Dawwas Ghadeer K. (Orcid ID: 0000-0002-7982-7419)
Connors Jean M (Orcid ID: 0000-0001-6445-582X)

CORRESPONDENCE

Apixaban has Superior Effectiveness and Safety Compared to Rivaroxaban in Patients with Commercial Healthcare Coverage: A Population-Based Analysis in Response to CVS 2022 Formulary Changes

Ghadeer K. Dawwas, MSc, MBA, PhD[1,2,3], Adam Cuker, MD, MS[4,5] Jean Marie Connors, MD[6],

Geoffrey D. Barnes, MD, MSc[7]

1. Center for Pharmacoepidemiology Research and Training, Center for Clinical Epidemiology and Biostatistics, Perelman School of Medicine, University of Pennsylvania (Philadelphia, Pennsylvania)
2. Department of Biostatistics, Epidemiology and Informatics, Perelman School of Medicine, University of Pennsylvania (Philadelphia, Pennsylvania)
3. Leonard Davis Institute of Health Economics, University of Pennsylvania (Philadelphia, Pennsylvania)
4. Department of Medicine, Perelman School of Medicine, University of Pennsylvania (Philadelphia, Pennsylvania)
5. Department of Pathology and Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania (Philadelphia, Pennsylvania)
6. Division of Hematology, Brigham and Women's Hospital, Harvard Medical School (Boston, Massachusetts)
7. Department of Internal Medicine, Frankel Cardiovascular Center, University of Michigan (Ann Arbor, Michigan)

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Correspondence

Ghadeer K. Dawwas, Department of Biostatistics, Epidemiology, and Informatics, Perelman School of Medicine, University of Pennsylvania, 423 Guardian Drive, Philadelphia, Pennsylvania 19104-4865, USA; Email: gkdawwas@pennmedicine.upenn.edu

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To the Editor:

CVS Caremark, part of CVS Health, announced the exclusion of apixaban (Eliquis®) from the CVS 2022 Caremark Preferred Drug List contracted with some insurers. Warfarin and rivaroxaban are listed as preferred alternatives. Apixaban is a direct oral anticoagulant (DOAC) indicated for the prevention and treatment of venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE). One factor that may have influenced the exclusion of apixaban from CVS formulary coverage was the limited evidence comparing apixaban to other DOACs specifically in younger patients with commercial healthcare coverage. Recently, researchers showed a lower rate of thromboembolic and bleeding events with apixaban compared to rivaroxaban.[1,2] However, these studies focused on Medicare beneficiaries 65 years or older,[2] or included commercially insured adults with dual enrollment in Medicare.[1] To address this policy-relevant gap in evidence, we examined the effectiveness and safety of apixaban compared to rivaroxaban in a new-user cohort of VTE patients with commercial healthcare coverage, excluding patients with dual Medicare enrollment, overall, and stratified by age group.

We used commercial data from Optum's de-identified Clinformatics® Data Mart Database, which captures the healthcare experience of a privately insured population in the United States. The administrative database includes de-identified individual-level data on enrollment, patient demographics, outpatient claims, inpatient claims, prescription drug claims, and laboratory data for a subset of beneficiaries. Studies using the Optum Clinformatics Data Mart Database are categorized as exempt from Institutional Review Board approval at the University of Pennsylvania.

We conducted a new-user active comparator cohort study. The study design, methods, and outcomes definitions are described in our recent study.[1] We included patients ≥18 years, who had ≥1 prescription of apixaban or rivaroxaban dispensed within 30 days of VTE diagnosis, and 12 months of continuous enrollment in medical and pharmacy benefits prior to treatment initiation (i.e., lookback period). To create a cohort of commercially insured patients, we excluded patients with dual enrollment (i.e., use of both commercial and Medicare insurance). We excluded patients with a prescription for any anticoagulant (i.e., dabigatran, edoxaban, and warfarin) during the lookback period and those who had diagnosis of PE or DVT prior to their

index VTE. The primary effectiveness outcome was recurrent VTE, a composite of DVT and PE. The primary safety outcome was a composite of gastrointestinal (GI) and intracranial bleeding. Follow-up began on treatment initiation and ended at the earliest occurrence of an outcome of interest, treatment discontinuation, initiation of the comparator, disenrollment from the health plan, or end of the study period. We used propensity score matching to adjust for potential differences in baseline demographics and disease risk factors between new-users of apixaban and rivaroxaban. After propensity score 1:1 matching, we estimated marginal hazard ratios (HRs) and corresponding 95% CI via Cox proportional-hazards regression using a robust variance estimator while adjusting for calendar year. We assessed the potential for effect modification by age group (<65 years and ≥ 65 years). We performed matching again within each of the selected subgroups. We conducted all analyses using SAS v9.4 (SAS Institute Inc.: Cary, NC).

The analysis included 42,143 patients with VTE with commercial healthcare coverage who were new-users of apixaban or rivaroxaban **(Appendix Table 1**). In the matched cohort (n=15,453 for apixaban and n=15,453 for rivaroxaban), the mean age was 67 years. Approximately 39% of patients were younger than 65 years (n=6,049 for apixaban and n= 5,952 for rivaroxaban). Covariates were well-balanced after matching including male sex (48% vs. 48%), anemia (13% vs. 13%), chronic lung disease (31% vs. 31%), diabetes (28% vs. 28%), and peripheral vascular disease (20% vs. 20%). In the propensity score-matched cohort of VTE patients, the incidence rate of VTE per 100 person-years of follow-up was 8.9 among apixaban users and 11.2 among rivaroxaban users. After propensity-score matching, use of apixaban (vs. rivaroxaban) was associated with a lower rate of recurrent VTE (adjusted HR, 0.78 [95% CI, 0.69 to 0.90]) **(Table 1)**. The results for the individual effectiveness outcome were similar for DVT (HR, 0.84 [95% CI, 0.73 to 0.97]) and PE (HR, 0.56 [95% CI, 0.31 to 1.01]). The incidence rate of GI and intracranial bleeding per 100 person-years of follow-up was 7.6 among apixaban users and 10.7 among rivaroxaban users. After propensity-score matching, use of apixaban (vs. rivaroxaban) was associated with a lower rate of GI and intracranial bleeding (HR, 0.70 [95% CI, 0.61 to 0.80]) **(Table 1)**. The results were similar for GI bleeding (HR, 0.66 [95% CI, 0.57 to 0.76]) and intracranial bleeding (HR, 0.79 [95% CI, 0.24 to 2.57]). We did not find evidence of effect modification by age among users of apixaban (vs. rivaroxaban) for recurrent VTE (P-value for interaction=0.64) or bleeding (P-value for interaction=0.20) **(Table 1)**.

In this large, propensity score-matched cohort of commercially-insured patients with VTE, we found that apixaban use was associated with a lower rate of recurrent VTE, intracranial bleeding, and GI bleeding compared with rivaroxaban; results did not vary with age. Our results confirm and extend recent findings from observational studies.[1,2] Specifically, our findings suggest that benefits associated with apixaban use to treat VTE are a) realized by patients with commercial insurance coverage and are not limited to those with Medicare coverage; and b) extend across age groups including those younger than 65 years.

Use of DOACs is guideline-recommended over warfarin therapy given their improved safety-efficacy profile and ease of use.[3,4] There are clinical situations in which rivaroxaban may be the most appropriate DOAC (e.g., patients who cannot reliably take twice-daily medications). However, based on the results of our analysis, there is compelling evidence favoring apixaban as compared to rivaroxaban in commercially insured patients with VTE. It is critical that insurance formulary coverage decisions follow the best available evidence and prioritize easy access to treatments with the highest degree of efficacy and safety. Formulary coverage decisions that are not evidence-based may have unintended consequences including inferior outcomes and increased overall healthcare costs.

REFERENCES

(1) Dawwas GK, Leonard CE, Lewis JD, Cuker A. Risk for Recurrent Venous Thromboembolism and Bleeding With Apixaban Compared With Rivaroxaban: An Analysis of Real-World Data. Annals of internal medicine 2021 Dec 7,.

(2) Ray WA, Chung CP, Stein CM, Smalley W, Zimmerman E, Dupont WD, et al. Association of Rivaroxaban vs Apixaban With Major Ischemic or Hemorrhagic Events in Patients With Atrial Fibrillation. JAMA 2021 December 21;326(23):2395-2404.

(3) Ortel TL, Neumann I, Ageno W, Beyth R, Clark NP, Cuker A, et al. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. Blood Adv 2020 /10/13;4(19):4693-4738.

(4) Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. Chest 2016 February 01;149(2):315-352.

Table 1. Risk of recurrent VTE and bleeding comparing apixaban and rivaroxaban among VTE patients with commercial healthcare coverage, excluding patients with dual Medicare enrollment, overall, and by age group

Primary analysis		**Apixaban**				**Rivaroxaban**			
Outcome	**N**	**Events, n**	**PYs follow-up, n**	**Incidence rate per 100 PYs**	**N**	**Events, n**	**PYs of follow-up, n**	**Incidence rate per 100 PYs**	**Adjusted marginal HR (95% CI)**
			Apixaban				Rivaroxaban		
Recurrent VTE	15,453	387	4,365	8.9	15,453	478	4,251	11.2	0.78 (0.69, 0.90)
DVT		369	4368	8.4		445	4,257	10.5	0.84 (0.73, 0.97)
PE		18	4,322	0.4		33	4,426	0.7	0.56 (0.31, 1.01)
Bleeding	15,453	333	4,390	7.6	15,453	459	4,278	10.7	0.70 (0.61, 0.80)
Intracranial		6	4,323	0.1		6	4,426	0.1	0.79 (0.24, 2.57)
GI		327	4,323	7.0		423	4,426	9.6	0.66 (0.57, 0.76)

Subgroup analysis

Examination of effect modification by age	N apixaban	N rivaroxaban	Recurrent VTE aHR for apixaban compared to rivaroxaban (95% CI)	P-value for interaction	Bleeding events aHR for apixaban compared to rivaroxaban (95% CI)	P-value for interaction
<65 years	5,867	5,867	0.78 (0.62, 0.98)	0.64	0.77 (0.56, 1.06)	0.20
≥ 65 years	9,351	9,351	0.76 (0.64, 0.90)		0.59 (0.50, 0.70)	

CI= confidence interval; DVT= deep vein thrombosis; GI= gastrointestinal; HR= hazard ratio; PE= pulmonary embolism; PYs= person-years, VTE= venous thromboembolism

Results from Cox proportional hazard models after PS 1:1 matching without replacement using a caliper of 0.1 of the standard deviation of the logit of PS

Appendix Table 1. Demographic and clinical characteristics of new users of apixaban and rivaroxaban among VTE patients with commercial healthcare coverage, excluding patients with dual Medicare enrollment

Characteristic	Prematching cohort					Postmatching cohort				
	Apixaban (n= 25,116)		Rivaroxaban (n= 17,027)		Standardized Difference	Apixaban (n= 15,453)		Rivaroxaban (n= 15,453)		Standardized Difference
Demographic characteristics										
Mean age (SD), *y*	70.1	(14.4)	65.4	(15.6)	0.33	66.6	(15.4)	66.7	(15.0)	0.01
Male sex, *n (%)*	11502	(45.8)	8308	(48.8)	0.06	7431	(48.1)	7441	(48.2)	0.00
Division, *n (%)*										
East North Central	3528	(14.1)	2911	(17.1)		2518	(16.3)	2539	(16.4)	
East South Central	1339	(5.3)	655	(3.9)		622	(4.0)	634	(4.1)	
Middle Atlantic	1896	(7.6)	1407	(8.3)		1283	(8.3)	1246	(8.1)	
Mountain	2444	(9.7)	1987	(11.7)		1767	(11.4)	1732	(11.2)	
New England	782	(3.1)	550	(3.2)		517	(3.4)	500	(3.2)	
Pacific	7567	(30.1)	4332	(25.4)		4069	(26.3)	4102	(26.6)	
South Atlantic	1563	(6.2)	1532	(9.0)		1219	(7.9)	1235	(8.0)	
West North Central	3471	(13.8)	2019	(11.9)		1939	(12.6)	1928	(12.5)	
West South Central										
Unknown					0.03					0.00
Insurance type, *n (%)*	970	(3.9)	796	(4.7)		704	(4.6)	710	(4.6)	
Exclusive provider organization	7444	(29.6)	5018	(29.5)		4636	(30.0)	4620	(29.9)	
Health maintenance organization	189	(0.8)	107	(0.6)		107	(0.7)	102	(0.7)	
Indemnity	8637	(34.4)	4331	(25.4)		4139	(26.8)	4224	(27.3)	
Other	4591	(18.3)	4737	(27.8)		3952	(25.6)	3874	(25.1)	
Point of service	3285	(13.1)	2038	(12.0)		1915	(12.4)	1923	(12.4)	
Preferred provider organization										
Baseline comorbid conditions, *n (%)*										
Alcohol misuse disorder	1080	(4.3)	709	(4.2)	0.01	678	(4.4)	659	(4.3)	0.01
Anemia	4060	(16.2)	2151	(12.6)	0.10	2028	(13.1)	2036	(13.2)	0.00
Angina	650	(2.6)	325	(1.9)	0.04	314	(2.0)	318	(2.1)	0.00
Cancer	5699	(22.7)	3832	(22.5)	0.00	3399	(22.0)	3556	(23.0)	0.02
Chronic kidney disease	10107	(40.2)	4806	(28.2)	0.25	4630	(30.0)	4670	(30.2)	0.01
Chronic lung disease	8713	(34.7)	5063	(29.7)	0.10	4714	(30.5)	4724	(30.6)	0.00
Coronary artery disease	265	(1.1)	109	(0.6)	0.04	115	(0.7)	107	(0.7)	0.01
Diabetes	8557	(34.1)	4533	(26.6)	0.16	4314	(27.9)	4341	(28.1)	0.00
Drug misuse disorder	1220	(4.9)	749	(4.4)	0.02	701	(4.5)	690	(4.5)	0.00
End stage renal disease	511	(2.0)	61	(0.4)	0.12	200	(1.3)	60	(0.4)	0.08
Heart failure	6635	(26.4)	2878	(16.9)	0.22	2853	(18.5)	2831	(18.3)	0.00
Hemophilia	10	(0.1)	11	(0.1)	0.01	10	(0.1)	6	(0.1)	0.01
Human immunodeficiency virus	104	(0.4)	63	(0.4)	0.01	60	(0.4)	57	(0.4)	0.00
Hyperlipidemia	12935	(51.5)	7439	(43.7)	0.16	7041	(45.6)	7024	(45.5)	0.00
Hypertension	18919	(75.3)	11024	(64.7)	0.25	10365	(67.1)	10410	(67.4)	0.01
Liver Disease	3163	(12.6)	2061	(12.1)	0.01	1879	(12.2)	1903	(12.3)	0.00
Peripheral vascular disease	6713	(26.7)	3261	(19.2)	0.17	3158	(20.4)	3150	(20.4)	0.00
Stroke	46	(0.2)	11	(0.1)	0.03	9	(0.1)	11	(0.1)	0.01
Tobacco use	3354	(13.4)	2411	(14.2)	0.02	2184	(14.1)	2148	(13.9)	0.01

Transient ischemic attack	2288	(9.1)	1026	(6.0)	0.11	973	(6.3)	987	(6.4)	0.00
Ulcer	806	(3.2)	398	(2.3)	0.05	390	(2.5)	383	(2.5)	0.00
Baseline medications, *n (%)*										
ACE inhibitors	7148	(28.5)	4094	(24.0)	0.10	3880	(25.1)	3856	(25.0)	0.00
Aldosterone antagonists	1215	(4.8)	570	(3.4)	0.07	528	(3.4)	541	(3.5)	0.00
a-Adrenergic blockers	3067	(12.2)	1641	(9.6)	0.08	1552	(10.0)	1574	(10.2)	0.00
Antiplatelet	4252	(8.5)	1844	(5.4)	0.11	1782	(5.8)	1806	(5.8)	0.00
ARBs	5424	(21.6)	2956	(17.4)	0.10	2827	(18.3)	2822	(18.3)	0.00
b-Blockers	8392	(33.4)	4206	(24.7)	0.18	4033	(26.1)	4059	(26.3)	0.00
CCBs	7304	(29.1)	3593	(21.1)	0.18	3442	(22.3)	3491	(22.6)	0.01
Direct vasodilators	951	(3.8)	281	(1.7)	0.11	280	(1.8)	280	(1.8)	0.00
Loop diuretics	5575	(22.2)	2582	(15.2)	0.17	2538	(16.4)	2514	(16.3)	0.00
NSAIDs	4929	(19.6)	3631	(21.3)	0.04	3247	(21.0)	3231	(20.9)	0.00
Potassium diuretics	1275	(5.1)	595	(3.5)	0.07	552	(3.6)	565	(3.7)	0.00
PPIs	7992	(31.8)	4594	(27.0)	0.10	4310	(27.9)	4306	(27.9)	0.00
SSRIs	4597	(18.3)	2814	(16.5)	0.05	2602	(16.8)	2615	(16.9)	0.00
Statins	11908	(47.4)	6519	(38.3)	0.18	6227	(40.3)	6225	(40.3)	0.00
Thiazide diuretics	6011	(23.9)	3582	(21.0)	0.07	3364	(21.8)	3374	(21.8)	0.00
Measures of health care use										
Mean inpatient visits (SD), *n*	1.6	(1.5)	1.3	(1.3)	0.24	1.3	(1.2)	1.3	(1.4)	0.01
Mean prescriptions (SD), *n*	36.7	(43.3)	32.2	(32.2)	0.16	32.3	(32.7)	32.2	(32.5)	0.03
Mean procedures (SD), *n*	1.9	(2.8)	1.8	(2.5)	0.05	1.8	(2.7)	1.8	(2.5)	0.00

ACE= angiotensin converting enzymes; ARBs= angiotensin-receptor blocker; CCB = calcium-channel blocker; NSAID = nonsteroidal anti-inflammatory drug; PPI = proton-pump inhibitor; SSRI = selective serotonin reuptake inhibitor; SD= standard deviation