Comparative Effectiveness of Direct Oral Anticoagulants Versus Low-Molecular-Weight Heparins in Patients With Cancer

Yande S,[1,2] Toale KM,[3] Wanat MA,[1] Aparasu RR,[1] Abughosh S,[1] Johnson ML[1]

[1]University of Houston College of Pharmacy, Houston, TX, United States; [2]RTI Health Solutions, Research Triangle Park, NC, United States;
[3]University of Texas, MD Anderson Cancer Center, Houston, TX, United States

BACKGROUND

- Venous thromboembolism (VTE) is a fatal comorbidity prevalent in patients with cancer.[1,2] Low-molecular-weight heparins (LMWHs) have been the preferred treatment for cancer-associated thrombosis (CAT)[3]
- Direct oral anticoagulants (DOACs) are a relatively newer drug class used for treating CAT[4]
- Treatment guidelines provide inconsistent recommendations for the treatment of CAT, and there are limited real-world data on the safety and effectiveness of DOACs in patients with cancer[5,6]

OBJECTIVE

- To conduct a comparative effectiveness of DOACs versus LMWHs in patients with cancer

METHODS

Study Design

- This was a retrospective cohort study (Figure 1)
- Patients with a diagnosis of primary lung, breast, pancreatic, colorectal, prostate or stomach cancer 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 1)
- An intention-to-treat approach was employed in which patients were categorized into either of the anticoagulant groups depending on the first anticoagulant a patient was started on after CAT diagnosis
- Patients were followed for 12 months and time to recurrent VTE and bleeding events between these 2 cohorts were compared

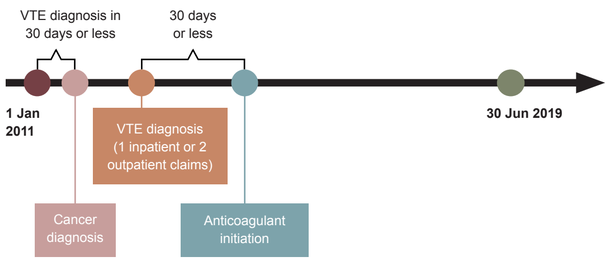
Study Measures and Data Analyses

- The primary effectiveness endpoint was recurrent VTE, and the safety outcome was major bleeding identified using the Cunningham algorithm[7]
- DOACs were compared with LMWHs as a group; inverse probability of treatment weights based on propensity scores was employed to compare the recurrence of VTE and major bleeding events among the 2 cohorts; stabilized weighting was used to balance the cohorts
- The observation period for the analysis spanned from the start of anticoagulant therapy until the end of 12 months or until the earliest event of interest, death, or end of data availability for the patient
- A sensitivity analysis was conducted where patients were censored at treatment switch or discontinuation (defined as gap of 60 days or more between end of days' supply of a previous fill and start of the next fill)
- A stratified analyses was also conducted by cancer to assess the effectiveness of these anticoagulation strategies in individual cancer types

Table 1. Patient Selection Criteria

Inclusion criteria	Exclusion criteria
Diagnosis lung, pancreatic, stomach, prostate, breast, or colorectal cancer	Received 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	Received both DOAC and LMWH in the 30 days after incident VTE diagnosis
Enrolled in Medicare Parts A, B and D at least 12 months before index VTE diagnosis	
Received either DOAC or LMWH in first 30 days after VTE diagnosis	

Figure 1. Study Design



RESULTS

- 9,972 patients with an eligible prescription of DOAC or LMWH met 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 2)
- 385 recurrent VTE events were identified from the 6 different cancers, and the maximum number of recurrent VTE cases occurred in the lung cancer cohort (n = 135)
- The intention-to-treat analyses found that the rate of recurrent VTE was significantly lower in the DOAC cohort (adjusted hazard ratio [adjHR] = 0.71; 95% CI, 0.56-0.88; $P \leq 0.0002$) compared with the LMWH cohort
- In the stratified analysis by cancer type, a significant reduction in hazard of VTE was found in patients with lung cancer (adjHR = 0.57; 95% CI, 0.38-0.86; $P \leq 0.0001$)
- 809 major bleeding events were identified across the 6 cancer types; major bleeding was more prevalent in patients with lung cancer
- In the intention-to-treat analyses, DOACs were associated with similar bleeding risk as LMWHs (adjHR = 0.86; 95% CI, 0.74-1.00; $P = 0.06$)
- In the stratified intention-to-treat analysis, a significant reduction in the risk of major bleeding was found only in patients with prostate (adjHR = 0.59; 95% CI, 0.38-0.93; $P = 0.02$) and pancreatic (adjHR = 0.61; 95% CI, 0.41-0.90; $P = 0.01$) cancers

Table 3. DOACs vs. LMWHs: Pooled Hazard Ratio Estimates for VTE Recurrence (All Cancers)

Approach	HR Estimate (95% CI)	*P* Value
Intention-to-treat analysis (12-month follow-up)	0.71 (0.56-0.88)	0.002
Censoring at treatment switch/discontinuation	0.71 (0.55-0.93)	0.01

Figure 2. Number of Events

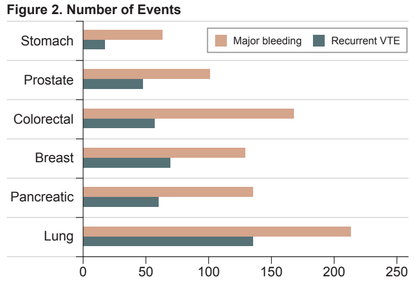


Table 4. DOACs vs. LMWH: Hazard Ratio Estimates for VTE Recurrence and Major Bleeding by Cancer Type (Intention-to-Treat Analysis)

Cancer Type	Point Estimate (95% CI) for VTE Recurrence	Point Estimate (95% CI) for Major Bleeding
Lung	0.57 (0.32-0.68)	0.97 (0.72-1.29)
Breast	0.89 (0.56-1.45)	1.14 (0.79-1.64)
Pancreatic	0.75 (0.46-1.30)	0.61 (0.41-0.90)
Colorectal	0.78 (0.45-1.27)	1.05 (0.73-1.50)
Prostate	0.57 (0.31-1.04)	0.59 (0.38-0.93)
Stomach	2.22 (0.67-7.29)	0.63 (0.36-1.11)

Table 5. DOACs vs. LMWH: Hazard Ratio Estimates for Major Bleeding (All Cancers)

Approach	HR Estimate (95% CI)	*P* Value
Intention-to-treat Analysis (12-month follow-up)	0.86 (0.74-1.00)	0.06
Censoring at treatment switch/discontinuation	0.89 (0.74-1.09)	0.27

Table 2. 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
Race				
Black	887 (8.89)	446 (9.12)	441 (8.68)	
White	8,643 (86.67)	4,206 (85.98)	4,437 (87.34)	< 0.0001
Other	432 (4.33)	230 (4.90)	202 (3.98)	
Anticoagulant				
LMWH				
Enoxaparin	4,849 (48.62)	4,843 (98.99)	–	–
Dalteparin	49 (0.49)	49 (1.001)	–	–
DOAC				
Rivaroxaban	3,012 (30.20)	–	3,012 (59.29)	–
Apixaban	1,948 (19.53)	–	1,948 (38.34)	–
Dabigatran	120 (1.20)	–	120 (2.36)	–
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)	
Time from cancer diagnosis to VTE (years)				
< 1	5,498 (55.13)	3,399 (69.48)	2,099 (41.32)	< 0.0001
1 to < 2	1,351 (13.54)	603 (12.33)	748 (14.72)	
2 to < 3	680 (6.81)	341 (6.97)	646 (12.72)	
> 3	2,136 (21.41)	549 (11.22)	1,587 (31.24)	
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[a]	2,425 (24.31)	1,346 (27.51)	1,079 (21.24)	< 0.0001
Antiplatelet drugs	243 (2.43)	107 (2.19)	136 (2.68)	0.112
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)	
Total duration of anticoagulation after discontinuation (mean days)	181.75	107.88	251.71	< 0.0001

[a] Calculated in the 30 days before index VTE

Figure 3. Kaplan-Meier Curves for Time (Days) to Recurrent VTE From Intention-to-Treat Analysis (12-Month Follow-up)

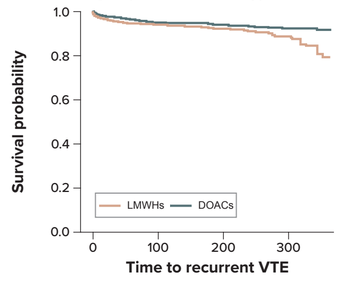


Figure 4. Kaplan-Meier Curves for Time (Days) to Recurrent VTE From Intention-to-Treat Analysis While Accounting for Discontinuation/Switching

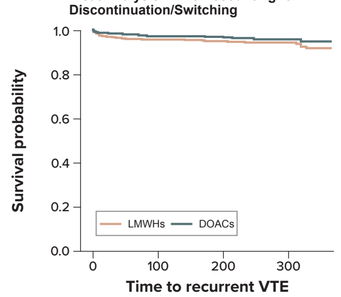


Figure 5. Kaplan-Meier Curves for Time to Major Bleeding From Intention-to-Treat Analysis (12-Month Follow-up)

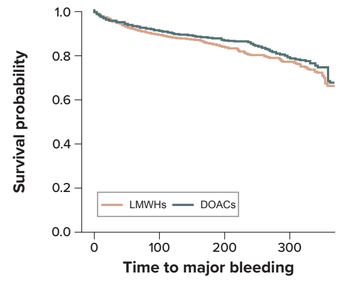
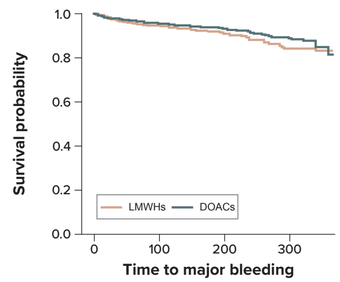


Figure 6. Kaplan-Meier Curves for Time to Major Bleeding While Accounting for Discontinuation/Switching



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
- Because of limitations in access to the SEER Medicare data, this study only included 6 cancers and thus had to exclude certain high-risk cancers such as head, neck, and brain cancer, which also have a high prevalence of VTE
- Sample size for some of the cancers, including lung and breast cancer, were high compared with stomach cancer. Thus some of the results in the stratified intention-to-treat analyses may be partially driven by the sample size of individual cancers and not may not have an actual causal link

CONCLUSIONS

- The overall results support the use of DOACs in patients with cancer and add to the existing pool of evidence regarding the safety and efficacy of these drugs
- This study found that DOACs are a safe and effective alternative for the treatment of CAT
- Current guidelines may be expanded to incorporate the use of DOACs in cancer populations

SELECTED REFERENCES

1. Farge D, et al. Lancet Oncol 2019; 20: e566-81.
2. Fernandes CJ, et al. Eur Respir Rev. 2019;28:180119.
3. O'Connell C, et al. Oncologist. 2021;26:e8-16.
4. Wumaier K, et al. Thromb J. 2021 Sep 29;19(1):68. doi: 10.1186/s12959-021-00319-1.
5. Key NS, et al. J Clin Oncol. 2020;38:496-520.
6. Khorana AA, et al. J Thromb Haemost. 2018;16:1891-4.
7. Cunningham A, et al. Pharmacoepidemiol Drug Saf 2011; 20: 560-6.

CONTACT INFORMATION

Soham Yande
Senior Health Outcomes Scientist, Health Economics

RTI Health Solutions
Research Triangle Park, NC,
United States

Email: syande@rti.org

Presented at: ISPOR 2024; 5-8 May 2024; Atlanta, GA, United States