NON-INTERVENTIONAL (NI) STUDY STATISTICAL ANALYSIS PLAN

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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1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACE	Angiotensin-converting enzyme
AE	Adverse Event
AIDS	Acquired immunodeficiency syndrome
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
HIV	Human immunodeficiency virus
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. AMENDMENTS AND UPDATES

Amendment number	Date	Statistical Analysis Plan section(s) changed	Summary of amendment(s)	Reason
Amendment 1 (V.2.0)	27Apr2022	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
		6. Research question and objectives	Added secondary objective of Phase I	Revised according to additional analysis in Phase I
		8.1 Study design	Updated Figure 1 and Figure 2	Amendment following Protocol Administrative Change Letter in Oct 22, 2021
		8.4 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	
		10. Statistical analysis	Added data analysis for secondary objective of Phase I	Revised according to additional analysis in Phase I
		12. List of tables	Revised Tables 1, 2, 5, and 6, and added Tables 3, 4, 7, 8, 11, and 12	
		13. List of figures	Added Figure 4	

5. INTRODUCTION

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 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 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.

6. 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 (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

7. 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%.

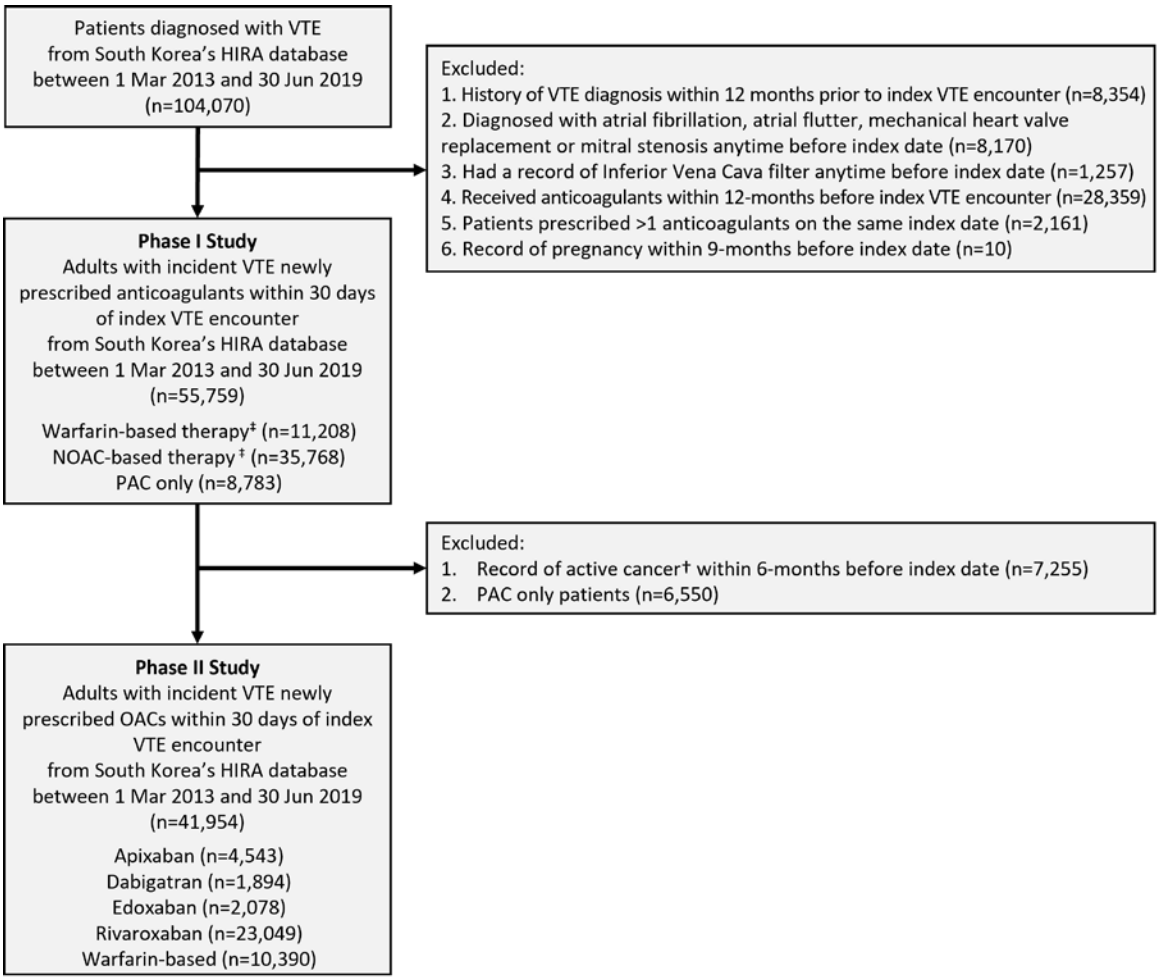
7.1. Data management

Data management (data programming and analysis) will be conducted on secure servers with regular backup provided by HIRA.

8. RESEARCH METHODS

8.1. 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).



Note: HIRA, Health Insurance and Review Assessment service; LMWH, low molecular weight heparin; NOAC, non-vitamin K antagonist; PAC, parenteral anticoagulants; VTE, venous thromboembolism; W, warfarin
†Record of active cancer is defined as first diagnosis of cancer with V code within the past 6 monts 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

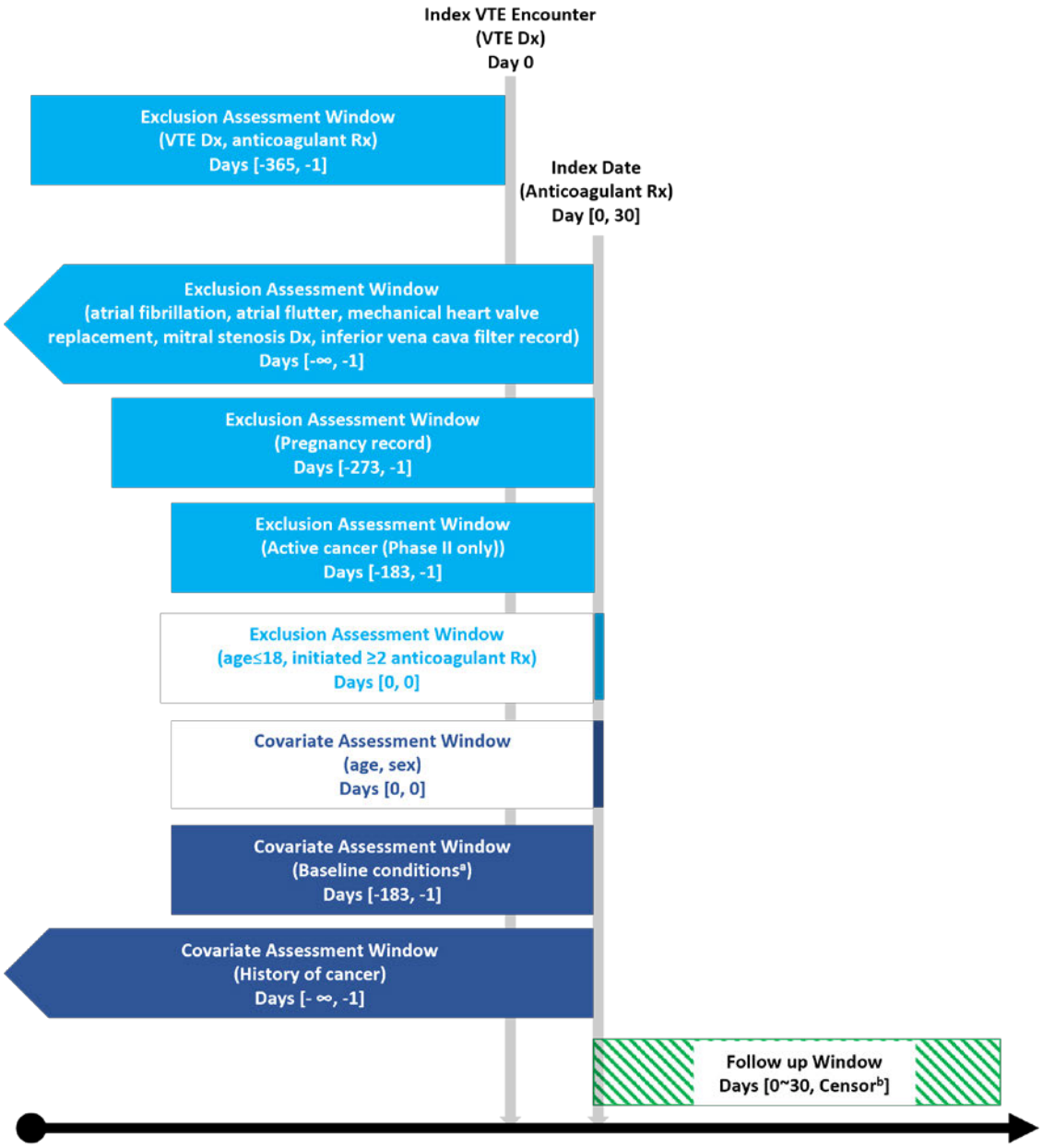
Figure 1. Study participants inclusion and exclusion criteria

8.2. Study population

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 specified in section 8.4 *Variables* (Figure 2).

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.



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
Figure 2. Overall study schematic

8.3. Setting

8.3.1. 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; 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)

3. Aged ≥18 years at index date

8.3.2. 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 monts 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 below table.

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)

8.4. 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.[1] 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 initated 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.[1]

- 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 Phase II)

  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

Clinical event preceding first treatment change	ICD-10 diagnosis code
Major bleeding	Defined in Phase II
Complications of VTE	
Post-thrombotic syndrome	I87.0
Chronic thromboembolic pulmonary hypertension	I27.2
Thromboembolism	
PE diagnosis	I26.0, I26.9
Aterial thromboembolism	I74
Ischemic stroke	I63
Transient ischemic attack	G45.9
Myocardial infarction	I21
Angina pectoris	I20
Major surgery	
Orthopedic surgeries	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, N4727
Cancer surgeries	Specified in 'cancer-related surgery' of section 8.3.2
Benign surgeries	R4123-R4129, R4421, R4430, R3975
Cancer-related event (active cancer)	C00-C97 (excluding non-melanoma skin cancer, C44) with V code (V011, V027, V193, V194)
Kidney function change	
Chronic kidney disease	N18, N19
Acute kidney injury	N17
Liver function change	
Liver disease	B15-B19, K70-K77
Abnormal liver function	R94.5, R74.0

- **Phase II of the study**

  - Major bleeding will be defined using primary or secondary diagnosis codes according to the ICD-10 dagnostic codes shown in below table and classified by site (intracranial, gastrointestinal [GI], all others).

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 [2] and HAS-BLED [3] scores will be measured within the 6-month period prior to the index date.

List of CCI	**Score**	**ICD-10 codes**
Cerebrovascular disease	1	G45, G46, H34, I60-I69
Congestive heart faiure	1	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5-I42.9, I43, I50, P29.0
Chronic pulmonary disease	1	I27.8, I27.9, J40–J47, J60–J67, J68.4, J70.1, J70.3

Dementia	1	F00–F03, F05.1, G30, G31.1
Diabetes without chronic complication	1	E10.0, E10.1, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9
Mild liver disease	1	B18, K70.0-K70.3, K70.9, K71.3-K71.5, K71.7, K73, K74, K76.0, K76.2-K76.4, K76.8, K76.9, Z94.4
Myocardial infarction	1	I21, I22, I25.2
Peipheral vascular disease	1	I70, I71, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9
Peptic ulcer diease	1	K25-K28
Rheumatologic disease	1	M05, M06, M32–M34, M31.5, M35.1, M35.3, M36.0
Diabetes with chronic complication	2	E10.2–E10.5, E10.7, E11.2–E11.5, E11.7, E12.2-E12.5, E12.7, E13.2–E13.5, E13.7, E14.2–E14.5, E14.7
Hemiplegia or paraplegia	2	G04.1, G11.4, G80.1, G80.2, G81, G82, G83.0-G83.4, G83.9
Any malignancy, including leukemia and lymphoma	2	C00–C26, C30–C34, C37–C41, C43, C45–C58, C60–C76, C81–C85, C88, C90–C97
Renal disease	2	I12.0, I13.1, N03.2-N03.7, N05.2-N05.7, N18, N19, N25.0, Z49.0-Z49.2, Z94.0, Z99.2
Moderate or severe liver disease	3	I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7
AIDS/HIV	6	B20–B22, B24
Metastatic solid tumor	6	C77-C80

List of HAS-BLED	**Score**	**ICD-10 codes**

Hypertension	1	I10-I15
Abnormal renal function	1	N18.3, N18.4, N18.5, N19, Z94.0, Z99.2
Abnormal liver function	1	B15-B19, C22, D68.4, I98.2, I98.3, K70-K77, Z94.4
Stroke	1	I63, I69.3, G45.9
Bleeding history	1	Intracranial and GI: I60, I61, I62, I69.0, I69.1, I69.2, S06.4, S06.5, S06.6, S06.8, I85.0, I98.3, K22.11, K22.6, K22.8, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.0, K31.81, K55.21, K62.5, K92.0, K92.1, K92.2 Other sites*: D62, H44.8, H35.72, H35.6, H31.3, H21.0, H11.3, H05.2, H47.0, H43.1, I31.2, N02.0-N02.9, N42.1, N83.1, N85.7, N92.0, N92.3, N93.0, N93.8, N93.9, M25.0, R23.3, R04.0, R04.1, R04.2, R04.8, R04.9, T79.2, T81.0, N95.0, R31.0, R31.1, R31.8, R58, T45.5, Y44.2, D68.3
Labile INR	1	Not applicable
Elderly > 65 years	1	
Drugs or alcohol concomitantly	1	Antiplatelet agents, NSAIDs
	1	Alcoholism: E24.4, F10, G31.2, G62.1, G72.1, I42.6, K29.2, K70, K86.0, O35.4, R78.0, T51.0, X45, X65, Y15, Y90, Y91, Z71.4, Z72.1

*Blood transfusion (Korean Procedure Codes: X1001, X1002, X2011, X2012, X2021, X2022, X2031, X2032, X2041, X2042, X2051, X2052, X2061, X2062, X2071, X2072, X2081, X2082, X2091, X2092, X2101, X2102, X2111, X2112, X2121, X2122, X2131, X2132, X2141, X2142, X3010) will also be used to define other site bleeding history.

- 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. 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.

10. STATISTICAL ANALYSIS

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.

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. NOAC-based (NOAC, only group, 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. 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) [4, 5]. 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 [ICD-10: I80.2, I80.3] vs. PE with or without DVT [I26.0, I26.9])
    - 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. Last, 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.[4]

- 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

10.1. 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.

11. REFERENCES

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12. LIST OF TABLES

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

Characteristics	**Warfarin-based therapy N= (%)**	**NOAC-based therapy N= (%)**	**PAC only N= (%)**	**p-value**
Follow-up (days; median, IQR)				
Age (years; mean±std)				
Age group (years; n, %)				
18-40				
40-65				
≥65				
Sex (n, %)				
Male				
Female				
Index VTE event (n, %)				
DVT only				
PE with or without DVT				
Major orthopedic surgery-provoked VTE (n, %)				
Health insurance type (n, %)				
National health insurance				
Medical aid				
Veterans				
Index year (n, %)				
2013				
2014				
2015				
2016				
2017				
2018				
2019				
CCI score (mean±std)				
HAS-BLED score (mean±std)				
Comorbidities (n, %)				
Antiphospholipid syndrome				
Asthma				
History of cancer				
COPD				
Chronic kidney disease				
Chronic liver disease				
Diabetes mellitus				
Fracture				
Heart failure				
Hyperlipidemia				

Hypertension	
Ischemic heart disease	
Myocardial infarction	
Stroke	
Trauma	
Previous use of medications (n, %)	
Corticosteroids	
NSAIDs	
ACE inhibitors	
Angiotensin II receptor blockers	
Antiplatelets	
β-blockers	
Calcium-channel blockers	
SSRI	
Proton pump inhibitors	
Diuretics	
Thiazides	
Vasodilators	
Estrogens	
Cyclooxygenase-2 inhibitors	
Triazole antifungal agents	
Outpatient visits (mean±std)	

Note: ACE, angiotensin-converting enzyme; CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; NOAC, non-vitamin K antagonist oral anticoagulant; NSAIDs, nonsteroidal anti-inflammatory drugs; PAC, parenteral anticoagulants; SSRI, selective serotonin reuptake inhibitors; std, standard deviation.

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

Characteristics	Warfarin-based therapy N= (%)	NOAC-based therapy N= (%)	PAC only N= (%)	p-value
Follow-up (days; median, IQR)				
Age (years; mean±std)				
Age group (years; n, %)				
18-40				
40-65				
≥65				
Sex (n, %)				
Male				
Female				
Index VTE event (n, %)				
DVT only				
PE with or without DVT				
Health insurance type (n, %)				
National health insurance				
Medical aid				
Veterans				
Index year (n, %)				
2013				
2014				
2015				
2016				
2017				
2018				
2019				
CCI score (mean±std)				
HAS-BLED score (mean±std)				
Comorbidities (n, %)				
Antiphospholipid syndrome				
Asthma				
History of cancer				
COPD				
Chronic kidney disease				
Chronic liver disease				
Diabetes mellitus				
Fracture				
Heart failure				
Hyperlipidemia				
Hypertension				
Ischemic heart disease				

Myocardial infarction	
Stroke	
Trauma	
Previous use of medications (n, %)	
Corticosteroids	
NSAIDs	
ACE inhibitors	
Angiotensin II receptor blockers	
Antiplatelets	
β-blockers	
Calcium-channel blockers	
SSRI	
Proton pump inhibitors	
Diuretics	
Thiazides	
Vasodilators	
Estrogens	
Cyclooxygenase-2 inhibitors	
Triazole antifungal agents	
Outpatient visits (mean±std)	

Note: ACE, angiotensin-converting enzyme; CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; NOAC, non-vitamin K antagonist oral anticoagulant; NSAIDs, nonsteroidal anti-inflammatory drugs; PAC, parenteral anticoagulants; SSRI, selective serotonin reuptake inhibitors; std, standard deviation.

Table 3. Baseline characteristics among venous thromboembolism patients without active cancer by their index non-vitamin K oral antagonist oral anticoagulant treatment

Characteristics	Apixaban N= (%)	Dabigatran N= (%)	Edoxaban N= (%)	Rivaroxaban N= (%)	p-value
Follow-up (days; median, IQR)					
Age (years; mean±std)					
Age group (years; n, %)					
18-40					
40-65					
≥65					
Sex (n, %)					
Male					
Female					
Index VTE event (n, %)					
DVT only					
PE with or without DVT					
Health insurance type (n, %)					
National health insurance					
Medical aid					
Veterans					
Index year (n, %)					
2013					
2014					
2015					
2016					
2017					
2018					
2019					
CCI score (mean±std)					
HAS-BLED score (mean±std)					
Comorbidities (n, %)					
Antiphospholipid syndrome					
Asthma					
History of cancer					
COPD					
Chronic kidney disease					
Chronic liver disease					
Diabetes mellitus					

Fracture					
Heart failure					
Hyperlipidemia					
Hypertension					
Ischemic heart disease					
Myocardial infarction					
Stroke					
Trauma					
Previous use of medications (n, %)					
Corticosteroids					
NSAIDs					
ACE inhibitors					
Angiotensin II receptor blockers					
Antiplatelets					
β-blockers					
Calcium-channel blockers					
SSRI					
Proton pump inhibitors					
Diuretics					
Thiazides					
Vasodilators					
Estrogens					
Cyclooxygenase-2 inhibitors					
Triazole antifungal agents					
Outpatient visits (mean±std)					

Table 4. Baseline characteristics among venous thromboembolism patients with active cancer by their index non-vitamin K antagonist oral anticoagulant treatment

Characteristics	**Apixaban**	**Dabigatran**	**Edoxaban**	**Rivaroxaban**	**p-value**
	N= (%)	**N= (%)**	**N= (%)**	**N= (%)**	
Follow-up (days; median, IQR)					
Age (years; mean±std)					
Age group (years; n, %)					
18-40					
40-65					
≥65					
Sex (n, %)					

- Male
- Female

Index VTE event (n, %)
- DVT only
- PE with or without DVT

Health insurance type (n, %)
- National health insurance
- Medical aid
- Veterans

Index year (n, %)
- 2013
- 2014
- 2015
- 2016
- 2017
- 2018
- 2019

CCI score (mean±std)

HAS-BLED score (mean±std)

Comorbidities (n, %)
- Antiphospholipid syndrome
- Asthma
- History of cancer
- COPD
- Chronic kidney disease
- Chronic liver disease
- Diabetes mellitus
- Fracture
- Heart failure
- Hyperlipidemia
- Hypertension
- Ischemic heart disease
- Myocardial infarction
- Stroke
- Trauma

Previous use of medications (n, %)
- Corticosteroids
- NSAIDs
- ACE inhibitors
- Angiotensin II receptor blockers

Antiplatelets	
β-blockers	
Calcium-channel blockers	
SSRI	
Proton pump inhibitors	
Diuretics	
Thiazides	
Vasodilators	
Estrogens	
Cyclooxygenase-2 inhibitors	
Triazole antifungal agents	
Outpatient visits (mean±std)	

Table 5. Treatment pattern of anticoagulant therapy among venous thromboembolism patients without active cancer for the treatment groups of interest

	Warfarin-based therapy N= (%)	**NOAC-based therapy N= (%)**	**PAC only N= (%)**
Overall treatment duration (days)			
Mean, std			
Median, IQR			
3-month persistence (%)			
6-month persistence (%)			
Treatment switching (n,%)			
Mean, std			
Median, IQR			
Treatment continuation (n,%)			
Mean, std			
Median, IQR			
Treatment discontinuation (n,%)			
Mean, std			
Median, IQR			
Treatment interruption (n,%)			
Mean, std			
Median, IQR			
Death (n,%)			
Mean, std			
Median, IQR			

Note: PAC, parenteral anticoagulants; NOAC, non-vitamin K antagonist oral anticoagulant; IQR, Interquartile range; std, standard deviation

Table 6. Treatment pattern of anticoagulant therapy among venous thromboembolism patients with active cancer for the treatment groups of interest

	Warfarin-based therapy N= (%)	**NOAC-based therapy N= (%)**	**PAC only N= (%)**
Overall treatment duration (days)			
Mean, std			
Median, IQR			
3-month persistence (%)			
6-month persistence (%)			
Treatment switching (n,%)			
Mean, std			
Median, IQR			
Treatment continuation (n,%)			
Mean, std			
Median, IQR			
Treatment discontinuation (n,%)			
Mean, std			
Median, IQR			
Treatment interruption (n,%)			
Mean, std			
Median, IQR			
Death (n,%)			
Mean, std			
Median, IQR			

Note: PAC, parenteral anticoagulants; NOAC, non-vitamin K antagonist oral anticoagulant; IQR, Interquartile range; std, standard deviation

Table 7. Treatment pattern of non-vitamin K antagonist therapy among venous thromboembolism patients without active cancer for the treatment groups of interest

	Apixaban N= (%)	**Dabigatran N= (%)**	**Edoxaban N= (%)**	**Rivaroxaban N= (%)**
Overall treatment duration (days)				
Mean, std				
Median, IQR				
3-month persistence (%)				
6-month persistence (%)				
Treatment switching (n,%)				
Mean, std				
Median, IQR				
Treatment continuation (n,%)				
Mean, std				
Median, IQR				
Treatment discontinuation (n,%)				
Mean, std				
Median, IQR				
Treatment interruption (n,%)				
Mean, std				
Median, IQR				
Death (n,%)				
Mean, std				
Median, IQR				

Note: IQR, Interquartile range; std, standard deviation

Table 8. Treatment pattern of non-vitamin K antagonist therapy among venous thromboembolism patients with active cancer for the treatment groups of interest

	Apixaban N= (%)	**Dabigatran N= (%)**	**Edoxaban N= (%)**	**Rivaroxaban N= (%)**
Overall treatment duration (days)				
Mean, std				
Median, IQR				
3-month persistence (%)				
6-month persistence (%)				
Treatment switching (n,%)				
Mean, std				
Median, IQR				
Treatment continuation (n,%)				
Mean, std				
Median, IQR				
Treatment discontinuation (n,%)				
Mean, std				
Median, IQR				
Treatment interruption (n,%)				
Mean, std				
Median, IQR				
Death (n,%)				
Mean, std				
Median, IQR				

Note: IQR, Interquartile range; std, standard deviation

Table 9. Treatment switch of anticoagulant therapy among venous thromboembolism patients without active cancer for the treatment groups of interest

Index drug		Switched to	Warfarin-based therapy	NOAC-based therapy	PAC only
Warfarin-based therapy (N=)	Patients	n (%)	–		
	Time to swtich	Mean, std			
		Median, IQR			
NOAC-based therapy (N=)	Patients	n (%)		–	
	Time to swtich	Mean, std			
		Median, IQR			
PAC only (N=)	Patients	n (%)			–
	Time to swtich	Mean, std			
		Median, IQR			

Note: PAC, parenteral anticoagulants; NOAC, non-vitamin K antagonist oral anticoagulant; IQR, Interquartile range; std, standard deviation

Table 10. Treatment switch of anticoagulant therapy among venous thromboembolism patients with active cancer for the treatment groups of interest

Index drug		Switched to	Warfarin-based therapy	NOAC-based therapy	PAC only
Warfarin-based therapy (N=)	Patients	n (%)	–		
	Time to swtich	Mean, std			
		Median, IQR			
NOAC-based therapy (N=)	Patients	n (%)		–	
	Time to swtich	Mean, std			
		Median, IQR			
PAC only (N=)	Patients	n (%)			–
	Time to swtich	Mean, std			
		Median, IQR			

Note: PAC, parenteral anticoagulants; NOAC, non-vitamin K antagonist oral anticoagulant; IQR, Interquartile range; std, standard deviation

Table 11. Treatment switch of overall anticoagulant therapy among venous thromboembolism patients without active cancer for the treatment groups of interest

Index drug		Switched to	Warfarin-based therapy	Apixaban	Dabigatran	Edoxaban	Rivaroxaban	PAC only
Warfarin-based therapy (N=)	Patients	n (%)	–					
	Time to swtich	Mean, std						
		Median, IQR						
Apixaban (N=)	Patients	n (%)		–				
	Time to swtich	Mean, std						
		Median, IQR						
Dabigatran	Patients	n (%)			-			
	Time to swtich	Mean, std						
		Median, IQR						
Edoxaban	Patients	n (%)				-		
	Time to swtich	Mean, std						
		Median, IQR						
Rivaroxaban	Patients	n (%)					-	
	Time to swtich	Mean, std						
		Median, IQR						
PAC only (N=)	Patients	n (%)						–
	Time to swtich	Mean, std						
		Median, IQR						

Note: PAC, parenteral anticoagulants; IQR, Interquartile range; std, standard deviation

Table 12. Treatment switch of overall anticoagulant therapy among venous thromboembolism patients with active cancer for the treatment groups of interest

Index drug		Switched to	Warfarin-based therapy	Apixaban	Dabigatran	Edoxaban	Rivaroxaban	PAC only
Warfarin-based therapy (N=)	Patients	n (%)	–					
	Time to swtich	Mean, std						
		Median, IQR						
Apixaban (N=)	Patients	n (%)		–				
	Time to swtich	Mean, std						
		Median, IQR						
Dabigatran	Patients	n (%)			-			
	Time to swtich	Mean, std						
		Median, IQR						
Edoxaban	Patients	n (%)				-		
	Time to swtich	Mean, std						
		Median, IQR						
Rivaroxaban	Patients	n (%)					-	
	Time to swtich	Mean, std						
		Median, IQR						
PAC only (N=)	Patients	n (%)						–
	Time to swtich	Mean, std						
		Median, IQR						

Note: PAC, parenteral anticoagulants; IQR, Interquartile range; std, standard deviation

Table 13. Pre- and post-weighted baseline characteristics of patients with venous thromboembolism who newly initiated apixaban and warfarin.

Characteristics	Pre-weighted			Post-weighted		
	Apixaban N= (%)	Warfarin-based therapy N= (%)	aSD	Apixaban N= (%)	Warfarin-based therapy N= (%)	aSD
Follow-up (days; median, IQR)						
Age (years; mean±std)						
Age group (years; n, %)						
18-40						
40-65						
≥65						
Sex (n, %)						
Male						
Female						
Health insurance type (n, %)						
National health insurance						
Medical aid						
Index year (n, %)						
2012						
2013						
2014						
2015						
2016						
2017						
2018						
2019						
CCI score (mean±std)						
HAS-BLED score (mean±std)						
Comorbidities (n, %)						
Antiphospholipid syndrome						
Asthma						
History of cancer						
COPD						
Chronic kidney disease						
Chronic liver disease						
Diabetes mellitus						
Fracture						

Heart failure	
Hyperlipidemia	
Hypertension	
Ischemic heart disease	
Myocardial infarction	
Stroke	
Trauma	
Previous use of medications (n, %)	
Corticosteroids	
NSAIDs	
ACE inhibitors	
Angiotensin II receptor blockers	
Aspirin	
β-blockers	
Calcium-channel blockers	
SSRI	
Proton pump inhibitors	
Diuretics	
Thiazides	
Vasodilators	
Estrogens	
Cyclooxygenase-2 inhibitors	
Outpatient visits (mean±std)	

Note: ACE, angiotensin-converting enzyme; aSD, absolute standardized difference; CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; NSAIDs, nonsteroidal anti-inflammatory drugs; PAC, parenteral anticoagulants; SSRI, selective serotonin reuptake inhibitors; std, standard deviation

Table 14. Pre- and post-weighted baseline characteristics of patients with venous thromboembolism who newly initiated rivaroxaban and warfarin.

Characteristics	Pre-weighted			Post-weighted		
	Rivaroxaban N= (%)	Warfarin-based therapy N= (%)	aSD	Rivaroxaban N= (%)	Warfarin-based therapy N= (%)	aSD
Follow-up (days; median, IQR)						
Age (years; mean±std)						
Age group (years; n, %)						
18-40						
40-65						
≥65						
Sex (n, %)						
Male						
Female						
Health insurance type (n, %)						
National health insurance						
Medical aid						
Index year (n, %)						
2012						
2013						
2014						
2015						
2016						
2017						
2018						
2019						
CCI score (mean±std)						
HAS-BLED score (mean±std)						
Comorbidities (n, %)						
Antiphospholipid syndrome						
Asthma						
History of cancer						
COPD						
Chronic kidney						

disease	
Chronic liver disease	
Diabetes mellitus	
Fracture	
Heart failure	
Hyperlipidemia	
Hypertension	
Ischemic heart disease	
Myocardial infarction	
Stroke	
Trauma	
Previous use of medications (n, %)	
Corticosteroids	
NSAIDs	
ACE inhibitors	
Angiotensin II receptor blockers	
Aspirin	
β-blockers	
Calcium-channel blockers	
SSRI	
Proton pump inhibitors	
Diuretics	
Thiazides	
Vasodilators	
Estrogens	
Cyclooxygenase-2 inhibitors	
Outpatient visits (mean±std)	

Note: ACE, angiotensin-converting enzyme; aSD, absolute standardized difference; CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; NSAIDs, nonsteroidal anti-inflammatory drugs; PAC, parenteral anticoagulants; SSRI, selective serotonin reuptake inhibitors; std, standard deviation

Table 15. Pre- and post-weighted baseline characteristics of patients with venous thromboembolism who newly initiated edoxaban and warfarin.

Characteristics	Pre-weighted			Post-weighted		
	Edoxaban N= (%)	Warfarin-based therapy N= (%)	aSD	Edoxaban N= (%)	Warfarin-based therapy N= (%)	aSD
Follow-up (days; median, IQR)						
Age (years; mean±std)						
Age group (years; n, %)						
18-40						
40-65						
≥65						
Sex (n, %)						
Male						
Female						
Health insurance type (n, %)						
National health insurance						
Medical aid						
Index year (n, %)						
2012						
2013						
2014						
2015						
2016						
2017						
2018						
2019						
CCI score (mean±std)						
HAS-BLED score (mean±std)						
Comorbidities (n, %)						
Antiphospholipid syndrome						
Asthma						
History of cancer						
COPD						
Chronic kidney disease						
Chronic liver disease						
Diabetes mellitus						
Fracture						

Heart failure	
Hyperlipidemia	
Hypertension	
Ischemic heart disease	
Myocardial infarction	
Stroke	
Trauma	
Previous use of medications (n, %)	
Corticosteroids	
NSAIDs	
ACE inhibitors	
Angiotensin II receptor blockers	
Aspirin	
β-blockers	
Calcium-channel blockers	
SSRI	
Proton pump inhibitors	
Diuretics	
Thiazides	
Vasodilators	
Estrogens	
Cyclooxygenase-2 inhibitors	
Outpatient visits (mean±std)	

Note: ACE, angiotensin-converting enzyme; aSD, absolute standardized difference; CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; NSAIDs, nonsteroidal anti-inflammatory drugs; PAC, parenteral anticoagulants; SSRI, selective serotonin reuptake inhibitors; std, standard deviation

Table 16. Pre- and post-weighted baseline characteristics of patients with venous thromboembolism who newly initiated dabigatran and warfarin.

Characteristics	Pre-weighted			Post-weighted		
	Dabigatran N= (%)	Warfarin-based therapy N= (%)	aSD	Dabigatran N= (%)	Warfarin-based therapy N= (%)	aSD
Follow-up (days; median, IQR)						
Age (years; mean±std)						
Age group (years; n, %)						
18-40						
40-65						
≥65						
Sex (n, %)						
Male						
Female						
Health insurance type (n, %)						
National health insurance						
Medical aid						
Index year (n, %)						
2012						
2013						
2014						
2015						
2016						
2017						
2018						
2019						
CCI score (mean±std)						
HAS-BLED score (mean±std)						
Comorbidities (n, %)						
Antiphospholipid syndrome						
Asthma						
History of cancer						
COPD						
Chronic kidney disease						
Chronic liver disease						
Diabetes mellitus						

Fracture	
Heart failure	
Hyperlipidemia	
Hypertension	
Ischemic heart disease	
Myocardial infarction	
Stroke	
Trauma	
Previous use of medications (n, %)	
Corticosteroids	
NSAIDs	
ACE inhibitors	
Angiotensin II receptor blockers	
Aspirin	
β-blockers	
Calcium-channel blockers	
SSRI	
Proton pump inhibitors	
Diuretics	
Thiazides	
Vasodilators	
Estrogens	
Cyclooxygenase-2 inhibitors	
Outpatient visits (mean±std)	

Note: ACE, angiotensin-converting enzyme; aSD, absolute standardized difference; CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; NSAIDs, nonsteroidal anti-inflammatory drugs; PAC, parenteral anticoagulants; SSRI, selective serotonin reuptake inhibitors; std, standard deviation

Table 17. Risk of major bleeding events in patients with venous thromboembolism who newly initiated oral anticoagulants associated with NOAC use versus warfarin

	No of Patients	No of Events	Person-years	Incidence rate* (95% CI)	Crude HR (95% CI)	IPT-Weighted HR (95% CI)
Warfarin-based					Reference (1.00)	
Apixaban						
Rivaroxaban						
Edoxaban						
Dabigatran						

Note: CI, confidence interval; HR, hazard ratio; IPT, inverse probability of treatment.
*Events per 1000 person years.

Table 18. Risk of major bleeding events by site, intracranial, gastrointestinal, all others, associated with NOAC use versus warfarin

	No of Patients	No of Events	Person-years	Incidence rate* (95% CI)	Crude HR (95% CI)	IPT-Weighted HR (95% CI)
Intracranial bleeding						
Warfarin-based					Reference (1.00)	
Apixaban						
Rivaroxaban						
Edoxaban						
Dabigatran						
Gastrointestinal bleeding						
Warfarin-based					Reference (1.00)	
Apixaban						
Rivaroxaban						
Edoxaban						
Dabigatran						
All other sites						
Warfarin-based					Reference (1.00)	
Apixaban						
Rivaroxaban						
Edoxaban						
Dabigatran						

Note: CI, confidence interval; HR, hazard ratio; IPT, inverse probability of treatment.
*Events per 1000 person years.

Table 19. Subgroup analyses for the risk of major bleeding events associated with NOAC use versus warfarin

	No. of Patients	No. of Events	IPT-Weighted HR (95% CI)	$P_{interaction}$*
Age				
<65 years				
Warfarin-based			Reference (1.00)	
Apixaban				
Rivaroxaban				
Edoxaban				
Dabigatran				
≥65 years				
Warfarin-based			Reference (1.00)	
Apixaban				
Rivaroxaban				
Edoxaban				
Dabigatran				
Sex				
Female				
Warfarin-based			Reference (1.00)	
Apixaban				
Rivaroxaban				
Edoxaban				
Dabigatran				
Male				
Warfarin-based			Reference (1.00)	
Apixaban				
Rivaroxaban				
Edoxaban				
Dabigatran				
VTE diagnosis setting				
Inpatient				
Warfarin-based			Reference (1.00)	
Apixaban				
Rivaroxaban				
Edoxaban				
Dabigatran				
Outpatient				
Warfarin-based			Reference (1.00)	
Apixaban				
Rivaroxaban				
Edoxaban				
Dabigatran				
Type of VTE				
DVT without PE				
Warfarin-based			Reference (1.00)	

Apixaban	
Rivaroxaban	
Edoxaban	
Dabigatran	
PE with or without DVT	
Warfarin-based	Reference (1.00)
Apixaban	
Rivaroxaban	
Edoxaban	
Dabigatran	
VTE etiology	
Major orthopedic surgery-provoked VTE	
Warfarin-based	Reference (1.00)
Apixaban	
Rivaroxaban	
Edoxaban	
Dabigatran	
Chronic kidney disease	
With CKD stage 3 or 4	
Warfarin-based	Reference (1.00)
Apixaban	
Rivaroxaban	
Edoxaban	
Dabigatran	
Without CKD stage 3 or 4	
Warfarin-based	Reference (1.00)
Apixaban	
Rivaroxaban	
Edoxaban	
Dabigatran	

Note: CI, confidence interval; DVT, deep vein thrombosis; HR, hazard ratio; IPT, inverse probability of treatment; PE, pulmonaryembolism; VTE, venous thromboembolism
*P for interaction will be calculated between warfarin-based therapy and each NOAC.

Table 20. Sensitivity analyses for the risk of major bleeding events associated with NOAC use versus warfarin

	No. of Patients	No. of Events	Hazard ratio (95% CI)
Treatment continuation grace period definition			
30 days (main analysis)			
Warfarin-based			Reference (1.00)
Apixaban			
Rivaroxaban			
Edoxaban			
Dabigatran			
15 days			
Warfarin-based			Reference (1.00)
Apixaban			
Rivaroxaban			
Edoxaban			
Dabigatran			
60 days			
Warfarin-based			Reference (1.00)
Apixaban			
Rivaroxaban			
Edoxaban			
Dabigatran			
Alternative approaches involving propensity scores			
IPT-weighted approach (main analysis)			
Warfarin-based			Reference (1.00)
Apixaban			
Rivaroxaban			
Edoxaban			
Dabigatran			
Varying the extreme value of PS in trimming process (extreme 5%)			
Warfarin-based			Reference (1.00)
Apixaban			
Rivaroxaban			
Edoxaban			
Dabigatran			
Varying the extreme value of PS in trimming process (extreme 10%)			
Warfarin-based			Reference (1.00)
Apixaban			
Rivaroxaban			
Edoxaban			
Dabigatran			
Adjusted as a covariate in the outcome model			
Warfarin-based			Reference (1.00)
Apixaban			
Rivaroxaban			

Edoxaban	
Dabigatran	
Stratifed on propensity scores in deciles	
Warfarin-based	Reference (1.00)
Apixaban	
Rivaroxaban	
Edoxaban	
Dabigatran	
Standardized mortality ratio-weighted approach	
Warfarin-based	Reference (1.00)
Apixaban	
Rivaroxaban	
Edoxaban	
Dabigatran	
Excluding patients with a history of bleeding during the 6-month pre-index date	
Warfarin-based	Reference (1.00)
Apixaban	
Rivaroxaban	
Edoxaban	
Dabigatran	

Note: CI, confidence interval; DVT, deep vein thrombosis; HR, hazard ratio; IPT, inverse probability of treatment; PE, pulmonaryembolism; VTE, venous thromboembolism

13. LIST OF FIGURES

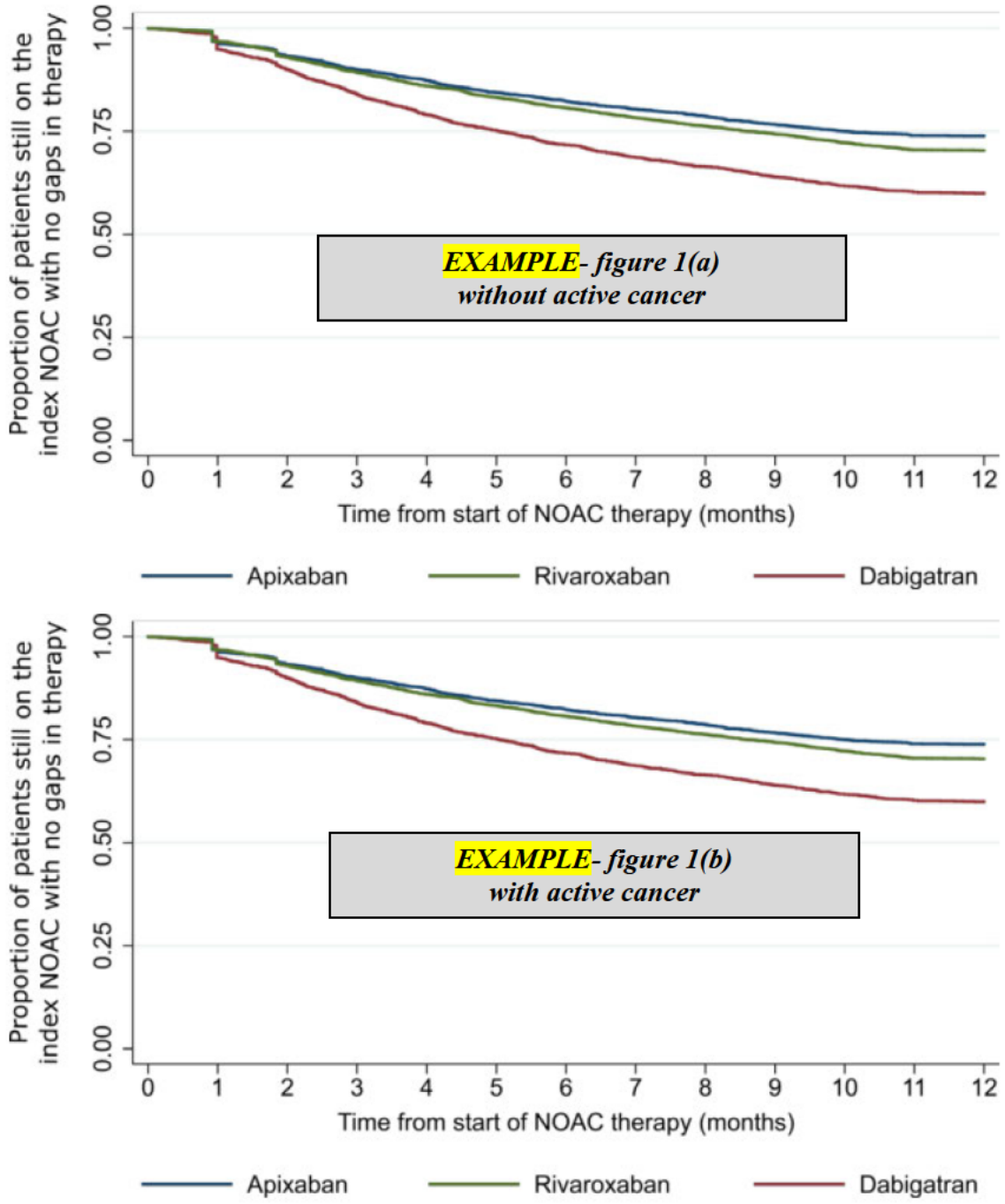

Figure 1. Kaplan-Meier plot showing time to anticoagulant therapy interruption in patients with venous thromboembolism according to presence of active cancer.

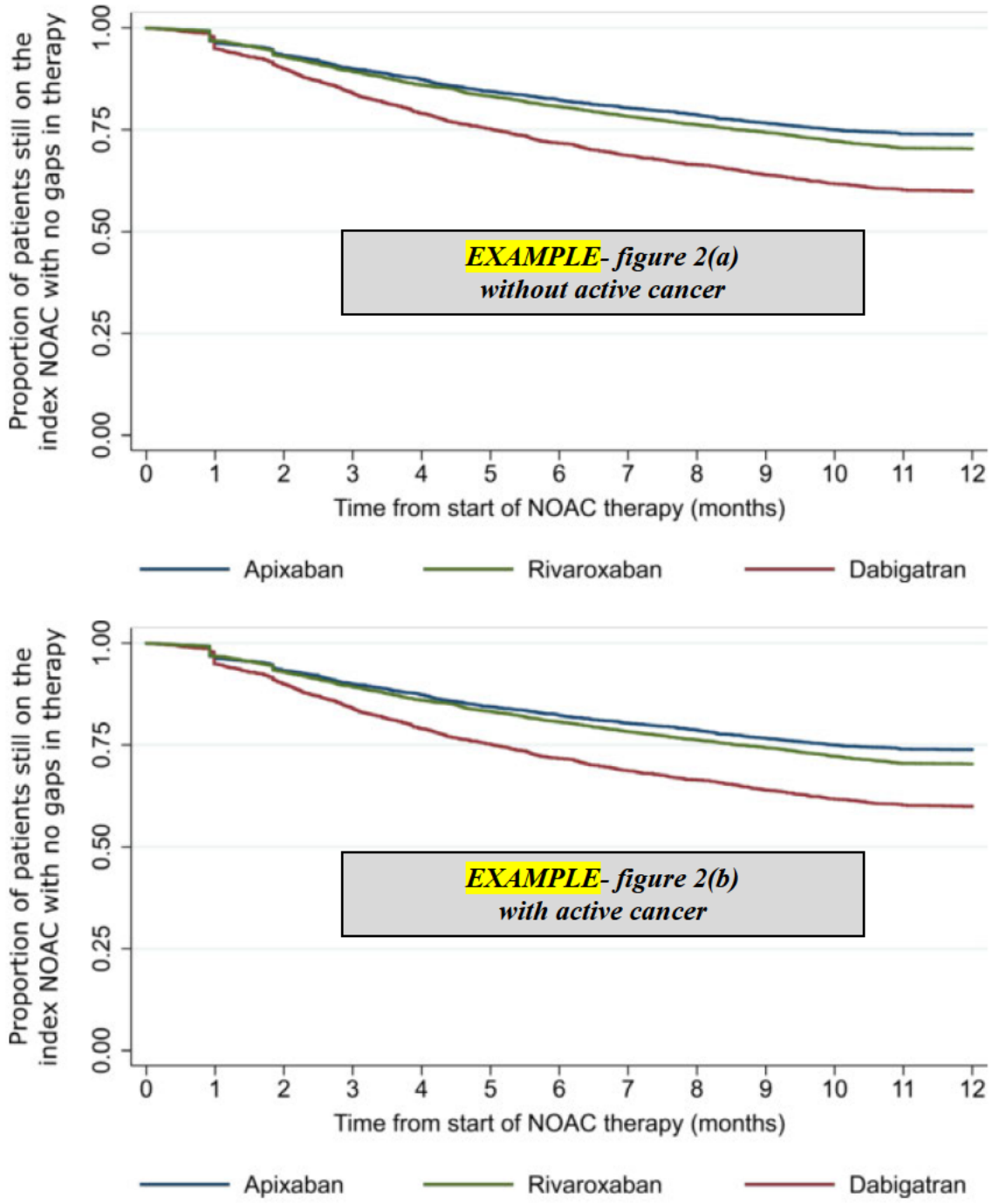

Figure 2. Kaplan-Meier plot showing time to anticoagulant therapy switching in patients with venous thromboembolism according to presence of active cancer.

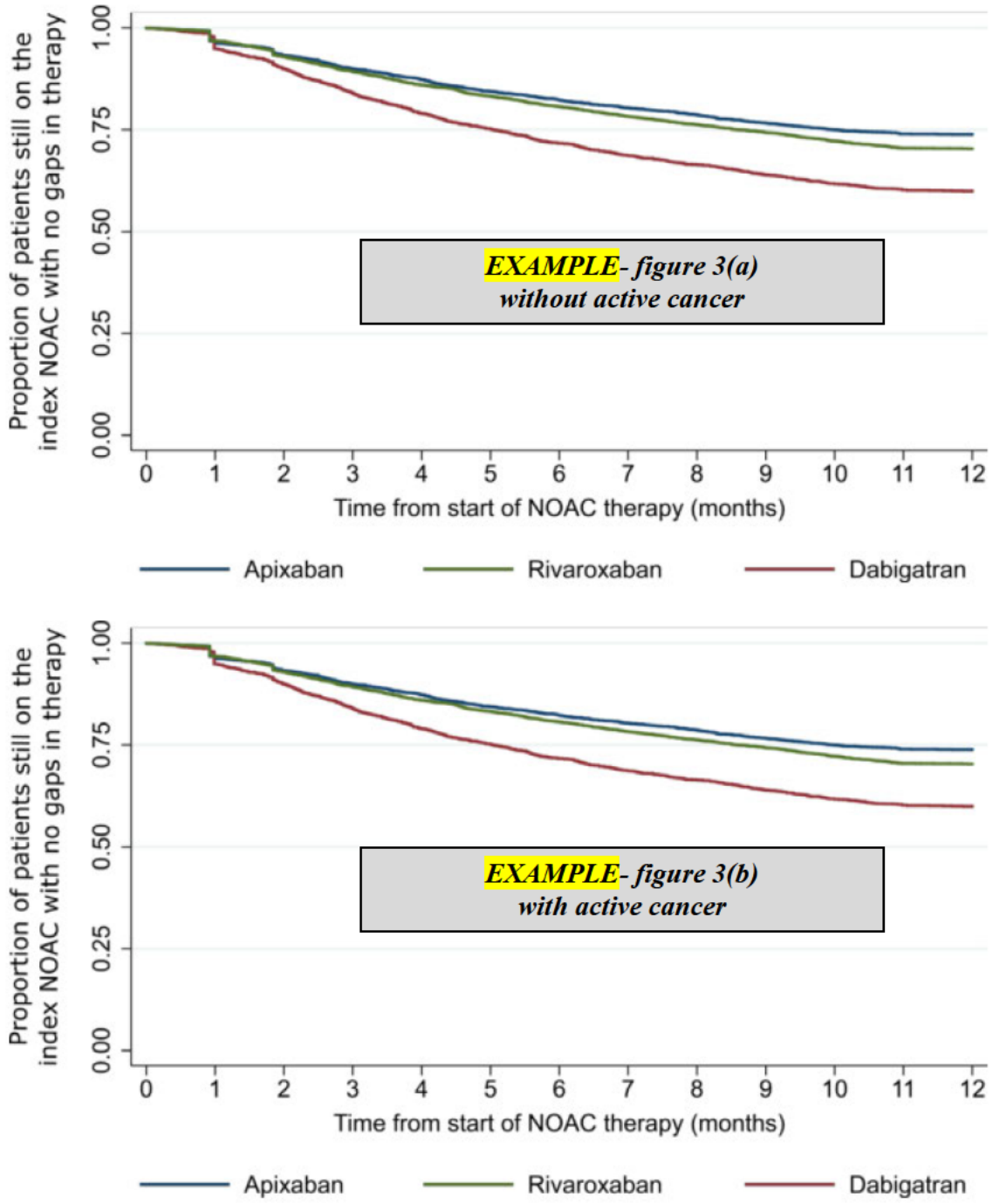

Figure 3. Kaplan-Meier plot showing time to anticoagulant therapy discontinuation in patients with venous thromboembolism according to presence of active cancer.

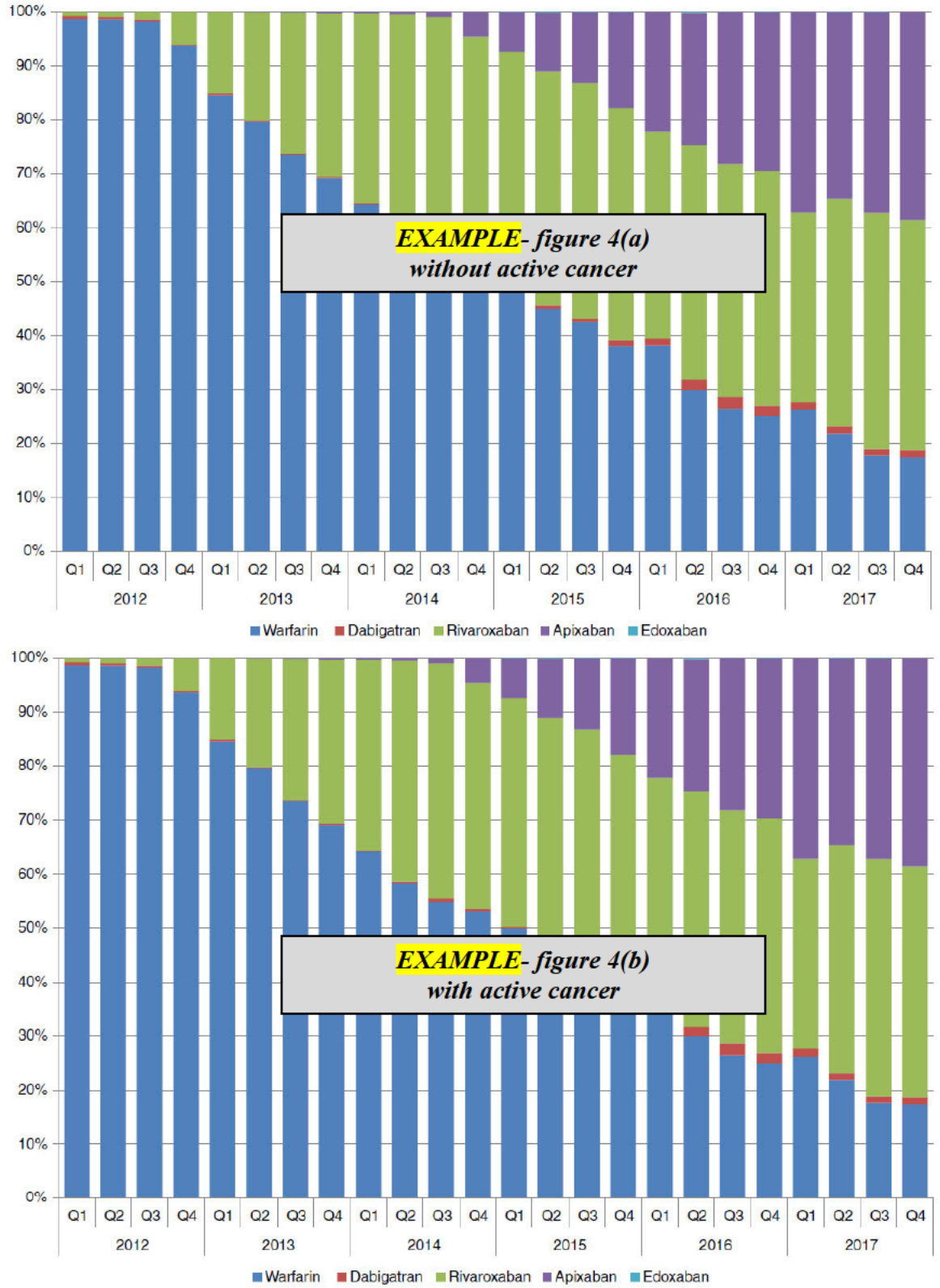

Figure 4. Trends in newly prescribed anticoagulants in patients with venous thromboembolism between Mar 2013 and Jun 2019.

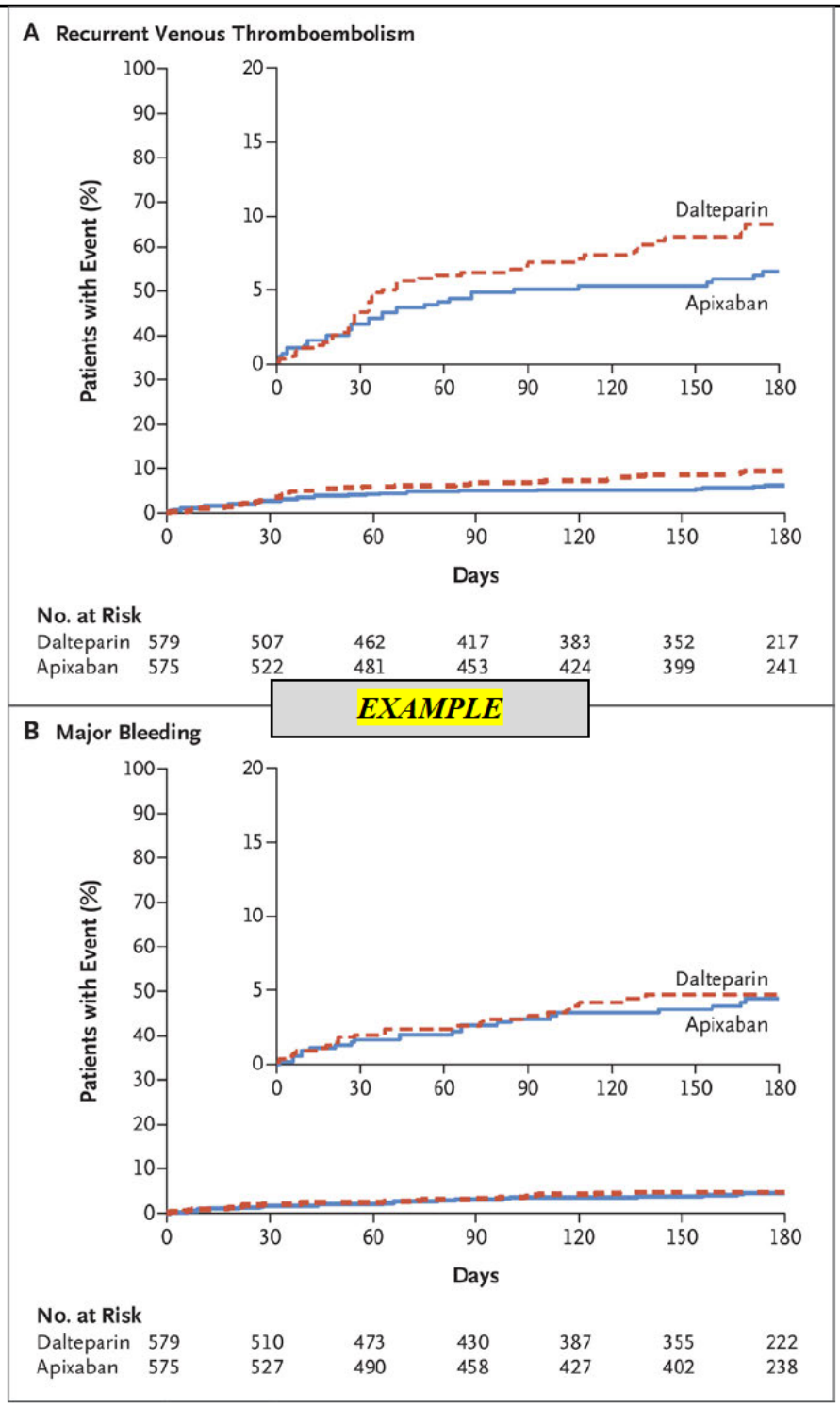

Figure 5. Cumulative incidence curves for the risk of major bleeding events associated with NOAC use versus warfarin

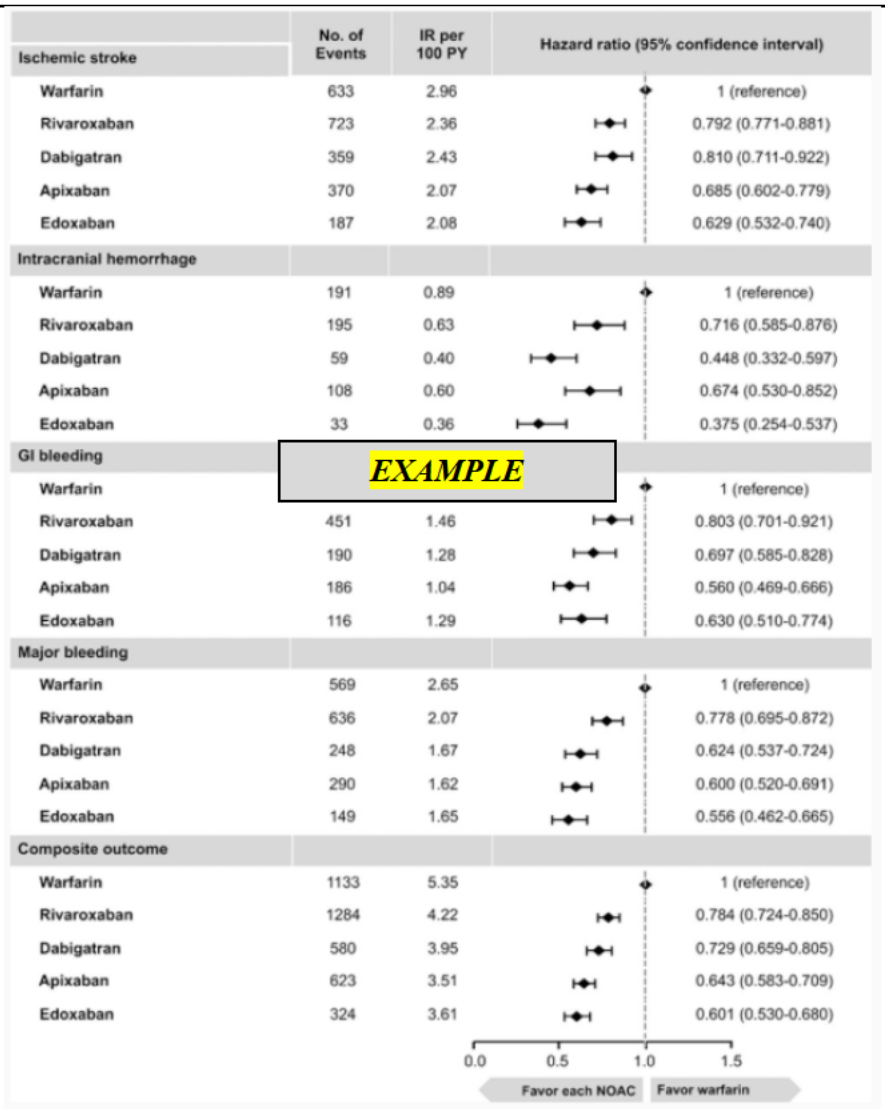

Figure 6. Number of weighted events, incidence rate, and hazard ratio of major bleeding events associated with NOAC use versus warfarin.

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

ANNEX 2. ADDITIONAL INFORMATION

Not applicable.