Risk of Cancer-Associated Thrombosis and Bleeding in Veterans With Malignancy Who Are Receiving Direct Oral Anticoagulants

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The low incidence of venous thromboembolism formation in this study and similar rates of bleeding in other clinical trials indicate that direct oral anticoagulant agents are safe alternatives in patients with cancer.

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Patients with cancer are at an increased risk of both venous thromboembolism (VTE) and bleeding complications. Risk factors for development of cancer-associated thrombosis (CAT) include indwelling lines, antineoplastic therapies, lack of mobility, and physical/chemical damage from the tumor.[1] Venous thromboembolism may manifest as either deep vein thrombosis (DVT) or pulmonary embolism (PE). Cancer-associated thrombosis can lead to significant mortality in patients with cancer and may increase health care costs for additional medications and hospitalizations.

Zullig and colleagues estimated that 46,666 veterans received cancer care from the US Department of Veteran Affairs (VA) health care system in 2010. This number equates to about 3% of all patients with cancer in the US who receive at least some of their health care from the VA health care system.[2] In addition to cancer care, these veterans receive treatment for various comorbid conditions. One such condition that is of concern in a prothrombotic state is atrial fibrillation (AF). For this condition, patients often require anticoagulation therapy with aspirin, warfarin, or one of the recently approved direct oral anticoagulant agents (DOACs), depending on risk factors.

BACKGROUND

Due to their ease of administration, limited monitoring requirements, and proven safety and efficacy in patients with AF requiring anticoagulation, the American Heart Association (AHA) and American College of Cardiology recently switched their recommendations for rivaroxaban and dabigatran for oral stroke prevention to a class 1/level B recommendation.[3]

The American College of Chest Physicians (ACCP) recommends treatment with DOACs over warfarin therapy for acute VTE in patients without cancer; however, the ACCP prefers low molecular-weight heparin (LMWH) over the DOACs for treatment of CAT.[4] Recently, the National Comprehensive Cancer Network (NCCN) updated its guidelines for the treatment of cancer-associated thromboembolic disease to recommend 2 of the DOACs (apixaban, rivaroxaban) for treatment of acute VTE over warfarin. These guidelines also recommend LMWH over DOACs for treatment of acute VTE in patients with cancer.[5] These NCCN recommendations are largely based on prespecified subgroup meta-analyses of the DOACs compared with those of LMWH or warfarin in the cancer population.

In addition to stroke prevention in patients with AF, DOACs have additional FDA-approved indications, including treatment of acute VTE, prevention of recurrent VTE, and postoperative VTE treatment and prophylaxis. Due to a lack of head-to-head, randomized controlled trials comparing LMWH with DOACs in patients with cancer, these agents have not found their formal place in the treatment or prevention of CAT. Several meta-analyses have suggested similar efficacy and safety outcomes in patients with cancer compared with those of LMWH.[6-8] These meta-analysis studies largely looked at subpopulations and compared the outcomes with those of the landmark CLOT (Randomized Comparison of Low-Molecular-Weight Heparin

versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer Investigators) and CATCH (Comparison of Acute Treatments in Cancer Hemostasis) trials.[9,10]

As it is still unclear whether the DOACs are effective and safe for treatment/prevention of CAT, some confusion remains regarding the best management of these at-risk patients. In patients with cancer on DOAC therapy for an approved indication, it is assumed that the therapeutic benefit seen in approved indications would translate to treatment and prevention of CAT. This study aims to determine the incidence of VTE and rates of major and clinically relevant nonmajor bleeding (CRNMB) in veterans with cancer who received a DOAC.

METHODS

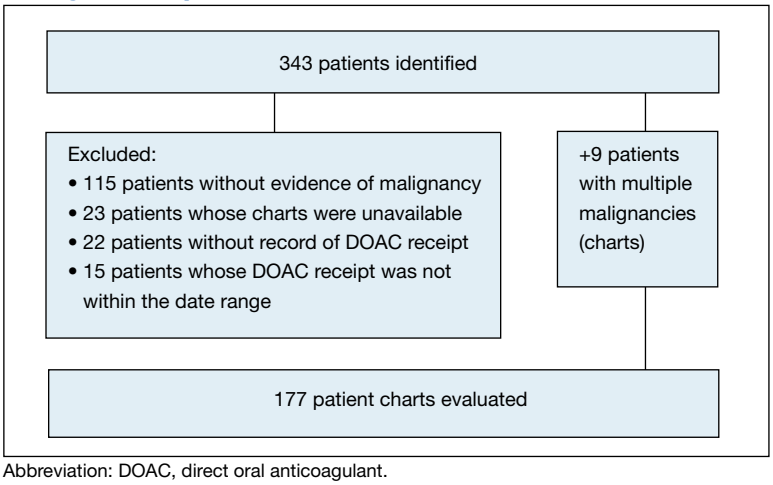
This retrospective, single-center chart review was approved by the local institutional review board and research safety committee. A search within the VA Corporate Data Warehouse identified patients who had an active prescription for one of the DOACs (apixaban, dabigatran, edoxaban, and rivaroxaban) along with an ICD 9 or ICD 10 code corresponding to a malignancy.

Patients were included in the final analysis if they were aged 18 to 89 years at time of DOAC receipt, undergoing active treatment for malignancy, had evidence of a history of malignancy (either diagnostic or charted evidence of previous treatment), or received cancer-related surgery within 30 days of DOAC prescription with curative intent. Patients were excluded from the final analysis if they did not receive a DOAC prescription or have any clear evidence of malignancy documented in the medical chart.

Patients' charts were evaluated for the following clinical endpoints: patient age, height (cm), weight (kg), type of malignancy, type of treatment for malignancy, serum creatinine (SCr), creatinine clearance (CrCl) calculated with the Cockcroft-Gault equation using actual body weight, serum hemoglobin, aspartate aminotransferase, alanine aminotransferase, total bilirubin, indication for DOAC, type of VTE, presence of a prior VTE, and diagnostic test performed for VTE. Major bleeding and CRNMB criteria were based on the definitions provided by the International Society on Thrombosis and Haemostasis (ISTH).[11] All laboratory values and demographic information were gathered at the time of initial DOAC prescription.

FIGURE

Study Participation Flowchart



Abbreviation: DOAC, direct oral anticoagulant.

The primary endpoint for this study was incidence of VTE. The secondary endpoints included major bleeding and CRNMB. All data collection and statistical analysis were done using Microsoft Excel 2016 (Redmond, WA). Comparisons of data between trials were done using the chi-squared calculation.

RESULTS

From initial FDA approval of dabigatran (first DOAC on the market) on October 15, 2012, to January 1, 2017, there were 343 patients who met initial inclusion criteria. Of those, 115 did not have any clear evidence of malignancy, 22 did not have any records of DOAC receipt, 15 did not receive a DOAC within the date range, and 23 patients' charts were unavailable. In addition, 9 of the patients identified had multiple malignancies. This resulted in 177 evaluable medical charts for this study (Figure).

The majority of the patients were males (96.6%), with an average age of 74.5 years. The average weight of all patients was 92.5 kg, with an average SCr of 1.1 mg/dL. This equated to an average CrCl of 85.5 mL/min based on the Cockcroft-Gault equation using actual bodyweight. Of the 177 patients evaluated, 30 (16.9%) were receiving active cancer treatment at time of DOAC initiation. Ninety patients (50.8%) received apixaban, 53 patients (29.9%) received dabigatran, and 34 patients (19.2%) received rivaroxaban; no patients received edoxaban therapy. Most of the patients (79.1%) received a DOAC for stroke prevention with AF/atrial flutter, and the remainder received a DOAC

TABLE 1
Baseline Demographics at DOAC Initiation

Characteristics	Results
Male, No. (%)	171.0 (96.6)
Age, mean (SD), y	74.5 (0.7)
Height, mean (SD), cm	175.7 (0.9)
Weight, mean (SD), kg	92.5 (1.8)
Body mass index, mean (SD), kg/m^2	30.0 (8)
Serum creatine, mean (SD), mg/dL	1.1 (0.3)
Creatinine clearance, mean (SD), (mL/min)[a]	85.5 (2.7)
Receiving cancer treatment, No. (%)	30.0 (16.9)
DOAC received, No. (%)	
Apixaban	90.0 (50.8)
Dabigatran	53.0 (29.9)
Edoxaban	0.0 (0)
Rivaroxaban	34.0 (19.2)
Indication for DOAC, No. (%)	
Acute venous thromboembolism	22 (12.4)
Atrial fibrillation/atrial flutter	140 (79.1)
History of venous thromboembolism	15 (8.5)
History of DVT, No. (%)	24 (13.6)

Abbreviations: DOAC, direct oral anticoagulant agents; DVT, deep vein thrombosis.
[a]Creatinine clearance calculated using Cockcroft-Gault equation with actual body weight.

for VTE treatment (12.4%) or VTE prophylaxis due to a history of prior VTE (8.5%). Baseline demographics are presented in Table 1 and are compared with the baseline demographics from the CLOT and CATCH trials in Table 2.

Two (1.1%) patients developed a VTE while receiving a DOAC. One patient was on rivaroxaban 20 mg daily for a prior VTE; the other was on dabigatran 150 mg twice daily for stroke prevention due to AF. Both patients developed a DVT, which was diagnosed by ultrasound (Table 3). The rate of VTE incidence in the CLOT trial was 8% and in the CATCH trial was 7.2%, both of which were much higher than the rate reported in this study ($P < .01$).[9,10]

Among the 177 evaluable patients in this study, there were 7 patients (4%) who developed a major bleed and 13 patients (7.3%) who developed a clinically relevant nonmajor bleed according to the definitions provided by ISTH.[11] The average time from first DOAC prescription to the bleeding event was about 9.6 months for a major bleed and 7.4 months for a CRNMB. Of the patients who had a major bleed, 3 were receiving apixaban, 2 were receiving dabigatran, and 2 were receiving rivaroxaban ($P = .79$ for all DOACs). Of the patients who developed CRNMB, 8 were receiving apixaban, 2 were receiving dabigatran, and 3 were receiving rivaroxaban ($P = .88$ for all DOACs). The breakdown of bleeding rates is presented in Table 4. The comparison of major and CRNMB rates in this study and the landmark trials are presented in Table 5.

As previously mentioned, only 30 of the patients were actively receiving treatment during DOAC administration. Most of the documented cases of malignancy were either a history of nonmelanoma skin cancer (NMSC) or prostate cancer. The most common method of treatment was surgical resection for both malignancies. Of the 30 patients who received active malignancy treatment while on a DOAC, there were 4 patients with multiple myeloma, 6 patients with NMSC, 4 patients with colon cancer, 1 patient with chronic lymphocytic leukemia (CLL), 1 patient with chronic myelogenous leukemia (CML), 1 patient with small lymphocytic leukemia (SLL), 4 patients with non-small cell lung cancer (NSCLC), 1 patient with unspecified brain cancer, and 1 patient with breast cancer. The various characteristics of these patients are presented in Table 6. Among these 30 patients, only 1 patient developed a DVT. Another patient developed a major bleed 12 months after initiating rivaroxaban 20 mg daily due to a history of prior VTE.

DISCUSSION

The CLOT and CATCH trials were chosen as historic comparators. Although the active treatment interventions and comparator arms were not similar between the patients included in this study and the CLOT and CATCH trials, the authors felt the comparison was appropriate as these trials were designed specifically for patients with malignancy. Additionally, these trials sought to assess rates of VTE formation and bleeding in the patient with malignancies—outcomes that aligned with this study. Alternative trials for comparison are the subgroup analyses of patients with malignancies in the AMPLIFY, RE-COVER, and EINSTEIN trials.[12-14] Although these trials were designed to stratify patients based on presence of malignancy, they were

TABLE 2
Comparison of Baseline Demographics Among Trials

	Study[a] (n = 177)	CLOT[b] Dalteparin (n = 338)	CLOT[b] Warfarin (n = 338)	CATCH[b] Tinazaparin (n = 449)	CATCH[b] Warfarin (n = 451)
Male, No. (%)	171 (96.6)	159 (47.0)	170 (50.3)	187 (48.6)	178 (39.5)
Age (SD), y	74.5 (0.7)	62 ± 12	63 ± 13	59.7 ± 12.7	58.8 ± 12.5
Weight (SD), kg	92.5 (1.8)	Not reported	Not reported	67.3 ± 17.3	67.1 ± 16.3
Receiving cancer treatment, No. (%)	30 (16.9)	266 (78.7)	259 (76.6)	228 (50.8)	248 (55)
History of DVT, No. (%)	24 (13.6)	39 (11.5)	36 (10.7)	27 (6)	30 (6.7)

Abbreviations: CATCH, Comparison of Acute Treatments in Cancer Hemostasis trial; CLOT, Randomized Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer Investigators trial; DVT, deep vein thrombosis.
[a]Descriptive statistics presented as mean + SEM unless otherwise noted.
[b]All data presented as mean + SD unless otherwise noted.

not powered to account for increased risk of VTE in patients with malignancies.

There are multiple risk factors that increase the risk of CAT. Khoranna and colleagues identified primary stomach, pancreas, brain, lung, lymphoma, gynecologic, bladder, testicular, and renal carcinomas as a high risk of VTE formation.[15] Additionally, Khoranna and colleagues noted that elderly patients and patients actively receiving treatment are at an increased risk of VTE formation.[15] The low rate of VTE formation (1.1%) in the patients in this study may be due to the low risk for VTE formation. As previously mentioned, only 30 of the patients (16.9%) in this study were receiving active treatment.

Additionally, there were only 42 patients (23.7%) who had a high-risk malignancy. The increased age of the patient population (74.5 years old) in this study is one risk factor that could largely skew the risks of VTE formation in the patient population. In addition to age, the average body mass index (BMI) of this study's patient population (30 kg/m^2) may further increase risk of VTE. Although Khoranna and colleagues identified a BMI of 35 kg/m^2 as the cutoff for increased risk of CAT, the increased risk based on a BMI of 30 kg/m^2 cannot be ignored in the patients in this study.[15]

Another risk inherent in the treatment of patients with cancer is pancytopenia, which may lead to increased risks of bleeding and infection. When patients are exposed to an anticoagulant agent in the setting of decreased platelets and hemoglobin (from treatment or disease process), the risk for major bleeds and CRNMB are increased drastically. In this patient population, the combined rate of bleeding (11.3%) was relatively decreased compared with that of the CLOT (16.5% for all bleeding events) and CATCH (15.7% for all bleeding events) trials.[9,10]

Compared with the oncology subgroup analysis of the AMPLIFY, RE-COVER, and EINSTEIN trials, the differences are more noticeable. The AMPLIFY trial reported a 1.1% incidence of bleeding in patients with cancer on apixaban, whereas the RE-COVER trial did not report bleeding rates, and the EINSTEIN trial reported a 14% incidence of bleeding in all patients with cancer on rivaroxaban for VTE treatment.[12-14] This study found a bleeding incidence of 12.2% with apixaban, 5.7% with dabigatran, and 14.7% with rivaroxaban. In this trial

TABLE 3
Characteristics of Patients Who Developed VTE While on a DOAC

Characteristics	DOAC	Malignancy (With Treatment)	Time to VTE
Male, 67 y Height: 196.9 cm Weight: 138.4 kg	Dabigatran 150 mg po bid for atrial fibrillation	Nonmelanoma skin cancer (excision, radiation and adjuvant capecitabine, topical fluorouracil)	25 mo
Male, 71 y Height: 175.3 cm Weight: 86.2 kg	Rivaroxaban 20 mg po daily for acute VTE	Rectal (Previously treated with radiation and adjuvant capecitabine)	11 mo

Abbreviations: DOAC, direct oral anticoagulant agent, VTE, venous thromboembolism.

TABLE 4
Bleeding Events

	Events, No.	Average Time to Event, mo	Apixaban, No. (%) (n = 90)	Dabigatran, No. (%) (n = 53)	Rivaroxaban, No. (%) (n = 34)
Total	20	8.2	11 (12.2)	4 (7.5)	5 (14.7)
Major	7	9.6	3 (3.3)	2 (3.8)	2 (5.9)
CRNMB	13	7.4	8 (8.9)	2 (3.8)	3 (8.8)

Abbreviation: CRNMB, clinically relevant nonmajor bleeding.

TABLE 5
Comparison of Bleeding Rates Among Trials

	Study (n = 177)	CLOT LMWH (n = 338)	CLOT Warfarin (n = 335)	CATCH LMWH (n = 449)	CATCH Warfarin (n = 451)	*P* Value[a]
Total	20	47	64	61	80	
Major	7	19	12	12	11	.03
CRNMB	13	28	52	49	69	.43
P value[a]		.02		.005		

Abbreviations: CATCH, Comparison of Acute Treatments in Cancer Hemostasis Trial; CLOT, Randomized Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer Investigators Trial; CRNMB, clinically relevant nonmajor bleeding; LMWH, low-molecular-weight heparin.
[a]*P* value is based on chi-squared comparison of each trial to study trial. Significance level set at $P < .05$.

the incidence of bleeding with rivaroxaban were similar; however, the incidence of bleeding with apixaban was markedly higher. There is no obvious explanation for this, as the dosing of apixaban was appropriate in all patients in this trial except for one. There was no documented bleed in this patient's medical chart.

A meta-analysis conducted by Vedovati and colleagues identified 6 studies in which patients with cancer received either a DOAC (with or without a heparin product) or vitamin K antagonist.[16] That analysis found a nonsignificant reduction in VTE recurrence (odds ratio [OR], 0.63; 95% confidence interval [CI], 0.31-1.1), major bleeding (OR, 0.77; 95% CI, 0.41-1.44), and CRNMB (OR, 0.85; 95% CI, 0.62-1.18).[16] The meta-analysis adds to the growing body of evidence in support of both safety and efficacy of DOACs in patients with cancer. Although the Vedovati and colleagues study does not directly compare rates between 2 treatment groups, the findings of similar rates of VTE recurrence, major bleed, and CRNMB are consistent with the current study. Despite differing patient characteristics, the meta-analysis by Vedovati and colleagues supports the ongoing use of DOACs in patients with malignancy, as does the current study.[16]

Limitations

Although it seems that apixaban, dabigatran, and rivaroxaban are effective in reducing the risk of VTE in veterans with malignancy, there are some inherent weaknesses in the current study. Most notably is the choice of comparator trials. The authors' believe that the CLOT and CATCH trials were the most appropriate based on similarities in population and outcomes. Considering the CLOT and CATCH trials compared LMWH to coumarin products for treatment of VTE, future studies should compare use of these agents with DOACs in the cancer population. In addition, the study did not include outcomes that would adequately assess risks of VTE and bleeding formation. This information would have been beneficial to more effectively categorize this study's patient population based on risks of each of its predetermined outcomes. Understanding safety and efficacy of DOACs in patients at various risks would help practitioners to choose more appropriate agents in practice. Last, this study

TABLE 6
Characteristics of Patients Receiving Active Treatment

Malignancy	Treatment Regimen	Metastatic	DOAC	DOAC Indication
Brain	Unknown	Yes	Apixaban	AF
Breast	Anastrozole, radiation therapy	No	Dabigatran	AF
CLL	Ibrutinib	Yes	Apixaban	AF
CML	Bosutinib	No	Apixaban	AF
Colon	Capecitabine, oxaliplatin	No	Rivaroxaban	Acute VTE
	Regorafenib	Yes	Apixaban	History of VTE
	Surgery	No	Apixaban	AF
	Capecitabine, oxaliplatin[a]	Yes	Rivaroxaban	Acute VTE
Multiple myeloma	Bortezomib, dexamethasone	Yes	Dabigatran	AF
	Bortezomib, cyclophosphamide, dexamethasone	No	Apixaban	Acute VTE
	Lenalidomide	Yes	Rivaroxaban	AF
	Lenalidomide, carfilzomib, dexamethasone	Yes	Rivaroxaban	Acute VTE
NMSC	Imiquimod topical	No	Apixaban	AF
	Resection	No	Apixaban	AF
	Excised	No	Dabigatran	AF
	Excised	No	Dabigatran	AF
	Excised, fluorouracil	No	Rivaroxaban	History of VTE
	Radiation, adjuvant capecitabine, excision, fluorouracil[b]	Yes	Dabigatran	AF
	Radiation	No	Apixaban	AF
	Erlotinib	No	Apixaban	AF
	Carboplatin-taxol, docetaxel, nivolumab	Yes	Dabigatran	AF
	Radiation	Yes	Rivaroxaban	Acute VTE
Prostate	Leuprolide	No	Apixaban	AF
	Leuprolide	No	Rivaroxaban	AF
	Radiation	No	Dabigatran	AF
	Bicalutamide, leuprolide	Yes	Apixaban	AF
	Docetaxel, bicalutamide	No	Dabigatran	AF
	Radiation, bicalutamide, leuprolide	No	Dabigatran	AF
	Radiation	No	Rivaroxaban	AF
SLL	Prednisone	No	Apixaban	AF

Abbreviations: AF, atrial fibrillation; CLL, chronic lymphocytic leukemia, CML, chronic myelogenous leukemia; DOAC, direct oral anticoagulant; NMSC, nonmelanoma skin cancer; NSCLC, non-small cell lung cancer; SLL, small lymphocytic lymphoma; VTE, venous thromboembolism.
[a]This patient developed a major bleed 12 months after DOAC initiation.
[b]This patient developed deep vein thrombosis.

did not assess the incidence of stroke in study patients. This is important because the DOACs were used mostly for stroke prevention in AF and atrial flutter. The increased risk of VTE in patients with cancer cannot directly correlate to risk of stroke with a comorbid cardiac condition, but the hypercoagulable state cannot be ignored in these patients.

CONCLUSION

This study provided some preliminary evidence for the safety and efficacy of DOACs in patients with cancer. The low incidence of VTE formation and similar rates of bleeding among other clinical trials indicate that DOACs are safe alternatives to currently recommended anticoagulation medication in patients with cancer.

AUTHOR DISCLOSURES

The authors report no actual or potential conflicts of interest with regard to this article.

DISCLAIMER

combinations—including indications, contraindications, warnings, and adverse effects—before administering pharmacologic therapy to patients.

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