






RECOMMENDATIONS AND GUIDELINES

Characteristics and outcomes of patients on concurrent direct oral anticoagulants and targeted anticancer therapies—TacDOAC registry: Communication from the ISTH SSC Subcommittee on Hemostasis and Malignancy

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Abstract

Background: Cancer patients are increasingly prescribed direct oral anticoagulants (DOACs) and targeted anticancer therapies, but limited data are available on the outcomes during concurrent use.

Objectives: We conducted an international registry through the Scientific and Standardization Committee of the ISTH to evaluate the characteristics, bleeding, and thrombotic outcomes in patients receiving concurrent DOACs and targeted anticancer therapies.

Patients/Methods: Patients receiving concurrent DOACs for venous thromboembolism (VTE) or atrial fibrillation and selected targeted anticancer therapies were followed for 6 months after the start of concurrent use. Data including patient and cancer characteristics, major bleeding, non-major bleeding events, and venous or arterial thromboses were collected.

Results: Two hundred and two patients were included from six institutions in the United States and Israel. The most common malignancies were hematologic ($N = 57$, 28.2%), followed by breast ($N = 50$, 24.8%) and lung ($N = 44$, 21.8%). The most common anticancer therapies were epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) inhibitors ($N = 43$, 21.3%), followed by Bruton's tyrosine kinase (BTK) inhibitors ($N = 42$, 20.8%) and palbociclib ($N = 42$, 20.8%). During follow-up, there were 9 major bleeding and 12 non-major bleeding events, corresponding to cumulative incidences of 4% (95% confidence interval [CI]: 2–8%) and 6% (95% CI: 3–10%), respectively. The cumulative incidence of major bleeding events was highest in BTK inhibitor users (10%). There were 3 VTE and 2 arterial thromboses, corresponding to cumulative incidences of 1.5% (95% CI: 0.4–4.0%) and 1.0% (95% CI: 0.2–3.3%), respectively.

Manuscript handled by: Joost Meijers

Final decision: Joost Meijers, 29 April 2021

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Funding information

International Society on Thrombosis and Haemostasis

Conclusions: In this cohort receiving concurrent DOACs and targeted anticancer therapies, the incidence of bleeding is higher compared to thrombosis, particularly with BTK inhibitors. Future larger prospective studies are needed.

KEYWORDS

anticoagulation, cancer-associated thrombosis, direct oral anticoagulants, drug-drug interaction, targeted anticancer therapy

1 | INTRODUCTION

Cancer patients have a 4- to 7-fold increased risk of venous thromboembolism (VTE) compared to patients without cancer.¹ In addition, they also have an increased risk of arterial thromboembolism (ATE), partially due to high rates of atrial fibrillation (AF).² In recent years, randomized controlled trials (RCTs) showed that direct oral coagulants (DOACs) are non-inferior to low molecular weight heparin (LMWH) for the treatment of cancer-associated thrombosis.³⁻⁶ Two additional RCTs established the role of DOACs for prevention of cancer-associated thrombosis in ambulatory cancer patients with intermediate to high risks of VTE (Khorana score ≥ 2).^{7,8} Clinical practice guidelines have since endorsed the use of DOACs in the prevention and treatment of cancer-associated thrombosis.⁹⁻¹² DOACs are also recommended as the preferred anticoagulant in cancer patients with newly diagnosed AF without high risks of gastrointestinal (GI) bleeding.¹³

Despite increasing utilization of DOACs in the management of VTE and AF in cancer patients, their safety with concurrent use of oral targeted anticancer therapies is largely unknown. DOACs are substrates of two predominant pathways: P-glycoprotein (P-gp) cell transporters and cytochrome P450 enzyme (CYP3A4) in the liver.¹⁴ Dabigatran and edoxaban are metabolized through the P-gp system but are independent of CYP3A4. Apixaban and rivaroxaban rely on both the P-gp and CYP3A4 metabolism. Concomitant medications that significantly inhibit or enhance P-gp and/or CYP3A4 pathways can potentially increase the risks of bleeding or thrombosis, respectively.^{15,16} In recent years, targeted anticancer therapies have been utilized in various cancer types, and many of these are tyrosine kinase inhibitors (TKI), which are also involved in the P-gp and/or CYP3A4 pathways. Limited pharmacokinetic studies have shown that concurrent use of medications involving both P-gp and CYP3A4 metabolism could influence DOAC drug levels *in vitro*, but whether these findings translate into clinically relevant events has not been established. For example, a recent large database analysis showed that the concurrent use of clarithromycin (increases DOAC levels) and DOACs led to an increase in clinically relevant bleeding events (adjusted hazard ratio [HR] 1.71, 95% confidence interval [CI] 1.20–2.45 for hemorrhage requiring hospitalization) compared to azithromycin (minimal effects on DOAC metabolism).¹⁷ However, data regarding concurrent use of DOACs and targeted anticancer therapies are limited. In addition, some targeted anticancer therapies such as ibrutinib can increase the risk of bleeding in the absence of

anticoagulants by other mechanisms.¹⁸ Vascular endothelial growth factor (VEGF) inhibitors can also increase the risk of both bleeding and thrombosis.^{19,20}

Currently, major international clinical practice guidelines and product inserts suggest caution and/or avoidance in using DOACs with potential interactions with anticancer therapies.⁹⁻¹¹ However, these recommendations are mainly based on *in vitro* pharmacokinetic studies and/or expert opinions, and there is little direct evidence from clinical studies on the effects of combined use of DOACs and targeted anticancer therapies. This lack of evidence has led to inconsistency and ambiguity with product labelling recommendations. For example, package inserts from Food and Drug Administration (FDA)-recommended dose reduction of apixaban (to 2.5 mg twice daily) for patients on strong dual inhibitors of CYP3A4 and P-gp pathways,²¹ while Canadian product monographs recommended against the use of apixaban in these patients.²² Edoxaban has dose-reduction recommendations in patients on P-gp inhibitors, while rivaroxaban and dabigatran do not. This creates uncertainty around pertinent clinical situations, such as the need for dose adjustment of anticancer therapies, DOACs, or both, upon concurrent use; the need to change to alternative anticoagulants; or monitoring strategies in patients on concurrent medications with potential interaction. Empiric dose adjustments of targeted anticancer therapies and/or anticoagulants might be done without evidence, which could result in increased risk of thrombosis or bleeding events if such adjustments are inappropriate. Therefore, it is of utmost importance and interest to investigate the outcomes of concurrent use of DOACs and targeted anticancer therapies.

The international registry of the safety and efficacy in cancer patients with concurrent use of direct oral anticoagulants and targeted anticancer therapies (TacDOAC registry) was approved by the subcommittee on Hemostasis and Malignancy of the international society on thrombosis and haemostasis (ISTH) and started enrollment in 2019. The aim of this observational international registry was to evaluate the patient and cancer characteristics, and bleeding and thrombotic outcomes in patients receiving concurrent DOACs and targeted anticancer therapies.

2 | METHODS

The registry was open for participation to all ISTH members. The registry was first announced at the Standardization and Scientific

Committees (SSC) meeting of the ISTH at the 2018 Congress and started enrollment in June 2019, with updated reports and reminders at the annual Congresses. Information about the registry was posted on the ISTH website (<https://www.isth.org/members/group.aspx?id=100352>). The enrollment was completed in October 2020. ISTH supported the registry with a grant and online REDCap platform for data collection. The funding agency had no influence on the design and conduct of the study, as well as analysis and presentation of the study results. The registry was approved by local institutional review boards or research ethics boards at each center as either prospective or retrospective study, depending on its choice and resources. For patients enrolled prospectively, each patient signed a written consent form.

Eligible patients included adult patients of 18 to 89 years of age with histologically confirmed active malignancy (defined as malignancy diagnosed or treated within 6 months of concurrent use or metastatic/recurrent malignancy) excluding in situ skin cancer, who had taken one of the listed targeted anticancer therapies of interest (Table 1) and any DOACs (dabigatran, rivaroxaban, apixaban, or edoxaban) concurrently. Given the large and growing number of targeted anticancer therapies, it was decided to limit to a selected list of targeted anticancer therapies (Table 1) for this registry. These anticancer therapies were selected based on potential drug-drug interactions involving the P-gp and/or CYP3A4 pathways, potential concern of excess bleeding risks given known characteristics of targeted anticancer therapies, and/or the frequency of use after consultation with oncologists. Each participating center identified eligible patients, and collected and input de-identified data on the standardized online REDCap case report forms. Data collected included patient characteristics (age, race, sex, weight, creatinine, platelet count, Eastern Cooperative Oncology Group [ECOG] performance status), characteristics of cancer and its treatment (site, histology, and stage of cancer; type, dose, and duration of targeted anticancer therapies), and characteristics of anticoagulation (type, dose, indication, and duration). Baseline characteristics were collected at the time of initiation of concurrent use (index date). Patients were then followed prospectively or data collected retrospectively for 6 months after the index date, regardless of the duration of concurrent use. The primary outcome of the study was major bleeding events, defined by ISTH major bleeding criteria, including fatal bleeding; bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal; overt bleeding with drop in hemoglobin of at least 2 g/dl or requiring at least two units of packed red blood cell transfusion.²³ Secondary outcomes included objectively confirmed recurrent VTE, ATE (by imaging studies and notes in medical records), and non-major bleeding events. Non-major bleeding events were events not meeting major bleeding criteria but prompted encounters with health-care teams, including phone calls, in-person visits, or hospitalizations and/or resulted in interventions (including any change in anticoagulant or anticancer therapies). Status of malignancy and vital status were recorded at 6 months. All outcome events were adjudicated by two physicians after reviewing relevant clinical notes, and imaging and laboratory studies.

2.1 | Statistical analysis

There was no formal sample size calculation as there were no reliable data on the rates of bleeding or thrombotic events in cancer patients receiving DOACs concurrently with various targeted anticancer therapies. A convenient sample size of 200 patients (100 for cancer-associated thrombosis and 100 for AF) was targeted. Descriptive statistics were used to present the results. Mean (standard deviation [SD]) or median (interquartile range [IQR]) was calculated for continuous variables, wherever appropriate, while count and percentage distribution were calculated for categorical variables. Kaplan-Meier analysis was used to calculate the 6-month cumulative incidences of major bleeding and non-major bleeding events, VTE and ATE, using death as a competing risk. Missing data were excluded from analysis. The statistical analyses were performed using SAS Enterprise Guide (version 7.15; SAS Institute Inc.) and R software (version 3.5.1).

3 | RESULTS

3.1 | Characteristics of the study population

Six centers from the United States and Israel (The Ohio State University, Versiti, Rabin Medical Center, University of Utah, University of Alabama at Birmingham, Washington University) enrolled a total of 202 patients in the study. Most data were collected retrospectively, except for 13 patients enrolled prospectively from the lead site (The Ohio State University). Consecutive patients with start of concurrent use between 2012 and 2020 were included. Table 2 summarizes data on patient, anticoagulation, and cancer characteristics. The median age was 67.5 (IQR 58–73) years. Approximately half (45.5%) of the patients were male. Most (84.6%) had a good ECOG performance status (0 or 1). The most common types of cancer in the study were hematologic ($N = 57$, 28.2%, including chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), and non-Hodgkin's lymphoma), followed by breast ($N = 50$, 24.8%) and lung cancer ($N = 44$, 21.8%). The majority (94.5%) of patients with solid tumor had metastatic disease at the time of concurrent use, with brain metastasis in 27.5% of patients.

Table 3 summarizes the number of patients and outcomes by anticancer therapies. The most common anticancer therapy regimens included epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) inhibitors ($N = 43$, 21.3%), Bruton's tyrosine kinase (BTK) inhibitors ($N = 42$, 20.8%), and cyclin-dependent kinase (CDK) inhibitor palbociclib ($N = 42$, 20.8%). For anticoagulation, 134 patients (66.3%) and 73 (36.1%) were prescribed DOACs for VTE and AF, respectively (five patients had both indications). Apixaban and rivaroxaban were the most common DOACs used, accounting for 96% (rivaroxaban: $N = 95$, apixaban: $N = 99$), while dabigatran was prescribed in 9 (4.5%) patients and edoxaban in 2 (1%) patients (3 patients had different DOACs at different time points). Most DOACs were prescribed at therapeutic dose (85.3%). In 31 patients treated with reduced anticoagulant dose, 12 (6% of

TABLE 1 Included targeted anticancer therapies in the current study and their mechanisms

Class	Targeted anticancer therapies	Drug	CYP3A4 pathway		P-gp pathway		Other hemostatic effects
			Type of effect	Putative effects on DOAC level	Type of effect	Putative effects on DOAC level	
EGFR, ALK inhibitors (lung cancer)		Osimertinib	Inhibitor (weak)	↑	None	None	Unknown
		Alectinib	None		Inhibitor	↑	Unknown
BTK inhibitors (CLL, lymphoma)		Ibrutinib	Inhibitor (weak)	↑	Inhibitor	↑	Anti-platelet effects causing bleeding
		Acalabrutinib	Inhibitor (weak)	↑	None	None	
Cyclin-dependent kinase inhibitor (breast cancer)		Palbociclib	Inhibitor (weak)	↑	None	None	Potentially thrombotic
VEGF inhibitors (mainly kidney cancer)		Sunitinib	None		? ^a		Thrombotic
		Cabozantinib	Inhibitor (weak)	↑	Inhibitor	↑	
BCR-ABL inhibitors (CML)		Imatinib	Inhibitor (moderate)	↑	? ^a		Thrombotic (arterial)
		Nilotinib	Inhibitor (moderate)	↑	Inhibitor	↑	
mTOR inhibitor (various cancer)		Everolimus	Inhibitor (weak)	↑	None	None	Unknown
HER2 inhibitors (breast cancer)		Lapatinib	Inhibitor (weak)	↑	Inhibitor	↑	Unknown
		Vemurafenib	Inducer (moderate)	↑	Inhibitor	↑	Unknown

Note: The information is obtained from FDA package inserts, Canadian product monographs, Lexicomp[®], and review articles.^{36,37}

Abbreviations: ALK, anaplastic lymphoma kinase; BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; CYP, cytochrome; DOAC, direct oral anticoagulant; EGFR, epidermal growth factor receptor; FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor 2; mTOR, mammalian target of rapamycin; P-gp: p-glycoprotein; VEGF: vascular endothelial growth factor.

^aNo effects reported in product labels nor Lexicomp[®] but in inhibiting effects commented in review articles cited above

TABLE 2 Patient and cancer characteristics at the time of concurrent use

Patient characteristics	
Age (years) median (IQR)	67.5 (58–73)
Male, N (%)	92 (45.5%)
Race, N (%) ^a	
White	150 (87.7%)
Black	14 (8.2%)
Asian	2 (1.2%)
Hispanic	2 (1.2%)
Other	3 (1.8%)
Weight (kg), median (IQR)	80.75 (69–101)
Creatinine (mg/dl), median (IQR)	0.97 (0.8–1.16)
Platelet count (K/ μ l), median (IQR)	213 (160–272)
ECOG ^a	
0	51 (30.4%)
I	91 (54.2%)
II	24 (14.3%)
III	2 (1.2%)
IV	0
Anticoagulation characteristics	
Indications (5 with both VTE and AF)	
VTE	134 (66.3%)
AF	73 (36.1%)
CHADSVASc score, median (IQR) ^a	3 (2.25–4)
Type (3 patients on different DOACs at different time)	
Dabigatran	9 (4.4%)
Rivaroxaban	95 (46.3%)
Apixaban	99 (48.3%)
Edoxaban	2 (1.0%)
Dose	
Therapeutic dose	174 (84.9%)
Reduced dose	31 (15.1%)
Cancer characteristics	
Cancer sites	
Breast	50 (24.8%)
Lung	44 (21.8%)
Gastrointestinal	12 (5.9%)
Genitourinary	27 (13.4%)
Gynecological	3 (1.5%)
Melanoma	1 (0.5%)
Hematologic	57 (28.2%)
Others ^b	9 (4.5%)
Cancer histology	
Adenocarcinoma	119 (58.9%)
Squamous	3 (1.5%)
Sarcoma	12 (5.9%)

(Continues)

TABLE 2 (Continued)

Cancer characteristics	
Chronic leukemia ^c	48 (23.8%)
Lymphoma	9 (4.5%)
Others ^d	12 (5.9%)
Stage (solid tumor)	N = 145
I	2/145 (1.4%)
II	1/145 (0.7%)
III	5/145 (3.4%)
IV	137/145 (94.5%)
Presence of brain metastasis (solid tumor) ^a	39/142 (27.5%)

Abbreviations: AF: atrial fibrillation; CLL: chronic lymphocytic leukemia; CML: chronic myelogenous leukemia; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; GIST: gastrointestinal stromal tumors; IQR: inter-quarter range; RCC, renal cell carcinoma; SD: standard deviation; VTE: venous thromboembolism.

^aExcluding unknown or missing values.

^bSarcoma: 2, thyroid: 3, neuroendocrine: 4.

^cCLL: 33, CML: 14, hairy cell leukemia: 1.

^dPapillary, anaplastic, neuroendocrine.

the overall population) were retrospectively deemed inappropriate based on package inserts (although rationales of dose reduction were often incompletely documented), mostly AF patients on apixaban. One patient received another concurrent interfering medication, dronedarone (moderate inhibitor of CYP3A4 and P-gp) with ibrutinib and apixaban; no other patients had reported concurrent use of other medications with CYP3A4 or P-gp interactions. Further details are available in Appendix Table A1 (indication of anticoagulation by cancer type) and Appendix Table A2 (DOACs and anticancer therapies combinations). Forty-one (20%) patients were taking concomitant aspirin and 6 (3%) had concomitant clopidogrel. The median duration of concurrent use during follow up was 6 (IQR 5.1–6) months.

3.2 | Bleeding events

Overall, nine major bleeding events were recorded within 6 months, including one fatal bleeding event, corresponding to a cumulative incidence of 4% (95% CI: 2–8%). There were 12 non-major bleeding events, with a cumulative incidence of 6% (95% CI: 3–10%). The incidences (95% CI) of major and non-major bleeding events were the highest in patients on BTK inhibitors (10% [3–21%] and 14% [6–27%], respectively), followed by 7% (1–21%) and 4% (0.2–16%) in VEGF inhibitor users, 5% (1–14%) and 7% (2–18%) in palbociclib users, and 2% (0.2–11%) and 2% (0.2–11%) in EGFR/ALK inhibitor users (Table 3). Appendix Figure A1 depicts the cumulative incidence of major bleeding events by anticancer therapies. Details of patient characteristics, bleeding events, and management in patients with major and non-major bleeding events are summarized in Appendix Tables A3 and A4, respectively.

TABLE 3 Bleeding and thrombotic outcomes by anticancer therapies

Anticancer therapies ^a	N = 202 (%)	Major bleeding		Non-major bleeding		VTE		ATE	
		N (%)	Cumulative incidence %, (95% CI)	N (%)	Cumulative incidence %, (95% CI)	N (%)	Cumulative incidence %, (95% CI)	N (%)	Cumulative incidence %, (95% CI)
EGFR and ALK inhibitors (osimertinib, alectinib)	43 (21.3%)	1/43 (2.3%)	2 (0.2-11)	1/43 (2.3%)	2 (0.2-11)	0		1/43 (2.3%)	2 (0.2-11)
BTK inhibitors (ibrutinib, acalabrutinib)	42 (20.8%)	4/42 (9.5%)	10 (3-21)	6/42 (14.3%)	14 (6-27)	0		0	
Cyclin-dependent kinase inhibitor (palbociclib)	42 (20.8%)	2/42 (4.8%)	5 (1-14)	3/42 (7.1%)	7 (2-18)	0		0	
VEGF inhibitors (sunitinib, cabozantinib)	28 (13.9%)	2/28 (7.1%)	7 (1-21)	1/28 (3.6%)	4 (0.2-16)	2/28 (7.1%)	7 (1-21)	0	
BCR-ABL inhibitors (imatinib, nilotinib)	22 (10.9%)	0		0		0		1/22 (4.6%)	5 (0.3-19)
mTOR inhibitor (everolimus)	18 (8.9%)	0		1/18 (5.6%)	6 (0.3-23)	0		0	
HER2 inhibitors (lapatinib)	4 (2.0%)	0		0		0		0	
BRAF inhibitors (dabrafenib, vemurafenib)	4 (2.0%)	0		0		1/4 (25%)	25 (0.3-71)	0	

Abbreviations: ALK, anaplastic lymphoma kinase; ATE, arterial thromboembolism; BTK, Bruton's tyrosine kinase; CI, confidence interval; DVT, deep vein thrombosis; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; mTOR, mammalian target of rapamycin; PE, pulmonary embolism; VEGF, vascular endothelial growth factor; VTE, venous thromboembolism.

^aOne patient was on palbociclib and everolimus at different time points.

3.3 | VTE and ATE events

During the 6-month follow-up period, three patients developed VTE, with a cumulative incidence of 1.5% (95% CI: 0.4–4.0%). Among the 134 patients on DOACs for cancer-associated thrombosis, the incidence of recurrent VTE was the same at 1.5%. Two patients developed ATE including one fatal stroke, corresponding to a cumulative incidence of 1.0% (95% CI: 0.2–3.3%). Thrombotic events occurred in various combinations of targeted anticancer therapies and anticoagulation. One PE occurred in a patient while taking an appropriately reduced dose of apixaban (based on product labelling for AF) and vemurafenib, the only CYP3A4 inducer among the included anticancer therapies. In the entire cohort, only two patients were on vemurafenib. None of the 12 patients with inappropriate dose reduction of DOACs had thrombotic events, but two developed non-major bleeding events. Details of patient characteristics, thrombotic events, and management are summarized in Appendix Table A5.

3.4 | Mortality and cancer status

At 6 months, the majority of patients ($N = 182$, 90.1%) were alive. No patients were lost to follow-up. Most patients had improved or stable cancer status ($N = 117$, 57.9%), while 33.2% ($N = 67$) had cancer progression.

4 | DISCUSSION

To the best of our knowledge, our study is the first multi-center, international study and the largest dedicated to investigating the clinical outcomes in patients receiving concurrent use of DOACs and targeted anticancer therapies. In the 202 enrolled patients, we found an incidence of major bleeding of 4% (95% CI: 2–8%), an incidence of non-major bleeding of 6% (95% CI: 3–10%), and low incidences of VTE and ATE at 6 months (1.5% and 1%, respectively).

It is reassuring that the incidence of overall major bleeding events found in our cohort during concurrent use was similar to the rate reported in meta-analysis of RCTs in cancer-associated thrombosis (4.3%),²⁴ although caution must be taken for cross-study comparison given the differences in patient population. A recent secondary analysis of the Caravaggio trial showed that concurrent use of anticancer agents was not associated with significant differences on recurrent VTE or major bleeding in patients treated with apixaban or dalteparin for cancer-associated thrombosis.²⁵ However, the number of patients on targeted kinase inhibitors and apixaban was small ($N = 31$) and at least 15 different tyrosine kinases were grouped and analyzed together. Our study has shown that the risk of bleeding varied greatly across different targeted anticancer therapies, which could provide important clinical implications.

Approximately half of bleeding events in our study occurred in patients on concurrent therapy with BTK inhibitors ($N = 10$, 47.6% of bleeding events). Ibrutinib alone is associated with increased

risks of bleeding and bruising even in the absence of anticoagulation.¹⁸ It is thought to be related to its off-target effects including the inhibition of collagen-mediated platelet aggregation and resultant reduced platelet adhesion on von Willebrand factors.^{26,27} As *in vitro* studies showed that ibrutinib and acalabrutinib are weak CYP3A4 inhibitors and ibrutinib is also a weak P-gp inhibitor,^{28,29} the increase in bleeding events associated with concurrent use of DOACs and BTK inhibitors was less likely due to interactions involving CYP3A4 and/or P-gp pathways, but more likely related to the additional antiplatelet effects of BTK inhibitors. In early clinical trials of ibrutinib, fatal intracranial bleeding events were observed in patients on concomitant ibrutinib and warfarin,³⁰ and therefore its concurrent use was excluded in subsequent clinical trials and cautioned against in product labels.²⁸ However, the risks of concurrent use of ibrutinib and other anticoagulants such as DOACs remain under-investigated and largely unknown. As ibrutinib is associated with an increased risk of AF³¹ and DOACs are recommended as preferred agents for cancer patients with AF,¹³ concurrent use of BTK inhibitors and DOACs is increasingly frequent and clinically relevant. Therefore, we included BTK inhibitors (hence the higher proportion of CLL patients included) in our study. One study reported bleeding rates in clinical trials of ibrutinib and showed a relatively low major bleeding rate (\geq grade 3 based on Common Terminology Criteria for Adverse Events [CTCAE] v4.0) of 9% over 21.1 months in treatment-naïve patients and 2% over 9.7 months in patients with prior therapy.³² However, in these trials, the most commonly used concurrent anticoagulant was LMWH in prophylactic doses over a short duration (<3 months), with only four patients treated with DOACs.³² More recently, a retrospective cohort study of 30 patients treated with ibrutinib and DOACs reported much higher bleeding rates: major bleeding events (grades 3 and 4) in 5 patients (16.6%) and overall bleeding events in 21 patients (73.3%) over a median follow-up of 13.4 months.³³ The newer generation BTK inhibitor, acalabrutinib, was designed to be more specific with presumably less off-target effects, but there were no data regarding its concurrent use with DOACs. In our study, we found a high rate of bleeding with concurrent use of BTK inhibitors and DOACs, with a 6-month incidence of major bleeding of 10% and that of non-major bleeding of 14%. The number of patients was too small to allow subgroup analysis on individual drug (ibrutinib vs. acalabrutinib). The utilization of different criteria to determine bleeding symptoms (CTCAE in oncology trials and ISTH criteria in our study and VTE trials) made it difficult to compare rates and interpret results among different studies. In future studies, standardized bleeding assessment with prospective data collection are recommended to allow a uniform evaluation of pertinent clinical outcomes.

VEGF inhibitors are associated with an increased risk of both bleeding and thrombosis.^{19,20} Indeed, in our study the risks of major bleeding and VTE were comparable. A recent retrospective study of 86 cancer patients showed that concurrent use of VEGF receptor TKIs and anti-Xa inhibitors (including LMWH and DOACs) significantly increased the risks of overall bleeding events (HR 2.45, 95%

CI 1.28–4.69, $P = 0.007$) compared to anti-Xa inhibitors alone.³⁴ Particularly, concurrent use of DOACs and VEGF receptor TKIs was associated with a HR of 4.15 (95% CI, 0.38–45.0 [$P = 0.24$]) in bleeding events compared to DOACs alone, although the number of DOAC users was small ($N = 20$). In our study of 28 patients receiving concurrent VEGF inhibitors (sunitinib or cabozantinib) and DOACs, a relatively high 6-month incidence of major bleeding (7%) was observed. In addition, VEGF inhibitors are known to be associated with increased risks of thrombotic complications, likely due to disturbance in the endothelial regulation, microvasculature, and coagulation cascade.²⁰ We observed two VTE in 28 patients receiving VEGF inhibitors, corresponding to a 6-month VTE incidence of 7% (95% CI: 1–21%). Given the small number of patients, this finding is preliminary with wide CI, and should be further evaluated in a larger population.

The 6-month incidence of VTE was low in our study (1.5%) compared to recent RCTs using DOACs for treatment of cancer-associated thrombosis (5.2% in meta-analysis).²⁴ First, our study included a mixed population, including 36% of patients who received DOACs for AF (although the risk of recurrent VTE is the same in the VTE cohort). In addition, patients in the VTE cohort could have received anticoagulation for a history of VTE for more than 3 months prior to the start of concurrent use and could have had a lower risk of recurrence. Patients included in our study also had a lower 6-month mortality rate of 10%, although close to 95% of patients with solid tumor had metastatic disease. Interestingly, although there were only two patients treated with vemurafenib, the only CYP3A4 inducer among the included anticancer therapies, one PE occurred in the setting of concurrent use of vemurafenib and apixaban at a reduced dose (which was appropriate given the presence of two AF dose-reduction criteria). Concurrent use of CYP3A4 or P-gp inducers could theoretically reduce DOAC concentrations and increase the risk of VTE, but literature on clinical outcomes with this combination in cancer patients was scarce.

Our study has limitations. Most patients included in the study were followed retrospectively. Therefore, bleeding events might be under-reported. We chose to include non-major bleeding events that prompted any encounter (including phone calls) or resulted in intervention, which is slightly different from the ISTH criteria of clinically relevant non-major bleeding (including only in-person encounters).³⁵ However, we believe that bleeding events prompting medical attention are clinically relevant. The study was observational, and individual treating physicians chose DOACs and targeted anticancer therapies, so inherent bias and confounders could be present, including potential bias in selecting patients perceived to be “lower risk of bleeding” for DOACs. Despite that, the study demonstrated a high rate of bleeding events with concurrent use of DOACs and certain anticancer therapies (such as BTK inhibitors and VEGF inhibitors). Some patients started anticoagulation prior to targeted anticancer therapies and some vice versa, and the duration of anticoagulation prior to targeted anticancer therapies was not consistently captured, which could have influenced the outcomes as the risks of recurrent VTE and/or bleeding is the highest in the first 3 months of anticoagulation

initiation. The number of targeted anticancer therapies did not represent all available agents, but we chose to concentrate on the agents with higher likelihood of bleeding or thrombotic complications or higher frequency of co-prescription for more clinical relevance. The majority of patients were treated with rivaroxaban or apixaban, so the data were not representative for dabigatran and edoxaban (for which the CYP pathway is not involved). Another limitation is the lack of a comparator arm such that we cannot conclude whether the rates of bleeding are greater than the administration of DOACs or targeted therapy alone or compared to other anticoagulants such as LMWH.

Despite these limitations, our study has strengths including the largest population of concurrent use of DOACs and targeted anticancer therapies, an international collaboration involving several academic institutions, and all thrombotic and bleeding outcomes were adjudicated with chart review by two physicians. We did not limit our investigation to interactions within CYP3A4 or P-gp pathways and intended to report outcomes of concurrent use that could be affected by other mechanisms. Our study provides important event rates on the clinical outcomes in patients receiving concomitant DOACs and targeted anticancer therapies, an area with very limited literature at this time. Our data revealed a high variability of bleeding risks with different anticancer therapies and can alert clinicians to maintain higher vigilance for bleeding complications in patients on certain combinations (such as DOACs and BTK inhibitors or VEGF inhibitors). In addition, our study showed low bleeding rates when DOACs were used with EGFR and ALK inhibitors or BCR-ABL inhibitors, which can be reassuring to clinicians when using these combinations. Our study is hypothesis generating and provides preliminary data for future research.

In conclusion, we report the results of the TacDOAC registry, which shows an incidence of major bleeding of 4% and non-major bleeding rate of 6%, and low incidences of VTE and ATE (1.5% and 1%, respectively) at 6 months. Concomitant use with different targeted anticancer therapies resulted in different bleeding risks, with BTK inhibitors and VEGF inhibitors found to be associated with higher risks. Our findings could be related to patient or cancer characteristics, or to DOAC use itself including involvement in the CYP/P-gp pathway or other mechanisms (such as antiplatelet effects from BTK inhibitors). Future larger prospective studies or analysis of large administrative databases are needed to improve our understanding and optimize care in patients receiving DOACs with targeted anticancer therapies. Based on the results of this study, future studies should focus on potential higher risk combinations such as concomitant anticoagulants and BTK inhibitors or VEGF inhibitors. Concurrent use with CYP3A4 or P-gp inducers is also an area with a significant knowledge gap requiring further investigation. Whether anti-Xa level measurement can be beneficial could also be of interest.

ACKNOWLEDGMENTS

We thank the Subcommittee on Hemostasis and Malignancy of the Scientific and Standardization Committee of the ISTH for

supporting and advertising the registry. The study was supported by Isth for REDCap and funding. We thank Abigail Bartosic, Megan Resetar, Vanessa Bonjour, and Aviv Sever for assistance in patient identification and data input. J. I. Zwicker is the recipient of CLOT UO1 from NHLBI (HL143365). M. Carrier is the recipient of Tier 1 Research Chair from the University of Ottawa in Cancer and Thrombosis.

CONFLICTS OF INTEREST

T.-F. Wang reports advisory board honoraria from Servier and grants from Leo Pharma. A. Leader reports advisory board honorarium from Pfizer, Bayer, Sanofi, and Novartis. G. Spectre reports honoraria/advisory boards: Pfizer, Bayer, Boehringer Ingelheim, Sanofi, and Novartis. M.Y. Lim has received advisory board honorarium from Sanofi Genzyme and Argenx. R. Gangaraju serves as a consultant for Sanofi-Genzyme and Alexion. K. Sanfilippo reports grant support from ACS-IRG and NHLBI. J.I. Zwicker reports research support from Incyte and Quercegen, consultancy: Sanofi, CSL, Parexel; honoraria/advisory boards: Pfizer/BMS, Portola, Daiichi. M. Carrier reports grants from BMS, Leo Pharma, and Pfizer; personal fees from BMS, Leo Pharma, Bayer, Pfizer, Servier, and Sanofi. The other authors report no conflicts of interest.

AUTHOR CONTRIBUTIONS

Study conception and design: T.-F. Wang, J.I. Zwicker, M. Carrier; patient inclusion and data acquisition: T.-F. Wang, L. Baumann Kreuziger, A. Leader, G. Spectre, M.Y. Lim, A. Gahagan, R. Gangaraju, and K. Sanfilippo; interpretation of the data: all authors; drafting of the manuscript: T.-F. Wang; critical revision of the manuscript for important intellectual content: all authors; final approval of the manuscript: all authors.

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How to cite this article: Wang T-F, Baumann Kreuziger L, Leader A, et al. Characteristics and outcomes of patients on concurrent direct oral anticoagulants and targeted anticancer therapies—TacDOAC registry: Communication from the ISTH SSC Subcommittee on Hemostasis and Malignancy. *J Thromb Haemost*. 2021;19:2068–2081. <https://doi.org/10.1111/jth.15367>

APPENDIX

TABLE A1 Indication of anticoagulation by cancer types and associated anticancer therapies

Cancer type	Anticancer therapies	Venous thromboembolism	Atrial fibrillation
Breast	Palbociclib, lapatinib	42	10
Lung	Osimertinib, alectinib	37	8
Gastrointestinal	Imatinib (mostly), sunitinib, everolimus, alectinib, cabozantinib	8	4
Genitourinary	Sunitinib, cabozantinib	22	7
Gynecological	Everolimus	3	0
Melanoma	Dabrafenib, vemurafenib	1	0
Hematologic	Ibrutinib, acalabrutinib, imatinib, nilotinib	15	42
Others	Everolimus (mostly), dabrafenib, vemurafenib, cabozantinib	7	2

Note: 2 breast cancer, 1 lung cancer, and 2 genitourinary cancer patients had both venous thromboembolism and atrial fibrillation.

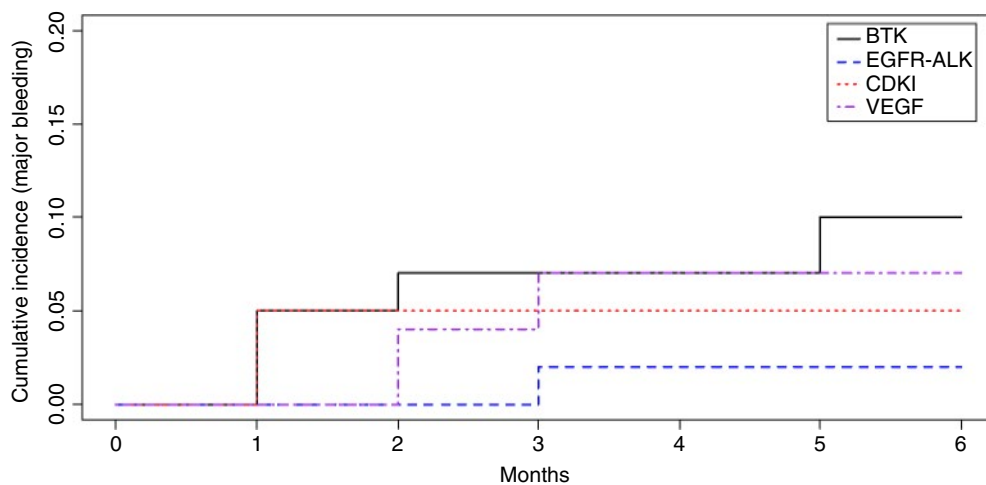


Figure A1 Cumulative incidence of major bleeding events by types of anticancer therapies. Abbreviations: ALK, anaplastic lymphoma kinase; BTK, Bruton's tyrosine kinase; CDKI, cyclin-dependent kinase inhibitor; EGFR, epidermal growth factor receptor; VEGF, vascular endothelial growth factor.

TABLE A2 Combinations of each direct oral anticoagulant and targeted anticancer therapy

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Osimertinib	1	19	15	0
Alectinib	0	7	2	0
Ibrutinib	3	8	19	0
Acalabrutinib	0	5	9	0
Palbociclib	1	22	19	1
Sunitinib	2	5	5	0
Cabozantinib	0	7	8	1
Imatinib	1	7	12	0
Nilotinib	0	1	1	0
Everolimus	1	10	8	0
Lapatinib	0	3	1	0
Dabrafenib	0	1	1	0
Vemurafenib	0	0	2	0

Note: One patient each on rivaroxaban and apixaban at different time periods with osimertinib, lapbociclib, and everolimus.

TABLE A3 Summary of patients with major bleeding events

N	Age	Sex	Type of cancer	Cancer stage	CrCl (ml/min)	Plt count (K/uL)	Cancer therapies	AC or antiplatelet	AC indication	Type of major bleeding	Time since concurrent use (weeks)	Treatment of bleeding event
1	59	M	CLL and CML	N/A	75	113	Ibrutinib 420 mg daily	Dabigatran 150 mg twice daily ASA 81 mg daily	AF	Bilateral subdural hematoma after a fall	19	Idarucizumab given, dabigatran stopped, Ibrutinib was discontinued
2	64	M	CLL	N/A	101	191	Ibrutinib 420 mg daily	Apixaban 5 mg twice daily	AF	Spontaneous ecchymoses at shoulder and upper chest, Hgb dropped by 5 g/dL	4	Surgical drainage of hematoma, Hold AC for one week, Ibrutinib stopped
3	68	M	Mantle cell lymphoma	N/A	99	209	Ibrutinib 560 mg daily	Rivaroxaban 20 mg daily	AF	Hemothorax after chest tube insertion for empyema, Hgb dropped by 3 g/dL	5	3 units RBC, hold Ibrutinib (AC was held at the time of procedure)
4	66	M	CLL	N/A	110	314	Acalabrutinib 100 mg bid	Apixaban 5 mg bid ASA 81 gm daily	AF	Inguinal hematoma after procedure, Hgb dropped 2.5 g/dL	3	Hospitalized, no transfusion nor change in meds
5	74	F	Breast	IV	31	309	Palbociclib 125 mg daily	Rivaroxaban 20 mg daily Clopidogrel 75 mg daily	PE	Symptomatic bleeding from superficial femoral artery, Hgb dropped by 1.8 g/dL	2 days	3 units RBC and plt transfusion, AC held, palbociclib continued Embolization of the bleeding vessel
6	73	F	Breast	IV	34	224	Palbociclib 125 mg 21 days on, 7 days off	Apixaban 5 mg twice daily	DVT upper limb	Hematochezia with Hgb down to 3.7 g/dL (dropped by 8 g/dL)	4	3 units RBC, colonoscopy showed a new colon mass, Palbociclib stopped
7	74	M	RCC	IV	44	263	Cabozantinib 60 mg daily	Rivaroxaban 20 mg daily	AF	Fatal massive hemoptysis	9	Death
8	42	M	RCC	IV	56	333	Sunitinib 50 mg daily 4 weeks on, 2 weeks off	Rivaroxaban 20 mg daily	PE	Gross hematuria, Hgb dropped by 1.5 g/dL	8	2 units RBC, AC was permanently discontinued
9	75	M	Lung	IV	95	196	Osimeitinib 80 mg daily	Apixaban 5 mg twice daily	DVT lower limb	Subdural hematoma and intraparenchymal bleed after a fall	12	PCC was given, AC discontinued, IVC filter inserted, Osimeitinib continued

Abbreviations: AC, anticoagulation; AF, atrial fibrillation; ASA, aspirin; ATE, arterial thrombosis; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; CrCl, creatinine clearance; DVT, deep vein thrombosis; F, female; Hgb, hemoglobin; IVC, inferior vena cava; M, male; N/A, not applicable; PCC, prothrombin complex concentrate; PE, pulmonary embolism; plt, platelet; RBC, red blood cell transfusions; RCC, renal cell carcinoma.

TABLE A4 Summary of patients with non-major bleeding events

N	Age	Sex	Type of cancer	Stage	CrCl (ml/min)	Plt count (K/uL)	Cancer therapies	AC	AC indication	Type of bleeding	Time since concurrent use (weeks)	Treatment
1	73	M	CLL	N/A	24	202	Ibrutinib 420 mg daily	Apixaban 2.5 mg twice daily	AF	Hemoptysis for 3–4 weeks	10	Ibrutinib stopped Referred to pulmonary and had bronchoscopy
2	74	M	CLL	N/A	80	293	Ibrutinib 420 mg daily	Rivaroxaban 15 mg daily	AF	Petechiae and ecchymoses on both hands	1	AC stopped 6 mo later due to ongoing hematoma
3	89	M	Mantle cell lymphoma	N/A	20	157	Ibrutinib 420 mg daily	Apixaban 2.5 mg twice daily ASA 75 mg daily	AF	Hemoptysis daily for 2 weeks, Hgb dropped by 1 g/dL	2	Hospitalization, AC held for 3 weeks and ibrutinib held for 2 weeks
4	71	M	Transformed diffuse large B cell lymphoma, thyroid cancer	N/A	107	108	Ibrutinib 420 mg daily	Apixaban 5 mg twice daily	PE	Epistaxis	8	AC was held for 3 days. ENT eval, 2 mo later another ENT eval for continued epistaxis
5	71	M	CLL	N/A	84	152	Ibrutinib 280 mg daily	Apixaban 5 mg twice daily	AF	Subconjunctival hemorrhage	13	No treatment
6	71	M	CLL	N/A	74	202	Acalabrutinib 200 mg daily	Rivaroxaban 20 mg daily ASA 81 mg daily	AF	R gluteal hematoma 6d after R femur fracture from fall and R hip hemiarthroplasty	3	1 unit RBC, changed to prophylactic enoxaparin for 6 weeks
7	76	F	Breast	IV	57	488	Palbociclib 125 mg daily	Rivaroxaban 20 mg daily ASA 81 mg daily	AF PE	Gross hematuria Hgb drop 1 g/dL	2	1 unit RBC, hospitalization, urethral stent exchanged
8	51	F	Breast	IV	111	194	Palbociclib 75 mg daily 21/28 days	Rivaroxaban 20 mg daily	RLE DVT	Persistent bleeding from minor trauma (finger cut)	16	Patient was sent to urgent care
9	82	F	Breast	IV	46	176	Palbociclib 125 mg daily	Rivaroxaban 20 mg daily	LLE DVT	Epistaxis	3 days	Patient called, AC changed to apixaban a few days later
10	42	M	RCC	IV	72	397	Sunitinib 50 mg daily 4 weeks on, 2 weeks off	Rivaroxaban 20 mg daily	PE	Mouth bleeding (bloody blister)	3	AC held for one day
11	47	M	Neuroendocrine tumor ileum	IV	64	112	Everolimus 10 mg daily	Rivaroxaban 20 mg daily	PE	Epistaxis	3	Increased epistaxis noted on follow-up 3 and 7 weeks after concurrent therapy, compression/ice
12	70	F	Lung	IV	61	180	Osimeitinib 80 mg daily	Rivaroxaban 20 mg daily	LUE DVT	Blood in underwear	12	Bleeding prompted visit; vaginal exam, AC changed to apixaban

Abbreviations: AC, anticoagulation; AF, atrial fibrillation; ASA, aspirin; ATE, arterial thrombosis; CLL, chronic lymphocytic leukemia; CrCl, creatinine clearance; DVT, deep vein thrombosis; ENT, ear, nose, throat; F, female; Hgb, hemoglobin; IVC, inferior vena cava; LLE, left lower extremity; LUE, left upper extremity; M, male; N/A, not applicable; PE, pulmonary embolism; plt, platelet; RBC, red blood cell transfusions; RCC, renal cell carcinoma; RLE, right lower extremity.

TABLE A5 Summary of patients with venous and arterial thromboses

N	Age	Sex	Type of cancer	Cancer stage	CrCl (ml/min)	Cancer therapies	AC	AC indication	Type of VTE/ATE	Time since concurrent use (weeks)	Treatment of VTE/ATE
1	82	M	Thyroid papillary cancer	IV	36	Vemurafenib 480 mg daily	Apixaban 2.5 mg twice daily	AF	PE	20	Increase apixaban to 5 mg twice daily
2	54	M	RCC	IV	147	Cabozantinib 40 mg daily	Rivaroxaban 20 mg daily	SVT of upper limb	PE	4	No change in AC
3	72	F	RCC	IV	41	Sunitinib 50 mg daily 14 days on, 14 off	Rivaroxaban 20 mg daily	PE	IVC thrombus	19	No change in AC
1	78	F	CML	N/A	48	Imatinib 400 daily	Apixaban 5 mg twice daily	SVT of lower limb	Stroke (diagnosed clinically)	23	AC stopped 4 weeks prior to the event, treated with aspirin
2	56	M	Lung	IV	166	Alectinib 600 mg daily	Apixaban 5 mg twice daily	PE	Stroke (confirmed by image)	18	Death

Abbreviations: AC, anticoagulation; AF, atrial fibrillation; ATE, arterial thrombosis; CML, chronic myelogenous leukemia; CrCl, creatinine clearance; F, female; IVC, inferior vena cava; M, male; N/A, not applicable; PE, pulmonary embolism; RCC, renal cell carcinoma; SVT, superficial thrombosis; VTE, venous thromboembolism.