RESEARCH ARTICLE

Safety of Direct Acting Oral Anticoagulants (DOACs) in Comparison to Enoxaparin in Gastrointestinal and Genito-Urinary Cancers

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ABSTRACT

Safety of Direct Oral Anticoagulants (DOAC) in Cancer Associated Thrombosis (CAT) in patients with Gastrointestinal (GI) and Genito-Urinary (GU) malignancies is uncertain. We identified patients with active GI and GU malignancies who received either enoxaparin or a DOAC (apixaban or rivaroxaban) for CAT from July 2001 to July 2020. Demographics, disease characteristics, thrombosis data, date of anticoagulation initiation, and bleeding events at one year were recorded and analysed. We identified 206 patients, 159 received DOAC (86 apixaban; 73 rivaroxaban) and 47 enoxaparin; 128 (62.1%) and 78 (37.9%) had GI and GU malignancies, respectively. Choice of anticoagulation varied significantly based on primary malignancy. Enoxaparin was preferred in GU tumors while DOACs were preferred in GI tumors (p=0.014). Within DOACs, rivaroxaban use was higher with GI cancers and apixaban was prescribed more often in GU malignancies (p=0.00049). Anticoagulated associated bleeding events in GI and GU cancers were common (22.2%). No difference in bleeding events was observed between enoxaparin (21.7%) and DOACs (22.4%) in patients with GI (p=0.56) or GU (p=0.74) tumors or for the combined CAT group (p=0.93). Apixaban and rivaroxaban had similar bleeding event rates. The majority of patients who experienced a bleeding event, 28/44 (63.6%), bled at the cancer site with a trend for increased bleeding in GU cancer patients on DOACs vs. enoxaparin (p=0.089). Anticoagulated associated bleeding in GI and GU cancers are common with enoxaparin and DOACs. There is a high percentage of bleeding at the tumour site in both malignancies irrespective of anticoagulant agent.

Keywords: Bleeding risk, DOAC, Gastrointestinal cancer, Genitourinary cancer, VTE

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INTRODUCTION

Venous Thromboembolic disease (VTE) is a common cause of morbidity and mortality in patients with cancer. The incidence of VTE in cancer patients is six-fold higher than in non-cancer patients [1]. Studies have shown that cancer patients with VTE have a poorer prognosis, decreased survival and increased high care cost burden as compared to cancer patients without VTE [2,3]. The landmark CLOT trial demonstrated the superiority of Low-Molecular-weight Heparins (LMWH) to vitamin K antagonists for treatment of Cancer Associated Thrombosis (CAT) and led to the adoption of LMWH by major guidelines for CAT for over a decade [4]. However, several aspects of LMWH including its parenteral administration, low renal clearance, relatively high cost and the lack of comparative evidence of its efficacy and safety when such treatment continues beyond 6 months has made its long-term use less than ideal [5]. The Direct Oral Anticoagulants (DOACs) including dabigatran, apixaban, rivaroxaban, and edoxaban are approved by the U.S. Food and Drug Administration (FDA) for treatment of VTE. The Hokusai-Cancer, SELECT-D, Caravaggio and ADAM VTE trials compared edoxaban, rivaroxaban and apixaban, respectively, to dalteparin for the treatment of cancer associated thrombosis [6-10]. While the results of these large randomized controlled trials seem to demonstrate that DOACs are non-inferior to LMWH for the prevention of recurrent VTE, a major point of concern is the elevated incidence of bleeding events, particularly in patients with GI malignancies. Given the findings from two RCTs-the SELECT-D trial and the Hokusai VTE-Cancer study-and multiple meta-analyses, DOACs were endorsed by multiple scientific society guidelines including American Society of Clinical Oncology (ASCO 2020 guidelines), American Society of Haematology (ASH 2021 guidelines), National Comprehensive Cancer Network (NCCN), International Society on Thrombosis and Haemostasis (ISTH) and International Clinical Practice guidelines for treatment of VTE in cancer patients. However, these guidelines also warrant caution regarding use of DOACs GI and GU malignancies [11-19]. The subgroup analyses of the Hokusai VTE-Cancer trial reported that GI cancer patients had a significantly higher bleeding rate in the edoxaban cohort versus dalteparin monotherapy [6]. The trial also observed that in the overall population (all cancer types), a trend toward higher rates of major bleeding with edoxaban was largely due to increases in the rate of GI and urogenital bleeds (patients with GI/GU bleeds, 4.8% *vs*. 1.1% for edoxaban *vs*. dalteparin arms) [6]. However, no data was provided about the site of the bleeding in GI and GU cancer patients. No separate subgroup analysis was reported for GU cancer patients either. Similarly in the SELECT-D trial no data was provided regarding the site of bleeding in GI and GU cancers. The reported that there was a signal that esophageal and gastroesophageal cancers were associated with major bleeding with rivaroxaban [10]. Given the paucity of data in DOACs in GI and GU cancers, we wanted to describe our single center experience and to compare the safety of DOACs in CAT in these patients.

MATERIALS AND METHODS

Data were obtained from Clinical Looking Glass (CLG), an interactive database software application developed at Montefiore Medical Center (Bronx, NY) that integrates demographic, clinical, and administrative datasets for statistical access. CLG was used to identify patients with malignancies involving the gastrointestinal, urothelial tract and prostate who received care within the Montefiore Health System from July 2001 until July 2020. Among the patients, only those with confirmed diagnosis of VTE during active cancer who received treatment with either enoxaparin or a DOAC (apixaban or rivaroxaban) were included in the study. Charts were reviewed to document additional demographic and clinical information as well as recurrent Venous Thromboembolism (VTE) and Bleeding Events (BE) while on anticoagulation during the follow-up period. Date of anticoagulation initiation was based on the first order and/or prescription. Follow-up period was defined as the

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time from first prescription date to the earliest of BE, one year from initiation or death. The study was approved by the Albert Einstein College of Medicine Institutional Review Board.

Study definitions

Active cancer at the time of VTE was defined as patients who were being actively treated with antineoplastic therapy when VTE was diagnosed. The GI cancers included in the study were esophageal, Gall Bladder (GB), gastric, duodenal and colorectal cancers. Esophageal, GB, gastric and duodenal cancers were grouped together as upper GI cancers. Colorectal cancers were categorized as lower GI cancers. The GU cancers included were renal, bladder, and prostate. Cancer diagnoses were confirmed by reviewing the pathology report. Active treatment at the time of VTE diagnosis was confirmed from the last Oncology documentation prior to the diagnosis. VTE diagnoses were confirmed from imaging findings including Computed Tomography Pulmonary Angiogram (CTPA), Ventilation Perfusion scan (V-Q scan) and/or duplex ultrasonography of the involved extremities. Patients were divided into two groups based on the type of anticoagulation used: DOAC group (apixaban and rivaroxaban) or enoxaparin group. All bleeding events were reviewed but only those that met the criteria for clinically relevant non-major bleeding and/or major bleeding according to the Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis were included [20,21].

Statistical methods

Means, counts and percentages of demographic and clinical variables (age, identifying gender, race, ethnicity, Eastern Cooperative Oncology Group (ECOG) status, Body Mass Index (BMI) were tabulated by anticoagulant. Type and stage of cancer, VTE site and associated recent surgeries were reviewed. Any BE risk factors, including other prescribed potentially interfering/contributing medications, were also recorded. Overall BE, BE at the cancer site and BE for each specific cancer were separately analysed. Each variable was compared between enoxaparin and DOAC (and between DOACs) cohorts using t-tests for continuous variables and chi-squared tests or Fisher's exact test for categorical variables. The distribution of time to bleeding was also compared across anticoagulation treatments in GI and GU using a proportional hazards regression model and then method of Fine and Gray (1999) to account for death as a competing risk. Results are presented as sub-distribution Hazard Ratios (HR) between treatment groups. Adjustment for the following potential confounders: BMI, ECOG status, race, cancer type and surgery prior to VTE event was accomplished by including them as additional covariates in the proportional hazards regression model. A two-tailed alpha of 0.05 was used to define statistical significance.

RESULTS

Study population

We identified total of 206 patients, 159 in the DOAC and 47 in the enoxaparin groups. Within the DOAC group, 86 patients were on apixaban and 73 were on rivaroxaban, describes the baseline characteristics of the study population by treatment group (Table 1). Median age of patients, gender and BMI were comparable for all groups. The enoxaparin group included a higher proportion of Blacks and lower proportion of Hispanics than the DOAC group (p=0.007). Patients given DOACs had better ECOG status than patients given enoxaparin (p=0.0023), but no difference in ECOG status was observed between DOACs (p=0.69). Most patients had metastatic disease, and the extent and stage of the cancer did not appear to be associated with anticoagulant choice (p=0.62). The majority of the VTE events were in the form of DVTs, with the enoxaparin group showing a higher but not significantly different proportion of DVTs compared to the DOAC group (74.4% *vs*. 58.4%; p=0.14). Concomitant aspirin intake was 9.4% in DOAC and 4.2% in enoxaparin groups, (p=0.26).

Table 1: Baseline characteristic of the study population.

Variables	All DOACs	Enoxaparin	P	Apixaban	Rivaroxaban	P
N	159	47	0	86	73	0
Age, mean (SD)	71.1 (12.4)	72.1 (11.4)	0.75	71.6 (12.2)	70.5 (12.6)	0.56
BMI, mean (SD)	26.6 (5.9)	24.8 (4.9)	0.07	26.3 (5.8)	27.0 (6.0)	0.38
% Male Identifying, n (%)	94 (59.1%)	29 (61.7%)	0.75	55 (63.9%)	39 (53.4%)	0.18
Surgery prior to VTE, n (%)	29 (18.2%)	5 (10.6%)	0.21	20 (23.2%)	9 (12.3%)	0.075
Concomitant Antiplatelet Use, n (%)	15 (9.4%)	2 (4.2%)	0.26	7 (8.1%)	8 (10.9%)	0.54
ECOG, n (%)						
0	33 (20.7%)	1 (2.1%)		15 (37.4%)	18 (24.6%)	
1	65 (40.8%)	13 (27.6%)		37 (43%)	28 (38.3%)	
2	28 (17.6%)	21 (44.6%)		16 (18.6%)	12 (16.4%)	
3	19 (11.9%)	8 (17%)		9 (10.4%)	10 (13.6%)	
4	14 (8.8%)	4 (8.5%)	0.0023	9 (10.4%)	5 (6.8%)	0.69
Self-Identified Race, n (%)						
White	23 (14.4%)	6 (12.7%)		11 (12.7%)	12 (16.4%)	
African/ American	55 (34.5%)	20 (42.5%)		28 (32.5%)	27 (36.9%)	
Other/ Refused	0	3 (6.3%)		0	0	
Hispanic	81 (50.9%)	18 (38.2%)	0.007	47 (54.6%)	34 (46.5%)	0.58
Cancer Stage, n (%)						
Early	15 (15.7%)	3 (6.3%)		12 (13.9%)	13 (17.8%)	
Locally Advanced	40 (25.1%)	13 (27.6%)		24 (27.9%)	16 (21.9%)	
Metastatic	94 (59.1%)	31 (65.9%)	0.75	50 (58.1%)	44 (60.2%)	0.62
Initial VTE site, n (%)						
DVT	93 (58.4%)	35 (74.4%)		53 (61.6%)	40 (54.7%)	
PE	42 (26.4%)	8 (17%)		24 (27.9%)	18 (24.6%)	
DVT&PE	24 (15.0%)	4 (8.5%)	0.14	9 (10.4%)	15 (20.5%)	0.21

Recurrent thrombotic events

There was one recurrent thrombosis in each of the apixaban (1/86) and the rivaroxaban (1/73) cohorts. There were no recurrent events in the enoxaparin (0/47) cohort.

Anticoagulation and cancer type

Among patients on DOACs, 106 (66.7%) and 53 (33.3%) had active GI and GU malignancy respectively, whereas in the enoxaparin group, 22(46.8%) and 25(53.2%) had active GI and GU malignancy respectively (p=0.014).The further breakdown of AC type and site of cancer (Table 2). When anticoagulation choice was examined by

primary tumour site, disproportionately more patients with GU tumors were placed on enoxaparin while more GI cancers were given a DOAC (p=0.014). Within the DOACs, differences in type of cancer were even greater, with over 80% of the rivaroxaban group comprising GI cancers versus 55% in the apixaban group (p=0.00049).

Table 2: Initial AC therapy choice in GI-GU cancer patients with thrombosis.

All	All DOACs	Enoxaparin	P	APixaban	Rivaroxaban	Rivaroxaban
	159 (77.2%)	47 (22.8%)		86 (41.1%)	73 (34.4%)	
GI primary	106 (66.7%)	22 (46.8%)		47 (54.7%)	59 (80.8%)	
Upper GI	28 (17.6%)	7 (14.9%)	0.014	16 (18.6%)	12 (16.5%)	
Colon	78 (49.1%)	15 (31.9%)		31 (36.1%)	47 (64.3%)	0.00049
GU primary	53 (33.3%)	25 (53.2%)		39 (45.3%)	14 (19.2%)	
Renal	27 (17%)	3 (6.4%)		20 (23.3%)	7 (9.6%)	
Bladder	14 (8.8%)	5 (10.6%)		11 (12.8%)	3 (4.1%)	
Prostate	12 (7.5%)	17 (36.2%)		8 (9.3%)	4 (5.5%)	

Bleeding events based on anticoagulation type

The bleeding event rates were 22.2% in the overall study population; 26.7% in GU cancers and 19.5% in GI cancers. The bleeding rates further stratified by primary malignancy and type of AC (Table 3). While comparing the type of anticoagulation, 22.4 % (34/152) of the bleeds were detected in patient on DOACs as compared to 21.7% (10/46) bleeds on enoxaparin, with no statistical significance (p=0.93). When examined by cancer type, no difference was noted in the incidence of bleeding between DOACs and enoxaparin in patients with GI (20.8% *vs* 13.6%, p=0.56) or GU (25.5% *vs*. 29.2%, p=0.74) tumors, respectively. Similarly no significant difference in the rate bleeding events was noted between apixaban and rivaroxaban in patients with GI (14.9% *vs*. 25.9%, p=0.17) or GU (66.7% *vs*. 75.0%, p=0.72) tumours or combined (18.8% *vs*. 26.9%, p=0.24) respectively. While examining the site of the bleeds, the majority of the bleeding events, 28/44 (63.6%), occurred at the primary cancer site, with no significant difference between the DOACs and enoxaparin, (67.6% *vs*. 50.0%, p=0.46) as shown in Table 3. However on stratifying the GI and GU cancers we noted a trend for increased cancer site bleeding events for GU cancers in patients on DOACs as compared enoxaparin (69.2% *vs*. 28.6%, p=0.089). Within the DOACs, no differences in bleeding at the cancer site was noted between the GI (85.7% *vs*. 57.1%, p=0.18) or the GU (66.7% *vs*. 75.0%, p=0.47) cancers and combined (75.0% *vs*. 61.1%, p=0.39).

Analysis of time to bleeding

In the analysis of time to bleeding accounting for death as a competing risk event, the hazard ratio for bleeding was non-significantly increased in the DOAC compared to enoxaparin group (Table 4; adjusted HR=2.04; 95% CI: 0.95-4.39; p=0.07) after controlling for cancer type, BMI, ECOG status and race. Cofounding variables were chosen based on the initial analysis between the DOAC and LMWH and between apixaban and rivaroxaban. The risk for bleeding was increased in the rivaroxaban group compared to the apixaban group but this also did not reach significance (Table 4; adjusted HR 2.06; 95% CI: 0.96-4.43; p=0.06) after controlling for surgery prior to VTE and cancer type. ECOG scores and surgery prior to VTE were significant predictors of bleeding risk (Table 4).

Table 3: Incidence of major/CRNM bleeding based on type of AC and primary site of cancer.

		All Major and CRNMB Hemorrhage					
All Bleeding per cancer type	**N**	**All DOACs**	**Enoxaparin**	**p**	**Apixaban**	**Rivaroxaban**	**p**
GI	24/123(19.5%)	21/101(20.8%)	3/22(13.6%)	0.56	7/47(14.9%)	14/54(25.9%)	0.17
GU	20/75(26.7%)	13/51(25.5%)	7/24(29.2%)	0.74	9/38(23.7%)	4/13(30.8%)	0.72
Total	44/198(22.2%)	34/152(22.4%)	10/46(21.7%)	0.93	16/85(18.8%)	18/67(26.9%)	0.24
Bleeding at primary cancer site/total bleeds per cancer type	N	All DOACs	Enoxaparin	p	Apixaban	Rivaroxaban	p
GI	17 (70.8%)	14/21 (66.7%)	3/3 (100%)	0.34	6/7 (85.7%)	8/14 (57.1%)	0.18
GU	11 (55.0%)	9/13 (69.2%)	2/7 (28.6%)	0.089	6/9 (66.7%)	3/4 (75.0%)	0.47
Total	28 (63.6%)	23/34 (67.6%)	5/10 (50.0%)	0.46	12/16 (75.0%)	11/18 (61.1%)	0.39

Table 4: Time to major/CRNMB bleeding.

		Hazard Ratio (95% CI)	p-value
Prior Surgery		3.2 (1.34-7.64)	0.009
BMI		0.99 (0.94-1.03)	0.54
ECOG Score	ECOG (1 *vs*. 0)	1.22 (0.42-3.57)	0.72
	ECOG (2 *vs*. 0)	3.14 (1.11-8.88)	0.03
	ECOG (3 *vs*. 0)	3.50 (1.16-10.56)	0.03
	ECOG (4 *vs*. 0)	3.00 (0.84-10.66)	0.09
Race/Ethnicity	African American *vs*. White	1.96 (0.7-5.53)	0.2
	Hispanic *vs*. White	1.59 (0.55-4.6)	0.39

Therapy (All Cancer Types)	DOAC *vs.* Enoxaparin	2.04 (0.95-4.39)	0.07
	Rivaroxaban *vs.* Apixaban	2.06 (0.96-4.43)	0.06
Cancer type (GU *vs.* GI)	DOAC *vs.* Enoxaparin	1.48 (0.82-2.66)	0.19
	Rivaroxaban *vs.* Apixaban	1.51 (0.76-3.0)	0.24

DISCUSSION

Systematic reviews and meta-analyses of some of the cancer associated thrombosis treatment trials have suggested that the risk of major bleeding in cancer patients is higher for patients using DOACs compared with LMWH [11,12,14,22]. The SELECT-D trial reported a three-fold relative increase in CRNMB with rivaroxaban compared with dalteparin and subgroup analysis of patients with GI malignancies showed increased risk of major bleeds with rivaroxaban compared to LMWH (36% *vs.* 11%). However the overall numbers were small and bleeding events were mostly low grade [7]. In the Hokusai-Cancer trial edoxaban was compared to LMWH and it reported a two-fold increased risk of major bleeding with edoxaban. Approximately one-third of subjects in each study arm had GI cancers. The subgroup analysis there showed equal events of upper and lower GI bleeds in patients with colorectal cancers [6]. The Caravaggio trial, in contrast, showed the frequencies of major bleeding were similar with apixaban and dalteparin, including major gastrointestinal bleeding [9]. These findings are in variance to the results of preceding studies, which demonstrated a higher incidence of bleeding with other direct oral anticoagulants than with dalteparin in a similar population. Non-major bleeding events were higher with apixaban, similar to what has been observed in previous RTCs involving DOACs [8]. A prospective cohort study for cancer associated thrombosis conducted at Mayo Clinic also showed only non-statistically significant trends towards increased bleeding with DOACs compared with LMWH [23]. A cohort study of patients at the Cleveland Clinic reported statistically similar MB and CRNMB rates in the DOAC and LMWH arms, with GI bleeding representing the majority of cases [24].

In our retrospective cohort study concentrating on these two potentially problematic areas, we found that there was no significant difference in overall (major and CRNMB) bleeding events between DOACs and enoxaparin in patients with underlying GI or GU malignancies or when combined. Overall we noted that anticoagulated associated bleeding in GI and GU cancers is common and that bleeding at the cancer site occurs most often; however we could find no indication that one class of anticoagulation is significantly worse than another. When we examined time to event, using death as a competitive risk and adjusting for ECOG status, prior surgeries, race, ethnicity and BMI, a slightly different picture was found. Here again there was no difference per cancer type but when all cancer types were grouped together, the larger cohort allowed an almost significant difference to emerge between DOACs and enoxaparin and, particularly, between rivaroxaban and apixaban. The studies above, including ours, raise a question about grouping all DOACs together, since the higher bleeding incidences in prior cancer studies seem to have only occurred in the non-apixaban studies [25-29]. Indeed, non-cancer studies suggest that apixaban does have a significant safety advantage [30]. Recent data reported from the Mayo Clinic VTE registry reported that patients with underlying In GU cancers, apixaban has a lower rate of major bleeding as compared to rivaroxaban or enoxaparin [31]. It remains to be seen whether this also holds true for bleeding in patients with cancer associated thrombosis in future prospective study.

There are theoretical reasons for increased bleeding with DOACs. Anatomic considerations such as sites of drug absorption may be important considerations as may be local blood supply, rates of cell turnover, and mucosal cell disruption. Both rivaroxaban and apixaban are absorbed in the active state in the upper GI stomach and the duodenum, with apixaban reported to also have some absorption through the rest of the GI tract. This might argue for a higher local DOAC concentration there and therefore an enhanced bleeding propensity in the upper GI tract [32]. We might have expected this to make a difference in anticoagulant choice for GI tumour but it did not and we also did not detect a difference in bleeding outcomes, either in total bleeds or in bleeding at the GI tumour site itself. Similarly, in the GU tract, it has been argued that DOACs, while being excreted, remain active in the GI tracts while LMWH, needing antithrombin to exert maximum effect, might be more inert and cause less bleeding. This theoretical rationale may have been the explanation for the higher use of LMWH in patients with GU CAT. If a DOAC was chosen, the increased dependency of rivaroxaban on renal clearance may also have led physicians to prescribe apixaban more often in GU tumour. In our retrospective cohort study concentrating on these two potentially problematic areas, we found that, while there was no significant difference in overall (major and CRNMB) bleeding events between DOACs and enoxaparin in patients with underlying GI or GU malignancies, more studies are needed to determine whether the adjusted relative hazard risk data that we demonstrate are valid within a prospective randomized trial setting. We confirm that anticoagulated associated bleeding in GI and GU cancers are very common and that bleeding at the cancer site occurs most often. Thus the safety of DOACs shown in our study is consistent with, and contributes to, evidence for the treatment of venous thromboembolism in cancer patients with DOACs [6,7].

Limitations in our study include its retrospective nature, the small number of patients and the unequal distribution of anticoagulant choices in these cancers. However, while small, it is still larger than many studies examining these cancer subtypes. While we may have missed clinical outcomes that occurred at other health systems, we are the largest health system in the Bronx by far and encompass many of the outlying hospitals within our EPIC system. We also have 'Care Everywhere', which allows us to view data from most other nearby hospitals. A major strength of this patient data review is that the majority of the patient cohort constitutes Hispanic and African American population which have been a minority in all the major RCTs. Available research data support the efficacy of DOACs for treatment of CAT, though their safety is less consistent. The Scientific and Standardization Committee of the International Society of Thrombosis and Haemostasis has stated that DOACs may be considered for the treatment of CAT with several important caveats, including a warning against use in patients with intra-luminal GI cancers [33]. The clinical impact of these considerations to providers and patients is ultimately subjective, and shared decision making remains crucial. Future prospective trials in this area are warranted to fully determine the safety of DOACs in GI and GU cancer patients.

CONCLUSION

It is unclear whether BMP signalling affects the function of astrocytes in the hippocampus; thus, the involvement of BMP signalling in the function of astrocytes in the hippocampus requires further study. In this review, we mainly focused on the effects of BMP signalling on the neurogenesis of neural stem cells in the hippocampus. An increasing number of studies have suggested the involvement of the BMP signalling pathway in abnormal neurogenesis in the diseased hippocampus and

the action of antidepressants, which strongly highlights the importance of the BMP signalling pathway as a potential target for a new therapeutic strategy for psychiatric disorders, such as depression and anxiety.

AUTHOR CONTRIBUTIONS

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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