Study information

Title	The real world evidence on treatment patterns, effectiveness, and safety of drugs for stroke prevention in nonvalvular atrial fibrillation patients in Korea
Protocol number	X9001134
Protocol version identifier	V.3.0
Date of last version of protocol	03 May 2018
Active substance	Apixaban ((PF-04652577/BMS-562247) (617001ATB, 617002ATB)
Medicinal product	ELIQUIS®
Research question and objectives	This study seeks to address the following objectives: ● To explore baseline characteristics and drug utilization patterns in patients with nonvalvular atrial fibrillation (NVAF) newly prescribed with anti-thrombotic therapies. ● To compare the effectiveness of anti-thrombotic therapies in patients with NVAF ● To compare the safety of anti-thrombotic therapies.in patients with NVAF
Country(-ies) of study	South Korea
Author	PPD PharmD PPD PPD, Pfizer Korea

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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AIDS	Acquired immune deficiency syndrome
CABG	Coronary Artery Bypass Graft surgery
CHA_2DS_2-VASc	Clinical stroke risk prediction tool based on comorbidities of congestive heart failure, hypertension, elderly age, diabetes mellitus, prior stroke or thromboembolism, vascular disease, and gender.
HAS-BLED	Clinical major bleeding risk score based on comorbidities of hypertension, abnormal renal and liver function, prior stroke, bleeding history, labile international normalized ratio values of anticoagulation level, elderly age, and concomitant drug or alcohol use.
HIRA	Health Insurance Review & Assessment Service
HIV	Human immunodeficiency virus
ICD-10	International Classification of Diseases 10th revision
ICJME	International Committee of Medical Journal Editors
KCD-6	Korean Standard Classification of Diseases 6th revision
KCD-7	Korean Standard Classification of Diseases 7th revision
MI	Myocardial infarction
MPR	Medication possession ratio
NOAC	Non vitamin K antagonist oral anticoagulants
NSAIDs	Nonsteroidal anti-inflammatory drugs
NVAF	Nonvalvular atrial fibrillation
OAC	Oral anticoagulants
PCI	Percutaneous coronary intervention

Abbreviation	Definition
PPI	Proton pump inhibitor
TE	Thromboembolism
TIA	Transient ischemic attack

2. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation	Address
PPD , PharmD	PPD	Pfizer Pharmaceuticals Korea Ltd.	Seoul, Korea
PPD , MPharm, MA, PhD	PPD	PPD	PPD

3. ABSTRACT

Study title: Real world evidence on treatment patterns, effectiveness, and safety of drugs for stroke prevention in nonvalvular atrial fibrillation patients in Korea (Version 2.0, 10 Oct 2017)

PPD

Rationale and Background:

There have been far fewer real world studies on effectiveness and safety outcomes of antiplatelet therapy, warfarin and Non vitamin K antagonist oral anticoagulants (NOACs) in Asian populations. The nationwide claims database in Korea can provide an opportunity to study comparative effectiveness and safety outcomes of therapies to prevent thromboembolic events in patients with nonvalvular atrial fibrillation.

Research question and objectives:

Research question: What is the real world data on antiplatelet therapy, warfarin and NOACs that can be found in the nationwide claims database in Korea?

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

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

3. To compare safety including major bleeding of antithrombotic therapies in patients with NVAF with the following antithrombotic therapies: NOACs, warfarin, and aspirin

[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 doses versus reduced doses of NOACs

- Patterns 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)

Study design: Retrospective cohort study

Population: Subjects with atrial fibrillation diagnosed (from January 1, 2007 up to and including the index date*) who newly initiated antithrombotic therapies (NOACs (not including edoxaban), 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 during the intake period (from July 1, 2015 to November 30, 2016).*

Variables:

Exposure: The exposure to the following will be considered:

1. Aspirin
2. Aspirin-clopidogrel combination*
3. Clopidogrel*
4. Warfarin
5. NOACs

   - Apixaban, Rivaroxaban, Dabigtran

**[Note] Clopidogrel, Aspirin-clopidogrel will be included in descriptive analysis.*

Outcome variables: The following outcomes will be assessed:

1. Effectiveness outcomes
   - Primary outcome: Composite of hemorrhagic stroke, ischemic stroke, and systemic embolism
   - Secondary outcomes: Individual outcome of hemorrhagic stroke, ischemic stroke, and systemic embolism
2. Safety outcomes

- Primary safety outcome: Major bleeding including gastrointestinal bleeding or intracranial bleeding and other bleeding

- Secondary safety outcomes: Individual outcome of major bleeding

Key-Covariates: Variables, including, but not limited to, will be age, sex, types of health insurance, CHA_2DS_2-VASc score, HAS-BLED score, Charlson Comorbidity Index score, etc.

Data sources: The Korean Health Insurance Review & Assessment Service (HIRA) database from January 1, 2007 to November 30, 2016 will be used for the analysis. The HIRA database contains the data of universal health insurance system in Korea. The database contains patients' demographic information, their use of inpatient and outpatient services, and pharmacy dispensing claims.

Study size: Based on HIRA disease statistics, the number of patients with atrial fibrillation (KCD code: I48) were 148,130 and 169,259 in 2015 and 2016, respectively. Thus, the anticipated number of patients will be approximately 150,000 since we plan to include patients who already had atrial fibrillation and were prescribed with aspirin, warfarin, or NOACs from July 1, 2015 to November 30, 2016. However, the study size might change after applying inclusion and exclusion criteria.

Data analysis: Patients will be matched on demographic and clinical characteristics. All outcome variables will be summarized descriptively through the tabular and graphical display of mean values, medians, ranges, and standard deviations of continuous variables of interest and frequency distributions for categorical variables. Effectiveness and safety outcomes of treatments will be estimated from time-to-event models. The 95% confidence intervals for the estimates will be calculated and $p < 0.05$ will be considered significant. All analyses will be carried out using SAS version 9.4. Analysis and reporting will be compliant with Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations.

4. AMENDMENTS AND UPDATES

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
Amendment 01 (V.2.0)	31Jan2018	Administrative amendment	Author	PPD [redacted]	NI Study lead change
		Substantial amendment	Effectiveness Endpoints	- Add 'Hemorrhagic stroke'	Meet to Harmonized Protocol
		Substantial amendment	Safety Endpoints	-Change to 'Major bleeding' - Delete the 'Clinically relevant non-major bleeing'	Meet to Harmonized Protocol
		Administrative amendment	3. ABSTRACT	- Add the information of version, date of protocol, name and affilation of main author - Add the variables of Exposure - Correct the milestone	Required SOP
		Administrative amendment	5.MILESTONES	Change the milestones which meet SOP required	Required SOP
		Administrative amendment	3. ABSTRACT 7.RESEARCH QUESTION AND OBJECTIVES	Add research questions	Add research questions
		Administrative amendment	8.1 Study design	Add the endpoints	Required SOP
		Substantial amendment	8.2.2 Exclusion criteria	Delete the explains unnecessary Add the exclusion criteria	Delete the explains unnecessary Meet to Harmonized Protocol
		Administrative amendment	8.7. Data Analysis	Add the SOP recommendation words	Required SOP
		Administrative amendment	9.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) 9.4.Ethical Conduct of the Study	Change the SOP required words	Required SOP
Amendment 02 (V.3.0)	03May 2018	Administrative amendment	3. Abstract	Change the phrases of Research question and objectives	Amend protocol phrases consistently with SAP.
		Administrative	7. Research question and	Change the phrases of Research	Amend protocol phrases consistently

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
		amendment	objectives 8.1 Study design 8.2 Setting	question and objectives	with SAP.
		Administrative amendment	8.2.2 Exclusion criteria	Delete 'Hip or knee replacement' from #5.	Duplicate from exclusion criteria #1.
		Substantial amendment	8.3 Variables	Change the operational definitions	Redefinition of hemorrhagic stroke, ischemic stroke and systemic embolism
				Delete the variable of 'myocardial infarction' from effectiveness outcome.	Redefinition of effectiveness outcome
				Add variable of 'Individual outcome of major bleeding'	Redefinition of each major bleeding events
				Delete variables of 'Dose', 'Medical history' and 'Study drugs'	Delete unnecessary sections.
				Add codes on operational definitions of 'Valvular AF/ Prosthetic heart valves' and 'Hip or knee replacement'	Add procedure codes.
		Substantial amendment	8.7	Additional sensitivity analysis	Perform IPTW using the propensity score derived from multinomial model

5. MILESTONES

Milestone	Planned date
Completion of feasibility assessment	10 Apr 2017
Start of data collection	01 Feb 2018
End of data collection	31 Nov 2018
Interim report 1	30 Jun 2018
Interim report 2	31 Dec 2018
Final study report	28 Feb 2019

6. RATIONALE AND BACKGROUND

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 thromboembolic events and death (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 few 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.

7. RESEARCH QUESTION AND OBJECTIVES

Research question: What is the real world data on antiplatelet therapy, warfarin and NOACs that can be found in the nationwide claims database in Korea?

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

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

3. To compare safety including major bleeding of antithrombotic therapies in patients with NVAF with the following antithrombotic therapies: NOACs, warfarin, and aspirin

[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 doses versus low dose of NOACs
    - Patterns 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)

8. RESEARCH METHODS

8.1 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 evaluated 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.

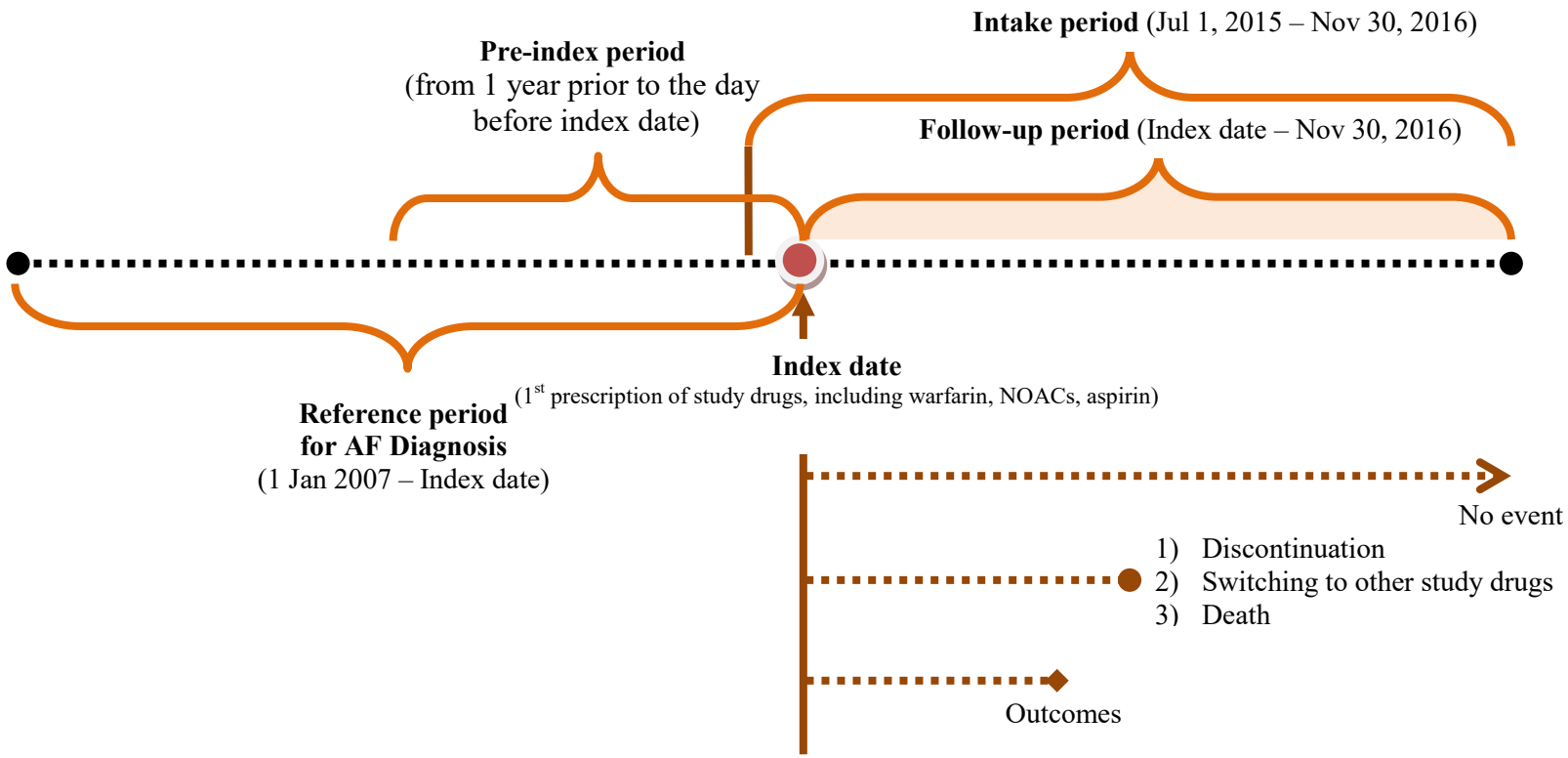

Figure 1. Study design scheme

8.2 Setting

8.2.1 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:

Table 1. 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 during intake period (from July 1, 2015 to November 30, 2016)
   [Note] NOACs include apixaban, dabigatran, and rivaroxaban.

8.2.2 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 other conditions 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.*

8.3 Variables

Variable	Role	Data source(s)	Operational definition
Composite of hemorrhagic stroke, ischemic stroke and systemic embolism	Primary effectiveness outcome	HIRA database	Claims with the following KCD codes in all diagnosis codes (main and sub-diagnosis codes) whichever came first (i.e., the first occurred event will be used): 1. Ischemic stroke: G459, I63, I693 2. Systemic embolism: I74 3. Hemorrhagic stroke: I60, I61, I62, I690, I691, I692 *[NOTE] Hospitalization and CT or MRI codes (brain CT or MRI for ischemic stroke and hemorrhagic stroke; any CT or MRI for systemic embolism) were also required for identification.* **Brain CT or MRI:* *CT: HA441, HA451, HA461, HA471, HA851* *MRI: HE101, HE102, HE135, HE201,*

Variable	Role	Data source(s)	Operational definition
			HE202, HE235, HE301, HE302, HE401, HE402, HE501, HE502, HE535 ***Any CT or 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, 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*

Variable	Role	Data source(s)	Operational definition
Individual outcome of primary outcome	Secondary effectiveness outcome	HIRA database	Claims with the following KCDcodes in all diagnosis codes (main and sub-diagnosis codes) whichever came first (i.e., the first occurred event will be used): 1. Ischemic stroke: G459, I63, I693 2. Systemic embolism: I74 3. Hemorrhagic stroke: I60, I61, I62, I690, I691, I692 *[NOTE] Hospitalization and CT or MRI codes (brain CT or MRI for ischemic stroke and hemorrhagic stroke; any CT or MRI for systemic embolism) were also required for identification. For CT or MRI codes, please see above.*
Major bleeding	Primary safety outcome	HIRA database	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. 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. - Intracranial (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)
Individual outcome of major bleeding	Secondary safety outcome	HIRA database	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). For codes, please see above.

Variable	Role	Data source(s)	Operational definition
Types of health insurance	Covariates	HIRA database	Types of health insurance divided as the following: 1. National Health Insurance 2. Medical aid
CHA_2DS_2-VASc	Covariates	HIRA database	CHA_2DS_2-VASc as continuous data or dichotomous data. The score will be calculated using the following KCD codes (refer to SAP-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. Sex (female)
HAS-BLED	Covariates	HIRA database	HAS-BLED as continuous data or dichotomous data. The score will be calculated using the following KCD codes (refer to SAP-Appendix 2, Table 10): 1. Hypertension 2. Abnormal renal function 3. Abnormal liver function 4. Stroke 5. Bleeding history or predisposition 6. Age > 65 7. Antiplatelet or NSAID use 8. Alcoholism
Charlson Comorbidity Index	Covariates	HIRA database	Charlson Comorbidity Index as continuous data or dichotomous data. The index will be calculated using the following KCD codes (Refer to SAP-Appendix 2, Table 11): 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

Variable	Role	Data source(s)	Operational definition
Medication use	Covariates	HIRA database	It will be consisted of the following: 1. History of NSAIDs 2. History of antiplatelet 3. History of PPI 4. History of H_2-receptor antagonists 5. History of antiarrhythmics 6. History of digoxin 7. History of statins
Exclusion criteria	Exclusion criteria	HIRA database	Claims with the following KCD codes or procedure codes: 1. 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 2. End-stage of chronic kidney disease/dialysis: N185, T824, Y602, Y612, Y622, Y841, Z49, Z992, E1022, E1122, E1222, E1322, E1422 3. Kidney transplant: Z940 4. Venous thromboembolism: I636, I676, I801, I802, I803, I808, I809, I81, I822, I823, I829, I26 5. Hip or knee replacement - Korean procedure codes: N0711, N0715, N1711, N1715, N1721, N1725, N2070, N2072, N2077, N2710, N2712, N2717, N3710, N3712, N3717, N3720, N3722, N3727, N4710, N4712, N4717, N4720, N4722, N4727 6. Thyrotoxicosis: E05 7. Pericarditis: I30, I31, I32 8. Hypertrophic cardiomyopathy: I422 9. Elective defibrillation, radiofrequency ablation, or left atrial appendage occlusion - Korean procedure codes: M5880, M6540, M6542, M6545, M6547, M6511
Follow-up period	Follow-up period	HIRA database	From the index date until the first occurrence of the following whichever came first: 1. Discontinuation: maximum of a 30-day gap after the calculated time to finishing the pack based on pack size and number of tablets per day. Switching: switch to any other study drugs 2. Outcome occurrence 3. Study ends: November 30, 2016

8.4 Data sources

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.

8.5 Study size

Based on the 2015-2016 HIRA disease statistics, there are 148,130 – 169,259 patients with atrial fibrillation (KCD code: I48). Thus, we anticipate getting the number of patients with approximately 150,000 since we plan to include patients who already had atrial fibrillation and were prescribed aspirin, warfarin, or NOACs from July 1, 2015 to November 30, 2016. However, the study size might change after applying inclusion and exclusion criteria.

8.6 Data management

Obtaining data files

Pusan National University team will submit the data request form to HIRA. After the HIRA committee review, the data will be uploaded in the server. The study team will access the data through the remote access using IP address. All medical or pharmacy claims and demographic information from January 1, 2007 to November 30, 2016 of patients with atrial fibrillation (KCD code: I48) from July 1, 2015 to November 30, 2016 will be accessed.

8.7 Data analysis

- All outcome variables will be summarized descriptively through the tabular and graphical display of mean values, medians, ranges, and standard deviations of continuous variables of interest and frequency distributions for categorical variables.

- 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, inverse probability of treatment weighting (IPTW)) will also be used. 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.

- Comparative analyses will be performed contingent on a feasibility assessment based on the descriptive analyses

- All analyses will be carried out using SAS version 9.4. The 95% confidence intervals for the estimates will be calculated and $p < 0.05$ considered significant.

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

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

8.8 Quality control

The HIRA data files are large and complex. The study analysts will thoroughly evaluate and assess the data quality—including review of data for accuracy, consistency, and completeness—by generating descriptive summaries of variables to be used for study analysis. To ensure the integrity and quality of data and study results, the study team will implement several practice standards for statistical programming, database management, and documentation for all projects involving database analyses. The following three steps will be undertaken to achieve this high level of quality:

- Documentation of SAS programming
    - To ensure smooth transition of analytic methods and work among programmers, reviewers, and other project personnel, documentation of the following information will be created for each SAS program: Project name; Program name; Program purpose; Program author; Date the program was completed;

Descriptions of subsequent changes and/or enhancements, with name of programmer and date for each.

- Validation of SAS programs
  - We will conduct following programming validation methods: Log review; Review of data listings and tables of summary statistics.
- Database storage and retention
  - The HIRA data is not allowed to be possessed by individual researcher. The data will be stored in the server owned by HIRA and will be only accessed through the remote access. Thus, the study team will not be able to store and possess the data. Two researchers will be allowed to access the data at once since only two IP addresses will be provided by HIRA. To ensure the integrity of the original data files, the data will be stored on a Linux server in a designated folder that cannot be overwritten. Data sets derived from the original files during the analysis process will be stored in a separate folder.

8.9 Limitations of the research methods

8.9.1 Measurement Error(s)/Misclassification(s)

In general, all study measures will be defined by information available in the claims data in the form of diagnosis codes, procedure codes, drug codes, and dates of service. Patients were identified for study inclusion on the prescription claims, which (as with all claims-based studies) are subject to coding error. Patient charts were not available to validate the accuracy of case identification.

8.9.2 Information Bias

Information bias is less likely to occur since the HIRA data is a population level data which covers the whole population in Korea which has a universal health insurance system.

8.9.3 Selection Bias

This study will include only those patients who filled a prescription through their insurance for aspirin, warfarin, or NOACs. Patients who did not fill a prescription through their insurer (i.e., patients who received free samples or paid for the medication out of pocket) cannot be evaluated in an administrative claims database.

Since the HIRA database does not include eligibility data and the complete mortality data for beneficiaries, the continuous health plan enrollment cannot be ensured and the deceased could be included in the analysis.

8.9.4 Analysis Limitations

The results of this study can be generalizable only to patients included in the HIRA population which is the entire Korean population. Results should not be generalized to other patient populations or healthcare systems outside Korea.

8.9.5 Missing and/or Incomplete Data

This study does not account for unobserved confounders. No information is provided in the database as to why patients may discontinue treatment. Further, no information is available regarding medications the patients may have received as over-the-counter treatment or as samples from the physician, as well as medications paid for out of pocket.

8.10 Other aspects

Not applicable.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Patient Information and Consent

Informed consent is not required for this study, because this study is secondary data collection study using fully anonymized data.

9.2. Patient withdrawal

Not Applicable.

9.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, and informed consent forms, and other relevant documents, (e.g., recruitment advertisements), if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

9.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences (CIOMS), management and REPORTING of adverse events/adverse reactions

This study includes unstructured data (e.g., narrative fields in the database) that will be converted to structured (i.e., coded) data solely by a computer using automated/algorithmic

methods and/or data that already exist as structured data in an electronic database. In these data sources, it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) are not available and AEs are not reportable as individual AE reports.

10. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The results of this research will be submitted for publication in a peer-reviewed journal and will be submitted for presentation in either poster or oral format at a medical or outcomes based research conference.

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICJME) Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, 3 and 4.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Pfizer for corporate review. The vendor agreement will detail the procedures for, and timing of, Pfizer's review of publications.

COMMUNICATION OF ISSUES

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

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this NI study protocol that the investigator becomes aware of.

11. REFERENCES

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1. LIST OF TABLES

2. LIST OF FIGURES

3. ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

4. ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable.

5. ANNEX 3. ADDITIONAL INFORMATION

Not applicable.

[redacted]