STATISTICAL ANALYSIS PLAN (SAP) TEMPLATE

FOR NON-INTERVENTIONAL STUDIES

[redacted]

Non-Interventional Study Protocol
<X9001134>

The real world evidence on treatment patterns, effectiveness, and safety of drugs for stroke prevention in nonvalvular atrial fibrillation patients in Korea

Statistical Analysis Plan
(SAP)

Version: 3.0

Author: PPD MPharm, MA, PhD PPD Korea)

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[redacted]

1 AMENDMENTS FROM PREVIOUS VERSION(S)

Amendment number	Date	Substantial or administrative amendment	SAP section(s) changed	Summary of amendment(s)	Reason
Amendment 01 (V2.0)	31Jan2018	Substantial amendment	2.1 STUDY DESIGN	Add "Comparative analyses will be performed contingent on a feasibility assessment based on the descriptive analyses." Clarify the reference period for AF diagnosis	Meet to Harmonized SAP
		Substantial amendment	2.2 STUDY OBJECTIVES	Change phrases aligned with protocol	According to protocol amendment
		Substantial amendment	3 ANALYSIS SETS/ POPULATIONS	Change Inclusion & Exclusion criteria	According to protocol amendment
		Substantial amendment	4.1 EFFICACY/ EFFECTIVENESS ENDPOINT(S)	Add 'Hemorrhagic stroke' in operational definition	Meet to Harmonized SAP
		Substantial amendment	4.2 SAFETY ENDPOINTS	Change to 'Major bleeding' Delete the 'Clinically relevant non-major bleeding'	Meet to Harmonized SAP
		Substantial amendment	5.1 STATISTICAL METHODS	Add Balance diagnostics & IPTW diagnostics	Specify the analysis method for propensity score
Amendment 02 (V3.0)	23Apr2018	Substantial amendment	2.Study design	Add 'other NOACs, new use of warfarin, and aspirin' Delete ' aspirin-clopidogrel combination, and clopidogrel'	More detailed description of the objectives
		Substantial amendment	2.2 study objectives	Delete ''to explore baseline characteristics and drug utilization patterns of antithrombotic therapies in special patients grougs (i.e., coronary intervention patients)	This secondary objective will have a separate protocol (in agreement with global HEOR team guidance)
		Administrative amendment	3.1 diagnosis codes for inclusion criteria	Add ' [NOTE] KCD code is based on ICD-10 and almost similar, but KCD code is slightly different from ICD-10 (e.g., ICD-10 is more subdivided and extensive than KCD code	More details on the difference between ICD-10 and KCD codes provided
		Administrative amendment	3. 1 Exclusion criteria	Delete ' hip or knee replacement' in medical claims indicating a diagnosis code of others during the 12-month baseline period	Conflicts with the exclusion criteria #1;duplicate
		Administrative amendment	3. 1 Exclusion criteria	Revise #6 as 'for the comparison of "NOAC versus NOAC", and "NOAC versus warfarin, patients with any OACs (apixaban, dabigatran, rivaroxaban, or warfarin)	More clear statements for NOAC vs NOAC and NOAC vs VKA comparison

Amendment number	Date	Substantial or administrative amendment	SAP section(s) changed	Summary of amendment(s)	Reason
				in the pre-index period	
		Substantial amendment	3.1 Exclusion criteria	Revise #7 as 'for the comparison of "NOAC versus aspirin", patients with following medications in the pre-index period (from 1 year prior to the day before index date)	More clear statements for NOAC vs aspirin
		Administrative amendment	3.1 Cohorts	Add statements on dataset for NOAC vs NOAC, NOAC vs warfarin, NOAC vs aspirin	Details provided for each comparison cohorts
		Administrative amendment	3.1 Cohorts	Delete ' [Note] clopidogrel, aspirin, clopidogrel will be included in descriptive analysis'	Deleted the statement for relocation
		Administrative amendment	3.2 Subgroups	Revise as 'subgroup analysis may be considered, including but not limited to subgroup analyses by…'	More broad statements to cover various topics for sub-analyses
		Substantial amendment	4.1 Efficacy/effectiveness endpoints	Revise to include hospitalization and CT/MRI imaging for all outcomes, more explanation on how the events were measured Add 'individual outcome of primary outcome' Deleted myocardial infarction	Corrected errors
		Substantial amendment	4.2 Safety endpoints	Add statement regarding main subdiagnosis codes being used Add ' hospitalization and brain CT/MRI to identify ICH' Add individual outcome of major bleeding, clinical events preceding each pattern, compliance	More clear statements added
		Administrative amendment	5.1 Descriptive analysis	Add ' the proportion of antithrombotics at index date will be examined'	More details on the treatment pattern provided
		Administrative amendment	5.1 Multivariate analysis	Specific comparison cohorts for analysis Add statements on covariate adjustment propensity score Delete references used under IPTW diagnostics Add statements for each comparison cohorts	More clear statements included
			5.1 Statistical methods	Additional sensitivity analysis	Perform IPTW using the propensity score derived from multinomial model
		Substantial amendment	5.2 Statistical analyses	Add ' other propensity score method will also be used'	More clear statements included

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Amendment number	Date	Substantial or administrative amendment	SAP section(s) changed	Summary of amendment(s)	Reason
		Administrative amendment	6.Summary of analyses	Delete 'myocardial infarction'	Removed for accuracy
		Administrative amendment	8. Appendix	Add statements regarding bleeding outcomes and procedures codes	More details provided
		Substantial amendment	Appendix 2. Data derivation details	Revise codes for effectiveness and safety outcomes codes	Input codes according to changes in the outcome endpoints
		Substantial amendment	Table 13. Exclusion criteria	Add codes for each conditions	More details provided
		Substantial amendment	Table 14. Blood transfusion codes	Add codes for Korean procedure codes used	More details provided

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2 INTRODUCTION

Atrial fibrillation (AF) is the most common persistent arrhythmia, and its prevalence has been estimated to be 1-2% of the general population, with a progressive increase (1). AF increases the risk of ischemic stroke by five-fold and is associated with 15% of stroke for all age groups and 30% in patients aged 80 years and older (2). Patients with AF-related ischemic stroke have higher recurrent risk, morbidity, and mortality as compared to patients with other types of stroke (3). Thus, current clinical guidelines for AF emphasize stroke prevention in patients with AF, in the presence of stroke risk factors (4). Effective stroke prevention essentially requires oral anticoagulants (OAC) therapy. Vitamin K antagonists (i.e., warfarin) effectively decrease the risk for thromboembolic events in patients with AF (5). However, vitamin K antagonists have several limitations, including need for regular blood monitoring and possibility for food or drug interactions. This had led to the quest for new OACs that would be more safe and effective than warfarin (6). In randomized controlled trials, NOACs demonstrated noninferior or superior reduction in stroke and systemic embolism when compared to warfarin (7-10).

Physicians now have a choice between the available NOACs but have relatively little evidence to guide their decision-making because of no head-to-head trials of these drugs. In addition, there have been far fewer studies on efficacy and safety outcomes of NOACs. The nationwide claims database in Korea can provide an opportunity to study comparative effectiveness and safety outcomes of NOACs in patients with atrial fibrillation in Korea.

2.1 STUDY DESIGN

This study will use a retrospective cohort design in which the treatment effectiveness and safety outcomes of new use of NOACs compared to other NOACs, new use of warfarin, and aspirin will be estimated in patients with atrial fibrillation using the Korean Health Insurance Review & Assessment Service (HIRA) database. Comparative analyses will be performed contingent on a feasibility assessment based on the descriptive analyses. Propensity score method and Cox proportional hazards models will be used to account for selection bias, differences in follow-up time, and right data censoring. This will allow us to minimize selection bias and confounding bias and provide outcome data amenable to rapid clinical interpretation (i.e., time-to-event analysis, hazard ratios). Furthermore, HIRA database will allow us to preserve the population-based longitudinal data collection advantages. The overall study design is described in Figure 1.

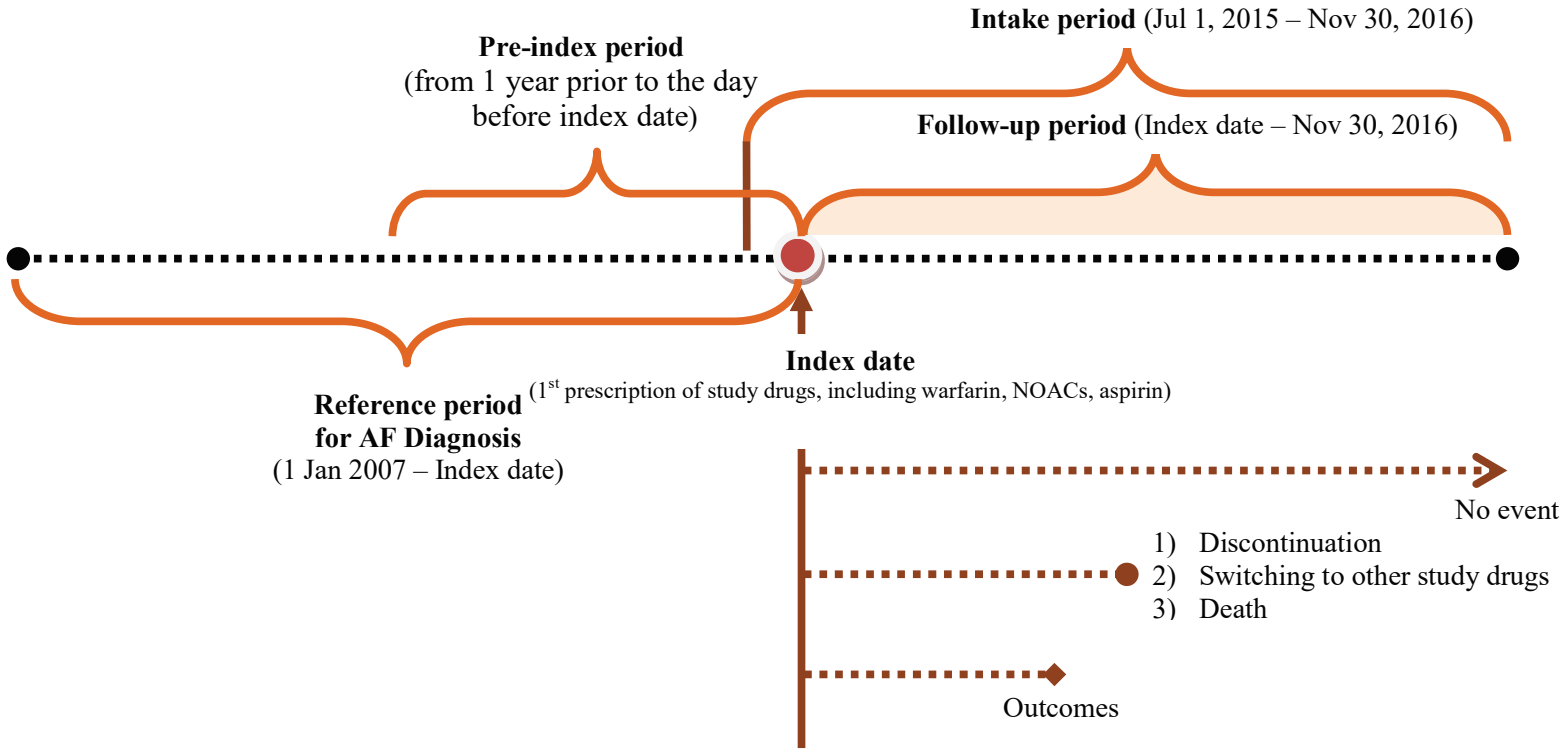

Figure 1. Study design scheme

Study population

Subjects with atrial fibrillation (between January 1, 2007 up to and including the index date*) who newly initiated NOACs, warfarin, or used aspirin between July 1, 2015 and November 30, 2016 in the Korean Health Insurance Review & Assessment Service (HIRA) database.

*Index date is the first prescription date of study drugs, including NOACs, warfarin, and aspirin.

Data source

South Korea has a universal health coverage system that the National Health Insurance covers approximately 97% of the overall South Korean population. The claims data of Health Insurance Review & Assessment Service (HIRA) contains 46 million patients per year that account for 90% of the total population in Korea and include claims from almost 80,000 healthcare service providers across South Korea as of 2011.

The claims data of HIRA includes patients' diagnosis, treatment, procedures, surgical history, and prescription drugs which provide a valuable resource for healthcare service research. Data elements captured in the HIRA database include patient-level demographic and plan enrollment information (e.g., start and stop dates of health plan enrollment), date-stamped (month and year) inpatient and outpatient medical claims (e.g., diagnosis codes, procedure codes, provider specialty), and pharmacy claims (e.g., prescription fill/refill dates, drug name/code, dosage). While procedure codes that identify patient receipt of laboratory tests are available, actual laboratory values and test results are not available.

The HIRA database has unique attributes that make it a useful data source for this study. The key advantage of the HIRA database relative to other potential data sources (e.g., medical chart review) is that it is a population level data including most of Korean population and it will provide a large analytic sample and provide accurate claim-level treatments pattern and health care utilization across all provider settings (e.g., inpatient, outpatient, pharmacy) in patients' spectrum of care.

One key limitation of the HIRA database is that it does not include clinical variables such as laboratory values and clinical markers. To overcome this limitation, the Charlson comorbidity index and overall healthcare utilization observed during the pre-index period will be used as proxy measures to incorporate the overall health status of the individual patients.

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2.2 STUDY OBJECTIVES

Primary objectives

1. To explore baseline characteristics and drug utilization patterns in patients with nonvalvular atrial fibrillation (NVAF) who newly initiated NOACs, warfarin, or used aspirin
    - Demographic and clinical characteristics: Age, sex, types of health insurance, CHA_2DS_2-VASc score, HAS-BLED score, Charlson Comorbidity Index score, etc.
    - Descriptions of index treatment: Types of medication received, index dose intensity
    - Drug utilization pattern: Each patient will be followed-up until the first treatment modification occurs, or study ends (November 30, 2016).
2. To compare effectiveness including hemorrhagic stroke, ischemic stroke and systemic embolism of antithrombotic therapies in patients with NVAF with the following antithrombotic therapies: NOACs, warfarin, and aspirin
    - Primary effectiveness outcome: Composite of hemorrhagic stroke, ischemic stroke, and systemic embolism
    - Secondary effectiveness outcomes: Individual outcome of hemorrhagic stroke, ischemic stroke, and systemic embolism
3. To compare safety of anti-thrombotic therapies in patients with NVAF with the following antithrombotic therapies: NOACs, warfarin, and aspirin
    - Primary safety outcome: Major bleeding including gastrointestinal bleeding or intracranial bleeding and other bleeding
    - Secondary safety outcomes: Individual outcome of major bleeding

[NOTE] comparative analyses will be performed contingent on a feasibility assessment based on the descriptive analyses.

Secondary objectives

1. To explore and understand more detailed drug utilization patterns
    - Standard dose versus reduced dose

- Pattern of usage (i.e., switching, discontinuation) and clinical events preceding the pattern
- Compliance (i.e., medication possession ratio)

2. To compare effectiveness and safety of antithrombotic therapies versus not using therapies among low risk patients (low score of CHA_2DS_2-VASc)

3 ANALYSIS SETS/ POPULATIONS

3.1 FULL ANALYSIS SET

Inclusion criteria

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

1. Patients aged 18 years or older on the index date
2. Patients had ≥1 medical claim for AF (refer to Table 1) before or on the index date with at least one hospitalization or at least two outpatient visits:

[Diagnosis codes for inclusion criteria]

KCD-6[1)]	KCD-7[2)]
I48 (Atrial fibrillation and flutter) I480 (Atrial fibrillation) I481 (Atrial flutter)	I48 (Atrial fibrillation and flutter) I480 (Paroxysmal atrial fibrillation) I481 (Persistent atrial fibrillation) I482 (Chronic atrial fibrillation) I483 (Typical atrial flutter) I484 (Atypical atrial flutter) I489 (Atrial fibrillation and atrial flutter, unspecified)

KCD-6, Korean version of ICD-10 (6th revision); KCD-7, Korean version of ICD-10 (7th revision)
1) KCD-6 diagnosis codes will be used from 1 July 2015 to 31 December 2015.
2) KCD-7 diagnosis codes will be used from 1 January 2016 to 30 November 2016.
[NOTE] KCD code is based on ICD-10 and almost similar, but KCD code is slightly different from ICD-10 (e.g., ICD-10 is more subdivided and extensive than KCD code).

3. Patients prescribed aspirin, warfarin, or NOACs in intake period (from July 1, 2015 to November 30, 2016)
   [Note] NOACs include apixaban, dabigatran and rivaroxaban.

Exclusion criteria

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

1. Medical claims indicating diagnosis or procedure for hip/knee replacement surgery within 6 weeks prior to index date

2. Medical claims indicating a diagnosis code indicative of rheumatic mitral valvular heart disease, mitral valve stenosis during the 12-month baseline period

   (Valvular AF / Prosthetic heart valves)

3. Medical claims indicating a diagnosis code of VTE (Venous thromboembolism) during the 12-month baseline period

4. Medical claims indicating a diagnosis or procedure code of transient AF, or cardiac surgery during the 12-month baseline period

   (Thyrotoxicosis, Hypertrophic cardiomyopathy, elective defibrillation, radiofrequency ablation, or left atrial appendage occlusion)

5. Medical claims indicating a diagnosis code of others during the 12-month baseline period

   - (End-stage chronic kidney disease / Kidney transplant / Dialysis / Pericarditis)

6. For the comparison of "NOAC versus NOAC", and "NOAC versus warfarin", patients with any OACs (apixaban, dabigatran, rivaroxaban, or warfarin) in the pre-index period (from 1 year prior to the day before index date)

   - *[NOTE] Patients prescribed antiplatelets in the pre-index period will not be excluded.*

7. For the comparison of "NOAC versus aspirin", patients with following medications in the pre-index period (from 1 year prior to the day before index date)

   - NOAC user: OACs (apixaban, dabigatran, rivaroxaban, warfarin)
   - Aspirin user: none
   - *[NOTE] NOAC user is defined as OAC naïve user and aspirin user is allowed to have OACs or antiplatelets in the pre-index period.*

[redacted]

Cohorts

To avoid increasing type I error when multiple comparisons occur, this full analysis set will be splitted into multiple sub-analysis sets as follows:

1. NOAC vs NOAC (both as OAC naïve users)
   A. Sub-dataset 1: patients with index treatment of apixaban and patients with index treatment of dabigatran
   B. Sub-dataset 2: patients with index treatment of apixaban and patients with index treatment of rivaroxaban
   C. Sub-dataset 3: patients with index treatment of dabigatran and patients with index treatment of rivaroxaban

[NOTE] The index date will be defined as date of the first prescription of NOAC in patients with NVAF. To identify new users, a look-back observation period from 1 year prior to the day before the index date will be used and must indicate no OAC use during this period. The diagnosis date of NVAF could occur from January 1, 2007 up to and including the index date.

2. NOAC vs warfarin (both as OAC naïve users)
   A. Sub-dataset 4: patients with index treatment of apixaban and patients with index treatment of warfarin
   B. Sub-dataset 5: patients with index treatment of dabigatran and patients with index treatment of warfarin
   C. Sub-dataset 6: patients with index treatment of rivaroxaban and patients with index treatment of warfarin

[NOTE] The index date will be defined as date of the first prescription of NOAC or warfarin in patients with NVAF. To identify new users, a look-back observation period from 1 year prior to the day before the index date will be used and must indicate no OAC use during this period. The diagnosis date of NVAF could occur from January 1, 2007 up to and including the index date.

3. NOAC (OAC naïve user) vs aspirin (no restrictions of antiplatelet or OAC use in the pre-index period)
   A. Sub-dataset 7: patients with index treatment of apixaban and patients with index treatment of aspirin
   B. Sub-dataset 8: patients with index treatment of dabigatran and patients with index treatment of aspirin
   C. Sub-dataset 9: patients with index treatment of rivaroxaban and patients with index treatment of aspirin

[NOTE] The index date will be defined as date of the first prescription of NOAC or aspirin in patients with NVAF during the intake period (from July 1, 2015 to November 30, 2016). To identify NOAC users, a look-back observation period from 1 year prior to the day before the index date will be used and must indicate no OAC use during this period. However, OAC use or antiplatelet use during a look-back observation period from 1 year prior to the day before the index date will be allowed for aspirin users. The diagnosis date of NVAF could occur from January 1, 2007 up to and including the index date.

Each patient was followed until discontinuation or switching of index treatment, outcome occurrence, or study ends (November 30, 2016).

3.2 SUBGROUPS

Subgroup analysis may be considered, including but not limited to subgroup analyses by CHA_2DS_2-VASc score, HAS-BLED score and the dose of index treatment.

4 ENDPOINTS AND COVARIATES

4.1 EFFICACY/ EFFECTIVENESS ENDPOINT(S)

Table 1. Effectiveness Endpoints

Variable	Role	Operational definition
Stroke/Systemic embolism	Primary effectiveness outcome	Hemorrhagic stroke, ischemic stroke and systemic embolism requiring hospitalization will be identified using hospital claims which had a hemorrhagic stroke, ischemic stroke or systemic embolism code whichever came first (i.e., the first occurred event will be used). All KCD diagnosis codes (main and sub-diagnosis codes) will be used. Especially, hospitalization and brain CT or MRI codes will be needed to identify ischemic stroke and hemorrhagic stroke. For systemic embolism, hospitalization and any CT or MRI codes will be used (Appendix 2, Table 7).
Individual outcome of primary outcome	Secondary effectiveness outcome	Individual outcome of hemorrhagic stroke (diagnosis codes in all main and sub-diagnosis codes + hospitalization + brain CT or MRI), ischemic stroke (diagnosis codes in all main and sub-diagnosis codes + hospitalization + brain CT or MRI), and systemic embolism (diagnosis codes

Variable	Role	Operational definition
		in all main and sub-diagnosis codes + hospitalization + any CT or MRI)

4.2 SAFETY ENDPOINTS

Table 2. Safety Endpoints

Variable	Role	Operational definition
Major bleeding	Primary safety outcome	Bleeding requiring hospitalization will be identified using hospital claims which had a bleeding diagnosis code as the first occurred KCD code and it will be consisted of intracranial hemorrhage (ICH) and gastrointestinal (GI) bleeding, and other bleeding (Appendix 2, Table 8). All KCD diagnosis codes (main and sub-diagnosis codes) will be used. Especially, hospitalization and brain CT or MRI codes will be needed to identify ICH.
Individual outcome of major bleeding	Secondary safety outcome	Individual outcome of ICH (diagnosis codes in all main and sub-diagnosis codes + hospitalization + brain CT or MRI), gastrointestinal bleeding (diagnosis codes in all main and sub-diagnosis codes + hospitalization), and other bleeding (diagnosis codes in all main and sub-diagnosis codes + hospitalization)

4.3 OTHER ENDPOINTS

Table 3. Other Endpoints

Variable	Role	Operational definition
Discontinuation	Outcome	Discontinuation is defined as the first day of a period of at least 30 consecutive days after the calculated time to finishing the pack based on pack size and number of tablets per day. The date of discontinuation will be the end date of the last filled prescription before the treatment gap.
Switching	Outcome	A switch among anticoagulants will be defined as a prescription filled for non-index OAC within 30

Variable	Role	Operational definition
		days after the date of discontinuation.
Clinical events preceding each pattern	Outcome	Types of event* preceding each pattern (i.e., discontinuation, switching) *[*Note] Events will include but not limited to (1) serious clinical events where physicians might consider changing anticoagulants (e.g., thromboembolic events (e.g., stroke/systemic embolism, venous thromboembolism [codes in Table 7]), major bleeding [codes in Table 8]); (2) the occurrence of a contraindication for OACs (e.g., valvular atrial fibrillation, severe kidney disease); and (3) procedure for atrial fibrillation that might not require OACs (e.g., elective defibrillation, radiofrequency ablation, and left atrial appendage occlusion [codes in Table 13]).*
Compliance (medication possession ratio, MPR)	Outcome	Medication possession ratio (MPR) will be calculated as total days of index treatment dispensed / 365 days of study follow-up. Patients with an MPR greater than 1 will be capped at 1.

4.4 COVARIATES

Table 4. Baseline Variables

Variable	Role	Operational definition
Age	Baseline characteristic and potential confounder	Age at index date
Sex	Baseline characteristic and potential confounder	1. Male 2. Female
Types of health insurance	Baseline characteristic and potential confounder	Types of health insurance divided as the following: 1. National Health Insurance 2. Medical aid

[redacted]

Variable	Role	Operational definition
CHA_2DS_2-VASc	Baseline characteristic and potential confounder	CHA_2DS_2-VASc as continuous data or dichotomous data. The score will be calculated using the following KCD codes (Appendix 2, Table 9): 1. Congestive heart failure 2. Hypertension 3. Diabetes mellitus 4. Stroke/TIA/TE 5. Vascular disease 6. Age ≥ 75 7. Age 65-74 8. Female
HAS-BLED	Baseline characteristic and potential confounder	HAS-BLED as continuous data or dichotomous data. The score will be calculated using the following KCD codes (Appendix 2, Table 10): 1. Hypertension 2. Abnormal renal function 3. Abnormal liver function 4. Stroke 5. Bleeding history or predisposition: refers to any bleeding codes 6. Age > 65 7. Antiplatelet or NSAID use 8. Alcoholism *[Note]* Labile international normalized ratio is not available in HIRA data and does not apply to patients on aspirin, or NOACs, so the modified HAS-BLED score has a maximum value of 8 instead of 9.
Charlson Comorbidity Index	Baseline characteristic and potential confounder	Charlson Comorbidity Index as continuous data or dichotomous data. The index will be calculated using the following KCD codes (Appendix 2, Table 11):

Variable	Role	Operational definition
		1. Myocardial infarction 2. Congestive heart failure 3. Peripheral vascular disease 4. Cerebrovascular disease 5. Dementia 6. Chronic pulmonary disease 7. Rheumatic disease 8. Peptic ulcer disease 9. Mild liver disease 10. Diabetes without chronic complication 11. Diabetes with chronic complication 12. Hemiplegia or paraplegia 13. Renal disease 14. Any malignancy, including lymphoma and leukemia, except malignant neoplasm of skin 15. Moderate or severe liver disease 16. Metastatic solid tumor 17. AIDS/HIV
Baseline Medication Use	Baseline characteristic and potential confounder	It will be consisted of the following (Appendix 2, Table 12): 1. NSAIDs 2. Antiplatelet 3. PPI 4. H_2-receptor antagonists 5. Antiarrhythmics 6. Digoxin

Variable	Role	Operational definition
		7. Statins

4.5 HANDLING OF MISSING VALUES

After examining the characteristics of missing values, we will determine whether we can remove observations with missing values from the dataset. Basically, subjects with missing values of covariates will not contribute to the analysis.

5 STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

5.1 STATISTICAL METHODS

Descriptive Analysis:

- All outcome variables will be summarized descriptively through the tabular and graphical display of mean values, medians, ranges, and standard deviations for continuous variables of interest and frequency distributions for categorical variables.
- The proportion of antithrombotics (aspirin, clopidogrel, aspirin and clopidogrel combination, warfarin, NOACs) at index date will be examined.
- Appropriate tests (e.g., t-test, chi-square test) will be used based on the distribution of the measure. The $p < 0.05$ considered significant.

Multivariate Analysis:

Propensity score method

The estimation of propensity score will be performed to control for confounders in each sub-dataset: (1) each NOAC versus NOAC; (2) each NOAC versus warfarin; (3) each NOAC versus aspirin.

Propensity scores are estimated by logistic regression analyses that incorporate potential treatment predictors as independent variables and types of index treatment as dependent variable (e.g., apixaban=1, warfarin=0). Covariates in the logistic regression model will

[redacted]

include variables such as age, sex, CCI score, CHA_2DS_2-VASc score, HAS-BLED score, and comorbidities, but the final list of these covariates will be discussed and determined after reviewing the results of descriptive analysis of the pre-matched datasets. Further, we will report the *c*-statistic of the propensity score that indicates the degree to which the propensity score model discriminates between treated patients and untreated patients.

After estimation of propensity score, we will perform propensity score matching (PSM). 1:1 matching without replacement will be performed.

The populations would be first matched using PSM according to their index treatment. For these matched populations we should then explore the proposed subgroups by: making an assessment of patient numbers in the subgroups and checking that patient characteristics are still similar between the index treatments in the subgroups. If they are similar, then conduct interaction term analysis is being conducted to determine whether the treatment effect varies between the subgroups. If the populations are no longer similar in characteristics, then re-matching via PSM will be performed for the subgroups.

Covariate adjustment using propensity score will also be performed. This approach has an advantage of using the whole observations whereas matching approach uses part of observations which were successfully matched.

Inverse probability of treatment weighted (IPTW)

We will perform an inverse probability of treatment weighted (IPTW) analysis. Every person will be weighted by the inverse of the probability of receiving the treatment actually received (i.e., PS in the treated and (1-PS) in the untreated).

Balance diagnostics

We will compare and assess the balance of baseline variables (e.g., continuous variable, dichotomous variable, interaction terms, or squares of continuous variable) between treated and control subjects in the weighted sample using standardized difference (Austin et al., 2015).

IPTW diagnostics

The distribution of weights will be carefully checked because some patients, those treated contrary to prediction, may receive very large weights (11, 12). To address the presence of extreme weights, we will consider several approaches, including use of stabilized weights, or trimmed or truncated weights (11-13). The stabilized weights will be implemented based on the following equation (11):

IPTW stabilized=E*PE/PS + (1-E)*(1-PE)/(1-PS)

- E: treatment (E=1), no treatment (E=0).
- PE: overall marginal prevalence of the treatment exposure.
- PS: estimated propensity score.

Balances between treatment groups will be evaluated by the standardized differences of all covariates, using a threshold of 0.1 to determine an imbalance.

Cox proportional hazards model

Cox proportional hazards model will be used to compare event rates between the treatment groups, with warfarin or antiplatelets as the primary reference in each sub-dataset: (1) each NOAC versus NOAC; (2) each NOAC versus warfarin; (3) each NOAC versus aspirin.

Cox model stratification (dummy variable method and true stratification method) will be performed to examine whether the stratum-to-stratum differences exist. To check the proportional hazards assumption, we will employ both the graphical methods (i.e., log-log plot, observed-expected plot, Schoenfeld residual plot) and statistical tests using the time-dependent covariate. If the assumption does not meet, we will employ either a stratified model or an interaction term between time and variable of interest (i.e., treatment indicator).

The variables included in the model will be finalized after attempting model building process. Potential interactions will also be considered.

The hazard ratio and 95% confidence interval will be provided.

Sensitivity Analysis

Sensitivity analysis of performing IPTW using the propensity score derived from multinomial model will be conducted.

5.2 STATISTICAL ANALYSES

- Patients with aspirin, warfarin, and NOACs will be matched via propensity-score method. Patients will be matched on patient demographics (i.e., age, sex) and clinical (i.e., CHA_2DS_2-VASc score, Charlson Comorbidity Index score, etc.) variables. Other propensity score method (i.e., covariate adjustment, IPTW) will

[redacted]

also be used. Standardized difference will be used to assess the balance of variables after matching. A standardized difference < 10% will be considered acceptable.

- A Cox proportional hazards model, to account for differences in follow-up time and right data censoring, will be used to compare effectiveness and safety outcomes between treatment groups.

[redacted]

6 SUMMARY OF ANALYSES

Outcome	Supports Protocol Objective Number	Statistical Method	Covariates/ Strata
Baseline characteristics and drug utilization patterns	1	Chi-square test, t-test	Demographic and clinical characteristics, including baseline comorbidities
Stroke/systemic embolism	2	Propensity score method, Cox proportional hazards model	Demographic and clinical characteristics, including baseline comorbidities
Major bleeding	3	Propensity score method, Cox proportional hazards model	Demographic and clinical characteristics, including baseline comorbidities

[redacted]

7 LIST OF TABLES

[redacted]

8 APPENDIX

8.1 APPENDIX 1. TABLE SHELLS

Table 5. Baseline characteristics *(example)*

	Apixaban (n=XX)	Warfarin (n=XX)
Age – mean, SD		
Gender		
Female		
Male		
Insurance type		
National Health Insurance		
Medical Aid		
CHA_2DS_2-VASc score		
Mean (SD)		
0-1		
2		
3		
4		
≥5		
HAS-BLED		
Mean (SD)		
0-2		
≥3		
Charlson Comorbidity Index		
Mean (SD)		
0-1		
2-3		
≥4		
Comorbidities		
Stroke/TIA		
Systemic embolism		
MI		
Bleeding*		
Hypertension		
Diabetes mellitus		
CAD		

[redacted]

	Apixaban (n=XX)	Warfarin (n=XX)
PAD		
Heart failure		
COPD		
Renal disease		
Medication use		
NSAIDs		
Antiplatelet		
PPI		
H2-receptor antagonist		
Digoxin		
Statin		
Antiarrhythmics		

*Bleeding will be identified as the same with the definition of major bleeding outcomes and the transfusion procedure codes (see Table 14 for codes).

Table 6. Hazard ratios for each comparison *(example)*

	Apixaban (n=XX) Event rate	Warfarin (n=XX) Event rate	Apixaban vs warfarin (n=XX) HR (95% CI)	*P* value
Effectiveness endpoints				
Stroke/systemic embolism				
Safety endpoints				
Major bleeding				

APPENDIX 2. DATA DERIVATION DETAILS

Table 7. Effectiveness Outcomes Codes

Type	KCD Code or Procedure Code
Hemorrhagic stroke*	I60, I61, I62, I690, I691, I692
Ischemic stroke*	G459, I63, I693
Systemic embolism**	I74
*Brain CT/MRI	CT: HA441, HA451, HA461, HA471, HA851 MRI: HE101, HE102, HE135, HE201, HE202, HE235, HE301, HE302, HE401, HE402, HE501, HE502, HE535
**Any CT/MRI	CT: HA401, HA402, HA403, HA404, HA405, HA406, HA407, HA408, HA409, HA410, HA411, HA412, HA413, HA414, HA415, HA416, HA424, HA425, HA434, HA435, HA443, HA444, HA445, HA446, HA447, HA448, HA449, HA453, HA456, HA457, HA458, HA459, HA463, HA464, HA465, HA466, HA467, HA468, HA469, HA473, HA474, HA475, HA476, HA477, HA478, HA479, HA496, HA497, HA801, HA805, HA809, HA813, HA834, HA835, HA853, HA856, HA857, HA858, HA859, S4852 MRI: HE103, HE104, HE105, HE106, HE107, HE108, HE109, HE110, HE111, HE112, HE113, HE114, HE115, HE116, HE117, HE118, HE119, HE120, HE121, HE122, HE123, HE124, HE125, HE126, HE127, HE128, HE129, HE130, HE131, HE132, HE133, HE134, HE136, HE137, HE138, HE139, HE140, HE141, HE142, HE203, HE204, HE205, HE206, HE207, HE208, HE209, HE210, HE211, HE212, HE213, HE214, HE215, HE216, HE217, HE218, HE219, HE220, HE221, HE222, HE223, HE224, HE225, HE226, HE227, HE228, HE229, HE230, HE231, HE232, HE233, HE234, HE236, HE237, HE238, HE239, HE240, HE241, HE303, HE304, HE305, HE306, HE307, HE308, HE309, HE310, HE311, HE312, HE313, HE314, HE315, HE316, HE317, HE318, HE319, HE320, HE321, HE322, HE323, HE324, HE325, HE326, HE327, HE328, HE329, HE330, HE331, HE332, HE333, HE334, HE403, HE404, HE405 ,HE406, HE407, HE408, HE409, HE410, HE411, HE412, HE413, HE414, HE415, HE416, HE417, HE418,

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	HE419, HE420, HE421, HE422, HE423, HE424, HE425, HE426, HE427, HE428, HE429, HE430, HE431, HE432, HE433, HE434, HE503, HE504, HE505, HE506, HE507, HE508, HE509, HE510, HE511, HE512, HE513, HE514, HE515, HE516, HE517, HE518, HE519, HE520, HE521, HE522, HE523, HE524, HE525, HE526, HE527, HE528, HE529, HE530, HE531, HE532, HE533, HE534, HE536, HE537, HE538, HE539, HE540, HE541, HF101, HF102, HF104, HF105, HF106, HF107, HF201, HF202, HF305, HF306

*Brain CT/MRI will be used to define hemorrhagic stroke and ischemic stroke.
**Any CT/MRI will be used to define systemic embolism.

Table 8. Safety Outcomes Codes

Type	KCD Code or Procedure Code
Intracranial haemorrhage*	I60, I61, I62, I690, I691, I692, S064, S065, S066, S068
Gastrointestinal 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
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
*Brain CT/MRI	CT: HA441, HA451, HA461, HA471, HA851 MRI: HE101, HE102, HE135, HE201, HE202, HE235, HE301, HE302, HE401, HE402, HE501, HE502, HE535

*Brain CT/MRI will be used to define intracranial hemorrhage.

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Table 9. CHA_2DS_2-VASc Score

Condition	KCD code	Point
Congestive heart failure	I50	1
Hypertension	I10-I15	1
Age	75+ years	2
Diabetes	E10-E14	1
Stroke	I63, I693 G459	2
Vascular disease	I21, I252, I70-I73	1
Age	65-74 years	1
Sex	Female	1

Table 10. HAS-BLED Score

Condition	KCD code	Point
Hypertension	I10-I15	1
Abnormal renal function	N183, N184	1
Abnormal liver function	B15-B19, C22, D684, I982, I983, K70-K77, Z944	1
Stroke	I63, I693, G459	1
Bleeding history or Predisposition*	Codes in Table 8	1
Labile INR	Not measurable	Not applicable
Elderly	65+ years	1
Drug therapy	Antiplatelets, NSAIDs	1
Alcoholism	E244, F10, G312, G621, G721, I426, K292, K70, K860, O354, P043, Q860, T510, X45, X65, Y15, Y90-Y91, Z502, Z714, Z721	1

* Blood transfusion will also be used to define other bleeding history (see Table 14 for blood transfusion codes).

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Table 11. Charlson Comorbidity Index

Condition	KCD code	Point
Cerebrovascular disease	G45.x, G46.x, H34.0, I60.x-I69.x	1
Congestive heart failure	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5-I42.9, I43.x, I50.x, P29.0	1
Chronic pulmonary disease	I27.8, I27.9, J40.x–J47.x, J60.x–J67.x, J68.4, J70.1, J70.3	1
Dementia	F00.x–F03.x, F05.1, G30.x, G31.1	1
Diabetes without chronic complication	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	1
Mild liver disease	B18.x, K70.0-K70.3, K70.9, K71.3-K71.5, K71.7, K73.x, K74.x, K76.0, K76.2-K76.4, K76.8, K76.9, Z94.4	1
Myocardial infection	I21.x, I22.x, I25.2	1
Peripheral vascular disease	I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9	1
Peptic ulcer disease	K25.x–K28.x,	1
Rheumatologic disease	M05.x, M06.x, M32.x–M34.x M31.5M35.1, M35.3, M36.0	1
Diabetes with chronic complication	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	2
Hemiplegia or paraplegia	G04.1, G11.4, G80.1, G80.2, G81.x, G82.x, G83.0-G83.4, G83.9	2
Any malignancy, including leukemia and lymphoma	C00.x–C26.x, C30.x–C34.x, C37.x–C41.x, C43.x, C45.x–C58.x, C60.x–C76.x, C81.x–C85.x, C88.x, C90.x–C97.x,	2
Renal disease	I12.0, I13.1, N03.2-N03.7, N05.2-N05.7, N18.x, N19.x, N25.0, Z49.0-Z49.2, Z94.0, Z99.2	2
Moderate or severe liver disease	I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7	3
AIDS/HIV	B20.x–B22.x, B24.x	6
Metastatic solid tumor	C77.x–C80.x	6

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Table 12. Baseline Medications

Class	Drug
NSAIDs	Bromfenac, Celecoxib, Diclofenac, Etodolac, Fenoprofen, Flurbiprofen, Ibuprofen, Indomethacin, Ketoprofen, Ketorolac, Naproxen, Meclofenamate, Mefenamic acid, Meloxicam, Nabumetone, Oxaprozin, Piroxicam, Sulindac, Tolmetin
Antiplatelets	Aspirin, Clopidogrel, Prasugrel, Ticlopidine, Cilostazol, Abciximab, Tirofiban, Dipyridamole, Ticagrelor
PPI	Omeprazole, Pantoprazole, Lansoprazole, Rabeprazole, Esomeprazole, Dexlansoprazole
H_2-receptor antagonists	Cimetidine, Ranitidine, Famotidine, Nizatidine, Roxatidine, Lafutidine
Antiarrhythmics	Quinidine, Procainamide, Mexiletine, Propafenone, Flecainide, Amiodarone, Bretylium, Dronedarone, Propranolol, Atenolol, Esmolol, Verapamil, Diltiazem, Sotalol
Digoxin	Digoxin
Statins	Atorvastatin, Fluvastatin, Lovastatin, Pitavastatin, Pravastatin, Roxuvastatin, Simvastatin

Table 13. Exclusion Criteria

Condition	KCD Code or Korean Procedure Codes
Valvular AF/ prosthetic heart valves	I05, I08, I09, I34, Q23, T820, T826, Z952, Z953, Z954 - Korean Procedure Codes: M6580, M6581, M6582, O1791, O1792, O1793, O1794, O1795, O1796, O1797, O1798, O1799, M6531, M6532, M6533, O1690, O1730, 1740, O1750, O1760, O1770, O1781, O1782, O1783, O1810, O1826
End-stage of chronic kidney disease/ dialysis/ kidney transplant	N185, T824, Y602, Y612, Y622, Y841, Z49, Z992, E1022, E1122, E1222, E1322, E1422, Z940
Venous thromboembolism	I636, I676, I801, I802, I803, I808, I809, I81, I822, I823, I829, I26
Thyrotoxicosis	E05
Pericarditis	I30, I31, I32
Hypertrophic	I422

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Condition	KCD Code or Korean Procedure Codes
cardiomyopathy	
Hip or knee replacement*	N0711, N0715, N1711, N1715, N1721, N1725, N2070, N2072, N2077, N2710, N2712, N2717, N3710, N3712, N3717, N3720, N3722, N3727, N4710, N4712, N4717, N4720, N4722, N4727
Elective defibrillation/ radiofrequency ablation/ left atrial appendage occlusion*	M5880, M6540, M6542, M6545, M6547, M6511

*[*Note] Hip or knee replacement, elective defibrillation, radiofrequency ablation, and left atrial appendage occlusion will be identified using procedure codes.*

Table 14. Blood Transfusion Codes

Condition	Korean procedure code
Whole Blood	X1001
Whole Blood	X1002
Fresh Liquid Plasma for Whole Blood 320ml	X2011
Fresh Liquid Plasma for Whole Blood 400ml	X2012
Packed RBC for Whole Blood 320ml	X2021
Packed RBC for Whole Blood 400ml	X2022
Washed RBC for Whole Blood 320ml	X2031
Washed RBC for Whole Blood 400ml	X2032
Fresh Frozen Plasma for Whole Blood 320ml	X2041
Fresh Frozen Plasma for Whole Blood 400ml	X2042
Frozen Plasma for Whole Blood 320ml	X2051
Frozen Plasma for Whole Blood 400ml	X2052
Cryoprecipitate for Whole Blood 320ml	X2061
Cryoprecipitate for Whole Blood 400ml	X2062
Platelet rich plasma for whole blood 320ml	X2071

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Condition	Korean procedure code
Platelet Rich Plasma for Whole Blood 400ml	X2072
Platelet Concentrate for Whole Blood 320ml	X2081
Platelet Concentrate for Whole Blood 400ml	X2082
Leukocyte Poor Packed RBC for Whole Blood 320ml	X2091
Leukocyte Poor Packed RBC for Whole Blood 400ml	X2092
Packed WBC for Whole Blood 320ml	X2101
Packed WBC for Whole Blood 400ml	X2102
Leukocyte Filtered Packed RBC for Whole Blood 320ml	X2111
Leukocyte Filtered Packed RBC for Whole Blood 400 ml	X2112
Leukocyte Filtered Packed Platelet Concentrate for Whole Blood 320ml	X2121
Leukocyte Filtered Packed Platelet Concentrate for Whole Blood 400ml	X2122
Red Blood Cells, Cryopreserved and Thawed for Whole blood 320ml	X2131
Red Blood Cells, Cryopreserved and Thawed for Whole blood 400ml	X2132
Plasma, Cryoprecipitate Reduced for Whole blood 320ml	X2141
Plasma, Cryoprecipitate Reduced for Whole blood 400ml	X2142
Fresh Blood	X3010

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9 REFERENCES

1. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart disease and stroke statistics--2015 update: a report from the American Heart Association. Circulation. 2015;131(4):e29-322.
2. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation: a major contributor to stroke in the elderly. The Framingham Study. Arch Intern Med. 1987;147(9):1561-4.
3. Savelieva I, Bajpai A, Camm AJ. Stroke in atrial fibrillation: update on pathophysiology, new antithrombotic therapies, and evolution of procedures and devices. Ann Med. 2007;39(5):371-91.
4. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, Jr., et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2014;64(21):e1-76.
5. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Annals of internal medicine. 2007;146(12):857-67.
6. Banerjee A, Marín F, Lip GY. A New Landscape for Stroke Prevention in Atrial Fibrillation. Stroke. 2011:STROKEAHA. 111.617886.
7. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl j Med. 2009;2009(361):1139-51.
8. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. New England Journal of Medicine. 2011;365(10):883-91.
9. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. New England Journal of Medicine. 2011;365(11):981-92.
10. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al. Edoxaban versus warfarin in patients with atrial fibrillation. New England Journal of Medicine. 2013;369(22):2093-104.
11. Stürmer T, Wyss R, Glynn RJ, Brookhart MA. Propensity scores for confounder adjustment when assessing the effects of medical interventions using nonexperimental study designs. Journal of internal medicine. 2014;275(6):570-80.
12. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. Statistics in medicine. 2015;34(28):3661-79.
13. Austin PC, Stuart EA. The performance of inverse probability of treatment weighting and full matching on the propensity score in the presence of model misspecification when estimating the effect of treatment on survival outcomes. Statistical methods in medical research. 2017;26(4):1654-70.