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Treatment Patterns and Clinical Outcomes in Korean Cancer Patients With Venous Thromboembolism: A Retrospective Cohort Study

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Abstract

This study assessed epidemiologic data and clinical outcomes, including venous thromboembolism (VTE) recurrence and bleeding events, in patients with cancer-associated VTE, and assessed factors associated with clinical outcomes. Data were extracted from retrospective medical-chart review of adult patients diagnosed with cancer-associated deep vein thrombosis or pulmonary embolism who received anticoagulation treatment for $\geq$3 months. Patients were classified by: low-molecular-weight heparin (LMWH), direct oral anticoagulants (DOACs), and other anticoagulants. First VTE recurrence and bleeding events, and factors associated with their occurrence, were assessed during the initial 6 months of treatment. Overall, 623 patients (age: 63.7 $\pm$ 11.3 years, 49.3% male) were included (119, 132, and 372 patients in LMWH, DOACs and other anticoagulants groups, respectively). The cumulative 6-month incidence of VTE recurrence was 16.6% (total), 8.3% (LMWH), 16.7% (DOACs), and 20.7% (other); respective bleeding events were 22.5%, 11.0%, 12.3%, and 30.7%). VTE recurrence and bleeding rates differed only between LMWH and other anticoagulants (HR 2.4, 95% CI: 1.2-5.0 and 3.6, 1.9-6.8, respectively). These results highlight the importance of initial VTE treatment choice for preventing VTE recurrence and bleeding events. LMWH or DOACs for $\geq$3 months can be considered for effective VTE management in cancer patients.

Keywords

cancer, venous thromboembolism, low-molecular-weight heparin, direct oral anticoagulants

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Introduction

Cancer is a major risk factor for the development of venous thromboembolism (VTE). The incidence of VTE is 4 times higher in cancer patients than in non-cancer patients.[1] The second leading cause of death in cancer patients is thromboembolism followed by cancer itself.[2] About 10% of cancer patients die due to thromboembolism.[2] Pancreas, stomach, uterus, kidney, lung, and primary brain tumors are associated with the highest rates of VTE.[3] In Korea, there is an increasing burden of cancer and VTE; the incidence of cancer and VTE increased 2-fold from 2001 to 2011.[4,5]

VTE management is challenging because the risk of recurrent VTE and bleeding are both increased in cancer patients. The incidences of VTE recurrence and bleeding in cancer patients are 3.2- and 2.2-fold higher than in non-cancer patients, indicating that prevention of VTE recurrence and bleeding during treatment is important for long-term survival in cancer patients.[6]

According to established clinical guidelines (e.g. American Society of Clinical Oncology [ASCO], National Comprehensive Cancer Network [NCCN], European Society for Medical Oncology [ESMO]), low-molecular-weight heparin (LMWH) is recommended as both short- and long-term treatment of VTE in cancer patients. For long-term treatment of VTE in cancer patients, LMWH monotherapy is recommended for at least 3 to 6 months.[7,8] Although guidelines recommend that LMWH be used over vitamin K antagonists or direct oral anticoagulants (DOACs), latest study findings suggest that DOACs can be considered an acceptable initial anticoagulant for the prevention of VTE recurrence, especially for patients without gastrointestinal or urogenital lesions which increase a substantial bleeding risk with DOACs.[9]

Although treatment guidelines are well established, a treatment gap between real-world practice and clinical guidelines has been reported.[10] Despite evidence from randomized controlled trials showing the usefulness of long-term LMWH, only approximately 50% of patients are treated according to established guideline recommendations.[10] Descriptions of real-world practice would improve the understanding of whether patients are being treated properly.

We aimed to describe real-world treatment patterns and clinical outcomes of VTE recurrence and bleeding in patients with cancer-associated VTE in the years 2013–2015. In addition, we compared the incidence rates of recurrent VTE and bleeding according to anticoagulants and assessed factors associated with VTE recurrence and bleeding. We further studied the demographic and clinical features of patients who continued anticoagulant treatment beyond 6 months.

Recently, the results from large-scale phase III trials have been published,[11-13] and both DOACs and LMWH are recommended for cancer-associated VTE according to patients' cancer types and organ functions.[14-17]

Methods

Study Design & Data Collection

This was a retrospective cohort study where 748 active cancer patients with VTE, diagnosed between January 2013 and December 2015, were enrolled at 8 university hospitals in Korea from January 2017 to July 2017. Medical records were reviewed retrospectively to collect all study data, including demographics, clinical features, and clinical outcomes. Clinical outcomes consisted of first-ever VTE recurrence events including deep vein thrombosis (DVT) and pulmonary embolism (PE), and first-ever major and minor bleeding events, from initial anticoagulant treatment to the end of 1-year observation. The grade of bleeding was retrospectively classified according to International Society of Thrombosis and Haemostasis criteria.[18]

Based on the nature of this retrospective study design, statistical estimation for sample size was not required. As the 8 participating study hospitals were representative in Korea, data from approximately 100 patients/hospital were considered as being representative of active cancer patients with VTE and anticoagulant treatment patterns.

Patients who met all of the following criteria were included in this study; 1) aged $\geq$19-years, 2) active cancer, defined as cancer: receiving active antimitotic treatment; or diagnosed within the past 6 months; or recurrent or metastatic,[19] 3) diagnosis of both/either DVT and/or PE which were documented radiologically by computed tomography or ultrasonography, 4) newly-started anticoagulation treatment between 1 January 2013 and 31 December 2015, 5) anticoagulation treatment for at least 15 days (if the reason for discontinuation of treatment within 15 days is bleeding or thrombosis (progression of VTE or the development of new arterial thrombosis), then it can be included this study), and 6) no history of anticoagulation treatment 1 month before VTE pharmacotherapy.

Patients who met at least 1 of the following criteria were excluded; 1) history of participation in a drug interventional clinical trial 1 month before study enrollment or during the study observation period, 2) diagnosis only with upper DVT (patients diagnosed with upper DVT were exceptionally eligible if either lower DVT or PE was combined), 3) VTE occurrence before active cancer diagnosis, 4) VTE not associated with cancer (e.g., catheter-related VTE), 5) other concomitant non-pharmacotherapy for VTE treatment (except for inferior cava filter and/or compression stockings), or 6) pregnant, breastfeeding women or any other patients who were determined not eligible by the investigators.

Patients were classified into 3 groups according to the treatments they received. If the patient temporarily stopped treatment within 3 months, due to bleeding or surgery, but began to receive the same treatment within two weeks, the patient was included in the group. Patients who started with LMWH monotherapy and continued it for the next 3 to 6 months, based on clinical guidelines, were defined as LMWH. Patients whose initial anticoagulant was DOAC monotherapy,

including patients who initially used any other types of anticoagulants for loading during the first 2 weeks, and treated for the following 3 to 6 months, were defined as DOACs. The remaining patients were classified as other anticoagulants. Recurrent VTE included both symptomatic and screening-detected VTE.

Statistical Analysis

Patient's demographic and clinical characteristics at baseline were summarized as frequencies and percentage for categorical variables, and mean (standard deviation) for continuous variables. Univariable comparisons among LMWH, DOACs and Other anticoagulants treatment groups were made using chi-squared test, Fisher's exact test or one-way analysis of variance (ANOVA), as appropriately. Cumulative incidence of clinical outcomes (first VTE recurrence and bleeding) during 6 months for all study patients were estimated by both Kaplan-Meier analysis and competing risk analysis which considered death as a competing event. Reflecting different exposure periods, 6-month event rates per 100 person-years of the first VTE recurrence and bleeding, along with Wald's 95% confidence intervals, were calculated. Further competing risk analysis, using sub-distributional hazard regression model along with Gray's test, was performed to compare 6-month cumulative incidences among the three treatment groups. Factors associated with the clinical outcomes were assessed by multiple competing risk analysis using the Fine-Gray's proportional sub-distribution hazard model. For this multivariable analysis, variables significantly affected by patient's baseline characteristics among groups ($P < .1$), as well as under clinical judgment, were selected. The model's adequacy was assessed by integrated time-dependent area under the curve (AUC), and its proportional hazard (PH) assumption was examined using both the Grambsch and Therneau test and a graphical examination of log cumulative hazard plot of Kaplan-Meier survival curves. For demographic and clinical features of patients who continued anticoagulant treatment over 6 months, only descriptive analyses were performed due to the limited number of subjects. All statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA). A two-sided P value of $< .05$ was considered as an indication of statistical significance.

Ethical Statement

The institutional review board (IRB) at each participating institution approved the study protocol (Seoul National University Hospital IRB approval number: B-1610-366-105). Patient consent was waived due to the retrospective nature of the study and lack of patient interaction. All of the study procedures were carried out in accordance with the ethical standards of the Helsinki Declaration (revised in 2013; World Medical Association).

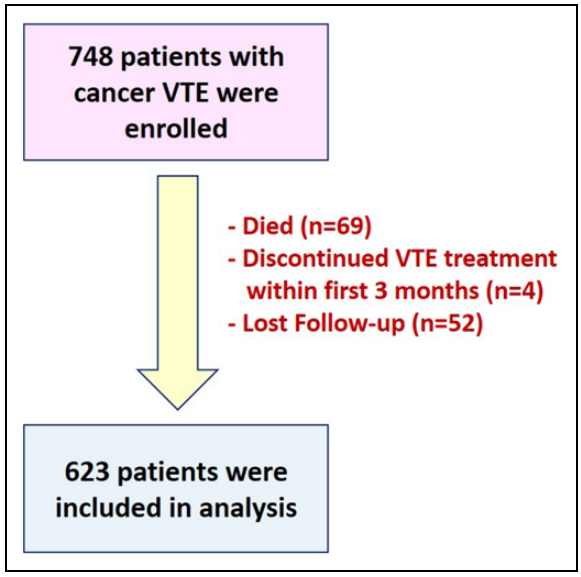

Figure 1. Study flow chart.

Results

Patients' Characteristics

Of 748 enrolled patients, 125 patients were lost to follow-up (n = 52), died (n = 69), or discontinued VTE treatment within the first 3 months (n = 4), and were excluded from the analysis (Figure 1). A total of 623 patients (aged 63.7 ± 11.3 years, male: 49.3%) were included. The proportions of patients with comorbidity, and with metastatic cancer, were highest in the LMWH group (84.9%, and 68.9%, respectively). Almost all patients (97.5%) in the LMWH group received cytotoxic therapy (Table 1). Major cancer types were lung (22.8%), colon-rectum (18.0%) and stomach (10.9%). 479 patients had PE with or without lower-extremity DVT and 144 patients had lower-extremity DVT alone. Among the 3 treatment groups, the proportion of patients with PE with or without lower-extremity DVT was highest (84%) in the LMWH group, but did not reach statistical significance ($p = 0.0888$). 555 patients had information about the anatomic sites of 861 involved vessels. 604 (70.2%) of 861 documented vessels were large vessels such as main or segmental pulmonary arteries and proximal veins of popliteal vein up to femoral and iliac vein.

Treatment Patterns of Anticoagulants

Most patients were prescribed LMWH as an initial therapy (57.5% of patients, n = 358) and the mean treatment duration was 80 ± 68 days. The number of patients who received initial LMWH treatment for the consecutive 3 to 6 months was 119, with a mean treatment duration of 154 ± 32 days. DOAC alone was initiated as first-line therapy in 19.1% (n = 121) of patients and continued for a mean of 112 ± 63 days. Of these, 79 patients continued with DOAC for 3 to 6 months (mean duration 153 ± 39 days). The remaining 42 patients were

Table 1. Patients' Characteristics at Baseline.

	LMWH	DOACs	Other anti-coagulants	Total	
	(N = 119)	(N = 132)	(N = 372)	(N = 623)	P value*
Age (years), mean (SD)	63.4 (10.8)	63.6 (10.7)	63.8 (11.8)	63.7 (11.3)	0.9308 (b)
Sex, number (%)					0.7417 (a)
Male	56 (47.1)	63 (47.7)	188 (50.5)	307 (49.3)	
Female	63 (52.9)	69 (52.3)	184 (49.5)	316 (50.7)	
Smoking, number (%)					0.7265 (a)
Current smoker	13 (10.9)	13 (9.9)	51 (13.7)	77 (12.4)	
Ex-smoker	25 (21.0)	27 (20.5)	73 (19.6)	125 (20.1)	
Nonsmoker	76 (63.9)	88 (66.7)	241 (64.8)	405 (65.0)	
ECOG performances					0.3379 (a)
3, 4	3 (2.5)	6 (4.5)	21 (5.6)	30 (4.8)	
0, 1, 2	116 (97.5)	126 (95.5)	351 (94.4)	593 (95.2)	
BMI (kg/m^2), mean (SD)	23.4 (2.9)	24.0 (3.2)	23.5 (3.4)	23.6 (3.3)	0.2811 (b)
D-dimer (μg/mL), mean (SD)¶	8.4 (7.6)	7.8 (7.0)	9.29 (10.3)	8.8 (9.3)	0.5434 (b)
Serum creatinine (mg/dL)	0.8 (0.2)	0.8 (0.2)	0.9 (0.7)	0.9 (0.6)	0.0587 (b)
Creatinine clearance rate (mL/min/1.73m2)					0.4785 (a)
<30.0	4 (3.4)	4 (3.0)	22 (5.9)	30 (4.8)	
30.0≤, <50.0	15 (12.6)	12 (9.1)	51 (13.7)	78 (12.5)	
50.0≤, <80.0	49 (41.2)	59 (44.7)	138 (37.1)	246 (39.5)	
≥80.0	51 (42.9)	57 (43.2)	161 (43.3)	269 (43.2)	
Platelet (x 10^3/μL), mean (SD)	226.5 (109.3)	237.8 (103.2)	219.24 (97.4)	224.56 (101.1)	0.1931 (b)
INR, mean (SD)	1.1 (0.3)	1.07 (0.2)	1.09 (0.2)	1.09 (0.2)	0.2979 (b)
Comorbidity, number (%)					**0.0006 (a)**
Yes	101 (84.9)	84 (63.6)	259 (69.6)	444 (71.3)	
No	18 (15.1)	48 (36.4)	113 (30.4)	179 (28.7)	
Cancer site, number (%)					0.1017 (a)
Very high risk$	*21 (17.6)*	*20 (15.1)*	*75 (20.2)*	*116 (18.6)*	
Stomach	15 (12.6)	13 (9.8)	40 (10.8)	68 (10.9)	
Pancreas	4 (3.4)	2 (1.5)	28 (7.5)	34 (5.5)	
Brain	2 (1.7)	5 (3.8)	7 (1.9)	14 (2.2)	
High risk$	*42 (35.3)*	*53 (40.2)*	*166 (44.6)*	*261 (41.9)*	
Lung	20 (16.9)	25 (18.9)	97 (26.1)	142 (22.8)	
Hematologic malignancies +	12 (10.1)	12 (9.1)	31 (8.3)	55 (8.8)	
Genitourinary tract #	10 (8.4)	9 (6.8)	20 (5.4)	39 (6.3)	
Gynecologic tract	0 (0.00)	7 (5.3)	18 (4.8)	25 (4.0)	
Neither very high nor high risk$	*56 (47.1)*	*59 (44.7)*	*131 ((35.2)*	*246 (39.5)*	
Breast	12 (10.1)	7 (5.3)	24 (6.5)	43 (6.9)	
Colorectum	31 (26.1)	30 (22.7)	51 (13.7)	112 (18.0)	
Hepatobiliary tract	8 (6.7)	9 (6.8)	30 (8.1)	47 (7.5)	
Others *^*	5 (4.2)	13 (9.9)	26 (7.0)	44 (7.1)	
Cytotoxic therapy					**0.0021** (a)
Yes	116 (97.5)	119 (90.2)	320 (86.0)	555 (89.1)	
No	3 (2.5)	13 (9.9)	52 (14.0)	68 (10.9)	
Hormonal replacement therapy					0.7133 (a)
Yes	0 (0.00)	0 (0.00)	1 (0.3)	1 (0.2)	
No	119 (100.0)	132 (100.0)	371 (99.7)	622 (99.8)	
Radiotherapy					0.4620 (a)
Yes	10 (8.4)	6 (4.6)	25 (6.7)	41 (6.6)	
No	109 (91.6)	126 (95.5)	347 (93.3)	582 (93.4)	
Major surgery					0.9663 (a)
Yes	3 (2.5)	3 (2.3)	10 (2.7)	16 (2.6)	
No	116 (97.5)	129 (97.7)	362 (97.3)	607 (97.4)	
Metastasis++, number (%)					**0.0003** (a)
M1	82 (68.9)	55 (41.7)	190 (51.1)	327 (52.5)	
M0	22 (18.5)	30 (22.7)	90 (24.2)	142 (22.8)	
Not applicable	15 (12.6)	47 (35.6)	90 (24.2)	152 (24.4)	
VTE events					0.0888 (a)

(continued)

Table 1. (continued)

	LMWH	DOACs	Other anti-coagulants	Total	
	(N = 119)	(N = 132)	(N = 372)	(N = 623)	P value*
PE with or without lower-extremity DVT	100 (84.0)	96 (72.7)	283 (76.1)	479 (76.9)	
Lower-extremity DVT alone	19 (16.0)	36 (27.3)	89 (23.9)	144 (23.1)	
Involved vessel¶¶					
Pulmonary artery					
Main	30 (25.2)	40 (30.3)	99 (26.6)	169 (27.1)	0.6236 (a)
Segmental	66 (55.5)	53 (40.2)	152 (40.9)	271 (43.5)	**0.0137** (a)
Sub-segmental	21 (17.7)	13 (9.9)	52 (14.0)	86 (13.8)	0.1997 (a)
Lower extremity deep vein					
Proximal vein	32 (26.9)	42 (31.8)	90 (24.2)	164 (26.3)	0.2294 (a)
Distal vein	28 (23.5)	39 (29.6)	104 (28.0)	171 (27.5)	(a)

* P-value among 3 different treatment groups.
(a) P-value by chi-square test or Fisher's exact test among 3 different treatment groups.
(b) P-value by one-way ANOVA.
¶ ± 3 days from VTE diagnosis.
$ Very high and high-risk of thrombosis classified according to the primary cancer site (Marc Carrier, et al. N Engl J Med 2019; 380:711-719).
+ Hematologic malignancies [total = 55]: leukemia (n = 4), lymphoma (n = 30), myeloma (n = 21).
# Genitourinary tract [total = 39]: kidney (n = 8), ureter (n = 9), bladder (n = 13), prostate (n = 6), testis (n = 2), seminoma (n = 1).
** Others [total = 44]: adrenal gland (n = 1), duodenum (n = 1), esophagus (n = 7), extrapulmonary small cell carcinoma (n = 1), head and neck (n = 13), jejunum (n = 1), melanoma (n = 3), mesothelioma (n = 2), metastasis of unknown origin (n = 1), neuroendocrine tumor (n = 2), sacral chordoma (n = 1), sarcoma (n = 7), thymoma (n = 4).
¶¶ Multiple response.
Note: Variables that were collected, but not presented herein, are provided in Supplementary Table 2.

switched to other anticoagulants before 3 months from drug initiation. 90.4% of the patients in this study were prescribed monotherapy as an initial treatment. The combination of warfarin and LMWH was the most commonly prescribed in combination therapy (n = 21), followed by combination of DOAC and LMWH (n = 14). After the first anticoagulation treatment, UFH was most commonly prescribed (29.0%, n = 183) for a mean of 6 ± 12 days, followed by DOAC (24.8%, n = 157) and LMWH (18.8%, n = 119) used for a mean of 94 ± 58 and 56 ± 59 days, respectively (Supplementary Table 1).

VTE Recurrence, Bleeding Event, and Risk Factors

Six-month cumulative VTE recurrence and bleeding incidences in all patients were 16.6% (SE 1.7%) and 22.5% (SE 1.8%), respectively (Figure 2A and B). Comparing groups, both events were highest in other anticoagulants group: 20.7% (SE 2.7%) and 30.7% (SE 2.7%), respectively. The other anticoagulants group had a 2.4- and 3.8-fold higher hazard of VTE recurrence and bleeding incidence, respectively, compared to the LMWH group (Figure 3A and B). The tendency toward a higher hazard for the incidence of both events in DOACs compared to LMWH (Hazard Ratio: 2.1 for VTE recurrence and 1.2 for bleeding incidence) was not statistically significant. The VTE recurrence rate in the LMWH group did not increase after 2 months (Figure 3A).

Regarding event rates per 100 person-years at 6 months, rates of first VTE recurrence and bleeding events were 34.5 (95% CI 27.9, 42.7) and 49.1 (95% CI 41.1, 58.6), respectively. Among groups, VTE recurrence and bleeding event rates at 6 months were lowest in the LMWH group: 16.8 (95% CI 8.7, 32.3) and 19.9 (95% CI (11.0, 35.9) 100 person-years, respectively. Non-LMWH (DOACs, other anticoagulants) groups showed the following event rates of VTE recurrence and bleeding: 42.8 (95% CI 32.8, 55.9), 77.1 (95% CI 63.1, 94.1) 100 person-years in the other anticoagulants group, and 33.0 (95% CI 21.5, 50.7), 21.8 (95% CI 13.2, 36.2) in the DOACs group.

We performed a sub-group analysis for DOACs users (N = 132). There was no difference in VTE recurrence and bleeding rate in patients with upper GI tract cancers versus other cancers. We also conducted a sub-group analysis for 21 multiple myeloma patients. Their 6 months' VTE recurrence and bleeding rate were 4.8% and 28.6%, respectively.

Risk factor associated with VTE recurrence was the involvement of the main pulmonary artery in initial VTE (Table 2). Meanwhile, bleeding events were associated with treatment of VTE with other anticoagulants (reference: LMWH group), and creatinine clearance less than 30mL/min (Table 3). Clinical and statistically significant variables (univariate analysis showed that variables with $P < 0.1$ were included) were included in the competing analysis model. The model's integrated time-dependent AUC was 0.728 for VTE recurrence and 0.757 for bleeding events. The competing risk model for VTE recurrence satisfied the global PH assumption among the three groups (Grambsch and Themeau test's global $P = 0.164$). Further, the PH assumptions for the DOAC group compared with the LMWH group ($P = 0.365$), and for Other anticoagulants

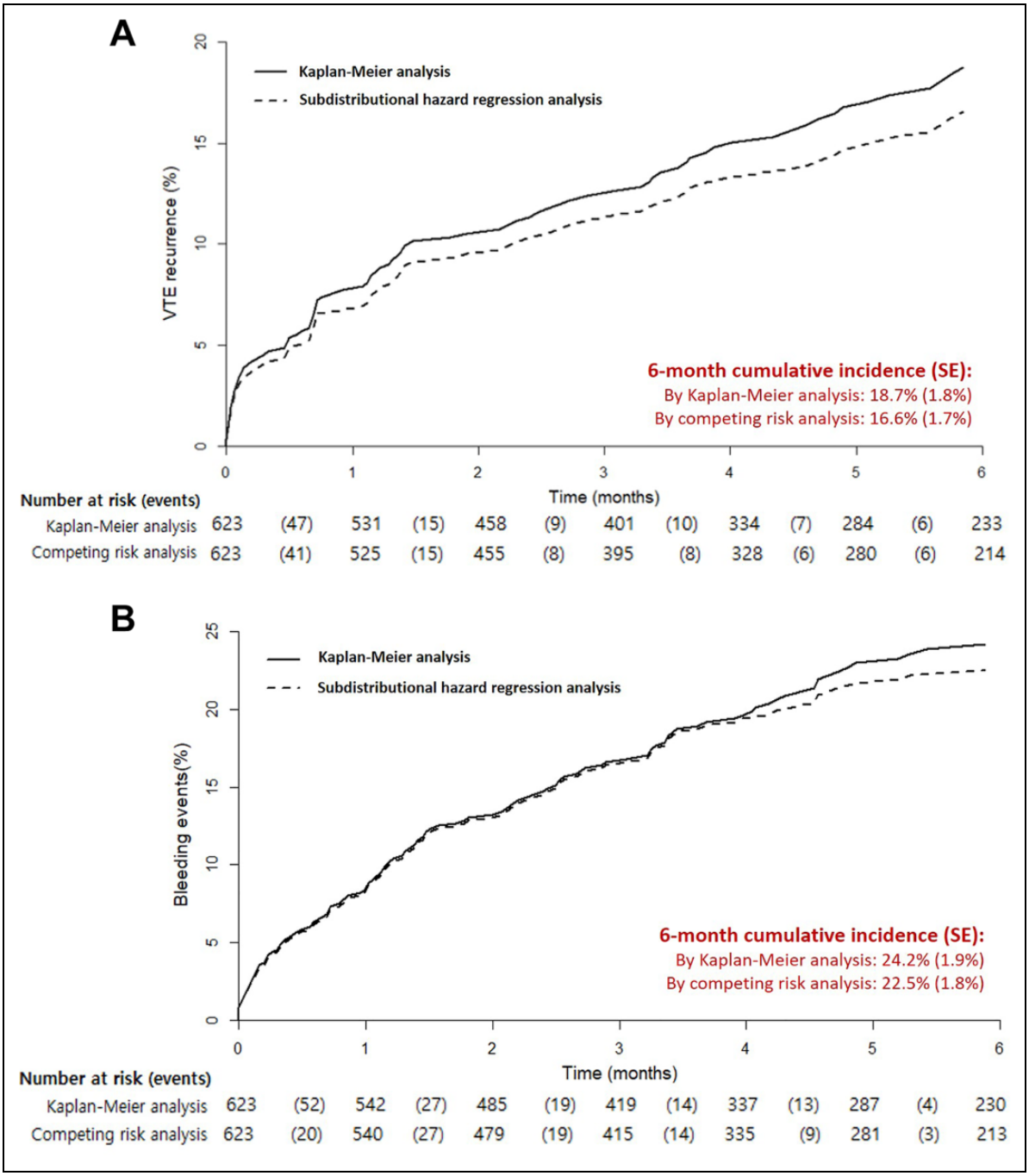

Figure 2. Cumulative VTE recurrence (A) and bleeding event (B) incidence.

compared with the LMWH group (P = 0.078), were also satisfied. For bleeding event competing risk model, although the PH assumption did not hold globally (P = 0.017), that for the DOAC group compared with the LMWH group was marginally satisfied (P = 0.053), but not for Other anticoagulants compared with the LMWH group (P = 0.004), so that a cautious interpretation of risk factors associated with bleeding events is needed. Graphical examinations of log cumulative hazard plots of Kaplan-Meier survival curves for two models also support the Grambsch and Themeau test results.

After 6-Months From Initial Therapy

The proportion of patients with comorbidities also increased at 6 months. In particular, in the DOACs and other anticoagulants groups, which had the definite increased proportion of patients with comorbidities from initial 63.6% and 69.6% to 94.7% and 84.1%. The proportion on cytotoxic chemotherapy decreased from initial 89.1% to 80.7% (Supplementary Table 3). 12-month cumulative VTE recurrence and bleeding incidences in 501 and 464 patients were 33.1% (SE 5.1%) and 12.0% (SE 3.2%), respectively (landmark competing risk analyses).

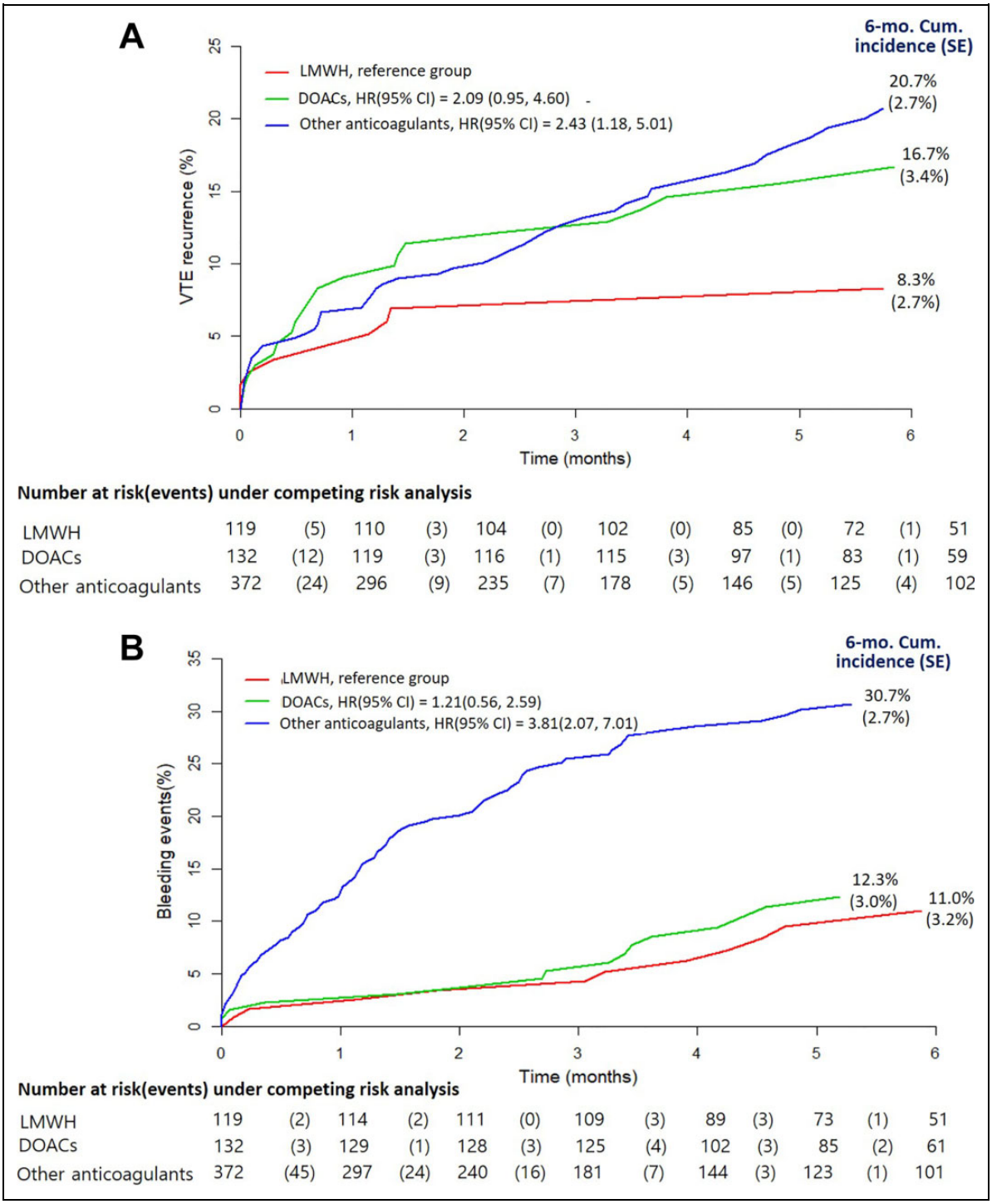

Figure 3. Cumulative VTE recurrence rate (A) and bleeding event incidence (B); comparison between 3 groups).

Discussion

This study described real-world treatment patterns and clinical outcomes of VTE recurrence and bleeding in patients with cancer-associated VTE for 12 months. We also compared the cumulative incidence rates of recurrent VTE and bleeding according to treatment groups and assessed factors associated with VTE recurrence and bleeding.

In this study, only 19.1% of cancer VTE patients were treated with LMWH. This is considerably lower compared with findings from previous studies which reported the non-LMWH rate for VTE treatment in cancer patients as 33%-52%.[20,21] On the other hand, due to the appearance of new anticoagulants, decreasing tendency of using LMWH as 1st line therapy for cancer VTE patients reported from 48.5% in 2009-2013 to

Table 2. Factors Associated With VTE Recurrence.

N = 623	Events	Rate of events per 100 P-Y (95% CI)[†]	HR (95% CI)	P-value *
Group				
LMWH	27	50.39 (34.56, 73.48)	Ref	-
DOACs	35	55.05 (39.53, 76.67)	1.79 (0.78, 4.13)	0.1716
Other anticoagulants	98	77.62 (63.67, 94.61)	2.10 (0.96, 4.62)	0.0638
Age				
< 63.7	87	81.12 (65.75, 100.09)	Ref	-
≥63.7	73	53.61 (42.62, 67.43)	0.77 (0.48, 1.22)	0.2662
Sex				
Female	85	68.86 (55.67, 85.18)	Ref	-
Male	75	62.51 (49.85, 78.38)	0.63 (0.40, 0.98)	0.0397
Primary site of Cancer				
Stomach or pancreas	36	107.23 (77.35, 148.66)	1.13 (0.64, 2.00)	0.6629
Others	124	59.09 (49.55, 70.46)	Ref	-
Cancer treatment				
Insertion of central venous catheter				
No	124	57.62 (48.32, 68.71)	Ref	-
Yes	36	127.50 (91.97, 176.76)	0.96 (0.53, 1.76)	0.8974
Radiation therapy				
No	150	66.98 (57.07, 78.60)	Ref	-
Yes	10	51.38 (27.64, 95.49)	0.55 (0.21, 1.41)	0.2104
Admission for treatment				
No	112	55.56 (46.17, 66.87)	Ref	-
Yes	48	114.69 (86.43, 152.18)	1.40 (0.83, 2.36)	0.2034
Hormone replacement therapy				
No	156	64.78 (55.37, 75.79)	Ref	-
Yes	4	152.98 (57.42, 407.62)	2.10 (0.48, 9.15)	0.3246
Inferior vena cava filter				
No	131	56.24 (47.39, 66.75)	Ref	-
Yes	29	276.06 (191.84, 397.25)	1.62 (0.73, 3.60)	0.2392
Compression stocking				
No	138	61.53 (52.07, 72.70)	0.68 (0.34, 1.39)	0.2919
Yes	22	114.97 (75.70, 174.61)	Ref	-
Recent major surgery within 6 months				
No	140	62.24 (52.74, 73.45)	Ref	-
Yes	20	108.24 (69.83, 167.77)	1.76 (0.95, 3.26)	0.0727
ECOG performance status				
0, 1, 2	147	63.04 (53.63, 74.10)	Ref	-
3, 4	13	127.09 (73.80, 218.88)	1.39 (0.55, 3.53)	0.4873
BMI				
< 23.6	81	70.86 (57.00, 88.10)	Ref	-
≥23.6	79	61.18 (49.08, 76.28)	0.71 (0.45, 1.12)	0.1392
Creatinine clearance				
< 30.0	6	50.75 (22.80, 112.97)	0.35 (0.09, 1.41)	0.1392
30.0≤, < 50.0	13	44.65 (25.93, 76.90)	0.28 (0.11, 0.73)	**0.0087**
50.0≤, < 80.0	66	62.98 (49.48, 80.16)	0.66 (0.41, 1.06)	0.0841
≥ 80.0	75	76.78 (61.23, 96.28)	Ref	-
Involved vessel[#]				
Pulmonary artery				
Main	59	90.08 (69.80, 116.27)	1.70 (1.04, 2.76)	**0.0336**
Segmental	53	50.90 (38.89, 66.63)	0.73 (0.43, 1.24)	0.2396
Subsegmental	16	49.66 (30.42, 81.05)	0.80 (0.39, 1.66)	0.5534
Lower extremity deep vein				
Proximal vein	50	71.11 (53.89, 93.82)	0.99 (0.59, 1.64)	0.9553
Distal vein	57	81.18 (62.62, 105.25)	1.26 (0.77, 2.08)	0.3604

* Wald's confidence interval (Rothman et al. (2008) Modern epidemiology, 3 rd ed., Lippincott Williams & Wilkins, PA USA, p.242).
[†] By multivariable competing risk analysis using the Fine-Gray proportional sub-distribution hazards model.
Multiple response.

Table 3. Factors Associated With Bleeding.

N = 612	Events	Rate of events per 100 P-Y (95% CI)*	HR (95% CI)	P-value†
Group				
LMWH	11	19.85 (10.99, 35.84)	Ref	-
DOACs	15	21.84 (13.17, 36.23)	1.02 (0.47, 2.21)	0.9505
Other anticoagulants	96	77.07 (63.09, 94.13)	3.20 (1.70, 6.02)	**0.0003**
Age				
< 63.7	62	55.14 (42.99, 70.73)	Ref	-
≥63.7	60	44.04 (34.20, 56.72)	0.76 (0.50, 1.17)	0.2104
Sex				
Female	60	47.10 (36.57, 60.67)	Ref	-
Male	62	51.12 (39.85, 65.57)	1.07 (0.73, 1.57)	0.7267
Primary site of Cancer				
Esophagus, stomach, or colorectum	38	46.22 (33.63, 63.52)	1.07 (0.71, 1.61)	0.7532
Others	84	50.46 (40.75, 62.50)	Ref	-
Cancer treatment				
Insertion of central venous catheter				
No	91	41.17 (33.52, 50.56)	Ref	-
Yes	31	112.22 (78.92, 159.57)	0.48 (0.30, 0.77)	**0.0022**
Radiation therapy				
No	117	51.33 (42.82, 61.53)	Ref	-
Yes	5	24.12 (10.04, 57.95)	0.41 (0.14, 1.19)	0.1023
Admission for treatment				
No	95	46.69 (38.19, 57.09)	Ref	-
Yes	27	59.73 (40.96, 87.10)	1.11 (0.68, 1.81)	0.6730
Hormone replacement therapy				
No	121	49.15 (41.13, 58.74)	Ref	-
Yes	1	40.27 (5.67, 285.89)	1.31 (0.11, 15.24)	0.8291
Inferior vena cava filter				
No	112	47.62 (39.57, 57.31)	Ref	-
Yes	10	74.22 (39.94, 137.95)	0.70 (0.33, 1.49)	0.3548
Compression stocking				
No	111	48.08 (39.92, 57.92)	0.73 (0.35, 1.51)	0.3974
Yes	11	61.73 (34.18, 111.46)	Ref	-
Recent major surgery within 6 months				
No	111	48.67 (40.41, 58.62)	Ref	-
Yes	11	53.42 (29.58, 96.46)	1.20 (0.59, 2.46)	0.6167
ECOG performance status				
0, 1, 2	113	47.66 (39.63, 57.31)	Ref	-
3, 4	9	77.88 (40.52, 149.68)	1.27 (0.54, 2.99)	0.5818
BMI				
< 23.6	70	60.03 (47.50, 75.88)	Ref	-
≥23.6	52	39.37 (30.00, 51.67)	0.75 (0.51, 1.12)	0.1607
Creatinine clearance				
< 30.0	10	112.01 (60.26, 208.17)	3.18 (1.47, 6.89)	**0.0033**
30.0≤, < 50.0	22	80.52 (53.02, 122.29)	1.63 (0.90, 2.95)	0.1041
50.0≤, < 80.0	36	33.10 (23.88, 45.89)	0.69 (0.42, 1.14)	0.1512
≥ 80.0	54	52.09 (39.90, 68.02)	Ref	-
Platelet (x $10^3/\mu L$)				
< 50	1	30.95 (4.36, 219.75)	0.55 (0.06, 5.16)	0.6007
≥ 50	119	49.22 (41.13, 58.91)	Ref	-
Involved vessel#				
Pulmonary artery				
Main	30	42.58 (29.77, 60.90)	0.93 (0.59, 1.46)	0.7554
Segmental	45	42.99 (32.10, 57.58)	1.05 (0.67, 1.63)	0.8358
Subsegmental	13	39.75 (23.08, 68.45)	0.77 (0.41, 1.47)	0.4303
Lower extremity deep vein				
Proximal vein	40	56.63 (41.54, 77.21)	1.23 (0.75, 2.02)	0.4059

(continued)

Table 3. (continued)

N = 612	Events	Rate of events per 100 P-Y (95% CI)*	HR (95% CI)	P-value†
Distal vein	43	60.08 (44.56, 81.01)	1.31 (0.80, 2.13)	0.2846

* Wald's confidence interval (Rothman et al. (2008) Modern epidemiology, 3 rd ed., Lippincott Williams & Wilkins, PA USA, p.242).
† By multivariable competing risk analysis using the Fine-Gray proportional sub-distribution hazards model.
# Multiple response.

around 25% in 2013-2014.[22] Importantly, more than half of all patients in this study started anticoagulants other than LMWH or DOAC or discontinued initial therapy before 3 months (defined as DOACs or other anticoagulants groups). This variation may reflect physicians' decisions according to the individual patients' conditions, insufficient awareness of clinical guidelines, or physicians' own negative perceptions of recommended treatment patterns.

Cumulative incidence rates of first VTE recurrence and bleeding events were 16.6% and 22.5% in this study which are a little higher than reported rates in the literature.[3-5] In a population-based cohort study, the cumulative incidence rate of VTE recurrence was 21.4% at 6 months[3]; in a prospective study, these rates were around 15% and 8%, respectively.[4] Based on real-word experience, the recurrence rate of VTE at 6 months was 13.2% for DOACs and 17.1% for LMWH.[23] We assume that the differences may reflect the very heterogeneous duration of treatment exposures and various patients' cancer stages reflecting real-world practice in Korea.

Concerning the comparison of VTE recurrence and bleeding events by treatment groups, patients treated with LMWH showed the lowest tendency for VTE recurrence and bleeding events, although there was no significant difference between LMWH and DOACs. These findings are consistent with results from previous studies.[5-7] A meta-analysis comparing the efficacy and safety of LMWH and DOACs for cancer VTE concluded that no definitive differences in efficacy and safety exist between the 2 anticoagulants.[8]

In our study, a few factors, including involvement of main pulmonary arteries, and coagulant patterns, and brain cancer when compared to lung cancer, were associated with VTE recurrence and bleeding events which reflect the limitations of retrospective design. Nevertheless, these results can provide concrete evidence to support previous study findings which reported the following related factors: patient-related factors included younger age (<65 years), female gender, or prior history of VTE,[9,10,24] and cancer-related factors were malignancy within 3 months of VTE events, locally advanced or metastatic cancer, primary tumor site (lung, hepatobiliary), or venous compression secondary to tumor or malignant adenopathy.[7,25,26]

Our study reflects actual patterns of anticoagulant use that are currently in practice. Therefore, the study can help to enhance the level of understanding of real-world practice and pinpoint unmet medical needs in anticoagulation treatment. Our results can also provide a strong foundation for understanding real-world practice beyond 6 months.

Because of the nature of the study design, a retrospective chart review, the patterns of anticoagulants were heterogeneous. and it was difficult to investigate all variables affecting patients. In particular, the time in therapeutic range (TTR), a variable that may be an important factor to event occurrence in the other coagulants group receiving warfarin, could not be investigated. Furthermore, incidence rates of VTE recurrence and bleeding should be interpreted cautiously given that they could have been under/overestimated due to the time lapse between the actual treatment period and time-to-event.

Conclusion

These real-world study results highlight the importance of initial VTE treatment choice regarding the prevention of VTE recurrence and bleeding events in cancer patients. LMWH or DOAC monotherapy as first-line treatment can be considered for at least 3 months to effectively manage VTE in cancer patients.

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Conceptualization: Kim YJ. Methodology: Kang JH, Bang SM, Kim YJ. Validation: Gil HY. formal analysis: Lee J, Park EL. Investigation: Kang JH, Bang SM, Hong MH, Ahn JS, Oh SY, Baek JH, Choi YJ, Shin SH. data curation: Kang JH, Bang SM, Gil HY, Kim YJ. Writing—original draft preparation: Gil HY. Writing—review and editing: Kang JH, Bang SM, Hong MH, Ahn JS, Oh SY, Baek JH, Choi YJ, Shin SH, Gil HY, Park HE, Kim YJ.

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