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Dynamic Patterns and Persistence of Anticoagulation Therapy in Patients with Venous Thromboembolism in South Korea: A Nationwide Cohort Study

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Abstract

Background Venous thromboembolism (VTE) is associated with increased morbidity, mortality, and health care expenditure. However, the comprehensive utilization of anticoagulation therapy in patients with VTE, especially regarding active cancer, in real-world practice remains unclear.

Objective To describe the prescription, persistence, and patterns of anticoagulation therapy among patients with VTE stratified according to active cancer.

Methods Using Korean nationwide claims data, we identified an incident, treatment-naïve cohort of patients with VTE from 2013 to 2019 and classified them according to the presence/absence of active cancer. We explored the secular trends, treatment patterns (e.g., discontinuation, interruption, and switch), and persistence of anticoagulation therapy.

Results There were 48,504 and 7,255 patients without and with active cancer, respectively. Non-vitamin K antagonist oral anticoagulants (NOACs) were the most common anticoagulant in both groups (65.1 and 57.9%, respectively). The prescription of NOACs increased steeply over time, regardless of active cancer, whereas parenteral anticoagulants (PACs) plateaued and warfarin decreased sharply. A heterogeneous pattern was observed between the groups without and with active cancer (3-month persistence was 60.8, 62.9, 57.2, and 3.4%, respectively; 6-month persistence was 42.3, 33.5, 25.9, and 1.2% vs. 9.9%). Median durations of continuous anticoagulant therapy for warfarin, NOAC, and PAC were 183, 147, and 3 days in nonactive cancer patients, and 121, 117, and 44 days in active cancer patients.

Conclusion Our findings suggest that there were substantial differences in persistence, patterns, and patient characteristics of anticoagulant therapy based on index anticoagulant and active cancer.

Keywords
- venous thromboembolism
- anticoagulants
- NOACs
- treatment patterns
- cancer

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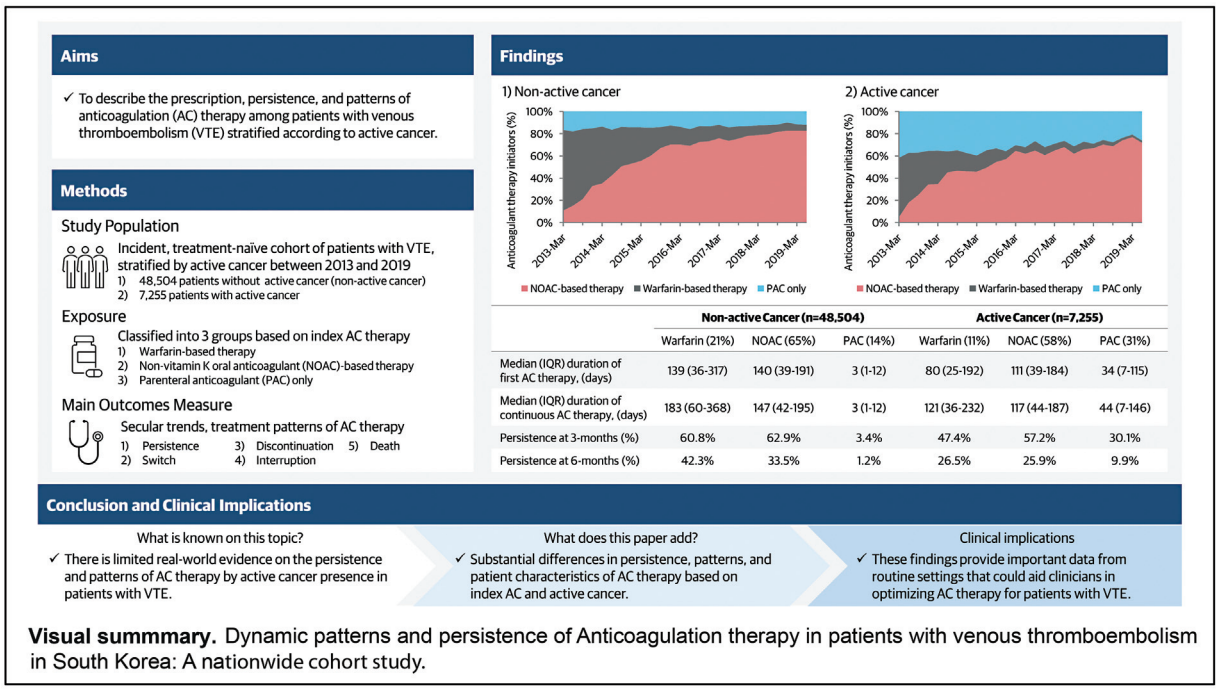

Visual summmary. Dynamic patterns and persistence of Anticoagulation therapy in patients with venous thromboembolism in South Korea: A nationwide cohort study.

Introduction

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is a major cause of increased morbidity, mortality, and health care expenditure. The incidence of VTE in the Asian population is much lower than that of the global population (15 vs. 100–200 cases per 100,000 people),[1] indicating the presence of substantial underlying differences between the Asian and Western populations and the relative uncommonness of VTE in Asia.[2] Nevertheless, with the increase of VTE incidence in Asia,[3] there has been a growing interest in the therapeutic management of VTE in recent years. Regarding the pharmacological treatment of VTE, the conventional guidelines have recommended parenteral anticoagulants (PACs), followed by vitamin K antagonists (VKAs). However, the introduction of non-VKA oral anticoagulants (NOACs), which have exhibited a noninferior efficacy and safety compared with conventional therapy in several trials, has dramatically shifted the therapeutic paradigm in the context of VTE.[4–7]

In a transitional phase of the changes being made to relevant guidelines for VTE, NOACs have attained the optimal therapeutic position; however, the recommendations for patients with active cancer have remained inconclusive because of the complicated status of each patient and their distinct hemodynamic characteristics compared with the general population, as well as a lack of large-sized randomized clinical trials addressing patients with active cancer exclusively.[8–10] Because active cancer is an irrefutable risk factor that increases the risk of VTE by more than twofold,[11] appropriate prevention and management of VTE using more convenient anticoagulants than PACs are highly imperative. Fortunately, three large-scale phase III studies comparing three NOACs with low-molecular-weight heparin (LMWH) were conducted.[12–14] Based on these results, the current guidelines recommend the use of NOACs in patients with active cancer without gastroesophageal lesions that cause severe bleeding.[15–17] However, the current guidelines are generally based on data from Western populations, thus rendering it challenging to apply them to the Asian population directly; evidence from this population would be beneficial for filling knowledge gaps and guiding clinicians toward better decision-making. Currently, as previous studies were limited to specific populations or focused on either epidemiology or patterns,[3,18,19] there is a strong need for comprehensive research that reflects the persistence and patterns of anticoagulant treatment according to the presence/absence of active cancer in routine clinical practice.

Because of the limited real-world evidence on the treatment patterns of different anticoagulants according to the presence/absence of active cancer, especially among the Asian population, we aimed to describe the sociodemographic and clinical characteristics of patients with VTE stratified according to active cancer regarding their index VTE treatment (warfarin-based, NOAC-based, and PAC-only therapy) and to investigate the utilization of anticoagulants, as well as the persistence, patterns, and overall duration of treatment with these agents, in South Korea.

Methods

Data Sources

We used the records of the Health Insurance Review and Assessment Service (HIRA) database of South Korea. The

HIRA database includes health care utilization information for all residents in South Korea, with anonymized patient identifiers. Information on age, sex, diagnosis (ICD-10 [International Classification of Diseases, 10th revision] diagnostic code, date of diagnosis, setting [inpatient, outpatient, emergency department], and other parameters), and medications dispensed/prescribed (national drug chemical code based on the active ingredient, date of prescription, days' supply, dose, route of administration, and other parameters) is available in the HIRA database. A previous validation study that compared the diagnosis codes recorded in HIRA with those recorded in electronic medical records found an overall positive predictive value of 82.3%.[20]

Study Population

A retrospective, observational, nationwide population-based cohort study was conducted to describe the persistence and patterns of anticoagulants prescribed to patients with VTE. The study cohort comprised patients aged ≥18 years at their incident diagnosis of VTE from an inpatient or outpatient setting between March 1, 2013 and June 30, 2019 who received anticoagulation therapy within 30 days of their VTE diagnosis (the detailed codes for identifying patients with VTE are provided in ►**Supplementary Table S1** [available in the online version]). Cohort entry was defined as the date of diagnosis of incident VTE, and the index date was defined as the date of first prescription of anticoagulants, within 30 days after the cohort entry. Among these eligible patients, the patients with the following characteristics were excluded: a record of VTE diagnosis within the 12-month period prior to cohort entry; a diagnosis of atrial fibrillation, atrial flutter, mechanical heart valve replacement, or mitral stenosis any time prior to the index date; a record of inferior vena cava filter any time prior to the index date; prescription of anticoagulatory therapy within the 12-month period prior to cohort entry; a record of pregnancy within the 9-month period before the index date; and prescription of two different anticoagulants at the index date.

The baseline sociodemographic characteristics (e.g., age and sex) were assessed at the index date, whereas the clinical characteristics (i.e., comorbidities, use of co-medications, Charlson comorbidity index [CCI], HAS-BLED scores, initial presentation of VTE, and number of outpatient visits) were assessed during the 6-month period prior to the index date. As the diagnosis of antiphospholipid syndrome is usually established after VTE diagnosis using additional diagnostic procedures, antiphospholipid syndrome was evaluated within the 6-month period after the index date (the overall study scheme is depicted in ►**Supplementary Fig. S1** [available in the online version]).

Design and Settings

All analyses were performed in two separate cohorts that were stratified according to the presence/absence of active cancer, because the hemodynamic status and treatment guidelines in patients with active cancer differ considerably from those of the general population. Active cancer was defined as a first diagnosis of cancer (excluding nonmelanoma skin cancer) with a unique domestic V code within the 6-month period prior to the index date, or ongoing anticancer treatment (chemotherapy, radiation therapy, or cancer-related surgery) accompanied by a cancer diagnosis with a V code within the 6 months preceding the index date. The V code was attributed to patients with a cancer diagnosis that was confirmed by histopathological, cytological, radiological, and immunological findings, as certified by the Korean Ministry of Health and Welfare for reimbursement purposes (the definitions of anticancer treatment are summarized in ►**Supplementary Table S2** [available in the online version]).

Within each cohort, after stratification according to active cancer, we described the patterns of anticoagulant therapy throughout the follow-up, which was defined as the period from the index date to the end of the study period (December 31, 2019; a minimum 6-month follow-up period is secured on all study populations). Each individual was discretely classified into three groups based on their index anticoagulant treatment: (1) warfarin-based therapy, defined as warfarin alone or onset of warfarin therapy within 14 days of PAC therapy; (2) NOAC-based therapy (i.e., apixaban, dabigatran, rivaroxaban, and edoxaban), defined as NOAC alone or PAC followed by NOAC within 14 days; and (3) PAC-only therapy, defined as the use of unfractionated heparin or LMWH for more than 14 days. Because in real-world practice PACs can be initiated at an acute stage of DVT/PE, before the clinical decision to use oral anticoagulants, we introduced a 2-week window to distinguish between PAC bridging therapy and PAC-only treatment.

Treatment Patterns

The treatment patterns were classified into five mutually exclusive events based on the occurrence of the first treatment episode: (1) switch, defined as a prescription of another anticoagulant therapy that was started after the initiation of treatment with the index anticoagulant and within 30 days after the estimated end of the supply of the index anticoagulant drug (exposure to the new anticoagulant treatment must have lasted for at least 30 days for its consideration as a treatment switch); (2) discontinuation (complete discontinuation; no re-initiation), defined as patients who ended their first continuous treatment episode with the index anticoagulant treatment without switching, and subsequently had no further prescriptions for that specific anticoagulant treatment during all available follow-up time; (3) interruption (re-initiation), defined as patients who had a gap with no new treatment within 30 days of the estimated end of the drug supply, but subsequently restarted the index treatment after this period; (4) death, defined as patients who died during the first anticoagulant treatment episode; and (5) persistence, defined as patients who were repeatedly prescribed the index anticoagulant until the end of the study period and did not experience any of the above events (treatment switch, discontinuation, interruption, or death). The duration of the first anticoagulant therapy was defined as the period from the index date to the earliest of the treatment events, i.e., switch, discontinuation, interruption, death, or the end of the study period (persistence). Moreover, we calculated the duration of continuous anticoagulant therapy,

which was defined as the persistence of treatment while allowing for switching between anticoagulants. This estimate provides an accurate representation of the actual treatment duration for patients with VTE.

Statistical Analysis

The baseline characteristics were summarized using the mean value with standard deviation or the median value with interquartile range (IQR) for continuous variables, and using counts (proportions) for categorical variables in the three treatment groups of interest: the warfarin-based group, the NOAC-based group, and the PAC-only group. An analysis of variance and the chi-squared test were used to analyze continuous and categorical variables, respectively. We assessed the temporal trend in the anticoagulation therapy for VTE between March 1, 2013 and June 30, 2019. The proportions of the index oral anticoagulants were estimated according to calendar year and quarters. To describe the patterns of anticoagulant therapy, we summarized the number and proportion of patients who experienced treatment switch, discontinuation, and interruption during their follow-up according to the index anticoagulant treatment. The duration of the first anticoagulant therapy and the duration of continuous anticoagulant therapy for each of the index anticoagulant treatments were summarized using the median [IQR]. We analyzed treatment persistence for each anticoagulant using the Kaplan–Meier method, to derive the treatment distribution over time. The treatment persistence rate was calculated at 3 and 6 months, with the log-rank test being used at these time points to assess the statistical significance of the differences between the survival curves. p-Values <0.05 were regarded as statistically significant. All analyses were performed using SAS Enterprise Guide 7.1 (SAS Institute Inc., Cary, North Carolina, United States).

Results

Study Populations and Characteristics

Of the 104,470 patients with VTE recorded in South Korea between 2013 and 2019 who were eligible, we identified 55,759 incident patients who initiated anticoagulant therapy within 30 days of diagnosis (►**Fig. 1**). There were 48,504 and 7,255 patients in the groups without and with active cancer, respectively. Most patients were aged ≥65 years, regardless of cancer status, and the female sex was more common in the group without active cancer; in contrast, patients with active cancer exhibited similar sex proportions. NOAC-based

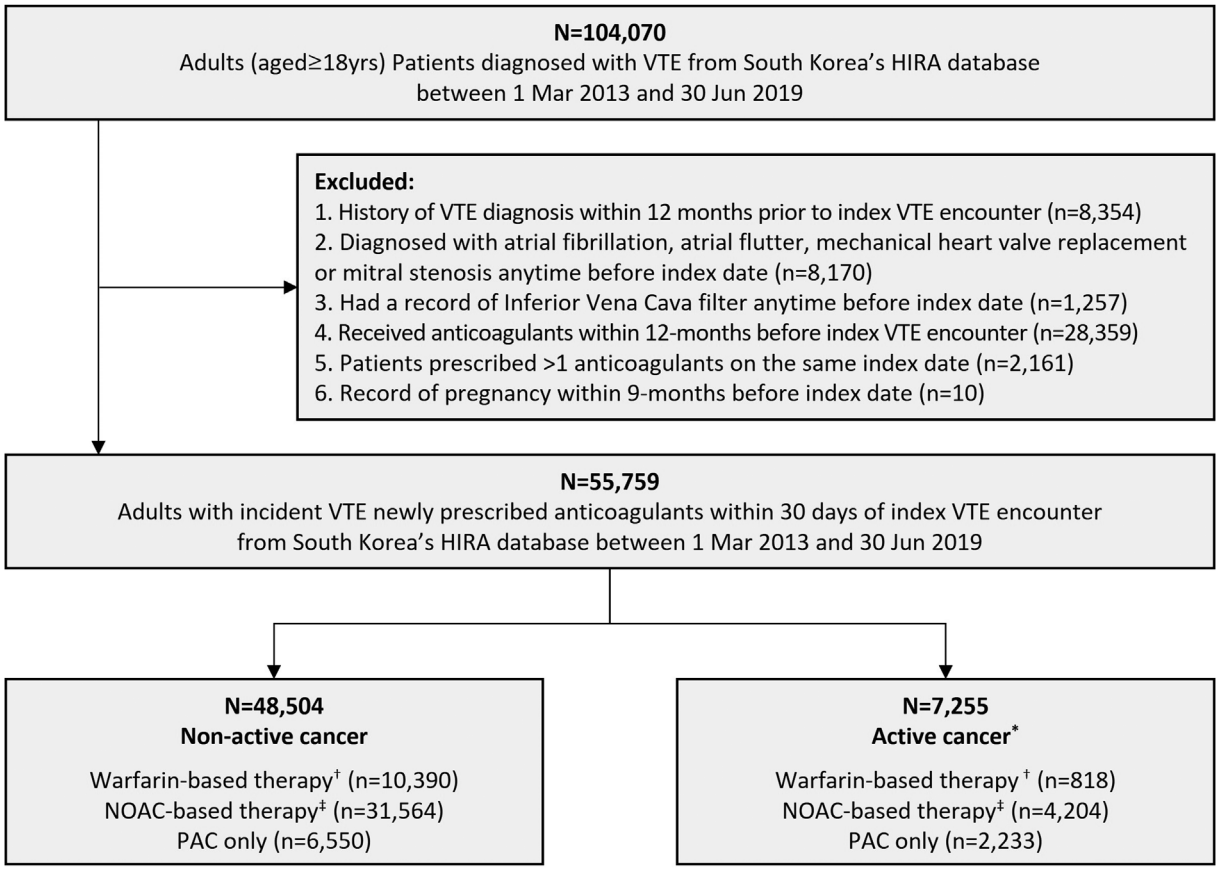

Fig. 1 Inclusion and exclusion criteria of the study. *Record of active cancer was defined as a first diagnosis of cancer with a V code within the 6-month period prior to the index date; or receiving anticancer treatment under a cancer diagnosis with a V code within the 6-month period prior to the index date. †Warfarin-based therapy included either a PAC with warfarin or warfarin alone. ‡NOAC-based therapy included either a PAC with a NOAC or a NOAC alone. HIRA, Health Insurance and Review Assessment service; LMWH, low-molecular-weight heparin; NOAC, non-vitamin K antagonist; PACs, parenteral anticoagulants; VTE, venous thromboembolism.

Table 1 Baseline characteristics among venous thromboembolism patients without active cancer by their index anticoagulant treatment

Characteristics	Warfarin-based therapy		NOAC-based therapy		PAC only		*p*-Value[a]
	N = 10,390 (21.4%)		*N* = 31,564 (65.1%)		*N* = 6,550 (13.5%)		
Age (y; mean ± SD)	66.4	16.7	67.5	16.1	68.9	16.3	<0.0001
Age group (y; *n*, %)							
18–40	974	9.37	2,591	8.20	527	8.04	<0.0001
40–65	2,920	28.1	8,414	26.6	1,643	25.0	
≥65	6,496	62.5	20,559	65.1	4,380	66.8	
Sex (*n*, %)							
Male	4,412	42.4	12,694	40.2	2,879	43.9	<0.0001
Female	5,978	57.5	18,870	59.7	3,671	56.0	
Index VTE event (*n*, %)							
DVT only	4,232	40.7	14,372	45.5	2,822	43.1	<0.0001
PE with/without DVT	6,158	59.3	17,192	54.5	3,728	56.9	
Major orthopaedic surgery-provoked VTE	183	1.76	654	2.07	119	1.82	0.0891
Index year (*n*, %)							
2013	3,035	29.2	1,089	3.45	804	12.2	<0.0001
2014	2,631	25.3	2,999	9.50	955	14.5	
2015	1,664	16.0	4,608	14.5	1,012	15.4	
2016	1,188	11.4	5,719	18.1	1,118	17.0	
2017	939	9.03	6,443	20.4	1,116	17.0	
2018	679	6.53	7,063	22.3	1,021	15.5	
2019	254	2.44	3,643	11.5	524	8	
HAS-BLED score (mean ± SD)	2.19	1.16	2.19	1.11	2.26	1.18	<0.0001

Abbreviations: IQR, interquartile range; NOAC, non-vitamin K antagonist oral anticoagulant; PAC, parenteral anticoagulants; SD, standard deviation.
[a]Analysis of variance (ANOVA) was conducted for continuous variables; Chi-square tests were conducted for categorical variables.

therapy was the predominant anticoagulant therapy in both patient groups, without ($n = 31,564$ [65.1%]) and with ($n = 4,204$ [57.9%]) active cancer; the proportion of initial PAC therapy was more frequent (twofold) among patients with compared with those without active cancer, thus revealing distinct patterns according to the presence of active cancer (30.8 vs. 13.5%) (►**Tables 1** and **2**).

Clear differences in patient characteristics were observed according to the presence of active cancer; for instance, PE as the index VTE event was more common in patients with active cancer than in those without it (~70 vs. 60%). In the group without active cancer, patients who received initial PAC therapy were the oldest (mean age: 68.9 years), had the highest CCI (mean: 1.45) and HAS-BLED (mean: 2.26) scores. In turn, in the active cancer group, patients who received initial PAC therapy were the youngest (mean age: 65.4 years) and had the lowest HAS-BLED score (mean: 2.23). The characteristics of patients who received initial warfarin- or NOAC-based therapies were largely similar, regardless of the presence of active cancer.

Secular Trends in Initial Anticoagulant Therapy Over Time

Regardless of the presence of active cancer, the most common anticoagulant treatment was NOAC-based therapy, with a steep increase of initial therapy using these agents noted over time (►**Fig. 2**). In contrast, a relative trend toward a plateau was observed in patients who received initial PAC-only therapy, and a sharply decreasing trend was observed for those who received initial warfarin treatment. Since their introduction, NOACs have replaced the market share of warfarin. Among the patients without active cancer, approximately 10% initiated therapy with NOACs in the first quarter of 2013; in turn, over time, this proportion increased to approximately 80%. This trend was also observed in patients with active cancer; however, the proportion of patients who received initial PAC therapy in the active cancer group was approximately 30 to 40%, indicating differences compared with the group without active cancer. Among the patients who received NOACs initially, rivaroxaban was the most common agent, followed by apixaban, edoxaban, and

Table 2 Baseline characteristics among venous thromboembolism patients with active cancer by their index anticoagulant treatment

Characteristics	Warfarin-based therapy		NOAC-based therapy		PAC only		*p*-Value[a]
	N = 818 (11.3%)		*N* = 4,204 (57.9%)		*N* = 2,233 (30.8%)		
Age (y; mean ± SD)	69.4	11.0	68.3	11.4	65.4	11.7	<0.0001
Age group (y; *n*, %)							
18–40	7	0.85	78	1.85	59	2.64	<0.0001
40–65	232	28.3	1,322	31.4	927	41.5	
≥65	579	70.7	2,804	66.6	1,247	55.8	
Sex (*n*, %)							
Male	424	51.8	2,204	52.4	1,138	50.9	0.5344
Female	394	48.1	2,000	47.5	1,095	49.0	
Index VTE event (*n*, %)							
DVT only	264	32.3	1,197	28.5	735	32.9	0.0005
PE with/without DVT	554	67.7	3,007	71.5	1,498	67.1	
Major orthopaedic surgery-provoked VTE	2	0.24	14	0.33	6	0.27	0.8586
Index year (*n*, %)							
2013	253	30.9	165	3.9	244	10.9	<0.0001
2014	213	26.0	441	10.5	366	16.4	
2015	131	16.0	554	13.2	381	17.1	
2016	79	9.7	747	17.8	361	16.2	
2017	79	9.7	810	19.3	355	15.9	
2018	47	5.8	945	22.5	358	16.0	
2019	16	2.0	541	12.9	168	7.5	
HAS-BLED score (mean ± SD)	2.45	1.11	2.39	1.12	2.23	1.17	<0.0001

Abbreviations: IQR, interquartile range; NOAC, non-vitamin K antagonist oral anticoagulant; PAC, parenteral anticoagulants; SD, standard deviation.
[a]Analysis of variance (ANOVA) was conducted for continuous variables; Chi-square tests were conducted for categorical variables.

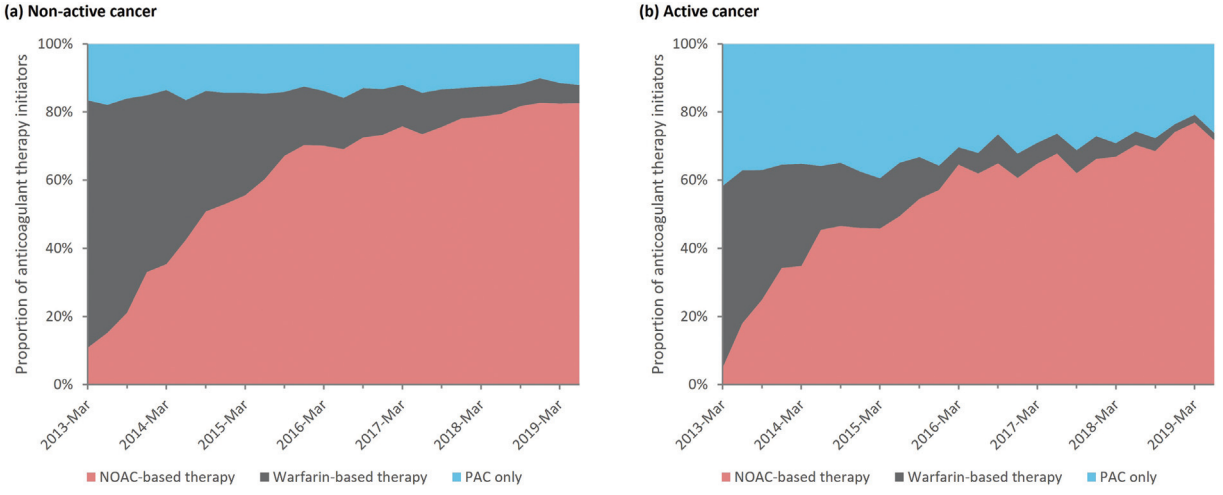

Fig. 2 Secular trends in the initial anticoagulant therapy in patients with venous thromboembolism stratified according to the presence/absence of active cancer.

dabigatran, regardless of active cancer, with apixaban and edoxaban showing increasing trends after reimbursement for VTE in the second quarter of 2015 (►**Supplementary Fig. S2,** available in the online version).

Persistence and Patterns of Anticoagulant Therapy

Treatment persistence was highest in the NOAC group at 3 months (62.9 and 57.2%), followed by warfarin at 6 months (42.3 and 26.5%) in patients with and without active cancer, respectively

Table 3 Treatment patterns of anticoagulant therapy among venous thromboembolism patients with or without active cancer by the treatment group of interests

	Nonactive cancer						Active cancer					
	Warfarin-based therapy		NOAC-based therapy		PAC only		Warfarin-based therapy		NOAC-based therapy		PAC only	
	N = 10,390 (21.4%)		*N* = 31,564 (65.1%)		*N* = 6,550 (13.5%)		*N* = 818 (11.3%)		*N* = 4,204 (57.9%)		*N* = 2,233 (30.8%)	
Median duration of the first anticoagulant therapy[a] (IQR, days)	139	36–317	140	39–191	3	1–12	80	25–192	111	39–184	34	7–115
Median duration of continuous anticoagulant therapy[b] (IQR, days)	183	60–368	147	42–195	3	1–12	121	36–232	117	44–187	44	7–146
Treatment patterns within 3 months of initial therapy (*n*, %)												
Persistence	6,313	60.8	19,848	62.9	222	3.4	388	47.4	2,405	57.2	673	30.1
Switch	913	8.8	393	1.3	500	7.6	102	12.5	100	2.4	150	6.7
Discontinuation	1,895	18.2	7,864	24.9	4,410	67.3	238	29.1	1,157	27.5	1,065	47.7
Interruption	1,186	11.4	3,177	10.1	1,175	17.9	64	7.8	349	8.3	227	10.2
Death	83	0.8	282	0.9	243	3.7	26	3.2	193	4.6	118	5.3
Treatment patterns within 6 months of initial therapy (*n*, %)												
Persistence	4,394	42.3	10,563	33.5	75	1.2	217	26.5	1,089	25.9	221	9.9
Switch	1,156	11.1	705	2.2	524	8.0	124	15.2	143	3.4	193	8.6
Discontinuation	2,870	27.6	14,271	45.2	4,491	68.6	332	40.6	1,998	47.5	1,322	59.2
Interruption	1,855	17.9	5,624	17.8	1,208	18.4	113	13.8	680	16.2	345	15.5
Death	115	1.1	401	1.3	252	3.9	32	3.9	294	7.0	152	6.8

Abbreviations: IQR, Interquartile range; NOAC, non-vitamin K antagonist oral anticoagulant; PAC, parenteral anticoagulants.

[a]First anticoagulant therapy was defined as the duration between the index date and the earliest day of treatment nonpersistence (switch, discontinuation, interruption, or death).

[b]Continuous anticoagulant therapy was defined as treatment persistence with allowing switching between the treatment group of interests, which indicates the actual treatment duration for venous thromboembolism treatment.

(►**Table 3**). In patients without active cancer, a remarkably low persistence was observed at 3 (3.4%) and 6 (1.2%) months, whereas the 3- and 6-month persistence in patients with active cancer was 30.1 and 9.9%, respectively, indicating clear disparities according to the presence/absence of active cancer. Treatment patterns within 3 or 6 months of initial therapy showed decreasing trends of persistence and increasing trends of discontinuation over time, regardless of active cancer. The median duration of first anticoagulant therapy was similar between warfarin (139 days) and NOAC (140 days) users, whereas a relatively short duration was observed in PAC-only users (3 days). In patients with active cancer, the median duration of first anticoagulant therapy was shorter than that observed in patients without active cancer, with the exception of PAC-only users (34 days). However, the median duration of continuous anticoagulant therapy among warfarin, NOAC, and PAC were 183, 147, and 3 days in nonactive cancer patients, and 121, 117, and 44 days in active cancer patients, respectively, showing the longer duration of treatment when considering treatment switch. Kaplan–Meier plots of the persistence of the index anticoagulant exhibited similar curves between users of warfarin and NOACs until 6 months in the patients without active cancer, whereas a steep decrease in persistence was observed in NOAC users at 6 months because of changes in the reimbursement criteria in South Korea, as NOAC therapy prescribed for >6 months was not reimbursed before 2019 (►**Fig. 3**). Among patients with active cancer, NOACs showed a higher persistence compared with warfarin; nevertheless, a similar decreasing trend was observed after 6 months. Kaplan–Meier plots of the time to nonpersistence for all types of treatment patterns are presented in (►**Supplementary Fig. S3** available in the online version).

Among the treatment-naïve anticoagulant users, 45,240 (93.3%) patients without active cancer and 6,522 (89.9%) patients with active cancer did not remain on their index anticoagulant during the follow-up. Treatment discontinuation was the most common type of treatment nonpersistence in both groups, followed by treatment interruption and switch. The rate of discontinuation was highest among PAC users in both groups (~65%), whereas that of interruption was highest among warfarin users (33%) in the group without active cancer, but was similar (~20%) between anticoagulants in the group with active cancer. Treatment switch was most frequent in warfarin users in both the groups without (14.8%) and with (17.6%) active cancer (►**Supplementary Tables S3,** available in the online version), with 95.4 and 68.1% of patients switching to NOAC-based therapy, respectively (►**Supplementary Table S4,** available in the online version). Most patients who received NOAC therapy initially (90.7%) switched to warfarin in the group without active cancer, whereas only half of them (48.6%) switched to warfarin in the active cancer group. In turn, PAC-only users mostly switched to NOACs in the groups without (77.6%) and with (82.7%) active cancer. The proportion of patients who switched to PAC therapy from other initial anticoagulant therapies was relatively higher in patients with active cancer compared with those without active cancer.

Discussion

This nationwide cohort study including more than 55,000 patients with VTE who were stratified according to the presence/absence of active cancer found that NOACs held a dominant position in the management of VTE, regardless of the presence of active cancer, in routine clinical practice. Although patients in the group without active cancer who received NOAC and warfarin therapy initially presented a similar 3-month persistence level (62.9 and 60.8%, respectively), the 3-month persistence of NOAC therapy (57.2%) was higher than that of warfarin (47.4%) in the group with active cancer. In nonactive cancer patients, the median duration of continuous anticoagulant therapy was relatively longer for warfarin and NOAC compared with that of active cancer patients (183 vs. 121 days for warfarin and 147 vs. 117 days for NOAC). On the other hand, the duration for PAC initiators in active cancer patients was longer than that in

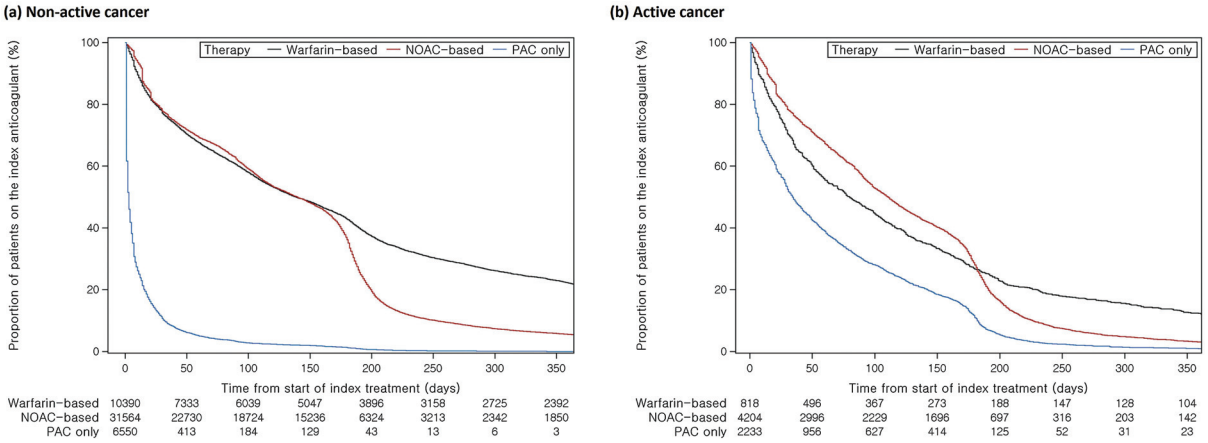

Fig. 3 Kaplan–Meier plot showing the persistence of treatment with the index anticoagulant among patients with venous thromboembolism who were stratified according to the presence/absence of active cancer. *p*-Values for the overall Kaplan–Meier curve and for each individual index anticoagulant comparison were <0.0001 at 3 and 6 months, regardless of active cancer. The Scheffé's method was applied to adjust multiple comparisons for the log-rank test. NOAC, non-vitamin K antagonist oral anticoagulant; PAC, parenteral anticoagulant.

nonactive cancer patients (44 vs. 3 days). The patterns of treatment switch varied according to the presence/absence of active cancer, as follows: <10% of the patients who received warfarin or NOACs initially switched to PACs in the group without active cancer, whereas >30% of these patients switched to PACs in the group with active cancer; the rate of switching to NOACs from warfarin or PACs was also lower in the latter group.

The temporal trends of initial anticoagulant therapy in the group without active cancer indicated decreases for warfarin but increases for NOACs, a trend that was consistent with that reported in several previous studies.[21–24] In particular, rivaroxaban was the most prescribed NOAC across all studies, likely because of the rapid market access and preference toward a once-daily dosing regimen.[25] Sizeable proportions of noncancer patients who initiated PAC were observed in our study. Based on a previous study in Korea, 19.5% of noncancer patients initiated PACs, supporting our findings and representing routine clinical practice of PAC utilization.[26] Interestingly, initial PAC therapy in patients with VTE with active cancer was substantial, which may be a good reflection of the clinical guidelines for optimizing anticoagulation therapy.[27,28] However, because the recently amended American Society of Hematology guidelines now recommend NOACs over PACs as the initial and short-term treatment for patients with VTE with active cancer,[29] slightly different trends that reflect these guideline updates are expected, thus warranting further research using more recent data.

Differential trends of PAC initial therapy were observed across countries. Although the patients who received PAC therapy initially in this study presented largely consistent trends (~20%), a U.S. study found a dramatic threefold increase in PAC use (from ~20 to 60%) between 2010 and 2017.[30] In turn, regardless of active cancer, initial therapy with apixaban and edoxaban exhibited increasing trends after reimbursement for VTE in this study. These trends could be explained by the growing body of evidence suggesting better comparative effectiveness and safety for apixaban versus rivaroxaban,[31,32] whereas for edoxaban, better safety profiles have been demonstrated in previous trials that included relatively larger proportions of Asian individuals.[6]

The observed 3- and 6-month persistence of each anticoagulation therapy was somewhat lower than that reported previously. One systematic review that included 12 observational studies of anticoagulant persistence reported values of 83 and 62% at 3 and 6 months, respectively.[33] In line with the results of the systematic review, the 3- and 6-month treatment persistence for VTE indication was greater than 90 and 70%, respectively, in a Danish study.[34] However, those studies were based on Western populations. Thus, the difference in persistence observed between our study and previous studies likely suggests potential gaps in knowledge in routine practice. Another possible explanation for the substantially low 6-month persistence of NOACs could be the reimbursement criteria implemented in South Korea, as NOACs prescribed for >6 months were not reimbursed until recently (February 2019). Regarding PACs, the persistence of this therapy was considerably lower than that detected for the other anticoagulants, especially among the patients with VTE without active cancer, resulting in a high rate of discontinuation. This finding may be attributed to either a poor compliance with injection regimens or the occurrence of premature death following fatal PE or active cancer.[35,36] Lastly, the high discontinuation rate observed for NOAC-based therapy may reflect the current guidelines recommending discontinuation after 3 to 6 months of initial anticoagulation therapy.[27,29]

The strengths of this study included the fact that, to our knowledge, this was the first study that investigated the various treatment patterns, including persistence, discontinuation, interruption, and switch, of anticoagulant treatment for VTE according to the presence/absence of active cancer. Second, we also used a nationwide database that provided comprehensive health care-related information for all domestic residents of Korea, accompanied by a highly accurate code to define active cancer, thereby assuring the validity of this study. Third, our study provides evidence on the treatment patterns of anticoagulants in both cancer and noncancer patients. Fourth, as most anticoagulant usage guidelines are based on Western populations, presenting the utilization patterns of anticoagulants in non-Western populations can help bridge the knowledge gap between these two populations. However, this study also had limitations. First, exposure misclassification was possible during the classification of the index anticoagulants and the assessment of treatment patterns. For instance, oral anticoagulants can be prescribed after 5 to 10 days of PAC bridging therapy in real-world practice.[28] However, we minimized exposure misclassification by setting this bridging therapy period as 2 weeks. Second, because of the inherent nature of claims data, we could not evaluate whether the patient actually took the drug that was prescribed/dispensed; this could have resulted in differences between the observed values and the real-world situation. Third, we could not accurately investigate the exact reasons behind each type of anticoagulant treatment nonpersistence, i.e., whether those decisions were made by clinicians because of the occurrence of adverse events or whether they were based on other causes. However, our findings were largely consistent with the previous research using electronic medical records from eight tertiary hospitals in Korea with respect to the proportion of anticoagulant initiators and treatment duration.[18] Fourth, the reimbursement criteria for NOACs that were in place during our study period could limit the validity of long-term persistence in this study. However, because the recommended treatment period for NOACs in most clinical practice settings is <6 months, this effect was likely minimal; nevertheless, further research is needed to reflect those reimbursement criteria. Another potential limitation of our study is that health care practitioners' prescribing behavior may have been influenced by changes in the guidelines for VTE treatment over time, particularly with the introduction of NOAC. This may have affected the overall duration of treatment and should be considered when interpreting our results. Finally, despite the use of nationwide data, the number of patients

with VTE was relatively small, which may limit the generalizability of the findings to Asian patient populations of other ethnicities or in other clinical settings.

Conclusion

These findings revealed the distinct persistence and patterns of anticoagulant treatment initiation and subsequent treatment nonpersistence in patients with VTE according to the presence/absence of active cancer. Although the treatment patterns were largely consistent with the contemporary guidelines, continuous research aimed at facilitating the improved adoption and application of evolving guidelines in clinical practice would be needed. Given the limited data available on this clinically significant issue, especially in patients with VTE with active cancer, these findings provide important data from routine care settings that could aid clinicians in optimizing anticoagulation therapy for patients with VTE with and without active cancer.

What is known about this topic?

- The incidence of VTE in Asian populations is considerably lower than that of the Western, with recent data indicating a rising trend.
- The current guidelines for VTE management are primarily based on data from Western populations, rendering it challenging to extend them to Asian populations, particularly among patients with active cancer.
- The real-world evidence on the prescription, persistence, and patterns of anticoagulation therapy according to the presence of active cancer in patients with VTE is limited.

What does this paper add?

- NOACs are cornerstone pharmacotherapeutics for managing VTE, regardless of active cancer; moreover, the initiation of apixaban and edoxaban therapy has increased since their market release.
- The 3-month persistence of NOACs (62.9 vs. 57.2%) and warfarin (60.8 vs. 47.4%) in patients without active cancer was modestly higher than that in those with active cancer.
- The comprehensive exploration of the prescription, persistence, pattern, and patient characteristics of anticoagulation therapy revealed substantial differences regarding index anticoagulants and active cancer.

Conflict of Interest
The authors J.-Y. S. and S.-M.B. received honoraria as speakers and/or consultants from Pfizer and Bristol Myers Squibb. S.C. is a previous employee of Pfizer Korea.

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