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TITLE: REAL-WORLD EFFECTIVENESS AND SAFETY OF DIRECT ORAL ANTICOAGULANTS AND WARFARIN IN PATIENTS WITH NONVALVULAR ATRIAL FIBRILLATION

Research Proposal

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Real-world effectiveness and safety of direct oral anticoagulants and warfarin in patients with atrial fibrillation

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CHAPTER I
BACKGROUND & RATIONALE

1.1 Background and Rationale

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia with increasing prevalence over the past decades.[1, 2] Patients with AF increased risk for hospitalization, morbidity and mortality attributable to stroke, thromboembolism and heart failure.[2-6] AF is defined as a supraventricular tachyarrhythmia with uncoordinated atrial electrical activation and consequently ineffective atrial contraction.[7] It is diagnosed by $\geq$ 30 seconds 12-lead electrocardiogram (ECG) documentation of absence of distinct repeating P waves and irregular R-R intervals (when atrioventricular conduction is not impaired).[7] One of cornerstones of AF management is long-term oral anticoagulation to reduce the risk of thromboembolism.

1.1.1 Magnitude of problems

Prevalence and incidence rates of AF vary with age, gender, race, geography and time period. AF is more prevalent in older population, men, and whites.[1, 8-12] The worldwide prevalence of AF in 2017 was estimated to be 0.51% (37,574 million cases of worldwide population).[13] In the United States, prevalent AF was 5.2 million in 2010 and is expected to reach 12.1 million in 2030.[14] Data from the Rotterdam Study showed that the prevalence of AF among adults aged $\geq$ 55 years was 7.7%, and the number of AF in the European Union will double from approximately 8.8 million in 2010 to 17.9 million by 2060 for those $\geq$ 55 years of age.[15] Compared with studies from Western countries, the prevalence estimates for AF across Asia were lower. The prevalence of AF in South Korea was 0.73% (269,448 patients) and 1.53% (639,349 patients) in 2006 and 2015, respectively with a trend toward increased prevalence at 5.81% (2.3 million) in 2060.[16]

In Thailand, the prevalence of AF varies from 1.9%-2.2% in elderly aged more than 60-65 years.[17, 18] Recently AF prevalence estimates obtained from the community-based study of 2.7% has been reported in Thai people aged 65 and over.[19]

The worldwide incidence rate of AF in 2017 was 403/millions inhabitants (total of 3046 million new cases).[13] In a community-based Multi-Ethnic Study in the United States from 2000 to 2002, the age- and sex-adjusted incidence rates per 1000 person-years were 11.23 (9.82-12.84) for non-Hispanic white, 3.94 (2.54-6.11) for Chinese, 5.77 (4.75-7.02) for non-Hispanic blacks and 6.07 (4.71-7.84) for Hispanics.[20]

The number of new AF cases in the UK was projected from 5.9 (5.8 to 6.1) per 1000 person-years in 2001 to 6.9 (6.8 to 7.1) per 1000 person-years in 2013.[21] The magnitude of the increase in incidence was greater with advancing age. In a study using the entire Korean adult population, per 1000 person-years, the overall incidence was 1.77 and the absolute rate increased in those aged $\geq$ 85 years.[16] However, AF incidence data for Thai population is very limited.

A Systematic review of the epidemiology of AF reported the prevalence and incidence of stroke in AF in regions outside North America.[22] The prevalence of stroke ranged from 3.1% to 24.2% in hospital-based cohorts and 13.0% to 15.4% in community-based cohort studies in China, Japan, Singapore, and Taiwan. A systematic review of cohort studies and RCTs found overall annual stroke rates varied from 0.45% to 9.28% per year among patients with nonvalvular AF not treated with oral anticoagulants.[23] The incidence of stroke and embolic events among paitnets with AF ranged from 1.7% per year to 5.6% in hospital-based studies. The annual risk of ischemic stroke in AF from community-based studies was 1.90% (-0.36%-4.17%).[24] Incidence of bleeding complications in patients treated with long-term anticoagulant was 3.8% (95% CI 3.8%–3.9%) per person-year.[25] A systematic review of real world studies carried out prior 2010, major bleeding rates for non-OAC-treated AF patients ranged between 0.0 and 3.9 per 100 person-years and between 0.0 and 7.2 per 100 person-years for AF patients treated with OAC therapy in an optimal treatment setting (anticoagulation clinics).[26]

1.1.2 Burden of stroke in AF patients

The currently estimated lifetime risk of AF was 1 in 3 individuals of European ancestry at index age of 55 years, whereas approximately the risk was 1 in 5 in Chinese population and 1 in 7 in Taiwanese adults.[27-29] The burden of AF does not only affect on patients individually, but also has direct and indirect broad impacts on society and economy. The worldwide economic burden of AF was 5976 million disability-adjusted life years (DALYs) in 2017, a 77% increase since 1997.[13]

The major adverse consequences of AF include stroke, systemic embolization (e.g., thromboembolic events in the aorta and the renal, mesenteric, pelvic, and extremity arteries), heart failure, cognitive impairment, dementia, depression, impaired quality of life, hospitalization and all-cause mortality.[30] Patients with AF who developed stroke has a huge negative impact on the survivors and caregivers owing to poor long term outcome, high recurrence rate, residual disability, and mortality.[31] In the Framingham study, risk of stroke was 5-fold increase in AF group compared with those without AF.[32] Previous studies reported prevalence of AF in patients with ischemic stroke of about 15-30%.[33-36] Data from 3 European observational studies suggested that the cost of AF-related stroke was 7-20% more than non-AF-related stroke and was attributable to hospital care and re-hospitalization.[37] Using the national public/private hospital database in France (2012), investigators estimated burden of cardiovascular complications in 533,044 hospitalized AF patients, 6.9% stroke/ TIA/systemic embolism, and 1.3% hemorrhages.[38] The annual total cost for all hospitalized cardiovascular events was €1.94 billion, of which stroke represented €362 million, and haemorrhage €48 million. Results from a systematic review of 16 studies in 2015 revealed that stroke-related health care costs were $8184, $12895, and $41420 for lower-middle–, middle-, and high-income economies, respectively.[39] However, the major cost component was from hospitalization.

Moreover, in the original Framingham Heart Study of AF population (55-94 years of age) reported 1.5-1.9-fold increase in mortality over 40 years of follow-up.[40] Among 272,186 hospital-based patients with AF included in the Swedish National Patient Registry, the mortality rates per 1000 person- years in the 3 age categories (< 65, 65-74 and 75-85 years) were 25.0, 63.5, and 152.1; and 27.5, 80.0, and 185.4 in women and men,

respectively.[41] According to population-based longitudinal survey of Scottish adults, women have a 2.2-fold higher long-term risk of all-cause mortality and 1.5-fold higher in men.[42]

1.1.3 Treatments & goals of treatments

The main objectives of AF treatment are symptoms control, prevention of cardiac dysfunction and thromboembolic events, particularly stroke.

Thrombosis-related clinical events in AF are attributed to thrombus formation in the left atrium with subsequently peripheral embolization. The pathogenesis of thrombosis, as proposed by Virchow, includes alterations in the blood constituents, abnormalities in blood flow and blood vessels wall.[43] Dilated left atrium, impaired left atrial function, and impaired left ventricular systolic function leading to blood stasis are related to risk of stroke and thromboembolism. Furthermore, hypercoagulable state, and endothelial dysfunction may contribute to development of thrombosis.

Long-term anticoagulation is a cornerstone of the treatment of AF. Vitamin K antagonist (VKA) such as warfarin inhibits vitamin K–dependent clotting factors II, VII, IX, X, proteins C and protein S synthesis by blocking the vitamin K epoxide reductase.[44] VKA has been extensively studied and demonstrated to be of significant efficacy compared with aspirin. An individual patient meta-analysis of 4052 patients with nonvalvular AF pooled from 6 randomized clinical trials (RCTs), patients receiving adjusted-dose warfarin with international normalized ratio (INR) target 2 to 3 were at a decreased risk of ischemic stroke (HR, 0.48; 95% CI, 0.37-0.63), but increased risk of major bleeding (HR, 1.71; 95% CI, 1.21-2.41) compared with aspirin.[45] Nonetheless, use of warfarin in clinical practice remains very challenging because of narrow therapeutic range, poor medication adherence, many adverse food and drug interactions, genetic variation in warfarin metabolism and frequent INR monitoring.

Current evidences of high-quality RCTs have demonstrated benefits of direct oral anticoagulant (DOAC) treatment (dabigatran, rivaroxaban, apixaban, edoxaban) on long-term consequences (e.g., stroke, systemic embolism, all-cause mortality), along with reducing complications of treatment (e.g., intracerebral hemorrhage, major bleeding, non-

major bleeding). These studies directly comparing between efficacy of warfarin and DOAC among patients with nonvalvular AF have shown similar or higher efficacy of DOAC, whereas risk of major bleeding, and intracranial hemorrhage were lower, compared with adjusted-dose warfarin.[46-49] A meta-analysis of a randomized control study showed benefit of DOAC as compared with warfarin in 19% reduction in stroke or systematic embolism (RR, 0.81; 95% CI, 0.73, 0.91) with 14% reduction in major bleeding (RR, 0.86; 95% CI, 0.73, 1.00) and 51% reduction in hemorrhagic stroke (RR, 0.49; 95% CI, 0.38, 0.64;.[50] Findings were similar in previous meta-analysis studies of phase II and phase III RCTs.[51-53] The efficacy and safety of DOACs were observed regardless of age, renal function, presence of diabetes mellitus or heart failure, prior VKA use or previous cerebrovascular events.[54, 55] A few meta-analysis of randomized trials focusing Asians has been consistently shown in previous meta-analyses.[56, 57] DOACs was associated with reduced risks of stroke or systematic embolism (RR, 0.73; 95% CI, 0.59, 0.90) and major bleeding (RR, 0.59; 95% CI, 0.48, 0.72).[57]

A meta-analysis of Japanese populations concluded that DOACs are at a reduced risk of stroke and systemic thromboembolism (RR, 0.45; 95% CI: 0.24, 0.85), major bleeding (RR, 0.66; 95% CI: 0.29, 1.47), and intracranial bleeding (RR, 0.46; 95% CI, 0.18, 1.16).[58] However, there is no RCTs directly comparing efficacy and safety among different type of DOACs.

RCTs are usually considered as the higher level (quality) of evidence compared to observational studies, also data from RCTs are incorporated for developing the guidelines and recommendations for clinicians. RCTs can reduce confounding, prevent selection bias based on treatment allocation, and directly estimate the causal effect. Nevertheless, the disadvantages of RCTs are related to the generalizability of the study because of strict study design and setting, specific patient selection which do not reflect real-world populations. Also, in the presence of cost, time, logistics, and ethical concerns, real world data can be used to mimic a RCT and will provide estimates of the causal treatment effect. Additionally, tight control setting, highly selected patient populations, narrow inclusion criteria, strict prestudy treatment protocol of RCT leads to the limit of generalizability of DOAC use in the real-world practice. Under “real-world” circumstances, there is variation across patient

demographics and characteristic (e.g., ethnicity, population risks), the use of anticoagulation (e.g., type of anticoagulant, dosage, regimen) and outcome of interest. These leads to different pharmacokinetic and pharmacodynamic compared to RCTs. Additionally, there is no head-to-head RCT for a direct effectiveness and safety comparison between the individual DOAC.

Thus, using real world evidence (RWE) in assessing real-world clinical safety and effectiveness will provide better valuable information on treatment practices and resource utilization, especially for low resource health care systems. For example, RCT tend to exclude patients who have fewer comorbidities, whereas real-world population tend to have major comorbidities, various dose adjustment, poor treatment adherence, and INR monitoring of warfarin. RWE study will able to capture real-time clinical treatment and relevant clinical outcomes (e.g., health-related quality of life, physical functioning, symptom severity) from multiple data sources such as electronic health record, patient registries, administrative and claims database, etc. Additionally, RWE can support health economic evaluation applied to clinical decision-making, treatment allocations and re-imbursement scheme by clinicians, health care administrators and policy makers.

RWE from large pragmatic, observational studies also support DOAC using in clinical practice and monitor the postmarket drug safety. In a meta-analysis pooling data from 28 studies of dabigatran, rivaroxaban, and apixaban compared with VKA in the real-world setting. There was no statistical difference between dabigatran and VKA for the outcomes of ischemic stroke or systemic embolism (HR, 1.17; 95% CI, 0.92, 1.50), and major bleeding (HR, 0.83; 95% CI, 0.65, 1.05). Compared with VKA, rivaroxaban was associated with similar risk of ischemic stroke or systemic embolism (HR, 0.73; 95% CI, 0.52, 1.04) and major bleeding (HR, 1.00; 95% CI, 0.92–1.08). Compared with VKA, apixaban was associated with lower risk for ischemic stroke or systemic embolism (HR, 1.07; 95% CI, 0.87, 1.31) and major bleeding (HR, 0.55; 95% CI, 0.48, 0.63).[59]

A recent meta-analysis of 15 observational studies demonstrated head-to-head comparison between DOACs.[60] In comparison between rivaroxaban versus dabigatran, a risk of stroke or systemic embolism is similar (HR, 1.00; 95% CI, 0.91, 1.10), but risk of major bleeding increased for rivaroxaban compared with dabigatran (HR, 1.39; 95% CI

1.28, 1.50). In comparison between rivaroxaban versus apixaban, risk of stroke or systemic embolism is similar (HR, 1.09; 95% CI, 0.96, 1.24), but risk of major bleeding increased for rivaroxaban compared with dabigatran (HR, 1.71; 95% CI 1.51, 1.94). In comparison between apixaban versus dabigatran, risk of stroke or systemic embolism is similar (HR, 0.94; 95% CI 0.83, 1.06), but risk of major bleeding decreased for rivaroxaban compared with dabigatran (HR, 0.80; 95% CI 0.68, 0.95). Consistent with the previous finding, apixaban is likely to be the most favorable option in relation to any major bleeding with the exception of conflicting results in stroke or systemic embolism for any pair of DOACs comparison are seen.[60-64]

A meta-analysis of real-world studies in Asian patients reported that compared with warfarin, DOAC was associated with decreased risk of thromboembolism (HR, 0.70; 95% CI, 0.63, 0.78), all-cause mortality (HR, 0.62; 95% CI, 0.56, 0.69), major bleeding (HR, 0.59; 95% CI, 0.50, 0.69), and intracranial hemorrhage (HR, 0.50; 95% CI, 0.40, 0.62).[65] Only one meta-analysis using evidences from the real-world data directly compared the efficacy and safety between DOAC and DOAC in Asian.[66] There were no differences between dabigatran versus rivaroxaban, and dabigatran versus apixaban for the efficacy and safety outcomes including stroke or systemic embolism, and major bleeding. In comparison with rivaroxaban, apixaban was associated with reduced risks of stroke or systemic embolism but similar rate of bleeding events.

Conflicting data derived from previous network meta-analyses have been reported on the ranking of each DOAC for efficacy and safety.[67, 68] Furthermore, previous studies were mostly conducted in high-income and developed countries, the evidence from real-world data for informing health policy development in low-income and middle-income countries (LMICs) are limited.

In a comparative study of effectiveness and safety of DOACs (dabigatran, rivaroxaban and apixaban) versus warfarin among 2,055 patients with nonvalvular AF in Thailand, risk of major bleeding was significantly lower across either the DOAC group or each individual DOAC.[69] Applying propensity score-based, marginal mean weighting through stratification-weighted Cox proportional hazard regression

for multivariate analysis with hospital stratification to compare risk of thromboembolism and major bleeding of DOAC with warfarin users with poor time in therapeutic range (TTR), risk of thromboembolism decreased for apixaban (adjusted HR, 0.48; 95% CI, 0.26–0.86) and dabigatran (adjusted HR, 0.44; 95% CI, 0.21–0.90). However, there were limitations from small sample size, lack of data on edoxaban and missing cases of death.

Through our study, we will explore the effectiveness and safety of warfarin and the currently available DOACs (dabigatran, rivaroxaban, apixaban and edoxaban) from real-world data in Thailand with different characteristics at patient-level and country-level, compared to previous observational studies in which conducted in high income and developed countries. Regarding the challenges in future trend and growth rate in AF prevalence, the result of this study in Thai setting will provide useful data to improve quality of care and drive policy implementation in resource-limited settings.

1.2 Research Question

Are DOACs (dabigatran, rivaroxaban, apixaban, edoxaban) effective and safe for prevention of thromboembolism in real-world patients with AF?

1.3 Research Objectives

1.3.1 Primary Objective

To estimate the treatment effectiveness for lowering all stroke and systemic embolism, and risk of major bleeding between

- all DOACs group (dabigatran, rivaroxaban, apixaban, and edoxaban) and warfarin
- each DOAC and warfarin
- any comparison pair of DOACs (the individual DOAC and any other different DOAC)

1.3.2 Secondary Objectives

To compare rates of ischemic stroke, unspecified stroke, hemorrhagic stroke, intracranial bleeding, gastrointestinal bleeding, clinically relevant non-major (CRNM)

bleeding, hospitalization, all-cause mortality, composite outcome of stroke, systemic embolism and all-cause mortality between groups as above.

CHAPTER II
LITERATURE REVIEW

2.1 Atrial fibrillation

AF is the most commonly treated sustained cardiac arrhythmia. AF is caused by an interaction between a trigger and the underlying substrate.[70, 71] Mechanical and anatomical change of the atria, particularly atrial dilatation plays a important role in the development of a substrate for AF. Then a rapid electrical firing in the atria or from the pulmonary veins trigger AF. However, the mechanism for AF development is poorly understood. Age, diabetes, hypertension, metabolic syndrome, hyperthyroidism, obesity, obstructive sleep apnea, venous thromboembolic disease alcohol excess, cardiac surgery, left atrial size and underlying heart diseases, e.g., coronary disease, valvular heart disease, heart failure, congenital heart disease are associated with an increased risk of the development of AF.[72-81]

Diagnosis of AF requires 12-lead ECG or a single-lead ECG recording of $\geq$ 30 seconds showing heart rhythm with no distinct repeating P waves, irregular atrial activations and irregular R-R intervals (when atrioventricular conduction is not impaired).[7] It is divided into four categories: paroxysmal AF, persistent AF, and permanent AF. Patients can range from asymptomatic or symptomatic including palpitations, fatigue, weakness, dizziness, lightheadedness, reduced exercise capacity, increased urination, or dyspnea, chest pain, presyncope. Furthermore, some patients present with complications, e.g., stroke or other systemic embolization or heart failure.

2.2 Oral anticoagulants for stroke prevention

The Atrial fibrillation Better Care (ABC) holistic pathway ('A' Anticoagulation/Avoid stroke; 'B' Better symptom management; 'C' Cardiovascular risk factors and comorbid conditions management) has been proposed as an integrated approach

to improve the integrated management of AF patients. Focusing on stroke prevention using anticoagulation using VKA or DOACs, therefore B (better symptom control) and C (cardiovascular and comorbidity optimization) are beyond the scope of this document.

Guideline recommendations for oral anticoagulantion in AF patients are based on the CHA2DS2-VASc stroke risk point scores. According to 2020 European Society of Cardiology (ESC) Guidelines for the diagnosis and management of atrial fibrillation, long OAC therapy is indicated for AF patients with CHA2DS2-VASc score of ≥2 in males or ≥3 in females (Class I, level A) ; and for a CHA2DS2-VASc score of 1 in males and 2 in females (Class IIa, level B). Moreover, DOAC is preferable in those with poor anticoagulation control (TTR < 70 %) or intorable.[7]

2.2.1 VKA

VKAs are the first anticoagulants used for long-term oral anticoagulation in patients with AF. VKAs (warfarin and acenocoumarol) inhibit the vitamin K dependent synthesis of clotting factors via depleting the reduced form of vitamin K that serves as a cofactor for gamma carboxylation in the liver.[82] It is indicated for use in patients with a mechanical heart valve or rheumatic mitral stenosis. It is preferable for patients with chronic severe kidney disease whose creatinine clearance less than 25-30 mL/min. The anticoagulant effect of warfarin is depend on the individual variability of pharmacokinetics and pharmacodynamics effects. Therefore, the dosage of warfarin should be attained to opitimized TTR with therapeutic INR in the range of 2 to 3. A meta-analysis of 29 RCTs including 28,044 patients with AF showed that adjusted-dose warfarin reduces stroke by 64% and mortality by 26%, and be more efficacious (by approximately 40%) than antiplatelet therapy.[83] The advantages of warfarin includes clinician familiarity, low cost, wide availability, and a variety of anticoagulation reversal methods. However, warfarin use is related to bleeding, drug and food interaction, narrow therapeutic range and require frequent drug monitoring.

2.2.2 DOACs

DOACs directly and selectively inhibit specific coagulation factor of the coagulation cascade: factor II (thrombin), in the case of dabigatran, or activated factor X

(Xa), in the case of rivaroxaban, apixaban and edoxaban. DOACs either direct thrombin inhibitor or factor Xa inhibitors are options for anticoagulation for preventing thromboembolic disease with similar or lower rates of both ischemic stroke and major bleeding compared with VKA.

Dabigatran etexilate is an orally administered prodrug that is converted in to active dabigatran, a reversible competitive direct thrombin inhibitor, with a half-life of approximately 12-17 hours in patients with normal renal function. Dabigatran is metabolized by P-glycoprotein and 80% is eliminated via the kidneys. Therefore, it should not be used in individual with creatinine clearance (CrCl) <30 mL/minute. Dabigatran was the first of the available DOACs which was approved since 2010 in the United States and has been approved by the Thai Food and Drug Administration (FDA) in 2009.

Rivaroxaban is an orally active factor Xa inhibitor with a once daily dosing regimen with a half-life in the range of 5 to 9 hours. It is metabolized by P-glycoprotein, and 65% is excreted via fecal route using CYP3A4 and CYP212, and 35% through the kidneys. It is recommended to reduce dose in individuals with CrCl 15-50 mL/minute and avoided in patients with CrCl <15 mL/minute. Rivaroxaban has been approved in the United States in 2011, then the Thai FDA has given approval in 2012.

Apixaban is an orally direct factor Xa inhibitor with a 12-hour half-life. CYP3A4-type cytochrome P450-dependent elimination is about 73% and 27% is eliminated via feces and urine, respectively. It is reco mmended to reduce dose in individuals with CrCl 15-50 mL/minute and avoided in patients with CrCl <15 mL/minute. Both US FDA and Thai FDA have given approval in 2012.

Edoxaban was the most recent Thai FDA approval for DOACs in 2016. It is a direct oral factor Xa inhibitor with a plasma half-life of approximately 10-14 hours. Edoxaban is metabolized by CYP3A4-type cytochrome P450, of which half is eliminated by the urine excretion and the other half in feces.

2.3 Clinical effectiveness and safety of oral anticoagulant for stroke and embolism prevention

2.3.1 Randomized control studies

Four large phase III RCTs have been conducted for comparing efficacy and safety between each DOAC (dabigatran, rivaroxaban, apixaban, edoxaban) and VKA in nonvalvular AF patients (Table 2.1). The primary efficacy endpoint of these studies included stroke and systemic embolism, whereas the primary safety endpoint was major bleeding or major bleeding plus CRNM bleeding.

2.3.1.1 Dabigatran versus Warfarin in Patients with Atrial Fibrillation[46] (RE-LY trial)

RE-LY trial is a parallel-group, open-label, multicenter clinical trial with blinded end-point adjudication (PROBE design). It was performed from December 22, 2005, through December 15, 2007, with a median follow-up of 2 years, at 951 centers in 44 countries. The investigators included 18,113 patients with nonvalvular AF documented on electrocardiography and met at least one of the following: previous stroke or TIA or systemic embolism, a left ventricular ejection fraction of less than 40%, New York Heart Association (NYHA) class II or higher heart-failure symptoms within 6 months before screening, and an age of at least 75 years or an age of 65-74 years plus diabetes mellitus, hypertension, or coronary artery disease (CAD). In this noninferiority trial, fixed doses of dabigatran (110 mg or 150 mg twice daily) or adjusted-dose warfarin was randomly assigned. Of the randomized 18,113 patients with AF, rate of stroke or systemic embolism was similar for dabigatran 110 mg group (1.53%/year versus 1.69%/year; risk ratio (RR), 0.91; 95% CI, 0.74-1.11; $P<0.001$ for noninferiority) and lower for dabigatran 150 mg group (1.11%/year versus 1.69%/year; RR, 0.66; 95% CI, 0.53-0.82; $P<0.001$ for superiority). The rate of major bleeding was lower for dabigatran 110 mg group (2.71%/year versus 3.36%/year; $P=0.003$) and similar for dabigatran 150 mg group (3.11%/year versus 3.36%/year; $P=0.31$). The rate of hemorrhagic stroke was lower for both 110 mg of dabigatran (0.12%/year versus 0.38%/year; $P<0.001$) and 150 mg of dabigatran (0.1%/year versus 0.38%/year; $P<0.001$). The mortality rate was not significantly different

for both 110 mg of dabigatran (3.75%/year versus 4.13%/year; P=0.13) and 150 mg of dabigatran (3.64%/year versus 4.13%/year; P=0.051).

2.3.1.2 Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation[47] (ROCKET AF trial)

ROCKET AF trial is a randomized, double-blind, double-dummy study conducted at 1,178 participating sites in 45 countries between December 18, 2006, and June 17, 2009. A total of 14,264 patients with nonvalvular AF and moderate-to-high risk for stroke were randomly assigned either rivaroxaban (at a dose of 20 mg daily) or dose-adjusted warfarin. Patients are considered to be at elevated risk if they have history of stroke, TIA, or systemic embolism or at least 2 of the following risk factors: heart failure and/or a left ventricular ejection fraction of 35% or less, hypertension, an age of $\geq$ 75 years, or the presence of diabetes mellitus (i.e., a CHADS2 score of $\geq$ 2, on a scale ranging from 1 to 6, with higher scores indicating a greater risk of stroke). The median duration of follow-up was 707 days. In the intention-to-treat analysis, the rate of stroke or systemic embolism was 2.1% per year in the rivaroxaban group, as compared with 2.4% per year in the warfarin group (HR with rivaroxaban, 0.88; 95% CI, 0.74-1.03; P<0.001 for noninferiority; P=0.12 for superiority). Major and nonmajor clinically relevant bleeding was 14.9% per year in the rivaroxaban group and 14.5% per year in the warfarin group (HR, 1.03; 95% CI, 0.96-1.11; P=0.44). The annualized rate of intracranial hemorrhage (0.5% versus 0.7%, P=0.02) and fatal bleeding (0.2% versus 0.5%, P=0.003) in the rivaroxaban group.

2.3.1.3 Apixaban versus Warfarin in Patients with Atrial Fibrillation[48] (ARISTOTLE trial)

ARISTOTLE trial is a randomized, double-blind, double-dummy trial comparing apixaban at a dose of 5 mg twice daily with warfarin in 18,201 patients with NVAF and at least 1 additional risk factor for stroke (median follow-up, 1.8 years). The annualized rate of the primary outcome (ischemic or hemorrhagic stroke or systemic embolism) was 1.27% with apixaban, as compared with 1.6% with warfarin (HR, 0.79; 95% CI, 0.66-0.95; P<0.001 for noninferiority; P=0.01 for superiority). The annualized rate of major bleeding was 2.13 % with apixaban, as compared with 3.19% with warfarin (HR,

0.69; 95% CI, 0.60-0.80; P<0.001). The annualized rate of hemorrhagic stroke was 0.24% with apixaban, as compared with 0.47% with warfarin (HR, 0.51; 95% CI, 0.35 to 0.75; P<0.001).

2.3.1.4 Edoxaban versus Warfarin in Patients with Atrial Fibrillation[49] (ENGAGE AF-TIMI 48 trial)

ENGAGE AF-TIMI 48 trial is a randomized, double-blind, double-dummy trial recruiting 21,105 patients with NVAF and CHADS2 risk score $\geq$ 2 in approximately 1,393 centers across 46 countries. Two once-daily regimens of edoxaban (60 mg or 30 mg) were compared with warfarin. Over a 2.8-year follow-up period, rate of the primary efficacy end point (stroke or systemic embolism) was 1.5% per year in the warfarin group, as compared with 1.18% per year in the group that received 60 mg of edoxaban (HR, 0.79; 97.5% CI, 0.63-0.99; P<0.001 for noninferiority) and 1.61% per year in the group that received 30 mg of edoxaban (HR, 1.07; 95% CI, 0.87-1.31; P=0.005 for noninferiority). Rate of major bleeding was 3.43% per year with warfarin versus 2.75% with 60 mg of edoxaban (HR, 0.80; 95% CI, 0.7-0.91; P<0.001) and 1.61% with 30 mg of edoxaban (HR, 0.47; 95% CI, 0.41-0.55; P<0.001).

2.3.1.5 Meta-analysis of RCTs [50]

The systematic review and meta-analysis of 4 RCTs including RE-LY, ROCKET AF, ARISTOTLE, and ENGAGE AF–TIMI 48 trials that compared 42,411 patients receiving a DOAC and 29,272 patients receiving warfarin. Patients randomized to DOAC had a decreased risk for stroke or systemic embolism (RR, 0.81; 95%CI, 0.73–0.91; P<0.0001), intracranial hemorrhage (RR 0.48, 95%CI, 0.39-0.59; P<0.0001) and all-cause mortality (RR, 0.90; 95 % CI, 0.85-0.95; P=0.0003) with an increased risk for gastrointestinal bleeding (RR, 1.25; 95%CI, 1.01-1.55; P=0·04).

2.3.1.6 Network meta-analysis of RCTs

Oral anticoagulants for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis, and cost effectiveness analysis[84]

A network meta-analysis was conducted to compare the efficacy, safety and cost effectiveness of DOACs, including data from 23 randomized studies involving 94,656 patients. Thirteen studies compared a DOAC with warfarin.

Apixaban 5 mg twice daily (OR, 0.7; 95% CI, 0.66-0.94) and dabigatran 150 mg twice daily (OR, 0.65; 95% CI, 0.52-0.81) had significantly lower risks of stroke or systemic embolism compared with therapeutic doses of warfarin (INR range 2.0-3.0). Between the DOACs, edoxaban 60 mg once daily (OR, 1.33; 95% CI, 1.02-1.75) was associated with higher risk of stroke or systemic embolism compared with dabigatran 150 mg twice daily, whereas rivaroxaban 20 mg once daily had significant higher risk of stroke or systemic embolism (OR, 1.35; 95% CI, 1.03-1.78) but lower risk of myocardial infarction (OR, 0.62; 95% CI, 0.41-0.93) compared with dabigatran 150 mg twice daily. There was little evidence of differences between the effects of recommended dose DOACs on all-cause mortality.

Compared with warfarin INR 2.0-3.0, apixaban 5 mg twice daily (OR, 0.71; 95% CI, 0.61-0.81), dabigatran 110 mg twice daily (OR, 0.80; 95% CI, 0.69 to 0.93), edoxaban 30 mg once daily (OR, 0.46; 95% CI, 0.40-0.54), and edoxaban 60 mg once daily (OR, 0.78; 95% CI, 0.69-0.90) were associated with less major bleeding. The odds for major bleeding outcome were higher for dabigatran 150 mg twice daily compared with apixaban 5 mg twice daily (OR, 1.33; 95% CI, 1.09-1.62), for rivaroxaban 20 mg twice daily compared with apixaban 5 mg twice daily (OR, 1.45; 95% CI, 1.19-1.78), and for rivaroxaban 20 mg twice daily compared with edoxaban 60 mg once daily (OR, 1.31; 95% CI, 1.07-1.59). In addition, apixaban 5 mg twice daily, dabigatran 110 mg twice daily, dabigatran 150 mg twice daily, edoxaban 30 mg once daily, edoxaban 60 mg once daily, and rivaroxaban 20 mg once daily had more favorable odds for ICH when comparing with warfarin INR 2.0-3.0. The use of apixaban 5 mg twice daily had the lowest odds for ICH and gastrointestinal bleeding among the recommended dose DOACs.

Apixaban 5 mg twice daily was the most effective anticoagulant for prevention of stroke or systemic embolism, myocardial infarction, and all-cause mortality, and the safest anticoagulant for major and gastrointestinal bleeding.

2.3.1.6 Limitations of RCTs

All four phase III studies (RE-LY, ROCKET AF, ARISTOTLE, and ENGAGE AF) demonstrated efficacy and safety of DOACs (dabigatran, rivaroxaban, apixaban and edoxaban, respectively) compared with warfarin for the AF population.
Since there are no randomized head-to-head comparisons of different DOACs for stroke, bleeding, or mortality outcomes in patients with NVAF, the meta-analyses and network meta-analyses were applied for direct and indirect comparisons of treatments, respectively. Most of these studies showed benefits of DOACs treatment for stroke/systemic embolism, intracranial bleeding and major bleeding reduction. However,
there were methodological differences in study design, AF definition, patient characteristics, and safety endpoints leading to challenges in interpretation of these phase III studies and meta-analytic data.[46-49, 85]

1) Differences in study design

The study design used for these phase III studies was based on multicentre, randomized controlled, non-inferiority trials. Double-blind and double-dummy technique was used for all studies except for RE-LY study which used PROBE design (Prospective Randomized Open, Blinded End-point).

2) Differences in patient demographics and characteristics

Baseline patient characteristics of the intention-to-treat populations of these RCTs was shown (Table 2.2). All studies focused on patients with nonvalvular AF without moderate to severe mitral stensosis (usually of rheumatic origin) and mechanical prosthetic valve. In RE-LY, NVAF documented on ECG within 6 months of screening was used in patients with at least one of the following criteria: stroke/TIA, LVEF <40%, heart failure symptoms (NYHA class II or above) in 6 months before screening, age $\geq$ 75 or 65–74 years with diabetes mellitus, hypertension, or CAD).[46] In ROCKET AF, patients with NVAF documented on ECG were used with any of the following criteria: previous stroke/TIA or

systemic embolism or ≥ 2 of the following: heart failure or LVEF ≤ 35%, hypertension, age ≥ 75 years, or diabetes mellitus (i.e., CHADS2 score ≥ 2).[47] Patients with NVAF or flutter at enrolment or ≥ 2 incidences of AF or flutter, ≥ 2 weeks apart in the 12 months before enrolment; ≥ 1 risk factors were included in ARISTOTLE.[48] Patients with NVAF <12 months and CHADS2 score ≥ 2 were eligible in ENGAGE AF.[49]

3) Differences in DOACs dose regimen

The standard dose of DOACs (dabigatran 150 mg twice daily/110 mg twice daily, apixaban 5 mg twice daily, rivaroxaban 20 mg once daily, and edoxaban 60 mg once daily) were used in RCTs. Importantly, a DOAC dose reduction was applied for ROCKET AF, ARISTOTLE, and ENGAGE AF based on the patient demographics and characteristics (Table 2), giving low-dosed patients of 21.0%, 4.7% and 32.4%, respectively in these trials. By contrast, in RE-LY, dose adjustment was not used, but dabigatran 150 or 110 mg twice daily were randomized to the treatment arm of the trial.[47-49] Furthermore, all of these RCTs recruited only new oral anticoagulant (OAC) users or OAC naive patients.

4) Differences in endpoint and outcome definitions

The primary efficacy endpoint for all phase III RCTs was stroke or systemic embolism. The primary safety endpoint in RELY, ARISTOTLE, and ENGAGE AF was major bleeding, whereas ROCKET AF included major bleeding and CRNM bleeding for primary safety outcome. Nonetheless, there was a variation in the definitions of stroke, major bleeding, and CRNM bleeding among studies. For example, RELY did not specify any minimum timeframe for defining a stroke, whereas the other three studies specified a minimum of 24 hours for persistent symptoms to be diagnosed stroke. Furthermore, there was a difference in defining major bleeding events. ARISTOTLE specified a 24 hour time window for a Hb decrease of ≥ 2 g/dL or transfusion of ≥ 2 units of packed red cells to be included as a major bleeding event. RELY, ROCKET AF and ENGAGE AF, in contrast, did not specify a limited timeframe but specify transfusion of ≥ 2 units of packed red cells or whole blood for defining a major bleeding.

2.3.2 Observations studies

Observational studies on real-world data in DOACs rapidly increase in the last decade. Tables 3 shows these RWE studies on the use of DOACs. The study characteristics, data source, comparators, follow-up duration, main outcomes and statistical analysis were reviewed.

In a retrospective, cohort study of 2,055 NVAF patients from 9 tertiary-care hospitals across 4 provinces in Thailand, 3 DOACs (dabigatran, rivaroxaban, and apixaban) were more effective in reducing major bleeding (adjusted HR 0.46; 95% CI, 0.34–0.62). The superiority in thromboembolism (stroke or systemic embolism) prevention and reduction of major bleeding were more pronounced when compared with warfarin users with poor time in TTR, adjusted HR 0.44 (95% CI, 0.21–0.90) and 0.26 (95% CI, 0.12-0.58) for dabigatran, and adjusted HR 0.48 (95% CI, 0.26–0.86) and 0.36 (95% CI, 0.18–0.73) for apixaban. However, there were some limitations 1) limited numbers of study population and outcome events 2) not included edoxaban 3) more than 50% of sample sized taking a low dose of DOAC 4) no clear explantion about switching treatment.

2.3.2.1 Meta-analysis of observational studies

Twenty-eight studies from real-world setting until January 7, 2017 have been included in the final meta-analysis to compare efficacy and safety between DOACs and VKA. The risk of ischemic stroke, ischemic stroke or systemic embolism, any stroke or systemic embolism, myocardial infarction, intracranial hemorrhage, major hemorrhage, gastrointestinal hemorrhage, and death were estimated. For the risk of ischemic stroke and ischemic stroke or systemic embolism, the HRs were 1.05 (95% CI, 0.75–1.19) and 1.08 (95% CI, 0.95–1.22) for apixaban versus 0.96 (95% CI, 0.80–1.16) and 1.17 (95% CI, 0.92–1.50) for dabigatran versus 0.89 (95% CI, 0.76–1.04) and 0.73 (95% CI, 0.52–1.04) for rivaroxaban). For the risk of intracranial hemorrhage, the HRs were 0.45 (95% CI, 0.31–0.63) for apixaban versus 0.42 (95% CI, 0.37–0.49) for dabigatran versus 0.64 (95% CI, 0.47–0.86) for rivaroxaban.

2.3.2.2 An updated meta-analysis in Asians[86]

A total of 12 observational studies of 441,450 Asian patients with NVAF were included in this meta-analysis. Compared with warfarin, dabigatran, rivaroxaban, and apixaban were associated with a reduction of ischemic stroke (HR, 0.78; 95% CI, 0.65-0.94; HR, 0.79; 95% CI 0.74-0.85; HR, 0.70; 95%CI, 0.62-0.78; respectively), all-cause mortality (HR, 0.68; 95%CI, 0.56-0.83; HR, 0.66; 95%CI, 0.52-0.84; HR, 0.66; 95%CI, 0.49-0.90, respectively), and major bleeding (HR, 0.61; 95%CI, 0.54-0.69; HR = 0.70, 95%CI: 0.54-0.90; HR = 0.58, 95%CI: 0.43-0.78; respectively).

2.3.2.3 Network meta-analysis[87]

Ten real-world studies including 312,827 Asian patients receiving DOACs (apixaban, dabigatran, rivaroxaban) or warfarin were identified. The risks of ischemic stroke, all-cause death, and major bleeding were lower for all DOACs treatment compared with warfarin. The risk of ischemic stroke was lower with apixaban (HR, 0.59; 95% CI, 0.40–0.85) than dabigatran, and was higher with rivaroxaban (HR, 1.61; 95% CI, 1.08–2.41) than apixaban. Moreover, the risk of major bleeding was higher with rivaroxaban (HR, 1.39; 95% CI, 1.02-1.90) than apixaban.

2.3.2.4 Limitations 'Real-world' observational studies

Although real world data can complement the evidences from RCTs by improving generalizability of research findings, allowing larger sample sizes and longer follow-up time, reducing overall cost, and including less common outcomes. The real-world observational studies carry significant limitations, for example, prone to selection bias, information bias and unmeasured confounding, especially when implemented the results for treatment effectiveness.

Most of real-world evidences in DOACs therapy were conducted in United States and high-income countries in Europe and East Asia. A few studies were conducted in upper middle-income countries such as Thailand, Malaysia. The retrospective studies using data sources based on nationwide or regional registries, medical claims and insurance data, hospital cohorts, investigator-initiated and industry-sponsored studies were frequently performed. However, these are more susceptible to investigator bias,

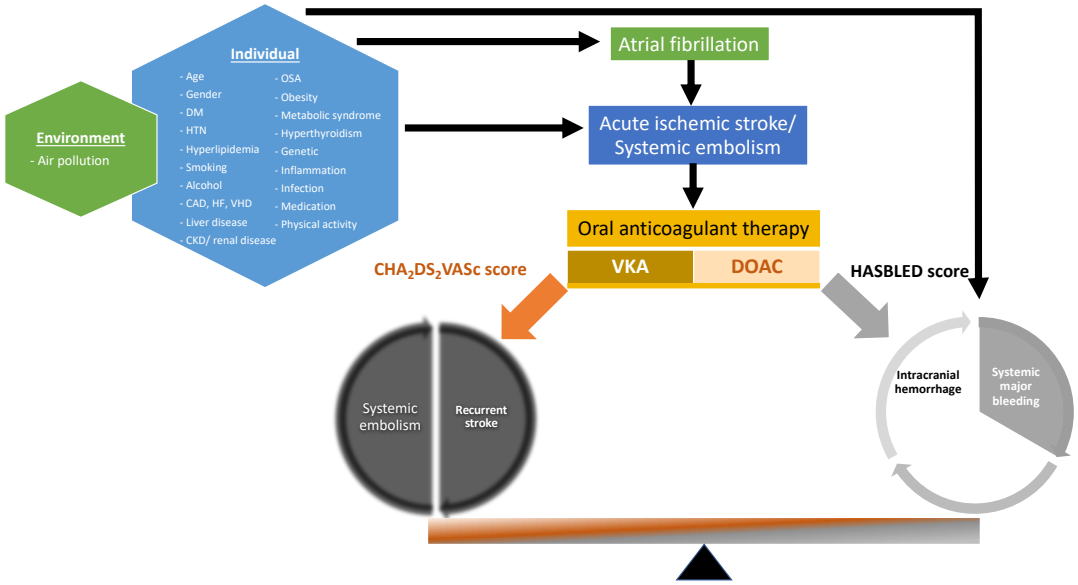
immortal bias, low quality of data and confounding when compared with prospective studies. The biases were related to doctor/patient preferences, different standard of care, dose-reduction strategies, drug availability and accessibility, patient insurance/budget, healthc care systems. Furthermore, the outcome definition used in these studies varied and may not be systematically collected and endpoint adjudication.

The previous real-world studies have expanded from warfarin-controlled to compare the DOACs to each other, predominantly in the earlier FDA-approved DOACs including dabigatran, rivaroxaban, and apixaban. However, the comparative studies for edoxaban were limited.

The commonly used statistical modelling are 1) Cox proportional hazard model, 2) propensity scores matching with same or very similar probability in two groups, but sometimes suffering from unknown or unmeasured confounders, incomplete match and smaller sample size and 3) propensity stratified models that used covariates to calculate the probability of receiving one of two treatments, for example, inverse probability of treatment weighting (IPTW) regarding time-to-event analyses.

The validity and heterogeneity of the meta-analysis or network meta-analyses were concerned when using observational studies rather than RCTs. There were higher risks of bias and confounding because the confounding factor probably not measured and controlled properly in the individual studies. Therefore, reporting and methodological quality of conducting meta-analyses of non-randomized studies need to be improved.

2.4 Conceptual framework



CAD; coronary artery disease, CKD; chronic kidney disease, DM; diabetic mellitus, HF; heart failure, HTN; hypertension, OSA; obstructive sleep apnea, VHD; valvular heart disease

TABLE

Table 2.1. Comparison of the 4 DOACs RCTs

	RE-LY	**ROCKET AF**	**ARISTOTLE**	**ENGAGE AF**
Design	Randomized, PROBE design	Randomized, Double-blind, double-dummy	Randomized, Double-blind, double-dummy	Randomized, Double-blind, double-dummy
Inclusion criteria	Age > 18 years NVAF documented by ECG within 6 months of screening ≥ 1 of the following: - previous stroke/TIA or systemic embolism - LVEF <40%, - symptomatic heart failure (NYHA ≥ class II) in the last 6 months - age ≥ 75 years - age 65–74 years + diabetes mellitus, hypertension, or CAD	Age > 18 years NVAF documented by ECG within 30 days of randomization History of prior ischemic stroke, TIA or non-CNS systemic embolism ≥ 2 of the following: - heart failure and/or LVEF ≤ 35% - hypertension - age ≥ 75 years - diabetes mellitus	Age ≥ 18 years NVAF or atrial flutter documented by ECG at enrollment or ≥ 2 incidences of AF or flutter, ≥ 2 weeks apart in the 12 months before enrolment ≥ 1 risk factors: - age ≥ 75 years - prior ischemic stroke, TIA or systemic embolism - symptomatic heart failure within 3 months or LVEF ≤ 40% - diabetes mellitus - hypertension	Age ≥ 21 years NVAF documented by ECG within the prior 12 months $CHADS_2$ index score ≥ 2
Study drugs	Dabigatran 150 mg or 110 mg twice daily	Rivaroxaban 20 mg once daily	Apixaban 5 mg twice daily	Edoxaban 60 mg or 30 mg once daily

	RE-LY	ROCKET AF	ARISTOTLE	ENGAGE AF
Dose reduction	-	15 mg once daily if CrCl ≤ 15-49 mL/min	2.5 mg twice daily if two out of three fulfilled: - weight ≤ 60 kg - age ≥ 80 years - serum creatinine ≥ 133 mmol/L (1.5 mg/dL) (or single criterion: if CrCl 15-29 mL/min)	30 mg once daily if: - weight ≤ 60 kg or - CrCl 15-49 mL/min or - concomitant therapy with strong P-Gp inhibitor

CAD, coronary artery disease; CNS, central nervous system; CrCl, creatinine clearance; ECG, electrocardiogram; kg, kilogram; LVEF, left ventricular ejection fraction; mg, milligrams; mg/dL, milligrams/decilitre; mL/min, milliliters per minute; NVAF, nonvalvular AF; NYHA, New York Heart Association; P-Gp, P-glycoprotein; PROBE, Prospective Randomized Open Blinded End-point; TIA, transient ischemic attack

Table 2.2 Baseline patient characteristics of the intention-to-treat populations of these RCTs[85]

	RE-LY			**ROCKET AF**		**ARISTOTLE**		**ENGAGE AF**		
	Dabigatran 150 mg (n=6,076)	Dabigatran 110 mg (n=6,015)	Warfarin (n=6,022)	Rivaroxaban (n=7,131)	Warfarin (n=7,133)	Apixaban (n=9,120)	Warfarin (n=9,081)	Edoxaban 60 mg (n=7,035)	Edoxaban 30 mg (n=7,034)	Warfarin (n=7,036)
Age ≥ 75 yr	40	38	39	43	43	31	31	41	40	40
Women	37	36	37	40	40	36	35	38	39	38
CHADS2 score, mean	2.2 (1.2)	2.1 (1.1)	2.1 (1.1)	3.5 (0.9)	3.5 (1.0)	2.1 (1.1)	2.1 (1.1)	2.8 (1.0)	2.8 (1.0)	2.8 (1.0)
Previous stroke or TIA	20	20	20	55	55	19	20	28	29	28
Heart failure	32	32	32	63	62	36	35	58	57	58
Diabetes	23	23	23	40	40	25	25	36	36	36
Hypertension	79	79	79	90	91	87	88	94	94	94
CrCl <50 mL/min	19	19	19	21	21	17	17	20	19	19
Follow-up, yr	2.0	2.0	2.0	1.9	1.9	1.8	1.8	2.8	2.8	2.8
TTR, median (IQR)	NA	NA	67 (54-78)	NA	58 (43-71)	NA	66 (52-77)	NA	NA	68 (57-77)

CHAPTER III
METHODOLOGY

3.1 Study design and setting

This retrospective cohort study using real world data will be based on data from Ramathibodi Hospital Database from January 1, 2010 through December 31, 2020. We will emulate RCTs and create a target trial using the observational data. The key design elements include 1) eligibility criteria, 2) treatment assignment and randomization, 3) specification of "time zero", 4) outcomes, 5) follow-up, 6) causal contrasts (intention-to-treat versus per protocol), and 7) statistical analyses.[88, 89] A framework for comparative effectiveness research will be applied as previously described.

3.2 Study patients

The first element of the target trial framework is establishing a patient's eligibility for study inclusion. The original DOAC RCTs (RE-LY, ROCKETAF, ARISTOTLE, and ENGAGE AF trials) recruited a specific non-valvular AF with different patient characteristics (Table 3.1).

Adults patients with AF who received either a DOAC or warfarin during January 1, 2010 through December 31, 2020 at Ramathibodi hospital will included if they meeting the following criteria.

3.2.1 Inclusion criteria

1) Aged ≥ 18 years

2) Diagnosis A F by 12-lead ECG on the day of starting anticoagulant treatment or before the study period (January 1, 2011 to December 31, 2020)

3) Receiving warfarin or at least one DOAC (dabigatran, rivaroxaban, apixaban, edoxaban) was initiated

4) Have follow up after receiving DOAC or warfarin at least 2 years

3.2.2 Exclusion criteria

1) Patients who diagnosed with moderate or severe mitral stenosis

2) Patients who had history of a mechanical prosthetic valve

3) Patients who have received oral anticoagulant for other than atrial fibrillation (e.g., venous thromboembolism, deep vein thrombosis, pulmonary embolism) before a diagnosis of atrial fibrillation has been made

4) Patients underwent hip or knee replacement surgery

5) Patients who had reversible causes of AF such as thyrotoxicosis

3.3 Study factors and measurement

The study factors of interest are warfarin, dabigatran, rivaroxaban, apixaban, edoxaban. The concept of 'treatment assignment' in RCT will be mimicked by using first treatment prescribed (e.g., new users). The index date is the first date when the patient has been initiated any OAC treatment (assumed to be the first date of prescription). The start and stop date of treatment were defined as the the date the patient started and stoped their OAC. Duration of treatment will be calculated by the interval in days between first and last prescription with the same OAC as recorded in the medication database. (Treatment duration (days) = (Treatment stop date – Treatment start date + the prescription length of the final treatment date (days)). The dosage, frequency and amount of these medications prescribed will be measured.

3.3.1 Warfarin

Warfarin was used to maintain a target INR of 2.0–3.0 for prevention of stroke and systemic embolism.

3.3.2 DOACs

1) Dabigatran

2) Rivaroxaban

3) Apixaban

4) Edoxaban

According to the 2020 ESC guidelines, the reduced doses were recommend for patients with impaired with renal function (Table 2).

3.4 Outcomes and measurement

3.4.1 Effectiveness outcome

The primary effectiveness outcome is stroke or systemic embolism.

3.4.2 Safety outcome

The primary safety outcome is major bleeding.

3.4.3 Secondary outcomes

The secondary outcomes include ischemic stroke, hemorrhagic stroke, undetermined stroke, intracranial hemorrhage (ICH), CRNM bleeding, gastrointestinal bleeding and all-cause mortality. The ICD-10 codes that identify all study outcomes are summarized (Table 3.4).

3.4.4 Composite outcomes

1) A composite of stroke, systemic embolism and all-cause mortality

2) A composite of major and CRNM bleeding

3) Major adverse cardiovascular event (MACE) is a composite of acute myocardial infarction, acute coronary syndrome/ischemic heart disease, stroke, heart failure, and all-cause mortality

3.4.5 Definition of outcomes

Stroke includes all stroke (ischemic stroke and hemorrhagic stroke).

Ischemic stroke is defined as an episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction.[90]

Hemorrhagic stroke is defined as an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage.[91]

Undetermined stroke is defined as stroke not specified as haemorrhage or infarction.

Systemic embolism is defined as a clinical history consistent with an acute loss of blood flow to a peripheral artery (or arteries) supported by evidence of embolism from surgical specimens, autopsy, angiography (conventional/ computed tomography angiography (CTA)/ magnetic resonance angiogram (MRA), vascular imaging, or other objective testing.[48] Histopathological findings of the surgical specimens or tissue specimens from autopsy were reported by experienced pathologists. Computed tomography (CT) and magnetic resonance imaging (MRI) scanning as described above were used for CTA and MRA study in the diagnosis of embolism. Vascular imaging was interpreted by experienced radiologist.

Major bleeding[92] is defined as

1) Fatal bleeding, and/or

2) Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome, and/or

3) Bleeding causing a fall in hemoglobin level of 20 g L^{-1} (1.24 mmol L^{-1}) or more, or leading to transfusion of two or more units of whole blood or red cells. Hemoglobin level was analyzed by using Sysmex S-1000i automated blood cell counter (Sysmex, Kobe, Japan).

Intracranial hemorrhage is defined as bleeding within the skull. CT scanning was performed with a 128-slice scanner (Aquilion CX, Tochigi, Japan) using conventional CT technique (120 KV, 300 mA, 0.75 s scanning time, and 0.5×64 mm scan thickness). MRI imaging was performed with a 3.0-Tesla whole body imager (Acheiva; Phillips Medical Systems, Best, the Netherlands). All neuroimaging was reviewed and reported by two independent experienced radiologists.

Gastrointestinal bleeding is defined as bleeding arising from a source any location within the gastrointestinal tract.

Clinically relevant non-major (CRNM) bleeding[93] is defined as any sign or symptom of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the

criteria for the International Society on Thrombosis and Haemostasis (ISTH) definition of major bleeding but does meet at least one of the following criteria:

1) Requiring medical intervention by a healthcare professional

2) Leading to hospitalization or increased level of care

3) Prompting a face to face (i.e., not just a telephone or electronic communication) evaluation

Non-fatal myocardial infarction is defined as myocardial infraction denoted the presence of acute myocardial injury detected by abnormal cardiac biomarkers in the setting of evidence of acute myocardial ischemia but does not cause death.[94]

All-cause mortality is defined as death from any causes.

3.5 Other covariates and measurement

3.5.1 Demographic factors

- Date of birth
- Gender
- Race
- Health insurance programs (e.g., Universal Coverage Scheme, the Civil Servant Medical Benefit Scheme, the Social Security Scheme)

3.5.2 Risk factors and comorbid conditions

Diabetes mellitus is defined as fasting plasma glucose (FPG) level >126 mg/dL preprandial on 2 examinations, glucose level >200 mg/dL postprandial, or 2-h plasma glucose ≥200 mg/dL during an oral glucose tolerance test or HbA1c >6.5% or under antidiabetic treatment.[95, 96] FPG and HbA1c were measured using hexokinase/ Glucose-6-Phosphate Dehydrogenase (Abbot Laboratory, Chicago, IL, USA) and turbidimetric inhibition immunoassay (Roche Diagnostics, Mannheim, Germany), respectively.

Hypertension is defined as blood pressure ≥140 mmHg systolic and/or ≥90 diastolic and/or currently taking antihypertensive medications.[97] Blood pressure was

measured by trained nurses using technique described previously.[98] Either a mercury sphygmomanometer or a validated standardized electronic device was applied.

Hyperlipidemia is defined as cholesterol < 200 mg/dl, high-density lipoprotein-cholesterol (HDL-C) > 40mg/dl, low-density lipoprotein- cholesterol (LDL-C) < 160mg/dl, and triglycerides < 200mg/dl. The levels of cholesterol, HDL-C, LDL-C were measured by the Siemens enzymatic methods (Siemens Medical Solution Diagnostics, Tarrytown, NY). The laboratory was standardized by the Centers for Disease Control and Prevention-National Heart, Lung, and Blood Institute Lipid Standardization Program.

Ischemic heart disease is defined as an inadequate blood and oxygen supply of the myocardium.

Heart failure is a condition in which the heart is unable to pump enough blood to meet the body's needs. The clinical syndromes consist of dyspnea, orthopnea, edema, hepatic congestion, ascites, fatigue, weakness.

Transient ischemic attack (TIA) is defined as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia without acute infarction.[99] Based on the findings from brain imaging: intracranial hemorrhage (ICH) was defined as a high-density area in CT or a high-intensity area in MRI images, indicating bleeding in the brain parenchyma.

Anemia is defined as a reduction in red blood cell mass, as measured by hemoglobin concentration, hematocrit, or red blood cell count. According to the World Health Organization (WHO) criteria, anemia in adult is defined as hemoglobin concentration of less than 13 and 12 g/dL in men and women, respectively.[100]

Alcoholism is defined as a primary, chronic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by impaired control over drinking, preoccupation with the drug alcohol, use of alcohol despite adverse consequences, and distortions in thinking, most notably denial.[101]

Chronic kidney disease is defined as kidney damage or glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 for 3 months or more.[102]

Peripheral artery disease (PAD) is defined as partial or complete obstruction of ≥1 peripheral arteries. An ankle-brachial index (ABI) with a value of ≤ 0.90 is widely used in both clinical practice and epidemiological studies to diagnose PAD.[103]

CHA_2DS_2-VASc score[104]:

- Congestive heart failure (clinical heart failure, or objective evidence of moderate to severe left ventricular dysfunction or hypertrophic cardiomyopathy)
- Hypertension or on antihypertensive therapy
- Age ≥75 years (doubled)
- Diabetes mellitus or treatment with oral hypoglycaemic drugs and/or insulin or fasting blood glucose >125 mg/dL
- Prior stroke or TIA or thromboembolism (doubled)
- Vascular disease (peripheral artery disease or myocardial infarction or aortic plaque)
- Age 65-74 years
- Sex category (female)

HAS-BLED bleeding risk score[105]:

- Uncontrolled hypertension (systolic blood pressure >160 mmHg)
- Abnormal renal and liver function (dialysis, transplant, serum creatinine >200 mmol/L, cirrhosis, bilirubin > × 2 upper limit of normal, aspartate aminotransferase (AST)/ alanine aminotransferase (ALT)/ alkaline phosphatase (ALP) >3 × upper limit of normal) (1 point for each)
- Stroke (previous ischemic or hemorrhagic stroke)
- Bleeding tendency or predisposition (previous major hemorrhage or anemia or severe thrombocytopenia)
- Labile INR or time in therapeutic range (TTR) <60% in patient taking warfarin
- Elderly (age greater than 65 years)
- Drugs (concomitant use of antiplatelet or non-steroidal antiinflammatory drugs (NSAIDs); and/or excessive alcohol per week) (1 point for each)

The ICD-9-CM and ICD-10 codes that identify all risk factors, comorbidities and concomitant diseases are summarized in Table 4.

3.5.3 Patient characteristics

The anthropometric measurements of height and weight will be used to calculate body mass index (BMI). Additionally, vital signs and stroke severity assessed by National Institutes of Health Stroke Scale (NIHSS)[106] will be obtained from local information systems and medical records.

3.5.4 Laboratory data

Laboratories values from

- Complete blood count: hemoglobin, hematocrit, mean corpuscular volume, platelet count
- Ferritin, serum iron, total iron binding capacity
- Liver function test: AST, ALT, ALP, gamma-glutamyl transferase (GGT), direct bilirubin, total bilirubin, albumin
- Lipid profile: total cholesterol, HDL-C, LDL-C, triglyceride
- Blood sugar, HbA1C
- Renal function (creatinine, glomerular filtration rate (GFR)) Creatinine clearance (CrCl) will be calculated using Cockcroft-Gault equation.[107] Then the appropriateness of dose reductions will be assessed according to dose-reduction criteria (Table 2.1).
- Prothrombin time, INR

Time in therapeutic range (TTR) on warfarin anticoagulant therapy will be calculated by using the Rosendaal technique as the percent of all INR values that were within the therapeutic range (2.0 to 3.0).[108]

3.6 Data management

3.6.1 Data sources

All data segments will be retrieved from multiple databases in Ramathibodi Hospital as following

- Demographic database: gender, date of birth, nationality
- Diagnosis database (from ICD-10, and ICD-9CM) for comorbidities and outcome of interest
- Medication database
- 12-leads ECG database
- 24- hour Holter monitoring database
- Echocardiography database
- Laboratory database including tests in hematology, chemistry, blood bank
- Vital signs database
- Billing database
- Death certificate database

The collected data will be completely anonymous and the research participant's personal identifying information will be protected. The data will be kept electronically on a personal password-protected laptop computer and set up backup system. Only authorized research team can access to the data.

3.6.2 Data retrieval

Our study population will mimic the eligibility criteria in the original RCTs by identifying all subjects with International Classification of Diseases, 10th revision (ICD-10) codes for AF. The study cohort will be generated by linkage of data from the ICD-10 system and data from a standard 12-lead electrocardiography. Patients with AF will be identified from 1) consecutive patients who were diagnosed with AF using ICD-10 code I48* between January 1, 2010, and December 31, 2020 in Ramathibodi Hospital, and 2) those who were diagnosed with AF based on automate interpretation of the 12-lead ECG between January 1, 2011, and November 11, 2021. Additionally, AF must be documented by ECG evidence from either standard 12-lead ECG or Holter monitor.

The subjects will be excluded from the merged dataset to emulate the original RCTs exclusions using a list of ICD-9 CM and ICD-10 codes. For example, our study will exclude subjects with moderate or severe mitral stenosis, mechanical prosthetic valve, taking oral anticoagulant for indications other than AF, knee/hip-replacement surgery within 35 days prior to time zero (t_0). Patients with reversible causes of AF, such as thyrotoxicosis will be also excluded. Figure 3.1 provides an overview of the AF cohort creation flow chart.

3.6.3 Data cleaning and checking

Before analyzing the data, identified AF target population will be validated by ECG interpretation. Automatic interpretation of the 12-lead ECG or 24-hour Holter monitoring of AF will be identified by using the terms 'Atrial Fibrillation', 'AFIB' and 'Atrial Flutter' for databases queries.The medical records of those with ICD-10 coding for AF but without ECG confirmation, and vice versa will be reviewed for validation of cases. Steps to indentify AF population are below.

1) The list of patients with 12- leads ECG or 24-hour Holter interpretation of AF will be created by merging between ECG and holter databases.

2) The AF patients identified from ICD-10 diagnostic codes will be cross-checked with those with ECG or Holter interpretation of AF.

3) The patients who had AF documented by ECG or holter will be eligible for the study. The patients with ICD-10 coded for AF without ECG or holter confirmation will be double-checked with the ECG and Holter databases to ensure those patients performed ECG or Holter.

4) Manual chart review will be performed to verify AF diagnosis in patients without information in ECG or holter database,

Additionally, we will check for missing data, errors and outliers. The frequency of each dependent and independent variables from the data set was explored. Outliers which were the extreme values were identified and rechecked. Missing values were replaced using multiple imputation with 10 imputed data sets. Available potential auxiliary variables were used to predict the missing values.

3.6.4 Data linkage

Tha data will be prepared in long format and the linking process between data sources consisted of the following steps

1) Diagnosis data will be created by using diagnosis database according to ICD-10 and ICD-9-CM codes, echocardiography and billing databases, regarding to exclusion criterion, risk factors, comorbidities and outcomes as previously described. These diagnosis data with date of diagnosis will be linked on HN.

2) After AF diagnosis is validated by ECG interpretation, patients from the target population will be exclude if there is any of the exclusion criteria. The list of AF patients' hospital number with the first date of AF diagnosis will be created as a main file for linking across datasets.

3) Medication database contains information on the dosage regimen, frequency and amount prescribed. The type with dosage of OAC, duration of treatment start and stop date will be collected. Only patients who were prescribed either warfarin or at least one DOACs (dabigatran, rivaroxaban, apixaban, edoxaban) will be included.

4) Laboratory and vital signs data will be explored and collapsed into the 3-, 6-months intervals. Then it will be matched to the patients' HN in the main file.

5) Administrative data (e.g., demographic), death certificate will be linked to the main file.

3.7 Sample size estimation

Sample size will be calculated for events of stroke or systemic events which are the primary effective outcome using a STATA version 16.0. An earlier cohort study reported the baseline rate of stroke or systemic embolism in the control group or warfarin of 3.31%.[109] The proportion of patients allocated to dabigatran, rivaroxaban, apixaban, edoxaban and warfarin groups will be varied based on a prestudy survey in the ratio of 6 : 6 : 6 : 2 : 80 respectively. From a previous systematic review and meta-analysis, the rate in the DOAC treatment group as hazard ratio are 0.77 (0.67-0.89), 0.76 (0.70-0.83), 0.67 (0.60-0.75), and 0.56 (0.44-0.70) for dabigatran, rivaroxaban, apixaban and edoxaban, compared to warfarin.[65] From the output (Figure 3.2), given the sample size of 417 are

required to detect the desired rate with 80% power using a 5%-level two-sided test. We need a sample of 713 subjects with additional 20% subjects adjusted for losses to follow-up, 43 per dabigatran group, 43 per rivaroxaban group, 43 per apixaban group, 14 per edoxaban group and 570 per warfarin group in a 10-year study. Nonetheless, all available patients who met inclusion/exclusion criteria for the study population will be included into the study analysis.

3.8 Data analysis

The statistical analysis of the study will be considered based on treatment approaches including intention to treat analysis, modified intention to treat analysis considering population whom received actual treatment in the time period, per-protocol analysis, and cases of a treatment switching, e.g., switched from warfarin to a DOAC.

3.8.1 Descriptive analysis

Demographics, comorbidities, and laboratory values between groups will be compared using χ^2 test (or Fisher's exact test where appropriate) for categorical outcome variables. Student's t test (or ANOVA where appropriate). Independent samples t-test (or Mann-Whitney test where appropriate) will be applied for continuous outcome variables.

Kaplan-Meier (KM) method with log rank test will be performed to compare time to 1) stroke or systemic embolism and 2) major bleeding.

3.8.2 Parametric survival model

Parametric regression survival-time models with appropriate distribution (e.g., Weibull, Exponential, gamma, log-normal distribution) will be performed with 'streg' command after stseting the data to the explore the effect of OAC therapy and other variables on survival by using time to event outcomes. This strategy is to perform a Cox model with time-varying covariates (an extended Cox model). Database will be prepared as "long format" data so one patient will have data in multiple records on each visit to the hospital. Some variables/categories will be re-categorized or collapsed to prevent overfitting problem and invalid model if there are small numbers of patients or events in that category. Only the first episode of interested outcome will be focused, then single

record and single event with censoring will be applied for. Starting date or index date will set as date of receiving any oral anticoagulant either VKA or DOAC treatment and the end date will be the date of diagnosis of interested events occurred or the end of study or the patient was switched from one OAC to another OAC or the date at the last follow-up if the patient has been lost to follow up. Akaike's Information Criterion (AIC) will be estimated for each distribution (AIC = -2log-likelihood + 2(number of model covariates + number of model-specific ancillary parameters + 1)) with the 'estat ic' postestimation command. The model with parametric survival distribution given the smallest AIC will be selected.

The covariables including demographic factors (e.g., gender, age, health insurance programs), risk factors and comorbidities (e.g., diabetes mellitus, hypertension, hyperlipidemia, ischemic heart disease, CHA_2DS_2 -VAS_c score, HAS-BLED bleeding risk score), clinical characteristics (e.g., body weight, BMI) and laboratory data (e.g., hemoglobin, creatinine clearance, INR) and anticoagulant treatment (e.g., warfarin, dabigatran, rivaroxaban, apixaban, edoxaban) will be included for univariate analysis. Those variables in which the p values in univariate analysis of less than 0.2 will be considered for stepwise method with backward elimination approach. The chosen model will include variables with statistically significant at the 5% level at least or clinically significant variables, and confounders.

3.8.3 Treatment effect model (counterfactual analysis)

The RCT limits generalizability because of ideal measures of treatment efficacy under restricted conditions whereas observational, nonrandomized study can demonstrate the real-world effectiveness under a wide range of clinical practice conditions. Statistical approaches for observational survival-time data or time-to-event data will be constructed based on the outcome and/or treatment and/or censor models chosen. These statistical methods should complement a Cox regression model which can produce biases if there is imbalance of the patient characteristics. The main advantage of the treatment effect model is estimating an average treatment effect with adjusting for censoring or missing-data.

After declaring data with ‘stset’ command, five estimators will be considered for estimating average treatment effects (ATEs), average treatment effects on the treated (ATETs), and potential-outcome means (POMs) for each treatment level (e.g., DOACs group versus warfarin, individual DOAC versus any other DOAC) with focusing on approaches including at least treatment and outcome models (LAC-IPWRA, WAC-IPWRA).

3.8.3.1 Regression adjustment (RA)

The RA estimator can handle the missing-data problem based on only outcome model without the treatment or censor models. Censoring is adjusted for in the log-likelihood function. We will implement ‘stteffects ra’ command to estimate the ATE by using averages of predicted outcomes.

3.8.3.2 Inverse-probability weights (IPW)

IPW estimator obtains the weights from treatment assignment and time-to-censoring models, giving weighted averages of the observed outcome to subsequently estimate the POMs and the ATE. The weights correct for missing potential outcome or the censoring when the data is lost or censored. We will use ‘stteffects ipw’ command to estimate the average time to outcome event.

3.8.3.3 Likelihood-adjusted-censoring inverse-probability-weighted regression adjustment (LAC-IPWRA)

LAC-IPWRA estimator model both treatment assignment and outcome models by combining IPW and RA without the time to censoring model. The censor time is handled by including a term in the log-likelihood function for the outcome model

3.8.3.4 Weighted-adjusted-censoring inverse-probability-weighted regression adjustment (WAC-IPWRA)

Unlike the LAC-IPWRA, the weight for censoring adjustment is obtained from the estimating parameters and WAC-IPWRA will be constructed under the outcome, treatment and censor models to estimate the ATE and control-level POM. The WAC-IPWRA estimator is less robust than the LAC-IPWRA estimator. The censoring time

which is accounted by using estimated weights must be random. We will use ‘stteffects ipwra’ command for WAC-IPWRA estimator.

3.8.3.5 Weighted regression adjustment (WRA)

WRA uses weights from a censor model to adjust for censoring in addition to the outcome model. This estimator is likely to be less robust because using weights is more restricted on the censoring process when compares to that including a term in the log-likelihood function for the outcome model. We will use ‘stteffects wra’ command to estimate averages of predicted outcomes and the POMs.

Under correct model specification, an outcome model, a model for the probability of treatment and a time-to-censoring model will be used.

1) Treatment assignment model

We will model and estimate the parameters of an OAC treatment assignment decision making. The inverse probability of treatment weights (IPTWs) will be estimated using a pooled multinomial logistic regression model adjusted covariate for the probability of being treated with any anticoagulant (warfarin, dabigatran, rivaroxaban, apixaban, edoxaban) conditional on selected baseline covariates (e.g., age, index date, health insurance program, body weight, history of anemia, GI bleeding, creatinine clearance).

2) Time-to-censoring model

We will model and estimate the parameters of a censoring time. The inverse probability of censoring weights (IPCWs) will be estimated using adjusted covariates for the probability of being censored (e.g., age, health insurance program, history of anemia, GI bleeding, INR, creatinine clearance). The covariables related to time-to-censoring model may be similar to those in outcome model.

3) Outcome model

The outcome model based on parametric survival analysis estimates the hazard ratios for each outcome among OACs treatment. The covariables for the outcome model include age, gender, diabetes mellitus, hypertension, heart failure, previous stroke,

alcoholism, CKD, history of anemia, GI bleeding, CHAD2VASC score, HAS-BLED score, INR and those variables in which are statistically significant in conventional analysis.

Assumption checking will be performed.

1) The conditional independence assumption to ensure that the potential outcomes are independent of the treatment assignment after conditioning on the covariates. Balance checks will be applied with ‘stteffects’ and ‘tebalance summarize’ command, respectively. The weighted standardized differences clos to 0, and the weighted variance ratios close to 1 indicate that the model-based treatment weights balanced the covariates. Overidentification test will be performed with ‘tebalance overid’ for command to check whether the treatment-assignment model is violated.

2) The sufficient overlap assumption to ensure that each patient have a sufficiently positive probability of being assigned to each treatment. We will use ‘teoverlap’ command to plot the densities of the probability of getting each treatment level and check whether the overlap assumption is violated.

3) The correct adjustment for censoring assumption to ensure that the the censoring time must be fixed or the process must be conditionally-on-covariates independent of the potential outcomes and the treatment-assignment process. Additionally, the censoring is random and the censoring process be correctly modeled for the IPW, WAC-IPWRA, and WRA estimators.

Sensitivity analysis will be performed by restricting patients with impaired kidney function, reduced DOAC dosage, and prior stroke. Additionally, E-value will be calculated to assess the robustness of study.

3.9 Ethics considerations

The protocol will be submitted for approval by the ethics committees of Ramathibodi Hospital to ensure that the study will be conducted safely and ethically on human subjects according to the principles of the Helsinki Declaration including respect for persons, beneficence and non-maleficence, and justice.

3.9.1 Respect for persons

The principle of respect for persons requires protecting and facilitating autonomy in persons. The patient enables self decision-making to treat or refuse treatment, and are given serious consideration. On the other hand, a substitute decision-maker was an accepted practice for vulnerable populations or an individuals who impaired decision-making capacity, for instance, patient with mental disorder. All participants were treated in a non-degrading manner out of respect for their dignity.

3.9.2 Beneficence and Non-maleficence

The principle of beneficence and non-maleficence is minimizing possible harms while maximizing benefits. The patients received the standard treatment; however, this study did not use any research intervention that may cause potential harm to the participants.

3.9.3 Justice

The principle of justice states that there should be an element of fairness in the distribution of the benefits and burdens of research, as well as equal distribution of scarce resources and new treatments. There are several widely accepted formulations of distribution; (1) to each person an equal share, (2) to each person according to individual need, (3) to each person according to individual effort, (4) to each person according to social contribution, and (5) to each person according to merit.[110]

3.10 Budget

Section/ Activity	Unit	No. of units	Unit costs (THB)	Total (THB)
1. Study-related costs				
1.1 Creating the protocol	Project	1	0	0
1.2 IRB submission	Site	1	0	0
1.3 Statistical plan and report				
1.3.1 Statistician consultation	Person	1	10,000	10,000
1.3.2 Statistic report of the results	Report	1	10,000	10,000
1.4 Manuscript preparation				
1.4.1 Writing manuscript	Document	2	5,000	10,000
1.4.2 English editing	Document	2	15,000	30,000
1.4.3 Submission fee	Document	2	50,000	100,000
Total cost: Section 1 Study-related				**160,000**
2. Patient-related costs	Case	0	0	0
3. Data-related costs				
3.1 Data entry (double entry) and cleaning	Person	20,000	2	40,000
3.2 Database management	Project	1	15,000	15,000
Total cost: Section 3 Data-related				**55,000**
4. Site-related costs				
4.1 Site initiation and training	Site	1	10,000	10,000
4.2 Investigator meeting	Site	1	10,000	10,000
4.3 Site monitoring	Site	1	5,000	5,000
4.4 Site closing	Site	1	5,000	5,000
Total cost: Section 4 Site-related				**30,000**
GRAND TOTAL				**245,000**

3.11 Time Frame

Activities	2022									2023									
	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10
Protocol development																			
Ethics committee submission																			
Data collection																			
Data cleaning and checking																			
Data analysis																			
Manuscript writing																			

TABLES

Table 3.1 Real-world evidences on the use of DOACs

Study, year	Country	Data source	DOACs	Sample size	Outcomes of interest	Follow up (days)	Statistical analysis
Abraham NS et al.[111], 2017	USA	Retrospective cohort, OptumLabs Data Warehouse	RIVA vs DABI APIXA vs DABI APIXA vs RIVA	15,787/15,787 6,542/6,542 6,565/6,565	GIB	113/120 89/120 89/106 (median)	PSM with Cox regression
Adeboyeje G et al.[112], 2017	USA	HealthCore Integrated Research Environment	Warfarin vs DABI vs APIXA vs RIVA	23,431/8,539/ 3,689/8,398	MB, GIB, ICH	285/212/ 139/169 (median)	PSW with Cox regression
Al-Khalili F et al.[113], 2016	Sweden, Retrospective cohort	Stockholm Heart Center (a cardiology outpatient clinic)	DABI vs RIVA vs APIXA	233/282/251	Discontinuation and bleeding	367/432/ 348 (median)	Cox regression
Amin et al.[114], 2018	USA	Medicare & Medicaid Services database	APIXA vs Warfarin APIXA vs DABI APIXA vs RIVA	20,803/20,803 15,418/15,418 20,804/20,804	IS, MB, SE, ICH, hemorrhagic stroke, GIB	115/122 115/113 115/133 (median)	PSM with Cox regression
Amin et al.[115], 2018	USA	OptumInsight Research Database	APIXA vs Warfarin APIXA vs DABI APIXA vs RIVA	8,328/8,328 3,557/3,557 8,440/8,440	all-cause hospitalization and hospitalizations due to stroke/ SE and MB	NA	PSM with Cox regression

Study, year	Country	Data source	DOACs	Sample size	Outcomes of interest	Follow up (days)	Statistical analysis
Andersson et al.[116], 2018	Denmark	Danish nation-wide administrative registries	APIXA vs DABI APIXA vs RIVA RIVA vs DABI	3,235/3,235 3,676/3,676 2,720/2,720	IS, MB, SE, ICH, hemorrhagic stroke, GIB	210/241 212/201 204/243 (mean)	PSM with Cox regression
Blin P et al.[117], 2019	France	French Healthcare Database	DABI vs RIVA	8,290/8,290	IS, MB, all-cause mortality, SE, MI, ICH, GIB, CRB, urogenital bleeding	730	PSM
Cha MJ et al.[118], 2017	Korea	Korean National Health Insurance Service database	RIVA vs DABI vs APIXA vs Warfarin	5,681/3,741/2,189/23,222	IS, ICH, or all-cause mortality	183/201/146/551 (mean)	PSM
Chan LX et al., 2018	Singapore	Tan Tock Seng Hospital	Warfarin vs DABI vs RIVA	128/110/145	Stroke, all cause death, MB, ICH, GIB	365 (median)	Cox regression
Chan YH et al.[119], 2016	Taiwan	Taiwan National Health Insurance Research Database	DABI vs Warfarin	9,940/9,913	IS, ICH, MB, all-cause mortality	245 (median)	IPTW
Chan YH et al.[120], 2016	Taiwan	Taiwan National Health Insurance Research Database	DABI vs RIVA vs Warfarin	5,921/3,916/5,251	Thromboembolic events, bleeding, and mortality	NA (short follow-up period)	IPTW
Chan YH et al.[121], 2018	Taiwan	Taiwan National Health Insurance Research Database	APIXA vs DABI vs RIVA vs Warfarin	5,843/20,079/27,777/19,375	All-cause mortality, ICH, GIB, MB	278, 566, 453, 537 (mean)	IPTW

Study, year	Country	Data source	DOACs	Sample size	Outcomes of interest	Follow up (days)	Statistical analysis
Chan YH et al.[122], 2019	Taiwan	Taiwan National Health Insurance Research Database	EDOXA vs APIXA vs RIVA vs DABI vs Warfarin	4,577/9,952/33,022/22,371/19,761	IS, SE, fatal ischemic stroke, acute MI, ICH, GIB, fatal bleeding, MB	NA	IPTW
Cho MS et al.[123], 2018	Korea	Korean National Health Insurance Service	Warfarin vs DABI vs RIVA vs APIXA	10,409/12,593/21,000/12,502	IS and SE, all-cause mortality, MB	458	IPTW
Deitelzweig S et al.[124], 2016	USA	Premier Hospital Database, Cerner database	DABI vs RIVA vs APIXA DABI vs RIVA vs APIXA	32,838/37,754/4,138 5,753/6,635/1,813	Bleeding-related hospital readmission	NA	Multivariable logistic regression
Ellis MH et al.[125], 2016	Israel	Healthcare Database	Warfarin vs DABI vs RIVA	9,564/5,976/2,709	MB	NA	Cox regression
Fralick M et al.[126], 2020	USA	U.S. nationwide commercial health care claims database	RIVA vs APIXA	39,351/39,351	IS, SE, ICH, GI	291/288 (mean)	PSM with Cox regression
Gorst-Rasmussen A et al.[127], 2016	Denmark	Danish National Prescription Registry, Danish National Patient Register, and Danish Civil Registration System	DABI vs RIVA vs Warfarin	8,908/2,405/11,045	Stroke, mortality, bleeding	394 (median)	PSW with Cox regression

Study, year	Country	Data source	DOACs	Sample size	Outcomes of interest	Follow up (days)	Statistical analysis
Graham DJ et al.[128], 2016	USA	Medicare databases	DABI vs RIVA	52,240/66,651	Thromboembolic stroke, ICH, major extracranial bleeding	108/111 (mean)	IPTW
Graham DJ et al.[129], 2019	USA	Medicare databases	RIVA vs DABI APIXA vs DABI APIXA vs RIVA	106,369/86,293 72,921/86,293 72,291/106,369	IS, all-cause mortality, ICH, GIB, major extracranial bleeding	130 (mean)	PSM with Cox regression
Gupta et al.[130], 2018	USA	Department of Defense Military Health System	APIXA vs Warfarin APIXA vs DABI APIXA vs RIVA	7,607/ 7,607 4,129/4,129 11,284/11,284	MB	NA	PSM with Cox regression
Hernandez I and Zhang Y[131], 2017	USA	Medicare Part D data from the Centers for Medicare and Medicaid Services	DABI150 vs RIVA20 DABI75 vs RIVA15	7,322/ 5,799 1,816/2,568	Stroke, thromboembolic events, death, MB	385/251 357/239 (mean)	PSW with Cox regression
Hernandez I, Zhang Y, Saba S[132], 2017	USA	Medicare	APIXA vs DABI vs RIVA vs Warfarin	2,358/1,415/ 5,139/ 12,353	IS, ICH, GIB, any bleeding	185/294/255/274 (mean)	Cox regression
Ho JCS et al.[133], 2012	Hong Kong	Prince of Wales Hospital	DABI vs Warfarin	122/122	SE, IS, all cause death, MB, ICH, GIB	310 (median)	Cox regression

Study, year	Country	Data source	DOACs	Sample size	Outcomes of interest	Follow up (days)	Statistical analysis
Huang HY et al.[134], 2018	Taiwan	Taiwan National Health Insurance Research Database	RIVA vs Warfarin	9,637/9,637	IS, ICH, GIB	350/431	PSM with Cox regression
Jeong HK et al.[135], 2019	Korea	Chonnam National University Hospital	RIVA vs Warfarin	804/804	IS, MB, GIB, ICH, all-cause mortality	365	PSM with Cox regression
Kodani E et al.[136], 2016	Japan	J-RHYTHM Registry 2	Warfarin vs DABI vs RIVA vs APIXA	3,964/325/403/184	SE, IS, All cause death, MB, ICH, GIB	1,935	Multivariate logistic regression
Kohsaka S et al.[137], 2017	Japan	275 acute care hospitals across Japan	Warfarin vs APIXA Warfarin vs DABI Warfarin vs RIVA	5,977/5,977 5,090/5,090 6,726/6,726	MB	365	PSM
Kohsaka S et al.[138], 2018	Japn	Medical Data Vision Database	APIXA vs Warfarin	11,972/11,972 36,990/ 36,990	SE, MB	NA	PSM with Cox regression
Koretsune Y et al.[139], 2019	Japan	Hospital Information systems and administration database by Medical Data Vision	DABI vs Warfarin	4,606/4,606	Stroke, SE, ICH, MB, GIB	212/180	PSM with Cox regression
Lai CL et al.[140], 2017	Taiwan	Taiwan National Health Insurance Research Database	RIVA vs DABI	4,600/4,600	IS, all-cause mortality, MI, SE, ICH, GIB	329 (mean)	PSM

Study, year	Country	Data source	DOACs	Sample size	Outcomes of interest	Follow up (days)	Statistical analysis
Lamberts M et al.[141], 2017	Denmark	Danish nationwide administrative registries	APIXA vs DABI vs RIVA vs Warfarin	7,963/15,413/6,715/24,230	MB	214/392/230/251 (median)	Cox regression
Larsen TB et al.[142], 2016	Denmark	Danish nation-wide databases	APIXA vs DABI vs RIVA vs Warfarin	6,349/ 12,701/ 7,192/35,436	IS, SE, death, any bleeding, ICH, MB	694 (mean)	IPTW
Lau WC et al.[143], 2017	China and Hong Kong	Clinical Data Analysis and Reporting System	DABI vs Warfarin	2,580/2,580	ICH, GIB	425	PSM with Cox regression
Lee KH et al.[144], 2017	Korea	Chonnam National University Hospital	Warfarin vs DABI	549/549	SE, IS, all cause death, MB, ICH, GIB	NA	PSM with Cox regression
Lee SR et al.[145], 2018	Korea	National Health Insurance Service	Warfarin vs EDOXA	12,183/4,061	IS, all cause death, MB, ICH, GIB	329/110(median)	PSM with Cox regression, IPTW
Lee SR et al.[146], 2019	Korea	Korean Health Insurance Review Database	Warfarin vs RIVA vs DABI vs APIXA vs EDOXA	25,420/35,965/17,745/22,177/15,496	IS, ICH, GIB, MB	300/318/318/292/208	IPTW
Li WH et al.[147], 2017	China	Hospital-based AF registry in Queen Mary Hospital	DABI vs RIVA vs Warfarin	467/669/963	IS, ICH	662 (mean)	Cox regression

Study, year	Country	Data source	DOACs	Sample size	Outcomes of interest	Follow up (days)	Statistical analysis
Lin J, Trocio J, Gupta K[148], 2017	USA	IMS Pharmetrics Plus	APIXA vs RIVA APIXA vs DABI APIXA vs Warfarin	4,062/4,062 2,684/2,684 4,847/4,847	MB	92/92 122/92 92/92 (median)	PSM with Cox regression
Lip GYH et al.[149], 2016	USA	Truven MarketScan®Commercial and Medicare supplemental US claims database	Warfarin vs APIXA Warfarin vs DABI Warfarin vs RIVA APIXA vs DABI APIXA vs RIVA DABI vs RIVA	6,964/6,964 4,515/4,515 12,625/12,625 4,407/4,407 7,399/7,399 4,657/4,657	MB	100/96 97/100 100/113 93/103 95/116 100/111 (median)	PSM
Lip GYH et al.[150], 2018	USA	Healthcare claims databases	APIXA vs Warfarin DABI vs Warfarin RIVA vs Warfarin APIXA vs DABI APIXA vs RIVA DABI vs RIVA	100,977/100,977 36,990/36,990 125,068/125,068 37,314/37,314 107,236/107,236 37,693/37,693	Stroke, SE, MB (GIB, ICH, and MB at other key sites)	126/158 124/156 146/159 124/123 125/145 123/143 (median)	PSM with Cox regression
Mitsuntisuk P et al.[69], 2021	Thailand	Hospital database	Warfarin vs APIXA vs DABI vs RIVA	605/405/441/604	Stroke or SE, MB, and net adverse clinical events	1029/694/913/799 (mean)	IPTW
Norby FL et al.[151], 2017	USA	MarketScan	RIVA vs DABI RIVA vs Warfarin	16,957/16,957 32,495/ 45,496	IS, MI, ICH, GIB	320 (median)	PSM with Cox regression

Study, year	Country	Data source	DOACs	Sample size	Outcomes of interest	Follow up (days)	Statistical analysis
Nosewort hy PA et al.[152], 2016	USA	Optum Labs Data Warehouse	RIVA vs DABI APIXA vs DABI APIXA vs RIVA	15,787/15,787 6,542/6,542 6,565/6,565	Stroke, SE, MB	NA	PSM with Cox regression
Okumura Y et al.[153], 2018	Japan	63 institutions in the Tokyo area	Warfarin vs DABI vs RIVA vs APIXA vs EDOXA	1,561/456/761/428/31	Stroke or SE, ICH, MB, all-cause mortality	1,199 (median)	PSM with Cox regression
Rutherford OW et al.[154], 2020	Norway	Nationwide registries	DABI vs RIVA DABI vs APIXA APIXA vs RIVA	10,252/10,252 10,413/10,413 13,699/13,699	Stroke, MB, CRNM bleeding, major or CRNM bleeding, GIB, and ICH	567/555 555/372 552/381	PSM with Cox regression
Shiga T et al.[155], 2015	Japan	Tokyo Women's Medical University Hospital	DABI vs RIVA vs APIXA vs Warfarin	192/107/102/200	SE, IS, MB, ICH, GIB	732/732/671/732	Chi-square test
Staerk L et al.[156], 2018	Denmark	Danish nationwide administrative registries	RIVA vs DABI APIXA vs DABI APIXA vs RIVA	6,868/7,078 7,203/7,078 7,203/6,868	IS, MB, ICH, GIB	730	Cox regressions
Villines TC et al.[157], 2019	USA	Department of Defense Military Health System	RIVA vs DABI APIXA vs DABI	12,763/12,763 4,802/4,802	IS, MB, all-cause mortality, MI, ICH, hemorrhagic stroke, GIB, major	417/422 358/350 (mean)	PSM with Cox regression

Study, year	Country	Data source	DOACs	Sample size	Outcomes of interest	Follow up (days)	Statistical analysis
					extracranial bleeding		
Vinogradova Y et al.[158], 2018	UK	QResearch Clinical Practice research Datalink	Warfarin vs DABI vs RIVA vs APIXA Warfarin vs DABI vs RIVA vs APIXA	53,921/4,534/ 13,597/9,199 16,664/1,003/ 2,950/1,402	IS, MB, all-cause mortality, ICH, GIB, urogenital bleeding	491/402/336/297 412/323/228/200	Cox regression
Yap LB et al.[159], 2016	Malaysia	Malaysia's National Heart Institute	DABI vs Warfarin	500/500	IS, MB	355/315 (mean)	Cox regression

APIXA, apixaban; DABI, dabigatran; EDOXA, edoxaban; RIVA, rivaroxaban

CRB, clinically relevant bleeding; CRNM bleeding, clinically relevant non-major bleeding; GIB, gastrointestinal bleeding; IPTW, inverse probability of treatment weights; MB, major bleeding; MI, myocardial infarction; PSM, propensity score matching; PSW, propensity score weighting; ICH, intracranial hemorrhage; IS, ischemic stroke; SE, systemic emboli

Table 3.4. ICD-9 CM and ICD-10 codes used in identifying target population, definitions of comorbidities and outcomes.

	ICD-9 CM and ICD-10 codes
Target population	
Atrial fibrillation	ICD-10: I48*
Additional diagnoses to identify valvular atrial fibrillation	
Mitral stenosis	ICD-10: I050, I052, I342
Pulmonary embolism	ICD-10: I26*
Venous thromboembolism and deep vein thrombosis	ICD-10: I821, I822, I823, I828, I829, I802, O223, O871
Presence of prosthetic heart valve	ICD-10: Z952, Z953, Z954
Thyrotoxicosis	ICD-10: E05*
Hip replacement surgery	ICD-9 CM: 8151, 8153, 70, 71, 72, 73
Knee replacement surgery	ICD-9 CM: 8154, 8155, 80, 81, 82, 83, 84
Comorbidities	
Diabetic mellitus	ICD-10: E11*
Hypertension	ICD-10: I10, I11*, I12*, I13*, I15*
Hyperlipidemia	ICD-10: E78*

	ICD-9 CM and ICD-10 codes
Ischemic heart disease	ICD-10: I20*, I21*, I22*, I23*, I24*, I25*
Heart failure	ICD-10: I110, I130, I132, I50*
Previous stroke/ transient ischemic attack (TIA)	ICD-10: G45*, I63*, I64, I61*, I60*
Previous intracranial hemorrhage	ICD-10: I60*, I61*, I62*
Previous gastrointestinal bleeding	ICD-10: I850, K221, K228, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K290, K528, K625, K920, K921, K922
Anemia	ICD-10: D50*, D500, D51*, D52*, D53*, D55*, D56*, D57*, D58*, D59*, D60*, D61*, D62*, D63*, D64*
Alcoholism	ICD-10: E244, F10*, G312, G621, G721, I426, K292, K70*, K860, O354, T51*, Z714, Z721
Liver disease	ICD-10: B15*, B16*, B17*, B18*, B19*, K70*, K72*, K76.6
Chronic kidney disease (CKD)	ICD-10: N18*, I770, T824, T825, T827, T828, T829, Z992, Z49, Z490, Z4901, Z492, T824, Z4902, T85611, T85621, T85631, T85691, T8571, T861, Z940 ICD-9-CM: 3895, 3893, 3927, 3942, 3943, 3953, 3995, 5493, 5498, 5569, 5561
CKD stage 1	ICD-10: N181
CKD stage 2	ICD-10: N182

	ICD-9 CM and ICD-10 codes
CKD stage 3	ICD-10: N183
CKD stage 4	ICD-10: N184
CKD stage 5	ICD-10: N185
Hemodialysis	ICD-10: N186, I770, T824, T825, T827, T828, T829, Z992, Z49, Z490, Z4901, Z492, T824 ICD-9-CM: 3895, 3893, 3927, 3942, 3943, 3953, 3995
Peritoneal dialysis	ICD-10: N186, Z4902, T85611, T85621, T85631, T85691, T8571, Z992, Z492, Z490, Z49 ICD-9-CM: 5493, 5498
Renal replacement therapy (hemodialysis or peritoneal dialysis)	ICD-10: N186, I770, T824, T825, T827, T828, T829, Z992, Z49, Z490, Z4901, Z492, T824, Z4902, T85611, T85621, T85631, T85691, T8571 ICD-9-CM: 3895, 3893, 3927, 3942, 3943, 3953, 3995, 5493, 5498
Renal disease	ICD-10: I12*, I13*, N00*, N01*, N02*, N03*, N04*, N05*, N06*, N07*, N11*, N14*, N17*, N18*, N19, Q61*, N180, N181, N182, N183, N184, N185
Kidney transplant	ICD-10: T861, Z940 ICD-9-CM: 5569, 5561
End stage renal disease (ESRD)	ICD-10: N180, N186, I770, T824, T825, T827, T828, T829, Z992, Z49, Z490, Z4901, Z492, T824, Z4902, T85611, T85621, T85631, T85691, T8571, T861, Z940

	ICD-9 CM and ICD-10 codes
	ICD-9-CM: 3895, 3893, 3927, 3942, 3943, 3953, 3995, 5493, 5498, 5569, 5561
Peripheral artery disease	ICD-10: I702*, I708*, I709*, I71*, I739
Cancer	ICD-10: C00*, C01, C02*, C03*, C04*, C05*, C06*, C07, C08*, C09*, C10*, C11*, C12*, C13*, C14*, C15*, C16*, C17*, C18*, C19, C20, C21*, C22*, C23*, C24*, C25*, C26*, C30*, C31*, C32*, C33, C34*, C37, C38*, C39*, C40*, C41*, C43*, C44*, C45*, C46*, C47*, C48*, C49*, C50*, C51*, C52, C53*, C54*, C55, C56, C57*, C58, C60*, C61, C62*, C63*, C64, C65, C66, C67*, C68*, C69*, C70*, C71*, C72*, C73, C74*, C75*, C76*, C77*, C78*, C79*, C80*, C81*, C82*, C83*, C84*, C85*, C86*, C88*, C90*, C91*, C92*, C93*, C94*, C95*, C96*, C97
Outcomes	
Stroke	ICD-10: I63*, I64, I61*, I60*
Ischemic stroke	ICD-10: I63*
Hemorrhagic stroke	ICD-10: I61*, I60*
Undetermined Stroke	ICD-10: I64
Subarachnoid hemorrhage	ICD-10: I60*
Intracerebral hemorrhage	ICD-10: I61*

	ICD-9 CM and ICD-10 codes
Other nontraumatic intracranial haemorrhage	ICD-10: I62*
Intracranial hemorrhage	ICD-10: I60*, I61*, I62*
Systemic embolism	ICD-10: I74*
Major bleeding	ICD-10: H313, H356, H431, H450, I23, I230, I312, J942, K661, M250, S064, S065, S066, S068
Gastrointestinal bleeding	ICD-10: I850, K221, K228, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K290, K528, K625, K920, K921, K922
Clinically relevant non-major (CRNM) bleeding	ICD-10: A985, D500, D62*, D683, D698, D699, H113, I850, K221, K228, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K290, K528, K625, K922, N02*, N421, N836, N837, N857, N92*, N93*, O721, R04*, R31, R58, T14*
Major adverse cardiovascular event (MACE)	ICD-10: I21*, I22*, I24*, I63*, I65*, I66*, I110, I50*, I971

FIGURES

Figure 3.1. AF cohort creation flow chart

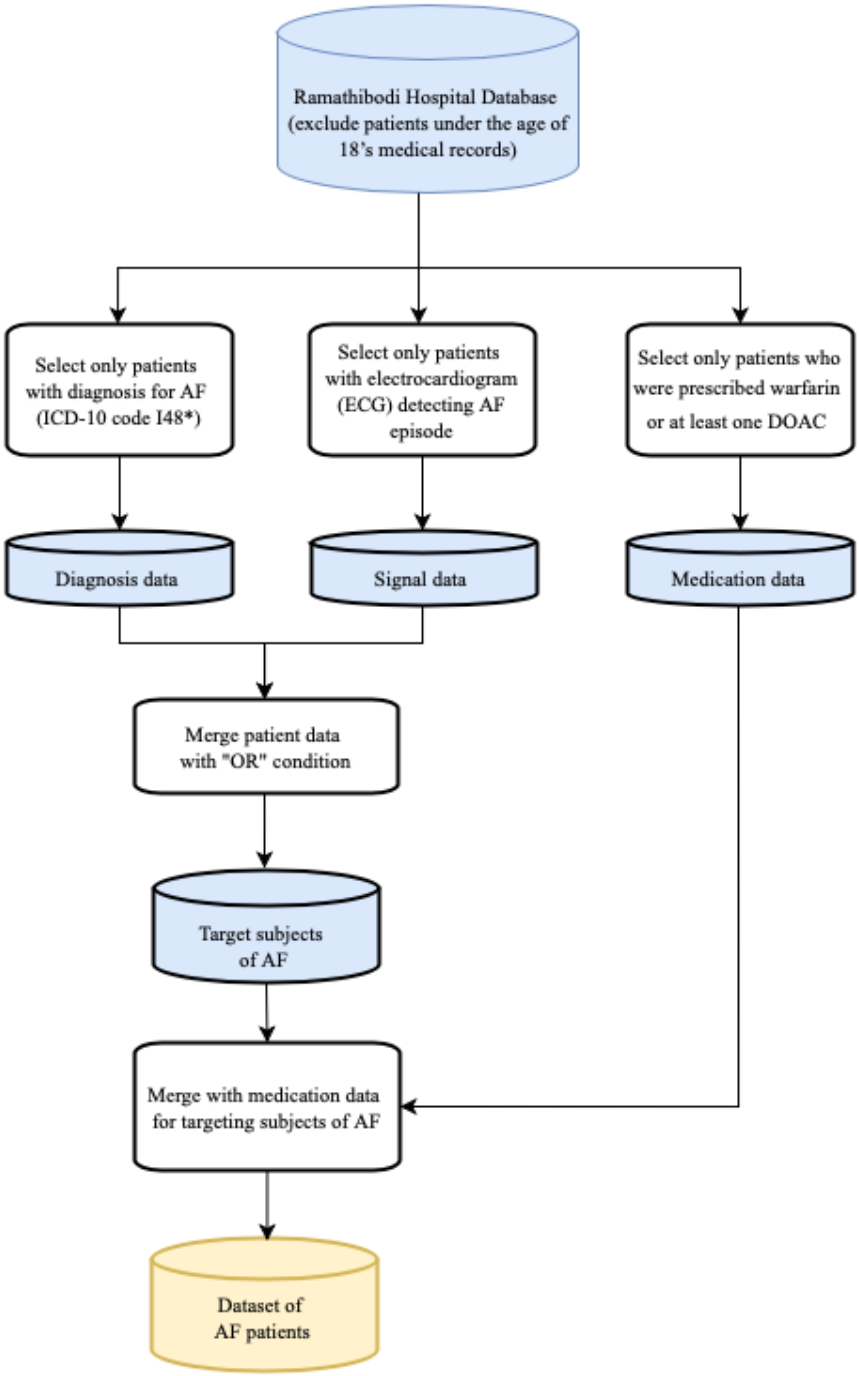


Figure 3.2. Sample size estimation for stroke or systemic embolism events

```
. artsurv, method(l) nperiod(10) ngroups(5) fp(0) edf0(0.0331, ) hratio(0.77, 0.76, 0.67, 0.56, 1) alpha(0.05) power(0.8)
>  aratios(6 6 6 6 80 ) recrt(0 0, 1, 0 ) distant(0) detail(0) onesided(0) ni(0) tunit(1) trend(0)

ART - ANALYSIS OF RESOURCES FOR TRIALS        (version 1.0.7, 19 October 2009)
-------------------------------------------------------------------------------
A sample size program by Abdel Babiker, Patrick Royston & Friederike Barthel,
MRC Clinical Trials Unit, London NW1 2DA, UK.
-------------------------------------------------------------------------------
Type of trial                           Superiority - time-to-event outcome
Statistical test assumed                Unweighted logrank test (local)
Number of groups                        5
Allocation ratio                        6.00:6.00:6.00:6.00:80.00
Global test

Total number of periods                 10
Length of each period                   One year

Survival probs per period (group 1)     0.072 0.005 0.000 0.000 0.000 0.000
                                         0.000 0.000 0.000 0.000
Survival probs per period (group 2)     0.075 0.006 0.000 0.000 0.000 0.000
                                         0.000 0.000 0.000 0.000
Survival probs per period (group 3)     0.102 0.010 0.001 0.000 0.000 0.000
                                         0.000 0.000 0.000 0.000
Survival probs per period (group 4)     0.148 0.022 0.003 0.000 0.000 0.000
                                         0.000 0.000 0.000 0.000
Survival probs per period (group 5)     0.033 0.001 0.000 0.000 0.000 0.000
                                         0.000 0.000 0.000 0.000
Number of recruitment periods           0
Number of follow-up periods             10
Method of accrual                       Uniform

Hazard ratios as entered (groups 1,..,5) 0.77, 0.76, 0.67, 0.56, 1
Alpha                                   0.050 (two-sided)
Power (designed)                        0.800

Total sample size (calculated)          417
Expected total number of events         417
-------------------------------------------------------------------------------
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