Comparative Effectiveness and Safety of Direct-acting Oral Anticoagulants and Warfarin in Patients with Venous Thromboembolism and Active Cancer: An Observational Analysis

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ABSTRACT

Purpose: There is limited evidence to support the use of direct-acting oral anticoagulants (DOACs) in patients with venous thromboembolism (VTE) and active cancer. This study aimed to assess the effectiveness of DOACs versus warfarin for the prevention of recurrent VTE and major bleeding events in patients with VTE and active cancer.

Methods: We identified patients with incident VTE and active cancer who newly initiated treatment with DOACs or warfarin from Truven Health MarketScan Commercial Claims and Medicare supplemental databases. Patients were followed up from treatment initiation (index date) until the occurrence of >7-day gap in treatment, the start of the study comparator, an outcome of interest (recurrent VTE or major bleeding), inpatient death, disenrollment, or end of the study period, whichever occurred first. We controlled for confounders via propensity score matching and estimated the hazard ratios (HRs) using Cox proportional hazards regression models.

Findings: A total of 9952 patients were included in the matched cohort (4976 DOACs users and 4976 warfarin users). Patient characteristics were well balanced after matching. We observed a lower incidence of recurrent VTE (3 vs 5 per 100 person-years) and major bleeding events (2 vs 3 per 100 person-years) in the DOAC group compared to warfarin group, respectively. In Cox regression models, use of DOACs (vs warfarin) was associated with a lower risk of recurrent VTE (hazard ratio (HR), 0.59; 95% CI, 0.42−0.82) and major bleeding events (HR, 0.64; 95% CI, 0.44−0.94).

Implications: On the basis of our findings, among patients with VTE and active cancer, DOACs offer superior effectiveness with a lower risk of bleeding when compared with warfarin for the secondary prevention of VTE. (*Clin Ther*. 2020;42:e161−e176)

Key words: cancer, DOACs, safety, thrombosis, venous thromboembolism, warfarin.

INTRODUCTION

Venous thromboembolism (VTE), including pulmonary embolism (PE) and deep vein thrombosis (DVT), affects 200,000 individuals each year, incurring substantial societal and economic burden.[1] Risk of VTE increases with age, use of estrogen, prolonged immobility, major trauma, and cancer, with the latter accounting for approximately 20% of

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VTE cases.[2,3] Compared with patients with VTE without cancer, those with cancer have higher rates of recurrent events and adverse bleeding complications,[4] even with standard anticoagulation regimens.[5] This finding can be partially explained by complications related to factors such as surgical interventions, chemotherapy, and prolonged immobilization.[6]

The American College of Chest Physicians guidelines recommend low-molecular-weight heparin (LMWH) for secondary prevention of VTE in patients with cancer, yet most such patients are treated with vitamin K antagonists (ie, warfarin) or direct-acting oral anticoagulants (DOACs) in routine clinical practice.[7,8] Because long-term treatment is recommended in patients with cancer, practical issues with the use of LMWH, including cost, route of administration, and quality of life, make other alternatives (eg, DOACs and vitamin K antagonists) an attractive option for the treatment of patients with cancer-related VTE.[9] Although warfarin is inexpensive relative to other anticoagulants, drugs, including anticancer medications or chemotherapy, may interact with warfarin, which can lead to wide fluctuation in the international normalized ratio.[6,10]

DOACs (eg, apixaban, rivaroxaban, and dabigatran) are administered orally, do not require frequent monitoring, and are less susceptible to drug–drug or drug–food interactions.[11] However, there is limited evidence to guide the selection between DOACs and vitamin K antagonists within this population. Patients with cancer and VTE are often underrepresented in randomized clinical trials (RCTs), accounting for <5% of patients enrolled in these trials.[9] Furthermore, the evidence generated from a meta-analysis of RCTs, which was limited by the small sample size, found no differences in the risk of recurrent VTE and major bleeding between DOACs and warfarin.[9]

Therefore, we primarily aimed to (1) assess the effectiveness of DOACs versus warfarin for the prevention of recurrent VTE and (2) examine the risk of major bleeding between DOACs and warfarin among patients with VTE and active cancer. Secondarily, we aimed to assess the comparative effectiveness and safety of the individual DOACs compared with warfarin among patients with VTE and active cancer.

METHODS

Data Source

This was a retrospective cohort analysis using data from Truven Health MarketScan Commercial Claims and Medicare supplemental insurance between January 2013 and December 2016. The commercial data include employer-based health care coverage of employees and their dependents, representing >57 million covered lives. The Medicare supplemental files represent retirees who are covered by Medicare supplemental insurance. The database provides information on inpatient admissions, outpatient visits, prescription claims, enrollment, and health expenditures. The data are deidentified and compliant with the Health Insurance Portability and Accountability Act of 1996.

Study Design and Participants

An incident disease, new-user cohort was created by selecting patients with newly diagnosed VTE (ie, no prior diagnosis of VTE or use of anticoagulants within a 12-month lookback period) who initiated anticoagulation treatment within 30 days of their first VTE diagnosis. Patients were selected between January 2014 and November 2016 but followed up through December 2016 (Figure). We restricted the cohort to patients with active cancer who were new users at the time of their first VTE to avoid the bias that resulted from the inclusion of prevalent users, such as the underascertainment of events that occur early in treatment.[12] VTE was defined based on the presence of diagnoses of DVT or PE presenting on inpatient discharge claims or outpatient claims (2 diagnoses within 1 year). *International Classification of Diseases, Ninth Revision* (ICD-9) and *International Classification of Diseases, Tenth Revision* (ICD-10) codes for VTE diagnosis, (ICD-9: 415.1, 451.1, 453.2, 453.4, 453.5, 453.8, 453.9; ICD-10: I80.2, I80.3, I80.1, I82.8, I80.9, I82.9, I80.8, O22.3, O22.9, O87.1, I26.9, I26.0) were validated previously.[13] We considered the date of the first claim to be the diagnosis date of VTE (ie, first of inpatient claims or the earliest date of 2 outpatient claims if VTE was captured based on 2 outpatient claims within 1 year).

Among eligible patients, we identified those with diagnoses of active cancer based on the presence of a cancer diagnosis (any position) within the 6 months preceding their first VTE diagnosis. Patients were also

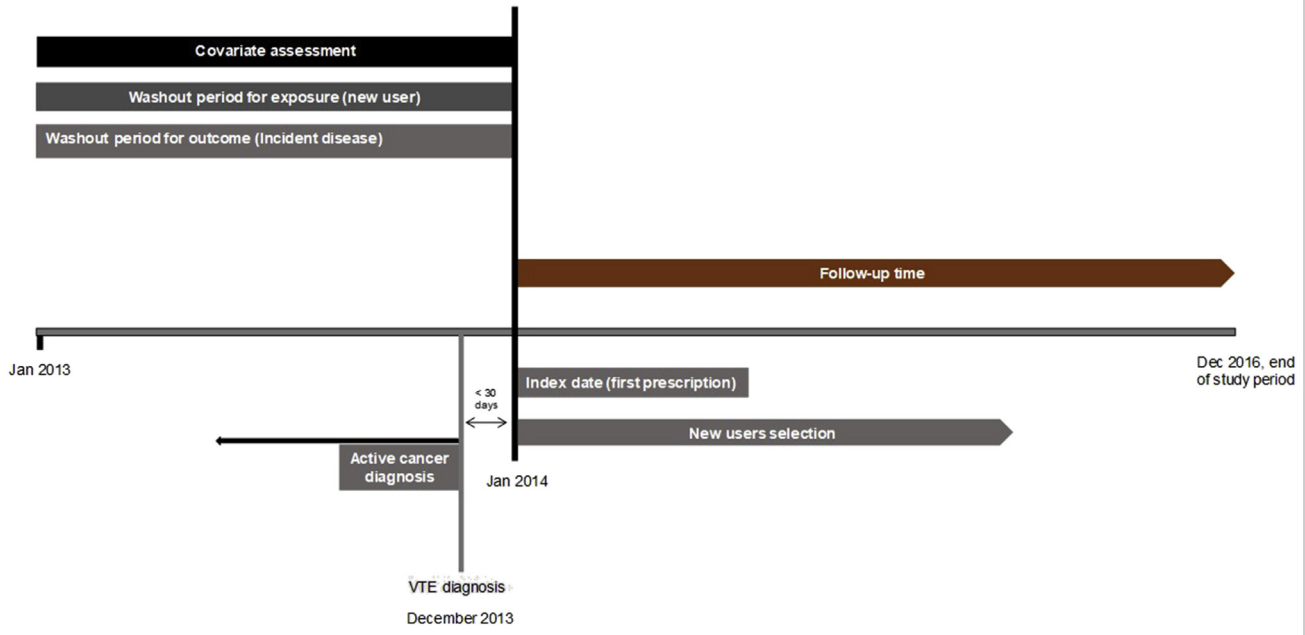

Figure. Study design. VTE = venous thromboembolism.

required to be treated with radiotherapy, surgery, or chemotherapy.[14]

Exposure and Covariates

Exposure was defined by the anticoagulant dispensed on the index date. Patients were classified into 2 groups: new users of DOACs (apixaban, rivaroxaban, dabigatran) or new users of warfarin. We did not have an adequate sample size to evaluate edoxaban because of its recent introduction into the US market. We selected warfarin as the active comparator because (1) warfarin remains the most widely used anticoagulant and (2) treatment guidelines at the time of the study (January 2013 to December 2016) used to give preference to warfarin in patients with cancer-related VTE. Patients were considered continuously exposed as long as they continued to refill their prescriptions, allowing a gap of $\leq$7 days between refills. We excluded patients who initiated use of DOACs and warfarin on the same date and those with <12 months of continuous enrollment in medical and pharmacy benefits before treatment initiation.

Confounders were prespecified and identified from prior studies that evaluated the risk of recurrent VTE in patients with VTE or major bleeding in patients receiving anticoagulants.[15–18] Covariates included demographic characteristics, baseline measures of health care utilization (eg, total number of outpatient visits during the prior year), baseline drug exposure (eg, nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, aspirin, and β-blockers), baseline comorbidities (eg, ischemic heart disease, myocardial infarction, and chronic kidney disease), and the type of cancer treatment during baseline (chemotherapy, radiotherapy, and surgery). Because certain types of cancers may increase the risk of VTE, we classified cancer into risk categories as very high-risk for VTE (stomach, pancreas, and brain), high risk for VTE (lung, lymphoma, gynecologic, bladder, testicular, and renal), and low risk for VTE (thyroid, prostate, oral, leukemia, larynx, kidney, esophagus, colon, breast, and bone).[19,20] This classification is based on the Khorana risk score for the prediction of VTE in patients with cancer.[20] In addition, because bleeding is more common in patients with gastrointestinal cancers, we classified patients into 2 groups: gastrointestinal cancers and nongastrointestinal cancers.[21]

Study Outcomes

The primary outcomes of interest were recurrent VTE and major bleeding events presenting on hospital discharge diagnosis (primary disposition only). Recurrent VTE events, DVT and PE, were identified based on the presence of primary discharge diagnosis indicative of VTE. This definition, which has been validated in inpatient and ambulatory care administrative databases, was found to have a positive predictive value between 73.3% and 83.1%.[22] The major bleeding outcome included a composite of intracranial hemorrhage, gastrointestinal bleeding, and other major bleeding events. The ICD-9 and ICD-10 codes for major bleeding were used and validated in prior studies.[23,24]

Follow-up started from the date of the first prescription (index date) until (1) discontinuation of index medication (ie, presence of a gap >7 days in therapy); (2) start of the study comparator (ie, a DOAC user starts warfarin therapy); (3) an outcome of interest (recurrent VTE or major bleeding); (4) inpatient death; (5) disenrollment defined as the presence of a gap ≥31 days in health care coverage; or (6) end of the study period (December 2016), whichever occurred first. For the secondary analysis, switching among the individual DOACs terminated follow-up because we aimed to assess the comparative effectiveness and safety of the individual DOACs (apixaban, rivaroxaban, and dabigatran) compared with warfarin.

Statistical Analysis

We summarized patients' baseline demographic and clinical characteristics and assessed the differences between users of DOACs and warfarin via absolute standardized differences. We used the propensity score matching (PSM) method to reduce the effect of measured confounders. Incident users of DOACs were 1:1 matched to an incident user of warfarin based on a caliper of 0.01. We used Cox proportional hazards models to estimate the hazard ratios (HRs), and the proportional hazards assumption was tested using Schoenfeld residuals.

In the subgroup analysis, we stratified the primary analysis by age (<65 vs ≥ 65 years), cancer-related VTE risk category (very high risk for VTE, high risk for VTE, or low risk for VTE) for the recurrent VTE outcome, and gastrointestinal cancers versus non-gastrointestinal cancers for the major bleeding outcome. We performed the matching again within each of the selected subgroups to preserve the balance in baseline characteristics (eg, within patients aged <65 years). We conducted sensitivity analyses to examine the robustness of the study findings. All analyses were performed using SAS software, version 9.4 (SAS Institute Inc, Cary, North Carolina).

RESULTS

A flow diagram of the study population is presented in Supplemental Figure 1. We identified a total of 5622 new users of DOACs and 6750 new users of warfarin before PSM (Table I and Supplemental Figure 2). After 1:1 matching, a total of 9952 patients were included in the matched cohort (4976 DOAC users and 4976 warfarin users) (Table II and Supplemental Figure 3). After PSM, patients' demographic and clinical characteristics were well balanced between the DOAC and warfarin groups, including mean age (64.2 vs 64.3 years), proportion of men (49.2% vs 49.7%), history of bleeding (17.9% vs 18.1%), chronic kidney disease (15.6% vs 16.0%), and use of antiplatelet (5.5% vs 5.6%). All absolute standardized differences were <0.1. In addition, there was an equal distribution of cancer types between the 2 groups (Supplemental Table I).

Recurrent VTE

A Kaplan–Meier curve in the matched sample and the incidence rates of recurrent VTE are presented in Supplemental Figure 4 and Table III. After adjustment, the use of DOACs was associated with a lower risk of recurrent VTE compared with warfarin (HR, 0.59; 95% CI, 0.42–0.82). The results from the prespecified subgroup analyses were consistent with the primary analysis when stratifying by age ($P = 0.39$ for interaction), cancer VTE-related risk category (P = 0.32 for interaction), and within the individual DOACs, including apixaban (vs warfarin) (HR, 0.32; 95% CI, 0.12–0.88) and rivaroxaban (vs warfarin) (HR, 0.68; 95% CI, 0.49–0.97) (Tables III and IV). We were unable to examine dabigatran because of the limited sample size (n = 95).

Incident Bleeding

A Kaplan–Meier curve in the matched sample and the incidence rates of major bleeding are presented in Supplemental Figure 5 and Table III. After adjustment, the use of DOACs was associated with a

Table I. Demographic and clinical characteristics of new users of DOACs and warfarin before propensity score matching.*

Characteristic	DOACs (n = 5622)	Warfarin (n = 6750)	Absolute STD
Age, mean (SD), y	63.4 (13.5)	65.7 (13.2)	0.17
Sex			
Male	2712 (48.2)	3449 (51.1)	0.06
Female	2910 (51.8)	3301 (48.9)	
Comorbidities			
Trauma	1738 (30.9)	1973 (29.2)	0.04
Hyperlipidemia	2544 (45.3)	3051 (45.2)	0.00
Tobacco use	517 (9.2)	641 (9.5)	0.01
Respiratory diseases	1679 (29.9)	2081 (30.8)	0.02
Liver disease	632 (11.2)	588 (8.7)	0.08
CKD	794 (14.1)	1387 (20.5)	0.18
Anemia	1553 (27.6)	2118 (31.4)	0.08
Alcohol use disorder	83 (1.5)	118 (1.7)	0.02
Drug use disorder	165 (2.9)	199 (2.9)	0.00
History of bleeding	986 (17.5)	1323 (19.6)	0.05
Ischemic heart disease	1133 (20.2)	1523 (22.6)	0.06
Myocardial infarction	187 (3.3)	284 (4.2)	0.05
Stroke	451 (8.0)	648 (9.6)	0.06
Heart failure	387 (6.9)	503 (7.5)	0.02
Thrombocytopenia	119 (2.1)	86 (1.3)	0.06
Varicose vein	74 (1.3)	58 (0.9)	0.04
Baseline medications			
Antiplatelet agents	308 (5.5)	358 (5.3)	0.01
NSAIDs	1112 (19.8)	1100 (16.3)	0.09
ACEIs	1035 (18.4)	1357 (20.1)	0.04
Aspirin	69 (1.2)	99 (1.5)	0.02
β-Blockers	1554 (27.6)	1953 (28.9)	0.03
Calcium channel blockers	1203 (21.4)	1471 (21.8)	0.01
SSRIs	806 (14.3)	941 (13.9)	0.01
PPIs	1937 (34.5)	2030 (30.1)	0.09
Loop diuretics	854 (15.2)	1115 (16.5)	0.04
Potassium-sparing diuretics	170 (3.0)	203 (3)	0.00
Thiazide	69 (1.2)	117 (1.7)	0.05
Vasodilators	86 (1.5)	132 (2.0)	0.03
Corticosteroids	2835 (50.4)	2903 (43.0)	0.15
COX-2 inhibitors	146 (2.6)	153 (2.3)	0.02
HAS-BLED score, mean (SD)	0.3 (0.5)	0.3 (0.4)	0.08
Outpatient visits, mean (SD)	35.5 (25.4)	30.7 (26.3)	0.18

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Table I. (*Continued*)

Characteristic	DOACs (n = 5622)	Warfarin (n = 6750)	Absolute STD
Treatment received for cancer			
Chemotherapy	5548 (98.7)	6641 (98.4)	0.03
Radiotherapy	1127 (20.0)	1117 (16.5)	0.00
Surgery	1625 (28.9)	2121 (31.4)	0.06

ACEIs = angiotensin-converting enzyme inhibitors; CKD = chronic kidney disease; COX = cyclooxygenase; DOACs = direct-acting oral anticoagulants; HAS-BLED = hypertension, abnormal renal/liver function (1 or 2 points), stroke, bleeding history or predisposition, labile international normalized ratio, elderly (>65 years of age), drugs/alcohol concomitantly (1 or 2 points); PPIs = proton-pump inhibitors; NSAIDs = nonsteroidal anti-inflammatory drugs; SSRIs = selective serotonin reuptake inhibitors; STD = standardized difference.

* Data are presented as number (percentage) of patients unless otherwise indicated.

lower risk of major bleeding compared with warfarin (HR, 0.64; 95% CI, 0.44−0.94) (Table III). The results from the prespecified subgroup analyses were consistent with the primary analysis when stratifying by age (P = 0.98 for interaction), cancer type, including gastrointestinal cancer and nongastrointestinal cancer (P = 0.79 for interaction), and across the individual DOACs, including rivaroxaban (vs warfarin) (HR, 0.65; 95% CI, 0.43−0.98) and apixaban (vs warfarin) (HR, 0.48; 95% CI, 0.17−1.39), although the latter comparison was not statistically significant (Tables III and IV).

The study results remained consistent after excluding patients who used LMWH (N = 80 [45 DOAC users and 35 warfarin users]) for recurrent VTE (HR, 0.59; 95% CI, 0.43−0.83) and major bleeding (HR, 0.63; 95% CI, 0.43−0.93) and after requiring patients to have at least 2 diagnosis of VTE (based on outpatient claims) before treatment initiation (recurrent VTE: HR, 0.55; 95% CI, 0.39−0.76; major bleeding: HR, 0.64; 95% CI, 0.51−0.80).

DISCUSSION

In this population-based analysis of patients with VTE and active cancer who were not previously treated with anticoagulants, the use of DOACs was associated with a lower risk of recurrent VTE and major bleeding events compared with warfarin. This association remained consistent when comparing rivaroxaban and warfarin and when comparing apixaban and warfarin, although the low number of events in the latter comparison for the major bleeding outcome resulted in a wide CI crossing the null. We were not able to assess risks and benefits of dabigatran (n = 95) and edoxaban (n = < 10) because of the limited sample size.

Patients with active cancer are at an increased risk for VTE, and the selection of anticoagulant in this population remains a challenge in part because of the small proportion of patients with cancer who were included in RCTs.[25] Treatment guidelines consider LMWH to be the treatment of choice for the prevention of cancer-related VTE but note that warfarin or a DOAC may be a reasonable alternative in patients who refuse or have compelling reasons to avoid LMWH, such as pain related to injections, inconvenience related to LMWH administration, or the cost of LMWH therapy.[8,25]

Despite the steady increase in the use of DOACs among the general VTE population, their uptake in patients with cancer-associated VTE remains limited, presumably because of the relative paucity of evidence. Recently, DOACs were compared with LMWH among cancer patients in RCTs.[26,27] The Hokusai VTE Cancer trial found that edoxaban was noninferior to LMWH for the prevention of recurrent VTE but was associated with higher bleeding risk.[27] Similarly, the Anticoagulation Therapy in Selected Cancer Patients at Risk of Recurrence of Venous Thromboembolism (SELECT-D) trial reported that rivaroxaban, compared with LMWH, was associated with a lower risk of recurrent VTE (HR, 0.43; 95% CI, 0.19−0.99) but a higher risk of clinically relevant nonmajor bleeding (HR, 3.76; 95% CI, 1.63−8.69). The results from these trials prompted the National

Table II. Demographic and clinical characteristics of new users of DOACs and warfarin after propensity score matching.*

Characteristic	DOACs (n = 4976)	Warfarin (n = 4976)	Absolute STD
Age, mean (SD), y	64.2 (13.3)	64.3 (13.3)	0.01
Sex			
Male	2450 (49.2)	2471 (49.7)	0.01
Female	2526 (50.8)	2505 (50.3)	
Comorbidities			
Trauma	1522 (30.6)	1481 (29.8)	0.02
Hyperlipidemia	2249 (45.2)	2244 (45.1)	0.00
Tobacco use	549 (11.0)	455 (9.1)	0.00
Respiratory diseases	1492 (30.0)	1494 (30.0)	0.00
Liver disease	496 (10.0)	500 (10.0)	0.00
CKD	778 (15.6)	798 (16.0)	0.01
Anemia	1427 (28.7)	1425 (28.6)	0.00
Alcohol use disorder	77 (1.5)	78 (1.6)	0.00
Drug use disorder	138 (2.8)	142 (2.9)	0.00
History of bleeding	893 (17.9)	902 (18.1)	0.00
Ischemic heart disease	1033 (20.8)	1053 (21.2)	0.01
Myocardial infarction	178 (3.6)	182 (3.7)	0.00
Stroke	422 (8.5)	438 (8.8)	0.01
Heart failure	339 (6.8)	260 (5.2)	0.01
Baseline medications			
Antiplatelet agents	273 (5.5)	280 (5.6)	0.01
NSAIDs	926 (18.6)	922 (18.5)	0.00
ACEIs	944 (19.0)	961 (19.3)	0.01
Aspirin	64 (1.3)	65 (1.3)	0.00
β-Blockers	1385 (27.8)	1400 (28.1)	0.01
Calcium channel blockers	1052 (21.1)	1055 (21.2)	0.00
SSRIs	703 (14.1)	691 (13.9)	0.01
PPIs	1610 (32.4)	1640 (33.0)	0.01
Loop diuretics	767 (15.4)	779 (15.7)	0.01
Potassium-sparing diuretics	153 (3.1)	159 (3.2)	0.01
Thiazide	67 (1.3)	64 (1.3)	0.01
Vasodilators	81 (1.6)	78 (1.6)	0.00
COX-2 inhibitors	120 (2.4)	118 (2.4)	0.00
No. of outpatient visits, mean (SD)	33.1 (23.3)	32.9 (27.6)	0.01
Type of cancer			
Very high risk	431 (8.7)	420 (8.4)	0.01

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Table II. (*Continued*)

Characteristic	DOACs (n = 4976)	Warfarin (n = 4976)	Absolute STD
High risk	1512 (30.4)	1502 (30.2)	0.00
Treatment received for cancer			
Chemotherapy	4907 (98.6)	4907 (98.6)	0.00
Radiotherapy	903 (18.1)	911 (18.3)	0.00
Surgery	1485 (29.8)	1469 (29.5)	0.01

ACEIs = angiotensin-converting enzyme inhibitors; CKD = chronic kidney disease; COX = cyclooxygenase; DOACs = direct-acting oral anticoagulants; PPIs = proton pump inhibitors; NSAIDs = nonsteroidal anti-inflammatory drugs; SSRIs = selective serotonin reuptake inhibitors; STD = standardized difference.
* Data are presented as number (percentage) of patients unless otherwise indicated.

Comprehensive Cancer Network to include DOACs in their most recent updated version of treatment guidelines as a second-line treatment option behind LMWH for the prevention of VTE.[28] Although the recommendations encourage the use of edoxaban in combination with LMWH (Level of

Table III. Risk of recurrent venous thromboembolism and major bleeding with DOACs compared with warfarin in propensity score–matched analyses.

Medications	No. of Patients	No. of Pearson-years	No. of Events	Crude Incidence per 100 Person-years	HR (95% CI)
Recurrent VTE					
DOACs	4976	1954	56	3	0.59 (0.42–0.82)
Warfarin	4976	1957	96	5	Reference
Secondary analysis					
Apixaban	975	332	5	2	0.32 (0.12–0.88)
Warfarin	975	392	16	4	Reference
Rivaroxaban	4204	1674	55	3	0.68 (0.49, 0.97)
Warfarin	4204	1609	80	5	Reference
Major bleeding					
DOACs	4976	1963	43	2	0.64 (0.44–0.94)
Warfarin	4976	1961	68	3	Reference
Secondary analysis					
Apixaban	975	352	5	1	0.48 (0.17–1.39)
Warfarin	975	303	11	4	Reference
Rivaroxaban	4204	1687	37	2	0.65 (0.43, 0.98)
Warfarin	4204	1612	56	3	Reference

DOACs = direct-acting oral anticoagulants; HR = hazard ratio; VTE = venous thromboembolism.

Table IV. Risk of recurrent VTE and major bleeding events with DOACs versus warfarin in propensity score–matched subgroup analyses.

Medications	No. of Patients	No. of Person-years	No. of Events	Crude Incidence per 100 Person-years	HR (95% CI)	*P* for Interaction
Recurrent VTE						
Age <65 y						
DOACs	2785	1056	45	4	0.67 (0.56–0.97)	0.39
Warfarin	2785	1023	67	7	Reference	
Age ≥65 y						
DOACs	2134	886	13	1	0.54 (0.28–1.07)	
Warfarin	2134	895	24	3	Reference	
Very high risk for VTE						
DOACs	371	121	3	2	0.33 (0.07–1.21)	0.32
Warfarin	371	100	9	9	Reference	
High risk for VTE						
DOACs	1410	549	16	3	0.47 (0.26–0.86)	
Warfarin	1410	514	33	6	Reference	
Low risk for VTE						
DOACs	3073	1248	32	6	0.79 (0.50–1.26)	
Warfarin	3073	1274	41	6	Reference	
Major Bleeding						
Age <65 y						
DOACs	2785	1065	29	3	0.89 (0.54–1.48)	0.98
Warfarin	2785	1030	32	3	Reference	
Age ≥65 y						
DOACs	2134	888	15	2	0.59 (0.31–1.11)	
Warfarin	2134	898	26	3	Reference	
GI cancer						
DOACs	919	368	12	3	0.73 (0.34–1.56)	0.79
Warfarin	919	322	15	3	Reference	
Non-GI cancer						
DOACs	4004	1578	32	32	0.67 (0.42–1.02)	
Warfarin	4004	1600	50	50	Reference	

DOACs = direct acting oral anticoagulants; GI = gastrointestinal; HR = hazard ratio; VTE = venous thromboembolism.

Recommendation: A), the use of other DOACs, such as apixaban and rivaroxaban, is recommended when patients refuse or have contraindications for LMWH.[28]

Our findings are important because thrombotic events are the second leading cause of mortality in patients with cancer.[29] Because of the high cost of LMWH, its inconvenient route of administration, and a lower risk of cancer reported with warfarin in recent evidence, warfarin remains the most widely used anticoagulant among patients with cancer.[30] For instance, results from a recent analysis reported that 47.7% of patients with cancer initiated treatment with warfarin compared with 25% with LMWH and 24.1% with rivaroxaban.[7] Given their rapid onset of action, short half-life, and convenient route of administration, our data support that DOACs can be an effective and tolerable alternative to warfarin for the secondary prevention of VTE in patients with active cancer who are unwilling or unable to use LMWH, in those >65 years of age, and in cancer types that are considered very high or high risk for VTE.

There are several limitations of the current analysis. First, although the study adjusted for several measured confounders, information on laboratory measures (eg, international normalized ratio), disease risk factors (eg, immobility), and over-the-counter medications (eg, aspirin) were not available in the current data. Second, there is the potential of coding error when specifying ICD codes in administrative databases. As a result, it is possible that VTE recurrence events identified using discharge diagnosis code might be originated from previous VTE events (rather than new recurrence), which would have resulted in an overestimation of the risk of recurrent VTE. Thus, we used an outcome definition based on primary hospital discharge diagnosis only, which has been validated in previous studies. In addition, any misclassification is likely nondifferential between the DOAC and warfarin groups.

Third, although we used the PSM to mimic randomization, the potential for selection bias remains, for example, if a physicians' choice to prescribe DOACs versus warfarin was predicated on their perception of a patient's baseline disease risk. However, we expect this to have a minimal effect on the observed estimates because most of the baseline covariates, including a number of well-known risk factors for recurrent VTE and bleeding, were comparable between the treatment groups even before PSM. Fourth, although the risk of VTE may vary between primary and secondary cancer, we were not able to differentiate between the treatment groups because of the nature of the database used in this study. Fifth, the current data are representative of the patients with VTE who have active cancer and are covered by commercial or Medicare supplemental insurance. The study results are applicable for secondary prevention of VTE (ie, recurrent VTE) rather than primary prevention in patients with cancer.

Despite these limitations, the present study has several strengths. First, we only included treatment-naive patients and used a robust adjustment method to minimize differences in baseline covariates. Second, we had a large sample of patients with cancer and VTE, which allowed for the assessment of the risks and benefits of the individual DOACs (eg, apixaban and rivaroxaban).

CONCLUSION

On the basis of our findings, DOACs offer superior effectiveness for the prevention of recurrent VTE and have a lower risk of bleeding when compared with warfarin among patients with VTE and active cancer.

DISCLOSURES

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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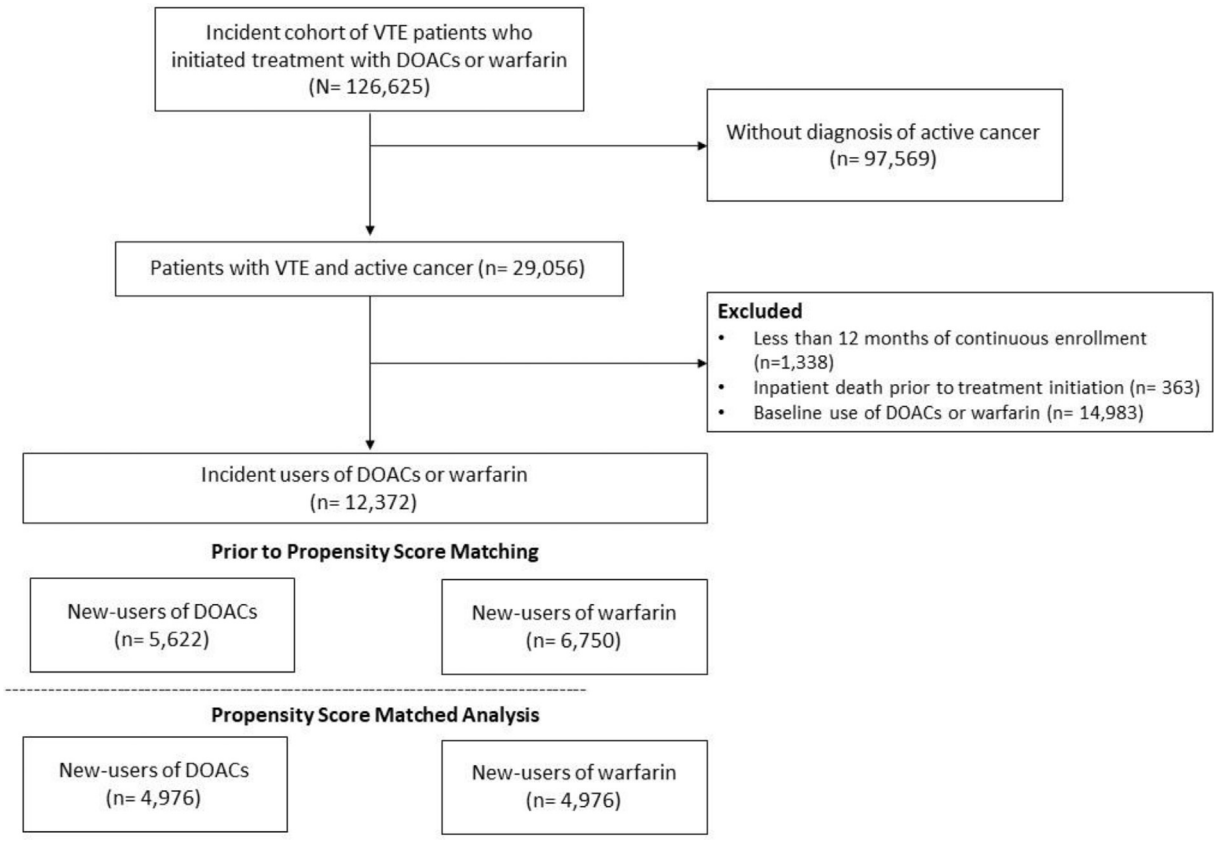
APPENDIX



Supplemental Figure S1. Flow diagram of the study population.

Supplemental Table S1. Distribution of each cancer type based on venous thromboembolism risk among new-users of direct-acting oral anticoagulants and warfarin in patients with venous thromboembolism and cancer.

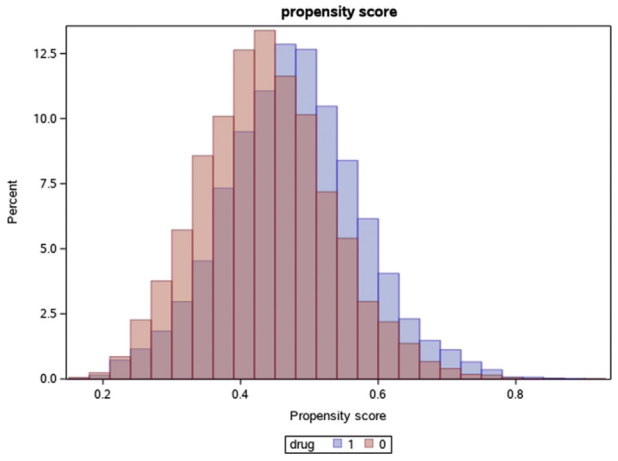
Patient characteristics before PS matching	DOACs	n= 5,622	Warfarin	n= 6,750	Absolute STD
Very high risk*					
Stomach	93	1.7	164	2.4	0.04
Pancreas	201	3.6	233	3.5	0.00
Brain	173	3.1	260	3.9	0.04
High risk*					
Lung	738	13.1	938	13.9	0.02

(*continued on next page*)

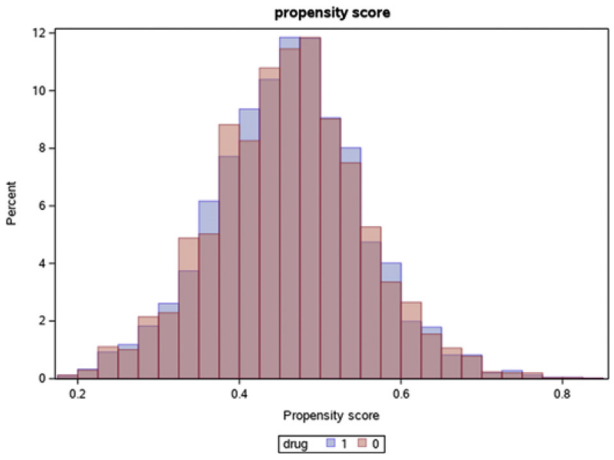
Supplemental Table S1. (*Continued*)

Patient characteristics before PS matching	DOACs	n= 5,622	Warfarin	n= 6,750	Absolute STD
Lymphoma	397	7.1	482	7.1	0.00
Gynecologic	247	4.4	289	4.3	0.00
Bladder	198	3.5	337	5.0	0.08
Testicular	37	0.7	36	0.5	0.02
Renal	166	3.0	334	5.0	0.18
Other types of cancer					
Thyroid	83	1.5	84	1.2	0.02
Prostate	582	10.4	836	12.4	0.07
Oral	126	2.2	161	2.4	0.01
Leukemia	119	2.1	127	1.9	0.02
Larynx	33	0.6	39	0.6	0.00
Kidney	166	3.0	334	4.9	0.12
Esophagus	81	1.4	134	2.0	0.05
Colon	504	9.0	732	10.8	0.07
Breast	890	15.8	977	14.5	0.04
Bone	81	1.4	112	1.7	0.02

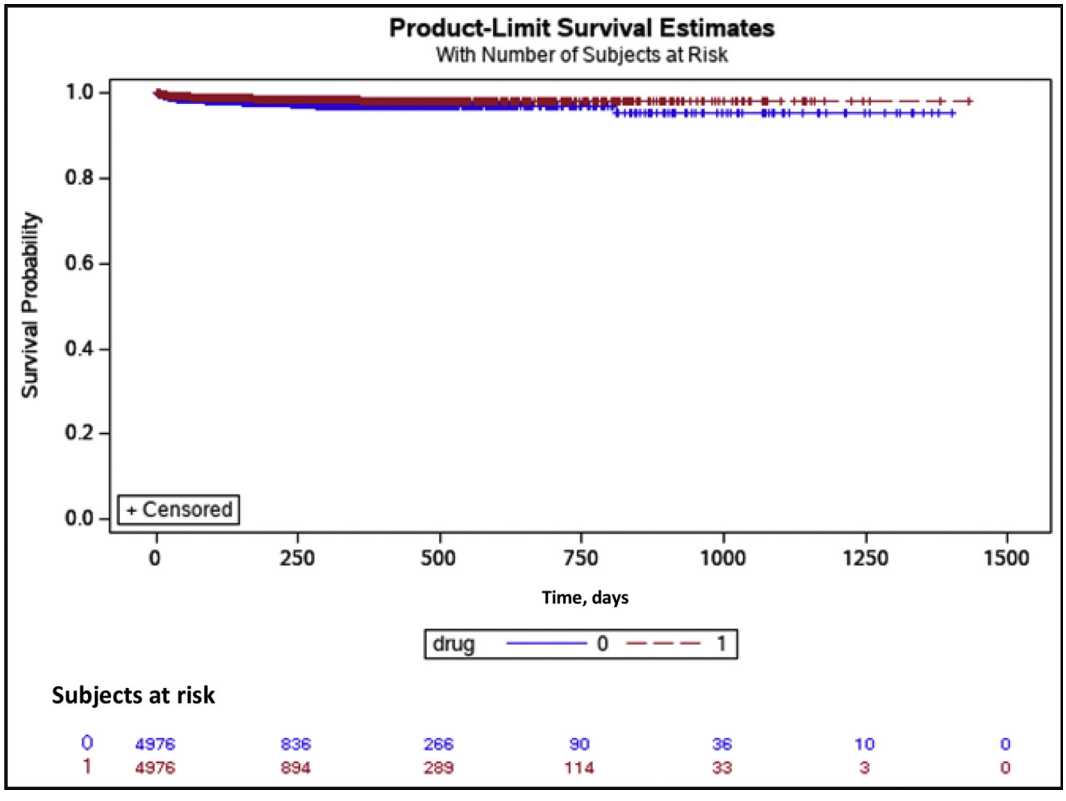
Direct-acting oral anticoagulants, DOACs, propensity score, PS, standardized difference, STD
* Cancer was classified based on the risk of developing venous thromboembolism into very-high risk, high-risk, and others based on prior published research.



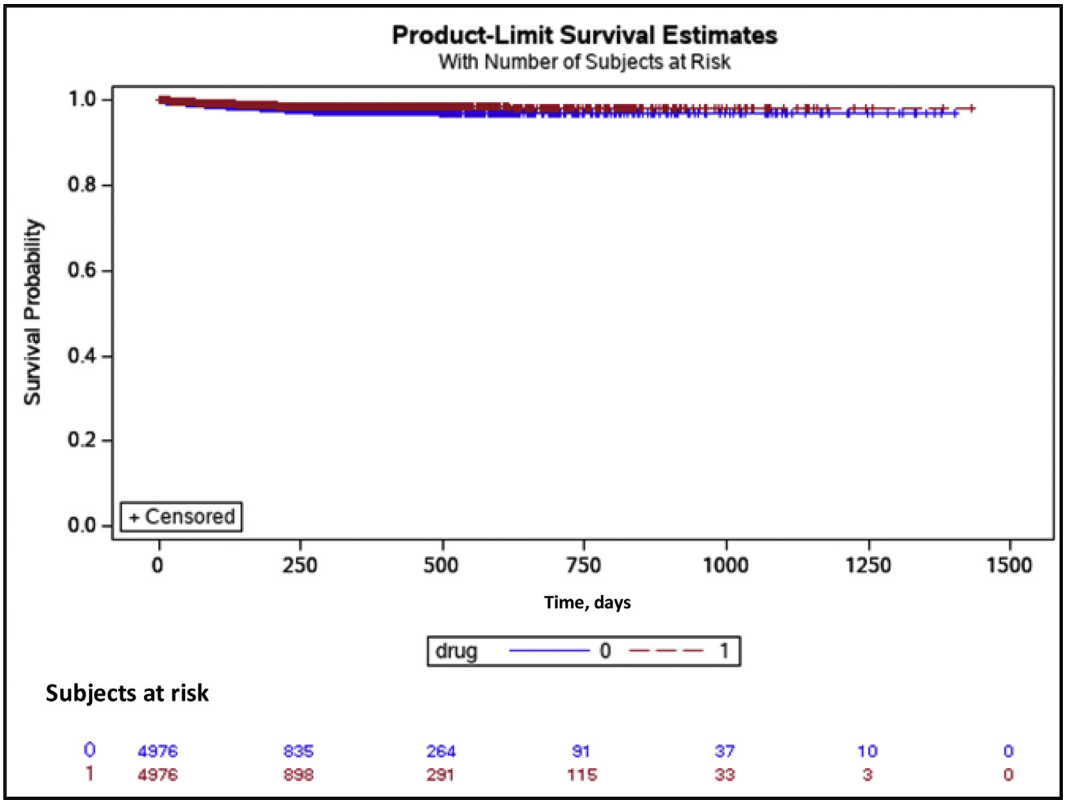
Supplemental Figure S2. Distribution of propensity score prior to matching. *Group 1 refers to new-users of direct-acting oral anticoagulants, group 0 refers to new-users of warfarin.



Supplemental Figure S3. Distribution of propensity score after matching. *Group 1 refers to new-users of direct-acting oral anticoagulants, group 0 refers to new-users of warfarin.



Supplemental Figure S4. Kaplan Meier survival curve comparing the risk of recurrent venous thromboembolism between direct-acting oral anticoagulants and warfarin among patients with venous thromboembolism and active cancer. *Group 1 refers to new-users of direct-acting oral anticoagulants, group 0 refers to new-users of warfarin.



Supplemental Figure S5. Kaplan Meier survival curve comparing the risk of major bleeding events between direct-acting oral anticoagulants and warfarin among patients with venous thromboembolism and active cancer. *Group 1 refers to new-users of direct-acting oral anticoagulants, group 0 refers to new-users of warfarin.