Prevalence and Factors Associated With the Use of Direct Oral Anticoagulants (DOACs) and Low-Molecular-Weight Heparins (LMWHs) in Patients With Cancer

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BACKGROUND

- Venous thromboembolism (VTE) is a fatal comorbidity prevalent in patients with cancer[1-3]
- LMWHs have been the preferred treatment for cancer-associated thrombosis (CAT)[4]
- DOACs are a relatively newer drug class used for treating CAT[5]
- Treatment guidelines provide inconsistent recommendations for the treatment of CAT (Table 1)

Table 1. Summary of Treatment Guidelines for CAT[6-8]

Guidelines	Recommendations
American Society of Clinical Oncology (ASCO) 2020	Initial anticoagulation: LMWH, UFH, fondaparinux or rivaroxaban Long-term (up to 6 months): LMWH, edoxaban, or rivaroxaban. VKA can be used if accessibility is an issue for the others. Increased bleeding risk with DOACs, particularly in gastrointestinal and potentially genitourinary malignancies.
International Society of Thrombosis and Hemostasis (ISTH) 2018[7]	Acute VTE: edoxaban/rivaroxaban if low bleeding risk and no drug-drug interactions; LMWH for patients with drug-drug interactions and bleeding risk.
National Comprehensive Cancer Network (NCCN) 2022[8]	Category 1: apixaban, edoxaban, dalteparin Category 2A: rivaroxaban, dabigatran, enoxaparin LMWH preferred for patients with gastric or gastroesophageal lesions. Apixaban may be safer than edoxaban or rivaroxaban for patients with gastric or gastric esophageal lesions (Category 2B).
International Initiative on Thrombosis and Cancer (ITAC) 2022	LMWH is recommended over UFH for initial treatment unless CrCl < 30 mL/min; rivaroxaban/edoxaban can be used for initial treatment if CrCl ≥ 30 mL/min. LMWH or DOAC should be continued for at least 6 months.
American Society of Hematology (ASH) 2021	DOAC (apixaban or rivaroxaban) or LMWH can be used for initial treatment (first week) of VTE. For short-term treatment, DOAC (apixaban, edoxaban, or rivaroxaban) is preferred over LMWH or VKA.

CrCl = creatinine clearance; UFH = unfractionated heparin; VKA = vitamin K antagonist.

OBJECTIVE

- To study the prevalence and factors associated with the use of DOACs versus LMWHs in CAT

METHODS

Study Design

- This was a retrospective cohort study (Figure 1)
- Patients with a primary cancer of lung, breast, pancreatic, colorectal, prostate or stomach cancer diagnosis were identified from the SEER-Medicare linked database cancer file from 1 January 2011 through the end of Medicare claims on 30 June 2019 to ensure adequate data to identify VTE and drug exposure (Table 2)

Study Measures and Data Analyses

- Bivariate tests were carried out to assess the unadjusted association of choice of anticoagulant and the baseline covariates
- Multivariable logistic regression model was conducted with an indicator variable for the receipt of anticoagulant as the dependent variable to assess the factors associated with the use of DOAC versus LMWH in these patients with cancer

Figure 1. Study Design

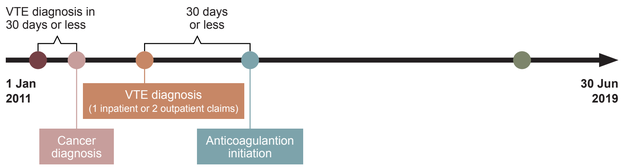


Table 2. Patient Selection Criteria

Inclusion criteria	Exclusion criteria
Diagnosis of cancer (lung, pancreatic, stomach, prostate, breast, colorectal)	Patients on LMWH therapy for fewer than 10 days (no misclassification, excluding bridging therapy)
Diagnosis of VTE after the cancer diagnosis or fewer than 30 days before the cancer diagnosis	Patients on both DOAC and LMWH in the 30 days after incident VTE diagnosis
Enrolled in Medicare Part A and B & D at least 12 months before index VTE diagnosis	
Patients on either DOAC or LMWH in first 30 days	

RESULTS

- A total of 9,972 patients were identified with an eligible prescription of DOAC or LMWH after meeting the inclusion and exclusion criteria; 4,892 and 5,080 patients initiated LMWH and DOAC therapy, respectively, within the first 30 days after incident VTE diagnosis (Table 3)
- Sociodemographic characteristics including age (odds ratio [OR], 1.02; 95% confidence interval [CI], 1.01-1.03) and being a female (OR, 1.15; 95% CI, 1.03-1.29) were found to be significant predictors for the use of DOACs
- As the cancer advanced from early to advanced stages, use of DOACs declined significantly (OR, 0.69; 95% CI, 0.53-0.90 and OR, 0.54; 95% CI, 0.41-0.70 for regional and distant stages, respectively)
- Prevalence of surgery 30 days before VTE diagnosis reduced the odds of being on DOAC compared with being on LMWH (OR, 0.74; 95% CI, 0.66-0.83)
- Year of VTE diagnosis was the strongest predictor of DOAC; patients were significantly more likely to be on DOAC than LMWH in 2019 versus 2011 (OR, 106.39; 95% CI, 42.19-268.28), ORs for other years can be found in Table 4

Table 4. Table 2: Factors Associated With the Use of DOACs Versus LMWH

Predictors of DOAC vs. LMWH use	Adjusted OR (95%CI)	*P* value
Age of VTE diagnosis	1.02(1.01-1.03)	< 0.0001
Race		
Black vs. White	0.89 (0.76-1.04)	0.17
Other vs. White	0.80 (0.63-1.02)	0.07
Sex		
Female vs. male	1.15(1.03-1.29)	0.01
Stage[a]		
Localized vs. in situ	0.94 (0.72-1.23)	0.66
Regional vs. in situ	0.69 (0.53-0.90)	0.01
Distant vs. in situ	0.54 (0.41-0.70)	< 0.0001
Cancer type		
Pancreatic vs. lung	0.78 (0.66-0.91)	0.001
Breast vs. lung	1.93 (1.65-2.25)	< 0.0001
Colorectal vs. lung	1.50 (1.18-1.90)	< 0.0001
Prostate vs. lung	2.11 (1.77-2.51)	< 0.0001
Stomach vs. lung	0.83 (0.64-1.07)	0.14
Cancer therapy (yes vs. no)	0.74 (0.67-0.81)	< 0.0001
Surgery (yes vs. no)[b]	0.74(0.67-0.83)	< 0.0001
Time from cancer diagnosis to index VTE (years)		
1 to < 2 vs. 1	1.12(0.97-1.28)	0.11
2 to < 3 vs. 1	1.37 (1.17-1.60)	< 0.0001
> 3 vs. 1	1.29 (1.12-1.48)	< 0.0001
Type of VTE		
Both DVT and PE vs. only DVT	0.81 (0.73-0.91)	< 0.0001
Only PE vs. only DVT	0.75 (0.66-0.84)	< 0.0001
Year of VTE diagnosis		
2012 vs. 2011	1.94 (0.72-5.24)	0.19
2013 vs. 2011	15.60 (6.30-38.62)	< 0.0001
2014 vs. 2011	25.44 (10.35-62.51)	< 0.0001
2015 vs. 2011	31.12 (12.68-76.35)	< 0.0001
2016 vs. 2011	43.78 (17.86-107.33)	< 0.0001
2017 vs. 2011	48.82 (19.91-119.68)	< 0.0001
2018 vs. 2011	77.48 (31.42-191.04)	< 0.0001
2019 vs. 2011	106.39 (42.15-268.28)	< 0.0001
Antiplatelet drug use	1.20 (0.89-1.60)	0.22
Previous bleed	0.88 (0.69-1.08)	0.21
Comorbidities[c]		
Thrombocytopenia (yes vs. no)	0.97 (0.80-1.15)	0.70
Renal disease (yes vs. no)	1.12 (0.99-1.26)	0.05
CHF (yes vs. no)	1.16 (1.03-1.31)	0.01
COPD (yes vs. no)	1.12 (1.02-1.24)	0.02
Dementia (yes vs. no)	1.39 (1.12-1.72)	0.002
Liver disease, mild (yes vs. no)	0.79 (0.71-0.88)	< 0.0001
Ulcers (yes vs. no)	0.80 (0.65-0.98)	0.03
Atrial fibrillation (yes vs. no)	0.72 (0.62-0.83)	< 0.0001

CHF = congestive heart failure; PVD = peripheral vascular disease.
[a] Indicates that some values were missing.
[b] Calculated in the 30 days before the index VTE.
[c] Only statistically significant variables included.

Table 3. Patient Characteristics

Characteristics	Total (n = 9,972)	LMWH (n = 4,892)	DOAC (n = 5,080)	*P* value
Median age at index VTE diagnosis (CAT)	74 (6.5)	73 (6.2)	74 (6.8)	< 0.0001
Sex				
Female	5,550 (55.56)	2,671 (54.60)	2,879 (56.69)	0.038
Anticoagulant				
LMWH				
Enoxaparin	4,849 (48.62)	4,843 (98.99)	–	–
Dalteparin	49 (0.49)	49 (1.001)	–	–
DOAC				
Rivaroxaban	3,012 (30.20)	–	3012(59.29)	–
Apixaban	1,948 (19.53)	–	1,948 (38.34)	–
Dabigatran	120 (1.20)	–	120 (2.36)	–
Cancer stage at diagnosis[a]				
In situ	369 (3.70)	113 (2.86)	256 (6.18)	< 0.0001
Localized	2,652 (26.59)	848 (21.45)	1,804 (43.54)	
Regional	2,001 (20.06)	1,026 (25.95)	975 (23.53)	
Distant	2,816 (28.23)	1,858 (47)	958 (23.12)	
Not applicable/unstaged	258 (2.58)	108 (2.73)	150 (3.62)	
Primary cancer type				
Lung	3,236 (32.45)	1,937 (39.60)	1,299 (25.57)	< 0.0001
Pancreas	1,412 (14.15)	980 (20.03)	432 (8.50)	
Breast	1,918 (19.23)	567 (11.59)	1,351 (26.59)	
Colorectal	1,575 (15.79)	755 (15.43)	820 (16.14)	
Prostate	1,445 (14.49)	402 (8.22)	1,043 (20.53)	
Stomach	386 (3.87)	251 (5.13)	135 (2.66)	
Year of VTE diagnosis				
2011-2013	1,465 (14.69)	1,238 (25.30)	227 (4.46)	< 0.0001
2014-2016	4,477 (44.89)	2,334 (47.71)	2,143 (42.18)	
2017-2019	4,030 (40.41)	1,320 (26.98)	2,710 (53.34)	
Thrombocytopenia	780 (7.82)	342 (6.99)	438 (8.62)	< 0.0001
Active cancer therapy	5,637 (56.52)	2,958 (60.46)	2,679 (52.73)	< 0.0001
Prior surgery[b]	2,425 (24.31)	1,346 (27.51)	1,079 (21.24)	< 0.0001
Type of VTE				
Both DVT and PE	2,053 (20.58)	1,080 (22.07)	973 (19.15)	0.01
Only DVT	5,393 (54.08)	2,541 (51.94)	2,852 (56.14)	
Only PE	2,526 (25.33)	1,271 (25.98)	1,255 (24.70)	
Duration, anticoagulation after discontinuation (days)	181.75	107.88	251.71	< 0.0001
Select Charlson comorbidities[c]				
Acute MI	560 (5.61)	252 (5.15)	308 (6.06)	0.048
Congestive heart failure	2,090 (20.95)	935 (19.11)	1,155 (22.74)	< 0.0001
COPD	4,398 (44.10)	2,214 (45.26)	2,184 (42.99)	0.022
Peripheral vascular disease	2,918 (29.26)	1,372 (28.05)	1,546 (30.43)	0.008
Cerebrovascular disease	2,170 (21.76)	1,110 (22.69)	1,060 (20.87)	0.027
Dementia	577 (5.78)	187 (3.82)	390 (7.68)	< 0.0001
Paralysis	253 (2.53)	140 (2.86)	113 (2.22)	0.043
Diabetes	3,551 (35.60)	1,814 (37.08)	1,737 (34.19)	0.002
Diabetes with complications	1,332 (13.35)	616 (12.59)	716 (14.09)	0.027
Renal disease	1,956 (19.61)	846 (17.29)	1,110 (21.85)	< 0.0001
Liver disease (mild)	2,533 (25.40)	1,500 (30.66)	1,033 (20.33)	< 0.0001
Liver disease (moderate-severe)	142 (1.42)	86 (1.76)	56 (1.10)	0.005
Peptic ulcer disease	550 (5.51)	338 (6.91)	212 (4.17)	< 0.0001
Atrial fibrillation	1,223 (12.26)	670 (13.70)	553 (10.89)	< 0.0001

COPD = chronic obstructive pulmonary disease; DVT = deep vein thrombosis; MI = myocardial infarction; PE = pulmonary embolism.
[a] Indicates that some values were missing. [b] Calculated in the 30 days before index VTE. [c] Only statistically significant variables included.

Figure 2. Type of Venous Thromboembolism

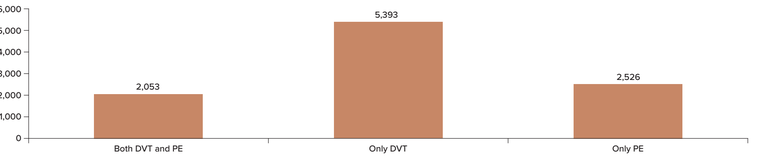


Figure 3. Low-Molecular-Weight Heparins

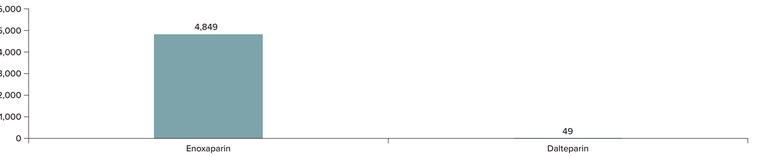
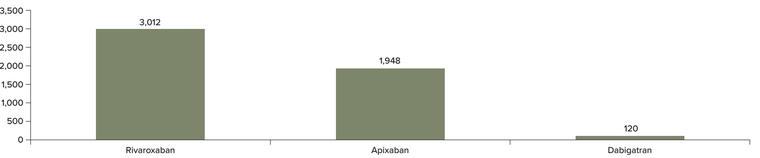


Figure 4. Direct Oral Anticoagulants



LIMITATIONS

- The use of retrospective databases to capture diagnostic information in the form of International Classification of Diseases (ICD-9 and ICD-10-CM) codes could cause overdiagnosis or underdiagnosis depending on the validity of the coding schema. To reduce the impact of this limitation, we used a validated coding scheme with an acceptable positive predictive value.
- Our study results are limited the population aged ≥ 65 years and cannot be generalized to other populations.
- Another limitation inherent of claims data is the inability to capture clinical parameters.
- It is also possible that the number of recurrent VTE events was underestimated due to undercoding of VTE events. To reduce this bias, the inclusion of thrombotic events was limited to the presence of at least one of the validated sets of VTE-associated billing codes restricted to the primary position.

CONCLUSIONS

- Our results highlight certain factors that might drive selection of DOAC versus LMWH.
- Both are reliable options for the treatment of CAT.
- Current guidelines recommend the use of DOACs in carefully selected patients.
- Further real-world evidence studies need to be carried out using newer data to understand the factors that might drive selection in these patients and their subsequent effect on clinical outcomes.

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Presented at: ISPOR 2023; 7-10 May 2023; Boston, Massachusetts, United States