.85%
Renal disease (CKD or CrCl < 50 ml/min)	17,980	51.88%	17,724	51.14%	4852	48.39%	4877	48.64%	20,386	50.21%	20,193	49.74%

Table 1 continued

	Apixaban cohort		Warfarin cohort		Dabigatran cohort		Warfarin cohort		Rivaroxaban cohort		Warfarin cohort	
	N/mean	%/SD	*N*/mean	%/SD	*N*/mean	%/SD	*N*/mean	%/SD	*N*/mean	%/SD	*N*/mean	%/SD
Anemia	18,603	53.68%	18,168	52.42%	5033	50.19%	4965	49.52%	21,440	52.81%	21,141	52.07%
Malignancy	8425	24.31%	8021	23.14%	2241	22.35%	2283	22.77%	9926	24.45%	9484	23.36%
Dose of the index prescription												
Standard dose[b]	22,624	65.28%			7338	73.18%			24,092	59.34%		
Low dose[c]	12,034	34.72%			2689	26.82%			16,509	40.66%		

CAD coronary artery disease, *CHA_2DS_2-VASc* congestive heart failure, hypertension, aged ≥ 75 years, diabetes mellitus, prior stroke or transient ischemic attack, or thromboembolism, *CKD* chronic kidney disease, *COPD* chronic obstructive pulmonary disease, *CrCl* creatinine clearance, *CVD* cardiovascular disease, *GERD* gastroesophageal reflux disease, *GI* gastrointestinal, *HAS-BLED* hypertension, abnormal renal and liver function, stroke, bleeding, labile international normalized ratio, elderly, drugs or alcohol, *MI* myocardial infarction, *NOAC* non-vitamin K antagonist oral anticoagulants, *NVAF* non-valvular atrial fibrillation, *PAD* peripheral artery disease, *PCI/CABG* percutaneous coronary intervention/coronary artery bypass grafting, *PUD* peptic ulcer disease, *PVD* peripheral vascular disease, *SD* standard deviation, *SE* systemic embolism, *TIA* transient ischemic attack

[a] Cells with values < 11 are not reported

[b] 5 mg apixaban, 150 mg dabigatran, 20 mg rivaroxaban

[c] 2.5 mg apixaban, 75 mg dabigatran, 10 or 15 mg rivaroxaban; 3035 and 13,474 patients received 10 mg and 15 mg rivaroxaban, respectively, in the rivaroxaban-warfarin matched cohort

Table 2 Baseline characteristics among multimorbid patients with NVAF after propensity score matching among NOACs vs NOACs

	Apixaban cohort		Dabigatran cohort		Apixaban cohort		Rivaroxaban cohort		Dabigatran cohort		Rivaroxaban cohort	
	N/ mean	%/SD	*N*/ mean	%/SD	*N*/ mean	%/SD	*N*/ mean	%/SD	*N*/ mean	%/SD	*N*/ mean	%/SD
Sample size	9962	100%	9962	100%	35,126	100%	35,126	100%	10,156	100%	10,156	100%
Age	77.27	8.59	77.06	8.39	78.33	8.67	78.16	8.58	76.84	8.53	76.96	8.66
18–54	96	0.96%	97	0.97%	298	0.85%	299	0.85%	111	1.09%	110	1.08%
55–64	397	3.99%	386	3.87%	1196	3.40%	1198	3.41%	474	4.67%	459	4.52%
65–74	3364	33.77%	3406	34.19%	10,340	29.44%	10,392	29.58%	3468	34.15%	3502	34.48%
≥ 75	6105	61.28%	6073	60.96%	23,292	66.31%	23,237	66.15%	6103	60.09%	6085	59.92%
Gender												
Male	4837	48.55%	4863	48.82%	16475	46.90%	16,430	46.77%	5004	49.27%	4976	49.00%
Female	5125	51.45%	5099	51.18%	18,651	53.10%	18,696	53.23%	5152	50.73%	5180	51.00%
Baseline comorbidity												
Deyo-Charlson Comorbidity Index	4.95	2.64	4.92	2.59	5.08	2.64	5.07	2.61	4.91	2.58	4.89	2.59
CHA_2DS_2-VASc score[a]	4.86	1.45	4.86	1.46	4.94	1.45	4.94	1.45	4.84	1.48	4.83	1.46
0												
1	39	0.39%	41	0.41%	105	0.30%	128	0.36%	49	0.48%	58	0.57%
2	354	3.55%	347	3.48%	1120	3.19%	1057	3.01%	393	3.87%	366	3.60%
3	1307	13.12%	1326	13.31%	4283	12.19%	4316	12.29%	1385	13.64%	1420	13.98%
4+	8261	82.93%	8246	82.77%	29,611	84.30%	29,617	84.32%	8325	81.97%	8312	81.84%
HAS-BLED score[a]	3.92	1.15	3.91	1.15	4.01	1.15	4.01	1.14	3.89	1.16	3.89	1.15
0												
1	93	0.93%	90	0.90%	249	0.7%	234	0.7%	104	1.02%	104	1.02%

Table 2 continued

	Apixaban cohort		Dabigatran cohort		Apixaban cohort		Rivaroxaban cohort		Dabigatran cohort		Rivaroxaban cohort	
	N/ mean	%/SD	*N*/ mean	%/SD	*N*/ mean	%/SD	*N*/ mean	%/SD	*N*/ mean	%/SD	*N*/ mean	%/SD
2	959	9.63%	967	9.71%	2970	8.5%	2921	8.3%	1025	10.09%	986	9.71%
3+	8909	89.43%	8904	89.38%	31,904	90.8%	31,963	91.0%	9026	88.87%	9064	89.25%
Bleeding history	2923	29.34%	2922	29.33%	10,718	30.51%	10,740	30.58%	2970	29.24%	3062	30.15%
Stroke/SE	2082	20.90%	2085	20.93%	7493	21.33%	7443	21.19%	2108	20.76%	2127	20.94%
Comorbidities for multimorbidity definition												
CAD (CAD, prior MI, PCI/CABG)	7122	71.49%	7121	71.48%	25,146	71.59%	24,877	70.82%	7254	71.43%	7098	69.89%
Congestive heart failure	5259	52.79%	5215	52.35%	18,408	52.41%	18,428	52.46%	5299	52.18%	5278	51.97%
Valvular disease	2878	28.89%	2682	26.92%	10,368	29.52%	9643	27.45%	2709	26.67%	2692	26.51%
Hypertension	9756	97.93%	9760	97.97%	34,504	98.23%	34,500	98.22%	9948	97.95%	9948	97.95%
PVD (PAD or aortic aneurysm)	4189	42.05%	4193	42.09%	15,174	43.20%	15,469	44.04%	4244	41.79%	4362	42.95%
CVD (carotid stenosis, TIA, stroke)	3791	38.05%	3717	37.31%	13,582	38.67%	13,489	38.40%	3759	37.01%	3795	37.37%
Depression (diagnosis or antidepressants) or dementia	5125	51.45%	5217	52.37%	18,182	51.76%	18,675	53.17%	5314	52.32%	5339	52.57%
Pulmonary (COPD, asthma)	3479	34.92%	3572	35.86%	12,224	34.80%	12,771	36.36%	3644	35.88%	3658	36.02%
Sleep apnea	2689	26.99%	2599	26.09%	8800	25.05%	8066	22.96%	2694	26.53%	2528	24.89%
GI disorder (dyspepsia, GERD, PUD)	6143	61.66%	6090	61.13%	21,900	62.35%	21,921	62.41%	6208	61.13%	6254	61.58%
Chronic liver disease	549	5.51%	538	5.40%	1759	5.01%	1827	5.20%	558	5.49%	551	5.43%
Hypo- or hyperthyroidism	4011	40.26%	3924	39.39%	14,091	40.12%	13,924	39.64%	3976	39.15%	3993	39.32%
Diabetes	5871	58.93%	5902	59.25%	19,871	56.57%	19,910	56.68%	6040	59.47%	6046	59.53%
Musculoskeletal (falls, osteoporosis)	2478	24.87%	2482	24.91%	9281	26.42%	9581	27.28%	2499	24.61%	2692	26.51%

Table 2 continued

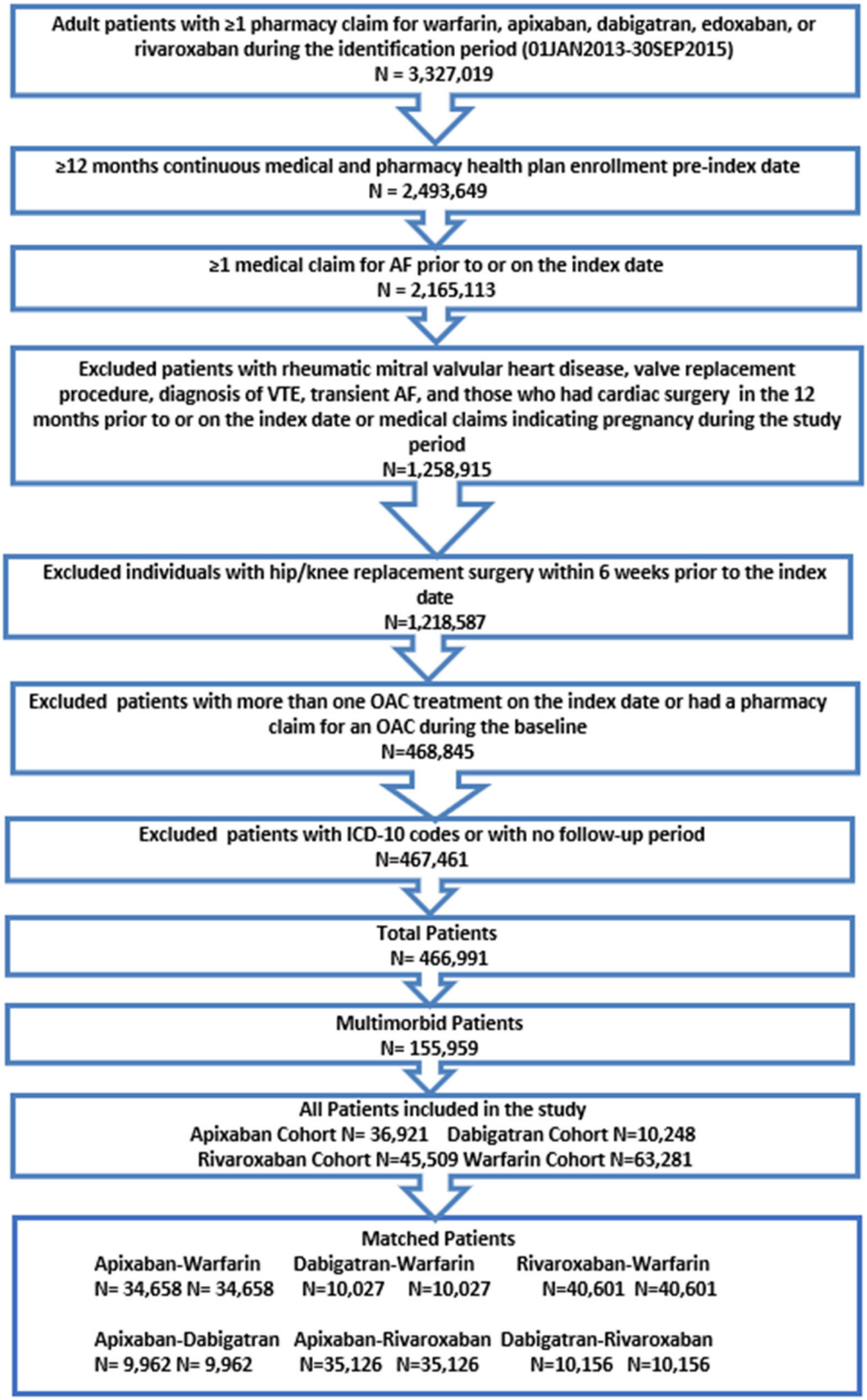
	Apixaban cohort		Dabigatran cohort		Apixaban cohort		Rivaroxaban cohort		Dabigatran cohort		Rivaroxaban cohort	
	N/ mean	%/SD	*N*/ mean	%/SD	*N*/ mean	%/SD	*N*/ mean	%/SD	*N*/ mean	%/SD	*N*/ mean	%/SD
Renal disease (CKD or CrCl < 50 ml/min)	4858	48.77%	4800	48.18%	17,882	50.91%	17,719	50.44%	4892	48.17%	4880	48.05%
Anemia	4944	49.63%	4967	49.86%	18,250	51.96%	18,260	51.98%	5043	49.66%	5060	49.82%
Malignancy	2364	23.73%	2210	22.18%	8532	24.29%	8447	24.05%	2256	22.21%	2411	23.74%
Dose of the index prescription												
Standard dose[b]	7017	70.44%	7288	73.16%	23,378	66.55%	20,504	58.37%	7462	73.47%	6336	62.39%
Low dose[c]	2945	29.56%	2674	26.84%	11,748	33.45%	14,622	41.63%	2694	26.53%	3820	37.61%

CAD coronary artery disease, *CHA_2DS_2-VASc* congestive heart failure, hypertension, aged ≥ 75 years, diabetes mellitus, prior stroke or transient ischemic attack, or thromboembolism, *CKD* chronic kidney disease, *COPD* chronic obstructive pulmonary disease, *CrCl* creatinine clearance, *CVD* cardiovascular disease, *GERD* gastroesophageal reflux disease, *GI* gastrointestinal, *HAS-BLED* hypertension, abnormal renal and liver function, stroke, bleeding, labile international normalized ratio, elderly, drugs or alcohol, *MI* myocardial infarction, *NOAC* non-vitamin K antagonist oral anticoagulants, *NVAF* non-valvular atrial fibrillation, *PAD* peripheral artery disease, *PCI/CABG* percutaneous coronary intervention/coronary artery bypass grafting, *PUD* peptic ulcer disease, *PVD* peripheral vascular disease, *SD* standard deviation, *SE* systemic embolism, *TIA* transient ischemic attack

[a] Cells with values < 11 are not reported

[b] 5 mg apixaban, 150 mg dabigatran, 20 mg rivaroxaban

[c] 2.5 mg apixaban, 75 mg dabigatran, 10 or 15 mg rivaroxaban. 2615 and 12,007 patients received 10 mg and 15 mg rivaroxaban, respectively, in the apixaban-rivaroxaban matched cohort and 704 and 3116 patients received 10 mg and 15 mg rivaroxaban, respectively, in the dabigatran-rivaroxaban matched cohort


Adult patients with ≥1 pharmacy claim for warfarin, apixaban, dabigatran, edoxaban, or rivaroxaban during the identification period (01JAN2013-30SEP2015)
N = 3,327,019
≥12 months continuous medical and pharmacy health plan enrollment pre-index date
N = 2,493,649
≥1 medical claim for AF prior to or on the index date
N = 2,165,113
Excluded patients with rheumatic mitral valvular heart disease, valve replacement procedure, diagnosis of VTE, transient AF, and those who had cardiac surgery in the 12 months prior to or on the index date or medical claims indicating pregnancy during the study period
N=1,258,915
Excluded individuals with hip/knee replacement surgery within 6 weeks prior to the index date
N=1,218,587
Excluded patients with more than one OAC treatment on the index date or had a pharmacy claim for an OAC during the baseline
N=468,845
Excluded patients with ICD-10 codes or with no follow-up period
N=467,461
Total Patients
N= 466,991
Multimorbid Patients
N= 155,959
All Patients included in the study
Apixaban Cohort N= 36,921 Dabigatran Cohort N=10,248
Rivaroxaban Cohort N=45,509 Warfarin Cohort N=63,281
Matched Patients
Apixaban-Warfarin Dabigatran-Warfarin Rivaroxaban-Warfarin
N= 34,658 N= 34,658 N=10,027 N=10,027 N=40,601 N=40,601
Apixaban-Dabigatran Apixaban-Rivaroxaban Dabigatran-Rivaroxaban
N= 9,962 N= 9,962 N=35,126 N=35,126 N=10,156 N=10,156

◀**Fig. 1** Study selection. AF atrial fibrillation; Clinical Modification, OAC oral anticoagulant, VTE venous thromboembolism

1 day post-index date to the first of 30 days after discontinuation, switch date, death, end of continuous medical or pharmacy plan enrollment, or end of study.

Statistical Methods

Propensity score matching (PSM) was conducted between NOAC and warfarin cohorts and between the NOAC cohorts. Patients were matched 1:1 in each dataset based on the propensity scores generated by logistic regression using demographics, Charlson Comorbidity Index (CCI) scores [14], comorbidities that were documented risk factors for stroke/SE or MB, and baseline co-medications. Patients were matched by nearest neighbor matching without replacement using a caliper of 0.01. Covariate balance was checked through standardized differences, with a threshold of 10% [15]. Patients from the five matched datasets were pooled for the final analysis.

Risk of stroke/SE and risk of MB were evaluated using Cox proportional hazard models, with robust sandwich estimates ($\alpha = 0.05$) [16]. OAC treatment was included as the independent variable; no other covariates were included as the cohorts were balanced.

All statistical analyses were performed using SAS version 9.4.

Subgroup Analyses

An interaction analysis was conducted between treatment and comorbidity level among patients with 6–8 comorbidities vs patients with 9+ comorbidities. The statistical significance ($p < 0.10$) of the interaction between treatment and comorbidity level was evaluated. Further, PSM and Cox proportional hazard models were separately completed for patients prescribed standard dose NOACs (apixaban 5 mg, dabigatran 150 mg, rivaroxaban 20 mg) and low dose NOACs (apixaban 2.5 mg, dabigatran 75 mg, rivaroxaban 10 or 15 mg).

Compliance with Ethics Guidelines

Since the core study described herein did not involve the collection, use, or transmittal of individual identifiable data, institutional review board (IRB) approval to conduct this study was not required. The security of the data meets the requirements of the Health Insurance Portability and Accountability Act (HIPAA) of 1996. The study protocol was reviewed and determined to be exempt from the Office for Human Research Protections (OHRP's) Regulations for the Protection of Human Subjects (45 CFR 46) under the following category: Exemption 4: Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

RESULTS

After applying the selection criteria, 33.4% ($n = 155,959$) of the NVAF population newly initiated on OACs ($n = 466,991$) had multimorbidity; 36,921 (23.7%) initiated apixaban, 10,248 (6.6%) dabigatran, 45,509 (29.2%) rivaroxaban, and 63,281 (40.6%) warfarin (Fig. 1). The mean number of comorbidities ranged from 7.5 to 7.8 across the drug cohorts. Before PSM, apixaban patients were older and warfarin patients had higher CCI, CHA_2DS_2-VASc, and HAS-BLED scores compared to NOAC patients (Supplementary Table S2).

The unadjusted incidence rates of stroke/SE per 100 person-years were 3.7 (warfarin), 2.4 (apixaban), 2.8 (dabigatran), and 2.4 (rivaroxaban). The unadjusted rates for MB per 100 person-years were 11.5 (warfarin), 6.9 (apixaban), 7.2 (dabigatran), and 10.5 (rivaroxaban) (Supplementary Table S3).

After PSM, 34,658 apixaban-warfarin, 10,027 dabigatran-warfarin, and 40,601 rivaroxaban-warfarin patient pairs were studied. Matching

for NOAC comparisons included 9962 patient pairs for the apixaban-dabigatran, 35,126 pairs for the apixaban-rivaroxaban, and 10,156 pairs for the dabigatran-rivaroxaban cohorts (Fig. 1). Coronary artery disease, hypertension, and GI disorders were among some of the most prevalent comorbid conditions. The baseline characteristics of the matched populations are shown in Tables 1 and 2.

NOAC vs Warfarin Comparisons

Compared to warfarin, apixaban and rivaroxaban were associated with a lower risk of stroke/SE (apixaban: hazard ratio [HR] 0.63, 95% confidence interval [CI] 0.54–0.74; rivaroxaban: HR 0.70, 95% CI 0.64–0.77). Dabigatran was associated with a similar risk of stroke/SE (HR 0.91, 95% CI 0.75–1.10) compared to warfarin. Apixaban and dabigatran were associated with a lower risk of MB compared to warfarin (HR 0.61, 95% CI 0.56–0.67; HR 0.75, 95% CI 0.66–0.86, respectively) while rivaroxaban patients had a higher risk of MB (HR 1.06, 95% CI 1.01–1.12; Fig. 2a).

NOAC vs NOAC Comparisons

Compared to dabigatran, apixaban was associated with a lower risk of stroke/SE (HR 0.81, 95% CI 0.65–1.00) and MB (HR 0.82, 95% CI 0.69–0.98). Dabigatran was associated with a higher risk of stroke/SE versus rivaroxaban (HR 1.29, 95% CI 1.02–1.62). Apixaban and dabigatran were associated with lower risks of MB versus rivaroxaban (HR 0.57, 95% CI 0.52–0.63; HR 0.72, 95% CI 0.64–0.81, respectively) (Fig. 2b). The Kaplan–Meier curves for cumulative incidence rates of stroke/SE and MB in the matched populations are shown in Supplementary Figs. S1A–S1L.

Subgroup Analyses

Significant interactions were observed for treatment and number of comorbidities among some of the analyses for stroke/SE and MB. For apixaban vs warfarin and apixaban vs rivaroxaban, patients with 6–8 comorbidities experienced a greater relative magnitude of reduction in the risk of MB compared to patients with 9+ comorbidities (Tables 3 and 4). A significant interaction was also found for apixaban vs rivaroxaban for stroke/SE ($p = 0.064$) where apixaban patients with 6–8 comorbidities had a similar risk of stroke/SE, but apixaban patients with 9+ comorbidities trended towards a lower risk of stroke/SE compared with rivaroxaban patients (Table 4). The results of the dose analyses were generally consistent with the main analysis. In the standard dose comparison, all NOACs demonstrated a lower risk of stroke/SE compared to warfarin (Supplementary Figs. S2 and S3).

Fig. 2 Incidence rates and hazard ratios for stroke and major bleeding: **a** NOACs vs warfarin; **b** NOACs vs NOACs. CI confidence interval, GI gastrointestinal, NOAC non-vitamin K antagonist oral anticoagulant, SE systemic embolism. [a]The upper confidence interval was rounded from 0.999 to 1

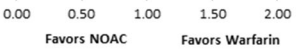
DISCUSSION

This ARISTOPHANES subgroup analysis is the largest study to date that evaluates the effectiveness and safety of OAC treatment in a multimorbid (at least six comorbidities) patient population with NVAF. Overall, NOACs were found to be associated with varying risk of stroke/SE and MB compared to warfarin and differential risk of stroke/SE and MB was also observed between NOACs. Further analyses in key subgroups, including NOAC low- and standard-dose populations and patients with 6–8 vs 9+ comorbidities, showed generally consistent findings.

Multimorbidity is common in patients with NVAF, and proportionally becoming more prevalent in recent years [17]. The presence of multimorbidity is associated with an increased risk of stroke, bleeding, and death [17]. The results of the present study are similar to the findings from related post hoc analyses of the ARISTOTLE trial. Therein, patients were included on the basis of the number of comorbidities and classified as no multimorbidity (0–2

a

	Comparator Incidence per 100 person-years	Warfarin Incidence per 100 person-years	Hazard Ratio (95% CI)	P-value
Apixaban vs Warfarin	(N=34,658 vs. N=34,658)			
Stroke/SE	2.40	3.47	0.63 (0.54-0.74)	<0.001
Ischemic	1.95	2.50	0.70 (0.63-0.79)	<0.001
Hemorrhagic	0.37	0.81	0.43 (0.27-0.67)	<0.001
Systemic Embolism	0.10	0.17	0.54 (0.32-0.91)	0.021
Major Bleeding	7.06	10.54	0.61 (0.56-0.67)	<0.001
GI Bleeding	3.43	4.95	0.63 (0.56-0.71)	<0.001
Intracranial Hemorrhage	0.82	1.42	0.55 (0.42-0.72)	<0.001
Other sites	3.12	4.77	0.60 (0.54-0.66)	<0.001
Dabigatran vs Warfarin	(N=10,027 vs. N=10,027)			
Stroke/SE	2.79	3.07	0.91 (0.75-1.10)	0.329
Ischemic	2.34	2.27	1.03 (0.83-1.28)	0.787
Hemorrhagic	0.33	0.73	0.45 (0.28-0.73)	0.001
Systemic Embolism	0.12	0.08	1.46 (0.56-3.81)	0.437
Major Bleeding	7.27	9.67	0.75 (0.66-0.86)	<0.001
GI Bleeding	4.40	4.45	0.99 (0.85-1.15)	0.876
Intracranial Hemorrhage	0.74	1.31	0.57 (0.41-0.78)	<0.001
Other sites	2.59	4.49	0.58 (0.48-0.70)	<0.001
Rivaroxaban vs Warfarin	(N=40,601 vs. N=40,601)			
Stroke/SE	2.33	3.27	0.70 (0.64-0.77)	<0.001
Ischemic	1.79	2.34	0.76 (0.68-0.84)	<0.001
Hemorrhagic	0.40	0.80	0.50 (0.39-0.64)	<0.001
Systemic Embolism	0.14	0.18	0.79 (0.55-1.14)	0.212
Major Bleeding	10.94	10.17	1.06 (1.01-1.12)	0.015
GI Bleeding	6.08	4.71	1.27 (1.19-1.36)	<0.001
Intracranial Hemorrhage	0.76	1.41	0.53 (0.45-0.63)	<0.001
Other sites	4.95	4.63	1.06 (0.98-1.14)	0.156



b

	Comparator Incidence per 100 person-years	Reference Incidence per 100 person-years	Hazard Ratio (95% CI)	P-value
Apixaban vs Dabigatran (ref.)	(N=9,962 vs. N=9,962)			
Stroke/SE	2.51	2.85	0.81 (0.65-1.00)	0.049
Ischemic	2.04	2.39	0.78 (0.63-0.97)	0.025
Hemorrhagic	0.32	0.32	0.96 (0.44-2.09)	0.918
Systemic Embolism	0.16	0.13	1.06 (0.48-2.36)	0.877
Major Bleeding	6.50	7.21	0.82 (0.69-0.98)	0.032
GI Bleeding	3.14	4.34	0.66 (0.53-0.82)	<0.001
Intracranial Hemorrhage	0.75	0.73	0.98 (0.63-1.53)	0.930
Other sites	2.90	2.60	1.00 (0.80-1.25)	0.991
Apixaban vs Rivaroxaban (ref.)	(N=35,126 vs. N=35,126)			
Stroke/SE	2.28	2.41	0.87 (0.74-1.02)	0.093
Ischemic	1.85	1.83	0.94 (0.83-1.07)	0.348
Hemorrhagic	0.34	0.45	0.70 (0.43-1.17)	0.173
Systemic Embolism	0.10	0.15	0.59 (0.35-0.99)	0.045
Major Bleeding	6.75	10.87	0.57 (0.52-0.63)	<0.001
GI Bleeding	3.24	6.02	0.49 (0.44-0.55)	<0.001
Intracranial Hemorrhage	0.77	0.84	0.87 (0.66-1.14)	0.300
Other sites	3.08	4.88	0.58 (0.53-0.65)	<0.001
Dabigatran vs Rivaroxaban (ref.)	(N=10,156 vs. N=10,156)			
Stroke/SE	2.79	2.19	1.29 (1.02-1.62)	0.034
Ischemic	2.33	1.73	1.36 (1.07-1.72)	0.010
Hemorrhagic	0.33	0.36	0.91 (0.53-1.57)	0.748
Systemic Embolism	0.13	0.13	1.01 (0.38-2.68)	0.984
Major Bleeding	7.15	9.97	0.72 (0.64-0.81)	<0.001
GI Bleeding	4.33	5.50	0.79 (0.68-0.92)	0.002
Intracranial Hemorrhage	0.72	0.70	1.02 (0.69-1.50)	0.923
Other sites	2.57	4.63	0.56 (0.47-0.67)	<0.001

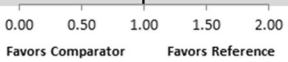


Table 3 Incidence and hazard ratios of stroke/SE and MB among patients with 6–8 comorbidities vs patients with 9+ comorbidities receiving NOACs vs warfarin

6–8 Comorbidities	Incidence per 100 person-years		Hazard ratio (95% CI)	9+ Comorbidities	Incidence per 100 person-years		Hazard ratio (95% CI)	Interaction *p* value
	Apixaban	Warfarin			Apixaban	Warfarin		
Stroke/SE	2.25	3.24	0.63 (0.52, 0.77)	Stroke/SE	2.85	4.24	0.62 (0.51, 0.76)	0.870
MB	5.55	8.97	0.57 (0.52, 0.62)	MB	11.72	15.99	0.68 (0.58, 0.79)	0.023
	Dabigatran	Warfarin			Dabigatran	Warfarin		
Stroke/SE	2.68	2.82	0.94 (0.74, 1.21)	Stroke/SE	3.18	4.06	0.81 (0.56, 1.15)	0.496
MB	5.93	8.35	0.71 (0.59, 0.84)	MB	12.06	15.03	0.83 (0.68, 1.01)	0.285
	Rivaroxaban	Warfarin			Rivaroxaban	Warfarin		
Stroke/SE	2.08	3.14	0.65 (0.59, 0.73)	Stroke/SE	3.13	3.73	0.84 (0.70, 1.00)	0.020
MB	9.49	8.73	1.07 (1.01, 1.14)	MB	15.68	15.42	1.01 (0.92, 1.11)	0.333

CI confidence interval, *MB* major bleeding, *NOAC* non-vitamin K antagonist oral anticoagulant, *SE* systemic embolism

Table 4 Incidence and hazard ratios on stroke/SE and MB among patients with 6–8 comorbidities vs patients with 9+ comorbidities receiving NOACs vs NOACs

6–8 Comorbidities	Incidence per 100 person-years		Hazard ratio (95% CI)	9+ Comorbidities	Incidence per 100 person-years		Hazard ratio (95% CI)	Interaction *p* value
	Apixaban	Dabigatran			Apixaban	Dabigatran		
Stroke/SE	2.38	2.75	0.80 (0.60, 1.05)	Stroke/SE	2.95	3.20	0.84 (0.56, 1.27)	0.853
MB	5.18	5.84	0.81 (0.64, 1.02)	MB	10.99	12.11	0.82 (0.66, 1.02)	0.951
	Apixaban	Rivaroxaban			Apixaban	Rivaroxaban		
Stroke/SE	2.13	2.11	0.93 (0.79, 1.11)	Stroke/SE	2.74	3.44	0.74 (0.59, 0.93)	0.064
MB	5.40	9.47	0.53 (0.48, 0.58)	MB	11.15	15.62	0.66 (0.57, 0.77)	0.002
	Dabigatran	Rivaroxaban			Dabigatran	Rivaroxaban		
Stroke/SE	2.71	2.06	1.32 (1.02, 1.71)	Stroke/SE	3.11	2.66	1.19 (0.79, 1.79)	0.636
MB	5.78	8.68	0.67 (0.58, 0.77)	MB	12.14	14.70	0.84 (0.66, 1.07)	0.134

CI confidence interval, *MB* major bleeding, *NOAC* non-vitamin K antagonist oral anticoagulant, *SE* systemic embolism

comorbidities), moderate multimorbidity (3–5 comorbidities), and high multimorbidity (at least 6 comorbidities), and the risks of stroke/SE and MB were elevated for patients in the high and moderate multimorbidity groups compared with the no multimorbidity group [9]. The ARISTOTLE post hoc analysis also found that multimorbid apixaban patients trended toward a lower risk of stroke/SE and MB compared to warfarin, which is consistent with both the main trial results and the present study [9].

Few real-world retrospective studies have evaluated the impact of OAC treatment in patients with AF and multimorbidity. One study done by Mentias et al. assessed the effectiveness of dabigatran, rivaroxaban, and warfarin among Medicare patients with AF where multimorbidity was indicated by CHA_2DS_2-VASc, HAS-BLED, and Gagne comorbidity scores rather than number of comorbid conditions at baseline [18]. Across the three comorbidity scores, the authors found that standard-dose dabigatran patients did not have a significantly different risk of stroke or MB compared to warfarin. This is inconsistent with the results of both the standard-dose subgroup analysis of this study and results from the RE-LY trial, which showed that dabigatran had a significantly lower risk of stroke/SE and MB compared to warfarin [19]. Mentias et al. (2018) found that standard-dose rivaroxaban patients had a higher risk of MB compared to dabigatran patients across all three scores, which is consistent with results of our main analysis and standard-dose subgroup analysis [18]. The discrepancy in trends may be due to the difference in defining multimorbidity.

Compared to previous studies, this ARISTOPHANES subgroup analysis provides a larger sample of patients with NVAF and multimorbidity from a more representative population, including both Medicare and commercially insured patients. The results are consistent with available RCT literature in showing that NOACs are associated with favorable benefit/risk profile when compared to warfarin.

Limitations

For this retrospective observational study, only statistical associations could be concluded, not causal relationships. Although cohorts were matched through PSM, there were potential residual confounders. As a result of the nature of claims studies, outcome measures could only be based on International Classification of Diseases—Ninth Revision—Clinical Modification (ICD-9-CM) codes without further adjustment with precise clinical criteria. In addition, laboratory values, such as hemoglobin or international normalized ratio (INR) measurements, are not available in the dataset so time in therapeutic range for patients prescribed warfarin was indeterminable. Nonetheless, the inclusion of patients with potentially poorer quality control of warfarin therapy in everyday clinical practice may enable the study findings to better reflect real-world situations. Additionally, previously verified mortality information was only available for Medicare patients, and although 62% of stroke deaths occur outside of an acute hospital setting, it is unlikely that the proportion of deaths would differ by cohort [20, 21].

This study used both the distribution of comorbidities at baseline and previously published ARISTOTLE trial subgroup analyses to define multimorbidity, but definition of multimorbidity differs from some other studies and presents a challenge to compare our findings with those of other studies. While all patients were required to have at least six comorbidities, the severity of conditions remained unknown and may not be equal among patients. Moreover, unobserved heterogeneity may exist across the five data sources. 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—on the basis of a published estimate of 0.5%—and therefore unlikely to have any significant effect on the results [22]. Finally, the results may not reflect the overall multimorbid NVAF population in the USA because the study did not include

uninsured patients and those solely covered by other public health insurance plans.

CONCLUSIONS

In the largest observational study of patients with NVAF and multimorbidity, we show that among patients with NVAF and six or more comorbid conditions, NOACs were associated with varying risk of stroke/SE and MB compared to warfarin and to each other. Rather than a "one drug fits all" approach, our results may be useful for selecting appropriate OAC treatment for multimorbid patients.

ACKNOWLEDGEMENTS

Funding. Sponsorship for this study and the journal's rapid service fee was provided by Bristol-Myers Squibb Company and Pfizer Inc.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Medical Writing, Editorial, and Other Assistance. Editorial assistance in the preparation of this article was provided by Michael Moriarty of STATinMED Research. Support for this assistance was funded by Bristol-Myers Squibb Company and Pfizer Inc.

Disclosures. Steven Deitelzweig is a consultant for BMS/Pfizer, Daiichi-Sankyo, Portola, and Boehringer Ingelheim, and has been on the speakers' bureau for Janssen, Bristol Myers Squibb Company/Pfizer Inc., and Boehringer Ingelheim. Gregory Y.H. Lip is a consultant for Bayer/Janssen, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Verseon and Daiichi-Sankyo. Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo. No fees are directly received personally. Huseyin Yuce has nothing to disclose. Allison Keshishian is a paid employee of STATinMED Research which is a paid consultant to Bristol-Myers Squibb Company and Pfizer Inc. Amiee Kang, Amol Dhamane, Christian Klem, Lisa Rosenblatt and Jenny Jiang are paid employees of Bristol-Myers Squibb Company. Xuemei Luo and Jack Mardekian are paid employees of Pfizer Inc.

Compliance with Ethics Guidelines. Since the core study described herein did not involve the collection, use, or transmittal of individual identifiable data, institutional review board (IRB) approval to conduct this study was not required. The security of the data meets the requirements of the Health Insurance Portability and Accountability Act (HIPAA) of 1996. The study protocol was reviewed and determined to be exempt from the Office for Human Research Protections (OHRP's) Regulations for the Protection of Human Subjects (45 CFR 46) under the following category: Exemption 4: Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects. This study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments.

Data Availability. The raw data on which these analyses were based were obtained from the Centers for Medicare & Medicaid Services (CMS) and four US commercial claims databases: the IBM MarketScan® Commercial Claims and Encounter Database, the IQVIA PharMetrics Plus™ Database, the Optum Clinformatics™ Data Mart, and the Humana Research Database. These data are available from the respective organizations upon request.

REFERENCES

1. Zoni-Berisso M, Lercari F, Carazza T, Domenicucci S. Epidemiology of atrial fibrillation: European perspective. Clin Epidemiol. 2014;6:213.

2. De Caterina R, Husted S, Wallentin L, et al. Vitamin K antagonists in heart disease: current status and perspectives (Section III). Position paper of the ESC Working Group on Thrombosis—Task Force on Anticoagulants in Heart Disease. Thromb Haemost. 2013;110:1087–107.

3. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet. 2014;383:955–62.

4. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2019;74(1):104–32.

5. Salive ME. Multimorbidity in older adults. Epidemiol Rev. 2016;35:75–83.

6. Parks AL, Fang MC. Anticoagulation in older adults with multimorbidity. Clin Geriatr Med. 2016;32:331–46.

7. Vanbeselaere V, Truyers C, Elli S, et al. Association between atrial fibrillation, anticoagulation, risk of cerebrovascular events and multimorbidity in general practice: a registry-based study. BMC Cardiovasc Dis. 2016;16(1):61.

8. Jani BD, Nicholl BI, McQueenie R, et al. Multimorbidity and co-morbidity in atrial fibrillation and effects on survival: findings from UK Biobank cohort. EP Europace. 2017;20(FI_3):f329–36.

9. Alexander KP, Brouwer MA, Mulder H, et al. Outcomes of apixaban versus warfarin in patients with atrial fibrillation and multi-morbidity: insights from the ARISTOTLE trial. Am Heart J. 2019;208:123–31.

10. Li X, Deitelzweig S, Keshishian A, et al. Effectiveness and safety of apixaban versus warfarin in non-valvular atrial fibrillation patients in "real-world" clinical practice. A propensity-matched analysis of 76,940 patients. Thromb Haemost. 2017;117(6):1072–82.

11. Lip GYH, Keshishian A, Li X, et al. Effectiveness and safety of oral anticoagulants among non-valvular atrial fibrillation patients: the ARISTOPHANES study. Stroke. 2018;49(12):2933–44.

12. Thigpen JL, Dillon C, Forster KB, 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.

13. Cunningham A, Stein CM, Chung CP, Daugherty JR, Smalley WE, Ray W. An automated database case definition for serious bleeding related to oral anticoagulant use. Pharmacoepidemiol Drug Saf. 2011;20(6):560–6.

14. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373–83.

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

16. Austin PC. The use of propensity score methods with survival or time-to-event outcomes: reporting measures of effect similar to those used in randomized experiments. Stat Med. 2014;33(7):1242–58.

17. Proietti M, Marzona I, Vannini T, et al. Long-term relationship between atrial fibrillation, multimorbidity and oral anticoagulant drug use. Mayo Clin Proc. 2019;94(12):2427–36.

18. Mentias A, Shantha G, Chaudhury P, Sarrazin MSV. Assessment of outcomes of treatment with oral anticoagulants in patients with atrial fibrillation and multiple chronic conditions: a comparative

effectiveness analysis. JAMA Netw Open. 2018;1(5):e182870–e182870.

19. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. New Engl J Med. 2009;361(12):1139–51.

20. Jarosek S. Death Information in the Research Identifiable Medicare Data. ResDAC. https://www.resdac.org/articles/death-information-research-identifiable-medicare-data. Accessed 1 Mar 2021

21. Virani SS, Alonso A, Aparicio HJ, et al. Heart disease and stroke statistics-2021 update: a report from the American Heart Association. Circulation. 2021;143(8):e254–743. https://doi.org/10.1161/CIR.0000000000000950.

22. Broder MS, Neary MP, Chang E, Cherepanov D, Katznelson L. Treatments, complications, and healthcare utilization associated with acromegaly: a study in two large United States databases. Pituitary. 2014;17(4):333–41.