OHDSI Comparative effectiveness and safety of direct ORal Anticoagulants in patients with atrial fibrillation: a standardiZed Observational data Network study (CORAZON)

**Version**: 2.1

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# List of abbreviations

AF Atrial fibrillation

DOAC Direct Oral Anticoagulant

OHDSI Observational Health Data Sciences and Informatics

# Abstract

Direct oral anticoagulants (DOACs) are the first-line treatment for stroke prevention in patients with atrial fibrillation (AF), a common cardiac arrythmia affecting over 33 million people worldwide. This study will compare the effectiveness and safety outcomes between all the DOACs available for use in current clinical practice: dabigatran, rivaroxaban, apixaban, and edoxaban, in order to establish evidences on optimal anticoagulant choice for patients with AF.

# Amendment and Updates

|  |  |  |  |
| --- | --- | --- | --- |
| Version | Date | Person | Changes |
| 1.0 | 24 April 2020 | Wallis Lau | Initial draft |
| 1.1 | 22 May 2020 | Wallis Lau | * Added the concept ids for exposures, outcomes, and inclusion criteria events * Changed the screening period for AF from 365 days to any time on or before index date * Added details on data sources * Added details on the propensity score covariates (the use of Cyclops package) * Revised the number of analyses required |
| 1.2 | 22 June 2020 | Wallis Lau | * Added subgroup analyses for patients with chronic kidney diseases and aged >=80 years * Revised the definition of time at risk for the subgroup analysis for different dosing of DOACs |
| 2.0 | 4 September 2020 | Wallis Lau | * Updated the concept ids and the control outcomes |
| 2.1 | 16 February 2021 | Wallis Lau | * Added the GitHub link to the concept ids for easier references |

# Rationale and Background

Atrial fibrillation (AF) is the most common cardiac arrhythmia affecting over 33 million people worldwide.[1](#_ENREF_1) AF is a leading cause of stroke, making up one-fourth of all strokes encountered in clinical practice.[2](#_ENREF_2) Warfarin is traditionally prescribed to patients with AF for stroke prevention, but it has a range of limitations (e.g. narrow therapeutic range, multiple drug-drug interactions, and requires frequent monitoring), posing several challenges to clinical management.

The limitations of warfarin have prompted the development of 4 direct oral anticoagulants (DOACs) over the past decade: dabigatran (2010),[3](#_ENREF_3) rivaroxaban (2011),[4](#_ENREF_4) apixaban (2012),[5](#_ENREF_5) and edoxaban (2015).[6](#_ENREF_6) In randomized controlled trials, all DOACs were at least non-inferior to warfarin for preventing stroke, with comparable or fewer major bleeding events. Therefore, current guidelines recommend the use of DOACs over warfarin for stroke prevention in AF.[7](#_ENREF_7), [8](#_ENREF_8) However, there is no further guidance on how to choose between the DOACs, because evidence from head-to-head trials of DOACs is not available. While a randomized controlled trial directly comparing dabigatran, rivaroxaban, and apixaban has been commenced in Taiwan, there has been no update of status since 2016.[9](#_ENREF_9) Based on the clinical trials comparing DOAC to warfarin,[3-6](#_ENREF_3) several network meta-analyses have been conducted to indirectly compare between the DOACs[10](#_ENREF_10); however, the validity of the results are limited by the heterogeneity of the designs and patient characteristics across the included trials. There have been observational studies that directly compared outcomes between the DOACs, but they did not include all the 4 DOACs, and the results were conflicting.[11](#_ENREF_11) To the best of our knowledge, no studies have been conducted to directly compare all the four DOACs in a population-based setting.

Therefore, the objective of this study is to compare the effectiveness and safety outcomes between dabigatran, rivaroxaban, apixaban, and edoxaban in patients with AF using multi-national databases, in order to establish evidence on optimal anticoagulant choice for patients with AF.

# Research Questions and Objectives

## Research Questions

In this study, we are interested in every pairwise comparison between any two DOACs (dabigatran, rivaroxaban, apixaban, and edoxaban). For each comparison, we are interested in the comparative effect on 1) a composite of ischemic stroke and systemic embolism; 2) intracranial bleeding; 3) gastrointestinal bleeding; and 4) all-cause mortality.

**Primary research question:**

* For each comparison between two DOACs, for each of the outcomes of interest, what is the hazard ratio?

**Secondary research question:**

* What is the incidence rate of each outcome of interest in each exposure group?

## Objectives

To compare the effectiveness and safety outcomes between dabigatran, rivaroxaban, apixaban, and edoxaban in patients with AF.

# Research methods

## Study Design

This will be a set of retrospective, observational, new-user cohort studies. The study period will commence in 2010 (the year when the first DOAC, dabigatran, was approved for use in clinical practice) and will end in 2019 (subject to data availability). The treatment and comparator cohorts will be patients with AF who initiates DOACs. Direct head-to-head comparison will be conducted for any two DOACs for a range of clinical outcomes. Differences in baseline confounders will be accounted for by propensity score modelling.

## Data Source(s)

The study will aim to be conducted using routinely collected electronic data from multiple databases across different countries. At the time of protocol preparation, the following data sources have been included:

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Data source** | **Country** | **Patient Count** | **History** | **Patient Type** | **Data collection** |
| LPD France EMR | France | 30.9 M | 2009 - | Outpatient / General population/ Patients seen in the primary care setting | Electronic health records in ambulatory setting |
| Disease Analyser Germany EMR | Germany | 39.2 M | 1992 - | Outpatient only / General population/Public and private insurance | Electronic health records in ambulatory setting |
| UK IMRD | United Kingdom | 12.7 M | 1994 - | General population / Primary care records with hospitalisation / referral information | Pseudonymised Electronic Medical Records collected from Patient Management software used within UK Primary Care |
| US Hospital Charge Master | United States | 94.5 M | 2001 - | Inpatient & outpatient hospital encounters, including Emergency Room visits / General population | Anonymized patient level data are sourced from hospital charge detail masters (CDM) and collected from resource management software within short-term, acute-care and non-federal hospitals |
| US Ambulatory EMR | United States | 75.7 M | 2006 – | Outpatient | Electronic health records in ambulatory setting |

## Study population

The study population will include patients with AF who had a prescription of any DOACs. The detailed definitions of the study population are described in **section 7.4 Exposures** below.

## Exposures

There are 4 drug exposures of interest: dabigatran, rivaroxaban, apixaban, and edoxaban.

**Table 1. Concept IDs for direct oral anticoagulants of interest (preliminary working list at time of protocol preparation)**

|  |  |  |
| --- | --- | --- |
| **Direct oral anticoagulants** | **Concept ID (and all the descendants are included)** | **Concept name** |
| Dabigatran | 40228152 | [dabigatran etexilate](http://atlas-demo.ohdsi.org/#/concept/40228152) |
| 45775372 | [dabigatran](http://atlas-demo.ohdsi.org/#/concept/45775372) |
| Rivaroxaban | 40241331 | [rivaroxaban](http://atlas-demo.ohdsi.org/#/concept/40241331) |
| Apixaban | 43013024 | [apixaban](http://atlas-demo.ohdsi.org/#/concept/43013024) |
| Edoxaban | 45892847 | edoxaban |

The cohort entry rules and inclusion rules for the drug exposure cohorts are listed below and illustrated in **Figure 1**. More concept IDs might be added after examining the orphan codes using CohortDiagnotics. GitHub repository contains the final concepts IDs used in the study (<https://github.com/ohdsi-studies/Corazon/tree/29b317b49cd8a8a2a5d703ef6265d869ce852af8/documents>).

Initial Event Cohort

People having any of the following:

* a drug exposure of a DOAC
  + for the first time in the person's history
  + occurrence start is on or after 2010-01-01
  + occurrence end is on or Before 2019-12-31
  + with age >= 18 years

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

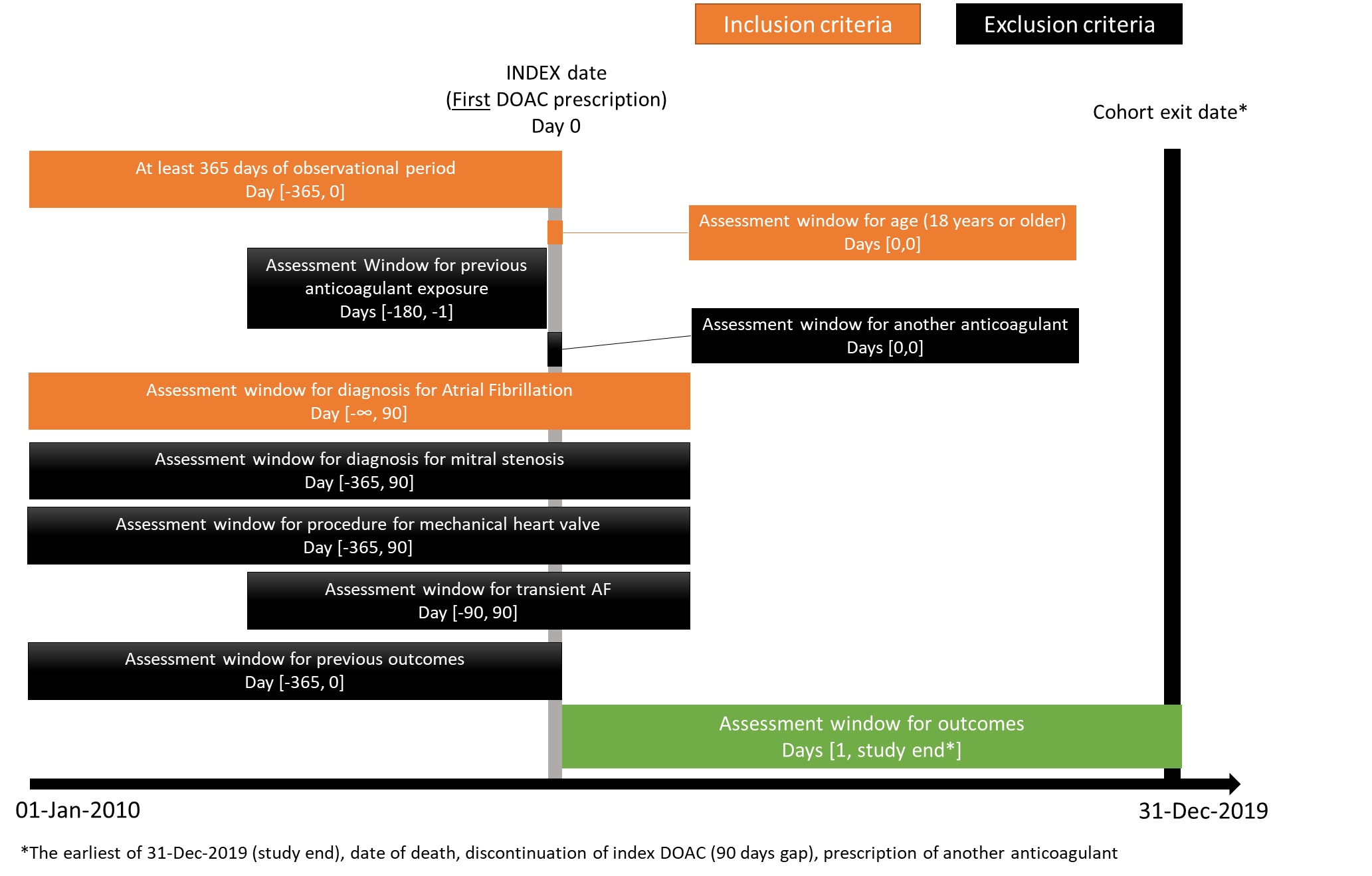
Inclusion rules (the index date is defined as the date of the first drug exposure)

* Had a diagnosis of AF anytime on or before the index date or within 90 days after the index date (to account for any delay in recording of diagnosis)
* No diagnosis of mitral stenosis or hyperthyroidism within 365 days on or before the index date or within 90 days after the index date (to account for any delay in recording of diagnosis)
* No procedure codes for mechanical heart valve within 365 days on or before the index date or within 90 days after the index date (to account for any delay in recording of the procedure)
* No records for transient AF (that is, those who had cardiac surgery or were diagnosed with myocarditis, pericarditis, or pulmonary embolism) within 90 days before index date or within 90 days after the index date
* No diagnosis of the outcome of interest within 365 days on or before the index date (to ensure incident events)
* No exposure of any oral anticoagulants (i.e. apixaban, dabigatran, edoxaban, rivaroxaban, and warfarin) with 180 days before the index date
* No exposure to another oral anticoagulant (i.e. other than the index anticoagulant) on the index date

The exit date of the exposure cohort is defined as the end of the index treatment (allowing for 90-day gaps between consecutive prescriptions), a prescription of an alternative oral anticoagulant, death, or study end (31st December 2019), whichever came first.

**Table 2. Concept IDs to define inclusion events (preliminary working list at time of protocol preparation; final version will be contained in GitHub repository)**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Atrial fibrillation** | | | | | | |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Exclude** | **Descendants** | **Mapped** |
| 4139517 | Transient cerebral ischemia due to atrial fibrillation | Condition | Standard | NO | YES | NO |
| 45769228 | Percutaneous transluminal ablation of atrial wall for atrial flutter | Procedure | Standard | NO | YES | NO |
| 42736318 | Operative incisions and reconstruction of atria for treatment of atrial fibrillation or atrial flutter (eg, maze procedure) | Procedure | Standard | NO | YES | NO |
| 4181800 | Maze procedure for atrial fibrillation | Procedure | Standard | NO | YES | NO |
| 42709991 | Insertion of pacemaker for control of atrial fibrillation | Procedure | Standard | NO | YES | NO |
| 4020234 | Implantation of intravenous pacemaker for atrial fibrillation | Procedure | Standard | NO | YES | NO |
| 4180108 | History of maze procedure for atrial fibrillation | Observation | Standard | NO | YES | NO |
| 4323077 | History of atrial flutter | Observation | Standard | NO | YES | NO |
| 4194288 | H/O: atrial fibrillation | Observation | Standard | NO | YES | NO |
| 40761369 | Ever told you have or had atrial fibrillation | Observation | Standard | NO | YES | NO |
| 4065288 | EKG: atrial flutter | Condition | Standard | NO | YES | NO |
| 4064452 | ECG: atrial fibrillation | Condition | Standard | NO | YES | NO |
| 2101903 | Documentation of permanent or persistent or paroxysmal atrial fibrillation (STR) | Observation | Standard | NO | YES | NO |
| 2617598 | Clinician documented that patient with heart failure and atrial fibrillation was not an eligible candidate for warfarin therapy measure | Observation | Standard | NO | YES | NO |
| 314665 | Atrial flutter | Condition | Standard | NO | YES | NO |
| 44803845 | Atrial fibrillation monitoring verbal invitation | Observation | Standard | NO | YES | NO |
| 44803702 | Atrial fibrillation monitoring third letter | Observation | Standard | NO | YES | NO |
| 44803786 | Atrial fibrillation monitoring telephone invitation | Observation | Standard | NO | YES | NO |
| 44803842 | Atrial fibrillation monitoring second letter | Observation | Standard | NO | YES | NO |
| 44803863 | Atrial fibrillation monitoring first letter | Observation | Standard | NO | YES | NO |
| 4047554 | Atrial fibrillation monitoring | Observation | Standard | NO | YES | NO |
| 44808026 | Atrial fibrillation care pathway | Observation | Standard | NO | YES | NO |
| 44790918 | Atrial fibrillation annual review | Observation | Standard | NO | YES | NO |
| 313217 | Atrial fibrillation | Condition | Standard | NO | YES | NO |
| 43528009 | Additional linear or focal intracardiac catheter ablation of the left or right atrium for treatment of atrial fibrillation remaining after completion of pulmonary vein isolation (List separately in addition to code for primary procedure) | Procedure | Standard | NO | YES | NO |
| **Mitral stenosis or hyperthyroidism** | | | | | | |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Exclude** | **Descendants** | **Mapped** |
| 4113641 | Thyrotoxicosis with or without goiter | Condition | Standard | NO | YES | NO |
| 1314419 | Patient has mitral stenosis or prosthetic heart valves or patient has transient or reversible cause of af (e.g., pneumonia, hyperthyroidism, pregnancy, cardiac surgery) | Observation | Standard | NO | YES | NO |
| 315273 | Mitral valve stenosis | Condition | Standard | NO | YES | NO |
| **Mechanical heart valves** | | | | | | |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Exclude** | **Descendants** | **Mapped** |
| 2001448 | Open and other replacement of unspecified heart valve | Procedure | Standard | NO | YES | NO |
| 2001456 | Open and other replacement of tricuspid valve | Procedure | Standard | NO | YES | NO |
| 2001454 | Open and other replacement of pulmonary valve | Procedure | Standard | NO | YES | NO |
| 2001452 | Open and other replacement of mitral valve | Procedure | Standard | NO | YES | NO |
| 2001450 | Open and other replacement of aortic valve | Procedure | Standard | NO | YES | NO |
| **Transient atrial fibrillation (cardiac surgery, pericarditis, myocarditis, pulmonary embolism)** | | | | | | |
| **Concept Id** | **Concept Name** | **Domain** | **Vocabulary** | **Exclude** | **Descendants** | **Mapped** |
| 4289908 | Viral pericarditis | Condition | Standard | NO | YES | NO |
| 42628681 | Valvuloplasty, aortic valve, open, with cardiopulmonary bypass; complex (eg, leaflet extension, leaflet resection, leaflet reconstruction, or annuloplasty) | Procedure | Standard | NO | YES | NO |
| 4338316 | Tricuspid annuloplasty using ring | Procedure | Standard | NO | YES | NO |
| 2727300 | Transplantation of Heart, Zooplastic, Open Approach | Procedure | Standard | NO | YES | NO |
| 2727299 | Transplantation of Heart, Syngeneic, Open Approach | Procedure | Standard | NO | YES | NO |
| 2727298 | Transplantation of Heart, Allogeneic, Open Approach | Procedure | Standard | NO | YES | NO |
| 4105593 | Transplantation of heart valve | Procedure | Standard | NO | YES | NO |
| 927088 | Transcatheter implantation of wireless pulmonary artery pressure sensor for long-term hemodynamic monitoring, including deployment and calibration of the sensor, right heart catheterization, selective pulmonary catheterization, radiological supervision an | Procedure | Standard | NO | YES | NO |
| 44816389 | Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; transapical exposure (eg, left thoracotomy) | Procedure | Standard | NO | YES | NO |
| 43527896 | Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; transaortic approach (eg, median sternotomy, mediastinotomy) | Procedure | Standard | NO | YES | NO |
| 43527919 | Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; percutaneous femoral artery approach | Procedure | Standard | NO | YES | NO |
| 43527895 | Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; open iliac artery approach | Procedure | Standard | NO | YES | NO |
| 43527893 | Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; open femoral artery approach | Procedure | Standard | NO | YES | NO |
| 43527894 | Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; open axillary artery approach | Procedure | Standard | NO | YES | NO |
| 43527897 | Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; cardiopulmonary bypass support with percutaneous peripheral arterial and venous cannulation (eg, femoral vessels) (List separately in addition to code for primary procedure) | Procedure | Standard | NO | YES | NO |
| 43527900 | Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; cardiopulmonary bypass support with open peripheral arterial and venous cannulation (eg, femoral, iliac, axillary vessels) (List separately in addition to code for primary procedure | Procedure | Standard | NO | YES | NO |
| 43527901 | Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; cardiopulmonary bypass support with central arterial and venous cannulation (eg, aorta, right atrium, pulmonary artery) (List separately in addition to code for primary procedure) | Procedure | Standard | NO | YES | NO |
| 4149913 | Systemic lupus erythematosus with pericarditis | Condition | Standard | NO | YES | NO |
| 320025 | Syphilitic pericarditis | Condition | Standard | NO | YES | NO |
| 444083 | Syphilitic myocarditis | Condition | Standard | NO | YES | NO |
| 4314708 | Subacute pericarditis | Condition | Standard | NO | YES | NO |
| 4237738 | Subacute effusive constrictive pericarditis | Condition | Standard | NO | YES | NO |
| 4030730 | Subacute constrictive pericarditis | Condition | Standard | NO | YES | NO |
| 42732622 | Right heart catheterization | Procedure | Standard | NO | YES | NO |
| 4155486 | Rheumatic pericarditis | Condition | Standard | NO | YES | NO |
| 320743 | Rheumatic myocarditis | Condition | Standard | NO | YES | NO |
| 42735929 | Repair of pulmonary atresia with ventricular septal defect, by unifocalization of pulmonary arteries; without cardiopulmonary bypass | Procedure | Standard | NO | YES | NO |
| 42735930 | Repair of pulmonary atresia with ventricular septal defect, by unifocalization of pulmonary arteries; with cardiopulmonary bypass | Procedure | Standard | NO | YES | NO |
| 725039 | Removal of a total replacement heart system (artificial heart) for heart transplantation (List separately in addition to code for primary procedure) | Procedure | Standard | NO | YES | NO |
| 4035033 | Pyogenic pericarditis | Condition | Standard | NO | YES | NO |
| 43530605 | Pulmonary embolism with pulmonary infarction | Condition | Standard | NO | YES | NO |
| 4239311 | Postpericardiotomy pericarditis | Condition | Standard | NO | YES | NO |
| 4276025 | Postcardiac injury pericarditis | Condition | Standard | NO | YES | NO |
| 4190901 | Post-traumatic pericarditis | Condition | Standard | NO | YES | NO |
| 4143776 | Post-radiation pericarditis | Condition | Standard | NO | YES | NO |
| 4121477 | Post-infarction pericarditis | Condition | Standard | NO | YES | NO |
| 4336595 | Plication annuloplasty of tricuspid valve | Procedure | Standard | NO | YES | NO |
| 4337747 | Plication annuloplasty of mitral valve | Procedure | Standard | NO | YES | NO |
| 4245386 | Pericarditis sicca | Condition | Standard | NO | YES | NO |
| 4196638 | Pericarditis secondary to uremia | Condition | Standard | NO | YES | NO |
| 4222722 | Pericarditis secondary to tumor metastatic to pericardium | Condition | Standard | NO | YES | NO |
| 4101469 | Pericarditis secondary to systemic lupus erythematosus | Condition | Standard | NO | YES | NO |
| 4337524 | Pericarditis secondary to scleroderma | Condition | Standard | NO | YES | NO |
| 4296152 | Pericarditis secondary to rheumatoid arthritis | Condition | Standard | NO | YES | NO |
| 4056843 | Pericarditis secondary to primary tumor | Condition | Standard | NO | YES | NO |
| 4056882 | Pericarditis secondary to penetrating trauma | Condition | Standard | NO | YES | NO |
| 4291329 | Pericarditis secondary to non-penetrating trauma | Condition | Standard | NO | YES | NO |
| 4155496 | Pericarditis secondary to neoplasia | Condition | Standard | NO | YES | NO |
| 4214249 | Pericarditis secondary to myxedema | Condition | Standard | NO | YES | NO |
| 4149568 | Pericarditis secondary to Mulibrey nanism | Condition | Standard | NO | YES | NO |
| 4185852 | Pericarditis secondary to malignant primary tumor | Condition | Standard | NO | YES | NO |
| 4238669 | Pericarditis secondary to collagen vascular disease | Condition | Standard | NO | YES | NO |
| 4189352 | Pericarditis secondary to aortic aneurysm | Condition | Standard | NO | YES | NO |
| 4322145 | Pericarditis secondary to acute myocardial infarction | Condition | Standard | NO | YES | NO |
| 45766217 | Pericarditis due to metabolic disease | Condition | Standard | NO | YES | NO |
| 37016749 | Pericarditis caused by toxin | Condition | Standard | NO | YES | NO |
| 4164723 | Pericarditis caused by deposits of cholesterol | Condition | Standard | NO | YES | NO |
| 4183718 | Pericarditis associated with severe chronic anemia | Condition | Standard | NO | YES | NO |
| 4277121 | Pericarditis associated with infectious mononucleosis | Condition | Standard | NO | YES | NO |
| 4006296 | Pericarditis associated with familial Mediterranean fever | Condition | Standard | NO | YES | NO |
| 4229749 | Pericarditis associated with atrial septal defect | Condition | Standard | NO | YES | NO |
| 4138837 | Pericarditis | Condition | Standard | NO | YES | NO |
| 2313807 | Percutaneous balloon valvuloplasty; pulmonary valve | Procedure | Standard | NO | YES | NO |
| 4187102 | Percutaneous balloon valvuloplasty of pulmonary valve | Procedure | Standard | NO | YES | NO |
| 4103844 | Parasitic pericarditis | Condition | Standard | NO | YES | NO |
| 2001528 | Other operations on heart and pericardium | Procedure | Standard | NO | YES | NO |
| 2000047 | Other cardiovascular procedures | Procedure | Standard | NO | YES | NO |
| 2001434 | Operations on valves and septa of heart | Procedure | Standard | NO | YES | NO |
| 4101252 | Operation on vessels of heart | Procedure | Standard | NO | YES | NO |
| 4218568 | Non-infectious pericarditis | Condition | Standard | NO | YES | NO |
| 442569 | Myocarditis due to acquired toxoplasmosis | Condition | Standard | NO | YES | NO |
| 314383 | Myocarditis | Condition | Standard | NO | YES | NO |
| 4196524 | Mycotic pericarditis | Condition | Standard | NO | YES | NO |
| 4337061 | Mitral annuloplasty using ring | Procedure | Standard | NO | YES | NO |
| 312543 | Meningococcal pericarditis | Condition | Standard | NO | YES | NO |
| 319720 | Meningococcal myocarditis | Condition | Standard | NO | YES | NO |
| 43021067 | Infective constrictive pericarditis | Condition | Standard | NO | YES | NO |
| 4217075 | Infectious pericarditis | Condition | Standard | NO | YES | NO |
| 35624116 | Idiopathic recurrent pericarditis | Condition | Standard | NO | YES | NO |
| 4189533 | Hydralazine-induced pericarditis | Condition | Standard | NO | YES | NO |
| 318072 | Histoplasmosis with pericarditis | Condition | Standard | NO | YES | NO |
| 439682 | Histoplasma duboisii with pericarditis | Condition | Standard | NO | YES | NO |
| 314867 | Histoplasma capsulatum with pericarditis | Condition | Standard | NO | YES | NO |
| 442112 | Gonococcal pericarditis | Condition | Standard | NO | YES | NO |
| 4252587 | Familial pericarditis | Condition | Standard | NO | YES | NO |
| 4031469 | Drug-induced pericarditis | Condition | Standard | NO | YES | NO |
| 443778 | Diphtheritic myocarditis | Condition | Standard | NO | YES | NO |
| 315469 | Coxsackie pericarditis | Condition | Standard | NO | YES | NO |
| 319728 | Coxsackie myocarditis | Condition | Standard | NO | YES | NO |
| 312334 | Constrictive pericarditis | Condition | Standard | NO | YES | NO |
| 42732628 | Combined right heart catheterization with left ventricular puncture (with or without retrograde left heart catheterization) | Procedure | Standard | NO | YES | NO |
| 42732627 | Combined right heart catheterization and transseptal left heart catheterization through intact septum (with or without retrograde left heart catheterization) | Procedure | Standard | NO | YES | NO |
| 42732626 | Combined right heart catheterization and retrograde left heart catheterization | Procedure | Standard | NO | YES | NO |
| 321307 | Chronic rheumatic pericarditis | Condition | Standard | NO | YES | NO |
| 4053008 | Chronic pericarditis | Condition | Standard | NO | YES | NO |
| 4119595 | Chronic infective pericarditis | Condition | Standard | NO | YES | NO |
| 4097815 | Chronic effusive pericarditis | Condition | Standard | NO | YES | NO |
| 4203625 | Chronic constrictive pericarditis | Condition | Standard | NO | YES | NO |
| 4181182 | Chronic adhesive pericarditis | Condition | Standard | NO | YES | NO |
| 45766036 | Carditis due to rheumatic fever | Condition | Standard | NO | YES | NO |
| 4124694 | Bacterial pericarditis | Condition | Standard | NO | YES | NO |
| 4144859 | Annuloplasty of tricuspid valve | Procedure | Standard | NO | YES | NO |
| 4020089 | Annuloplasty of mitral valve | Procedure | Standard | NO | YES | NO |
| 312928 | Adhesive pericarditis | Condition | Standard | NO | YES | NO |
| 321578 | Acute rheumatic myocarditis | Condition | Standard | NO | YES | NO |
| 320116 | Acute pericarditis | Condition | Standard | NO | YES | NO |
| 312653 | Acute myocarditis | Condition | Standard | NO | YES | NO |



**Figure 1. Exposure cohort design.**

### Patients subgroup analyses

In subgroup analyses, the drugs will be stratified into standard dose (resulting in 4 exposure cohorts) and reduced dose (another 4 exposure cohorts) (**Table 3**). We will compare the DOACs within the standard-dose group (e.g. apixaban 5mg twice daily vs rivaroxaban 20mg once daily) and within the reduced-dose group (e.g. apixaban 2.5mg twice daily vs rivaroxaban 15mg once daily).

**Table 3. Concept IDs for direct oral anticoagulants for subgroup analysis for standard-dose and reduced-dose groups (preliminary working list at time of protocol preparation; final list will be contained in the GitHub repository)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Direct oral anticoagulants** | **Standard dose** | **Concept ID (including all the descendants)** | **Concept name** |
| Apixaban | 5mg twice daily | 43013029 | apixaban 5 MG |
| Dabigatran | 150mg twice daily | 40228153 | [dabigatran etexilate 150 MG](http://atlas-demo.ohdsi.org/#/concept/40228153) |
| 36787982 | [dabigatran 150 MG](http://atlas-demo.ohdsi.org/#/concept/36787982) |
| Rivaroxaban | 20mg once daily | 40244447 | [rivaroxaban 20 MG](http://atlas-demo.ohdsi.org/#/concept/40244447) |
| Edoxaban | 60mg once daily | 45892859 | [edoxaban 60 MG](http://atlas-demo.ohdsi.org/#/concept/45892859) |
|  |  |  |  |
| **Direct oral anticoagulants** | **Reduced dose** | **Concept ID (including all the descendants)** | **Concept name** |
| Apixaban | 2.5mg twice daily | 43013025 | [apixaban 2.5 MG](http://atlas-demo.ohdsi.org/#/concept/43013025) |
| Dabigatran | 75mg twice daily (in the United States) | 40228160 | [dabigatran etexilate 75 MG](http://atlas-demo.ohdsi.org/#/concept/40228160) |
| 36787992 | [dabigatran 75 MG](http://atlas-demo.ohdsi.org/#/concept/36787992) |
| 110mg twice daily (outside the United States) | 35606207 | [dabigatran etexilate 110 MG](http://atlas-demo.ohdsi.org/#/concept/35606207) |
| 36787972 | [dabigatran 110 MG](http://atlas-demo.ohdsi.org/#/concept/36787972) |
| Rivaroxaban | 15mg once daily | 40244443 | [rivaroxaban 15 MG](http://atlas-demo.ohdsi.org/#/concept/40244443) |
| Edoxaban | 30mg once daily | 45892855 | [edoxaban 30 MG](http://atlas-demo.ohdsi.org/#/concept/45892855) |

Additional subgroup analyses will be conducted to compare the effects of DOACs among two important patient subgroups: 1) patients with chronic kidney disease (CKD) at cohort entry; 2) patients who were aged>=80 years at cohort entry.

The subgroup analysis for CKD will be conducted by repeating the main analysis and adding the following inclusion rule to all the DOACs cohorts, derived with reference to the LEGEND study[12](#_ENREF_12):

Having all of the following criteria:

* at least 1 occurrence of a condition occurrence of [LEGEND HTN] Chronic kidney disease

Having any of the following criteria:

* + - at least 1 occurrence of a condition occurrence of [LEGEND HTN] Chronic kidney disease

where event starts between 30 days After and all days After index start date

* + - or at least 2 occurrences of a procedure of [LEGEND HTN] Dialysis

where event starts between 0 days Before and all days After index start date

* + - or at least 2 occurrences of an observation of [LEGEND HTN] Dialysis

where event starts between 0 days Before and all days After index start date

where event starts between all days Before and 0 days After index start date

Limit qualifying cohort to: **all events per person.**

The Concept IDs of CKD are listed in **Table 4 and Table 5** below.

**Table 4. Concept IDs of chronic kidney diseases (preliminary working list at time of protocol preparation; final version will be contained in GitHub repository).**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Chronic Kidney Diseases** | | | | | | |
| **Concept Id** | **Concept Name** | **Domain** | **Standard Concept Caption** | **Exclude** | **Descendants** | **Mapped** |
| 197930 | Renal hypertension complicating pregnancy, childbirth and the puerperium | Condition | Standard | YES | YES | NO |
| 192359 | Renal failure syndrome | Condition | Standard | NO | YES | NO |
| 195014 | Renal failure following molar AND/OR ectopic pregnancy | Condition | Standard | YES | YES | NO |
| 37116834 | Postpartum acute renal failure | Condition | Standard | YES | YES | NO |
| 4066005 | Post-delivery acute renal failure with postnatal problem | Condition | Standard | YES | YES | NO |
| 195314 | Nephrotic syndrome | Condition | Standard | NO | YES | NO |
| 193253 | Nephritis | Condition | Standard | NO | NO | NO |
| 192279 | Kidney disorder due to diabetes mellitus | Condition | Standard | NO | YES | NO |
| 4103224 | Interstitial nephritis | Condition | Non-Standard | NO | YES | NO |
| 43530912 | Induced termination of pregnancy complicated by renal failure | Condition | Standard | YES | YES | NO |
| 201313 | Hypertensive renal disease | Condition | Standard | NO | YES | NO |
| 195737 | Hemorrhagic nephroso-nephritis | Condition | Non-Standard | YES | YES | NO |
| 195289 | Goodpasture's syndrome | Condition | Standard | YES | YES | NO |
| 261071 | Glomerulosclerosis | Condition | Standard | NO | YES | NO |
| 4263367 | Glomerulonephritis | Condition | Standard | NO | YES | NO |
| 46271022 | Chronic kidney disease | Condition | Standard | NO | YES | NO |
| 45769152 | Bartter syndrome | Condition | Standard | YES | YES | NO |
| 194385 | Aneurysm of renal artery | Condition | Standard | NO | YES | NO |
| 197320 | Acute renal failure syndrome | Condition | Standard | YES | YES | NO |

**Table 5. Concept IDs of dialysis (preliminary working list at time of protocol preparation; final version will be contained in GitHub repository).**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Dialysis** | | | | | | |
| Concept Id | Concept Name | Domain | Standard Concept Caption | Exclude | Descendants | Mapped |
| 45889365 | Dialysis Services and Procedures | Procedure | Classification | NO | YES | NO |
| 4032243 | Dialysis procedure | Procedure | Standard | NO | YES | NO |
| 4090651 | Dialysis finding | Observation | Standard | NO | YES | NO |

The subgroup analysis for aged>=80 years will be conducted by repeating the main analysis and revising the age criteria in the initial cohort entry event from aged 18 years to aged 80 years:

Initial Event Cohort

People having any of the following:

* a drug exposure of a DOAC
  + for the first time in the person's history
  + occurrence start is on or after 2010-01-01
  + occurrence end is on or Before 2019-12-31
  + with age >= 80 years

with continuous observation of at least 365 days prior and 0 days after event index date, and limit initial events to: earliest event per person.

## Outcomes

### Study outcomes

The outcomes of interest include a range of clinically concerned outcomes associated with DOAC use: 1) a composite of ischemic stroke and systemic embolism; 2) intracranial bleeding; 3) gastrointestinal bleeding; 4) all-cause mortality. The concept ids were derived based on previous studies[13](#_ENREF_13), [14](#_ENREF_14) and checking on the orphan concepts by running CohortDiagnotics. Only the first occurrence of an outcome following index date will be included and the follow-up of the patient will be censored by the first occurrence of an outcome.

**Table 5. Concept IDs of the outcomes (preliminary working list at time of protocol preparation; final version will be contained in GitHub repository)**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Ischemic stroke and/or systemic embolism** | | | | | | |
| **Concept Id** | **Concept Name** | **Domain** | **Standard Concept Caption** | **Exclude** | **Descendants** | **Mapped** |
| 37110765 | Ischemic stroke without residual deficits | Condition | Standard | NO | YES | NO |
| 43530670 | Ischemic stroke without coma | Condition | Standard | NO | YES | NO |
| 43530669 | Ischemic stroke with coma | Condition | Standard | NO | YES | NO |
| 4310996 | Ischemic stroke | Condition | Standard | NO | YES | NO |
| 4323292 | Embolism from thoracic aorta | Condition | Standard | NO | YES | NO |
| 4078667 | Embolism from abdominal aorta | Condition | Standard | NO | YES | NO |
| 4045734 | CVA - cerebrovascular accident due to cerebral artery occlusion | Condition | Standard | NO | YES | NO |
| 321037 | Cholesterol embolus syndrome | Condition | Standard | NO | YES | NO |
| 37110237 | Cerebral ischemic stroke due to small artery occlusion | Condition | Standard | NO | YES | NO |
| 37110238 | Cerebral ischemic stroke due to intracranial large artery atherosclerosis | Condition | Standard | NO | YES | NO |
| 37110239 | Cerebral ischemic stroke due to extracranial large artery atherosclerosis | Condition | Standard | NO | YES | NO |
| 374384 | Cerebral ischemia | Condition | Standard | NO | YES | NO |
| 443454 | Cerebral infarction | Condition | Standard | NO | YES | NO |
| 316437 | Cerebral atherosclerosis | Condition | Standard | NO | YES | NO |
| 372924 | Cerebral artery occlusion | Condition | Standard | NO | YES | NO |
| 4278217 | Arterial thrombosis | Condition | Standard | NO | YES | NO |
| 374060 | Acute ill-defined cerebrovascular disease | Condition | Standard | NO | YES | NO |
| **Intracranial bleeding** | | | | | | |
| **Concept Id** | **Concept Name** | **Domain** | **Standard Concept Caption** | **Exclude** | **Descendants** | **Mapped** |
| 432923 | Subarachnoid hemorrhage | Condition | Standard | NO | YES | NO |
| 439847 | Intracranial hemorrhage | Condition | Standard | NO | YES | NO |
| 376713 | Cerebral hemorrhage | Condition | Standard | NO | YES | NO |
| **Gastrointestinal bleeding** | | | | | | |
| **Concept Id** | **Concept Name** | **Domain** | **Standard Concept Caption** | **Exclude** | **Descendants** | **Mapped** |
| 4291649 | Upper gastrointestinal bleeding | Condition | Standard | NO | YES | NO |
| 43021552 | Suture plication of artery for control of rectal hemorrhage | Procedure | Standard | NO | YES | NO |
| 4212456 | Painless rectal bleeding | Condition | Standard | NO | YES | NO |
| 4189790 | Painful rectal bleeding | Condition | Standard | NO | YES | NO |
| 4242106 | Occult blood in stools | Condition | Standard | NO | YES | NO |
| 4103703 | Melena | Condition | Standard | NO | YES | NO |
| 45757654 | Intestinal hemorrhage due to angiodysplasia of intestine | Condition | Standard | NO | YES | NO |
| 40485318 | Incision of stomach and suture of bleeding gastric ulcer | Procedure | Standard | NO | YES | NO |
| 437027 | Hemorrhagic duodenitis | Condition | Standard | NO | YES | NO |
| 46270529 | Hemorrhage of small intestine with diverticulosis | Condition | Standard | NO | YES | NO |
| 46269901 | Hemorrhage of small intestine due to diverticulitis | Condition | Standard | NO | YES | NO |
| 197925 | Hemorrhage of rectum and anus | Condition | Standard | NO | YES | NO |
| 45757543 | Hemorrhage of colon due to diverticulosis | Condition | Standard | NO | YES | NO |
| 442190 | Hemorrhage of colon | Condition | Standard | NO | YES | NO |
| 443530 | Hematochezia | Condition | Standard | NO | YES | NO |
| 26727 | Hematemesis | Condition | Standard | NO | YES | NO |
| 192671 | Gastrointestinal hemorrhage | Condition | Standard | NO | YES | NO |
| 46269911 | Gastric hemorrhage due to hypertrophic gastritis | Condition | Standard | NO | YES | NO |
| 46270025 | Gastric hemorrhage due to eosinophilic gastritis | Condition | Standard | NO | YES | NO |
| 46270145 | Gastric hemorrhage due to atrophic gastritis | Condition | Standard | NO | YES | NO |
| 45757783 | Gastric hemorrhage due to alcoholic gastritis | Condition | Standard | NO | YES | NO |
| 193250 | Gastric hemorrhage | Condition | Standard | NO | YES | NO |
| 4152684 | Feces: fresh blood present | Condition | Standard | NO | YES | NO |
| 4195152 | Endoscopic control of gastric bleeding | Procedure | Standard | NO | YES | NO |
| 4031954 | Duodenal ulcer with hemorrhage AND perforation | Condition | Standard | NO | YES | NO |
| 198798 | Dieulafoy's vascular malformation | Condition | Standard | NO | YES | NO |
| 4148536 | Dark stools | Condition | Standard | NO | YES | NO |
| 4247008 | Chronic peptic ulcer with hemorrhage AND perforation | Condition | Standard | NO | YES | NO |
| 4174044 | Chronic peptic ulcer with hemorrhage | Condition | Standard | NO | YES | NO |
| 437326 | Chronic gastrojejunal ulcer with hemorrhage AND with perforation but without obstruction | Condition | Standard | NO | YES | NO |
| 433515 | Chronic gastrojejunal ulcer with hemorrhage | Condition | Standard | NO | YES | NO |
| 4294973 | Chronic gastric ulcer with hemorrhage AND with perforation | Condition | Standard | NO | YES | NO |
| 4211001 | Chronic gastric ulcer with hemorrhage | Condition | Standard | NO | YES | NO |
| 4232181 | Chronic duodenal ulcer with hemorrhage | Condition | Standard | NO | YES | NO |
| 4155093 | C/O - melena | Condition | Standard | NO | YES | NO |
| 4092938 | Blood in vomit - symptom | Condition | Standard | NO | YES | NO |
| 4149861 | Black feces | Condition | Standard | NO | YES | NO |
| 4006994 | Acute peptic ulcer with hemorrhage and perforation | Condition | Standard | NO | YES | NO |
| 4046500 | Acute peptic ulcer with hemorrhage | Condition | Standard | NO | YES | NO |
| 193249 | Acute hemorrhagic gastritis | Condition | Standard | NO | YES | NO |
| 4217947 | Acute gastrojejunal ulcer with hemorrhage AND perforation | Condition | Standard | NO | YES | NO |
| 4274491 | Acute gastrojejunal ulcer with hemorrhage | Condition | Standard | NO | YES | NO |
| 4169592 | Acute gastric ulcer with hemorrhage AND perforation | Condition | Standard | NO | YES | NO |
| 4231580 | Acute gastric ulcer with hemorrhage | Condition | Standard | NO | YES | NO |
| 4336230 | Acute duodenal ulcer with hemorrhage AND perforation | Condition | Standard | NO | YES | NO |
| 4027729 | Acute duodenal ulcer with hemorrhage | Condition | Standard | NO | YES | NO |

### Negative control outcomes

Negative controls will be selected using a semiautomated procedure used in OHDSI.[15](#_ENREF_15) The procedure will include automatically extracting and synthesizing the information from literature, product labels regarding adverse drug events, and spontaneous reporting of adverse drug events to produce a list of negative control candidates. This list will then be reviewed to verify the appropriateness and biological plausibility.

## Covariates

### Propensity score covariates

To address potential bias due to nonrandomized treatment allocation, propensity scores matching will be used to construct a cohort of patients who differed with respect to treatment with anticoagulants but were similar with respect to other measured characteristics. The propensity score is defined as the probability of receiving the targeted treatment vs the comparator treatment, given the observed patient characteristics. The Cyclops package (<https://ohdsi.github.io/Cyclops>) will be used to construct the propensity score based on a range of baseline covariates derived from the data, including all drugs, condition, procedures, and summary scores such as CHA2DS2-VASc score and Charlson Comorbidity Index.

* Demographics
  + Gender
  + Age group (5-year bands)
  + Index year
* Conditions, procedures, and device exposure records
  + In 365d prior to and including index date (excluding AF)
* Recent drugs use
  + In 30d prior to and including index date (excluding the target treatment and comparator treatment)
* Measurements (including laboratories tests) within, above, and below normal range
  + In 365d prior to and including index date
* Comorbidity scores
  + CHA2DS2-VASc
  + Charlson Comorbidity Index

Any covariates that are found in fewer than 0.1% of the study population will not be included in the propensity score model fitting to enhance computational efficiency.

# Data Analysis Plan

## Calculation of time-at risk

Two time-at-risk periods will be used:

* On-treatment (primary analysis): Commences from the index date and ends on the date of discontinuation of index treatment (allowing for 90-day gaps between consecutive prescriptions), a prescription of an alternative oral anticoagulant, changing of dose (applies to the subgroup analysis for DOAC doses only; defined as a prescription of the same DOAC but of different dose, e.g. dabigatran 110mg 🡪 dabigatran 150mg), death, the first occurrence of an outcome, or study end (31st December 2019), whichever came first.
* Intention-to-treat (secondary analysis): Commences from the index date and ends on the date of death, the first occurrence of an outcome, or study end (31st December 2019), whichever came first.

## Model Specification

The occurrence of outcomes will be captured among the target cohort and comparator cohort during the time-at-risk periods as specified in section 7.1. The hazards of the outcomes will be compared between the cohorts using Cox proportional hazards regression model. The number of outcomes and incidence of the outcomes will be calculated in each drug exposure cohorts during the entire follow-up period. The number of people at risk and cumulative incidence of the outcomes in each drug exposure cohort will be calculated at 1, 2, 3 years of follow-up.

Propensity score matching with variable target-to-comparator ratio[16](#_ENREF_16) will be used to address the potential baseline differences in characteristics between comparison groups. A caliper of 0.2 standard deviations of the propensity score on the logit scale will be used for matching. Propensity score will be estimated for each patient using a data-driven, regularized logistic regression model available in OHDSI. The covariates to be included in the propensity score model fitting are listed in **section 6.6.1**.

### Pooling effect estimates across databases

The effect estimates will be pooled across databases in a meta-analysis using a random-effect model. The estimates for negative controls will be pooled before performing empirical calibration on the pooled estimates.

## Analyses to perform

### Comparative analyses

The following comparative analyses will be performed if sufficient data is present (e.g. if at least 1,000 subjects are observed in both target and comparator cohort):

* N= 30 treatment comparisons for each outcome:
  + Primary analysis at drug level: 4 DOACs = 4C2= 6 comparisons
  + Four subgroup analysis (standard dose, reduced dose, CKD, aged 80+) = 4\*6 = 24 comparisons
* N=4 outcomes of interest
* N=2 time-at-risk definitions: on-treatment and intention-to-treat
* N=2 models: Cox regression using propensity score matching and Cox regression using stratifications of propensity score

The total number of analyses is therefore 30\*4\*2\*2 = 480 analyses per database.

### Descriptive analyses

Baseline characteristics, including age (mean and standard deviation), sex, disease history, and recent drug use will be reported for each drug cohorts of interest. The number of outcome events and incidences of the outcome events during the entire time-at-risk periods will be calculated. The number of people at risk and cumulative incidence of the outcomes will be calculated in the end of the 1st year, 2nd year, and 3rd year of time-at-risk.

## Output

Summary statistics on baseline characteristics, incidences of the outcomes; hazard ratios, cumulative incidence/Kaplan-Meier plots.

## Evidence Evaluation

The comparability between the target cohorts and comparator cohorts will be evaluated by examining the propensity score distributions. Covariate balance before and after propensity score modelling will be evaluated using standardized differences, where a value of <0.10 is considered negligible.

# Strengths and Limitations of the Research Methods

Strengths

To our knowledge, this will be the largest and most comprehensive study to provide evidence about the comparative effectiveness and safety of all the 4 DOACs available for use in clinical practice. We will use a new-user cohort study design to eliminate the residual effect of previous drug exposure on the outcomes. Propensity score matching will also be used to address potential confounding factors. Several measures (e.g. negative controls, confidence interval calibrations) will be used to evaluate the robustness and validity of the study results.

Limitations

Due to the observational nature of the study, we cannot exclude the possibility of residual confounding factors. To overcome this potential limitation, all known confounding variables for which there is adequate information available will be included in the study. Also, we will use propensity score modelling to control for possible prescribing bias and confounding by accounting for the observed differences between groups.

# Protection of Human Subjects

This study will only use de-identified patient data which will not involve any direct contact or primary collection of individual human subject data. The study results will be aggregated and presented in tabular form that omits subject identification. Any publications will not include subject identifiers. Cells with patient counts <5 will be masked to prevent unintentional disclosure of patient identity.

# Management and Reporting of Adverse Events and Adverse Reactions

There is no potential to collect adverse events or adverse reactions during the conduct of this research, as the minimum criteria needed to report adverse events (e.g. an identifiable patient) are not available in any databases.

# Plans for Disseminating and Communicating Study Results

The study results will be made available in the OHDSI website after completion of the study. We intend to publish our findings in a peer reviewed journal as well as to present them at relevant scientific conferences.

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