



Aalborg Universitet

AALBORG UNIVERSITY
DENMARK

Effectiveness and Safety of Oral Anticoagulants Among Nonvalvular Atrial Fibrillation Patients With Active Cancer

Deitelzweig, Steven; Keshishian, Allison V; Zhang, Yan; Kang, Amiee; Dhamane, Amol D; Luo, Xuemei; Klem, Christian; Ferri, Mauricio; Jiang, Jenny; Yuce, Huseyin; Lip, Gregory Y H

Published in:
JACC: CardioOncology

DOI (link to publication from Publisher):
[10.1016/j.jacc.2021.06.004](https://doi.org/10.1016/j.jacc.2021.06.004)

Creative Commons License
CC BY-NC-ND 4.0

Publication date:
2021

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

[Link to publication from Aalborg University](#)

Citation for published version (APA):
Deitelzweig, S., Keshishian, A. V., Zhang, Y., Kang, A., Dhamane, A. D., Luo, X., Klem, C., Ferri, M., Jiang, J., Yuce, H., & Lip, G. Y. H. (2021). Effectiveness and Safety of Oral Anticoagulants Among Nonvalvular Atrial Fibrillation Patients With Active Cancer. *JACC: CardioOncology*, 3(3), 411-424.
<https://doi.org/10.1016/j.jacc.2021.06.004>

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal -

Take down policy

If you believe that this document breaches copyright please contact us at vbn@aub.aau.dk providing details, and we will remove access to the work immediately and investigate your claim.

ORIGINAL RESEARCH

Effectiveness and Safety of Oral Anticoagulants Among Nonvalvular Atrial Fibrillation Patients With Active Cancer



Steven Deitelzweig, MD,^{a,b} Allison V. Keshishian, MPH,^{c,d} Yan Zhang, PhD,^e Amiee Kang, MPH,^e Amol D. Dhamane, MS,^e Xuemei Luo, PhD,^f Christian Klem, PHARM D,^e Mauricio Ferri, MD,^e Jenny Jiang, MS,^e Huseyin Yuce, PhD,^d Gregory Y.H. Lip, MD^{g,h}

ABSTRACT

BACKGROUND Patients with cancer are more likely to develop nonvalvular atrial fibrillation (NVAf). Currently there are no definitive clinical trials or treatment guidelines for NVAf patients with concurrent cancer.

OBJECTIVES This subgroup analysis of the ARISTOPHANES study compared the risk of stroke/systemic embolism (stroke/SE) and major bleeding (MB) among NVAf patients with active cancer who were prescribed non-vitamin K antagonist oral anticoagulants (NOACs) or warfarin.

METHODS A retrospective observational study was conducted in NVAf patients with active cancer who newly initiated apixaban, dabigatran, rivaroxaban, or warfarin from January 1, 2013, through September 30, 2015, with the use of Medicare and 4 U.S. commercial claims databases. Cox models were used to estimate the risk of stroke/SE and MB in the pooled propensity score-matched cohorts.

RESULTS A total of 40,271 patients were included, with main cancer types of prostate (29%), female breast (17%), genitourinary (14%), and lung (13%). Compared with warfarin, apixaban was associated with a lower risk of stroke/SE (hazard ratio [HR]: 0.59; 95% confidence interval [CI]: 0.45-0.78) and MB (HR: 0.58; 95% CI: 0.50-0.68); dabigatran and rivaroxaban had similar risks of stroke/SE (dabigatran: HR: 0.88 [95% CI: 0.54-1.41]; rivaroxaban: HR: 0.82 [95% CI: 0.62-1.08]) and MB (dabigatran: HR: 0.76 [95% CI: 0.57-1.01]; rivaroxaban: HR: 0.95 [95% CI: 0.85-1.06]). Risks of stroke/SE and MB varied among NOAC-NOAC comparisons, while consistent treatment effects were seen for all treatment comparisons across key cancer types.

CONCLUSIONS Among this cohort of NVAf patients with active cancer, the risk of stroke/SE and MB varied among oral anticoagulants and were consistent across cancer types. (J Am Coll Cardiol CardioOnc 2021;3:411-424) © 2021 Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

From the ^aOchsner Clinic Foundation, Department of Hospital Medicine, New Orleans, Louisiana, USA; ^bUniversity of Queensland School of Medicine—Ochsner Clinical School, New Orleans, Louisiana, USA; ^cSTATinMED Research, Ann Arbor, Michigan, USA; ^dNew York City College of Technology, City University of New York, New York, New York, USA; ^eBristol Myers Squibb Company, Lawrenceville, New Jersey, USA; ^fPfizer, Inc., Groton, Connecticut, USA; ^gLiverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart and Chest Hospital, Liverpool, United Kingdom; and the ^hAalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

Manuscript received December 16, 2020; accepted June 13, 2021.

ISSN 2666-0873

<https://doi.org/10.1016/j.jacc.2021.06.004>

Downloaded for Anonymous User (n/a) at Aalborg University Hospital from ClinicalKey.com by Elsevier on October 28, 2021. For personal use only. No other uses without permission. Copyright ©2021. Elsevier Inc. All rights reserved.

ABBREVIATIONS AND ACRONYMS

AF	= atrial fibrillation
GI	= gastrointestinal
GU	= genitourinary
ICH	= intracranial hemorrhage
MB	= major bleeding
NOAC	= non-vitamin K antagonist oral anticoagulant
NVAF	= nonvalvular atrial fibrillation
PSM	= propensity score matching
SE	= systemic embolism
VTE	= venous thromboembolism

Atrial fibrillation (AF) is a heart rhythm condition that may lead to substantial morbidity and mortality, specifically in aging populations (1). In the U.S., 2.3 million individuals are considered to have AF, with an expected increase to 5.6 million by 2050 (1,2). AF occurs with many coexisting health conditions, including hypertension, coronary heart disease, chronic kidney disease, and diabetes mellitus (3). In addition, there is accumulated evidence suggesting an association between the incidence of AF and cancer (4,5).

A recent systematic review and meta-analysis of the association between cancer and AF revealed that patients with solid cancer were at a higher risk of developing AF compared with noncancer patients (4). Similarly, in the REGARDS (Reasons for Geographic and Racial Differences in Stroke Study), cancer patients were more likely to have prevalent AF than those without cancer (5). In addition, gastric, ovarian and cervical cancer patients have been associated with a higher risk of ischemic stroke compared to non-cancer patients (6-8), and it has been reported that major bleeding (MB) occurs in ~10% of all cancer patients (9).

Traditionally AF has been managed with the use of oral anticoagulants (OACs), such as vitamin K antagonists, but non-vitamin K antagonist oral anticoagulants (NOACs) are increasingly being used. However, there are no specific clinical trials or guidelines for AF treatment in cancer patients (10). Post hoc analyses of clinical trials such as the ROCKET AF (An Efficacy and Safety Study of Rivaroxaban With Warfarin for the Prevention of Stroke and Non-Central Nervous System Systemic Embolism in Patients With Nonvalvular Atrial Fibrillation; NCT00403767) and ARISTOTLE (Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation; NCT00412984) trials have shown that the relative efficacy and safety of NOACs do not statistically differ from warfarin in patients with and without a history of cancer for the prevention of stroke/systemic embolism (SE) and the occurrence of MB (11,12). There was, however, a greater benefit seen in the composite of thrombotic events (stroke/SE, myocardial infarction, and death) among apixaban users with active cancer versus no cancer when compared to warfarin users in the ARISTOTLE trial (12).

Real-world studies, though limited, have also shown largely consistent results with the clinical trials regarding the generally uniform benefits seen among NOAC users regardless of cancer status (13-16). Increased risk of cardiac complications, such as stroke and MB, among AF patients with cancer (4-9)

necessitates a comprehensive evaluation of available treatment strategies for this population. This subgroup analysis of ARISTOPHANES (Anticoagulants for Reduction In Stroke: Observational Pooled Analysis on Health Outcomes and Experience of Patients; NCT03087487), through the use of several data sources, aimed to respectively compare the risk of stroke/SE and MB among the nonvalvular AF (NVAF) population with active cancer newly prescribed to apixaban, dabigatran, rivaroxaban, or warfarin.

METHODS

DATA SOURCES AND PATIENT SELECTION. NVAF patients with active cancer who were newly treated with apixaban, dabigatran, rivaroxaban, edoxaban, or warfarin were selected (17). Data were pooled from the U.S. Centers for Medicare and Medicaid Services (CMS) database and 4 U.S. 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. Patients prescribed edoxaban were not included in this study given an insufficient sample size. Detailed data description and pooling processes can be found in previously published ARISTOPHANES reports (17,18).

From the ARISTOPHANES study population, NVAF patients with active cancer were selected if they had at least 1 OAC pharmacy claim from January 1, 2013, to September 30, 2015 (identification period). Active cancer was identified in patients who had at least 2 claims for cancer diagnosis or 1 claim for cancer diagnosis plus at least 1 claim for cancer treatment (eg, chemotherapy, radiation, cancer-related surgery) within 6 months before OAC treatment initiation (Supplemental Table 1). The first NOAC pharmacy claim during the identification period was designated as the index date for patients with any NOAC claim; the first warfarin prescription date was designated as the index date for those without a NOAC claim (19). Patients were required to have an AF diagnosis before or on the index date and needed continuous medical and pharmacy health plan enrollment for ≥12 months before the index date (baseline period). Patients were not required to be newly diagnosed with AF or cancer, but patients with OAC use during the baseline period were excluded. Detailed exclusion criteria are listed in Figure 1.

OUTCOME MEASURES. The primary outcomes were time to first stroke/SE and time to first MB. Hospitalizations with stroke/SE or MB as the principal or first-listed diagnosis were used as the primary outcome measures. The primary effectiveness

outcome of stroke/SE was further stratified by ischemic stroke, hemorrhagic stroke, and SE. The primary safety outcome of MB was further stratified by gastrointestinal (GI) bleeding, intracranial hemorrhage (ICH), and MB in other key sites (17,20,21). Patients were followed from the day after the index date to the earliest of 30 days after the date of discontinuation, switch, end of continuous medical and pharmacy enrollment, death (all-cause deaths from Medicare and hospitalization deaths from commercial datasets), or end of study period (September 30, 2015). Discontinuation was defined as no evidence of index OAC prescription for 30 days from the last day of the last filled prescription days' supply.

STATISTICAL ANALYSIS. All variables were stratified by cohort and analyzed descriptively. Mean \pm SD were provided for continuous variables. Frequencies and percentages were provided for categorical variables. One-to-one propensity score matching (PSM) was conducted in each database for all comparisons before the datasets were pooled: NOAC versus warfarin (apixaban vs warfarin, dabigatran vs warfarin, and rivaroxaban vs warfarin) and NOAC versus NOAC (apixaban vs dabigatran, apixaban vs rivaroxaban, and dabigatran vs rivaroxaban) (17,18). Propensity scores were generated by logistic regression with the use of the following variables: demographics, Deyo-Charlson comorbidity index (CCI), comorbidities, baseline medications, cancer metastasis, and cancer-related treatment (variables are listed in Tables 1, 2, 3, and 4). Patients were matched by nearest neighbor matching without replacement (with a caliper of 0.01). The PSM-adjusted baseline variables were compared based on standardized differences, with a threshold of 10% for balance (22).

Kaplan-Meier curves were used to illustrate cumulative incidence rates, and log-rank tests were used to compare the curves across cohorts. Cox proportional hazard models were used to evaluate the risk of stroke/SE and MB with robust sandwich estimates to account for correlation within the matched populations (23). All matched confounders were balanced after PSM; therefore, only OAC treatment was included as an independent variable in the Cox models. Hazard ratios (HRs) are expressed with 95% confidence intervals (CIs). P values of <0.05 were considered as statistically significant. Data analysis was performed with the use of SAS statistical software version 9.4 (SAS Institute).

SUBGROUP ANALYSIS. Subgroup analysis was conducted for the following key cancer types across the OAC cohorts: breast cancer, lung cancer, hematologic cancer, genitourinary (GU) cancer, and upper/lower

GI cancer. Patients in the dabigatran cohort and those with other cancer types were not included for the subgroup analysis owing to limited sample size. The PSM cohorts were stratified by the included cancer type, and interactions between treatment comparisons and cancer types on stroke/SE and MB were evaluated. P values of <0.10 were considered as statistically significant for the interaction analysis.

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

RESULTS

After applying the selection criteria, a total of 40,271 NVAF patients in the pooled datasets were identified as also having active cancer, accounting for 9% of the total ARISTOPHANES NVAF patient population ($N = 466,991$) (Figure 1). Among the NVAF patients with active cancer, the index users of warfarin, apixaban, dabigatran, and rivaroxaban numbered 15,371 (38%), 9,517 (24%), 2,742 (7%), and 12,641 (31%), respectively.

Before PSM, the majority of patients included in the analysis had solid nonhematologic tumors (92%), with prostate cancer being the most common cancer site (29%), followed by female breast cancer (17%), GU cancer (14%), lung cancer (13%), and GI cancer (13%). More than one-half of the patients in each cohort reported receiving a cancer-related treatment 6 months before or on the index date (Supplemental Table 2). Furthermore, the majority of apixaban, dabigatran, and rivaroxaban users (73%, 81%, and 69%, respectively) were on standard doses of each medication. Before PSM, the incidence rates (per 100 person-years) for stroke/SE and MB, respectively, were as follows: warfarin: 2.64 and 10.56; apixaban: 1.45 and 6.01; dabigatran: 1.92 and 5.38; and rivaroxaban: 1.72 and 8.01.

After 1:1 PSM, the following NOAC-warfarin comparison cohorts were formed: apixaban-warfarin with 8,236 pairs, dabigatran-warfarin with 2,470 pairs, and rivaroxaban-warfarin with 9,988 pairs (Table 1 and 2). The NOAC-NOAC comparison cohorts were formed as apixaban-dabigatran with 2,413 pairs, apixaban-rivaroxaban with 8,608 pairs, and dabigatran-rivaroxaban with 2,553 pairs (Table 3 and 4). The mean follow-up time for the 6 matched cohorts ranged

TABLE 1 Post-PSM Baseline Characteristics of NOAC-Warfarin Cohorts

	Apixaban vs Warfarin				Dabigatran vs Warfarin				Rivaroxaban vs Warfarin			
	Apixaban		Warfarin		Dabigatran		Warfarin		Rivaroxaban		Warfarin	
	n	or Mean % or SD	n	or Mean % or SD	n	or Mean % or SD	n	or Mean % or SD	n	or Mean % or SD	n	or Mean % or SD
Sample size	8,236	100%	8,236	100%	2,470	100%	2,470	100%	9,988	100%	9,988	100%
Age, y ^a	78.00	7.60	77.90	7.51	76.67	7.41	76.78	7.61	77.41	7.45	77.40	7.55
18-54	24	0.29%	25	0.30%	12	0.49%	14	0.57%	24	0.24%	34	0.34%
55-64	174	2.11%	160	1.94%	67	2.71%	76	3.08%	258	2.58%	252	2.52%
65-74	2,617	31.78%	2,633	31.97%	905	36.64%	888	35.95%	3,358	33.62%	3,341	33.45%
≥75	5,421	65.82%	5,418	65.78%	1,486	60.16%	1,492	60.40%	6,348	63.56%	6,361	63.69%
Sex ^a												
Male	4,945	60.04%	4,961	60.24%	1,503	60.85%	1,523	61.66%	6,023	60.30%	6,016	60.23%
Female	3,291	39.96%	3,275	39.76%	967	39.15%	947	38.34%	3,965	39.70%	3,972	39.77%
U.S. geographic region ^a												
Northeast	1,636	19.86%	1,620	19.67%	541	21.90%	528	21.38%	2,093	20.96%	2,052	20.54%
Midwest	1,838	22.32%	1,865	22.64%	559	22.63%	593	24.01%	2,510	25.13%	2,536	25.39%
South	3,353	40.71%	3,331	40.44%	896	36.28%	872	35.30%	3,662	36.66%	3,684	36.88%
West	1,394	16.93%	1,406	17.07%	472	19.11%	476	19.27%	1,703	17.05%	1,697	16.99%
Other	15	0.18%	14	0.17%	NR	NR	NR	NR	20	0.20%	19	0.19%
Baseline comorbidity												
Deyo-Charlson comorbidity index ^a	4.64	3.56	4.62	3.55	4.12	3.42	4.08	3.35	4.61	3.55	4.62	3.58
CHA ₂ DS ₂ -VAsC score	4.12	1.48	4.13	1.46	3.92	1.50	3.92	1.45	4.06	1.48	4.07	1.46
0	25	0.30%	21	0.25%	19	0.77%	13	0.53%	37	0.37%	48	0.48%
1	133	1.61%	138	1.68%	61	2.47%	58	2.35%	212	2.12%	196	1.96%
2	833	10.11%	750	9.11%	305	12.35%	290	11.74%	1,040	10.41%	945	9.46%
3	1,981	24.05%	2,019	24.51%	645	26.11%	656	26.56%	2,491	24.94%	2,460	24.63%
≥4	5,264	63.91%	5,308	64.45%	1,440	58.30%	1,453	58.83%	6,208	62.15%	6,339	63.47%
HAS-BLED score	3.58	1.29	3.57	1.28	3.37	1.26	3.32	1.24	3.53	1.26	3.52	1.28
0	17.00	0.21%	15	0.18%	15	0.61%	10	0.40%	28	0.28%	31	0.31%
1	274	3.33%	281	3.41%	108	4.37%	114	4.62%	356	3.56%	361	3.61%
2	1,500	18.21%	1,507	18.30%	521	21.09%	547	22.15%	1,785	17.87%	1,883	18.85%
≥3	6,445	78.25%	6,433	78.11%	1,826	73.93%	1,799	72.83%	7,819	78.28%	7,713	77.22%
Bleeding history ^a	2,889	35.08%	2,904	35.26%	812	32.87%	782	31.66%	3,569	35.73%	3,564	35.68%
Heart failure ^a	2,666	32.37%	2,661	32.31%	716	28.99%	729	29.51%	3,114	31.18%	3,123	31.27%
Diabetes mellitus ^a	3,129	37.99%	3,085	37.46%	938	37.98%	938	37.98%	3,894	38.99%	3,863	38.68%
Hypertension ^a	7,514	91.23%	7,503	91.10%	2,197	88.95%	2,185	88.46%	9,068	90.79%	9,031	90.42%
Renal disease ^a	2,656	32.25%	2,614	31.74%	567	22.96%	559	22.63%	2,881	28.84%	2,889	28.92%
Liver disease ^a	799	9.70%	776	9.42%	207	8.38%	187	7.57%	1,062	10.63%	1,078	10.79%
Myocardial infarction ^a	861	10.45%	898	10.90%	204	8.26%	222	8.99%	1,019	10.20%	1,047	10.48%
Dyspepsia or stomach discomfort ^a	2,367	28.74%	2,340	28.41%	654	26.48%	637	25.79%	2,808	28.11%	2,807	28.10%
Non-stroke/SE peripheral vascular disease ^a	4,952	60.13%	4,956	60.17%	1,408	57.00%	1,402	56.76%	5,914	59.21%	5,906	59.13%
Stroke/SE ^a	1,121	13.61%	1,158	14.06%	283	11.46%	298	12.06%	1,243	12.44%	1,277	12.79%
Transient ischemic attack ^a	673	8.17%	712	8.64%	183	7.41%	168	6.80%	766	7.67%	777	7.78%
Anemia and coagulation defects ^a	3,680	44.68%	3,648	44.29%	997	40.36%	958	38.79%	4,358	43.63%	4,379	43.84%
Alcoholism ^a	179	2.17%	168	2.04%	60	2.43%	51	2.06%	229	2.29%	239	2.39%
Peripheral artery disease	2,121	25.75%	2,130	25.86%	597	24.17%	582	23.56%	2,505	25.08%	2,575	25.78%
Coronary artery disease	4,252	51.63%	4,295	52.15%	1,169	47.33%	1,205	48.79%	5,074	50.80%	5,046	50.52%
Dose of the index prescription												
Standard dose ^b	5,920	71.88%	NA	NA	1,973	79.88%	NA	NA	6,619	66.27%	NA	NA
Low dose ^c	2,316	28.12%	NA	NA	497	20.12%	NA	NA	3,369	33.73%	NA	NA

Continued on the next page

from 6 to 8 months. All baseline variables included in the PSM logistic model were balanced with a standardized difference of <10%, resulting in well balanced demographic and clinical characteristics between pairs. The Kaplan-Meier curves for cumulative

incidence rates of stroke/SE and MB in the matched populations can be seen in [Supplemental Figures 1 to 12](#).

NOAC-WARFARIN COMPARISONS. Among the NOAC cohorts, apixaban patients had a lower risk for stroke/

TABLE 1 Continued

	Apixaban vs Warfarin				Dabigatran vs Warfarin				Rivaroxaban vs Warfarin			
	Apixaban		Warfarin		Dabigatran		Warfarin		Rivaroxaban		Warfarin	
	n or Mean	% or SD	n or Mean	% or SD	n or Mean	% or SD	n or Mean	% or SD	n or Mean	% or SD	n or Mean	% or SD
Follow-up time, days	181.10	165.61	228.54	214.08	222.27	223.36	229.25	214.07	214.88	207.85	227.94	212.57
Median	120		145		121		147		129		145	
Reasons for censoring												
Discontinuation	3,183	38.65%	4,835	58.71%	1,442	58.38%	1,460	59.11%	5,206	52.12%	5,952	59.59%
Switch	320	3.89%	NA	NA	269	10.89%	NA	NA	677	6.78%	NA	NA
Death	461	5.60%	801	9.73%	160	6.48%	208	8.42%	711	7.12%	962	9.63%
End of continuous medical/pharmacy enrollment	98	1.19%	168	2.04%	40	1.62%	61	2.47%	230	2.30%	222	2.22%
End of study period	4,174	50.68%	2,432	29.53%	559	22.63%	741	30.00%	3,164	31.68%	2,852	28.55%

Cells with n < 11 are not reported (NR). ^aVariable used in propensity score matching. ^b5 mg apixaban, 150 mg dabigatran, 20 mg rivaroxaban. ^c2.5 mg apixaban, 75 mg dabigatran, 10 or 15 mg rivaroxaban; 560 and 2,809 patients received 10 mg and 15 mg rivaroxaban, respectively, in the rivaroxaban-warfarin matched cohort.

CHA₂DS₂-Vasc = congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischemic attack (TIA), vascular disease, age 65 to 74 years, sex category; HAS-BLED = Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly; NA = not applicable; NOAC = non-vitamin K antagonist oral anticoagulant; PSM = propensity score matching; SD = standard deviation; SE = systemic embolism.

SE compared with those prescribed warfarin (HR: 0.59; 95% CI: 0.45-0.78) (**Central Illustration**). Dabigatran and rivaroxaban patients had a similar risk for stroke/SE compared with warfarin patients (dabigatran: HR: 0.88 [95% CI: 0.54-1.41]; rivaroxaban: HR: 0.82 [95% CI: 0.62-1.08]). Ischemic stroke was the most common embolic event, with a lower risk in apixaban patients (HR: 0.72; 95% CI: 0.52-0.99) and similar risks in dabigatran (HR: 0.95; 95% CI: 0.54-1.66) and rivaroxaban (HR: 1.02; 95% CI: 0.76-1.37) patients compared with warfarin patients.

The apixaban cohort was the only cohort that had a significantly lower risk for MB compared with the warfarin cohort (HR: 0.58; 95% CI: 0.50-0.68). Dabigatran and rivaroxaban patients had a similar risk of MB compared with warfarin patients (dabigatran: HR: 0.76 [95% CI: 0.57-1.01]; rivaroxaban: HR: 0.95 [95% CI: 0.85-1.06]).

Apixaban patients experienced a lower risk for all 3 types of MB compared with warfarin patients. Dabigatran patients had a lower risk for other MB compared with warfarin patients (HR: 0.65; 95% CI: 0.44-0.95), and rivaroxaban patients had a reduced risk for ICH compared with warfarin patients (HR: 0.49; 95% CI: 0.35-0.69).

NOAC-NOAC COMPARISONS. Apixaban patients had a lower risk for stroke/SE compared with dabigatran patients (HR: 0.41; 95% CI: 0.22-0.77) (**Figure 2**). Similar risks for stroke/SE were seen in the apixaban-rivaroxaban comparison (HR: 0.81; 95% CI: 0.60-1.08) and the dabigatran-rivaroxaban comparison (HR: 0.90; 95% CI: 0.50-1.63).

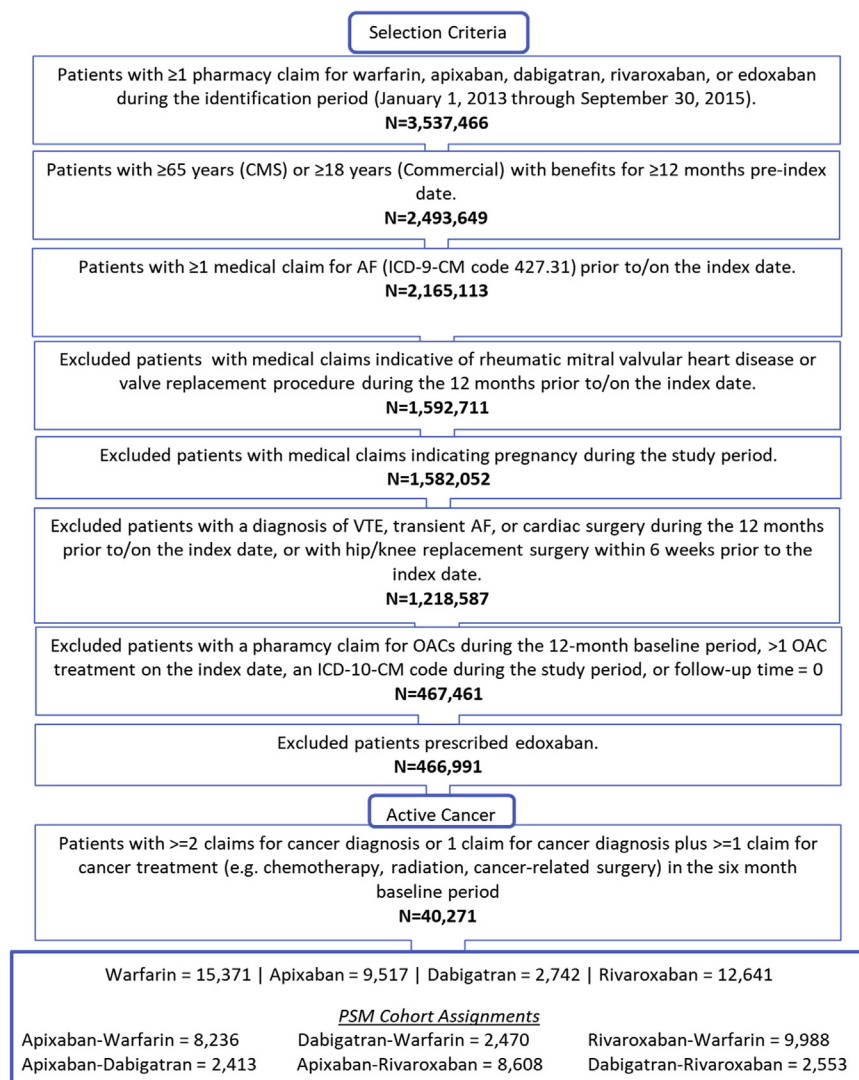
When evaluating MB, apixaban patients had a lower risk compared with rivaroxaban patients (HR: 0.66; 95% CI: 0.54-0.80) and a similar risk

compared with dabigatran patients (HR: 0.83; 95% CI: 0.58-1.19). Dabigatran patients also experienced a lower risk for MB compared with those prescribed rivaroxaban (HR: 0.71; 95% CI: 0.52-0.95). The apixaban cohort continued to show a lower risk for MB compared with the rivaroxaban cohort in terms of GI bleeding (HR: 0.56; 95% CI: 0.45-0.69) and bleeding in other major sites (HR: 0.70; 95% CI: 0.54-0.91). The other NOAC-NOAC comparisons for the MB components all yielded similar risks to one another.

SUBGROUP ANALYSIS. No significant interactions were seen between treatment comparisons and the included cancer types for stroke/SE and MB. Treatment effects were consistent across different cancer types (**Figures 3 and 4**). Owing to the small sample size of patients with the included cancer types, the subgroup analysis was not evaluated for the dabigatran cohorts.

DISCUSSION

As far as we are aware, this is the largest contemporary cohort of NVAF patients with active cancer treated with NOACs and warfarin. Our principal findings in this subgroup analysis of the ARISTOPHANES study of NVAF patients with active cancer are that compared with warfarin, apixaban was associated with a lower risk of stroke/SE and MB and dabigatran and rivaroxaban had similar risks of stroke/SE and MB. Second, risks of stroke/SE and MB varied among NOAC-NOAC comparisons: apixaban patients had a lower risk of stroke/SE compared with dabigatran users, and a lower risk of MB compared with rivaroxaban users; and dabigatran patients experienced a lower risk in MB compared with those prescribed rivaroxaban. Third, when evaluating

FIGURE 1 Selection Criteria

The inclusion and exclusion criteria of this study yielded over 466,000 patients with nonvalvular atrial fibrillation, of which 40,271 had active cancer. These patients were matched into NOAC-warfarin and NOAC-NOAC cohorts via propensity score matching. AF = atrial fibrillation; CMS = U.S. Centers for Medicare and Medicaid Services; ICD-9/10-CM = International Classification of Diseases-9th/-10th Revision, Clinical Modification; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulant; PSM = propensity score matching; VTE = venous thromboembolism.

patients according to major cancer types, consistent treatment effects on stroke/SE or MB were seen for the NOAC-warfarin and NOAC-NOAC comparisons across the different cancer types. As an ad hoc analysis of the ARISTOPHANES study focusing on patients with active cancer, the results of this analysis were generally consistent with the findings of the main ARISTOPHANES analysis on the whole patient population regardless of active cancer status (17). Both

analyses showed that NOACs were associated with better or similar safety and effectiveness compared with warfarin. In addition, the present analysis showed consistent treatment effects across key cancer types.

Active cancer patients are more susceptible to developing not only cardiac disturbances such as NVAf, but also other thromboembolic and bleeding complications, such as ischemic stroke and MB,

TABLE 2 Post-PSM Cancer-Related Baseline Characteristics of NOAC-Warfarin Cohorts

	Apixaban vs Warfarin				Dabigatran vs Warfarin				Rivaroxaban vs Warfarin			
	Apixaban		Warfarin		Dabigatran		Warfarin		Rivaroxaban		Warfarin	
	n	%	n	%	n	%	n	%	n	%	n	%
Sample size	8,236	100	8,236	100	2,470	100	2,470	100	9,988	100	9,988	100
Cancer site												
Prostate	2,483	30.15	2,343	28.45	745	30.16	740	29.96	2,938	29.42	2,780	27.83
Female breast	1,497	18.18	1,398	16.97	468	18.95	430	17.41	1,757	17.59	1,704	17.06
Gastrointestinal(GI) ^a	1,004	12.19	1,100	13.36	288	11.66	312	12.63	1,338	13.40	1,403	14.05
Lung	946	11.49	1,156	14.04	269	10.89	357	14.45	1,228	12.29	1,448	14.50
Lymphoma	935	11.35	895	10.87	285	11.54	266	10.77	1,160	11.61	1,094	10.95
Lower GI ^b	751	9.12	792	9.62	200	8.10	219	8.87	972	9.73	1,000	10.01
Bladder	669	8.12	703	8.54	204	8.26	171	6.92	789	7.90	792	7.93
Leukemia	479	5.82	480	5.83	144	5.83	132	5.34	559	5.60	561	5.62
Renal cell carcinoma	368	4.47	386	4.69	90	3.64	99	4.01	408	4.08	453	4.54
Gynecologic ^c	256	3.11	255	3.10	80	3.24	79	3.20	350	3.50	326	3.26
Multiple myeloma	217	2.63	250	3.04	71	2.87	69	2.79	285	2.85	295	2.95
Upper GI ^d	133	1.61	169	2.05	37	1.50	52	2.11	193	1.93	209	2.09
Pancreas	79	0.96	106	1.29	31	1.26	31	1.26	120	1.20	128	1.28
Stomach	66	0.80	98	1.19	24	0.97	33	1.34	96	0.96	130	1.30
Brain tumor	67	0.81	73	0.89	28	1.13	20	0.81	87	0.87	96	0.96
Testicular	11	0.13	NR	NR	NR	NR	NR	NR	24	0.24	11	0.11
Cancer metastasis ^e	1,231	14.95	1,237	15.02	308	12.47	306	12.39	1,612	16.14	1,601	16.03
Cancer type												
Hematologic	1,328	16.12	1,293	15.70	400	16.19	379	15.34	1,591	15.93	1,567	15.69
Nonhematologic	7,621	92.53	7,618	92.50	2,260	91.50	2,284	92.47	9,257	92.68	9,221	92.32
Cancer-related treatment	4,458	54.13	4,399	53.41	1,258	50.93	1,239	50.16	5,411	54.18	5,423	54.30
Chemotherapy ^e	3,793	46.05	3,753	45.57	1,033	41.82	1,018	41.21	4,583	45.89	4,572	45.77
Hormone therapy ^e	593	7.20	565	6.86	189	7.65	191	7.73	722	7.23	716	7.17
Radiation ^e	708	8.60	697	8.46	217	8.79	214	8.66	936	9.37	922	9.23
Cancer-related surgery ^e	245	2.97	224	2.72	66	2.67	63	2.55	323	3.23	313	3.13

Cells with n < 11 are not reported (NR). Immunotherapy was also assessed as a cancer-related treatment but had too few patients to report (n < 11). ^aGI cancer includes esophagus, stomach, biliary system, pancreas, small intestine, large intestine, rectum, and anus cancers. ^bLower GI cancer includes small intestine, large intestine, rectum, and anus cancers. ^cGynecologic cancer includes uterus, cervix, placenta, ovary, and other female genital organ cancers. ^dUpper GI cancer includes esophagus and stomach cancers. ^eVariable used in propensity score matching.

Abbreviations as in Table 1.

compared with noncancer individuals (4-9). Owing to these increased risks, this patient population poses a unique challenge regarding anticoagulation management (24). However, current AF guidelines for cancer patients have yet to strongly recommend any specific treatment owing to the lack of evidence and research conducted within this at-risk patient population (25,26). This underscores the urgency in evaluating the potential risks and benefits of available treatment strategies for NVAF active cancer patients.

A recent systematic review and meta-analysis of post hoc analyses from the ROCKET AF, ENGAGE AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis In Myocardial Infarction 48), and ARISTOTLE trials, and 2 other cohort studies that compared NOACs with warfarin among AF patients with cancer showed results similar to those found in our analysis (25). The meta-analysis found that NOAC use was significantly

associated with a reduced risk of stroke/SE (risk ratio [RR]: 0.52; 95% CI: 0.28-0.99) and a decreased risk of intracranial or GI bleeding (RR: 0.65; 95% CI: 0.42-0.98). In addition, NOAC use had a tendency toward significantly reducing the risk of MB (RR: 0.73; 95% CI: 0.53-1.00) in NVAF cancer patients.

Real-world studies that have investigated the impact of NOAC treatments in NVAF patients with active cancer are limited (13-16). In a Korean retrospective study, NVAF active cancer patients using NOACs (apixaban, dabigatran, and rivaroxaban) experienced lower stroke/SE, MB, and all-cause death incidence rates than those in the PSM warfarin cohort (13). A U.S. study using the MarketScan claims database identified 16,096 AF patients who were actively treated for cancer during the time of anticoagulation initiation (15). In that MarketScan study, patients initiating apixaban had significantly lower rates of severe bleeding (HR: 0.37; 95% CI:

TABLE 3 Post-PSM Baseline Characteristics of NOAC-NOAC Cohorts

	Apixaban vs Dabigatran				Apixaban vs Rivaroxaban				Dabigatran vs Rivaroxaban			
	Apixaban		Dabigatran		Apixaban		Rivaroxaban		Dabigatran		Rivaroxaban	
	n or Mean	% or SD	n or Mean	% or SD	n or Mean	% or SD	n or Mean	% or SD	n or Mean	% or SD	n or Mean	% or SD
Sample size	2,413	100%	2,413	100%	8,608	100%	8,608	100%	2,553	100%	2,553	100%
Age, y ^a	76.95	7.51	76.58	7.49	77.43	7.80	77.39	7.68	76.13	7.73	76.17	7.70
18-54	NR	NR	NR	NR	47	0.55%	42	0.49%	11	0.43%	19	0.74%
55-64	71	2.94%	71	2.94%	273	3.17%	258	3.00%	125	4.90%	114	4.47%
65-74	893	37.01%	897	37.17%	2,840	32.99%	2,836	32.95%	947	37.09%	957	37.49%
≥75	1,442	59.76%	1,435	59.47%	5,448	63.29%	5,472	63.57%	1,470	57.58%	1,463	57.31%
Sex ^a												
Male	1,498	62.08%	1,457	60.38%	5,209	60.51%	5,191	60.30%	1,558	61.03%	1,581	61.93%
Female	915	37.92%	956	39.62%	3,399	39.49%	3,417	39.70%	995	38.97%	972	38.07%
U.S. geographic region ^a												
Northeast	513	21.26%	514	21.30%	1,629	18.92%	1,671	19.41%	549	21.50%	550	21.54%
Midwest	518	21.47%	539	22.34%	1,817	21.11%	1,825	21.20%	576	22.56%	600	23.50%
South	932	38.62%	927	38.42%	3,756	43.63%	3,733	43.37%	958	37.52%	960	37.60%
West	449	18.61%	431	17.86%	1,390	16.15%	1,365	15.86%	467	18.29%	441	17.27%
Other	NR	NR	NR	NR	16	0.19%	14	0.16%	NR	NR	NR	NR
Baseline comorbidity												
Deyo-Charlson comorbidity index ^a	4.06	3.40	4.00	3.38	4.42	3.53	4.42	3.52	3.94	3.37	3.99	3.27
CHA ₂ DS ₂ -VAsC score	3.90	1.47	3.91	1.50	4.02	1.49	4.02	1.51	3.83	1.53	3.84	1.51
0	11	0.46%	13	0.54%	42	0.49%	53	0.62%	29	1.14%	18	0.71%
1	63	2.61%	67	2.78%	188	2.18%	205	2.38%	85	3.33%	93	3.64%
2	294	12.18%	305	12.64%	974	11.32%	961	11.16%	344	13.47%	356	13.94%
3	650	26.94%	639	26.48%	2,127	24.71%	2,139	24.85%	672	26.32%	642	25.15%
≥4	1,395	57.81%	1,389	57.56%	5,277	61.30%	5,250	60.99%	1,423	55.74%	1,444	56.56%
HAS-BLED score	3.40	1.26	3.38	1.26	3.50	1.28	3.50	1.27	3.32	1.29	3.31	1.25
0	9	0.37%	15	0.62%	26	0.30%	33	0.38%	23	0.90%	12	0.47%
1	101	4.19%	103	4.27%	348	4.04%	349	4.05%	138	5.41%	133	5.21%
2	508	21.05%	505	20.93%	1,646	19.12%	1,559	18.11%	552	21.62%	556	21.78%
≥3	1,795	74.39%	1,790	74.18%	6,588	76.53%	6,667	77.45%	1,840	72.07%	1,852	72.54%
Bleeding history ^a	782	32.41%	780	32.32%	2,878	33.43%	2,844	33.04%	811	31.77%	780	30.55%
Heart failure ^a	698	28.93%	696	28.84%	2,613	30.36%	2,609	30.31%	712	27.89%	722	28.28%
Diabetes mellitus ^a	893	37.01%	893	37.01%	3,145	36.54%	3,169	36.81%	933	36.55%	957	37.49%
Hypertension ^a	2,152	89.18%	2,153	89.23%	7,813	90.76%	7,805	90.67%	2,262	88.60%	2,277	89.19%
Renal disease ^a	555	23.00%	542	22.46%	2,455	28.52%	2,449	28.45%	551	21.58%	563	22.05%
Liver disease ^a	225	9.32%	199	8.25%	803	9.33%	800	9.29%	205	8.03%	190	7.44%
Myocardial infarction ^a	219	9.08%	199	8.25%	838	9.74%	852	9.90%	202	7.91%	213	8.34%
Dyspepsia or stomach discomfort ^a	658	27.27%	636	26.36%	2,402	27.90%	2,410	28.00%	653	25.58%	665	26.05%
Non-stroke/SE peripheral vascular disease ^a	1,342	55.62%	1,363	56.49%	5,081	59.03%	5,109	59.35%	1,421	55.66%	1,429	55.97%
Stroke/SE ^a	270	11.19%	272	11.27%	1,087	12.63%	1,088	12.64%	281	11.01%	282	11.05%
Transient ischemic attack ^a	159	6.59%	179	7.42%	714	8.29%	703	8.17%	186	7.29%	179	7.01%
Anemia and coagulation defects ^a	972	40.28%	965	39.99%	3,602	41.84%	3,631	42.18%	1,001	39.21%	967	37.88%
Alcoholism ^a	63	2.61%	57	2.36%	180	2.09%	172	2.00%	66	2.59%	68	2.66%
Peripheral artery disease	552	22.88%	580	24.04%	2,130	24.74%	2,145	24.92%	604	23.66%	609	23.85%
Coronary artery disease	1,160	48.07%	1,139	47.20%	4,355	50.59%	4,396	51.07%	1,179	46.18%	1,209	47.36%
Dose of the index prescription												
Standard dose ^b	1,862	77.17%	1,940	80.40%	6,346	73.72%	5,728	66.54%	2,058	80.61%	1,793	70.23%
Low dose ^c	551	22.83%	473	19.60%	2,262	26.28%	2,880	33.46%	495	19.39%	760	29.77%

Continued on the next page

0.17-0.79) and had similar rates of ischemic stroke and other bleeding compared with warfarin users. Dabigatran and rivaroxaban had similar rates of ischemic stroke and severe bleeding compared with warfarin users. These MarketScan results are

generally consistent with those of our study; however, our analysis included significantly more patients and additional comparisons.

STUDY LIMITATIONS. To the best of our knowledge, this study represents the largest cohort of NVAf

TABLE 3 Continued

	Apixaban vs Dabigatran				Apixaban vs Rivaroxaban				Dabigatran vs Rivaroxaban			
	Apixaban		Dabigatran		Apixaban		Rivaroxaban		Dabigatran		Rivaroxaban	
	n or Mean	% or SD	n or Mean	% or SD	n or Mean	% or SD	n or Mean	% or SD	n or Mean	% or SD	n or Mean	% or SD
Follow-up time, days	186.88	169.89	224.31	224.61	182.10	166.01	217.29	209.18	224.44	225.79	220.97	210.09
Median	122		122		121		132		120		139	
Reasons for censoring												
Discontinuation	930	38.54%	1,407	58.31%	3,344	38.85%	4,531	52.64%	1,495	58.56%	1,327	51.98%
Switch	87	3.61%	255	10.57%	337	3.91%	557	6.47%	274	10.73%	197	7.72%
Death	96	3.98%	158	6.55%	453	5.26%	599	6.96%	157	6.15%	137	5.37%
End of continuous medical/pharmacy enrollment	27	1.12%	35	1.45%	125	1.45%	201	2.34%	49	1.92%	69	2.70%
End of study period	1,273	52.76%	558	23.12%	4,349	50.52%	2,720	31.60%	578	22.64%	823	32.24%

Cells with n < 11 are not reported (NR). ^aVariable used in propensity score matching. ^b5 mg apixaban, 150 mg dabigatran, 20 mg rivaroxaban. ^c2.5 mg apixaban, 75 mg dabigatran, 10 or 15 mg rivaroxaban. 507 and 2,373 patients received 10 mg and 15 mg rivaroxaban, respectively, in the apixaban-rivaroxaban matched cohort and 133 and 627 patients received 10 mg and 15 mg rivaroxaban, respectively, in the dabigatran-rivaroxaban matched cohort.

Abbreviations as in Table 1.

TABLE 4 Post-PSM Cancer Related Baseline Characteristics of NOAC-NOAC Cohorts

	Apixaban vs Dabigatran				Apixaban vs Rivaroxaban				Dabigatran vs Rivaroxaban			
	Apixaban		Dabigatran		Apixaban		Rivaroxaban		Dabigatran		Rivaroxaban	
	n	%	n	%	n	%	n	%	n	%	n	%
Sample size	2,413	100	2,413	100	8,608	100	8,608	100	2,553	100	2,553	100
Cancer site												
Prostate	762	31.58	738	30.58	2,650	30.79	2,573	29.89	782	30.63	760	29.77
Female breast	446	18.48	467	19.35	1,593	18.51	1,536	17.84	485	19.00	451	17.67
Gastrointestinal(GI) ^a	286	11.85	286	11.85	1,015	11.79	1,120	13.01	300	11.75	280	10.97
Lung	268	11.11	263	10.90	962	11.18	997	11.58	282	11.05	298	11.67
Lymphoma	276	11.44	253	10.48	991	11.51	1,032	11.99	267	10.46	320	12.53
Lower GI ^b	218	9.03	204	8.45	756	8.78	830	9.64	214	8.38	215	8.42
Bladder	188	7.79	194	8.04	671	7.80	682	7.92	210	8.23	193	7.56
Leukemia	139	5.76	138	5.72	480	5.58	466	5.41	145	5.68	170	6.66
Renal cell carcinoma	98	4.06	89	3.69	372	4.32	341	3.96	89	3.49	108	4.23
Gynecologic ^c	75	3.11	79	3.27	265	3.08	289	3.36	81	3.17	73	2.86
Multiple myeloma	57	2.36	67	2.78	218	2.53	238	2.76	69	2.70	71	2.78
Upper GI ^d	40	1.66	34	1.41	140	1.63	178	2.07	36	1.41	23	0.90
Pancreas	19	0.79	29	1.20	82	0.95	88	1.02	31	1.21	32	1.25
Stomach	15	0.62	28	1.16	68	0.79	70	0.81	30	1.18	19	0.74
Brain tumor	18	0.75	22	0.91	72	0.84	89	1.03	23	0.90	13	0.51
Testicular	NR	NR	NR	NR	14	0.16	19	0.22	NR	NR	NR	NR
Cancer metastasis ^e	296	12.27	283	11.73	1,242	14.43	1,233	14.32	297	11.63	299	11.71
Cancer type												
Hematologic	384	15.91	373	15.46	1,357	15.76	1,363	15.83	399	15.63	431	16.88
Nonhematologic	2,243	92.95	2,222	92.08	7,975	92.65	7,971	92.60	2,341	91.70	2,334	91.42
Cancer-related treatment	1,228	50.89	1,230	50.97	4,608	53.53	4,629	53.78	1,297	50.80	1,294	50.69
Chemotherapy ^f	1,017	42.15	1,003	41.57	3,883	45.11	3,896	45.26	1,052	41.21	1,049	41.09
Hormone therapy ^g	165	6.84	187	7.75	656	7.62	641	7.45	195	7.64	183	7.17
Radiation ^h	231	9.57	213	8.83	762	8.85	764	8.88	238	9.32	255	9.99
Cancer-related surgery ⁱ	66	2.74	70	2.90	257	2.99	265	3.08	68	2.66	77	3.02

Cells with n < 11 are not reported (NR). Immunotherapy was also assessed as a cancer-related treatment but had too few patients to report (n < 11). ^aGI cancer includes esophagus, stomach, biliary system, pancreas, small intestine, large intestine, rectum, and anus cancers. ^bLower GI cancer includes small intestine, large intestine, rectum, and anus cancers. ^cGynecologic cancer includes uterus, cervix, placenta, ovary, and other female genital organ cancers. ^dUpper GI cancer includes esophagus and stomach cancers. ^eVariable used in propensity score matching.

Abbreviations as in Table 1.

CENTRAL ILLUSTRATION NOAC Versus Warfarin: PSM Incidence Rates and Hazard Ratios of Stroke/SE and MB**ARISTOPHANES Substudy****Active Cancer**

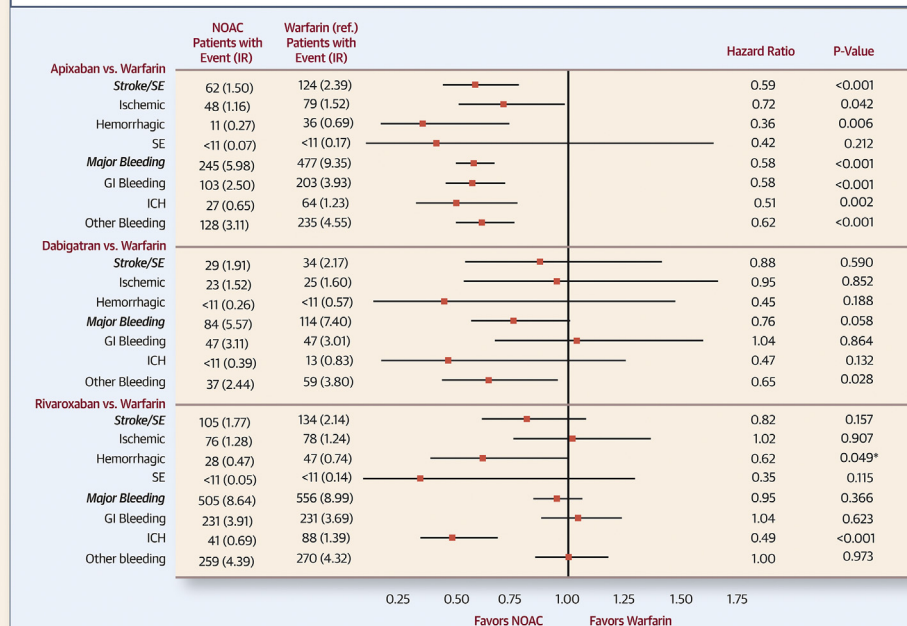
Patients with ≥ 2 claims for cancer diagnosis or 1 claim for cancer diagnosis plus ≥ 1 claim for cancer treatment (e.g. chemotherapy, radiation, cancer-related surgery) in the six month baseline period

N=40,271

Warfarin=15,371 / Apixaban=9,517 / Dabigatran=2,742 / Rivaroxaban=12,641

Propensity Score Matched Cohort Assignments

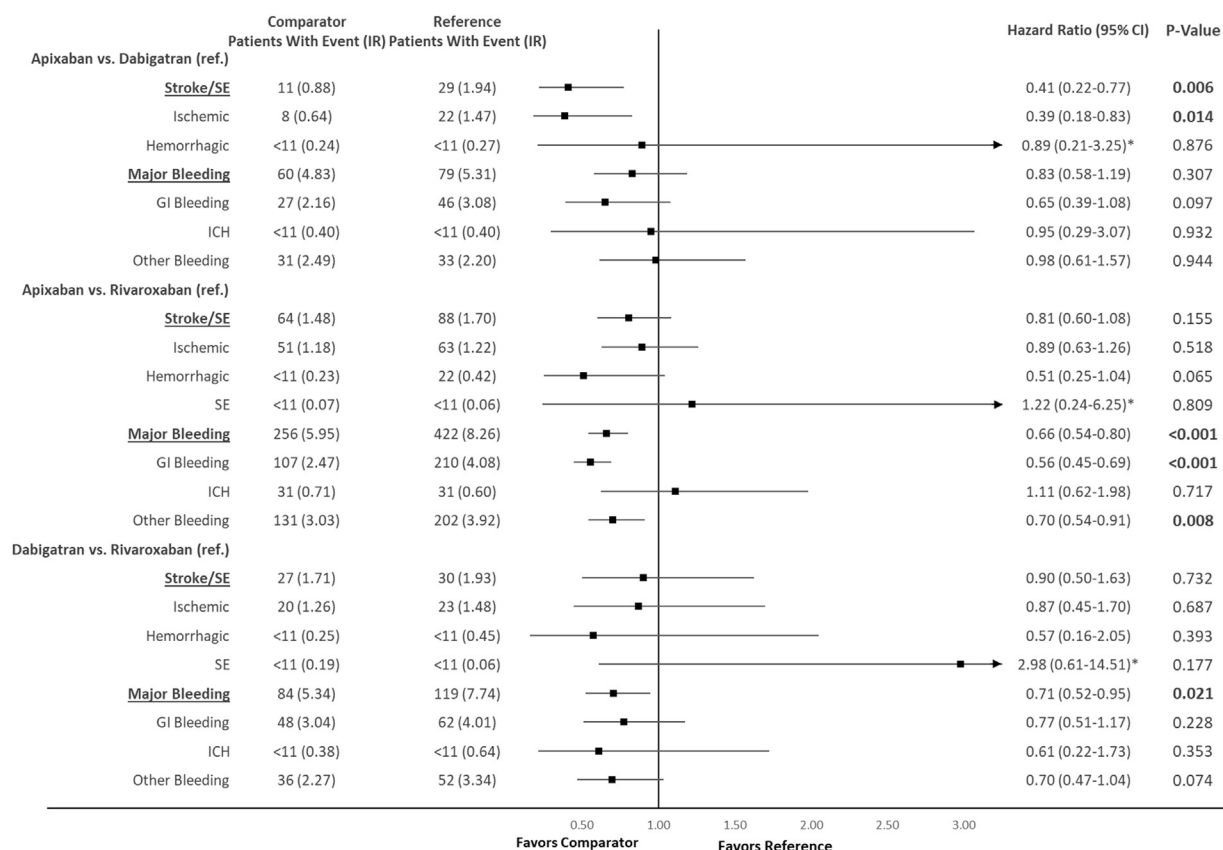
Apixaban-Warfarin=8,236 Dabigatran-Warfarin=2,470 Rivaroxaban-Warfarin=9,988
Apixaban-Dabigatran=2,413 Apixaban-Rivaroxaban=8,608 Dabigatran-Rivaroxaban=2,553

Risk of Stroke/Systemic Embolism (SE) or Major Bleeding

Deitelzweig, S. et al. *J Am Coll Cardiol CardioOnc.* 2021;3(3):411-424.

Incidence rates [IR] (per 100 person-years) and hazard ratios (with 95% confidence intervals [CIs]) of non-vitamin K oral anticoagulants (NOACs) vs warfarin. Apixaban was associated with a lower risk for stroke/systemic embolism (SE) and major bleeding (MB) compared with warfarin, and dabigatran and rivaroxaban were associated with similar risks for stroke/SE and MB compared with warfarin. Risk of SE is not reported for dabigatran versus warfarin comparison owing to small sample size. *P value is considered to be significant because the upper limit of the 95% CI was rounded from 0.997 to 1.00. GI = gastrointestinal; ICH = intracranial hemorrhage.

FIGURE 2 NOAC Versus NOAC: PSM Incidence Rates and Hazard Ratios of Stroke/SE and MB



Incidence rates (IRs) (per 100 person-years) and hazard ratios (HRs) (with 95% confidence intervals [CIs]) of NOACs vs NOACs. Apixaban was associated with a lower risk of stroke/SE compared with dabigatran users, and a lower risk of MB compared with rivaroxaban. Dabigatran was associated with a lower risk in MB compared with rivaroxaban. Risk of SE is not reported for apixaban vs dabigatran comparisons owing to small sample size. *Upper limit of 95% CI extends beyond chart.

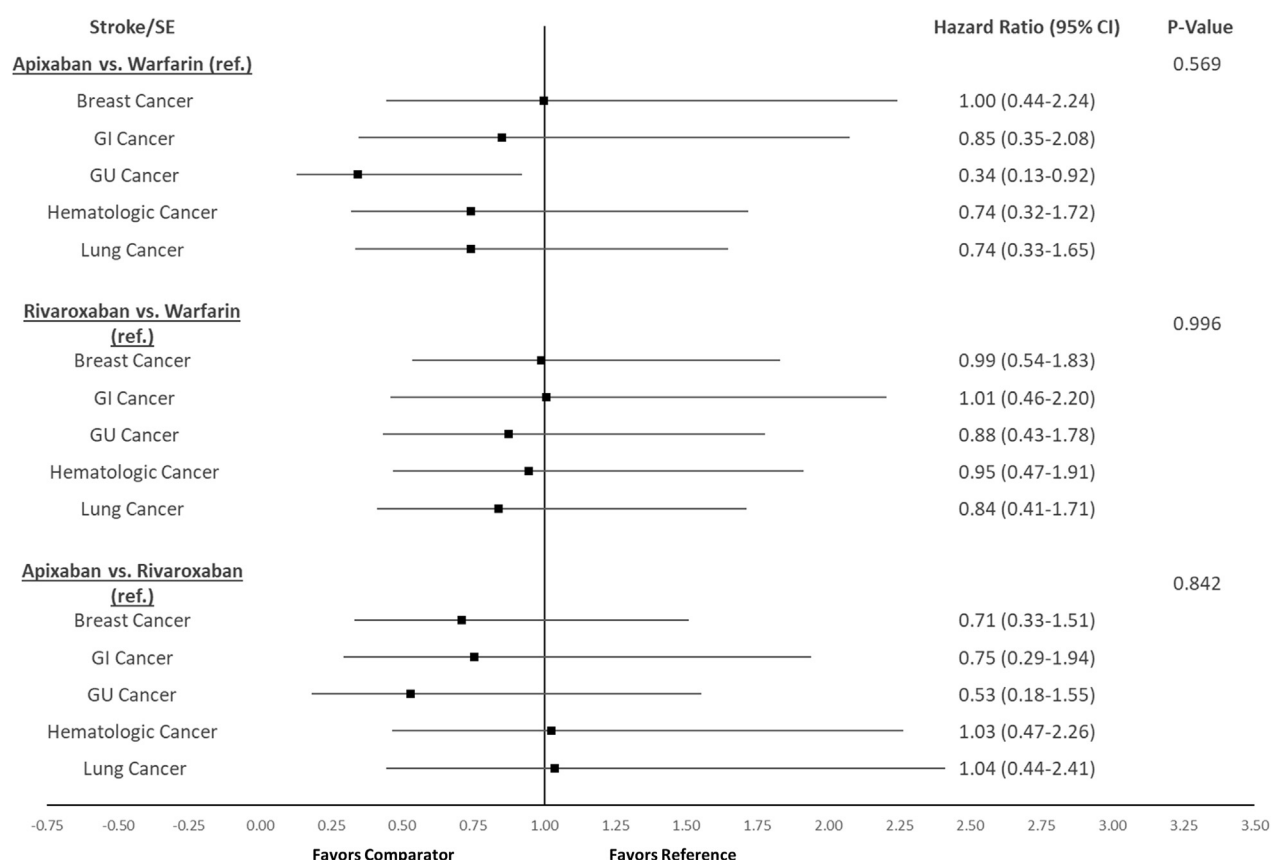
GI = gastrointestinal; ICH = intracranial hemorrhage; MB = major bleeding; SE = systemic embolism; other abbreviations as in Figure 1.

active cancer patients who have been treated with NOACs and warfarin. Using a pooled analysis of 5 U.S. claims databases, this study provides a significant sample size and sufficient statistical power. As a retrospective observational study, however, several limitations need to be noted for this analysis.

First, the results of this study can only be representative of statistical associations, not causal relationships, between the exposures of interest and study outcomes. Even with the use of PSM, the matched cohorts are subject to residual confounders, such as over-the-counter aspirin use or lack of laboratory values, which is especially important when interpreting NOAC-NOAC comparisons. These comparisons are primarily intended for hypothesis generation, given the lack of head-to-head clinical trials.

Second, claims database studies used only ICD-9-CM, CPT, and HCPCS codes to identify outcomes and clinical conditions. These codes lack crucial clinical information on pathology, and are prone to misclassification, which has been observed in cancer metastasis diagnosis (27,28). For example, detailed characteristics including cancer stage, progression, and primary versus secondary cancer diagnosis are lacking in our analysis, which may be pivotal in understanding potential variations in NVAF treatment outcomes as a result of severity of cancer status and/or type. The evaluation of label-adherent dosing for apixaban is also deterred because information on patient weight and renal function, which are needed to assess whether apixaban dose has been used appropriately or not, are not available in the claims data used in this study. Furthermore, because of the study period of this analysis, cancer treatment advancements that

FIGURE 3 PSM HRs of Stroke/SE for Cancer Subgroups



HRs (95% CIs) of stroke/SE for NOACs vs warfarin and NOACs vs NOACs within cancer subgroups. *P* value represents statistically significant interaction between treatment and cancer type. No significant interactions were observed; treatment effect was consistent across cancer types. GU = genitourinary; other abbreviations as in Figures 1 and 2.

have led to improvements in major health outcomes (eg, MB in hematologic cancers) also are not considered. In addition, this analysis had a relatively short mean follow-up time of 6-8 months.

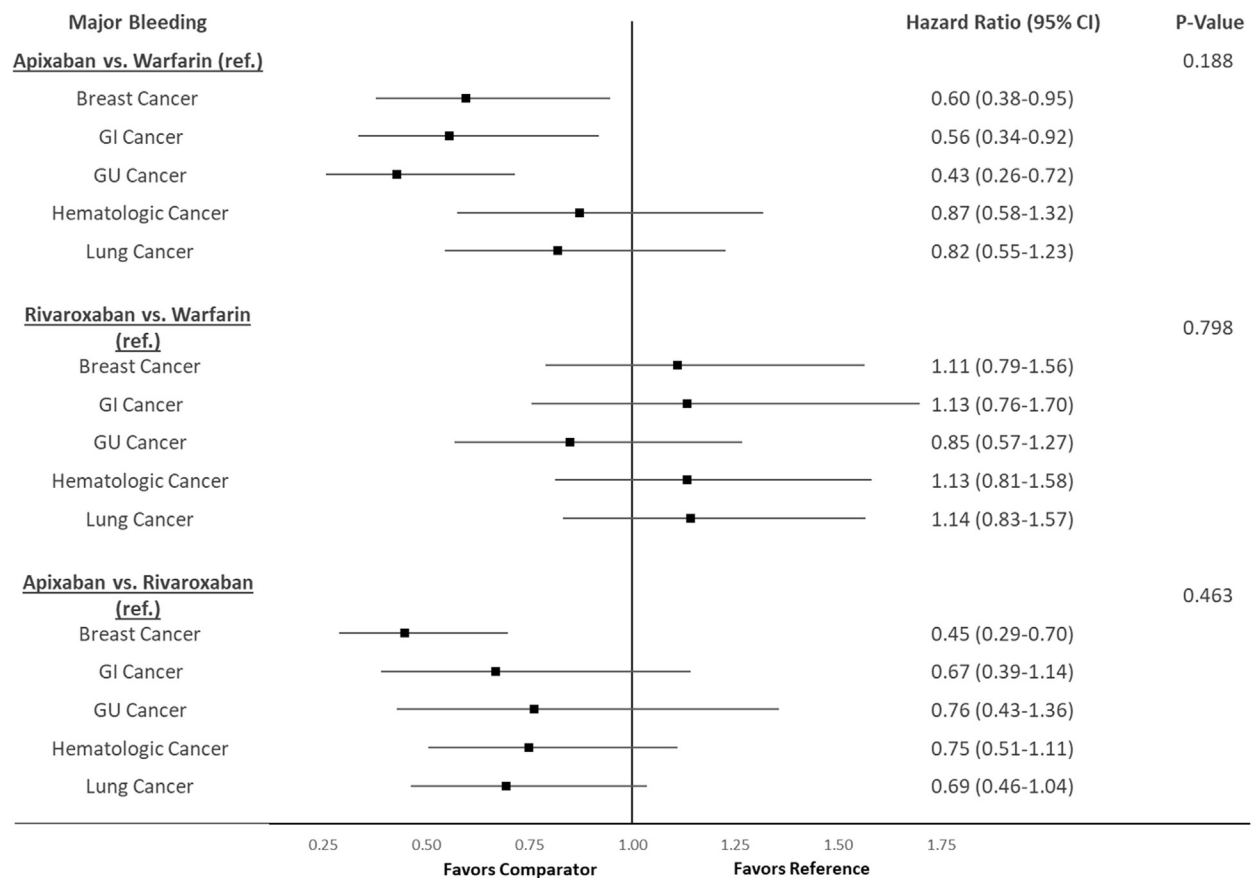
It should also be noted that unobserved heterogeneity may exist across the 5 datasets used in this analysis. The likelihood of duplicate observations is relatively low, researched to be 0.5%, and is not likely to have a significant impact on study results (29). Although this study represents the largest-to-date real-world retrospective claims study of NOAC versus warfarin and NOAC versus NOAC comparisons among active cancer patients with NVAF, it is not reflective of the overall active cancer NVAF population in the US. Uninsured patients and patients solely covered by other public health insurance plans were not included in this analysis. More studies are

needed to better understand the effectiveness and safety of OACs in specific cancer populations. Owing to limited sample size, especially for dabigatran patients, dose was not assessed in separate subgroup analyses. In addition, future analyses with increased sample sizes of dabigatran patients would allow more confidence in the present findings for this patient cohort (large confidence intervals in the risk estimates for dabigatran vs other OACs were observed because of small sample size).

CONCLUSIONS

Among NVAF patients with active cancer, apixaban was associated with a lower risk, and dabigatran and rivaroxaban with similar risks of stroke/SE and MB compared with warfarin. Apixaban users also had a

FIGURE 4 PSM HRs of Major Bleeding for Cancer Subgroups



HRs (95% CIs) of MB for NOACs vs warfarin and NOACs vs NOACs within cancer subgroups. *P* value represents statistically significant interaction between treatment and cancer type. No significant interactions were observed; treatment effect was consistent across cancer types. Abbreviations as in Figures 1 to 3.

lower risk of stroke/SE compared with dabigatran users and a lower risk of MB compared with rivaroxaban users. Dabigatran was associated with a lower risk of MB compared with rivaroxaban. Treatment effects were consistent across several common cancer types for NOAC-warfarin and NOAC-NOAC comparisons. Subsequent real-world studies are warranted to further study the impact of NOAC treatment options in the NVAF cancer population, specifically addressing NOAC treatment outcomes within specific cancer subtypes.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This study was funded by Pfizer and Bristol Myers Squibb. Although the authors have financial relationships with these companies, neither business entity influenced the design, conduct, or reporting of the research. Dr Deitelzweig is a consultant for Bristol Myers

Squibb Company/Pfizer Inc., Daiichi-Sankyo, Portola, and Boehringer Ingelheim; and has been on the Speakers Bureau for Janssen, Bristol Myers Squibb Company/Pfizer Inc., and Boehringer Ingelheim. Ms Keshishian is a paid employee of STATinMED Research, which is a paid consultant to Bristol Myers Squibb and Pfizer. Drs Kang, Zhang, Dhamane, Klem, Ferri, and Jiang are paid employees of Bristol Myers Squibb. Dr Luo is a paid employee of Pfizer. Dr Yuce has reported that he has no relationships relevant to the contents of this paper to disclose. Dr Lip is a consultant for Bayer/Janssen, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Verseen, and Daiichi-Sankyo; and is a speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo; no fees are directly received personally.

ADDRESS FOR CORRESPONDENCE: Dr Steven Deitelzweig, Ochsner Health 1514 Jefferson Highway, 11th floor, Hospital Medicine, New Orleans, Louisiana 70121, USA. E-mail: sdeitelzweig@ochsner.org. Twitter: [@statinmedresearch](https://twitter.com/statinmedresearch).

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In NVAf patients with active cancer, initiation of NOACs is associated with a similar or reduced risk in thromboembolic and bleeding complications compared with treatment with warfarin. These findings were consistent across several common cancer types.

TRANSLATIONAL OUTLOOK: Future studies are needed to further understand patient- and dosing-specific characteristics to enhance the safety and effectiveness of NOACs in the cancer population. A more detailed evaluation of NOAC treatment outcomes according to specific cancer types and disease severity is necessary.

REFERENCES

- Yadava M, Hughey AB, Crawford TC. Post-operative atrial fibrillation: incidence, mechanisms, and clinical correlates. *Heart Fail Clin*. 2016;12:299-308.
- Zimetbaum P. Atrial fibrillation. *Ann Intern Med*. 2017;166:ITC33-ITC48.
- Allan V, Honarbakhsh S, Casas JP, et al. Are cardiovascular risk factors also associated with the incidence of atrial fibrillation? A systematic review and field synopsis of 23 factors in 32 population-based cohorts of 20 million participants. *Thromb Haemost*. 2017;117:837-850.
- Yuan M, Zhang Z, Tse G, et al. Association of cancer and the risk of developing atrial fibrillation: a systematic review and meta-analysis. *Cardiol Res Pract*. 2019;2019:8985273.
- O'Neal WT, Lakoski SG, Qureshi W, et al. Relation between cancer and atrial fibrillation (from the Reasons for Geographic and Racial Differences in Stroke Study). *Am J Cardiol*. 2015;115:1090-1094.
- Kuan AS, Chen SC, Yeh CM, et al. Risk of ischemic stroke in patients with gastric cancer: a nationwide population-based cohort study. *Medicine (Baltimore)*. 2015;94:e1336.
- Kuan AS, Teng CJ, Wu H, et al. Risk of ischemic stroke in patients with ovarian cancer: a nationwide population-based study. *BMC Med*. 2014;12:53.
- Tsai SJ, Huang YS, Tung CH, et al. Increased risk of ischemic stroke in cervical cancer patients: a nationwide population-based study. *Radiat Oncol*. 2013;8:41.
- Kamphuisen PW, Beyer-Westendorf J. Bleeding complications during anticoagulant treatment in patients with cancer. *Thromb Res*. 2014;133(suppl 2):S49-S55.
- Farmakis D, Parissis J, Filippatos G. Insights into onco-cardiology: atrial fibrillation in cancer. *J Am Coll Cardiol*. 2014;63:945-953.
- Chen ST, Hellkamp AS, Becker RC, et al. Efficacy and safety of rivaroxaban vs warfarin in patients with non-valvular atrial fibrillation and a history of cancer: observations from ROCKET AF. *Eur Heart J Qual Care Clin Outcomes*. 2019;5:145-152.
- Melloni C, Dunning A, Granger CB, et al. Efficacy and safety of apixaban versus warfarin in patients with atrial fibrillation and a history of cancer: insights from the ARISTOTLE trial. *Am J Med*. 2017;130:1440-1448.e1.
- Kim K, Lee YJ, Kim TH, et al. Effect of non-vitamin K antagonist oral anticoagulants in atrial fibrillation patients with newly diagnosed cancer. *Korean Circ J*. 2018;48:406-417.
- Laube ES, Yu A, Gupta D, et al. Rivaroxaban for stroke prevention in patients with nonvalvular atrial fibrillation and active cancer. *Am J Cardiol*. 2017;120:213-217.
- Shah S, Norby FL, Datta YH, et al. Comparative effectiveness of direct oral anticoagulants and warfarin in patients with cancer and atrial fibrillation. *Blood Adv*. 2018;2:200-2009.
- Ording AG, Horváth-Puhó E, Adelborg K, Pedersen L, Prandoni P, Sørensen HT. Thromboembolic and bleeding complications during oral anticoagulation therapy in cancer patients with atrial fibrillation: a Danish nationwide population-based cohort study. *Cancer Med*. 2017;6:1165-1172.
- Lip GYH, Keshishian A, Li X, et al. Effectiveness and safety of oral anticoagulants among non-valvular atrial fibrillation patients. *Stroke*. 2018;49:2933-2944.
- Li XS, 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;117:1072-1082.
- Yao X, Abraham NS, Sangaralingham LR, et al. Effectiveness and safety of dabigatran, rivaroxaban, and apixaban versus warfarin in nonvalvular atrial fibrillation. *J Am Heart Assoc*. 2016;5:e003725.
- 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;8:8-14.
- Cunningham A, Stein CM, Chung CP, Daugherty JR, Smalley WE, Ray WA. An automated database case definition for serious bleeding related to oral anticoagulant use. *Pharmacoepidemiol Drug Saf*. 2011;20:560-566.
- Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med*. 2009;28:3083-3107.
- 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;33:1242-1258.
- Malavasi VL, Fantecchi E, Gianolio L, et al. Atrial fibrillation in patients with active malignancy and use of anticoagulants: under-prescription but no adverse impact on all-cause mortality. *Eur J Intern Med*. 2019;59:27-33.
- Deng Y, Tong Y, Deng Y, Zou L, Li S, Chen H. Non-vitamin K antagonist oral anticoagulants versus warfarin in patients with cancer and atrial fibrillation: a systematic review and meta-analysis. *J Am Heart Assoc*. 2019;8:e012540.
- Zamorano JL, Lancellotti P, Rodriguez Muñoz D, et al. ESC Scientific Document Group. 2016 ESC position paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: the Task Force for Cancer Treatments and Cardiovascular Toxicity of the European Society of Cardiology (ESC). *Eur Heart J*. 2016;37:2768-2801.
- Jagsi R, Bekelman JE, Chen A, et al. Considerations for observational research using large data sets in radiation oncology. *Int J Radiat Oncol Biol Phys*. 2014;90:11-24.
- Chawla N, Yabroff KR, Mariotto A, et al. Limited validity of diagnosis codes in Medicare claims for identifying cancer metastases and inferring stage. *Ann Epidemiol*. 2014;24:666-672.
- 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;17:333-341.

KEY WORDS active cancer, anticoagulants, bleeding, nonvalvular atrial fibrillation, stroke

APPENDIX For supplemental tables and figures, please see the online version of this paper.