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Original Article

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Epidemiology of Venous Thromboembolism and Treatment Pattern of Oral Anticoagulation in Korea, 2009–2016: a Nationwide Study Based on the National Health Insurance Service Database

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Address for Correspondence:
Kye Hun Kim, MD, PhD
Department of Cardiovascular Medicine, Chonnam National University Hospital, Chonnam National University Medical School, 42 Jebong-ro, Dong-gu, Gwangju 61469, Korea.
E-mail: christiankyehun@hanmail.net

Sung-A Chang, MD, PhD
Department of Medicine, Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Korea.
E-mail: elisabet.chang@gmail.com

ORCID iDs
Hyung Yoon Kim
https://orcid.org/0000-0002-0692-5640
Sung-A Chang
https://orcid.org/0000-0001-5124-605X
Kye Hun Kim
https://orcid.org/0000-0002-6885-1501
Jae-Young Kim
https://orcid.org/0000-0001-9628-421X
Woo-Keun Seo
https://orcid.org/0000-0002-4004-8434

Hyung Yoon Kim, MD[1], Sung-A Chang, MD, PhD[2], Kye Hun Kim, MD, PhD[1], Jae-Young Kim, MS[3], Woo-Keun Seo, MD, PhD[3], Hyungseop Kim, MD, PhD[4], Jeong-Sook Seo, MD, PhD[5], Sung-Hee Shin, MD, PhD[6], Sang Jae Rhee, MD, PhD[7], Sun Hwa Lee, MD, PhD[8], and Jung Sun Cho, MD, PhD[9]; Venous Thromboembolism Research Group of Korean Society of Echocardiography

[1]Department of Cardiovascular Medicine, Chonnam National University Hospital, Chonnam National University Medical School, Gwangju, Korea
[2]Department of Internal Medicine, Cardiovascular Imaging Center, Heart, Vascular & Stroke Institute, Sungkyunkwan University School of Medicine, Seoul, Korea
[3]Department of Neurology and Stroke Center, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[4]Division of Cardiology, Department of Internal Medicine, Keimyung University Dongsan Medical Center, Daegu, Korea
[5]Division of Cardiology, Department of Internal Medicine, Busan Paik Hospital, Inje University, Busan, Korea
[6]Division of Cardiology, Department of Internal Medicine, Inha University Hospital, Incheon, Korea
[7]Department of Cardiovascular Medicine, Wonkwang University Hospital, Iksan, Korea
[8]Department of Cardiology in Internal Medicine, Jeonbuk National University Medical School and Hospital, Jeonju, Korea
[9]Department of Cardiology, College of Medicine, The Catholic University of Korea, Seoul, Korea

ABSTRACT

BACKGROUND: The annual incidence of venous thromboembolism (VTE) is increasing, and the treatment pattern of oral anticoagulants (OACs) has changed with introduction of new oral anticoagulants (NOACs). The aims of this study were to assess the annual incidence of VTE in a Korean population and the change of treatment pattern with availability of NOACs using a population-based database.
METHODS: Using the Korean National Health Insurance Services database, we identified patients diagnosed with VTE between 2009 and 2016. The annual prevalence of VTE and clinical characteristics and treatment pattern were investigated. The annual incidence of VTE was calculated using direct and indirect methods using the estimated Korean population in 2009 as the reference.
RESULTS: The annual incidence of VTE in Korean has increased yearly from 23.9 per 100,000 in 2009 to 42.2 in 2016. The overall rate of OAC prescription for VTE treatment increased from 55.9% to 68% in the same time period. The rate of initiation of NOAC treatment greatly increased, particularly from 2013 onwards, with a 20-fold increase from 2009 to 2016 (2.1% vs. 54.3%).

Journal of Cardiovascular Imaging JCVI

Hyungseop Kim
https://orcid.org/0000-0001-7056-4221
Jeong-Sook Seo
https://orcid.org/0000-0001-6724-4227
Sung-Hee Shin
https://orcid.org/0000-0002-8306-9622
Sang Jae Rhee
https://orcid.org/0000-0001-9738-0481
Sun Hwa Lee
https://orcid.org/0000-0001-9752-9717
Jung Sun Cho
https://orcid.org/0000-0002-0308-0021

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The authors have no financial conflicts of interest.

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CONCLUSIONS: The annual incidence of VTE in Korea increased by almost two-fold from 2009 to 2016. The rate of initiation of NOAC treatment has increased substantially since 2013, and these agents have surpassed VKAs as the anticoagulant of choice for VTE. This temporal pattern of OAC prescription is consistent with the current clinical guidelines, which indicate NOACs over the warfarin in patients with VTE.

Keywords: Annual incidence; Oral anticoagulants; NOACs; Temporal trend; Venous thromboembolism

INTRODUCTION

Venous thromboembolism (VTE) is the third leading cause of cardiovascular death following myocardial infarction and stroke.[1] Deep vein thrombosis (DVT) and pulmonary embolism (PE) are associated with reduced survival and increased re-hospitalization.[2][3] The economic burden of VTE is considerable, with estimated costs of VTE hospitalization of 16,644 dollars per patient per year in the USA.[4] VTE has become a growing public health problem largely due to the increasing aging population. The population of patients with VTE is smaller in Asian populations compared with Western populations (DVT, 5.3–30 vs. 78–269; PE, 3.9–11.7 vs. 45–189, per 100,000 population, Asian vs. Western populations).[2][5][6]

Vitamin K antagonists (VKAs) are currently the most commonly used treatment option for VTE. However, VKAs have several potential pitfalls in clinical use. VKAs have a narrow therapeutic index, and the intensity of the anticoagulation effect using the international normalized ratio should be closely monitored. Food intake and use of drugs are frequently limited in patients taking VKAs because of the predisposition to drug and food interactions, and the influence of VKAs on quality of life is not negligible.[17] With the introduction of new oral anticoagulants (NOACs), the conventional OAC warfarin is rapidly being replaced by NOACs because of titration-free preparation and lack of interactions with food and drugs. In Korea, the first NOAC (Rivaroxaban, Xarelto®) was approved by the KFDA on 13 April, 2009, followed by dabigatran (Pradaxa®, 18 February, 2011), apixaban (Eliquis®, 30 November, 2011), and edoxaban (Lixiana®, 25 August, 2015).[18] The Reimbursement by Public Health Insurance system for VTE was started in 2013, in the order of rivaroxaban (January 1, 2013), dabigatran (January 1, 2013), apixaban (May 1, 2015), and edoxaban (February 1, 2016).

In this study, we investigated the update on the annual incidence of VTE in Korea and how the treatment pattern of VTE in Korea changed according to the approval and reimbursement policy for treatment.

METHODS

Study population

Data were collected from the Korean National Health Insurance Service (NHIS) in Korea between 2009 and 2016. The NHIS covers 97% of the population in Korea. The other 3% of records from Medical Aid were not included in this study. Cases were extracted with the diagnostic code of VTE that is composed of DVT and PE. The diagnostic code was selected from the 10th revision of the International Statistical Classification of Disease and Related Health Problems (ICD-10) that consisted of primary and secondary diagnoses

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Journal of Cardiovascular Imaging JCVI

Table 1. Diagnostic codes of venous thromboembolism

Variables	ICD-10	Venous thromboembolism
Venous thromboembolism		
Deep vein thrombosis of the lower extremity	I80.0	Deep vein thrombosis
	I80.2	Deep vein thrombosis, not otherwise specified
Pulmonary embolism	I26	Pulmonary thromboembolism
	I26.0	Pulmonary embolism with mention of acute cor pulmonale
	I26.9	Pulmonary embolism without mention of acute cor pulmonale
Other venous thrombosis	I82.2	Embolism and thrombosis of the vena cava
	I82.8	Embolism and thrombosis of other specified veins
	I82.9	Embolism and thrombosis of an unspecified vein
	O22.3	Deep phlebothrombosis in pregnancy

ICD-10: 10th revision of the International Statistical Classification of Disease and Related Health Problems.

related to VTE as follows. DVT comprises deep vein thrombosis, not otherwise specified (I80.2) and embolism or thrombosis of a lower extremity (I80.3). PE comprises pulmonary thromboembolism (I26), PE with mention of acute cor pulmonale (I26.0), and PE without mention of acute cor pulmonale (I26.9). VTE is composed of embolism and thrombosis of the vena cava (I82.2), embolism and thrombosis of other specified veins (I82.8), embolism and thrombosis of an unspecified vein (I82.9), and deep phlebothrombosis in pregnancy (O22.3) as well as the above diagnosed DVT and PE (**Table 1**). Venous thrombosis of other sites, such as upper extremities and intra-abdominal sites, was not included in this study. A patient who was included in the data was excluded from the data of the following year. If a patient had both diagnostic codes of DVT and PE, the patient was classified as PE. The data consisted of main and secondary diagnoses related to VTE.

Data collection

Demographic and clinical data were age, sex, prior surgery within 6 months, and previous medical history. The previous medical history was determined by ICD-10 codes as follows: diabetes mellitus (E10.x, E11.x, E12.x, E13.x, E14.x), hypertension (I10.x, I11.x-I13.x, I15.x), malignancy (C00.x-C26.x, C30.x-C34.x, C37.x-C41.x, C43.x, C45.x-C58.x, C60.x-C76.x, C81.x-C85.x, C88.x, C90.x-C97.x), heart failure (I09.9, I11.0, I13.0, I13.2, I25.2, I42.0, I42.5-I42.9, I43.x, I50.x, P29.0), and cerebral vascular accident (G45.x, G46.x, H34.0, I60.x-169.x). Lipid lowering agents were investigated by medication codes and categorized as statins, ezetimibe, omega 3, and fenofibrate.

All OACs prescribed between 2009 and 2016 were investigated, comprising warfarin (2 mg and 5 mg), rivaroxaban (10, 15, and 20 mg), dabigatran (75, 110, and 150 mg), apixaban (2.5 and 5 mg), and edoxaban (15, 30, and 60 mg). Drugs prescribed before approval by Korean Ministry of Food & Drug Safety (MFDS) for the purpose of research were excluded from the investigation. Aspirin use was investigated to examine the temporal trend of OAC use according to the initiation of insurance coverage.

Statistical methods

The annual incidence of VTE in adults was calculated as a crude rate of number of events divided by a specified population, usually expressed as number of patients per 100,000 population at risk. We also calculated the age-standardized annual incidence of VTE with the direct method using the estimated Korean population and with the indirect method using the crude incidence rate in 2009 as the reference.[19)20)] The rates of OAC prescription were calculated as the number of new OAC cases divided by a specific disease population by year.

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Journal of Cardiovascular Imaging JCVI

Ethics

This study protocol was exempted by the Institutional Review Board (IRB) of Samsung Medical Center (IRB File No: 2018-03-027).

RESULTS

Patient characteristics

Between 2009 and 2016, a total of 133,956 patients was newly diagnosed with VTE, 65,982 patients were diagnosed with PE, and 79,762 patients were diagnosed with DVT. The descriptive characteristics of the cases including venous thromboembolic risk factors are summarized in **Table 2**. Among the investigated risk factors for VTE, prior admission within 6 months was most prevalent (54%), followed by previous surgery within 6 months (22.1%), malignancy (15%), hypertension (7.1%), DM (3.3%), and prior history of cerebral vascular accident within 6 months (2.2%).

Incidence of VTE, PE, and DVT between 2009 and 2016 in Korea

A total of 133,956 cases was newly diagnosed with VTE in Korea between 2009 and 2016; of these cases, 58,808 (43.9%) were men and 75,148 (56.1%) were women. The number of cases substantially increased from 12,064 cases in 2009 to 22,039 cases in 2016.

The total crude incidence rate in 2016 was 42.16 for VTE, 21.42 for PE, and 24.75 for DVT per 100,000 population (0.042%, 0.021%, and 0.024%, respectively) (**Table 3**).

Age-standardized incidence rates are shown in **Table 3**. The age-standardized incidence rate of VTE steadily increased by about 5% annually, from 23.98 per 100,000 population (0.024%) in 2009 to 33.98 per 100,000 population (0.034%) in 2016. The age-standardized annual incidence of PE and DVT also gradually increased from 2009 to 2016, from 11.19 to 21.42 per 100,000 (0.011% to 0.021%) for PE and from 14.47 to 24.75 per 100,000 (0.014% to 0.024%) for DVT. The overall annual incidence of DVT was higher than that of PE (**Table 3** and **Figure 1A**).

Table 2. Descriptive characteristics including venous thromboembolic risk factors in patients diagnosed between 2009 and 2016

Variables	VTE	PE	DVT
Number of cases	133,956	65,982	79,762
DM	4,408 (3.3)	2,268 (3.4)	2,780 (3.5)
Hypertension	9,488 (7.1)	5,442 (8.2)	5,503 (6.9)
Malignancy	20,078 (15)	14,076 (21.3)	7,771 (9.7)
Previous surgery (within 6 months)	29,650 (22.1)	16,961 (25.7)	16,586 (20.8)
Previous admission (within 6 months)	72,282 (54)	47,260 (71.6)	33,465 (42)
Heart failure	2,209 (1.6)	1,817 (2.8)	662 (0.8)
Previous CVA (within 6 months)	3,008 (2.2)	1,852 (2.8)	1,560 (2)
Pregnancy (within 6 months)	75 (0.1)	62 (0.1)	16 (0)
Medications			
Statins	83,315 (62.2)	49,900 (75.6)	54,570 (68.4)
Ezetimibe	1,904 (1.4)	1,039 (1.6)	1,395 (1.7)
Omega 3	1,207 (0.9)	723 (1.1)	708 (0.9)
Fenofibrate	517 (0.4)	319 (0.5)	288 (0.4)

Data are presented as number (%). CVA: cerebral vascular accident, DM: diabetes mellitus, DVT: deep vein thrombosis, PE: pulmonary embolism, VTE: venous thromboembolism.

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Journal of Cardiovascular Imaging JCVI

Table 3. Crude and age-standardized annual incidence of venous thromboembolism (per 100,000): crude and age-standardized annual incidence of venous thromboembolism: overall and by sex

Variables	2009 (n = 50,290,771)			2010 (n = 50,581,191)			2011 (n = 50,908,646)			2012 (n = 51,169,141)		
	Crude	Direct standardized	Indirect standardized	Crude	Direct standardized	Indirect standardized	Crude	Direct standardized	Indirect standardized	Crude	Direct standardized	Indirect standardized
Venous thrombo-embolism												
All	23.988	23.988	23.988	25.895	25.100	25.128	29.455	27.715	27.758	32.387	29.357	29.452
Men	21.877	21.877	21.877	22.514	21.774	21.794	25.673	24.039	24.070	28.853	25.946	26.011
Women	26.116	26.116	26.116	29.299	28.461	28.495	33.261	31.437	31.487	35.938	32.797	32.923
Pulmonary embolism												
All	11.191	11.191	11.191	12.232	11.813	11.829	14.070	13.160	13.167	15.744	14.133	14.131
Men	9.897	9.897	9.897	10.568	10.193	10.202	12.335	11.493	11.498	14.473	12.902	12.902
Women	12.495	12.495	12.495	13.908	13.452	13.475	15.817	14.846	14.860	17.021	15.358	15.378
Deep vein thrombosis												
All	14.478	14.478	14.478	15.719	15.285	15.295	17.801	16.829	16.868	19.127	17.485	17.571
Men	13.553	13.553	13.553	13.755	13.340	13.349	15.546	14.625	14.653	16.821	15.264	15.313
Women	15.409	15.409	15.409	17.697	17.251	17.259	20.070	19.067	19.105	21.444	19.739	19.849

	2013 (n = 51,448,491)			2014 (n = 51,757,146)			2015 (n = 52,034,424)			2016 (n = 52,272,755)		
	Crude	Direct standardized	Indirect standardized	Crude	Direct standardized	Indirect standardized	Crude	Direct standardized	Indirect standardized	Crude	Direct standardized	Indirect standardized
Venous thrombo-embolism												
All	32.850	28.933	29.074	35.359	30.148	30.427	38.409	31.930	32.129	42.162	33.985	34.302
Men	28.766	25.146	25.169	30.762	25.950	26.086	33.454	27.529	27.489	36.302	28.803	28.895
Women	36.952	32.777	33.011	39.977	34.386	34.802	43.383	36.414	36.793	48.038	39.277	39.740
Pulmonary embolism												
All	16.411	14.287	14.282	18.040	15.167	15.207	19.158	15.624	15.640	21.424	16.959	16.941
Men	14.313	12.403	12.341	15.867	13.224	13.208	16.815	13.597	13.512	19.072	14.911	14.783
Women	18.517	16.205	16.253	20.223	17.121	17.231	21.510	17.679	17.791	23.783	19.022	19.112
Deep vein thrombosis												
All	19.635	17.472	17.608	20.701	17.877	18.108	22.919	19.365	19.553	24.753	20.315	20.609
Men	17.215	15.206	15.257	18.057	15.441	15.562	19.884	16.662	16.661	20.932	16.937	17.050
Women	22.066	19.776	19.975	23.356	20.346	20.668	25.966	22.135	22.455	28.585	23.795	24.192

Age-standardized incidence rates of venous thromboembolism were calculated using age groups according to direct and indirect methods using the estimated Korean population in 2009 as a reference.

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Journal of Cardiovascular Imaging JCVI

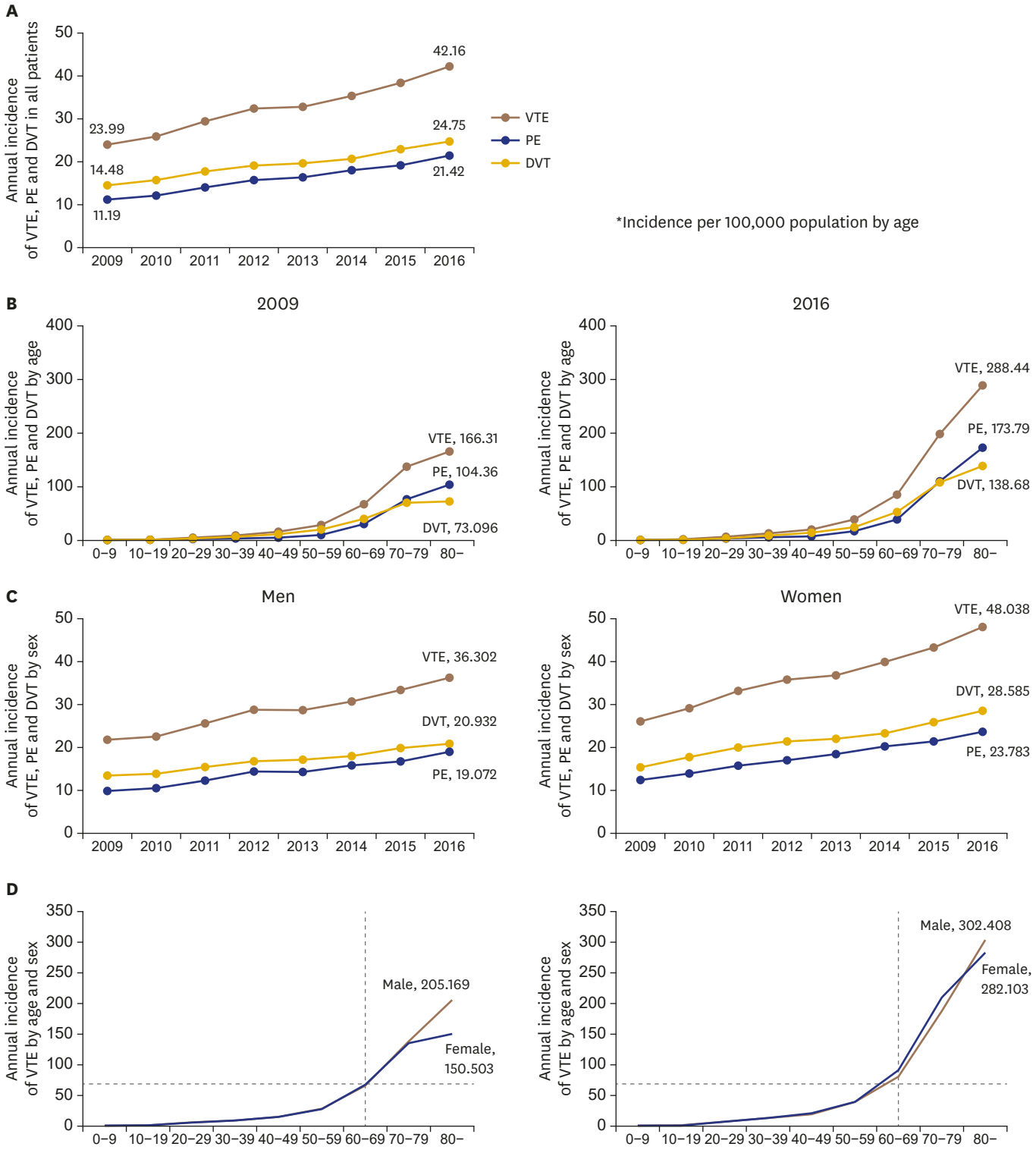

Figure 1. Annual incidence of VTE, PE, and DVT in all patients (A), patients classified by age (B), patients classified by sex (C), and patients classified by age and sex in Korea between 2009 and 2016 (D). (A) Annual incidence of VTE, PE, and DVT in all patients. (B) Annual incidence of VTE, PE, and DVT by age. (C) Annual incidence of VTE, PE, and DVT by sex. (D) Annual incidence of VTE by age and sex.
DVT: deep vein thrombosis, PE: pulmonary embolism, VTE: venous thromboembolism.

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Annual trends in incidence by age, sex, and disease category

The annual incidence of VTE increased markedly with age. VTE is very rare before the age of 20 years (**Supplementary Table 1**). The annual incidence of VTE in elderly people older than 60 years was approximately 13–14 times greater than that of younger people and 5 times greater than that of the middle aged group (**Table 4** and **Figure 1B**).

Comparison of the incidence rates of each disease according to age showed that the incidence of DVT was almost twice that of PE in patients younger than 60 years. However, the incidence of PE increased steeply after the age of 60, and the incidence of PE was higher than that of DVT after age 70 (**Table 4**, **Supplementary Table 1** and **Figure 1B**).

Women showed higher annual incidences of disease than men. The crude annual incidence rates for women were approximately 1.3 times greater than that of men (48.0 vs. 36.3 for VTE, 23.8 vs. 19.1 for PE, and 28.6 vs. 20.9 for DVT in 2016; **Table 3** and **Figure 1C**). The crude incidence rates of VTE, PE, and DVT increased in all age and sex categories from 2009 to 2016 (**Table 4**). The incidence of VTE was similar between the sexes younger than 50 years; in patients older than 60 years, the incidence of disease in women was higher than that of men; in patients 80 years and older, the incidence of disease in men was higher than that of women (**Supplementary Table 1** and **Figure 1D**).

Table 4. Crude and age-standardized annual incidence of venous thromboembolism (per 100,000): crude annual incidence of venous thromboembolism, classified by sex and age

Variables	2009 (n = 50,290,771)			2010 (n = 50,581,191)			2011 (n = 50,908,646)			2012 (n = 51,169,141)		
	All	Men	Women	All	Men	Women	All	Men	Women	All	Men	Women
Venous thrombo-embolism												
All	23.99	21.88	26.12	25.90	22.51	29.30	29.45	25.67	33.26	32.39	28.85	35.94
20 to < 40	7.32	7.63	6.99	7.43	7.30	7.57	8.38	8.61	8.15	8.59	8.49	8.71
40 to < 60	20.88	21.33	20.42	21.67	20.43	22.94	23.36	23.12	23.61	24.99	24.91	25.08
60–	101.85	99.50	103.62	109.14	103.49	113.42	122.96	113.53	130.15	132.03	126.22	136.51
Pulmonary embolism												
All	11.19	9.90	12.50	12.23	10.57	13.91	14.07	12.34	15.82	15.74	14.47	17.02
20 to < 40	2.49	2.83	2.13	2.45	2.82	2.06	3.18	3.73	2.59	3.27	3.53	2.98
40 to < 60	7.14	7.93	6.34	7.54	7.94	7.12	8.68	9.31	8.04	9.91	10.99	8.81
60–	55.10	50.93	58.23	59.53	54.29	63.50	65.63	60.05	69.88	70.50	68.60	71.97
Deep vein thrombosis												
All	14.48	13.55	15.41	15.72	13.76	17.70	17.80	15.55	20.07	19.13	16.82	21.44
20 to < 40	5.44	5.77	5.08	5.82	5.55	6.10	5.91	5.88	5.95	6.20	6.15	6.25
40 to < 60	15.07	14.84	15.30	15.65	14.10	17.23	16.57	16.03	17.13	16.82	15.95	17.71
60–	53.99	54.91	53.31	58.24	56.48	59.58	67.52	62.20	71.59	71.59	67.42	74.81

	2013 (n = 51,448,491)			2014 (n = 51,757,146)			2015 (n = 52,034,424)			2016 (n = 52,272,755)		
	All	Men	Women	All	Men	Women	All	Men	Women	All	Men	Women
Venous thrombo-embolism												
All	32.85	28.77	36.95	35.36	30.76	39.98	38.41	33.45	43.38	42.16	36.30	48.04
20 to < 40	8.54	8.88	8.16	8.66	9.02	8.26	9.82	10.20	9.40	10.43	10.54	10.32
40 to < 60	24.39	24.35	24.43	25.27	23.79	26.77	25.96	25.72	26.19	29.33	28.63	30.04
60–	130.96	120.30	139.24	137.89	128.55	145.22	143.74	130.73	154.04	151.18	135.71	163.55
Pulmonary embolism												
All	16.41	14.31	18.52	18.04	15.87	20.22	19.16	16.82	21.51	21.42	19.07	23.78
20 to < 40	3.42	3.92	2.88	3.59	4.01	3.12	4.03	4.60	3.40	4.43	4.93	3.88
40 to < 60	9.88	10.52	9.22	10.54	10.93	10.14	10.85	11.59	10.08	12.70	13.49	11.88
60–	71.55	64.58	76.96	76.36	70.60	80.87	77.41	70.29	83.04	82.10	75.59	87.30
Deep vein thrombosis												
All	19.64	17.21	22.07	20.70	18.06	23.36	22.92	19.88	25.97	24.75	20.93	28.58
20 to < 40	6.11	6.27	5.93	6.00	6.23	5.74	6.91	7.11	6.68	7.33	7.34	7.31
40 to < 60	16.72	16.21	17.25	17.13	15.66	18.64	17.63	16.89	18.38	19.33	18.20	20.49
60–	72.18	66.13	76.87	74.59	69.82	78.32	79.89	71.85	86.26	83.16	72.56	91.63

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Journal of Cardiovascular Imaging JCVI

A distinct increase was observed in the annual incidence of PE over time, with a substantial increase in PE in elderly patients. The incidence of PE in 2009 was higher in women younger than 50 years but was higher in men in their 60s and 70s; in patients older than 80 years, the incidence of disease in women was higher than that in men. In contrast, the incidence of PE was higher in men than women in patients younger than 50 years, and the incidence in 2016 was higher in women after 60 years of age (**Supplementary Table 1**). The annual incidence of DVT in women increased considerably over time compared to that of men, with a remarkable increase in elderly patients.

Trends in OAC prescription for VTE, PE, and DVT

Between 2009 and 2016, a total of 86,033 cases were newly prescribed an OAC for VTE, 52,580 cases for PE, and 47,085 cases for DVT. Furthermore, 51,069 (40.7%) cases were initiated on VKAs and 34,964 (22.5%) cases were initiated on NOACs for VTE; 31,849 (52.1%) on VKAs and 20,731 (26.4%) on NOACs for PE; and 27,330 (37.7%) on VKAs and 19,755 (21.9%) on NOACs for DVT.

The mean crude rate of OAC prescription was 63.3% for VTE, 78.4% for PE, and 59.5% for DVT, and these rates gradually increased during the study period. The rate of NOAC use increased over the study period by 52.1% for VTE, 64.2% for PE, and 46.5% for DVT. In contrast, the rate of VKA use decreased by 40.0%, 51%, and 33.4% for VTE, PE, and DVT, respectively (**Figure 2**). These changes were noticeable after onset of insurance coverage for NOACs (**Table 5**). In 2016, the rate of NOAC prescription was 54.3%, 66.6%, and 48.9% of VTE, PE, and DVT cases, respectively, whereas the rate of VKA prescription was 13.7%, 16.9%, and 14.1% of cases. The total number of prescriptions for OACs and time trend of OAC use are summarized in **Figure 3**.

The average prescription rate of aspirin was 25% for all cases and decreased slightly over the study period (25.3% in 2009 and 17.4% in 2016, average of all VTE, PE, and DVT cases, **Table 5**).

Temporal trends in NOAC choice

Rivaroxaban was the most commonly prescribed OAC during the entire study period, with 20.1% of OAC prescriptions. Of the total NOAC prescriptions during the study period, rivaroxaban accounted for the largest portion (84.1%), followed by dabigatran (7.8%), apixaban (6.7%), and edoxaban (1.5%) (**Table 5** and **Figure 4**).

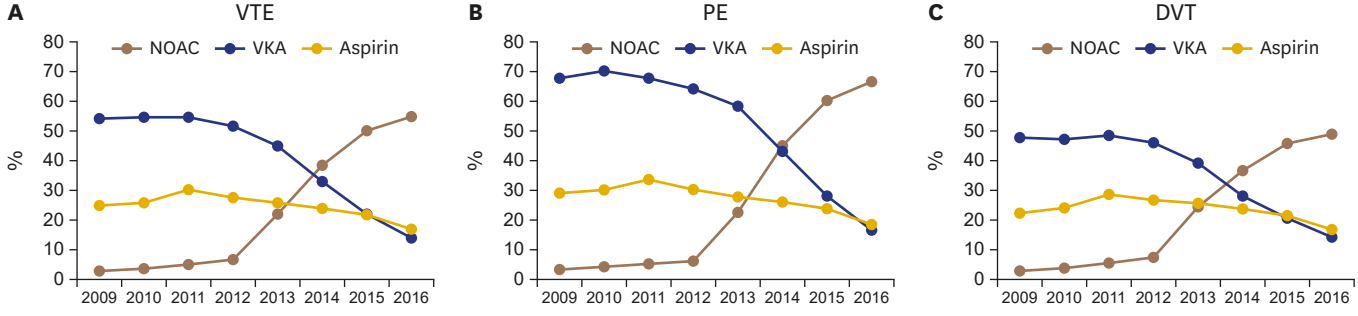

Figure 2. Time trends in oral anticoagulant choice for VTE (A), PE (B), and DVT (C) from 2009 to 2016.
DVT: deep vein thrombosis, PE: pulmonary embolism, VTE: venous thromboembolism.

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Table 5. Trends of oral anticoagulant prescription for VTE, PE, and DVT from 2009 to 2016

Diagnosis	Medication	2009	2010	2011	2012	2013	2014	2015	2016
VTE	Number of cases	12,064	13,098	14,995	16,572	16,907	18,301	19,986	22,039
	NOAC	260 (2.16)	380 (2.90)	724 (4.83)	1,061 (6.40)	3,690 (21.8)	6,948 (38.0)	9,934 (49.7)	11,967 (54.3)
	Rivaroxaban	260 (2.16)	380 (2.90)	621 (4.14)	944 (5.70)	3,503 (20.7)	6,716 (36.7)	8,348 (41.8)	8,626 (39.1)
	Dabigatran	-	-	67 (0.45)	74 (0.45)	125 (0.74)	123 (0.67)	984 (4.92)	1,318 (5.98)
	Apixaban	-	-	36 (0.24)	43 (0.26)	62 (0.37)	109 (0.60)	561 (2.81)	1,555 (7.06)
	Edoxaban	-	-	-	-	-	-	41 (0.21)	468 (2.12)
	Vitamin K antagonist	6,478 (53.7)	7,115 (54.3)	8,105 (54.1)	8,490 (51.2)	7,548 (44.6)	5,964 (32.6)	4,345 (21.7)	3,024 (13.7)
	Aspirin	2,966 (24.6)	3,362 (25.7)	4,484 (29.9)	4,536 (27.4)	4,322 (25.6)	4,368 (23.9)	4,297 (21.5)	3,703 (16.8)
PE	Number of cases	5,628	6,187	7,163	8,056	8,443	9,337	9,969	11,199
	NOAC	136 (2.42)	205 (3.31)	357 (4.98)	504 (6.24)	1,892 (22.4)	4,188 (44.8)	5,988 (60.1)	7,461 (66.6)
	Rivaroxaban	136 (2.42)	205 (3.31)	293 (4.09)	424 (5.26)	1,767 (20.9)	4,036 (43.2)	4,963 (49.8)	5,355 (47.8)
	Dabigatran	-	-	43 (0.60)	47 (0.58)	87 (1.03)	86 (0.92)	727 (7.29)	957 (8.55)
	Apixaban	-	-	21 (0.29)	33 (0.41)	38 (0.45)	66 (0.71)	269 (2.70)	801 (7.15)
	Edoxaban	-	-	-	-	-	-	29 (0.29)	348 (3.11)
	Vitamin K antagonist	3,820 (67.9)	4,346 (70.2)	4,848 (67.7)	5,165 (64.1)	4,942 (58.5)	4,042 (43.3)	2,799 (28.1)	1,887 (16.9)
	Aspirin	1,641 (29.2)	1,872 (30.3)	2,409 (33.6)	2,446 (30.4)	2,355 (27.9)	2,447 (26.2)	2,393 (24.0)	2,071 (18.5)
DVT	Number of cases	7,281	7,951	9,062	9,787	10,102	10,714	11,926	12,939
	NOAC	174 (2.39)	251 (3.16)	485 (5.35)	715 (8.95)	2,448 (24.2)	3,889 (36.3)	5,469 (45.9)	6,324 (48.9)
	Rivaroxaban	174 (2.39)	251 (3.16)	428 (4.72)	657 (8.22)	2,342 (23.2)	3,765 (35.1)	4,638 (38.9)	4,589 (35.5)
	Dabigatran	-	-	37 (0.41)	38 (0.48)	70 (0.69)	58 (0.54)	434 (3.64)	598 (4.62)
	Apixaban	-	-	20 (0.22)	20 (0.25)	36 (0.36)	66 (0.62)	376 (3.15)	941 (7.27)
	Edoxaban	-	-	-	-	-	-	21 (0.18)	196 (1.51)
	Vitamin K antagonist	3,464 (47.6)	3,749 (47.2)	4,386 (48.4)	4,496 (56.3)	3,947 (39.1)	2,998 (28.0)	2,462 (20.6)	1,828 (14.1)
	Aspirin	1,622 (22.3)	1,921 (24.2)	2,582 (28.5)	2,607 (32.6)	2,599 (25.7)	2,534 (23.7)	2,567 (21.5)	2,187 (16.9)

Data are presented as number (%). Gray shading indicates cases after initiation of insurance coverage for each drug. DVT: deep vein thrombosis, NOAC: new oral anticoagulant, PE: pulmonary embolism, VTE: venous thromboembolism.

Rivaroxaban and dabigatran were covered by medical insurance starting in 2013, which is two years earlier than other NOACs, so the prescription rate of these two drugs increased markedly starting in 2013. Apixaban was not covered by medical insurance until 2015 despite approval from the MFDS in 2011, so the prescription rate of apixaban was relatively low. However, apixaban and edoxaban were covered by medical insurance since 2015 and 2016, respectively, after which the prescription rates increased significantly.

DISCUSSION

The present study investigated the annual incidence of VTE, PE, and DVT and evaluated the treatment pattern of OACs using data from the NHIS in Korea from 2009 through 2016.

The mean age-standardized annual incidence of VTE during the study period was 0.028% (range 0.024% in 2009 to 0.034% in 2016). This is much lower compared with the reported annual incidence of approximately 0.1%–0.2% in Western populations.[2)9)11)13)21)] However, recent studies have reported gradual increases in the incidence of VTE in Asian populations.[7)14)22)] In our study, the annual incidence increased by 5% annually from 2009 to 2016. The rate increased nearly two-fold during the 7 years of the study period, especially in patients older than 60 years. The increasing incidence of VTE might be due to the increase in the elderly population and the associated increase in comorbidities. Increased access to medical services for elderly patients could also contribute to the increased incidence. The wide and increased use of non-invasive imaging such as computed tomographic angiography and echocardiography and the improved imaging quality of non-invasive imaging also are important contributing factors for the increased prevalence of VTE in Korea.

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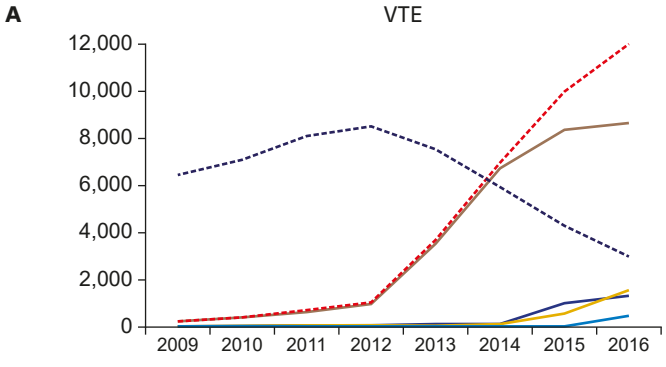
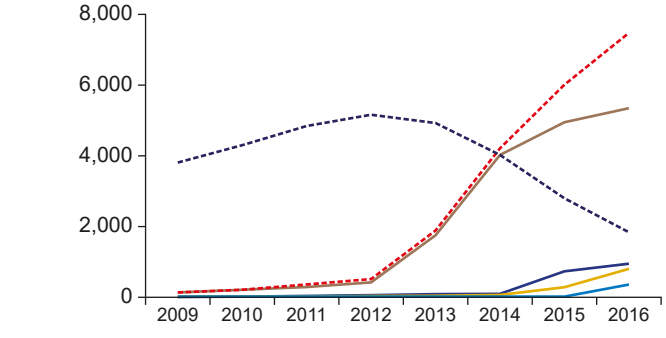


	2009	2010	2011	2012	2013	2014	2015	2016
Rivaroxaban	260	380	621	944	3,503	6,716	8,348	8,626
Dabigatran	0	0	67	74	125	123	984	1,318
Apixaban	0	0	36	43	62	109	561	1,555
Edoxaban	0	0	0	0	0	0	41	468
NOAC	260	380	724	1,061	3,690	6,948	9,934	11,967
Warfarin	6,478	7,115	8,105	8,490	7,548	5,964	4,345	3,024



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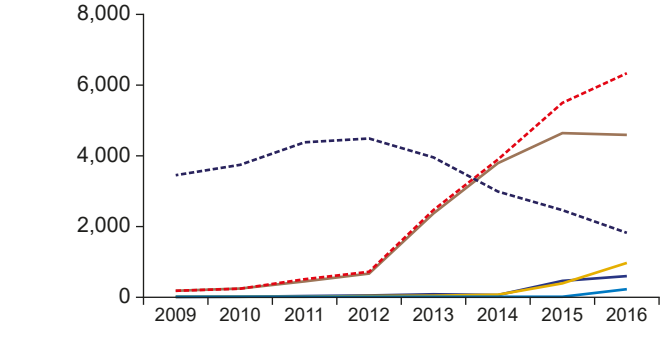
Dabigatran	0	0	43	47	87	86	727	957
Apixaban	0	0	21	33	38	66	269	801
Edoxaban	0	0	0	0	0	0	29	348
NOAC	136	205	357	504	1,892	4,188	5,988	7,461
Warfarin	3,820	4,346	4,848	5,165	4,942	4,042	2,799	1,887



	2009	2010	2011	2012	2013	2014	2015	2016
Rivaroxaban	174	251	428	657	2,342	3,765	4,638	4,589
Dabigatran	0	0	37	38	70	58	434	598
Apixaban	0	0	20	20	36	66	376	941
Edoxaban	0	0	0	0	0	0	21	196
NOAC	174	251	485	715	2,448	3,889	5,469	6,324
Warfarin	3,464	3,749	4,386	4,496	3,947	2,998	2,462	1,828

Figure 3. Total number of prescriptions for OACs and time trends of OAC use from 2009 to 2016. (A) VTE, (B) PE, (C) DVT.
DVT: deep vein thrombosis, NOACs: new oral anticoagulants, OACs: oral anticoagulants, PE: pulmonary embolism, VTE: venous thromboembolism.

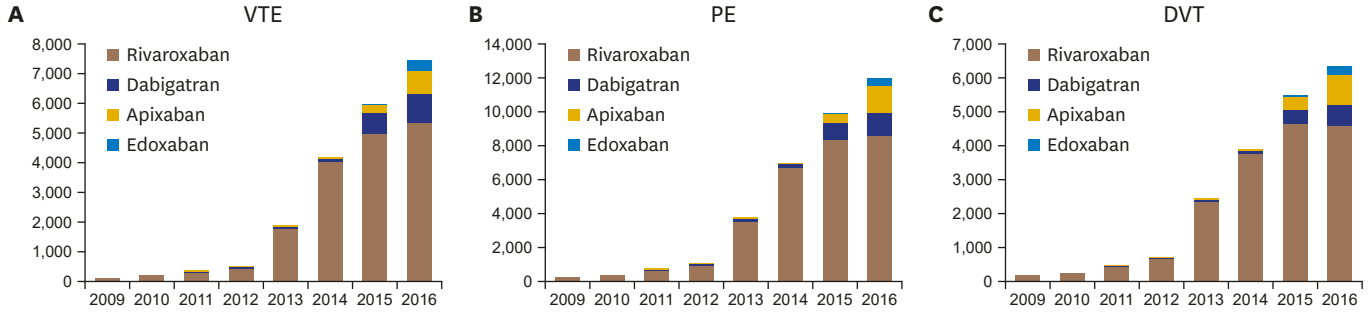


Figure 4. Time trends in NOAC choice for VTE (A), PE (B), and DVT (C) from 2009 to 2016.
DVT: deep vein thrombosis, NOACs: new oral anticoagulants, PE: pulmonary embolism, VTE: venous thromboembolism.

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In a previous study by Hong et al.,[22] there was a steady increase in the annual incidence of VTE. The authors reported that the annual incidence rate of VTE in Korea between 2009 and 2013 was 0.024% (range 0.021 to 0.029%), which is slightly lower than the finding of the current study. In the present study, we adopted a wider range of diagnosis codes compared with the previous study; this might have contributed to the difference in annual incidence rate between studies. We also used the NHIS database, whereas the previous study used the Health Insurance Review and Assessment Service (HIRA) database, which uses different data sources.

In our study, the incidence of VTE increased markedly with increasing age, which is similar to the pattern reported in previous studies.[23] The incidence of DVT was higher than that of PE in most age groups except 70 years and older. DVT is a milder form of VTE, and PE is considered to develop from DVT even though co-existing cases were reported in 50% of DVT cases in a previous study. PE is more fatal than is DVT, and elderly patients older than 70 years showed a higher incidence of PE, which suggests that fatalities from VTE increased in elderly patients.[24] An increased incidence of VTE in the elderly could be associated with increased risk with aging. Our data also showed that men and women had different patterns of VTE incidence in increasing age categories. The possible explanations for these disparities are likely multifactorial. There are several well-recognized clinical risk factors for VTE in women such as oral contraceptive use, hormone replacement therapy, estrogen receptor modulator therapy, and pregnancy.

In Korea, the absolute number of NOAC prescriptions has drastically increased, as has the ratio, accounting for more than 50% of all OAC prescriptions in 2016. Conversely, there was substantial decrease in the rate of VKA prescriptions, which corresponded to 15% of all OAC prescriptions in 2016. Similar prescribing trends were reported in western countries, although the healthcare system and reimbursement by insurance differ by country.[25-27] Evidence for NOAC use in the treatment of VTE shows a clear trend for replacing VKA use.[28-31] Physician awareness on the efficacy and safety of NOACs is important to initiate NOAC prescription; however, the clinical availability of NOACs in real clinical practice is affected out-of-pocket patient cost. Our data showed that use of NOACs increased significantly with initiation of insurance coverage of rivaroxaban and dabigatran in 2013, and exceeded use of VKAs in treatment for VTE, PE, and DVT. The increase of NOAC use was most likely attributed to insurance coverage in Korea.

Among NOACs, rivaroxaban was the most prescribed, consisting of 84% of the total NOAC use in the current study. These prescription trends are a consequence of several factors, such as increased physician experience, increased evidence of efficacy and safety of NOACs, and most importantly, initiation of insurance coverage of NOACs since 2013 in Korea. With a slight increase of apixaban and edoxaban use after insurance coverage starting in 2015 and 2016, the portion of rivaroxaban use among NOAC prescriptions slightly decreased to 72% in 2016. Dabigatran was the second most commonly used NOAC, and the prescription rate remained steady over time, which is thought to be relevant to the earlier initiation of insurance coverage. The prescription of apixaban surpassed that of dabigatran after introduction of insurance coverage of apixaban.

To the best of our knowledge, this is the first study that investigated the trend of NOAC use after initiation of insurance coverage in Korea. The effect of initiation of insurance coverage on apixaban and edoxaban might not yet be fully reflected in prescription rates. Further studies will explore further the impact of recent insurance coverage on NOAC prescription trends in Korea.

This study has several limitations. First, subjects with a diagnostic code of VTE other than the main and second diagnostic codes were not included in the study. Second, there was no risk assessment in the current study. We investigated only comorbid conditions using diagnostic codes, so accurate risk assessment could not be performed using the NHIS database. Of the known risk factors of VTE, medical history of diabetic mellitus and hypertension, malignancy, postoperation, prior admission, and pregnancy were analyzed. Other important risk factors such as infection, obesity, estrogen therapy, and thrombophilia could not be retrieved. Third, patients who switched anticoagulation treatment from VKAs to NOACs or from NOACs to VKAs could not be analyzed in this study. The majority of patients received only VKAs or NOACs, but 10% of patients were excluded from the study to avoid misinterpretation.

In conclusion, the incidence of VTE, PE, and DVT in the Korean population is lower compared with that in Western countries but has increased substantially from 2009 to 2016. This suggests that the incidence of VTE is growing in Asia along with increasing age and changes in lifestyle accompanied by gradual improvements of socioeconomic status. The treatment pattern of VTE is rapidly changing from VKA to NOAC and is greatly affected by insurance reimbursement and the physician's clinical experience.

ACKNOWLEDGMENTS

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SUPPLEMENTARY MATERIAL

Supplementary Table 1

Crude annual incidence of venous thromboembolism by sex and age in 2009 and 2016 (per 100,000)

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