


# Retrospective Review of Prescribing Patterns in Cancer-Associated Thrombosis: A Single Center Experience in Edmonton, Alberta, Canada

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## Abstract

Low molecular weight heparin (LMWH) is the standard of care for treating cancer-associated thrombosis (CAT), although new evidence for direct oral anticoagulants (DOACs) supports use in specific cancer populations. In this retrospective review at a specialty CAT clinic from 2016 to 2019, we report the use of anticoagulants (LMWH, DOACs, warfarin, anticoagulant class change) in the acute and chronic phases of CAT and compare use before/after publication of the Hokusai-VTE Cancer trial. Death, venous thromboembolism (VTE) recurrence and bleeding was also reported. Of the 221 included, median age was 69 years, with 57.5% having metastatic disease. In the acute phase, 80.1% were prescribed LMWH, 4.1% DOAC, and 14.5% had an anticoagulant class change (LMWH to DOAC; 78.1%). In the chronic phase, 35.8% were prescribed LMWH, 11.3% DOAC, and 42.9% had an anticoagulant class change (LMWH to DOAC; 90.1%). Use of DOACs in the acute and chronic phase prior to the Hokusai-VTE trial was 1.0% and 2.0%, respectively, and following publication was 6.8% and 19.6%. Death occurred for 22.6% patients, recurrent VTE in 7.2%, and bleeding in 5.0%. DOAC use is increasing with time; real-world data may help to guide optimization of the care of complex patients.

## Keywords

anticoagulants, Canada, cancer-associated thrombosis, heparins, practice guideline, venous thromboembolism

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## Introduction

Venous thromboembolism (VTE) is comprised of deep vein thrombosis (DVT) and pulmonary embolism (PE) and the baseline risk is 1 in 1000 per year in the general adult population.<sup>1</sup> Cancer increases this risk by 4 fold, and those having chemotherapy have an increased risk of 6.5 fold. After cancer progression, VTE is the second leading cause of death among patients with cancer.<sup>1-8</sup> Anticoagulation management in cancer-associated thrombosis (CAT) is complicated in that cancer patients have both an increased risk of thrombosis and bleeding relative to patients experiencing VTE without cancer.<sup>4-7,9</sup> Guidelines as recent as 2016 recommend low molecular weight heparin (LMWH) as the standard of care for the treatment and prevention of CAT.<sup>10-12</sup> This is based on clinical trials comparing LMWH to warfarin which collectively

showed that LMWH is both more effective and safer than warfarin in this challenging population.

New evidence for direct oral anticoagulants (DOACs) compared to dalteparin in the CAT population emerged in February 2018 in the Hokusai-VTE Cancer trial (edoxaban), which was followed by select-d (rivaroxaban), and CARAVAGGIO

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(apixaban).<sup>13-15</sup> Hokusai-VTE Cancer was a randomized trial (n = 1050) that demonstrated edoxaban was non-inferior to dalteparin in the acute phase treatment of CAT in the studied population, but also had a statistically significant increased risk of major bleeding particularly in patients with gastrointestinal (GI) cancers.<sup>13</sup> Select-d was a pilot randomized trial (n = 406) that also showed likely equal efficacy of rivaroxaban and dalteparin for acute phase CAT treatment in the studied population.<sup>14</sup> There was increased GI and genitourinary (GU) bleeding with major upper GI bleeding resulting in a protocol change that excluded all patients with upper GI cancers from further enrolment about half way through the trial. CARAVAGGIO is the most recent large randomized trial and showed that apixaban was statistically non-inferior to dalteparin for acute phase treatment of CAT in the studied population.<sup>15</sup> Interestingly, this study also demonstrated similar rates of major bleeding between apixaban and dalteparin. There was an increased rate of clinically relevant non-major bleeding in the GU tract and lungs. Unfortunately, bleeding by cancer type was not shown in the reported data and so it remains unclear if there is a signal for bleeding in GI cancer patients as seen with the other 2 DOACs. Although these trials are heterogeneous in their results and applicability to patient populations, guidelines have now incorporated the use of DOACs into their recommendations, with caveats regarding risk of bleeding and drug-drug interactions.<sup>16-20</sup>

With evolving evidence and changing guidelines for the treatment of CAT, there is merit to assess the application of this data in the real world. Limited data is available on anticoagulant prescribing practices or what factors influence patient and clinician decisions in choosing a treatment regimen. As such, our study sought to determine the patterns of practice for use of anticoagulants for patients seen in the specialty CAT clinic at the University of Alberta Hospital, spanning the years prior to and after the publication of the Hokusai-VTE Cancer trial.

## Methods

### Study Design

This study was a retrospective record review of patients referred to the CAT clinic at the University of Alberta Hospital, Edmonton, Canada. Patients are referred to the clinic after experiencing a thrombotic event associated with previously known, or newly diagnosed cancer. Patients are seen by a hematologist in the clinic after their thrombosis diagnosis, and most are followed every 3 months until stable, and then every 6-12 months thereafter.

To be eligible, patients had to be Alberta residents 18 years of age or older with a diagnosis of active cancer who had an initial appointment at the CAT clinic between September 1, 2016 and August 31, 2019. Active cancer was defined as cancer diagnosed within the previous 6 months; regionally, advanced or metastatic cancer; cancer for which treatment had been administered within 6 months; or hematological cancer that was not in complete remission. Patients had to have a

confirmed acute venous thromboembolism (VTE) within 1 month prior to their initial CAT clinic appointment and at least 1 follow-up visit within the acute phase of VTE treatment (3 months  $\pm$  1 month from index CAT date) in order to capture CAT clinic practices. Eligible acute VTE events included: symptomatic or incidentally detected deep vein thrombosis (DVT) of the leg (proximal or distal); symptomatic or incidental pulmonary embolism (PE) that was confirmed by means of diagnostic imaging involving subsegmental, segmental or more proximal pulmonary arteries. Patients were excluded if they had another indication for anticoagulation therapy, a superficial venous thrombosis, an atypical thrombus in locations other than the leg or lung, a tumor thrombus, an arterial thrombus, if they died within 3 months of the index CAT or there was insufficient data/documentation available to capture the primary outcome. Ethics approval was obtained via the University of Alberta Research Ethics Board (Pro00094698).

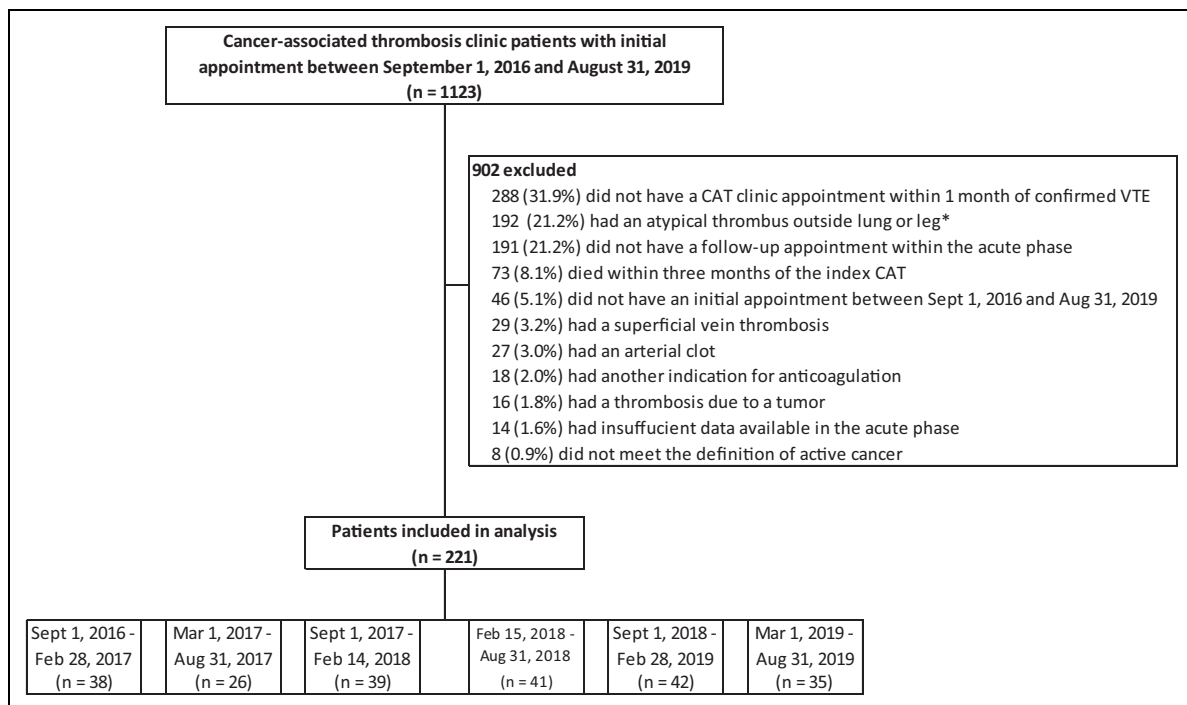
Patients were followed for a maximum of 1 year from their index CAT, or until the occurrence of a recurrent VTE, bleeding requiring a therapy change, or death. At the point of recurrent VTE or bleeding, ongoing follow up was not performed for these patients as further therapy decisions would be based on this new event, rather than the index CAT.

### Outcomes

The primary outcome was to report the proportion of different anticoagulants used for the acute phase treatment of CAT, classified as being treated with *LMWH only*, *warfarin only* (including the initial LMWH overlap), *DOAC only* (including LMWH lead in for edoxaban), or an *anticoagulant class change*. The timing and rationale for dose or agent changes were captured. Secondary outcomes included the proportion of different anticoagulants used for the chronic phase treatment (3 months to 1 year) of CAT. A comparison of anticoagulant practice patterns in the acute and chronic phases before and after February 15, 2018 (publication of the Hokusai-VTE cancer trial) was also reported. Those with an initial CAT clinic visit before February 15, 2018 were considered in the “before” group while those with an initial CAT clinic visit on or after February 15, 2018 were considered in the “after” group. All-cause death, recurrent VTE, and bleeding events requiring a therapy change were recorded within the 1 year follow-up period.

### Data Analysis

Medians ( $\pm$  interquartile ranges [IQR]) were reported for continuous data. Frequencies and proportions are reported for categorical variables. Comparing use of therapies before and after the publication of the Hokusai-VTE Cancer trial was performed using a chi-square test. Fisher’s exact test was used when the cell frequencies were smaller than 5. Mann-Whitney U-test was used to compare the median values between the 2 groups. Two proportions between the 2 groups were conducted using an independent test of proportions. A p-value  $<0.05$  was used for all statistical significance.



**Figure 1.** Patient flow.

\*Of the 192 patients with atypical thrombus outside of the lung or legs, 97 had an arm DVT, 41 portal vein thrombosis, 16 superior/inferior mesenteric vein thrombosis, 14 IVC/SVC thrombosis, 7 ovarian or gonadal vein thrombosis, 7 renal vein thrombosis, and 10 were classified as other.

Statistical analysis was performed using SPSS (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.) version 25 software.

## Results

### Baseline Characteristics

Of 1123 patients screened, 221 (19.7%) were included, with most (53.1%) being excluded due to timing of the CAT clinic visits (Figure 1). Median age was 69 years (IQR 61-75), 47.1% were male, and pulmonary embolism (PE) was most common (71.9%) (Table 1). Most common cancer types were colorectal (17.2%), lung (15.8%), breast (13.1%) and genitourinary (12.2%). The majority (57.5%) had metastatic disease and 68.3% were on active therapy for cancer during the acute phase of CAT treatment. Patients were seen at the CAT clinic at a median of 16 days (IQR 11-23) from their index CAT diagnosis, and follow-up was a median of 365 days (IQR 235-365).

### Acute Phase

In the acute phase, most patients were prescribed LMWH only (177/221; 80.1%), and a few were prescribed DOACs only (9/221; 4.1%) (Table 2). Most of the remaining patients (32/221; 14.5%) had an anticoagulant class change at a median of 25 days (IQR 16-30). The majority of changes were from LMWH to a DOAC (25/32; 78.1%) with the rationale being most commonly patient preference (14/25), new evidence for

DOAC use in CAT (11/25), and that the patient was no longer on cancer therapy (6/25) (not mutually exclusive). In contrast, those changing from a DOAC to LMWH (5/32; 15.6%) cited LMWH to be first line therapy for CAT. Relative to those predominantly receiving parenteral therapy within the acute phase, the group on oral therapy had more patients with lung (36.7% vs. 12.6%) or breast (26.7% vs. 11.0%) cancers (Table 1). The parenteral group had more GI (33.0% vs. 10.0%) and GU (13.1% vs. 6.7%) cancers, as well as numerically more patients with metastatic disease (59.2% vs. 46.7%;  $P = 0.20$ ) and more patients who were on active therapy for cancer (70.2% vs. 56.7%;  $P = 0.14$ ). At the end of the acute phase, a total of 34/221 (15.4%) of patients were on DOAC therapy.

### Chronic Phase

In the chronic phase, anticoagulation therapy for patients consisted of LMWH only for 76/212 (35.8%), DOAC only for 24/212 (11.3%), and an anticoagulant class change in 91/212 (42.9%) (Table 3). Changing from a LMWH to a DOAC was most common (82/91; 90.1%), and occurred at a median of 121 days (IQR 110-191). Most commonly reported reasons for class change were no longer receiving cancer treatment (40/82), cancer remission (27/82), a sufficient duration of time had passed since CAT (27/82), patient preference (41/82), and new evidence with DOACs (30/82) (not mutually exclusive). In the chronic phase, there was an increase in the number of patients on DOAC only relative to the acute phase (11.3%

**Table 1.** Baseline Characteristics as Per Predominant Anticoagulant in Acute Phase.

Characteristic	Total cohort (n = 221)	Predominant anticoagulation in the acute phase of therapy*		p-value
		Parenteral (n = 191)	Oral (n = 30)	
Median age—years (IQR)	69 (61-75)	68 (61-75)	70 (65-78)	0.31
Male sex—no. (%)	104 (47.1)	96 (50.3)	8 (26.7)	0.02
Median weight—kg (IQR)	77 (67-93)	79 (67-95)	68 (63-77)	0.012
Median platelet count— $\times 10^9/L$ (IQR)	261 (200-339)	260 (200-355)	284 (229-317)	0.82
Median hemoglobin count—g/L (IQR)	119 (106-129)	119 (104-129)	122 (117-130)	0.15
Median creatinine clearance <sup>†</sup> —mL/min (IQR)	68 (51-90)	69 (51-93)	56 (48-70)	0.033
Type of index CAT—no. (%)				0.42
PE	159 (71.9)	136 (71.2)	23 (76.7)	
Leg DVT	49 (22.2)	42 (22.0)	7 (23.3)	
Both PE and leg DVT	13 (5.9)	13 (6.8)	0 (0.0)	
PE location—no. (%)				0.85
More proximal pulmonary arteries	55 (32.0)	49 (32.9)	6 (26.1)	
Segmental	109 (63.4)	93 (62.4)	16 (69.6)	
Subsegmental	8 (4.7)	7 (4.7)	1 (4.3)	
PE type—no. (%)				0.26
Symptomatic	82 (47.7)	74 (49.7)	8 (34.8)	
Incidental	90 (52.3)	75 (50.3)	15 (65.2)	
Leg DVT location—no. (%)				0.13
Proximal	56 (90.3)	50 (90.9)	6 (85.7)	
Femoral	28 (50.0)	27 (54.0)	1 (16.7)	
Iliac	14 (25.0)	12 (24.0)	2 (33.3)	
Popliteal	24 (25.0)	11 (22.0)	3 (50.0)	
Distal	6 (9.7)	5 (9.1)	1 (14.3)	0.82
Leg DVT type—no (%)				0.73
Symptomatic	57 (91.9)	50 (90.9)	7 (100.0)	
Incidental	5 (8.1)	5 (9.1)	0 (0.0)	
History of VTE prior to index event—no. (%)	35 (15.8)	32 (16.8)	3 (10.0)	0.35
If prior VTE, cancer-associated—no. (%)	16 (45.7)	14 (43.8)	2 (66.7)	0.90
Type of cancer—no. (%)				0.008
Solid tumor	196 (88.7)	169 (88.5)	27 (90.0)	
Colorectal	38 (17.2)	36 (18.8)	2 (6.7)	
Lung	35 (15.8)	24 (12.6)	11 (36.7)	
Genitourinary	27 (12.2)	25 (13.1)	2 (6.7)	
Breast	29 (13.1)	21 (11.0)	8 (26.7)	
Pancreatic or hepatobiliary	13 (5.9)	12 (6.3)	1 (3.3)	
Gynecological	26 (11.8)	24 (12.6)	2 (6.7)	
Upper gastrointestinal	15 (6.8)	15 (7.9)	0 (0.0)	
Other <sup>‡</sup>	13 (5.9)	12 (6.3)	1 (0.0)	
Hematological malignancy	25 (11.3)	22 (11.5)	3 (10.0)	0.81
Metastatic disease—no. (%)	127 (57.5)	113 (59.2)	14 (46.7)	0.20
Active cancer therapy during acute phase—no. (%)	151 (68.3)	134 (70.2)	17 (56.7)	0.14
Type of active therapy (may select more than 1)—no. (%)				0.27
Chemotherapy	97 (64.2)	89 (66.4)	8 (47.1)	
Hormonal therapy	23 (15.2)	20 (14.9)	3 (17.6)	
Immunotherapy	16 (10.6)	15 (11.2)	1 (5.9)	
Radiotherapy	20 (13.2)	18 (13.4)	2 (11.8)	
Surgery	3 (2.0)	2 (1.5)	1 (5.9)	
Targeted therapy	29 (19.2)	22 (16.4)	7 (41.2)	
Other	1 (0.7)	1 (0.7)	0 (0.0)	
Median time from index CAT to initial CAT clinic appointment—days (IQR)	16 (11-23)	16 (11-23)	16 (11-24)	0.95

CAT = cancer associated thrombosis; DOAC = direct oral anticoagulant; DVT = deep vein thrombosis; LMWH = low molecular weight heparin; PE = pulmonary embolism; VTE = venous thromboembolism.

\*Predominant anticoagulation for  $\geq 45$  days out of 90 days encompassing the acute phase of therapy. Parenteral is LMWH or fondaparinux; oral is a DOAC or warfarin.

<sup>†</sup> Creatinine clearance calculation using Cockcroft-Gault equation.

<sup>‡</sup> Other cancers include brain (3), head & neck (5), peripheral nerve sheath sarcoma, chondroid chordoma, retroperitoneal sarcoma, thyroid, and lung + colon (primary tumor unknown).

**Table 2.** Acute Phase Data.

Outcome	Total cohort (n = 221)	Divided before and after Hokusai-VTE Cancer publication date*		p-value	
		Before Feb 15, 2018 (n = 103)	On or after Feb 15, 2018 (n = 118)		
Anticoagulation in acute phase—no. (%)					
LMWH only	177 (80.1)	91 (88.3)	86 (72.9)	0.005	
Dalteparin	102 (57.6)	60 (65.9)	42 (48.8)		
same dose	96 (94.1)	55 (91.7)	41 (97.6)		
dose increase	5 (4.9)	4 (6.7)	1 (2.4)		
dose decrease	1 (1.0)	1 (1.7)	0 (0.0)		
Enoxaparin	5 (2.8)	3 (3.3)	2 (2.3)		
same dose	5 (100.0)	3 (100.0)	2 (100.0)		
Tinzaparin	43 (23.3)	12 (13.2)	31 (36.0)		
same dose	35 (81.4)	9 (75.0)	26 (83.9)		
dose increase	3 (7.0)	1 (8.3)	2 (6.5)		
dose decrease	5 (11.6)	2 (16.7)	3 (9.7)		
Switched agents	27 (15.3)	16 (17.6)	11 (12.8)		
dalteparin to tinzaparin	7 (25.9)	2 (12.5)	5 (45.5)		
enoxaparin to dalteparin	15 (55.6)	11 (68.8)	4 (36.4)		
enoxaparin to tinzaparin	4 (14.8)	3 (18.8)	1 (9.1)		
tinzaparin to dalteparin	1 (3.7)	0 (0.0)	1 (9.1)		
DOAC only	9 (4.1)	1 (1.0)	8 (6.8)	0.89	
Apixaban	1 (11.1)	0 (0.0)	1 (12.5)		
Rivaroxaban	8 (88.9)	1 (100.0)	7 (87.5)		
Warfarin only	1 (0.5)	1 (1.0)	0 (0.0)		NA
Anticoagulant class change	32 (14.5)	10 (9.7)	22 (18.6)		
LMWH to DOAC	25 (78.1)	6 (60.0)	19 (86.4)		0.055
DOAC to LMWH	5 (15.6)	3 (30.0)	2 (9.1)		
LMWH to fondaparinux†	2 (6.3)	1 (10.0)	1 (4.5)		
Anticoagulation discontinued	2 (0.9)	0 (0.0)	2 (1.7)		
LMWH	2 (100.0)	0 (0.0)	2 (100.0)		
Median time from index CAT to change—days (IQR)					
LMWH dose change	24 (15-42)	24 (13-43)	23 (17-39)	0.99	
LMWH agent switch	16 (14-23)	16 (13-24)	19 (15-23)		
Anticoagulant class change	25 (16-30)	28 (23-55)	24 (14-30)	0.54	
LMWH to DOAC	28 (16-31)	55 (35-56)	25 (15-30)		
DOAC to LMWH	22 (16-24)	22 (19-24)	18 (14-21)		
LMWH to fondaparinux	21 (17-24)	27 (NA)	14 (NA)		NA
Anticoagulation discontinued	78 (77-78)	NA	78 (77-78)		

DOAC = direct oral anticoagulant; LMWH = low molecular weight heparin; NA = not applicable; VTE = venous thromboembolism.

\*Secondary outcome.

†Both patients switched off of LMWH due to heparin induced thrombocytopenia (HIT).

vs. 4.1%) and in those experiencing an anticoagulant class change (42.9% vs. 14.5%). At the end of the chronic phase, 106/212 (50.0%) of patients were anticoagulated with a DOAC, in comparison to 15.4% on DOACs at the end of the acute phase ( $P < 0.0001$ ). Death occurred for 48/212 (22.6%) patients, at a median of 212 days (IQR 167-282).

### Before and after Hokusai-VTE Cancer Publication

Differences are noted in prescribing patterns in the acute phase before ( $n = 103$ ) and after ( $n = 118$ ) publication of the Hokusai-VTE Cancer trial. Before February 15, 2018, 91/

103 (88.3%) patients were prescribed LMWH only, in comparison to 86/118 (72.9%) after this date ( $P = 0.005$ ) (Table 2). Additionally, before publication, only 1/103 (1.0%) was prescribed DOAC only, compared to 8/118 (6.8%) after ( $P = 0.89$ ). Of the 25 patients that were switched from LMWH to DOAC in the acute phase overall, 19/25 (76%) of them were switched after Hokusai-VTE Cancer was published. These patients were also switched to DOACs sooner, at a median of 25 days (IQR 15-30) compared to 55 days (IQR 35-56) for patients switched from LMWH to DOAC before publication ( $P = 0.38$ ).

**Table 3.** Chronic Phase Data.

Outcome	Total cohort (n = 212)†	Divided before and after Hokusai-VTE Cancer publication date*		p-value
		Before Feb 15, 2018 (n = 100)	On or after Feb 15, 2018 (n = 112)	
Anticoagulation in chronic phase—no. (%)				
LMWH only	76 (35.8)	42 (42.0)	34 (30.4)	0.078
Dalteparin	45 (59.2)	29 (69.0)	16 (47.1)	
same dose	31 (68.9)	20 (69.0)	11 (68.8)	
dose increase	3 (6.7)	3 (10.3)	0 (0.0)	
dose decrease	11 (24.4)	6 (20.7)	5 (31.3)	
Tinzaparin	29 (38.2)	11 (26.2)	18 (52.9)	
same dose	20 (69.0)	8 (72.7)	12 (66.7)	
dose increase	1 (3.4)	0 (0.0)	1 (5.6)	
dose decrease	8 (27.6)	3 (27.3)	5 (27.8)	
Switched agents	2 (2.6)	2 (4.8)	0 (0.0)	
enoxaparin to dalteparin	2 (100.0)	2 (100.0)	-	
DOAC only	24 (11.3)	2 (2.0)	22 (19.6)	0.51
Apixaban	4 (16.7)	0 (0.0)	4 (18.2)	
Edoxaban	5 (20.8)	0 (0.0)	5 (22.7)	
same dose	4 (80.0)	-	4 (80.0)	
dose decrease	1 (20.0)	-	1 (20.0)	
Rivaroxaban	15 (62.5)	2 (100.0)	13 (59.1)	
Warfarin only	1 (0.5)	1 (1.0)	0 (0.0)	NA
Anticoagulant class change	91 (42.9)	38 (38.0)	53 (47.3)	0.02
LMWH to DOAC	82 (90.1)	33 (86.8)	49 (92.5)	
LMWH to warfarin	4 (4.4)	4 (10.5)	0 (0.0)	
DOAC to LMWH	3 (3.3)	0 (0.0)	3 (5.7)	
LMWH to DOAC to LMWH	2 (2.2)	1 (2.6)	1 (1.9)	
Anticoagulation discontinued	20 (9.4)	17 (17.0)	3 (2.7)	0.13
LMWH	10 (50.0)	10 (58.8)	0 (0.0)	
DOAC	7 (35.0)	5 (29.4)	2 (66.7)	
LMWH to DOAC	3 (15.0)	2 (11.8)	1 (33.3)	
Median time from index CAT to change—days (IQR)‡				
LMWH dose change	116 (113-238)	115 (109-230)	192 (115-238)	0.22
LMWH agent switch	110 (109-112)	110 (109-112)	NA	NA
DOAC dose change	122 (NA)	NA	122 (NA)	NA
Anticoagulant class change	120 (109-192)	188 (122-213)	113 (103-123)	<0.0001
LMWH to DOAC	121 (110-191)	188 (123-213)	114 (106-123)	<0.0001
LMWH to warfarin	146 (98-223)	146 (98-223)	NA	NA
DOAC to LMWH	97 (94-183)	NA	97 (94-183)	NA
Anticoagulation discontinued	195 (166-222)	182 (151-223)	210 (208-215)	0.22

DOAC = direct oral anticoagulant; LMWH = low molecular weight heparin; NA = not applicable; VTE = venous thromboembolism.

\*Secondary outcome.

† Nine patients had no chronic follow-up due to a bleed requiring therapy change or a recurrent VTE.

‡ Time to first change if multiple anticoagulant class changes were made; time to anticoagulation stopped regardless of whether multiple switches occurred previous to this occurring.

In the chronic phase, before February 15, 2018, 42/100 (42%) patients were on LMWH only therapy, in comparison to 34/112 (30.4%) after this date ( $P = 0.078$ ) (Table 3). Prior to Hokusai-VTE Cancer, only 2/100 (2.0%) patients were prescribed DOAC alone, compared to 22/112 (19.6%) after the trial was published ( $P = 0.51$ ). Of the 82 patients switched from a LMWH to a DOAC in the chronic phases overall, 49/82 (59.8%) occurred after the publication of the Hokusai-VTE Cancer trial, with a median time to switch of 114 days (IQR 106-123). This change occurred earlier than the median of 188

days (IQR 123-213) in those switched from LMWH to DOAC before Hokusai ( $P < 0.0001$ ).

### Recurrent VTE and Bleeding Requiring a Therapy Change

Of the 221 patients included in this retrospective record review, 16 (7.2%) had a recurrent VTE and 11 (5.0%) had bleeding requiring a therapy change. Of the 16 patients with recurrent VTE, the most frequent cancer types were colorectal (4/16; 25%), followed by pancreatic or hepatobiliary (3/16; 18.8%),

and gynecological (3/16; 18.8%). Nine patients (56.3%) had metastatic disease and 11 (68.8%) were on active cancer therapy at the time of recurrent VTE. The median time to recurrent VTE was 97 days (IQR 50-230), with 6/16 events occurring in the acute phase. At the time of recurrent VTE, 12/16 (75%) were anticoagulated with a LMWH and 4/16 (25%) with a DOAC. All of the patients with recurrent VTE in acute phase were on LMWH at that time. After experiencing a clot, the majority of patients (9/16; 56.3%) had the LMWH dose increased, or were switched from a DOAC to a LMWH (3/16; 18.8%).

Of the 11 patients with a bleeding event, the predominant cancer type was genitourinary (6/11; 54.5%). Seven patients (63.6%) had metastatic disease, and 8 (72.7%) were on active therapy for cancer at the time of the bleeding event. The median time from index CAT to bleed was 115 days (IQR 85-201), with most patients experiencing hematuria (6/11; 54.5%). There was one incident of non-fatal intracranial hemorrhage. At the time of the bleeding event, 9/11 (81.8%) were on a LMWH and 2/11 (18.2%) were on a DOAC. Of note, 3/11 (27.3%) bleeding events occurred in the acute phase, and all of the patients were on LMWH at that time. After experiencing a bleed, 5/11 (45.5%) had the LMWH dose decreased, 3/11 (27.3%) had their anticoagulation held for a period and then restarted at the same dose, and the 3/11 (27.3%) had their anticoagulation discontinued altogether.

## Discussion

In this retrospective record review, most patients were anticoagulated with LMWH in the acute phase after their index CAT, and anticoagulant class changes were most commonly from LMWH to DOAC. This class change occurred more often, and sooner after the index CAT once the Hokusai-VTE Cancer trial was published. Use of DOACs in the chronic phase was more prevalent than in the acute phase, with half of patients on these agents at 1 year.

A recent audit of the GARFIELD registry (May 2014-January 2017) reported patients with active cancer to have similar types of cancer as our study, with most patients at baseline being administered LMWH alone (57.8%), followed by DOACs (24.5%) and warfarin (14.2%).<sup>21</sup> Notably, these data report earlier usage of therapies, prior to the publication of efficacy/safety data and largely pre-date our data.

Similar to both the Hokusai-VTE Cancer, CARAVAGGIO and select-d trials, our study included those with both symptomatic and incidental PE and leg DVT (Table 4).<sup>13-15</sup> Moreover, our patients were of a similar age and weight, and had comparable portions having metastatic disease (57.5%) and receiving active cancer therapy (68.3%). Our patients also aligned with the most common cancer types from CAT trials (colorectal, lung, and breast).

This study had a death rate of 22.6% at 12 months, which is lower than in the DOAC in CAT trials.<sup>13-15,22</sup> However, we did exclude patients who died during the acute phase of treatment, which may have falsely decreased our death rate. Our rate of

recurrent VTE was 7.2%, which is comparable to the rates found in the RCTs. Our rate of bleeding requiring a therapy change was 5.0%, which is comparable or slightly higher than the major bleeding reported in the RCTs. There was a signal for increased bleeding that arose in the RCTs with DOAC use in patients with GI and GU cancers. This likely impacted physician decisions on use of DOACs in such patients and is reflected in our study results, which showed no patients with GI or GU cancers in the DOAC only group during the acute phase. Two patients with colorectal cancer, and 2 with GU cancers (prostate, bladder) were transitioned from LMWH to DOAC within the acute phase, but no patients with upper GI cancers were prescribed DOACs during this time.

In our study, when comparing patients predominantly on oral or parenteral therapy within the acute phase, those on parenteral therapy were more likely to have metastatic disease. This demonstrates that the severity of the cancer likely influenced prescribing decisions toward LMWH. This is not surprising given that patients enrolled into the CLOT trial were significantly sicker than in the more recent DOAC in CAT trials with respect to relative proportions of patients with metastatic disease, receiving active cancer treatment, having a higher ECOG status and a higher mortality. Additionally, in our study there were more DOACs prescribed in incidental rather than symptomatic PE. The CLOT trial did not include incidental clots. While some patients can still have symptomatic events that are discovered incidentally, incidental VTE will invariably include many events that are less severe and less acute. Incidental index events were included in the DOAC in CAT trials, potentially lending comfort for DOAC use in these situations.

Patients were often transitioned to a DOAC from a LMWH when they were deemed more stable—reflected in parameters such as time from index CAT, completion of active cancer treatment, or remission of cancer. However, the reasons why patients were not transitioned to a DOAC at all, or why that transition was delayed, was not explicitly captured in our study. DOAC consideration was noted as an option in clinic letters, but then disregarded most commonly due to concern for drug-drug interactions with cancer therapy. Additionally, clinicians appeared to be more comfortable with the perioperative use of LMWH, and thus DOACs were eliminated in patients requiring surgical interventions. Patients also remained on LMWH because of their cancer type (more hesitancy to use DOAC in GI/GU cancers), and poor renal function. A decision to remain on more well established treatment, especially in complex patients where limitations of newer data may leave uncertainties, is often the most pragmatic approach. As seen in this study, while DOAC use increased over time, this was more pronounced in the chronic phase of VTE treatment and when the patient was deemed more stable.

Although the first evidence for DOAC use in CAT was with edoxaban in the Hokusai-VTE Cancer trial, we see a lack of this agent prescribed in our study. Of those prescribed DOAC only in the acute phase, none were prescribed edoxaban. In the chronic phase, of those prescribed DOAC only, 5/24 were on edoxaban. For patients transitioned from LMWH to DOAC,

Table 4. Comparison of Retrospective Record Review to Literature.

	Hokusai VTE Cancer		select-d		CARAVAGGIO		CLOT		Retrospective record review	
	2018		2018		2020		2003		2016-2020	
<b>Anticoagulant</b>	<b>Edoxaban (n = 522)</b>	<b>Dalteparin (n = 524)</b>	<b>Rivaroxaban (n = 203)</b>	<b>Dalteparin (n = 203)</b>	<b>Apixaban (n = 576)</b>	<b>Dalteparin (n = 579)</b>	<b>Dalteparin (n = 338)</b>	<b>Warfarin (n = 338)</b>	<b>Oral<sup>§</sup> (n = 30)</b>	<b>Parenteral (n = 191)</b>
<b>Type of CAT</b>	Symptomatic or incidental (30%)		Symptomatic PE/DVT and incidental (50%) PE		Symptomatic or incidental (20%)		Only symptomatic PE/DVT		Symptomatic or incidental (41%)	
<b>Age (yrs)</b>	64.3*	63.7*	67 <sup>†</sup>	67 <sup>†</sup>	67.2*	62*	63*	63*	70 <sup>†</sup>	68 <sup>†</sup>
<b>Weight (kg)</b>	78.8*	79.1*	Reported as BMI		75.7*	76.1*	Renal (22%) = 64; Non-renal = 75.5 <sup>†</sup>	Renal (22%) = 65; Non-renal = 75 <sup>†</sup>	68 <sup>†</sup>	79 <sup>†</sup>
<b>Metastatic cancer (%)</b>	52.4	53.4	59	59	67.5 <sup>‡</sup>	66	68.6	46.7	59.2	59.2
<b>Cancer treatment (%)</b>	71.6	73.1	69	69	59.7	59.8	78.7	76.6	56.7	70.2
<b>Top 3 cancer types</b>	Colorectal		Colorectal		Colorectal		Breast	Breast	Colorectal	
	Lung		Lung		Lung		Colorectal	Colorectal	Lung	
	GU		Breast		Breast		Lung	Lung	Breast	
<b>Recurrent VTE (%)</b>	7.9	11.3	3.9	8.9	5.6	7.9	8.0	15.8	13.3	6.3
<b>Bleeding (%)</b>									6.7 <sup>†</sup>	4.7 <sup>†</sup>
<b>Major CRNMB</b>	6.9	4.0	5.4	3.0	3.8	4.0	5.6	3.6		
<b>CRNMB</b>	14.6	11.1	12.3	3.4	9.0	6.0	—	—		
<b>Death (%)</b>	39.5	36.6	30	25	23.4	26.4	39	41	6.7	24.1
	(12 mo.)	(12 mo.)	(6 mo.)	(6 mo.)	(~6 mo.)	(~6 mo.)	(6 mo.)	(6 mo.)	(12 mo.)	(12 mo.)

CAT = cancer-associated thrombosis; CRNMB = clinically relevant non-major bleeding; DVT = deep vein thrombosis; PE = pulmonary embolism; VTE = venous thromboembolism.

\* Presented as means.

† Presented as medians.

‡ Includes recurrent locally advanced cancer as well.

§ Of the oral options, 29 DOACs and 1 warfarin.

Our study captured bleeding requiring a therapy change, rather than as per the ISTH definitions.



20.8% were transitioned to edoxaban in the acute phase, and 17.1% in the chronic phase. It is likely that this finding can be attributed to 2 reasons. Firstly, the data on apixaban and rivaroxaban in VTE patients without cancer were published earlier than that for edoxaban, and the use of these agents was already more commonplace. The second is drug coverage; edoxaban was listed on the Alberta Drug Benefits list, which includes patients on government-sponsored plans (seniors, low-income, etc.), only as of March 1, 2019. Apixaban and rivaroxaban gained their Alberta Drug Benefits coverage in March 2014 and October 2012, respectively. Many cancer patients are older and/or no longer able to continue their prior employment which makes financial constraints a significant factor for treatment choices.

Our study has limitations, including the retrospective design which is subject to restricted data access in electronic health records, incomplete data and variability in data reporting. Secondly, our sample size was limited to 19.7% of the population seen at the CAT clinic during our study timeframe, however, our inclusion criteria ensured patients had sufficient follow-up within the acute phase of CAT treatment to elucidate changes made, and the rationale behind those changes.

With the emergence of new data, cancer patients are no longer limited to LMWH when requiring anticoagulation for CAT. DOAC use was less common in the acute phase of VTE treatment likely attributable to concerns regarding severity of the cancer and VTE as well as drug-drug interactions with active cancer treatment. As patients stabilized in the chronic phase, DOAC use increased. Studying the use of DOACs in “real world” CAT patients can identify these and other barriers to applying the emerging DOAC evidence to clinical practice. This can help to guide further research into optimizing the care of these complex patients.

### Author Contributions

HK participated in design, acquired all the data, and performed the analysis of the data. She drafted the manuscript, approved the final version to be published and agrees to be accountable for all aspects of the work. MM participated in the design and interpretation of the data. She revised the manuscript for important intellectual content, approved the final version to be published and agrees to be accountable for all aspects of the work. SQ put this forward as a research project and participated in the design of this study. He revised the manuscript for important intellectual content, approved the final version to be published and agrees to be accountable for all aspects of the work. SG participated in the analysis and interpretation of the data. She revised the manuscript for important intellectual content, approved the final version to be published and agrees to be accountable for all aspects of the work. CW participated in design, analysis and interpretation of the data. She revised the manuscript for important intellectual content, approved the final version to be published and agrees to be accountable for all aspects of the work. TJB conceived, participated in design, analysis and interpretation of the data. She revised the manuscript for important intellectual content, approved the final version to be published and agrees to be accountable for all aspects of the work.

### Availability of Data

Data collected for study is entered in Research Electronic Data Capture (REDCap) at the University of Alberta, Edmonton, Alberta, Canada.

### Declaration of Conflicting Interests

HK, MM, SQ, SG have nothing to disclose. CW has received honoraria and is on Advisory Boards for Pfizer, Leo Pharma, BMS-Pfizer, and Servier. She is also the Local Principal Investigator for clinical trials with funding from Bayer, BMS-Pfizer, Daiichi-Sankyo, CIHR, Heart and Stroke Foundation of Canada. These are all outside the work of this study. TJB has received unrestricted research grants from Leo Pharm and Pfizer, all outside the work of this study.


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