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Cancer-associated thrombosis: A meta-analysis and single-center experience

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ABSTRACT

Objectives: In this study, we present our clinical experience in patients with cancer-associated venous thrombosis (CAT) and aimed to conduct a meta-analysis to compare direct-acting oral anticoagulants (DOACs) with each other and low-molecular-weight heparin (LMWH).

Patients and methods: Between January 2010 and December 2020, a total of 98 patients (44 males, 54 females; mean age: 65.6±13.4 years; range, 21 to 91 years) diagnosed with both cancer and venous thromboembolism (VTE) were screened in the computer-based database system. Randomized-controlled trials and clinical trials conducted between 2016 and 2020, in which DOACs were compared with LMWH in the treatment of VTE in cancer patients, were screened using the MEDLINE database via PubMed and SCOPUS.

Results: Gynecological and gastrointestinal tract cancers were the most common malignancies in 22.4% and 28.6% of the patients, respectively). The rate of deep venous thrombosis (DVT) was higher (65.4%) and five patients had upper extremity DVT. Direct-acting oral anticoagulants were found to be more effective than LMWH in preventing recurrent VTE (risk ratio [RR]: 0.111; 95% confidence interval [CI]: 0.014-0.866; p=0.036 *vs.* RR: 0.444; 95% CI: 0.198-0.999; p=0.036, respectively).

Conclusion: Based on our clinical experience and meta-analysis results, DOACs can be considered a reasonable alternative in patients with CAT. Clinicians should keep in mind that treatment of CAT requires a multidisciplinary approach and interdisciplinary collaboration.

Keywords: Cancers, direct-acting oral anticoagulants, low-molecular-weight heparin, venous thromboembolism.

Venous thromboembolism (VTE) is one of the most common and serious cardiovascular diseases worldwide.[1-4] Cancer-associated venous thrombosis (CAT) is a difficult subgroup of VTE and a major cause of morbidity and mortality.[2-4] There is a clear correlation between cancer and thrombosis[5-8] and several variables play a role in this correlation. Cancer type, cancer degree, tumor treatment, and additional thrombogenic risk factors may contribute to clinical progress. The incidence of CAT is about 1 to 20%, risk of bleeding is 10%, and risk of recurrence is 10 to 20%.[7-13] These conditions can increase morbidity, and even can hinder cancer treatment, leading to an enormous financial healthcare burden.

Several studies have shown the efficacy of low-molecular-weight heparin (LMWH) in decreasing the risk of VTE in patients with cancer.[14,15] To date, large-scale randomized-controlled trials (RCTs) have been conducted in direct-acting oral anticoagulants (DOACs) and vitamin K antagonists (VKAs) in terms of efficacy and safety, and the results have been shown to be similarly effective and safe with VKA.[15-18] Due to the non-inferiority of DOACs over VKAs, the former has become the preferred treatment method

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in VTE.[6,8] Therefore, these recent RCTs involving cancer subgroups and primary CAT patients have shown that DOACs are as effective and safe as VKAs in CAT patients.[17-19] Recently, DOACs have been included in the guidelines for the treatment of cancer patients with a high level of recommendation.[3,6] However, there is no large-scale RCT to reveal which of these drugs prevent recurrence of VTE and have lower bleeding rates. In the present study, we share our clinical experience in patients with CAT and aimed to conduct a meta-analysis to compare DOACs with each other and LMWH.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at Başkent University Faculty of Medicine, Department of Cardiovascular Surgery between January 2010 and December 2020. All patients diagnosed with both cancer and VTE were screened in the computer-based database system of our institute. Throughout the screening period, 1,342 records were obtained. A total of 1,078 of these records were excluded due to the repetitive patient admissions. The patients with basal cell skin cancer, upper extremity superficial thrombophlebitis, and catheter thrombosis and those receiving prophylactic treatment were also excluded. The patients over the age of 18 years with active cancer and VTE were included in the study. Finally, a total of 98 patients with CAT (44 males, 54 females; mean age: 65.6±13.4 years; range, 21 to 91 years) were enrolled. Data including the index VTE type, cancer type, and medications applied, platelet counts (<100,000 mm^3), creatinine clearance (<50 mL/min), recurrent VTE (pulmonary embolism [PE]/deep venous thrombosis [DVT]), bleeding and death were recorded. Cancer types were classified as solid tumors including gynecological, gastrointestinal (GI), lung, central nervous system, urinary tract, breast and hematological malignancies, and others. The treatment applied was classified as LMWH, warfarin sodium, and DOACs and the duration of treatment was noted. It was confirmed that all follow-up controls were performed by a single team of vascular laboratory. Physical examination, Duplex ultrasound control, drug records, and collaboration with the related departments (e.g., oncology, gynecological oncology, and urology) was performed in each follow-up visit. A written informed consent was obtained from each patient. The study was approved by the institutional clinic. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Meta-analysis

All RCTs and clinical trials conducted between 2016 and 2020, in which DOACs were compared with LMWH in the treatment of VTE in cancer patients, were screened using the MEDLINE database of the United States National Library of Medicine via PubMed and SCOPUS. The keywords [(deep vein thrombosis-pulmonary embolism-venous thromboembolism) and (low-molecular-weight heparin-rivaroxaban-apixaban-edoxaban-dabigatran-anticoagulant) and (malignancy-neoplasm-cancer)] were screened in accordance with the Boolean operator for both databases.

Duplications and irrelevant data were removed. Prophylaxis, endovascular treatment, other treatment, subgroup analysis, catheter-related thrombosis, non-cancer-associated trials, ongoing trials, and trials including children were excluded (Figure 1).

Four RCTs were included in this meta-analysis. Four RCTs comparing a factor 10a inhibitor (rivaroxaban, apixaban or edoxaban) with a LMWH and including 2,907 patients with CAT were examined. Relevant articles were assessed by three authors and the following data were obtained from the studies and the data extraction table was created: patient demographic data, primary VTE, recurrent VTE, major bleeding, fatal bleeding, clinically relevant non-major bleeding (CRNMB), VTE-related mortality, and all-cause mortality.

Statistical analysis

Statistical analysis and meta-analysis were performed using the Comprehensive Meta-Analysis (CMA) Software version 2.2.064 (Biostat, Englewood, NJ, USA). Efficacy of outcomes were measured as the risk ratio (RR) and meta-analysis used a weighted average of the RR and 95% confidence interval (CI). Tests of heterogeneity were conducted among the studies using the Cochran's chi-square test (also called the Q test) and I-Squared statistic, where a p value of <0.05 was considered an indication of heterogeneity. Some RRs were pooled using the DerSimonian and Laird random effects model (REM), given that there was considerable variation across the studies and as a statistically significant heterogeneity was observed across the study results. Otherwise, the fixed effect model was used. Descriptive data were presented in

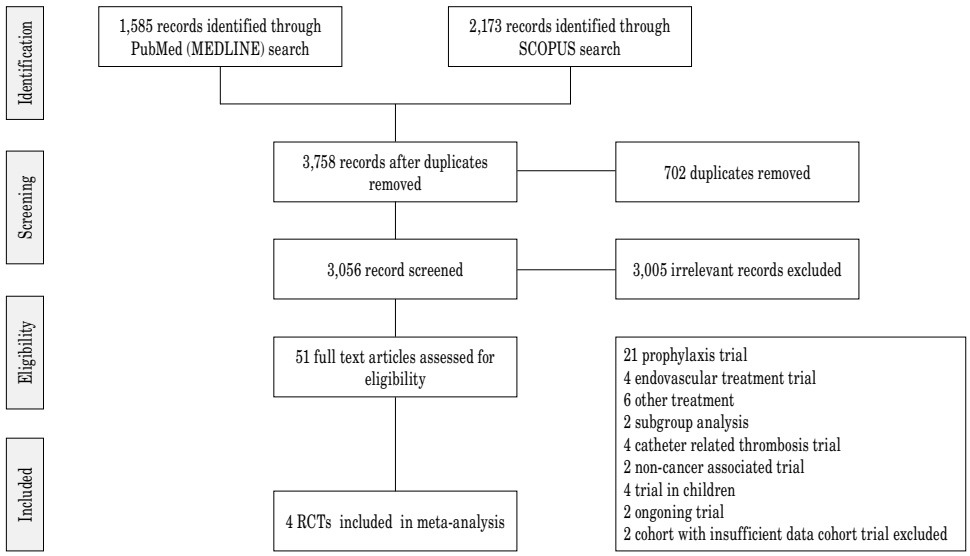

Figure 1. Flow diagram of study selection.

Medline:
(deep vein thrombosis OR pulmonary embolism OR venous thromboembolism) AND (low molecular weight heparin OR rivaroxaban OR apixaban OR edoxaban OR dabigatran OR anticoagulant) AND (malignancy OR neoplasm OR cancer)
Scopus:
TITLE-ABS-KEY
(deep AND vein AND thrombosis) OR (pulmonary AND embolism) OR (venous AND thromboembolism) AND (low AND molecular AND weight AND heparin) OR (rivaroxaban) OR (apixaban) OR (edoxaban) OR (dabigatran) OR (anticoagulant) AND (malignancy) OR (neoplasm) OR (cancer) AND PUBYEAR > 2009

Table 1. Baseline data of patients

	n	%	Mean±SD	Min-Max
Age (year)			65.6±13.4	21-91
Sex				
Female	54	55.1		
Cancer type				
Gynegologic	22	22.4		
Gastrointestinal	28	28.6		
Lung	8	8.2		
Central nervous system	2	2.0		
Urinary tract	11	11.2		
Breast	12	12.2		
Hematologic	12	12.2		
Others	3	3.1		
Trombocytopenia (<100,000/mm^3)	9	9.2		
GFR (<50 mL/min)	14	14.3		
Pulmonary embolism with or without DVT	34	34.6		
DVT only	64	65.4		
Symptomatic PE/DVT	86	87.8		
Incidental PE/DVT	8	8.2		
VTE history	6	6.1		
Drug				
LMWH	75	76.5		
Warfarin sodium	16	16.3		
DOACs	7	7.1		

SD: Standard deviation; GFR: Glomerular filtration rate; DVT: Deep vein thrombosis; PE: Pulmonary embolism; VTE: Venous thromboembolism; LMWH: Low molecular weight heparin; DOAC: Direct-acting oral anticoagulant.

Table 2. Follow-up results of CAT patients

	n	%	Median	Min-Max
Follow-up			8.61	1-45
Recurrent VTE	9	9.2		
Recurrent PE	6	6.1		
Recurrent DVT	7	7.1		
Fatal PE	3	3.1		
Major bleeding	5	5.1		
Major GIS bleeding	4	4.1		
Major non-GIS bleeding	1	1.0		
CRNMB	7	7.1		
Major bleeding or CRNMB	12	12.1		
Death	24	24.5		

CAT: Cancer-associated venous thrombosis; SD: Standard deviation; VTE: Venous thromboembolism; PE: Pulmonary embolism; DVT: Deep vein thrombosis; GIS: Gastrointestinal; CRNMB: Clinically relevant non-major bleeding.

mean ± standard deviation (SD), median (min-max) or number and frequency, where applicable.

RESULTS

Clinical results

Overall characteristics of the patients are summarized in Table 1. Gynecological and GI tract cancers were the most common malignancies in 22.4% and 28.6% of the patients, respectively. The rate of DVT was higher (65.4%) and five patients had upper extremity DVT. Totally, 86 (87.8%) patients of all VTEs were symptomatic. Of the patients, 75 (76.5%) used LMWH, 16 (16.3%) used warfarin sodium, and seven (7.1%) used DOACs.

Recurrent VTE was observed in nine patients, and six of them (6.1%) had PE, regardless of DVT and three (3.1%) patients had only lower extremity DVT. In addition, the total number of patients with recurrent DVT was seven (7.1%), and three (3.1%) patients died due to PE. Major bleeding was observed in five (5.1%) patients, and one (1%) of them had cerebrovascular bleeding, while the remaining four (4.1%) patients had major GI bleeding. The number of patients with major bleeding or CRNMB was 12 (12.2%) (Table 2). All major bleeding cases were observed in the LMWH group, nine patients with major bleeding or CRNMB were in the LMWH group, and the other three patients were in the warfarin sodium group. No bleeding or recurrence was observed in the DOAC group. A total of 24 patients died during the period of DVT treatment (24.5%). The reason for mortality was not related to DVT or PE. Recurrence and bleeding data are shown in Tables 2 and 3, respectively.

Meta-analysis

In all studies, the rate of the patients with active cancer was ≥97%. The included studies evaluated either apixaban 5 mg twice daily (ADAM-VTE and CARAVAGGIO),[10,11] edoxaban 60 mg once daily (Hokusai VTE Cancer),[8] or rivaroxaban 20 mg once daily (SELECT-D).[9] The patients in the control groups in all studies received subcutaneous dalteparin

Table 3. Comparison of drugs

	LMWH (n=75)		Warfarin sodium (n=16)		DOACs (n=7)	
	n	%	n	%	n	%
Recurrent VTE	7	9.3	2	12.5	0	0
Major bleeding	5	6.6	0	0	0	0
Major bleeding or CRNMB	9	12	3	18.7	0	0

LMWH: Low molecular weight heparin; DOAC: Direct-acting oral anticoagulant, VTE: Venous thromboembolism; CRNMB: Clinically relevant non-major bleeding.

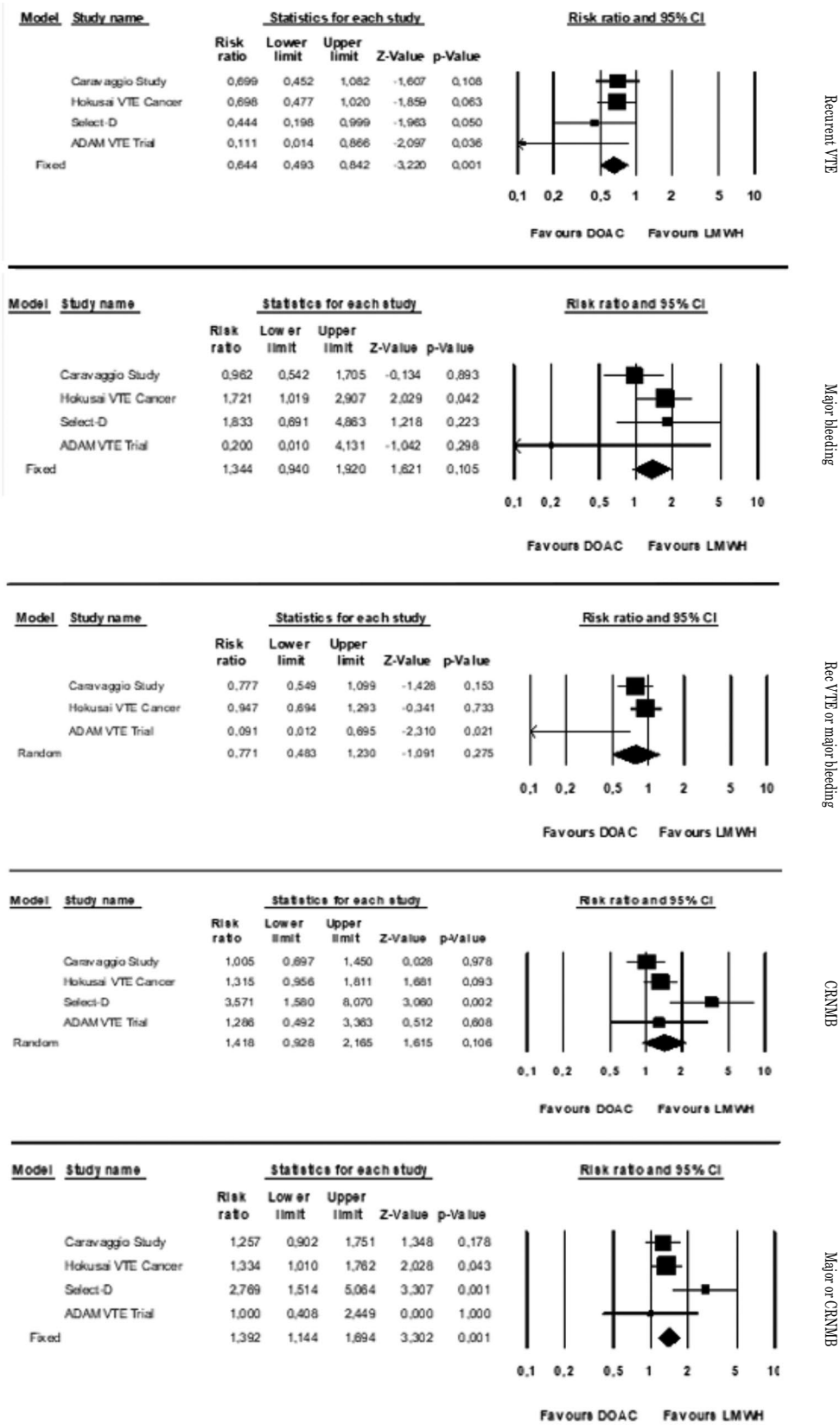

Figure 2. Forest plots of relative risks between DOACs and LMWH groups.
DOACs: Direct-acting oral anticoagulants; LMWH: Low-molecular-weight heparin.

sodium (200 IU per kg for the first 30 days, followed by 150 IU per kg thereafter). The follow-up periods varied between 6 and 12 months.[9-12] Recurrent VTE, major bleeding and CRNMB were compared (Figure 2).

Recurrence

Direct-acting oral anticoagulants were found to be more effective than LMWH in preventing recurrent VTE (RR: 0.111; 95% CI: 0.014-0.866; p=0.036 *vs.* RR: 0.444; 95% CI: 0.198-0.999; p=0.036, respectively). Also, the pooled (RR) was found to be statistically significant in favor of DOACs (RR: 0.644; 95% CI: 0.493-0.842; p=0.0001) (I^2=23.6; p=0.27). There was no significant difference in the incidence of recurrent VTE or major bleeding between the DOACs. However, the probability analysis showed that the incidence of recurrent VTE was slightly lower in the rivaroxaban group (RR: 0.672; 95% CI: 0.455-0.993; p=0.046) (I^2=24.8; p=0.26). In recurrent PE and comparison of the studies are shown in Figure 2 (RR: 0.333; 95% CI: 0.014-8.118; p=0.50 *vs.* RR: 0.444; 95% CI: 0.139-0.1420; p=0.171, respectively).

Bleeding

Considering major bleeding rates, it was clinically positive, although it was not statistically significant in favor of LMWH (pooled RR: 1.344; 95% CI: 0.940-1.920; p=0.105, I^2=26.4%; p=0.25). In the CARAVAGGIO and ADAM-VTE studies, there were controversial clinical results in favor of DOACs in bleeding rates (RR: 0.962; 95% CI: 0.542-1.705; p=0.893 *vs.* RR: 0.20; 95% CI: 0.010-4.131; p=0.298, respectively).

In terms of the CRNMB rates, LMWH was not statistically superior to DOACs; however, the rates were clinically in favor of LMWH (pooled RR: 1.418; 95% CI: 0.928-2.165; p=0.106, I^2=61.5%; p=0.05). Otherwise, the rates in the CARAVAGGIO study were more favorable in favor of DOACs, consistent with the major bleeding rates. The results comparing CRNMB are shown in Figure 2. However, it was also not statistically significant (RR: 1.005; 95% CI: 0.697-1.450; p=0.978).

The rates in terms of major bleeding or CRNMB were statistically significant in favor of LMWH and CARAVAGGIO and Hokusai studies had more favorable results among DOACs (RR: 1.257 and 1.334 *vs.* RR: 2.769, respectively). The results regarding major and CRNMB are shown in Figure 2.

Data regarding major GI bleeding were available in the CARAVAGGIO and SELECT-D studies. Although the rates were in favor of LMWH, there was no statistically significant difference (pooled RR: 1.352; 95% CI: 2.678-2.695; p= 0.392, I^2=0%; p=0.43). Therefore, between two studies, the CARAVAGGIO study had clinically more favorable results (RR: 1.106 *vs.* RR: 2.000, respectively) (Figure 3).

DISCUSSION

Anticoagulation therapy is the backbone of treatment in CAT due to the increased risk of VTE; however, the challenges in the treatment include the management of recurrent VTE and bleeding. The LMWHs are the treatment of choice in this vulnerable group of patients, as shown in a pivotal trial, namely the Comparison of Low-molecular-weight heparin versus Oral anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (CLOT) trial.[20] This study revealed lower rates of recurrent VTE at six months (9% *vs.* 17%, respectively; hazard ratio [HR]: 0.48; 95% CI: 0.30-0.77) and a similar risk of bleeding events (6% *vs.* 4%, respectively; p=0.27).

Direct-acting oral anticoagulants can be administered orally without routine monitoring with minimal interactions with other drugs and food. Therefore, their use in DVT and PE has increased in recent years owing to their efficacy and safety compared to VKAs. Recently, several RCTs have compared DOACs with LMWH for the treatment of VTE in patients with CAT.[9-12] These trials have various results, particularly in terms of bleeding. This variability is mostly due to the study types and the variability of patients such as stage of cancer, type of cancer, patient heterogeneity, and follow-up periods.

In the present study including 98 patients with CAT, we used consistent data with previous studies comparing LMWH and DOAC groups. Proportionally, the LMWH group constituted the vast of majority. In four studies included in the meta-analysis, the DOACs were found to be non-inferior to LMWH. Although no statistical comparison was made due to the low number of patients in the DOAC group, the absence of recurrence was partially consistent with the low recurrence rates in these studies. Similar results were found in terms of bleeding rates.

In these four studies comparing LMWH with DOACs, the same LMWH (dalteparin) was compared

with apixaban in two studies (ADAM-VTE and CARAVAGGIO), rivaroxaban (SELECT-D) in one study, and edoxaban in one study (Hokusai VTE Cancer). Since the comparison group was the same in all studies, this meta-analysis was conducted considering that DOACs would be compared with each other in terms of efficacy and safety, although it did not reach statistical significance, but it would reach a clinical significance. In the ADAM-VTE study, the inclusion of cerebral DVT and splenic DVT patients, which were not included in the other three studies, and the lower proportion of GI tract malignancy patients may lead to more favorable results in favor of DOAC. This is particularly important, as thrombosis in the portal or splenic veins may complicate management, particularly in patients with hepatocellular or pancreatic cancer.

In each of the studies, the patients were evaluated in case of the Eastern Cooperative Oncology Group (ECOG) classification. However, the patients who had ECOG Performance Status 0 had a higher rate in the ADAM-VTE study than the other three studies, and the ECOG 2 group had a lower rate. Therefore, the lower VTE recurrence rates in the ADAM-VTE are consistent with this result. Of note, although the ADAM-VTE study provides the criteria for inclusion in the meta-analysis, its extremely favorable rates in favor of DOAC may not reflect real-life data due to the aforementioned reasons in patients with CAT. In addition, although the positive aspects of this study are described, it may be more reasonable to compare other three studies, CARAVAGGIO, SELECT-D, and Hokusai VTE Cancer due to the lower sample size compared to other studies and the initial status of the included patients with carcinoma. In these pivotal studies, all DOACs were found to be non-inferior to LWMH in the prevention of recurrent VTE.

Bleeding is another important issue to be considered. Based on these findings, it is not likely to speculate that bleeding rates of LMWH is less than edoxaban and rivaroxaban. Gastrointestinal cancers may be an important reason for this result. However, there was no significant difference between apixaban and deltaparin, which may be an important advantage for apixaban in this frail patient population. A possible explanation may be the enrolment of fewer GI cancer patients who are prone to bleeding in the CARAVAGGIO and ADAM-VTE studies, which were conducted after seven publications of the other two DOAC (edoxaban and rivaroksaban) studies. Another explanation may be the documented relative advantage of apixaban, particularly its association with a lower risk of bleeding.[3,21] Also, it would be wise to emphasize that patients with brain lesions were excluded from the apixaban study, despite the inclusion of small sample size in other three studies. Nevertheless, the scarcity of the data makes it difficult to draw a firm conclusion on this subject.

Furthermore, DOACs seem to be more effective in terms of recurrent VTE. There may be several mechanisms. One of the reasons may be the ease of using DOACs in such a group of patients who are already exhausted of using several drugs. A subcutaneous injection may decrease the proper use of medication. Another reason which may be linked to the first one may be the reduction of the dose of LMWHs in the control arm of the studies.

Rivaroxaban was also statistically significantly superior to LMWH in terms of recurrent VTE and clinically superior compared to apixaban and edoxaban. The probable cause of this benefit was explained in the SELECT-D study, suggesting that rivaroxaban was a more potent factor 10a inhibitor than other serine proteases.[22] Considering the increased frequency of these two types of venous thrombosis in patients with cancer, it can be predicted that the frequency of VTE may increase in studies that were not specified.

In PE, the other major VTE type, proportional superiority and clinically positive results in the SELECT-D study were observed. However, the difference with the other studies, particularly compared to the other two previous results, appears with almost similar rates in the CARAVAGGIO study. In addition, the study emphasized the distribution of cancer in the population, and the high number of patients with this distribution can be combined with real-life data.

As in all types of diseases, a patient-based treatment strategy should be tailored in a multidisciplinary approach. These patients are a special group of patients and various parameters can interfere with the treatment. Drug interactions, malnutrition, vomiting, the use of myelosuppressive chemotherapy or radiation, full blood counts including platelets, renal/liver function and gastric protection with proton pump inhibitors or H2 receptor blockers should be considered in all such patients.

Nonetheless, this study presents the results of a single-center experience and a meta-analysis of pivotal studies in anticoagulant treatment of cancer patients. However, its retrospective design and heterogeneity

of the patients are the main limitations, particularly as most of the patients were treated with LMWH. Despite the encouraging results with DOACs, it is still difficult to make a definitive conclusion due to the small sample size. However, we can speculate that these findings seem to make a paradigm change in our current conservative approach, at least in selected CAT patients. Furthermore, insufficiency in detailing patient characteristics and heterogeneity in the cancer types are of the major limitations of this meta-analysis, as well as the limitation in analyzing the results of different studies. The interaction between cancer drugs and DOACs was unable to be evaluated in this meta-analysis. Further studies are needed to answer these questions. The use of LMWH can be regarded another limitation, as dosing and type of LMWH vary according to clinics.

In conclusion, based on our clinical experience and meta-analysis results and literature data, DOACs can be considered a reasonable alternative in patients with CAT. Clinicians should keep in mind that treatment of CAT requires a multidisciplinary approach and interdisciplinary collaboration.

Declaration of conflicting interests

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