NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	Treatment patterns and clinical outcomes among venous thromboembolism patients treated with anticoagulants after the entry of non-vitamin K antagonist oral anticoagulants in Korea
Protocol number	X9001305
Protocol version identifier	2.0
Date	27 April 2022
Active substance	B01AB01 (heparin) B01AB04 (dalteparin) B01AB05 (enoxaparin) B01AB06 (nadroparin) B01AB12 (bemiparin) B01AA03 (warfarin) B01AE07 (dabigatran) B01AF01 (rivaroxaban) B01AF02 (apixaban) B01AF03 (edoxaban)
Medicinal product	Eliquis® (apixaban)
Research question and objectives	• To describe the sociodemographic and clinical characteristics of patients with venous thromboembolism (VTE), overall and according to their index VTE treatment (parenteral anticoagulants [PAC] only, warfarin-based, non-vitamin K antagonist oral anticoagulants [NOAC]-based) • To describe index anticoagulant treatment patterns by investigating the

	utilization of different anticoagulants, treatment interruption, switches, discontinuations, and overall treatment duration • To examine the risk of clinical outcome (major bleeding) according to the specific type of oral anticoagulant (OAC)
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACE	Angiotensin-converting enzyme
AE	Adverse Event
ARB	Angiotensin II receptor blockers
ATC	Anatomical Therapeutic Chemical Classification System
CCI	Charlson Comorbidity Index
CI	Confidence Intervals
CIOMS	Council for International Organizations of Medical Sciences
COPD	Chronic Obstructive Pulmonary Disease
DOAC	Direct Oral Anticoagulants
DVT	Deep Vein Thrombosis
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
GEP	Good Epidemiological Practice
GPP	Guidelines for Good Pharmacoepidemiology Practices
GI	Gastrointestinal
HAS-BLED	Hypertension, Abnormal renal and liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio (INR), Elderly (> 65 years), Drugs or alcohol concomitantly
HIRA	Health Insurance Review and Assessment Service

HIRA-NPS	Health Insurance Review and Assessment Service-National Patient Sample
HR	Hazard Ratios
ICD-10	International Classification of Diseases, 10th Revision
IQR	Interquartile Range
IEA	International Epidemiological Association
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
LMWH	Low Molecular Weight Heparin
NDC	National Drug Code
NOAC	Non-vitamin K Antagonist Oral Anticoagulants
NSAIDs	Nonsteroidal Anti-inflammatory Drugs
NVAF	Non-Valvular Atrial Fibrillation
OAC	Oral Anticoagulant
PAC	Parenteral Anticoagulants
PASS	Post-Authorisation Safety Study
PE	Pulmonary Embolism
PPV	Positive Predictive Value
PS	Propensity Score
RCT	Randomized Controlled Trial
SD	Standardized Difference

SSRI	Selective serotonin reuptake inhibitors
STD	Standard Deviation
UFH	Unfractionated Heparin
VKA	Vitamin K Antagonist
VTE	Venous Thromboembolism

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

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4. ABSTRACT

- **Protocol title**

  Treatment patterns and clinical outcomes among venous thromboembolism patients treated with anticoagulants after the entry of non-vitamin K antagonist oral anticoagulants in Korea

- **Protocol version and date**

  2.0, 27 Apr 2022

- **Rationale and background**

  Venous Thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), is a major cause of morbidity, mortality and healthcare expenditure. Although the occurrence of VTE in the Asian population has been lower than that in Western populations, its incidence has been reported to have increased rapidly in recent years.

  For pharmacologic treatment of patients with VTE without cancer, the American College of Chest Physicians (CHEST) guidelines recommend the use of Non-Vitamin K antagonist oral anticoagulants (NOACs) over Vitamin K Antagonists (VKAs), with supporting evidences suggesting that each NOAC (e.g., apixaban) is effective at preventing recurrent VTE. In more recent treatment guidelines for the management of VTE released by the American Society of Hematology (ASH), NOACs are still recommended over VKAs for the initial management of VTE. NOACs are classified as a new generation of anticoagulants with approved indications of the risk reduction of stroke and embolism in nonvalvular atrial fibrillation (NVAF) as well as prophylaxis and treatment of DVT and PE.

  All NOACs became available as the first-line treatment of acute VTE in Korea after reimbursement expansion in May 2015. However, despite the increasing use of NOACs among VTE patients, there are still limited real-world evidence that assess treatment patterns as well as effectiveness and safety of the different anticoagulants especially among Asian population.

- **Research question and objectives**

  Research question

  - What is the real-world evidence of anticoagulant treatment for patients with VTE that can be found in the nationwide claims database in Korea?

  The current study will take place in two phases:

Phase I involves a descriptive assessment of VTE patient characteristics and treatment patterns in Korea as well as detailed power calculations for comparative analyses.

Phase II involves analyses of comparative safety between each NOAC and warfarin. These analyses will be implemented if there is sufficient power to enable scientifically valid inferences.

Primary objectives of Phase I of the study

- To describe the sociodemographic and clinical characteristics of patients with VTE, overall and according to ther index VTE treatment (parenteral anticoagulants [PAC] only, warfarin-based, NOAC-based)To describe index anticoagulant treatment patterns by investigating the utilization of different anticoagulants, treatment interruption, switches, discontinuations, and overall treatment duration

Primary objective of Phase II of the study

- To describe and compare the risk of clinical outcome (major bleeding) according to the specific type of OAC

[NOTE] Comparative analyses, especially NOAC vs NOAC direct comparisons, will be performed contingent on a feasibility assessment based on the descriptive analyses and the agreed opinion on scope after discussion with Eliquis Alliance Real World Data Review Committee.

Secondary objective of Phase I of the study

- To explore the relevant clinical events preceding treatment change from index anticoagulant

- **Study design**

  - Retrospective, observational, nationwide population-based cohort study

- **Population**

  Study period

  - 1 Mar 2012 to 31 Dec 2019

  Inclusion criteria

  - Incident VTE diagnosis in an inpatient or outpatient setting (International Classification of Diseases 10th Revision [ICD-10]: I26.0, I26.9, I80.2, I80.3) between 1 Mar 2013 and 30 Jun 2019.

- Received anticoagulation therapy (all medication codes for anticoagulants approved for VTE in Korea; unfractionated heparin [UFH], low molecular weight heparin [LMWH], warfarin, and NOACs) within 30 days of their VTE diagnosis (the index date will be defined as the date of treatment initiation with anticoagulants)

- Aged ≥18 years at index date

Exclusion criteria

- A record of VTE diagnosis within the 12-month period prior to the index VTE encounter

- Diagnosed with atrial fibrillation, atrial flutter, mechanical heart valve replacement or mitral stenosis anytime prior to index date

- Had a record of Inferior Vena Cava filter anytime prior to index date

- Received anticoagulation therapy within the 12-month period prior to index VTE encounter to restrict to new users of anticoagulation therapy

- Prescribed two different anticoagulants on the same index date to prevent exposure misclassification

- Had a record of pregnancy within the 9-month period prior to index date

Additional exclusion criteria for comparative analyses

- Had a record of active cancer, defined as first diagnosis of cancer with V code (a special code applied to patients with confirmed diagnosis of cancer by Korean Ministry of Health and Welfare for reimbursement for 5 years or longer if recurrent/metastatic) within the past 6 months of period prior to index date; or receiving anti-cancer treatment (chemotherapy, radiation therapy, or cancer-related surgery) under cancer diagnosis with V code within the past 6 months period prior to index date

Follow-up

- **Phase I of the study**: Patients will be followed-up from the index date until the earliest of in-hospital death or end of the study period (31 Dec 2019).

- **Phase II of the study**: Patients will be followed-up from the index date until the earliest of outcome occurrence (bleeding event), treatment discontinuation, switch to another anticoagulant, in-hospital death, or end of the study period (31 Dec 2019), where patients will be considered to have discontinued treatment when new prescription is absent within the 30-day grace period after the end of the former prescription.

- **Variables**

  Exposure(s)

  - Anticoagulant therapy (PAC [LMWH, UFH, others], NOACs [apixaban, dabigatran, rivaroxaban, edoxaban], warfarin).

  Outcome(s)

  - **Phase I of the study**: sociodemographic and clinical characteristics of patients with VTE, utilization of index anticoagulant treatment, treatment patterns (including treatment interruption, switching, complete discontinuation), overall treatment duration, and clinical events preceding first treatment change

  - **Phase II of the study**: Primary or secondary diagnosis with major bleeding (by site: intracranial, gastrointestinal [GI], and other sites) after the index date

  Covariate(s)

  - Sociodemographics (age, sex) will be assessed on the index date. Clinical characteristics including comorbidities, previous use of medications, and the number of outpatient visits will be assessed within the 6-month period prior to the index date

- **Data sources**

  - South Korea's Health Insurance and Review Assessment Service (HIRA) database

- **Study size**

  - The estimated number of incident patients with VTE and no history of active cancer from the 2018 HIRA-National Patient Sample (HIRA-NPS) database is 1,465, where the HIRA-NPS database is a 3% random sample of the entire Korean population of 50 million. Based on this estimation, the projected number of patients with VTE from the entire Korean population (HIRA database) of 2018 is 48,828 (1,465 * 33.33).

    - Excluding period for patients with previous OAC treatment,VTE history or a history of active cancer was set to prior 3 months because HIRA NPS database used in sample size estimation was constituted of one-year data only.

  1) Apixaban vs. warfarin

  - Among the above-mentioned number of incident patients with VTE and no history of active cancer, those who newly initiated apixaban or warfarin was estimated to be 211 patients (14.4%; 211/1,465), where patients had no prescription for OACs and no history of VTE within the 3-month period prior to VTE diagnosis. From these 211 patients, there were 83 (39.3%) apixaban users and 128 (60.7%) warfarin users

(based on 2018 HIRA-NPS data). Hence, the projected number of patients with VTE who newly initiated OACs to be present in the HIRA database in a single year is 7,032 patients (apixaban 2,766; warfarin 4,266). As this study aims to utilize data from 2013 to 2019 (7 years), the final projected number of patients with VTE who newly initiated apixaban or warfarin from the HIRA database is 49,224 patients (apixaban 19,362; warfarin 29,862).

- Considering a 95% for a two-sided CI level (α-error=0.05) and 80% power, the sample size for the comparative safety study for major bleeding events was calculated based on the following components:

  - HR for major bleeding events from previous literature: 0.31-0.75
  - Overall probability of major bleeding events from previous literature: 1.19%
  - Proportion of apixaban users among patients with VTE from the 2018 HIRA-NPS database: 39.3% (83 apixaban users; 128 warfarin users).
  - 2,013 patients with VTE treated with apixaban or warfarin are required to detect at 5% α-error, and 80% statistical power, and HR of 0.31 by sample size calculations for survival analysis; alternatively (more conservative estimate), 33,340 patients with VTE treated with apixaban or warfarin are required to detect at 5% α-error, and 80% statistical power, and HR of 0.75 by sample size calculations for survival analysis.
  - As this study is expected to include 49,224 patients with VTE, with 19,362 patients treated with apixaban from the nationwide HIRA database, this study will have enough statistical power to test the hypothesis of the association between apixaban use and risk of bleeding events among patients with VTE.

2) Rivaroxaban vs. warfarin

- Among the above-mentioned number of incident patients with VTE and no history of active cancer, those who newly initiated rivaroxaban or warfarin was estimated to be 382 patients (26.1%; 382/1,465), where patients had no prescription for OACs and no history of VTE within the 3-month period prior to VTE diagnosis. From these 382 patients, there were 264 (69.1%) rivaroxaban users and 118 (30.9%) warfarin users (based on 2018 HIRA-NPS data). Hence, the projected number of patients with VTE who newly initiated OACs to be present in the HIRA database in a single year is 12,732 patients (rivaroxaban 8,799; warfarin 3,933). As this study aims to utilize data from 2013 to 2019 (7 years), the final projected number of patients with VTE who newly initiated rivaroxaban or warfarin from the HIRA database is 89,124 patients (rivaroxaban 61,593; warfarin 27,531).

- Considering a 95% for a two-sided CI level (α-error=0.05) and 80% power, the sample size for the comparative safety study for major bleeding events was calculated based on the following components:

  - HR for major bleeding events from previous literature: 0.77-1.19
  - Overall probability of major bleeding events from previous literature: 8.1%
  - Proportion of rivaroxaban users among patients with VTE from the 2018 HIRA-NPS database: 69.1% (264 rivaroxaban users; 118 warfarin users).
  - 6,630 patients with VTE treated with rivaroxaban or warfarin are required to detect at 5% α-error, and 80% statistical power, and HR of 0.77 by sample size calculations for survival analysis; alternatively (more conservative estimate), 14,967 patients with VTE treated with rivaroxaban or warfarin are required to detect at 5% α-error, and 80% statistical power, and HR of 1.19 by sample size calculations for survival analysis.
  - As this study is expected to include 89,124 patients with VTE, with 61,593 patients treated with rivaroxaban from the nationwide HIRA database, this study will have enough statistical power to test the hypothesis of the association between rivaroxaban use and risk of bleeding events among patients with VTE.

3) Edoxaban vs. warfarin

- Among the above-mentioned number of incident patients with VTE and no history of active cancer, those who newly initiated edoxaban or warfarin was estimated to be 184 patients (12.6%; 184/1,465), where patients had no prescription for OACs and no history of VTE within the 3-month period prior to VTE diagnosis. From these 184 patients, there were 57 (31.0%) edoxaban users and 127 (69.0%) warfarin users (based on 2018 HIRA-NPS data). Hence, the projected number of patients with VTE who newly initiated OACs to be present in the HIRA database in a single year is 6,132 patients (edoxaban 1,900; warfarin 4,232). As this study aims to utilize data from 2013 to 2019 (7 years), the final projected number of patients with VTE who newly initiated edoxaban or warfarin from the HIRA database is 42,924 patients (edoxaban 13,300; warfarin 29,624).

- Considering a 95% for a two-sided CI level (α-error=0.05) and 80% power, the sample size for the comparative safety study for major bleeding events was calculated based on the following components:

  - HR for major bleeding events from previous literature: 0.56-0.81
  - Overall probability of major bleeding events from previous literature: 8.5%

- Proportion of edoxaban users among patients with VTE from the 2018 HIRA-NPS database: 31.0% (57 edoxaban users; 127 warfarin users).

- 1,282 patients with VTE treated with edoxaban or warfarin are required to detect at 5% α-error, and 80% statistical power, and HR of 0.56 by sample size calculations for survival analysis; alternatively (more conservative estimate), 9,703 patients with VTE treated with edoxaban or warfarin are required to detect at 5% α-error, and 80% statistical power, and HR of 0.81 by sample size calculations for survival analysis.

- As this study is expected to include 42,924 patients with VTE, with 13,300 patients treated with edoxaban from the nationwide HIRA database, this study will have enough statistical power to test the hypothesis of the association between edoxaban use and risk of bleeding events among patients with VTE.

4) Dabigatran vs. warfarin

- Among the above-mentioned number of incident patients with VTE and no history of active cancer, those who newly initiated dabigatran or warfarin was estimated to be 155 patients (10.6%; 155/1,465), where patients had no prescription for OACs and no history of VTE within the 3-month period prior to VTE diagnosis. From these 155 patients, there were 26 (16.8%) dabigatran users and 129 (83.2%) warfarin users (based on 2018 HIRA-NPS data). Hence, the projected number of patients with VTE who newly initiated OACs to be present in the HIRA database in a single year is 5,166 patients (dabigatran 866; warfarin 4,299). As this study aims to utilize data from 2013 to 2019 (7 years), the final projected number of patients with VTE who newly initiated dabigatran or warfarin from the HIRA database is 36,162 patients (dabigatran 6,062; warfarin 30,093).

- Considering a 95% for a two-sided CI level (α-error=0.05) and 80% power, the sample size for the comparative safety study for major bleeding events was calculated based on the following components:

  - HR for major bleeding events from previous literature: 0.52-0.69

  - Overall probability of major bleeding events from previous literature: 1.4%

  - Proportion of dabigatran users among patients with VTE from the 2018 HIRA-NPS database: 16.8% (26 dabigatran users; 129 warfarin users).

  - 9,361 patients with VTE treated with dabigatran or warfarin are required to detect at 5% α-error, and 80% statistical power, and HR of 0.52 by sample size calculations for survival analysis; alternatively (more conservative estimate), 29,071 patients with VTE treated with edoxaban or warfarin are required to

detect at 5% α-error, and 80% statistical power, and HR of 0.69 by sample size calculations for survival analysis.

- As this study is expected to include 36,162 patients with VTE, with 6,062 patients treated with dabigatran from the nationwide HIRA database, this study will have enough statistical power to test the hypothesis of the association between dabigatran use and risk of bleeding events among patients with VTE.

- **Data analysis**

  - Descriptive analysis will be conducted separately in two cohorts of non-cancer VTE and cancer VTE patients according to co-presence of active cancer.

  - We will use descriptive statistics to describe the baseline sociodemographic and clinical characteristics of patients with VTE and present them as mean and standard deviation (STD) for continuous variables or counts with proportions for categorical variables. Significance test will be conducted between the three treatment groups of interest using analysis of variance for continuous variables and chi-square test for categorical variables.

  - We will describe the utilization pattern of anticoagulant treatments among patients with VTE as counts with proportions. We will also estimate the treatment patterns (including treatment interruption, switches, discontinuation) and the overall treatment duration as median (interquartile range [IQR]) or mean (STD) by each index anticoagulant treatment. To identify potential reasons for treatment change, clinical events preceding the first treatment change will be measured within 30 days prior to the first date of treatment change.

  - We will calculate the incidence of major bleeding overall and by site per 1,000 person-years based on the Poisson distribution. We will estimate propensity scores (PS) using multivariable logistic regression models for the likelihood of receiving each NOAC or warfarin, conditioned on baseline sociodemographic and clinical characteristics. We will use multivariable Cox proportional hazard regression models to estimate HRs with 95% CIs for the risk of major bleeding associated with each OAC use, as compared with other OAC, with the PS applied as inverse probability of treatment weights to minimize residual confounding bias and increase comparability between treatment groups.

  - All analyses will be conducted using SAS Enterprise Guide 7.1 (SAS Institute Inc, Cary, NC), provided by HIRA through a virtual access machine.

- **Milestones**

- The results of this study are anticipated in Q2 2022. The expected completion date of preliminary analyis is Q3 2021 and the final report in Q3 2022. The milestones are dependent on receipt of requested dataset from HIRA.

5. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
Amendment 1 (V.2.0)	28Mar2022	Study information	Changed index treatment grouping to PAC only, warfarin-based, and NOAC-based therapy.	Amendment following Protocol Administrative Change Letter in Oct 22, 2021
			Updated author information	Revised due to author's title change
		4. Abstract	Changed index treatment grouping to PAC only, warfarin-based, and NOAC-based therapy.	Amendment following Protocol Administrative Change Letter in Oct 22, 2021
			Added secondary objective of Phase I	Revised according to additional analysis in Phase I
			Added outcome for secondary objective of Phase I	
			Revised data analysis for additional analyses	
		6. Milestones	Updated planned dates to study milestones	Revised due to change in study schedule
		8. Research question and objectives	Added secondary objective of Phase I	Revised according to additional analysis in Phase I
		9.1 Study design	Updated Figure 1 and Figure 2	Amendment following Protocol Administrative Change Letter in Oct 22, 2021
		9.3 Variables	Revised the sentence regarding heparin bridging period	Amendment following Protocol Administrative Change Letter in Oct 22, 2021 (acute heparin therapy to be considered in all OACs)
			Added outcome definition for secondary objective of Phase I	Added according to additional analysis in Phase I
			Revised evaluation period of comorbidies (APS, history of cancer)	Amendment following Protocol Administrative Change Letter in Oct 22, 2021 and detailed explanation
			Added antiplatelet agents and azole antifungal agents	
		9.7 Data analysis	Added data analysis for secondary objective of Phase I	Revised according to additional analysis in Phase I

6. MILESTONES

Milestone[†]	Planned date
Institutional Review Board (IRB) approval	1Q 2021
HIRA data application	1Q 2021
Study protocol development	1Q 2021
Study protocol finalization and approval	2Q 2021
HIRA data extraction and access	2Q 2021
Data analysis	3Q 2021
Preliminary results	3Q 2021
Data analysis for final	2Q 2022
Manuscript draft	2Q 2022
Final study report	3Q 2022
Manuscript finalization and approval	3Q 2022

[†]*Note that milestones are dependent on timely delivery of data provided by HIRA*

7. RATIONALE AND BACKGROUND

Venous thromboembolism (VTE) is a disorder that includes deep vein thrombosis (DVT) and pulmonary embolism (PE). Of VTE, DVT occurs when a blood clot forms in a deep vein, usually in the lower leg, thigh, or pelvis and PE occurs when a clot breaks loose and travels through the bloodstream to the lungs to eventually block an artery in the lung. Blood clots can develop in veins when damaged by surgery or trauma, or because of an inflammation in response to an infection or injury. Other risk factors for VTE include a history of a previous VTE event, comorbidities such as cancer or spinal cord injury, pregnancy, paralysis or long periods of immobilization, specific genes, and certain circumstances related to age, race, and sex. As a previous VTE event is a strong risk factor for the onset of VTE, recurrence of VTE is common, with a previous study reporting that approximately 30% of patients who experienced VTE will develop recurrent VTE within 10 years of their initial event [1]. With high rates of recurrence and mortality, as well as increased long-term morbidity and functional disability, VTE remains a major public health concern with a substantial disease burden [2] [3].

For pharmacologic treatment of patients with VTE without cancer, the American College of Chest Physicians (CHEST) guidelines recommend the use of non-vitamin K antagonist oral

anticoagulants (NOACs) over Vitamin K Antagonists (VKAs), with supporting evidence suggesting that each NOAC (e.g., apixaban) is effective at preventing recurrent VTE [4]. More recently, in the treatment guidelines for management of VTE released by the American Society of Hematology (ASH), NOACs are still recommended over VKAs for the initial management of VTE [5].

NOACs, or also known as direct oral anticoagulants (DOACs), are a relatively new generation of anticoagulants approved by the US FDA; dabigatran, rivaroxaban, apixaban, and edoxaban were approved in October 2010, July 2011, December 2012, and January 2015, respectively, for treatment indication of risk reduction of stroke and embolism in nonvalvular atrial fibrillation (NVAF) [6]. These NOACs have also been approved for prophylaxis and treatment of DVT and PE, which comprise VTE [7, 8]. Compared with VKAs, NOACs have fewer drug interactions, food interactions, and adverse effects and therefore, do not require frequent laboratory monitoring or dosage adjustments [4, 9]. Among NOACs, apixaban and rivaroxaban were approved as a single-drug approach for the treatment of VTE and do not require initial parenteral treatment with low molecular weight heparin (LMWH) or unfractionated heparin (UFH) [10, 11]. In actual real-world clinical practice, the two aforementioned NOACs are the most widely used and preferred treatments for VTE and preventing its recurrence [12-14]. Although NOACs demonstrated better safety profile than VKAs, concerns regarding their risk of adverse bleeding events remain due to their mechanism of action [15].

With both conventional and new anticoagulant therapies being used in real-world clinical practice, it is necessary to identify the utilization characteristics of individual anticoagulant treatments through the analysis of nationwide claims database. It is important to examine the treatment pattern and assess whether Korean patients are being treated appropriately based on the current treatment guidelines.

Several previous studies evaluated comparative effectiveness and safety of apixaban versus warfarin in patients with VTE. According to the AMPLIFY trial, the use of apixaban was non-inferior to conventional therapy for the treatment of VTE (relative risk [RR] 0.84, 95% confidence interval [CI] 0.60-1.18) and was superior to the bleeding event (RR 0.44, 95% CI 0.36-0.55) [10]. In the same manner as the results of the clinical trial, pharmacoepidemiologic studies reflecting real-world practice showed consistent results [16, 17]. However, those studies were focused on the western population, and the evidence on the effectiveness and safety of warfarin and apixaban from real-world clinical practice among the Asian population with venous thromboembolism is still limited. Of the NOACs, both apixaban and rivaroxaban are known to have low rates of major bleeding events[18, 19]. One US population-based retrospective cohort study compared the risk of major bleeding events between apixaban and rivaroxaban in patients with VTE [20]. According to the study's findings, the use of apixaban was associated with a reduced risk of major bleeding events when compared to rivaroxaban use (hazard ratio [HR] 0.54, 95% confidence interval [CI] 0.37-0.82). Although findings suggest a significant protective effect on major bleeding events associated with apixaban, more studies are needed to provide evidence on the different risk of major bleeding events between apixaban and other OACs in various ethnic populations.

Therefore, through this retrospective study utilizing Korean national claims database, we aim to 1) describe the clinical characteristics and anticoagulant treatment pattern of Korean VTE patients and 2) evaluate the safety outcome of current anticoagulant therapy regarding bleeding.

8. RESEARCH QUESTION AND OBJECTIVES

Research Question

What is the real-world evidence of anticoagulant treatment for patients with VTE that can be found in the nationwide claims database in Korea? The current study will take place in two phases:

Phase I involves a descriptive assessment of patient characteristics and treatment patterns in Korea as well as detailed power calculations for comparative study.

Phase II involves analyses of comparative safety between each NOAC and warfarin. These analyses will be implemented if there is sufficient power to enable scientifically valid inferences.

Primary Objectives of Phase I of the study

- To describe the sociodemographic and clinical characteristics of patietns with VTE, overall and according to ther index VTE treatment (PAC only, warfarin-based, NOAC-based)

- To describe index anticoagulant treatment patterns by investigating the utilization of different anticoagulants, treatment interruption, switches, discontinuations, and overall treatment duration

Primary Objective of Phase II of the study

- To describe and compare the risk of clinical outcome (major bleeding) according to the specific type of OAC

[NOTE] Comparative analyses, especially NOAC vs NOAC direct comparisons, will be performed contingent on a feasibility assessment based on the descriptive analyses and agreed opinion on scope after discussion with Eliquis Alliance Real World Data Review Committee.

Secondary objective of Phase I of the study

- To explore the relevant clinical events preceding treatment change from index anticoagulant

9. RESEARCH METHODS

9.1. Study design

A retrospective, observational, nationwide population-based cohort study will be conducted to describe the treatment patterns of anticoagulation therapies prescribed to patients with VTE in South Korea, and assess the risk of major bleeding associated with apixaban and other NOACs use, as compared with warfarin, by using the Health Insurance Review and Assessment Service (HIRA) database from 1 Mar 2012 to 31 Dec 2019 (Figure 1).

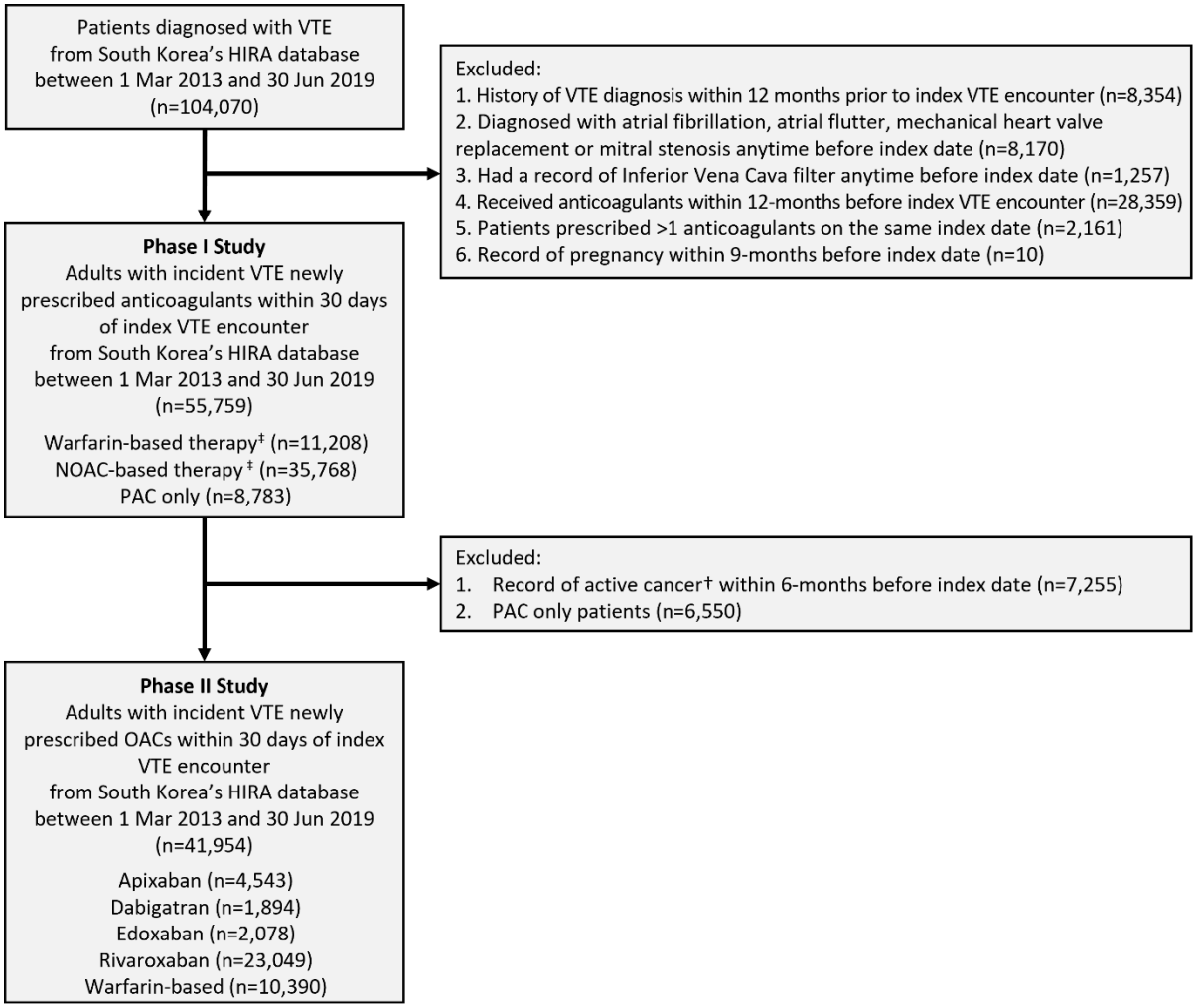

Figure 1. Study participants inclusion and exclusion criteria

Note: HIRA, Health Insurance and Review Assessment service; LMWH, low molecular weight heparin; NOAC, non-vitamin K antagonist; PAC, parenteral anticoagulants; VTE, venous thromboembolism

[†]Record of active cancer is defined as first diagnosis of cancer with V code within the past 6 months of period prior to index date; or receiving anti-cancer treatment under cancer diagnosis with V code within the past 6-month period prior to index date.
[‡]Warfarin-based and NOAC-based include either PAC with warfarin/NOAC or warfarin/NOAC only.

The study cohort will be defined as patients diagnosed with VTE between 1 Mar 2013 and 30 Jun 2019. The cohort entry will be defined as the date of incident VTE diagnosis. The index date will be defined as the date of first prescription for anticoagulants within 30 days after the index VTE event. The length of the exclusion assessment window will vary depending on the condition, from 12-months at minimum to anytime prior to index date. The following patients will be excluded: A record of VTE diagnosis within the 12-month period prior to the index VTE encounter, diagnosed with atrial fibrillation, atrial flutter, mechanical heart valve replacement or mitral stenosis anytime prior to index date, had a record of Inferior Vena Cava filter anytime prior to index date, received anticoagulatory therapy within the 12-month period prior to index VTE encounter to restrict to new users of anticoagulatory therapy, prescribed two different anticoagulants on the same index date to prevent exposure misclassification, had a record of pregnancy within the 9-month period prior to index date, and for the Phase II of the study only, had a record of active cancer within six months period prior to index date.

Baseline sociodemographic characteristics (e.g., age, sex) will be assessed on the index date, whereas clinical characteristics (comorbidities, previous use of medications, Charlson comorbidity index [CCI], HAS-BLED scores, initial presentation of VTE, number of outpatient visits) will be assessed in the 6-month period prior to the index date except when otherwise specfied in section 9.3 *Variables* (Figure 2).

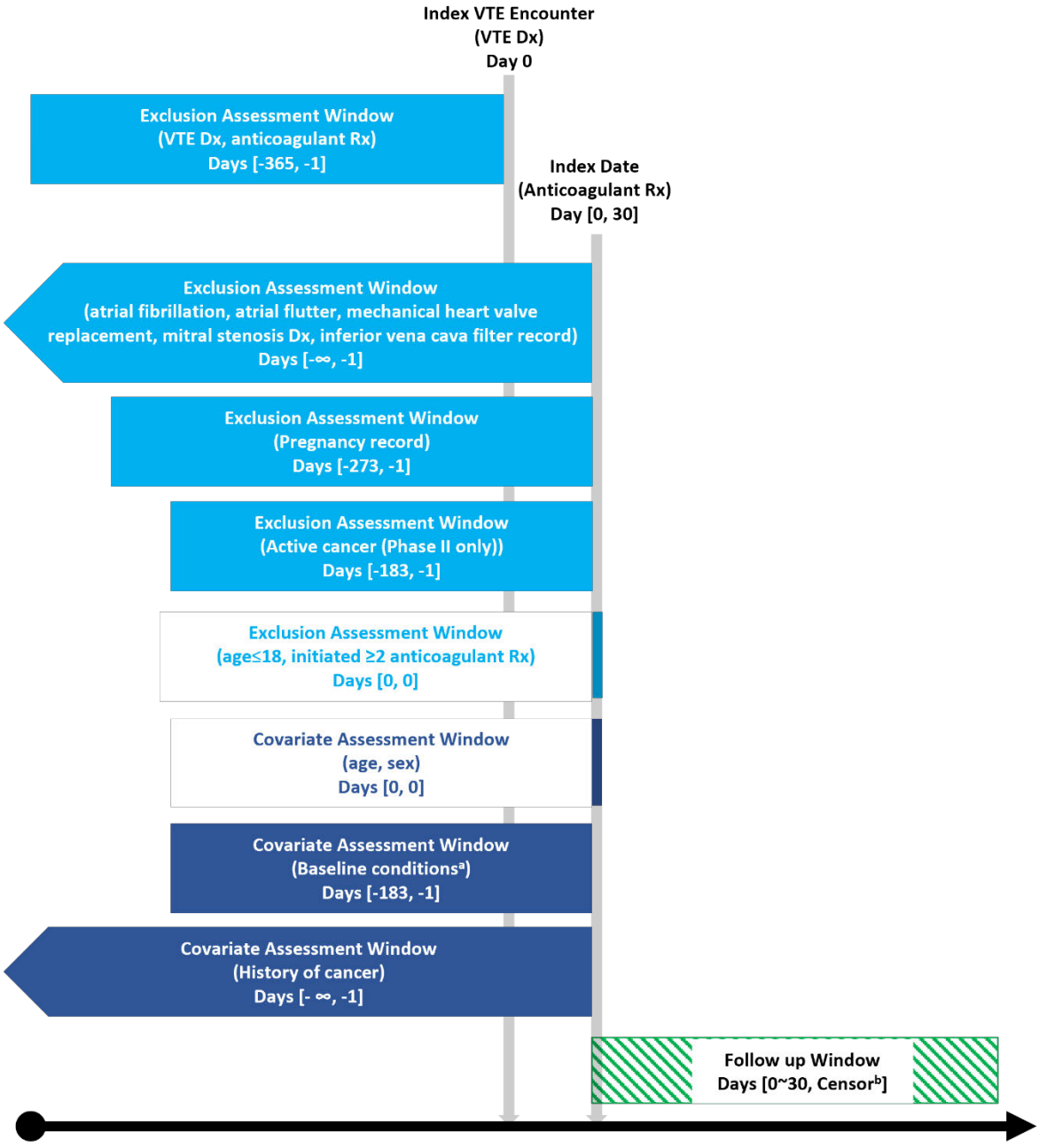

Figure 2. Overall study schematic

a. Baseline conditions included: Charlson comorbidity index, HAS-BLED scores, comorbidities (antiphospholipid syndrome, asthma, cancer, chronic obstructive pulmonary disease, chronic kidney disease, chronic liver disease, diabetes mellitus, fracture, heart failure, hyperlipidemia, hypertension, ischemic heart disease, myocardial infarction, stroke, trauma), previous use of medications (corticosteroids, nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors,

angiotensin II receptor blockers, antiplatelet agents, azole antifungal agents, β-blockers, calcium-channel blockers, selective serotonin reuptake inhibitors, proton pump inhibitors, diuretics, thiazides, vasodilators, estrogens, cyclooxygenase-2 inhibitors), initial presentation of VTE (DVT, PE, both DVT and PE), number of outpatient visits

b. Earliest of: outcome of interest (major bleeding event), treatment discontinuation, switch to another anticoagulant, in-hospital death, end of the study period (31 Dec 2019)

Note: Dx, diagnosis; NOAC, non-vitamin K antagonist oral anticoagulant; Rx, prescription; VTE, venous thromboembolism; PE, pulmonary embolism

Within this study cohort, we will describe the treatment patterns of anticoagulants prescribed for VTE treatment throughout the period of follow-up, defined as the period from the index date to the end of the study period. Moreover, if feasible, we will also examine the risk of major bleeding overall and by site, associated with each NOAC use, as compared with warfarin.

9.2. Setting

9.2.1. Inclusion criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Incident VTE diagnosis in an inpatient or outpatient setting (International Classification of Diseases 10th Revision [ICD-10]: I26.0, I26.9, I80.2, I80.3) between 1 Mar 2013 and 30 Jun 2019

2. Received anticoagulation therapy (all medication codes for anticoagulants approved for VTE in Korea; UFH, LMWH, warfarin, and NOACs) within 30 days of their VTE diagnosis (the index date will be defined as the date of treatment initiation with anticoagulants)

3. Aged ≥18 years at index date

9.2.2. Exclusion criteria

Patients meeting any of the following criteria will not be included in the study:

1. Had a record of VTE diagnosis (ICD-10: I26.0, I26.9, I80.2, I80.3) within the 12-month period prior to the index VTE encounter.

2. Diagnosed with atrial fibrillation/flutter (ICD-10: I48), mechanical heart valve replacement (National Procedure Code: Z952, M6531, M6532, M6533, O1781, O1782,

O1783, O1791, O1792, O1793, O1797, O1794, O1795, O1796, O1798, O1799) or mitral stenosis (ICD-10: I05.0, I05.2) anytime prior to index date

3. Had a record of Inferior Vena Cava filter (National Procedure Code: O2045, M6650) anytime prior to index date

4. Received anticoagulatory therapy within the 12-month period prior to index VTE encounter to restrict to new users of anticoagulatory therapy.

5. Prescribed two different anticoagulants on the same index date to prevent exposure misclassification.

6. Had a record of pregnancy (ICD-10: O03-O07, O10-O14, O16, O20-OO26, O28-O36, O41-O43, O46.8, O46.9, O61-O66, O67.8, O67.9, O69, O70-O75, O80-O92, O94-O99, P08, Z33-Z39) within the 9-month period prior to index date

7. Had a record of active cancer, defined as first diagnosis of cancer (ICD-10: C00-C97 [excluding non-melanoma skin cancer: C44]) with V code (V011, V027, V193, V194; a special code applied to patients with confirmed diagnosis of cancer by Korean Ministry of Health and Welfare for reimbursement for 5 years or longer if recurrent/metastasis) within the past 6 months of period prior to index date; or receiving anti-cancer treatment (chemotherapy, radiation therapy, or cancer-related surgery) under cancer diagnosis with V code within the past 6 months from index date (for Phase II of the study only). WHO-ATC codes and National Procedure Codes for anti-cancer treatment are shown in Table 1.

Table 1. WHO-ATC codes and National Procedure Codes for anti-cancer treatment

Anti-cancer treatment	WHO-ATC codes / National Procedure Codes
Chemotherapy	L01-04, H02AB02, H02AB04, H02AB06, H02AB07, H02AB09
Radiation therapy	HD051-HD059, HD061, HD071-HD073, HD080-HD089, HD091-HD093, HD110-HD115, HD121, HD150, HD160, HD211, HD212, HZ271
Cancer-related surgery	N0232, N0284-N0286, NA281-NA284, N0335, N0404, N0405, N0435-N0437, N0940, O0961-O0963, O1045, O1047, O1048, O1224-O1227, O1251, O1252, O1401, O1403-O1405, O1410, O1421-O1424, O1431, O1432, O1471, O1484, O1486, O1572, O1592, O1596, O1982, P2091, P2093, P2123, P2124, Q2150, Q2181-Q2183, Q2203, Q2206, Q2232, Q2292-Q2294, Q2346, Q2347, Q2348, Q2361, Q2362, Q2363, Q2365-Q2369, Q2401, Q2402, Q2403, Q2502, QA536, Q2533, Q2534, Q2536, Q2537, Q0251-Q0259, Q2594, Q2598, Q2601, Q2650,

	Q2651, QA671-QA673, QA679, Q1261, Q1262, Q2671-Q2673, Q2679, Q2761, Q2762, Q2791-Q2794, Q2796-Q2798, Q2890-Q2893, Q2901, Q0292, Q2921-Q2924, Q2927, Q2928, QA921-QA924, QA928, Q2925, Q2926, QA925, QA926, R3271, R3273, R3274, R3275, R3290, R3305, R3307, R3299, R3300, R3309, R3310, R3432, R3433, R3451, R3470, R3481, R3482, R3541-R3543, R3530, R3590, R3755, R3756, R3791, R3792, R3801, R3802, R3851, R3853, R3861, R3862, R3891, R3901, R3902, R3950, RZ512, R3960, R3975, R4003, R4004, R4067, R4068, R4071-R4074, R4140, R4143, R4144, R4147-R4149, R0141, R0142, R4154, R4155, R4156, R4250, R4331, R4332, R4423-R4428, P4543, P4551-P4554, P4561, P4571, P4572, S4616, S4634-S4639, S6691-6696, S4694-S4696, S4707-S4709, S4743, S4756-S4758, S4780, S4801-S4803, S4880, S4900, S4950, S5200, S5220, S5231, S5232, S5246, S5592, S5745, M6774, M6870, M6880, M6775, QZ841, M6890, M6900, M6991, M6910, Q0841, Q0842, N7136-N7139, N7140-N7153, Q7221-Q7225, Q7230, Q7280-Q7285, Q7342, Q7380, Q7410, Q7561-Q7567, Q7571, Q7572, Q7651-Q7654, Q7701-Q7703, QX706, Q7751, Q7752, Q7761-Q7763,Q7766, Q7771, Q7772, Q7775, Q7788, Q7789, U4811, U4812, U4881-U4883
Others	X5131-X5137 (hemopoietic cell transplantation)

9.3. Variables

Exposure

- **Phase I of the study:** PAC (UFH [Anatomical Therapeutic Chemical [ATC] code: B01AB01], LMWH [B01AB04, B01AB05, B01AB06, B01AB12]), VKA (warfarin [B01AA03]), NOACs (apixaban [B01AF02], rivaroxaban [B01AF01], edoxaban [B01AF03], dabigatran [B01AE07])

- **Phase II of the study:** Apixaban (B01AF02), Rivaroxaban (B01AF01), Edoxaban (B01AF03), Dabigatran (B01AE07), Warfarin (B01AA03)

Outcome(s)

- **Phase I of the study**

- Sociodemographic and clinical characteristics of patients with VTE who initiated anticoagulants.

- Utilization of different anticoagulants at treatment initiation. Patients will be classified based on their index anticoagulant treatment received within 30 days after being diagnosed with VTE.

- Treatment interruption from the index anticoagulant treatment, which will be defined as when a patient has a gap with no new treatment within 30 days of the estimated end of supply, but subsequently restarts the index treatment after this period.[21] The time to treatment interruption will be defined as the period from the index date to the date of treatment interruption.

- Treatment switching will be defined as a prescription of another anticoagulant therapy that is started after the treatment initiation of the index anticoagulant treatment and within 30 days after the estimated end of supply of the index anticoagulant drug (exposure to the new anticoagulant treatment must last for at least 30 days to be considered as a treatment switch). The time to treatment switch will be defined as the period from the index date to the date of treatment switch.

  Exemption: As heparin can be initiated at acute stage of DVT/PE before clinical decision to use OAC, a switch from initial heparin treatment to an OAC within 2 weeks after heparin treatment initiation will not be considered a treatment switch.

- Treatment discontinuation (complete discontinuation; no reinitiation) will be defined as when a patient who ended their first continuous treatment episode with the index anticoagulant treatment without switching, and subsequently have no further prescriptions for that respective anticoagulant treatment during all available follow-up time. The time to treatment discontinuation will be defined as the period from the index date to the date of treatment discontinuation.

- Overall anticoagulant treatment duration will be defined as the time period from the index date to the earliest of treatment interruption, switch, or discontinuation.

- If a patient has evidence of a repeat prescription within 30 days of the end of their prescription and does not experience any of the above events (treatment interruption, switch, or discontinuation), they will be assumed to be persistent on treatment.[21]

- Clinical event preceding first treatment change will be defined as occurrence of any event listed below within 30 days before treatment interruption, switch, or discontinuation. A new clinical event will be considered ‘new’ when it occurs for the first time within a 6-month period for acute conditions (arterial

thromboembolism, ischemic stroke, transient ischemic attack, myocardial infarction, angina pectoris, acute kidney injury, and abnormal liver function) and 5-years for chronic conditions (cancer, chronic kidney disease, and liver disease). A patient may contribute to multiple events.

① Major bleeding (as defined in Table 2)

② Complications of VTE: post-thrombotic syndrome and chronic thromboembolic pulmonary hypertension

③ Thromboembolism: PE diagnosis in patients with index event as DVT only, new diagnosis of arterial thromboembolism, ischemic stroke, transient ischemic attack, myocardial infarction, or angina pectoris

④ Major surgery: orthopedic surgeries (knee arthroplasty, hip arthroplasty, and hip fracture surgery), cancer surgeries (stomach, colorectal, hepatobiliary, pancreatic, breast, ovarian, cervical, renal, bladder, prostate, lung, and esophageal cancers, and brain tumors), and benign surgeries (myomectomy, oophorectomy, and transurethral resection of the prostate)

⑤ Cancer-related event (among non-active cancer patients only): new diagnosis of active cancer

⑥ Kidney function change: new diagnosis of chronic kidney disease or acute kidney injury

⑦ Liver function change: new diagnosis of liver disease or abnormal liver function

- **Phase II of the study**

  ■ Major bleeding will be defined using primary or secondary diagnosis codes according to the ICD-10 diagnostic codes shown in Table 2 and classified by site (intracranial, gastrointestinal [GI], and other sites) [22].

Table 2. Definition of major bleeding by site

Major bleeding	ICD-10 diagnosis code	Diagnostic definition
Intracranial hemorrhage	I60, I61, I62, I690, I691, I692, S064, S065, S066, S068	Diagnosis code + admission code + brain CT or MRI code **Brain CT or MRI: CT: HA441, HA451, HA461, HA471, HA851*

		MRI: HE101, HE102, HE135, HE201, HE202, HE235, HE301, HE302, HE401, HE402, HE501, HE502, HE535
GI bleeding	I850, I983, K2211, K226, K228, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K290, K3181, K5521, K625, K920, K921, K922	Diagnosis code + admission code
Other bleeding	D62, H448, H3572, H356, H313, H210, H113, H052, H470, H431, I312, N020-N029, N421, N831, N857, N920, N923, N930, N938, N939, M250, R233, R040, R041, R042, R048, R049, T792, T810, N950, R310, R311, R318, R58, T455, Y442, D683	Diagnosis code + admission code

- The earliest date of diagnosis of the major bleeding event after the index date will be defined as the outcome occurrence date.

- Patients will be followed up from the index date to the occurrence of an outcome, treatment discontinuation (30-day grace period), switch to another anticoagulants, in-hospital death, or end of the study period (31 Dec 2019) whichever comes first.

Potential Confounder(s)

- Sociodemographic characteristics such as age, sex, and index year will be assessed at the index date.

- CCI [23] and HAS-BLED [24] scores will be measured within the 6-month period prior to the index date.

- Initial presentation of VTE

  - DVT (I80.2, I80.3)

  - PE (I26.0, I26.9)

  - Both DVT and PE

- Comorbidities (ICD-10 diagnostic code) will be measured within the 6-month period prior to the index date.

- Antiphospholipid syndrome (D68.6, I82.9): As diagnosis of antiphospholipid syndrome is usually made after VTE diagnosis with subsequent diagnostic procedures, its presence will be evaulated within the 6-month period after the index date.
- Asthma (J45)
- Cancer (C00-C97): History of cancer (non-active) will be evaluated within a lifetime prior to the index date.
- Chronic obstructive pulmonary disease (COPD; J40-J44)
- Chronic kidney disease (N18, N19)
- Chronic liver disease (B18, B19, K70-K77)
- Diabetes mellitus (E10-E14)
- Fracture (S22, S32, S42, S52, S62, S72, S82, S92, T10, T12)
- Heart failure (I50)
- Hyperlipidemia (E78)
- Hypertension (I10-I15)
- Ischemic heart disease (I24, I25)
- Myocardial infarction (I21)
- Stroke (I60-I64, I69, G45)
- Trauma (T79, T98, V01–V99, W11–W17, W50–W52, W64, X34–X39, Y01–Y04, Y30–Y32)

- Previous use of medications (WHO-ATC code) will be measured within the 6-month period prior to the index date.
  - Corticosteroids (H02)
  - Nonsteroidal anti-inflammatory drugs (NSAIDs; M01A)
  - Angiotensin-converting enzyme (ACE) inhibitors (C09A, C09B)
  - Angiotensin II receptor blockers (ARBs; C09C, C09D)

- Antiplatelet agents (aspirin [N02BA01], aspirin/dipyridamole [B01AC30], abciximab [B01AC13], beraprost [B01AC19], cilostazol [B01AC23], clopidogrel [B01AC04], iloprost [B01AC11], indobufen [B01AC10], limaprost [C04AX], ozagrel [R03DX], prasugrel [B01AC22], sarpogrelate [B01AC], ticagrelor [B01AC24], ticlopidine [B01AC05], tirofiban [B01AC17], Treprostinil [B01AC21], triflusal [B01AC18])
- Azole antifungal agents (fluconazole [J02AC01], itraconazole [J02AC02], voriconazole [J02AC03], posaconazole [J02AC04])
- β-blockers (C07)
- Calcium-channel blockers (C08)
- Selective serotonin reuptake inhibitors (SSRIs; N06AB)
- Proton pump inhibitors (PPIs; A02BC)
- Diuretics (C03)
- Thiazides (C03A)
- Vasodilators (C01D, C04A)
- Estrogens (G03C)
- Cyclooxygenase (COX)-2 inhibitors (M01AH)

- Number of outpatient visits within the 6-month period prior to the index date.

9.4. Data sources

We will use the nationwide HIRA database of South Korea between 1 Mar 2012 and 31 Dec 2019 to identify all variables (exposure, outcome, covariates) needed to conduct this study. The HIRA database includes healthcare utilization information of residents of South Korea, with patient identifiers anonymized. Information on age, sex, diagnosis (ICD-10 diagnostic code, date of diagnosis, setting of diagnosis [inpatient, outpatient, emergency department], and others), medications dispensed/prescribed (national drug chemical code based on the active ingredient, date of prescription, days' supply, dose, route of administration, and others). Previous validation study that compared diagnosis codes recorded in the HIRA to those of recorded in electronic medical records found an overall positive predictive value (PPV) of 82.3%.

9.5. Study size

Phase I of the study (descriptive)

Not applicable as there are no specified *a priori* hypotheses

Phase II of the study (comparative)

- The estimated number of incident patients with VTE and no history of active cancer from the 2018 HIRA-National Patient Sample (HIRA-NPS) database is 1,465, where the HIRA-NPS database is a 3% random sample of the entire Korean population of 50 million. Based on this estimation, the projected number of patients with VTE from the entire Korean population (HIRA database) of 2018 is 48,828 (1,465 * 33.33).

    - Excluding period for patients with previous OAC treatment,VTE history or a history of active cancer was set to prior 3 months because HIRA NPS database used in sample size estimation was constituted of one-year data only.

1) Apixaban vs. warfarin

- Among the above-mentioned number of incident patients with VTE and no history of active cancer, those who newly initiated apixaban or warfarin was estimated to be 211 patients (14.4%; 211/1,465), where patients had no prescription for OACs and no history of VTE within the 3-month period prior to VTE diagnosis. From these 211 patients, there were 83 (39.3%) apixaban users and 128 (60.7%) warfarin users (based on 2018 HIRA-NPS data). Hence, the projected number of patients with VTE who newly initiated OACs to be present in the HIRA database in a single year is 7,032 patients (apixaban 2,766; warfarin 4,266). As this study aims to utilize data from 2013 to 2019 (7 years), the final projected number of patients with VTE who newly initiated apixaban or warfarin from the HIRA database is 49,224 patients (apixaban 19,362; warfarin 29,862).

- Considering a 95% for a two-sided CI level (α-error=0.05) and 80% power, the sample size for the comparative safety study for major bleeding events was calculated based on the following components:

    - HR for major bleeding events from previous literature: 0.31-0.75

    - Overall probability of major bleeding events from previous literature: 1.19%

    - Proportion of apixaban users among patients with VTE from the 2018 HIRA-NPS database: 39.3% (83 apixaban users; 128 warfarin users).

    - 2,013 patients with VTE treated with apixaban or warfarin are required to detect at 5% α-error, and 80% statistical power, and HR of 0.31 by sample size calculations for survival analysis; alternatively (more conservative estimate),

33,340 patients with VTE treated with apixaban or warfarin are required to detect at 5% α-error, and 80% statistical power, and HR of 0.75 by sample size calculations for survival analysis.

- As this study is expected to include 49,224 patients with VTE, with 19,362 patients treated with apixaban from the nationwide HIRA database, this study will have enough statistical power to test the hypothesis of the association between apixaban use and risk of bleeding events among patients with VTE.

2) Rivaroxaban vs. warfarin

- Among the above-mentioned number of incident patients with VTE and no history of active cancer, those who newly initiated rivaroxaban or warfarin was estimated to be 382 patients (26.1%; 382/1,465), where patients had no prescription for OACs and no history of VTE within the 3-month period prior to VTE diagnosis. From these 382 patients, there were 264 (69.1%) rivaroxaban users and 118 (30.9%) warfarin users (based on 2018 HIRA-NPS data). Hence, the projected number of patients with VTE who newly initiated OACs to be present in the HIRA database in a single year is 12,732 patients (rivaroxaban 8,799; warfarin 3,933). As this study aims to utilize data from 2013 to 2019 (7 years), the final projected number of patients with VTE who newly initiated rivaroxaban or warfarin from the HIRA database is 89,124 patients (rivaroxaban 61,593; warfarin 27,531).

- Considering a 95% for a two-sided CI level (α-error=0.05) and 80% power, the sample size for the comparative safety study for major bleeding events was calculated based on the following components:

  - HR for major bleeding events from previous literature: 0.77-1.19

  - Overall probability of major bleeding events from previous literature: 8.1%

  - Proportion of rivaroxaban users among patients with VTE from the 2018 HIRA-NPS database: 69.1% (264 rivaroxaban users; 118 warfarin users).

  - 6,630 patients with VTE treated with rivaroxaban or warfarin are required to detect at 5% α-error, and 80% statistical power, and HR of 0.77 by sample size calculations for survival analysis; alternatively (more conservative estimate), 14,967 patients with VTE treated with rivaroxaban or warfarin are required to detect at 5% α-error, and 80% statistical power, and HR of 1.19 by sample size calculations for survival analysis.

  - As this study is expected to include 89,124 patients with VTE, with 61,593 patients treated with rivaroxaban from the nationwide HIRA database, this study will have enough statistical power to test the hypothesis of the association between rivaroxaban use and risk of bleeding events among patients with VTE.

3) Edoxaban vs. warfarin

- Among the above-mentioned number of incident patients with VTE and no history of active cancer, those who newly initiated edoxaban or warfarin was estimated to be 184 patients (12.6%; 184/1,465), where patients had no prescription for OACs and no history of VTE within the 3-month period prior to VTE diagnosis. From these 184 patients, there were 57 (31.0%) edoxaban users and 127 (69.0%) warfarin users (based on 2018 HIRA-NPS data). Hence, the projected number of patients with VTE who newly initiated OACs to be present in the HIRA database in a single year is 6,132 patients (edoxaban 1,900; warfarin 4,232). As this study aims to utilize data from 2013 to 2019 (7 years), the final projected number of patients with VTE who newly initiated edoxaban or warfarin from the HIRA database is 42,924 patients (edoxaban 13,300; warfarin 29,624).

- Considering a 95% for a two-sided CI level (α-error=0.05) and 80% power, the sample size for the comparative safety study for major bleeding events was calculated based on the following components:

  - HR for major bleeding events from previous literature: 0.56-0.81
  - Overall probability of major bleeding events from previous literature: 8.5%
  - Proportion of edoxaban users among patients with VTE from the 2018 HIRA-NPS database: 31.0% (57 edoxaban users; 127 warfarin users).
  - 1,282 patients with VTE treated with edoxaban or warfarin are required to detect at 5% α-error, and 80% statistical power, and HR of 0.56 by sample size calculations for survival analysis; alternatively (more conservative estimate), 9,703 patients with VTE treated with edoxaban or warfarin are required to detect at 5% α-error, and 80% statistical power, and HR of 0.81 by sample size calculations for survival analysis.
  - As this study is expected to include 42,924 patients with VTE, with 13,300 patients treated with edoxaban from the nationwide HIRA database, this study will have enough statistical power to test the hypothesis of the association between edoxaban use and risk of bleeding events among patients with VTE.

4) Dabigatran vs. warfarin

- Among the above-mentioned number of incident patients with VTE and no history of active cancer, those who newly initiated dabigatran or warfarin was estimated to be 155 patients (10.6%; 155/1,465), where patients had no prescription for OACs and no history of VTE within the 3-month period prior to VTE diagnosis. From these 155 patients, there were 26 (16.8%) dabigatran users and 129 (83.2%) warfarin users (based on 2018 HIRA-NPS data). Hence, the projected number of patients with VTE

who newly initiated OACs to be present in the HIRA database in a single year is 5,166 patients (dabigatran 866; warfarin 4,299). As this study aims to utilize data from 2013 to 2019 (7 years), the final projected number of patients with VTE who newly initiated dabigatran or warfarin from the HIRA database is 36,162 patients (dabigatran 6,062; warfarin 30,093).

- Considering a 95% for a two-sided CI level (α-error=0.05) and 80% power, the sample size for the comparative safety study for major bleeding events was calculated based on the following components:

  - HR for major bleeding events from previous literature: 0.52-0.69
  - Overall probability of major bleeding events from previous literature: 1.4%
  - Proportion of dabigatran users among patients with VTE from the 2018 HIRA-NPS database: 16.8% (26 dabigatran users; 129 warfarin users).
  - 9,361 patients with VTE treated with dabigatran or warfarin are required to detect at 5% α-error, and 80% statistical power, and HR of 0.52 by sample size calculations for survival analysis; alternatively (more conservative estimate), 29,071 patients with VTE treated with edoxaban or warfarin are required to detect at 5% α-error, and 80% statistical power, and HR of 0.69 by sample size calculations for survival analysis.
  - As this study is expected to include 36,162 patients with VTE, with 6,062 patients treated with dabigatran from the nationwide HIRA database, this study will have enough statistical power to test the hypothesis of the association between dabigatran use and risk of bleeding events among patients with VTE.

9.6. Data management

Data management (data programming and analysis) will be conducted on secure servers with regular backup provided by HIRA. All statistical analyses will be performed using SAS Enterprise Guide 7.1 (SAS Institute Inc., Cary, NC, USA), provided by HIRA through a virtual access machine.

9.7. Data analysis

Phase I of the study (descriptive)

Main Analysis

- Descriptive analysis will be conducted separately in two cohorts of non-cancer VTE and cancer VTE patients according to co-presence of active cancer.

- Sociodemographic and clinical characteristics will be summarized with means (standard deviations [STD]) or median (interquartile range [IQR]) for continuous variables and with count (proportions) for categorical variables for the three treatment groups of interest: PAC only (UFH, LMWH, UFH+LMWH), warfarin-based (warfarin, PAC/warfarin) group, NOAC-based (NOAC, PAC/NOAC) group. Analysis of variance, and chi-square test will be conducted for continuous variables, and categorical variables, respectively.

    - In order to distinguish between PAC bridging therapy and PAC treatment, we will apply a time restriction of 2 weeks to PAC bridging therapy.

- Temporal trend in anticoagulation therapy for VTE will be presented between 1 Mar 2013 and 30 Jun 2019. Proportions of the index OACs will be estimated according to calendar year and quarter.

- The number and percentage of patients who discontinue treatment completely, experience treatment interruption and treatment switch during their follow-up will be described by the index anticoagulant treatment received. Results will be limited to the first of each of these events for each patient. For patients experiencing a treatment switch, the new treatment will be described at the time of their first switcher per individual drug.

- The duration of the index treatment by the index anticoagulant treatment received will also be summarized in terms of days using descriptive statistics (mean [STD], median [IQR]).

- The Kaplan-Meier method will be applied to derive the empirical distribution of time to each of the treatment endpoints of interest (e.g., treatment discontinuation or switch); these analyses will be performed per index anticoagulant treatment received and no comparisons will be made. Log-rank test will be conducted at the 3-, and 6 months after treatment initiation to assess statistical significance between the survival curves among three treatment groups of interest. Persistent rate will also be calculated at the same time point.

- In the NOAC-based group, all analyses will be repeated stratified by each individual NOAC class (e.g, apixaban, dabigatran, rivaroxaban, edoxaban) to identify the difference in baseline characteristics and treatment patterns between each NOAC class.

- To identify potential reasons for treatment change, clinical events preceding the first treatment change (major bleeding, thromboembolism diagnosis, complications of VTE, major surgery, active cancer, a new diagnosis of CKD or AKI, a new diagnosis

of liver disease or abnormal liver function) will be measured within 30 days prior to the first date of treatment change. Patients can contribute with multiple events.

- All analyses of treatment patterns will be presented stratified according to the index anticoagulant treatment, and not overall or per drug class.

Phase II of the study (comparative)

Propensity score analysis

- To balance and adjust for any potential differences in baseline sociodemographic and clinical characteristics between treatment groups, propensity score (PS) methods will be implemented.

    - A logistic regression model will be used to estimate the predicted probability (propensity) of initiating each NOAC compared with warfarin given baseline covariates mentioned above. By using the estimated PS, we will apply the PS based on the inverse probability of treatment weights (IPTW), where the treatment group of interest will be given a weight of 1/PS, and the comparator group will be given a weight of 1/(1-PS) [25, 26]. The most extreme 1% of PS values (IPTW with trimming) will be excluded to improve comparability between exposure groups.

Main Analysis

- Sociodemographic and clinical characteristics will be summarized with means (STD) or median (IQR) for continuous variables and with count (proportions) for categorical variables for the two treatment comparisons of: apixaban vs warfarin, rivaroxaban vs warfarin, edoxaban vs. warfarin and dabigatran vs. warfarin (and NOAC vs. NOAC, if scientifically feasible).

    - Differences in baseline covariates between users of different OACs will be assessed using the SD where the absolute SD <0.1 will be considered as well balanced.

- The incidence rate of major bleeding overall and by site will be presented as the total number of events per 1,000 person-years, with its 95% CIs estimated using the Poisson distribution.

- The risk of major bleeding according to the treatment of interest will be investigated in time-to-event analyses using standard Kaplan-Meier methods.

- Cox proportional hazards model will be used to compare the safety outcome between users of different OACs, weighted on the estimated PS according to the IPTW approach.

- Proportionality assumption will be tested by use of Schoenfeld residuals.

Subgroup Analysis

- The potential heterogeneity of treatment effects in selected subgroups of patients with VTE will be examined for the major bleeding as follows:
  - Aged <65 years vs. aged ≥65 years
  - Females vs. males
  - Setting of VTE diagnosis (inpatient vs. outpatient)
  - Type of VTE (DVT without PE vs. PE with or without DVT)
  - Major orthopedic surgery-provoked VTE
    - Major orthopedic surgery-provoked VTE is defined as an event preceded by knee arthroplasty, hip arthroplasty, or hip fracture surgery (National Procedure Codes: N0305, N0601, N0611, N0641, N0711, N2070, N0715, N2710, N0731, N0981, N0991, N1711, N3710, N1721, N3720, N1715,N4710, N1725, N4720, N2072, N2077, N2712, N2717, N3712, N3717, N3722, N3727, N4712, N4717, N4722 or N4727) within 3 months period prior to index date
  - With vs. without CKD stage 3 or 4 (N18.3, N18.4)
- P-for-interaction value <0.05 will be used to denote a significant difference between the two groups.

Sensitivity Analysis

- Vary the definition of treatment interruption/discontinuation to 15 and 60 days (allowing for varying non-adherence) to assess the effect this had on study outcomes.
- Four other approaches involving PS will be applied to determine the robustness of our study findings. First, we will vary the extreme value of PS in trimming process (most extreme 5%, and 10% will be excluded). Second, we will include the estimated PS, in addition to other covariates, into our multivariable Cox proportional hazards regression model. Third, we will stratify on the estimated PS in deciles. Lastly, we will apply another weighting approach, standardized mortality ratio weights, with the weights given as follows: 1 for the treatment group of interest and PS/(1 − PS) for the comparator group.[25]

- Exclude patients with a history of bleeding during the 6-month pre-index-date period in Phase II comparative analysis to evaluate the robustness of findings with respect to changes in underlying risk of patients

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a statistical analysis plan (SAP), which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

9.8. Quality control

All data will be checked for completeness and outlying values by research group with requisite background and experiences in pharmacoepidemiology. We will archive all data files and data management and statistical programs for quality control.

9.9. Limitations of the research methods

Information bias

- Outcome misclassification is possible as the records of diagnoses reported in the HIRA database may be different from their actual diagnoses recorded in the hospital's electronic medical records.

- To minimize any bias arising from exposure misclassification, analyses will be repeated by using a 15 and 60-day grace period definition for non-overlapping successive prescriptions.

Selection bias

- By using the nationwide HIRA database that encompasses the entire Korean population of 50 million, this study is unlikely to miss out any patients with VTE in South Korea.

Confounding bias

- Owing to the nature of observational studies, residual confounding from unmeasured or unaccounted confounders may be present.

- Nevertheless, to minimize confounding bias, we will apply various PS approaches, with the IPTW approach applied as our main analysis.

External validity of study design

- Our study results will achieve generalizability by using the nationwide HIRA database.

Analysis limitations

- Potential incompleteness of information on potential confounders such as laboratory data are unavailable for assessment due to inherent limitations of the HIRA database as its primary purpose is for administrative means.

- Sensitivity analysis using the E-value will be conducted to quantify the impact of residual confounding from unmeasured or unaccounted confounders on the risk estimates for the association between apixaban use and risk of VTE recurrence and bleeding events.

Limitations due to missing and/or incomplete data

- HIRA data are released for research only after thorough internal review, this would not be applicable to HIRA data.

9.10. Other aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient information

This study involves data that exist in anonymized structured format and contain no patient personal information.

10.2. Patient consent

As this study involves anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

10.3. Institutional review board (IRB)/Independent ethics committee (IEC)

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (e.g., informed consent forms if applicable) from the relevant IRBs/IECs. All correspondence with the IRB/IEC must be retained. Copies of IRB/IEC approvals must be forwarded to Pfizer.

We will obtain a customized HIRA database between 1 Mar 2012 and 31 Dec 2019. This study was approved by the Sungkyunkwan University's Institutional Review Board (SKKU-IRB-2020-12-010), which waived the requirement for informed consent.

10.4. Ethical conduct of the study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences (CIOMS) and the European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involved data that exist as structured data by the time of study start.

In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (e.g., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (e.g., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

Results of this study will be submitted for publication in an academic journal within one year after the end of the study. The target academic journals with their impact factors (as of 2019) are as below:

- European Heart Journal-Cardiovascular Pharmacotherapy (Impact Factor: 6.696)

- BMC Medicine (Impact Factor: 6.782)
- JAMA Network Open (Impact Factor: 5.032)
- Journal of Thrombosis and Haemostasis (Impact Factor: 4.157)
- Frontiers in Cardiovascular Medicine (Impact Factor: 3.915)

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14. LIST OF TABLES

15. LIST OF FIGURES

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

ANNEX 2. ADDITIONAL INFORMATION

Not applicable.