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Using primary care data to assess comparative effectiveness and safety of apixaban and rivaroxaban in patients with nonvalvular atrial fibrillation in the UK: an observational cohort study

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ABSTRACT

Objective To compare real-world effectiveness and safety of direct oral anticoagulants (DOACs) in patients with nonvalvular atrial fibrillation (AFib) for prevention of stroke.

Study design and setting A comparative cohort study in UK general practice data from The Health Improvement Network database.

Participants and interventions Before matching, 5655 patients ≥18 years with nonvalvular AFib who initiated at least one DOAC between 1 July 2014 and 31 December 2020 were included. DOACs of interest included apixaban, rivaroxaban, edoxaban and dabigatran, with the primary comparison between apixaban and rivaroxaban. Initiators of DOACs were defined as new users with no record of prescription for any DOAC during 12 months before index date.

Primary and secondary outcome measures The primary outcome was stroke (ischaemic or haemorrhagic). Secondary outcomes included the occurrence of all-cause mortality, myocardial infarction (MI), transient ischaemic attacks (TIA), major bleeding events and a composite angina/MI/stroke (AMS) endpoint.

Results Compared with rivaroxaban, patients initiating apixaban showed similar rates of stroke (HR: 0.93; 95% CI 0.64 to 1.34), all-cause mortality (HR: 1.03; 95% CI 0.87 to 1.22), MI (HR: 0.95; 95% CI 0.54 to 1.68), TIA (HR: 1.03; 95% CI 0.61 to 1.72) and AMS (HR: 0.96; 95% CI 0.72 to 1.27). Apixaban initiators showed lower rates of major bleeding events (HR: 0.60; 95% CI 0.47 to 0.75).

Conclusions Among patients with nonvalvular AFib, apixaban was as effective as rivaroxaban in reducing rate of stroke and safer in terms of major bleeding episodes. This head-to-head comparison supports conclusions drawn from indirect comparisons of DOAC trials against warfarin and demonstrates the potential for real-world evidence to fill evidence gaps and reduce uncertainty in both health technology assessment decision-making and clinical guideline development.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study performed head-to-head comparisons of direct oral anticoagulants rather than relying on indirect comparisons of trials with different designs.
⇒ This study used routinely collected data from electronic health records within a nationally representative UK database with good data recording and follow-up time.
⇒ Treatment assignment was not randomised; however, after propensity score matching, treatment groups were similar across 40 measured demographic and clinical characteristics, suggesting comparability between exposure groups.
⇒ Robustness of primary findings via propensity score matching was contextualised by use of alternative balancing approaches in sensitivity analyses, including propensity score weighting and high dimensional propensity score matching.
⇒ We did not link to secondary data for stroke outcome ascertainment but reporting of stroke and other conditions in the general practice record is incentivised by the Quality and Outcomes Framework.

INTRODUCTION

In the UK, atrial fibrillation (AFib) affects 1.4 million patients,[1] and between 0.9% and 1.6% of the UK's National Health Service spending is attributable to AFib, predominantly from hospitalisations.[2] The condition is associated with significant complications, including stroke—nonvalvular AFib increases an individual's risk of stroke by five times,[3] and between 20% and 30% of stroke cases are attributed to AFib.[4]

Anticoagulants, including vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs), are highly effective in the prevention and treatment of thromboembolic events associated with AFib. Nevertheless, VKAs like warfarin require frequent coagulation monitoring due to their narrow therapeutic index and have multiple drug and food interactions.

Alternatively, DOACs inhibit coagulation via direct and specific binding to active sites of thrombin (eg, dabigatran) or factor Xa (eg, apixaban, rivaroxaban and edoxaban) of the coagulation pathway. Compared with VKAs, DOACs have a wider therapeutic index, which permits use in fixed doses without coagulation monitoring, and relatively limited drug and food interactions. DOACs are the preferred anti-coagulants for patients with nonvalvular AFib in the UK.[5] The safety and efficacy of DOACs compared with VKAs for stroke prevention in patients with AFib have been established in randomised clinical trials (RCTs).[6 7] However, head-to-head RCTs of DOACs (eg, apixaban vs rivaroxaban) are not available, and relative safety and efficacy findings are based on indirect comparisons from network meta-analyses (NMA).[7–9]

Agencies, like the National Institute for Health and Care Excellence (NICE), evaluate the comparative effectiveness and cost-effectiveness of therapies to inform both reimbursement decisions and clinical guidelines. Between March 2012 and September 2015, NICE separately assessed and recommended four DOACs for stroke prevention in AFib: dabigatran, rivaroxaban, apixaban and edoxaban. Because no direct comparisons of DOACs were available, NICE's decision-making, which impacts patient health and clinical practice was based on RCTs of DOACs compared with warfarin and indirect comparisons to other DOACs. A NMA of indirect comparisons ranked rivaroxaban as the best DOAC for reducing myocardial infarction (MI) and all-cause mortality, while apixaban was ranked best for minimising the risk of bleeding and dabigatran was ranked best for reducing the rate of stroke.[5] However, the NMA rankings had probabilities that varied from 60% to 80% and most of the head-to-head ORs approached the null and/or had wide confidence intervals leading NICE to interpret the findings with caution. NICE noted heterogeneity among the trials on which the indirect comparisons were based, which limited the ability to differentiate between DOACs' effectiveness. These uncertainties were reflected in NICE's Atrial fibrillation: diagnosis and management guideline[5] where NICE decided to not recommend one DOAC over the others, but instead emphasised treatment should be personalised based on the patients' needs and preference.

Comparative effectiveness analysis in real-world data (RWD) has emerged as a potential strategy for supplementing clinical trials and for generating evidence on the effectiveness of products after launch.[10] There is a growing body of literature that has duplicated AFib RCT results in RWD,[11 12] which increases confidence in RWD studies that directly compare DOACs in RWD. However, there is heterogeneity in the results of RWE studies that directly compare DOACs. For example, a Scottish study in AFib patients found no differences between DOACs for stroke prevention.[13] These findings align with a French and Danish RWE study in nonvalvular AFib patients[14 15] but differ from a US-based study of Medicare patients with AFib, which found an increased risk of stroke for rivaroxaban patients compared with apixaban patients.[16] All-cause mortality findings are also mixed, with one study finding no difference between apixaban compared with rivaroxaban[14] and others finding increased mortality with rivaroxaban compared with apixaban[13 16] and dabigatran.[15] Only the French and Danish studies restricted to nonvalvular AFib[14 15] and the US-based study[16] was in patients >65 years old. Thus, it is unclear how generalisable these findings are to patients with nonvalvular AFib in the UK.

The objective of this study was to evaluate the comparative effectiveness and safety of the DOACs available in the UK (apixaban, rivaroxaban, edoxaban and dabigatran) through direct comparisons among adults with nonvalvular AFib at risk for stroke in the UK.

METHODS

Study design and objectives

We conducted an RWD cohort study to compare the rate of stroke among patients with nonvalvular AFib initiating DOACs, specifically, apixaban, rivaroxaban, edoxaban and dabigatran. Following the steps outlined by Gatto *et al*[17], we articulated the research question, conceptualised the underlying hypothetical target trial,[18] identified a fit-for-purpose data source, and posted the final protocol publicly on the EU PASS Register of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (EUPAS45073) prior to implementing the study.

Data source

This study used anonymised patient data from The Health Improvement Network (THIN) Database (A Cegedim Proprietary Database). The THIN Database is a primary care research database containing anonymised electronic health record data from around 850 UK general practices using the VISION clinical system (since 1994) and contains records for around 20 million patients. The THIN database has been well described, and the quality of data collection has been documented in multiple studies.[19 20] THIN has also been shown to be representative of the UK population with respect to demographics, major condition prevalence and mortality rates.[21]

Study population and treatment

We identified adults (≥18 years) with nonvalvular AFib newly initiating apixaban, rivaroxaban, edoxaban or dabigatran (with a 365-day washout for any prior DOAC use) between July 2014 and December 2020 (figure 1). Index date was assigned as the date of first qualifying treatment initiation. Patients were required to have at least one medical encounter in the 180 days prior to study index date, be at risk of stroke (general practitioner (GP) assessed CHA_2DS_2 VASc >1 for men and >2 for women), have no recorded history of study outcomes and have no prior diagnosis of cardiac valve disease, deep vein thrombosis, pulmonary embolism, angina or congenital heart

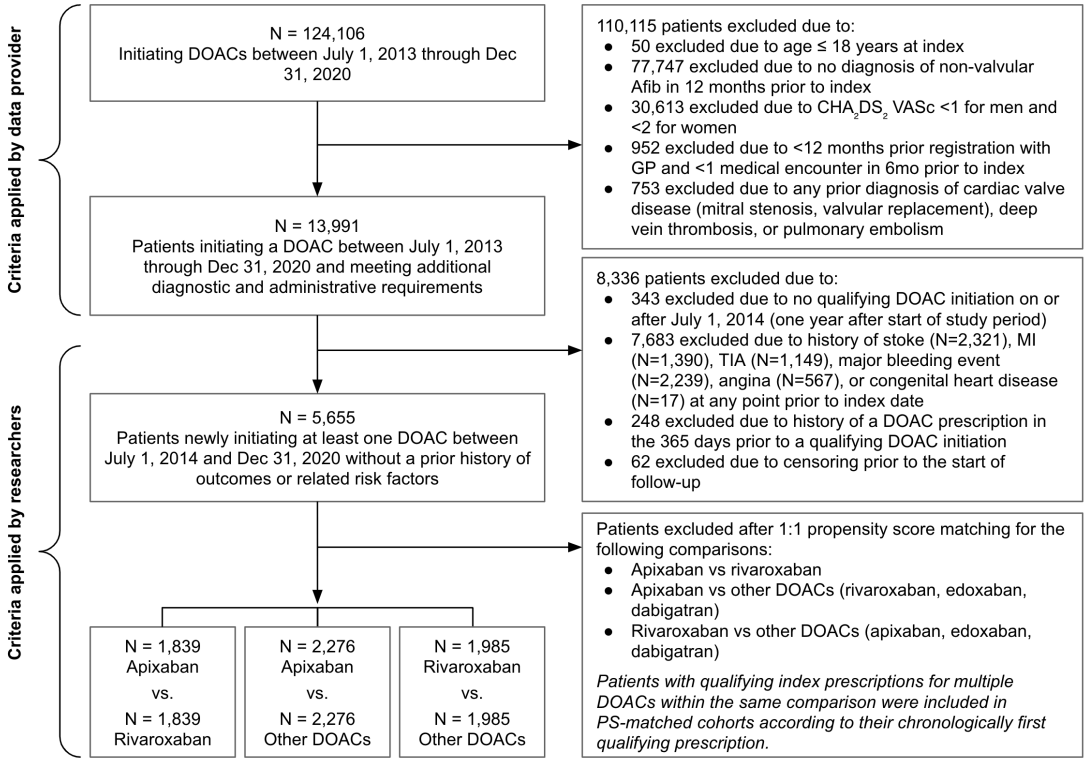

Figure 1 Study population for completed comparisons. DOACs, direct oral anticoagulants; GP, general practitioner; MI, myocardial infarction; PS, propensity score; TIA, transient ischaemic attack.

disease. History of congenital heart disease was an exclusion criterion because it is linked to valvular heart disease. Exposures of interest were defined by corresponding Anatomical Therapeutic Chemical (ATC) codes (online supplemental figure 1; online supplemental files 1 and 2).

The primary comparison of interest was apixaban initiators versus rivaroxaban initiators, the two most commonly prescribed DOACs in the UK.[22] Additional comparisons considered and completed are detailed in table 1. Patients with qualifying DOAC prescriptions from both medications or medication groups being compared (<0.5% of patients with qualifying prescriptions) were indexed according to the chronologically first qualifying prescription.

In the primary comparison, subgroup analyses were conducted by age group (<75 years vs ≥75 years), by CHA_2DS_2 VASc score (0–1, 2–3, ≥4), by gender, and among patients with vs without each of the following: concomitant aspirin use, prior warfarin use, diabetes mellitus and heart failure.

Table 1 Head-to-head comparisons considered and completed

	Rivaroxaban	Edoxaban	Dabigatran	DOACs class
Apixaban	Primary comparison *Completed*	Secondary comparison *Not completed due to insufficient sample size**	Secondary comparison *Not completed due to insufficient sample size**	Secondary comparison (rivaroxaban, edoxaban, dabigatran) *Completed*
Rivaroxaban	–	Secondary comparison *Not completed due to insufficient sample size**	Secondary comparison *Not completed due to insufficient sample size**	Secondary comparison (apixaban, edoxaban, dabigatran) *Completed*
DOACs class	–	Secondary comparison (apixaban, rivaroxaban, dabigatran) *Not completed due to insufficient sample size**	Secondary comparison (apixaban, rivaroxaban, edoxaban) *Not completed due to insufficient sample size**	--

*Did not meet the sample size criteria of greater than 500 patients per treatment group, and thus inferential analyses were not completed.
DOACs, direct oral anticoagulants.

Outcomes

The primary outcome was stroke (ischaemic or haemorrhagic). Secondary outcomes included all-cause mortality, MI, transient ischaemic attacks (TIA), major bleeding events and a composite of angina/MI/stroke (AMS). Major bleeding was defined as a composite of major intracranial (including haemorrhagic stroke), gastrointestinal and urogenital bleeds. Study outcomes were defined by corresponding Read Medical Codes and mapped International Classification of Disease, 10th version (ICD-10) diagnosis codes at the primary care setting (online supplemental files 1 and 2).

Covariates

Covariates included in the propensity score (PS) model (described below) included age, gender, CHA_2DS_2 VASc score,[23] year of treatment initiation and history of a number of diagnoses and treatments (see list in table 2). CHA_2DS_2 VASc score was estimated using patient history (online supplemental file 2) because the GP-assessed CHA_2DS_2 VASc was not available at time of analysis due to data availability constraints. All covariates were determined based on the literature and clinical knowledge regarding their relationship to the primary and secondary outcomes of interest.

Medication use was identified by ATC codes and assessed in the 12 months prior to and including the index date. Comorbidities were identified by Read Medical Codes and mapped ICD-10 diagnosis codes and were assessed over all available data prior to and including index date. Patient demographics were measured on the index date. High missingness (34%–98% missing; online supplemental table 1) in diagnostic assessments meant that we dropped some covariates that we planned to include in the PS models. This included marital status, cigarettes per day, alcohol glasses per day, body mass index, hemoglobin A1c (HbA1c), international normalised ratio, glomerular filtration rate and creatinine clearance as measures of renal function. Remaining covariates were assessed dichotomously based on the presence or absence of diagnostic or medication codes in the patient history. Patients were assumed to have had a diagnosis or prescription of the relevant code(s) was found among their records. Otherwise, it is assumed that the patient did not experience the event or was not prescribed the medication, thus resulting in no missing data for these variables. Additional dichotomous characteristics considered for inclusion in the PS model (eg, sepsis) capturing few (<1%) exposed or unexposed patients were not included in analytic models. See online supplemental file 2 for definitions of all covariates included in PS models.

The 1-year baseline period specified in the study protocol (EUPAS45073) for capture of baseline comorbidities was expanded to all prior available data after an observed under-capture of comorbid conditions (eg, hypertension) in baseline using the 1-year baseline period. Results corresponding to the protocol-specified 1-year baseline are reported in online supplemental tables 2 and 3.

PS matching

We used PS matching between exposure groups using 1:1 nearest neighbour matching without replacement (± a calliper of 0.01 of the PS). The PS model included a priori selected covariates assessed prior to treatment index, accounting for over-fitting, positivity violations and covariate instability.[24]

Diagnostic phase

In order to progress to the inferential analysis phase, each primary and secondary comparison had to pass a series of diagnostic checks (masked to treatment specific outcomes) including: positivity of variables, baseline confounder balance (an absolute standardised difference (ASD) ≤ 0.1),[25] sufficient population-level persistence on treatment (median persistence at least 1 year), and confirmation that models were not overfit (≥12 exposed patients per covariate). Adequacy of sample size was also assessed, but insufficient sample size per pre-specified power requirements did not preclude estimation,[26] as long as each PS matched comparator group had at least 500 patients. Comparisons passing all diagnostic criteria included apixaban versus rivaroxaban, apixaban versus other DOACs (rivaroxaban, edoxaban, dabigatran) and rivaroxaban versus other DOACs (apixaban, edoxaban, dabigatran).

Pre-specified inferential analysis

In the inferential phase, we executed Cox proportional hazards regression models to estimate HR and 95% CI after PS matching in the overall cohort and within each subgroup of interest. The incidence of stroke and secondary outcomes were assessed for the primary comparison of apixaban vs rivaroxaban. Incidence of stroke was compared for all secondary comparisons. Patients were followed in an 'intention to treat' (ITT) approach starting from the day after their index date. In analyses of stroke, MI, TIA, major bleeding events and AMS, patients were followed until the end of the study period (December 2020) or the first occurrence of the outcome, death or date of last contact with GP. In the analysis of all-cause mortality, follow-up was extended beyond the date of last contact to the date of a death if the death occurred within 90 days of a patient's last contact in order to capture deaths reported after a patient's last contact with their GP. Secondary analysis of the primary outcome in the apixaban versus rivaroxaban comparison included an 'as-treated' approach where in addition to the ITT censoring criteria, patients were censored on termination of exposure, crossover of exposure group, or addition of another DOAC. The exposure termination date was defined as the end of the last continuous prescription (allowing for up to 30-day gaps between end of previous and start of next prescription) plus a 30-day risk window.

Table 2 Baseline characteristics of patients with nonvalvular atrial fibrillation newly initiating a DOAC, before and after propensity score matching

	Patient characteristics before propensity score matching				Patient characteristics after propensity score matching								
	Apixaban	Rivaroxaban	Edoxaban	Dabigatran	Apixaban	Rivaroxaban	ASD	Apixaban	Other DOACs	ASD	Rivaroxaban	Other DOACs	ASD
Number of patients	2801	2221	398	261	1839	1839		2276	2276		1985	1985	
Year of cohort entry date							0.023			0.027			0.033
2014	76 (2.7%)	138 (6.2%)	0 (0.0%)	32 (12.3%)	76 (4.1%)	82 (4.5%)		76 (3.3%)	72 (3.2%)		100 (5.0%)	104 (5.2%)	
2015	365 (13.0%)	548 (24.7%)	0 (0.0%)	81 (31.0%)	361 (19.6%)	358 (19.5%)		360 (15.8%)	368 (16.2%)		428 (21.6%)	425 (21.4%)	
2016	571 (20.4%)	646 (29.1%)	11 (2.8%)	77 (29.5%)	527 (28.7%)	520 (28.3%)		553 (24.3%)	531 (23.3%)		575 (29.0%)	594 (29.9%)	
2017	546 (19.5%)	383 (17.2%)	20 (5.0%)	42 (16.1%)	382 (20.8%)	375 (20.4%)		426 (18.7%)	429 (18.8%)		378 (19.0%)	375 (18.9%)	
2018	530 (18.9%)	257 (11.6%)	115 (28.9%)	21 (8.0%)	249 (13.5%)	256 (13.9%)		377 (16.6%)	387 (17.0%)		256 (12.9%)	249 (12.5%)	
2019	423 (15.1%)	143 (6.4%)	129 (32.4%)	5 (1.9%)	141 (7.7%)	142 (7.7%)		266 (11.7%)	268 (11.8%)		142 (7.2%)	143 (7.2%)	
2020	290 (10.4%)	106 (4.8%)	123 (30.9%)	3 (1.1%)	103 (5.6%)	106 (5.8%)		218 (9.6%)	221 (9.7%)		106 (5.3%)	95 (4.8%)	
Age in years, mean (SD)	77.35 (8.54)	76.71 (8.62)	77.11 (8.35)	76.23 (8.56)	77.10 (8.69)	76.80 (8.40)	0.036	77.13 (8.55)	76.99 (8.34)	0.016	76.84 (8.54)	77.12 (8.54)	0.033
Female gender	1070 (38.2%)	785 (35.3%)	158 (39.7%)	81 (31.0%)	649 (35.3%)	665 (36.2%)	0.018	832 (36.6%)	841 (37.0%)	0.008	711 (35.8%)	696 (35.1%)	0.016
Non-major bleeding events	344 (12.3%)	252 (11.3%)	47 (11.8%)	34 (13.0%)	204 (11.1%)	210 (11.4%)	0.010	264 (11.6%)	271 (11.9%)	0.010	230 (11.6%)	223 (11.2%)	0.011
Anaemia	365 (13.0%)	276 (12.4%)	42 (10.6%)	21 (8.0%)	233 (12.7%)	235 (12.8%)	0.003	280 (12.3%)	272 (12.0%)	0.011	240 (12.1%)	233 (11.7%)	0.011
Diabetes mellitus	706 (25.2%)	657 (29.6%)	73 (18.3%)	74 (28.4%)	501 (27.2%)	502 (27.3%)	0.001	595 (26.1%)	582 (25.6%)	0.013	563 (28.4%)	539 (27.2%)	0.027
Hypertension	2046 (73.0%)	1654 (74.5%)	280 (70.4%)	205 (78.5%)	1373 (74.7%)	1349 (73.4%)	0.030	1680 (73.8%)	1659 (72.9%)	0.021	1473 (74.2%)	1464 (73.8%)	0.010
Heart failure	366 (13.1%)	287 (12.9%)	34 (8.5%)	25 (9.6%)	217 (11.8%)	236 (12.8%)	0.031	272 (12.0%)	272 (12.0%)	0.000	247 (12.4%)	261 (13.1%)	0.021
Osteoporosis and hip fractures	245 (8.7%)	145 (6.5%)	37 (9.3%)	16 (6.1%)	131 (7.1%)	132 (7.2%)	0.002	169 (7.4%)	165 (7.2%)	0.007	137 (6.9%)	138 (7.0%)	0.002
Malignant neoplasms	564 (20.1%)	477 (21.5%)	79 (19.8%)	54 (20.7%)	399 (21.7%)	365 (19.8%)	0.046	471 (20.7%)	470 (20.7%)	0.001	415 (20.9%)	431 (21.7%)	0.020
Acute kidney injury	82 (2.9%)	50 (2.3%)	5 (1.3%)	4 (1.5%)	52 (2.8%)	41 (2.2%)	0.038	55 (2.4%)	52 (2.3%)	0.009	45 (2.3%)	38 (1.9%)	0.025
Chronic kidney disease	695 (24.8%)	527 (23.7%)	84 (21.1%)	56 (21.5%)	450 (24.5%)	444 (24.1%)	0.008	555 (24.4%)	543 (23.9%)	0.012	469 (23.6%)	476 (24.0%)	0.008
Asthma and COPD	525 (18.7%)	451 (20.3%)	73 (18.3%)	52 (19.9%)	354 (19.2%)	346 (18.8%)	0.011	442 (19.4%)	434 (19.1%)	0.009	396 (19.9%)	356 (17.9%)	0.051
Dementia	75 (2.7%)	50 (2.3%)	7 (1.8%)	2 (0.8%)	45 (2.4%)	47 (2.6%)	0.007	52 (2.3%)	54 (2.4%)	0.006	46 (2.3%)	44 (2.2%)	0.007
Aspirin	824 (29.4%)	709 (31.9%)	89 (22.4%)	93 (35.6%)	570 (31.0%)	577 (31.4%)	0.008	686 (30.1%)	672 (29.5%)	0.013	615 (31.0%)	602 (30.3%)	0.014
Antiplatelets (other than aspirin)	164 (5.9%)	123 (5.5%)	18 (4.5%)	16 (6.1%)	105 (5.7%)	105 (5.7%)	0.000	125 (5.5%)	129 (5.7%)	0.008	115 (5.8%)	113 (5.7%)	0.004
Warfarin	391 (14.0%)	397 (17.9%)	53 (13.3%)	41 (15.7%)	289 (15.7%)	286 (15.6%)	0.004	348 (15.3%)	352 (15.5%)	0.005	333 (16.8%)	330 (16.6%)	0.004
Antianemic preparations	519 (18.5%)	334 (15.0%)	49 (12.3%)	33 (12.6%)	308 (16.7%)	289 (15.7%)	0.028	382 (16.8%)	368 (16.2%)	0.017	309 (15.6%)	310 (15.6%)	0.001
NSAIDs	340 (12.1%)	275 (12.4%)	50 (12.6%)	42 (16.1%)	242 (13.2%)	234 (12.7%)	0.013	289 (12.7%)	288 (12.7%)	0.001	249 (12.5%)	242 (12.2%)	0.011
Opioids	862 (30.8%)	640 (28.8%)	113 (28.4%)	73 (28.0%)	538 (29.3%)	532 (28.9%)	0.007	670 (29.4%)	659 (29.0%)	0.011	575 (29.0%)	550 (27.7%)	0.028
SSRIs	240 (8.6%)	181 (8.1%)	36 (9.0%)	17 (6.5%)	156 (8.5%)	150 (8.2%)	0.012	200 (8.8%)	193 (8.5%)	0.011	164 (8.3%)	154 (7.8%)	0.019
Antidepressants (other than SSRIs)	301 (10.7%)	235 (10.6%)	36 (9.0%)	26 (10.0%)	190 (10.3%)	199 (10.8%)	0.016	243 (10.7%)	245 (10.8%)	0.003	214 (10.8%)	204 (10.3%)	0.016
Antiepileptics	210 (7.5%)	150 (6.8%)	25 (6.3%)	19 (7.3%)	135 (7.3%)	127 (6.9%)	0.017	158 (6.9%)	165 (7.2%)	0.012	141 (7.1%)	134 (6.8%)	0.014

Continued

Table 2 Continued

	Patient characteristics before propensity score matching				Patient characteristics after propensity score matching								
	Apixaban	Rivaroxaban	Edoxaban	Dabigatran	Apixaban	Rivaroxaban	ASD	Apixaban	Other DOACs	ASD	Rivaroxaban	Other DOACs	ASD
Antipsychotics	141 (5.0%)	92 (4.1%)	20 (5.0%)	12 (4.6%)	83 (4.5%)	83 (4.5%)	0.000	107 (4.7%)	107 (4.7%)	0.000	86 (4.3%)	88 (4.4%)	0.005
Benzodiazepines	256 (9.1%)	182 (8.2%)	43 (10.8%)	23 (8.8%)	160 (8.7%)	157 (8.5%)	0.006	211 (9.3%)	201 (8.8%)	0.015	169 (8.5%)	169 (8.5%)	0.000
Lipid lowering drugs	1539 (54.9%)	1199 (54.0%)	191 (48.0%)	138 (52.9%)	1012 (55.0%)	1001 (54.4%)	0.012	1253 (55.1%)	1229 (54.0%)	0.021	1070 (53.9%)	1073 (54.1%)	0.003
Insulin	91 (3.2%)	80 (3.6%)	9 (2.3%)	5 (1.9%)	64 (3.5%)	55 (3.0%)	0.028	72 (3.2%)	68 (3.0%)	0.010	67 (3.4%)	69 (3.5%)	0.006
Antihyperglycemics other than insulins	525 (18.7%)	466 (21.0%)	51 (12.8%)	54 (20.7%)	363 (19.7%)	367 (20.0%)	0.005	432 (19.0%)	426 (18.7%)	0.007	410 (20.7%)	400 (20.2%)	0.013
Antihypertensives	2611 (93.2%)	2079 (93.6%)	366 (92.0%)	242 (92.7%)	1720 (93.5%)	1724 (93.7%)	0.009	2118 (93.1%)	2127 (93.5%)	0.016	1854 (93.4%)	1863 (93.9%)	0.019
Antiarrhythmics	94 (3.4%)	91 (4.1%)	10 (2.5%)	10 (3.8%)	69 (3.8%)	76 (4.1%)	0.020	81 (3.6%)	85 (3.7%)	0.009	81 (4.1%)	74 (3.7%)	0.018
Nitrates cardiac vasodilators	130 (4.6%)	99 (4.5%)	21 (5.3%)	9 (3.4%)	85 (4.6%)	87 (4.7%)	0.005	104 (4.6%)	99 (4.3%)	0.011	94 (4.7%)	85 (4.3%)	0.022
Cardiac stimulants	347 (12.4%)	272 (12.2%)	30 (7.5%)	17 (6.5%)	223 (12.1%)	219 (11.9%)	0.007	260 (11.4%)	249 (10.9%)	0.015	240 (12.1%)	247 (12.4%)	0.011
Gastrointestinal protective agents	1214 (43.3%)	893 (40.2%)	173 (43.5%)	106 (40.6%)	763 (41.5%)	753 (40.9%)	0.011	946 (41.6%)	943 (41.4%)	0.003	800 (40.3%)	786 (39.6%)	0.014
Bisphosphonates and other agents affecting bone structure	228 (8.1%)	171 (7.7%)	32 (8.0%)	15 (5.7%)	136 (7.4%)	139 (7.6%)	0.006	183 (8.0%)	169 (7.4%)	0.023	150 (7.6%)	148 (7.5%)	0.004
Systemic corticosteroids	442 (15.8%)	345 (15.5%)	53 (13.3%)	37 (14.2%)	285 (15.5%)	281 (15.3%)	0.006	346 (15.2%)	341 (15.0%)	0.006	313 (15.8%)	279 (14.1%)	0.048
Antineoplastics	140 (5.0%)	99 (4.5%)	21 (5.3%)	13 (5.0%)	83 (4.5%)	78 (4.2%)	0.013	103 (4.5%)	106 (4.7%)	0.006	96 (4.8%)	86 (4.3%)	0.024
Systemic antibiotics	1357 (48.4%)	1075 (48.4%)	177 (44.5%)	119 (45.6%)	873 (47.5%)	877 (47.7%)	0.004	1079 (47.4%)	1093 (48.0%)	0.012	951 (47.9%)	917 (46.2%)	0.034
Systemic antivirals	31 (1.1%)	32 (1.4%)	3 (0.8%)	3 (1.1%)	24 (1.3%)	24 (1.3%)	0.000	27 (1.2%)	25 (1.1%)	0.008	24 (1.2%)	23 (1.2%)	0.005
Vaccines and immunoglobulins	137 (4.9%)	204 (9.2%)	11 (2.8%)	24 (9.2%)	121 (6.6%)	136 (7.4%)	0.032	131 (5.8%)	137 (6.0%)	0.011	143 (7.2%)	132 (6.6%)	0.022
CHA2DS2 VASc score, mean (SD)	3.46 (1.12)	3.46 (1.09)	3.34 (1.12)	3.33 (1.11)	3.44 (1.09)	3.45 (1.09)	0.010	3.43 (1.10)	3.44 (1.10)	0.006	3.45 (1.09)	3.45 (1.11)	0.003

Characteristics reported as N (%) unless otherwise specified.
ASD, absolute standardised difference; COPD, Chronic Obstructive Pulmonary Disease; DOAC, directoral anticoagulant; NSAIDs, Non-steroidal anti-inflammatory drugs; SSRIs, Selective serotonin reuptake inhibitors.

Pre-specified sensitivity analysis

To evaluate the robustness of our findings, high-dimensional PS (HdPS) analysis was used to estimate the association between treatment with DOACs and the primary and secondary outcomes. The HdPS approach is a seven-step algorithm that empirically identifies a pool of covariates from different data dimensions (eg, diagnoses, procedures, medications) based on their prevalence and then selects a subset of the covariates for inclusion in a PS model based on their potential to bias the exposure-outcome association.[27]

Post-hoc analysis

Additional post-hoc analyses were conducted to further contextualise the study findings. Glaucoma, a condition not impacted by DOAC use, was assessed as a negative control outcome to assess the possibility of residual confounding after PS matching.[28] Inverse probability of treatment weighting (IPTW) and standardised mortality ratio weighting (SMR) methods were used to evaluate potential treatment effect heterogeneity in estimates of effect for primary and secondary outcomes and the robustness of results.[29] Primary analysis findings were additionally assessed by gender.

All data analyses were conducted using Aetion Evidence Platform V.4.45 (2021), software for RWD analysis. Aetion, Inc. https://www.aetion.com.

Patient and public involvement

There was no patient or public involvement in this study, including development of the research questions, selection of outcome measures, study design, conduct or dissemination of findings.

RESULTS

Out of a total of 5655 patients with new use of at least one DOAC before PS matching (figure 1), 2801 initiated apixaban, 2221 initiated rivaroxaban, 398 initiated edoxaban and 261 initiated dabigatran and met the criteria for inclusion (table 2).

Primary comparison: apixaban versus rivaroxaban

A total of 2221 rivaroxaban and 2801 apixaban patients were eligible for inclusion in PS-matched groups. Before PS matching, the apixaban group was more likely to initiate treatment after 2017 and more likely to be woman compared with rivaroxaban patients (table 2). After 1:1 PS matching, 1839 patients with apixaban and 1839 patients with rivaroxaban were identified (figure 1). Differences in covariate prevalence were minimal, with ASD below 0.1 for all characteristics (table 2). Due to sample size constraints, stratified analyses by dosage were not completed; dosages of index prescriptions are reported in online supplemental table 1. Median follow-up time in the ITT analysis was 845 days [IQR 340, 1368] in the apixaban group and 779 days [322, 1284] in the rivaroxaban group (online supplemental table 4). In the 'as-treated' approach, median follow-up time was shorter compared with ITT and longer in apixaban compared with rivaroxaban (506 days vs 412 days). Rivaroxaban patients were more likely to be censored for switching to another DOAC compared with apixaban patients (online supplemental table 4).

In the ITT analysis, the rate of stroke per 1000 person-years was 12.47 in the apixaban group and 13.48 in the rivaroxaban group (table 3). Compared with rivaroxaban, patients initiating apixaban showed similar rates of stroke (HR: 0.93; 95% CI 0.64 to 1.34; table 3, figure 2). Rates of secondary outcomes were also similar between apixaban versus rivaroxaban initiators: all-cause mortality (HR: 1.03; 95% CI 0.87 to 1.22), MI (HR: 0.95; 95% CI 0.54 to 1.68), TIA (HR: 1.03; 95% CI 0.61 to 1.72) and AMS (HR: 0.96; 95% CI0.72 to 1.27). Apixaban initiators showed lower rates of major bleeding events (HR: 0.60; 95% CI 0.47 to 0.75; table 3, figure 2). In secondary as-treated analysis, apixaban and rivaroxaban were similarly equivalent with respect to rates of stroke (HR: 0.95; 95% CI 0.59, 1.55; table 4).

In subgroup analyses, effects on stroke varied by concomitant aspirin use, history of warfarin use, and CHA_2DS_2 VASc score, though there was limited power to detect statistically significant differences (table 3). In HdPS-matched analyses of stroke and secondary outcomes, results were generally similar or trended toward lower outcome rates among patients with apixaban relative to PS-matched results (table 4, figure 2). Findings were also similar in post-hoc IPTW and SMR weighted analyses of primary and secondary outcomes (table 4, figure 2).

In ITT analysis of glaucoma as a negative control outcome, PS-matched and HdPS-matched rates of glaucoma were higher among patients with apixaban, though confidence intervals included the null (PS-matched: HR, 95% CI 1.22, 0.76 to 1.97; HdPS-matched: 1.48, 0.84 to 2.64).

Secondary comparison: apixaban versus other DOACs

After PS matching, 2276 patients with apixaban and 2276 patients with DOACs other than apixaban (rivaroxaban, edoxaban or dabigatran) were included (figure 1). Treatment groups were balanced after PS-matching, defined as ASD below 0.1 for all characteristics (table 2). Median follow-up time was longer in the apixaban group (median (IQR) 742 days [298, 1,259]) compared with the other DOACs group (681 days [296, 1170]) (online supplemental table 4). Similar rates of stroke were observed between groups (HR: 0.90; 95% CI 0.64 to 1.27; table 3).

Secondary comparison: rivaroxaban versus other DOACs

After PS matching, 1985 patients with rivaroxaban and 1985 patients with DOACs other than rivaroxaban (apixaban, edoxaban, dabigatran) were included (figure 1). Treatment groups were balanced after PS-matching, defined as ASD below 0.1 for all characteristics (table 2). Median follow-up time was shorter in the rivaroxaban group (median (IQR) 784 days [318, 1296]) compared

Table 3 HR of stroke and secondary outcomes among patients with nonvalvular atrial fibrillation newly initiating DOACs after propensity score matching: primary analyses

	Patients	Events	Rate per 1,000 PY	Patients	Events	Rate per 1000 PY	HR
Apixaban vs rivaroxaban: primary and secondary outcomes, intent to treat							
Outcome	Apixaban			Rivaroxaban			aHR (95% CI)
Stroke	1839	56	12.47	1839	57	13.48	0.93 (0.64 to 1.34)
All-cause mortality*	1837	288	62.72	1837	259	60.81	1.03 (0.87 to 1.22)
Myocardial infarction (MI)	1839	24	5.28	1839	24	5.63	0.95 (0.54 to 1.68)
Transient ischaemic attack (TIA)	1839	30	6.64	1839	28	6.57	1.03 (0.61 to 1.72)
Major bleeding event	1839	117	26.72	1839	183	45.86	0.60 (0.47 to 0.75)
Composite angina/MI/stroke endpoint (AMS)	1839	97	21.93	1839	96	23.12	0.96 (0.72 to 1.27)
Apixaban vs rivaroxaban: primary outcome (stroke) among subgroups, intent to treat							
Subgroup	Apixaban			Rivaroxaban			aHR (95% CI)
Age <75 years	621	11	6.49	621	9	5.80	1.10 (0.46 to 2.66)
Age ≥75 years	1172	41	15.24	1172	41	16.50	0.94 (0.61 to 1.44)
Concomitant aspirin use	409	14	13.16	409	5	5.04	2.54 (0.92 to 7.07)
No concomitant aspirin use	1389	41	12.31	1389	38	12.09	1.03 (0.66 to 1.60)
Prior warfarin use	263	6	9.83	263	8	14.27	0.69 (0.24 to 1.98)
No prior warfarin use	1516	46	12.35	1516	36	10.36	1.19 (0.77 to 1.85)
With diabetes	474	17	14.76	474	15	13.82	1.08 (0.54 to 2.16)
Without diabetes	1310	37	11.68	1310	33	11.12	1.05 (0.66 to 1.68)
With heart failure	189	7	17.81	189	7	17.50	1.04 (0.37 to 2.97)
Without heart failure	1611	52	13.02	1611	43	11.67	1.13 (0.76 to 1.70)
CHA2DS2 VASc 0–1	379	9	9.06	379	5	5.35	1.65 (0.55 to 4.92)
CHA2DS2 VASc 2–3	1312	40	12.67	1312	45	15.45	0.82 (0.54 to 1.26)
CHA2DS2 VASc 4+	69	1	6.28	69	1	6.58	0.91 (0.06 to 14.58)
Male	1158	33	11.56	1158	30	11.18	1.03 (0.63 to 1.69)
Female	650	19	12.23	650	21	14.49	0.86 (0.46 to 1.60)
Analysis of secondary comparisons: primary outcome (stroke), intent to treat							
Outcome	Apixaban			DOACs other than apixaban			aHR (95% CI)
Stroke	2276	65	12.57	2276	68	14.16	0.90 (0.64 to 1.27)
Outcome	Rivaroxaban			DOACs other than rivaroxaban			aHR (95% CI)
Stroke	1985	59	12.85	1985	65	13.36	0.96 (0.67 to 1.36)

PS model accounts for age, gender, CHA2DS2 VASc score, year of treatment initiation and the following diagnoses and treatments in baseline: non-major bleeding events, anaemia, diabetes, hypertension, heart failure, osteoporosis/hip fracture, malignant neoplasm, acute kidney injury, chronic kidney disease, asthma/COPD, dementia, aspirin, antiplatelets other than aspirin, warfarin, antimeric preparations, NSAIDs, opioids, SSRIs, antidepressants other than SSRIs, antiepileptics, antipsychotics, benzodiazepines, lipid lowering drugs, insulin, antihyperglycemics other than insulins, antihypertensives, antiarrhythmics, nitrates cardiac vasodilators, cardiac stimulants, gastrointestinal protective agents, bisphosphonates and other agents affecting bone structure, systemic corticosteroids, antineoplastics, systemic antibiotics, systemic antivirals, vaccines/immunoglobulins.
DOACs comprised apixaban, rivaroxaban, edoxaban, dabigatran.
In analysis of stroke, MI, TIA, major bleeding events, and AMS, patients were followed until occurrence of outcome, death, end of patient registration or end of study period (December 2020).
*In analysis of all-cause mortality, patients were followed until occurrence of outcome (death), end of study period (December/2020) or the later date of end of patient registration and any recorded death within 90 days of end of patient registration. Propensity score matched sample size for analysis of all-cause mortality differs from sample size in analysis of other outcomes because of differences in censoring criteria, which impact a small number of patients' eligibility for inclusion in analysis at the start of follow-up.
aHR, adjusted HR; PS, propensity score; PY, person years.

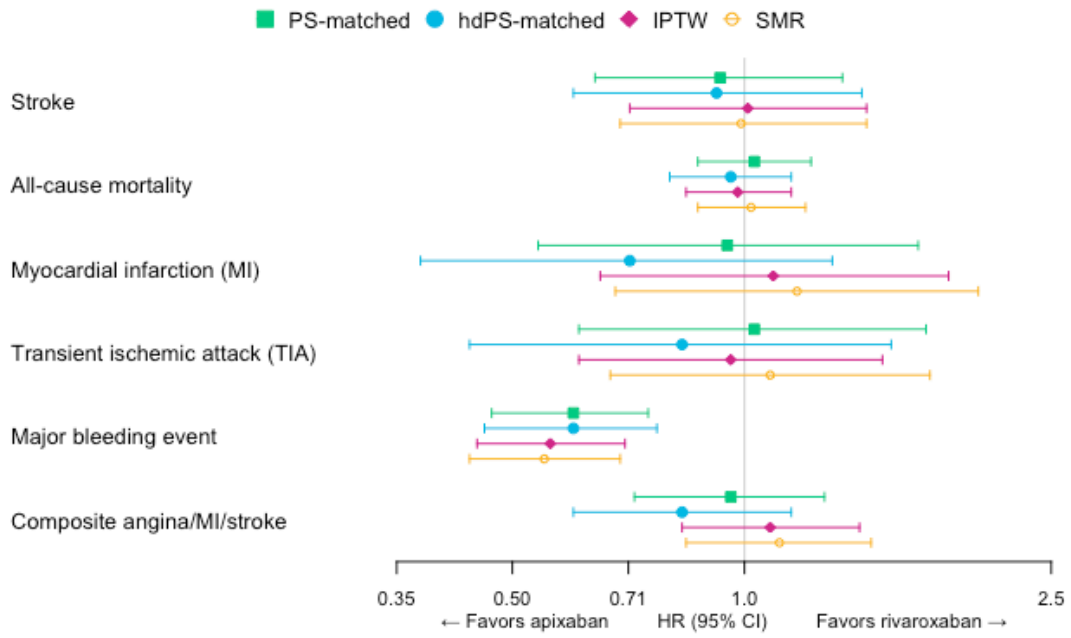

Figure 2 Hazard ratios of stroke and secondary outcomes, apixaban versus rivaroxaban, intent to treat analyses. PS model accounts for age, gender, CHA2DS2 VASc score, year of treatment initiation and the following diagnoses and treatments in baseline: non-major bleeding events, anaemia, diabetes, hypertension, heart failure, osteoporosis/hip fracture, malignant neoplasm, acute kidney injury, chronic kidney disease, asthma/chronic obstructive pulmonary disease, dementia, aspirin, antiplatelets other than aspirin, warfarin, antianemic preparations, non-steroidal anti-inflammatory drugs (NSAIDs), opioids, selective serotonic reuptake inhibitors (SSRIs), antidepressants other than SSRIs, antiepileptics, antipsychotics, benzodiazepines, lipid lowering drugs, insulin, antihyperglycemics other than insulins, antihypertensives, antiarrhythmics, nitrates cardiac vasodilators, cardiac stimulants, gastrointestinal protective agents, bisphosphonates and other agents affecting bone structure, systemic corticosteroids, antineoplastics, systemic antibiotics, systemic antivirals, vaccines/immunoglobulins Patients were followed until occurrence of outcome, death, end of patient registration, or end of study period (December 2020). HdPS, high dimensional propensity score; IPTW, inverse probability of treatment weighting; PS, propensity score; SMR, standardised mortality ratio weighting.

with the DOACs other than rivaroxaban (828 days [343, 1399]) (online supplemental table 4). There was no difference in rate of stroke between groups (HR: 0.96; 95% CI 0.67 to 1.36; table 3).

DISCUSSION

Among patients with nonvalvular AFib, apixaban was as effective as rivaroxaban in reducing the rate of stroke, all-cause mortality, MI, TIA and AMS, and was safer in terms of major bleeding episodes. Because there was heterogeneity across prior study results, our results align with some but not all prior research. The Scottish, Danish, and French studies also found similar effectiveness between apixaban and rivaroxaban,[13–15] while the US study found apixaban to be more effective.[16] Our effectiveness findings are also consistent with the indirect comparison of apixaban and rivaroxaban in the NMA used in NICE's 2021 clinical guidelines.[5] Prior research has consistently found apixaban to be safer in terms of major bleeding.[5 13 14 16] Some prior research found similar equivalencies with respect to all-cause mortality,[5 14] while others have found increased risk of all-cause mortality for rivaroxaban compared with apixaban.[13 16] In the secondary comparisons, the rate of stroke was similar between apixaban and other DOACs and rivaroxaban and other DOACs. These secondary comparisons offer an increase in referent group sample size with the inclusion of patients with edoxaban and dabigatran, noting that referent groups primarily comprised patients with rivaroxaban or apixaban. Apixaban and rivaroxaban were initiated more often than dabigatran and edoxaban, which is consistent with prescribing patterns in the UK[30] and aligns with the selection of the primary and secondary comparisons in the study. Because dabigatran and edoxaban were seldom used and sample sizes were small, head-to-head comparisons including these DOACs were not performed.

While RCTs demonstrate that DOACs are non-inferior to warfarin for stroke prevention in patients with nonvalvular AFib,[31–34] there is a lack of RCT head-to-head comparisons of individual DOACs. This uncertainty can make reimbursement, clinical decision-making and clinical guideline development challenging. NICE recently updated its AFib clinical guidelines,[5] relying on a NMA and indirect comparisons of individual DOACs for evidence on their comparative effectiveness and safety. This study addresses a known evidence gap and adds to the clinical evidence base from RCTs and NMAs to directly compare DOACs for stroke prevention in patients with

Table 4 HR of stroke and secondary outcomes among patients with nonvalvular atrial fibrillation newly initiating apixaban versus rivaroxaban after propensity score matching: sensitivity analyses

	HR (95% CI)				
Outcome	**Unadjusted**	**PS-matched**	**HdPS-matched**	**IPTW**	**SMR**
Stroke, all patients, by type of follow-up					
Stroke, intent-to-treat (ITT)	1.06 (0.76 to 1.49)	0.93 (0.64 to 1.34)	0.92 (0.60 to 1.42)	1.01 (0.71 to 1.44)	0.99 (0.69 to 1.44)
Stroke, as-treated (AT)	1.10 (0.71 to 1.71)	0.95 (0.59 to 1.55)	0.78 (0.44 to 1.38)	1.01 (0.64 to 1.62)	0.98 (0.60 to 1.60)
Secondary outcomes, all patients (ITT)					
All-cause mortality	1.07 (0.93 to 1.24)	1.03 (0.87 to 1.22)	0.96 (0.80 to 1.15)	0.98 (0.84 to 1.15)	1.02 (0.87 to 1.20)
Myocardial infarction (MI)	1.08 (0.65 to 1.79)	0.95 (0.54 to 1.68)	0.71 (0.38 to 1.30)	1.09 (0.65 to 1.84)	1.17 (0.68 to 2.01)
Transient ischaemic attack (TIA)	0.92 (0.59 to 1.42)	1.03 (0.61 to 1.72)	0.83 (0.44 to 1.55)	0.96 (0.61 to 1.51)	1.08 (0.67 to 1.74)
Major bleeding event	0.57 (0.47 to 0.70)	0.60 (0.47 to 0.75)	0.60 (0.46 to 0.77)	0.56 (0.45 to 0.70)	0.55 (0.44 to 0.69)
Composite angina/MI/stroke endpoint (AMS)	1.12 (0.87 to 1.43)	0.96 (0.72 to 1.27)	0.83 (0.60 to 1.15)	1.08 (0.83 to 1.41)	1.11 (0.84 to 1.46)

PS model accounts for age, gender, CHA2DS2 VASc score, year of treatment initiation and the following diagnoses and treatments in baseline: non-major bleeding events, anaemia, diabetes, hypertension, heart failure, osteoporosis/hip fracture, malignant neoplasm, acute kidney injury, chronic kidney disease, asthma/COPD, dementia, aspirin, antiplatelets other than aspirin, warfarin, antiameric preparations, NSAIDs, opioids, SSRIs, antidepressants other than SSRIs, antiepileptics, antipsychotics, benzodiazepines, lipid lowering drugs, insulin, antihyperglycemics other than insulins, antihypertensives, antiarrhythmics, nitrates cardiac vasodilators, cardiac stimulants, gastrointestina protective agents, bisphosphonates and other agents affecting bone structure, systemic corticosteroids, antieoplastics, systemic antibiotics, systemic antivirals, vaccines/immunoglobulins.
In assessment of stroke, MI, TIA, major bleeding events and AMS, patients were followed until occurrence of outcome, death, end of patient registration or end of study period (December 2020).
In assessment of all-cause mortality, patients were followed until occurrence of outcome (death), end of study period (December 2020) or the later date of end of patient registration and any recorded death within 90 days of end of patient registration.
HdPS, high dimensional propensity score; IPTW, inverse probability of treatment weighting; PS, propensity score; SMR, standardised mortality ratio weighting.

nonvalvular AFib in the UK. This additional evidence can help agencies like NICE contextualise the comparative effects of rivaroxaban and apixaban and inform its clinical decision-making.

This study has several strengths. The THIN data contain general practice records for over 20 million patient records in the UK and are likely reflective of typical patterns of treatment and care in the UK. Prescribing data are comprehensive and complete and are captured prospectively before outcome events. Nevertheless, this study is subject to several limitations. We did not link to secondary care data for stroke outcome ascertainment. However, stroke is included as part of the Quality and Outcomes Framework,[35] where general practices are incentivised to comprehensively document instances of stroke occurring in other care settings within patients' medical record. THIN data have been used and validated in published literature to evaluate AFib and stroke.[19 36–39] We were not sufficiently powered for any of the comparisons according to the protocol power guidelines. However, an underpowered study still provides valuable information on clinical outcomes. Indeed, Hernan argues that observational causal inference studies, which place little burden on patients, should proceed even if underpowered so that the evidence can be combined with that from other studies through meta-analysis.[26] For the evaluation of economic outcomes, that is, through a cost-effectiveness analysis, uncertainty in input parameter values is propagated through the use of probabilistic sensitivity analysis and thus properly reflected in the outputs. Our analysis of glaucoma as a negative control outcome indicates the possibility of residual confounding, with ITT estimates showing a higher rate of glaucoma for apixaban relative to rivaroxaban. Despite possible residual confounding resulting in bias away from the null, we still observed null findings across primary and sensitivity analyses in our primary outcome, stroke. As with the primary analysis, sample size was also a limitation of these sensitivity analyses.

THIN data contain records of prescriptions written, but it is not known whether medications were dispensed or taken. However, most patients initiating apixaban (80.9%) and rivaroxaban (76.8%) had a second prescription within 30 days of the end of their index prescription and the proportion of days covered in the follow-up period was high in both groups (mean 88.1% apixaban and mean 83.4% rivaroxaban), providing evidence that medications were being taken and refilled. Due to data availability constraints, in our analyses, we estimated patient CHA_2DS_2 VASc scores using patient history, which may deviate from a GP assessment-based score. However, 99.7% of female patients and 99.8% of male patients had patient history-estimated CHA_2DS_2 VASc scores, which aligned with the GP assessment-based score cutoffs imposed by the data vendor (≥2 and ≥1, respectively).

This study showed that among patients with nonvalvular AFib, apixaban was as effective as rivaroxaban in reducing rate of stroke and safer in terms of bleeding adverse events. This study demonstrates that comparative effectiveness RWE studies have the potential to fill evidence gaps and reduce uncertainty in HTA decision-making and clinical guideline development.

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Contributors AJ, SK, SR, SD, PJ and NG contributed to the conception and design of the study. AJ was responsible for the acquisition of the data. LG, AA, AP and PG carried out data analysis. AJ, LG, AA, AP and NG interpreted the results. AJ and LG drafted the manuscript. SK, SR, SD, MS, LK, AA, AP, PG, PJ and NG offered critical revisions and gave final sign off on the manuscript. AJ acted as the guarantor.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

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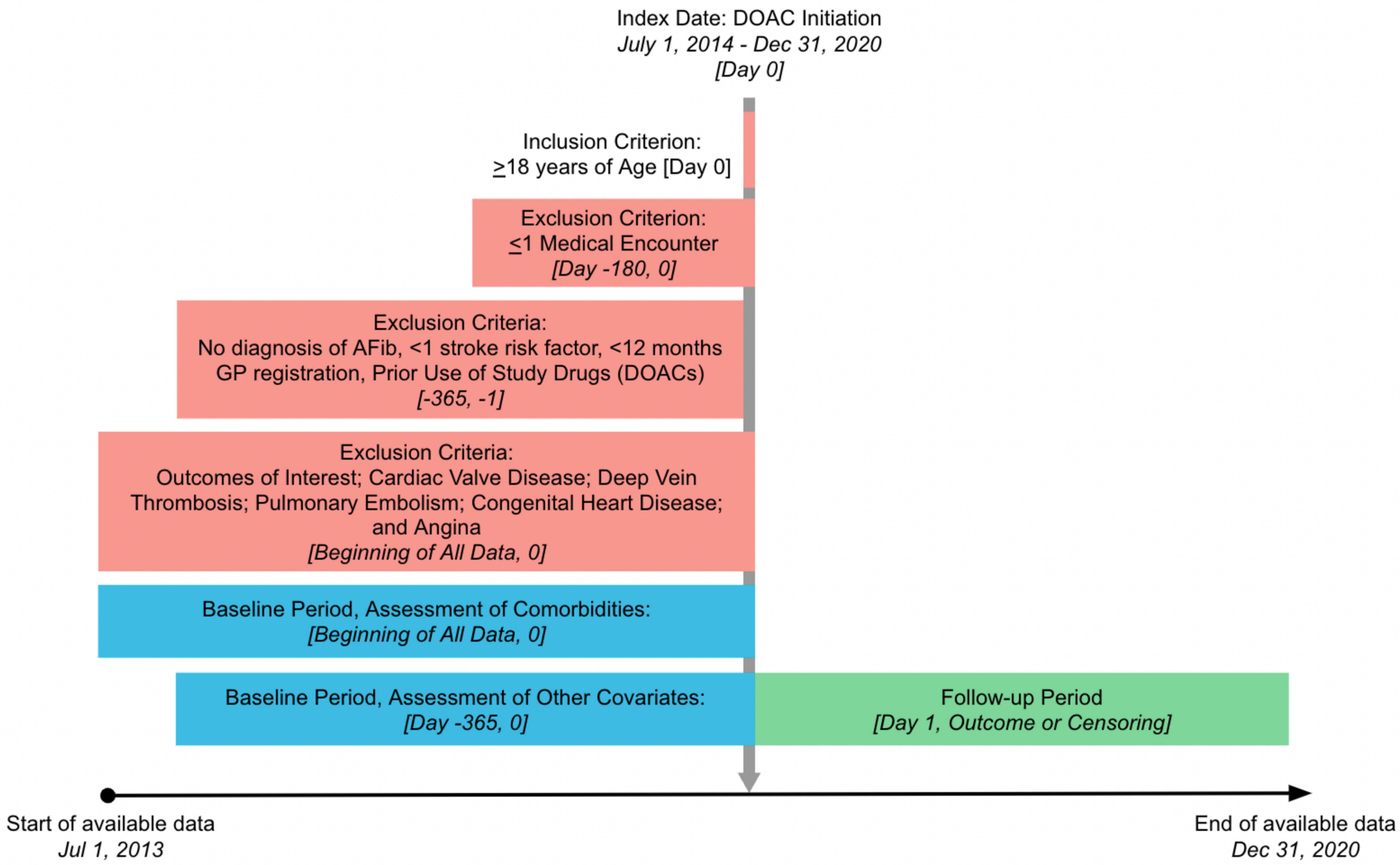
Index Date: DOAC Initiation
July 1, 2014 - Dec 31, 2020
[Day 0]
Inclusion Criterion:
≥18 years of Age [Day 0]
Exclusion Criterion:
≤1 Medical Encounter
[Day -180, 0]
Exclusion Criteria:
No diagnosis of AFib, <1 stroke risk factor, <12 months GP registration, Prior Use of Study Drugs (DOACs)
[-365, -1]
Exclusion Criteria:
Outcomes of Interest; Cardiac Valve Disease; Deep Vein Thrombosis; Pulmonary Embolism; Congenital Heart Disease; and Angina
[Beginning of All Data, 0]
Baseline Period, Assessment of Comorbidities:
[Beginning of All Data, 0]
Baseline Period, Assessment of Other Covariates:
[Day -365, 0]
Follow-up Period
[Day 1, Outcome or Censoring]
Start of available data
Jul 1, 2013
End of available data
Dec 31, 2020

Non-Interventional Study Protocol

Study Protocol Title	Comparative Effectiveness and Safety of Direct Oral Anticoagulants in Patients with Nonvalvular Atrial Fibrillation in the UK
Version Identifier	Number 1.0
Date of Last Version	22 December 2021
Study Type	Non-Interventional Retrospective Comparative Effectiveness Study
Research Question and Objectives	This study aims to evaluate the incidence of stroke and other outcomes in association with direct oral anticoagulants (DOACs) as compared to each other (i.e., direct comparisons) among patients with nonvalvular atrial fibrillation (AFib) in the UK. Individual DOACs of interest include apixaban, rivaroxaban, edoxaban, and dabigatran. The primary objective is to ● Estimate the incidence rates and evaluate the association of stroke (ischemic or hemorrhagic) for patients with nonvalvular AFib who initiated apixaban compared to rivaroxaban The secondary objectives are to ● Compare the incidence rates of stroke (ischemic or hemorrhagic) for patients with nonvalvular AFib who initiated: ○ apixaban compared to edoxaban, dabigatran, and DOACs class ○ rivaroxaban compared to edoxaban, dabigatran, and DOACs class ○ edoxaban compared to DOACs class ○ dabigatran compared to DOACs class ● Estimate the incidence rates and evaluate the association of all-cause mortality, myocardial infarction, transient ischemic attack, major bleeding events, and major adverse cardiovascular events (MACE) for patients with nonvalvular AFib who initiated individual DOACs compared to those who initiated other DOACs.
Country of Study	United Kingdom
Study Review Board	Nicolle Gatto, PhD, MPH Chief Science Officer Aetion, Inc. Pall Jonnson, PhD Programme Director - Data NICE
Study Implementation Team	Ayad Ali, PhD, SRPharmS Senior Principal Scientist Aetion, Inc. Amanda Patrick, MS Senior Principal Product Scientist Aetion, Inc. Ashley Jaksa, MPH Scientific Partnerships Lead Aetion, Inc. Seamus Kent, PhD Senior Advisor in Data and Analytics NICE Shaun Rowark, MSc Scientific Advisor in Data and Analytics NICE Stephen Duffield, PhD, MBChB Senior Analyst NICE

	Liza Gibbs, BS Scientist Aetion, Inc.

1. Table of Contents

2. List of Abbreviations

Abbreviation	Description
AEP	Aetion Evidence Platform
AFib	Atrial fibrillation
ATC	Anatomical Therapeutic Chemical
CHA_2DS_2 VASc	Congestive heart failure, Hypertension, Age ≥75, Diabetes, prior Stroke/transient ischemic attack, vascular disease
CI	Confidence interval
CPRD	Clinical Practice Research Datalink
DOACs	Direct oral anticoagulants
EU	European Union
GCP	Good clinical practices
GP	General practitioner
GPP	Good pharmacoepidemiology practices
HdPS	High dimensional propensity score
HR	Hazard ratio
HTA	Health technology assessment
ICD-10	International Statistical Classification of Diseases 10th edition
ICH	International conference on harmonization

ICSR	Individual case safety report
ITT	Intent to treat
MACE	Major adverse cardiovascular events
MI	Myocardial infarction
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NSAID	Non-steroidal anti-inflammatory drugs
ORBIT-AF	Outcomes Registry for Better Informed Treatment of Atrial Fibrillation
QOF	Quality outcomes framework
RCA	Research collaboration agreement
RWD	Real-world data
RWE	Real-world evidence
STaRT-RWE	Structured template and reporting tool for real world evidence
THIN®	The Health Improvement Network
TIA	Transient ischemic attack
UK	United Kingdom
VKA	Vitamin K antagonists

3. Amendments and Updates

Amendment or Update No.	Date	Section of Study Protocol	Amendment or Update	Reason

4. Milestones

Milestone	Planned Date
Start of Data Extraction	September 2021
End of Data Extraction	November 2021
Diagnostics for primary comparison	December 2021
Registration in the EU PAS Register	January 2022
Interim Report *	January 2022
Final Report of Study Results	February 2022

* The interim report will comprise descriptive and primary objective results for primary comparison.

5. Rationale and Background

Health Technology Assessment (HTA) agencies, like the National Institute for Health and Care Excellence (NICE), are turning toward coverage with evidence development and/or managed access programs to allow additional time for data on the effectiveness of products to mature or be collected. Real-world data (RWD) has emerged as a potential strategy to collect additional evidence on the effectiveness of products after launch. HTA bodies are in the process of adopting real-world evidence (RWE), evidence generated from RWD, into their decision-making processes and setting standards for its use.

As NICE develops best practices on real-world evidence (RWE) use, it is exploring RWD comparative effectiveness studies as a way to enhance its decision-making and address uncertainties in its assessments and guidelines.[1] As part of NICE's five-year strategic vision,[1] NICE is initiating RWE research projects to fill known evidence gaps, to inform when and how RWE can be used in its decision-making, and to determine when after drug launch sample size is sufficient for comparative effectiveness analysis and if the results are consistent over time. NICE is interested in a proof-of-concept RWE comparative effectiveness study to inform these best practices.

5.1. Aetion's Research Collaboration with NICE

Aetion entered a research collaboration agreement (RCA) with NICE in 2021 to evaluate how RWE studies can be used to fill evidence gaps and reduce uncertainties in NICE assessment and guideline development. Aetion is collaborating with NICE to identify research questions relevant to NICE's RWE standards workstreams. Using the comparative effectiveness study described below, Aetion and NICE are collaborating on identifying fit-for-purpose real-world data, developing the protocol, executing the study using the Aetion Evidence Platform® (2021), software for real-world data analysis (Aetion, Inc. https://www.aetion.com.), and piloting the Structured Template and Reporting Tool for Real World Evidence (STaRT-RWE)[2] for transparent reporting of study implementation.

5.2. Selection of Atrial Fibrillation as Proof of Concept Study

The safety and efficacy of direct oral anticoagulants (DOACs) compared to vitamin K antagonists (VKAs) in patients with atrial fibrillation (AFib) have been established in randomized clinical trials.[3] In Europe, the following DOACs are approved to prevent venous thromboembolism, deep vein thrombosis, pulmonary embolism, and stroke in adults with AFib: Apixaban (Eliquis®, first authorised in the EU and the UK May 2011); dabigatran (Pradaxa®, March 2008); rivaroxaban (Xarelto®, September 2008); and edoxaban (Lixiana®, June 2015).[4,5]

Between March 2012 and September 2015, NICE separately assessed and recommended four DOACs: dabigatran, rivaroxaban, apixaban, and edoxaban. Each submitted clinical trial compared the investigational DOACs to warfarin; however, there were no head-to-head clinical trials comparing the DOACs to each other at the time of NICE's assessments. Therefore, a network meta-analysis was completed for indirect comparison of individual DOACs agents using warfarin as the common comparator. NICE interpreted the network meta-analysis findings with caution noting the results were not sufficiently robust to differentiate between the products' effectiveness. These uncertainties were reiterated in NICE's 2014 AFib management guidelines in 2014 and 2021 updates.[6,7]

The lack of relevant direct comparisons driving uncertainty is common at the time of NICE assessment, and these uncertainties are not unique to AFib. The uncertainties in comparative effectiveness of AFib treatments impact downstream decisions by healthcare providers and patients as they try to identify the most effective, safe, and cost-effective treatment option for stroke prevention.

NICE has selected AFib for the proof-of-concept comparative effectiveness real-world effectiveness (RWE) study in part because there is a growing body of literature that has successfully validated the use of real-world data (RWD) in AFib,[8,9] and the burden of disease and cost to the healthcare system associated with AFib in the UK.[7] In addition, the DOACs for nonvalvular AFib included in this study were approved more than 5 years ago in the UK (edoxaban was approved in June 2015[10]), which allows us to explore how the value of RWE comparative effectiveness changes with length of follow-up. This can help inform optimal timing for reassessments.

This study will not only inform when and how NICE could use RWE to address uncertainties in the clinical evidence, but it could also inform NICE's AFib clinical guidelines.

5.3. DOACs Therapies for Atrial Fibrillation

Atrial fibrillation (AFib) is the most common type of cardiac conduction disorder accounting for up to 2.6% of healthcare costs in Europe, and about 9.5% of the European population is estimated to have AFib by 2060.[11] In the UK, AFib affects 1.4 million patients,[12] and between 0.9% to 1.6% of UK's National Health Service (NHS) spendings are attributable to AFib predominately from hospitalizations.[13] The condition is associated with significant complications, including stroke. Nonvalvular AFib increases an individual's risk of stroke by about five times,[14] and between 20% and 30% of stroke cases are attributed to AFib.[11]

Anticoagulants, including VKAs and DOACs, are highly effective in the prevention and treatment of thromboembolic events associated with AFib. Nevertheless, VKAs like warfarin are narrow therapeutic index drugs requiring frequent coagulation monitoring, and have multiple drug and food interactions. Alternatively, DOACs inhibit coagulation via direct and specific binding to active sites of thrombin (e.g., dabigatran) or factor Xa (e.g., apixaban, rivaroxaban, and edoxaban) of the coagulation pathway. Compared to VKAs, DOACs have a wider therapeutic index, which permits use in fixed doses without coagulation monitoring, and relatively limited drug and food interactions. Data from direct comparisons of DOACs (e.g., apixaban vs. dabigatran) are not available, and relative safety and efficacy findings are based on indirect comparisons from network meta-analyses.[15,16] Healthcare providers face challenges from uncertainties around DOACs treatment decisions for patients with AFib, particularly around which individual agent has the best benefit-risk profile within the class for mortality and cardiovascular risk reduction.

The current protocol details a study designed to evaluate the effectiveness and safety of the DOACs of interest (apixaban, rivaroxaban, edoxaban, and dabigatran) in direct comparisons, among adults with nonvalvular AFib at risk for stroke in the UK.

6. Research Objectives

This study evaluates the comparative effectiveness of apixaban versus rivaroxaban (primary objective) for reducing stroke among patients with nonvalvular AFib in the UK.

Secondary objectives included comparing the effectiveness of apixaban and rivaroxaban to the other DOACs (edoxaban, and dabigatran).

6.1. Hypothetical Target Trial

When planning and designing RWE studies, it is important to consider emulating a hypothetical target trial.[17] We sought to emulate a four-arm randomized trial that randomizes patients to apixaban, rivaroxaban, edoxaban, or dabigatran. The objective of the hypothetical trial is to compare apixaban to rivaroxaban, as the primary comparison, in the reduction of stroke among patients with nonvalvular AFib in the UK (Figure 6.1). The hypothetical target trial diagram is based on four clinical trials that evaluated the efficacy of respective DOACs in comparison with warfarin in patients with AFib (ARISTOTLE trial studied apixaban;[18] ROCKET AF studied rivaroxaban;[19] ENGAGE AF-TIMI 48 trial studied edoxaban;[20] and RE-LY trial studied dabigatran).[21] In addition, comparisons of individual DOACs to other DOACs as a pharmacological class will be included as secondary comparisons. The hypothetical target trial would be powered for the primary comparison of apixaban versus rivaroxaban, and the study designed to meet diagnostic criteria for the main analysis.

Within the UK, apixaban and rivaroxaban are the most frequently prescribed DOACs (Figure 6.2). Secondary comparisons will include comparing apixaban and rivaroxaban to the two other DOACs (edoxaban and dabigatran) (Table 6.1).

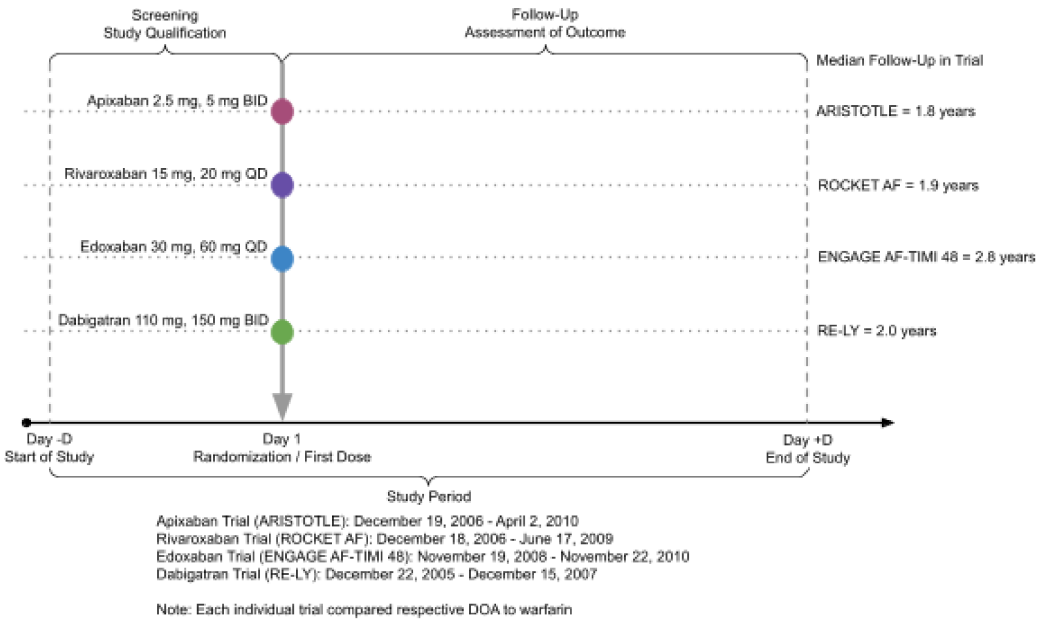

Figure 6.1 Hypothetical Target Trial Design

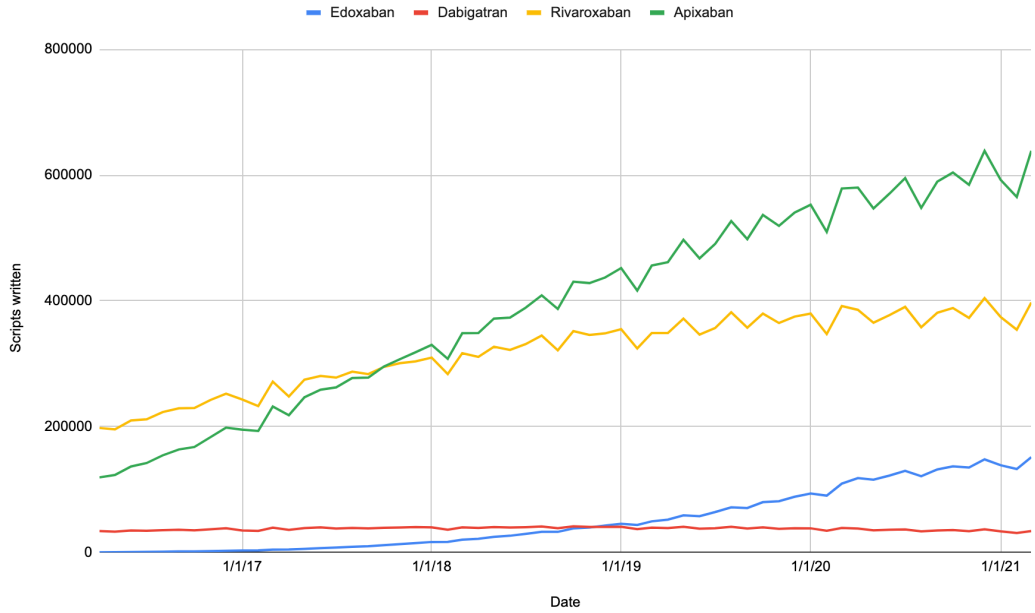

Figure 6.2 Utilization of DOACs in the UK (April 2016 - January 2021; Source: OpenPrescribing)

Table 6.1 Direct Comparisons of Study Exposures of Interest

	Rivaroxaban	Edoxaban	Dabigatran	DOACs Class
Apixaban	Primary	Secondary	Secondary	Secondary (rivaroxaban, edoxaban, dabigatran)
Rivaroxaban	-	Secondary	Secondary	Secondary (apixaban, edoxaban, dabigatran)
DOACs Class	-	Secondary (apixaban, rivaroxaban, dabigatran)	Secondary (apixaban, rivaroxaban, edoxaban)	-

6.2. Primary Objective

The primary objective is to estimate the incidence rates and analogous hazard ratio of stroke (ischemic or hemorrhagic) for patients with nonvalvular AFib who initiated apixaban compared to rivaroxaban (see Table 6.1).

6.3. Secondary Objectives

The secondary objectives are to:

- Estimate the incidence rates and analogous hazard ratios of stroke (ischemic or hemorrhagic) for patients with nonvalvular AFib who initiated:
    - apixaban compared to edoxaban, dabigatran, and DOACs class
    - rivaroxaban compared to edoxaban, dabigatran, and DOACs class
    - edoxaban compared to DOACs class
    - dabigatran compared to DOACs class

- Estimate the incidence rates and evaluate the analogous hazard ratio of all-cause mortality, myocardial infarction (MI), transient ischemic attack (TIA), major bleeding events, and major adverse cardiovascular events (MACE) for patients with nonvalvular AFib who initiated individual DOACs compared to those who initiated other DOACs (see Table 6.1).

7. Data Source

This study uses anonymized patient RWD from The Health Improvement Network (THIN®) Database (A Cegedim Proprietary Database). THIN® is an unobtrusive medical data collection scheme that collects anonymised patient data from its members. THIN® data is a primary care research database containing anonymised electronic health record data from around 850 UK general practices (GPs) using the VISION clinical system (since 1994), containing records around 20 million patients, of which 2.6 million are currently active. THIN® collates the computerized medical records of general practitioners (GPs) in the UK who act as the gatekeepers of healthcare and maintain patients' life-long electronic health records. As such they are responsible for primary healthcare and specialist referrals, and they also store information stemming from specialist referrals, and hospitalizations. GPs act as the first point of contact for any non-emergency health-related issues, which may then be managed within primary care and/or referred to secondary care as necessary. The THIN® database includes demographic, medical diagnosis, patient medical history, lifestyle factors, and written prescription information on individual patients. The Quality and Outcome Framework (QOF) rewards practices for the quality care they provide their patients, based on a number of indicators, including medical record data entry.

The THIN® database has been used for scientific publications in AF and stroke research[22-25] and has been validated and widely used in pharmacoepidemiologic studies.[22]

8. Research Methods

8.1. Study Design

This study is a non-interventional, retrospective cohort study utilising RWD from the UK to address the study objectives. Patients with nonvalvular AFib who initiated (i.e., new users of) DOACs during the observation period will comprise the study cohort. The exposure groups of interest will be patients initiating individual DOACs (apixaban, rivaroxaban, edoxaban, and dabigatran). All patients will be followed for the first occurrence of each of the study outcomes of interest.

8.2. Setting

This study will be conducted using an electronic anonymized patient RWD from The Health Improvement Network (THIN®) Database (A Cegedim Proprietary Database) that includes data collected in primary care settings in the UK.

8.2.1. Study Population

This study will be conducted using patient clinical data extracted from the THIN® database in the UK for adults with nonvalvular AFib at risk for stroke who initiated DOACs between July 1, 2014 and December 31, 2020. This period was selected to minimize potential effects on recommended treatment options due to changes in AFib management guidelines. The NICE AFib management guidelines, which recommend prescribing a DOACs (apixaban, rivaroxaban, edoxaban, or dabigatran) for stroke prevention were published in June 2014[6] and were not updated until April 2021[7], thus we believe treatment options to be stable during this period. Patients with AFib are identified by Read Medical Codes and ICD-10 diagnosis codes.

Patient selection criteria are described in the following sections and Figure 8.1.

8.2.1.1. Inclusion Criteria

The following are the inclusion criteria for the study cohort:

- ≥1 prescription for DOACs of interest (index date)

8.2.1.2. Exclusion Criteria

The following are the exclusion criteria for the study cohort:

- Exclusion criteria applied during selection of the data cut:
    - <1 diagnosis code for AFib on index date or in 12 months prior (applied during selection of the data cut)
    - <1 risk factor for stroke other than Afib on index date or in 12 months prior defined by CHA_2DS_2 VASc >1 for men and >2 for women[26]
    - <1 medical encounter in the 180 days prior to index date
    - ≥1 diagnosis code for the following conditions on index date or any time prior:
        - Cardiac valve disease (mitral stenosis, valvular replacement)
        - Deep vein thrombosis
        - Pulmonary embolism
- Exclusion criteria applied after selection of the data cut:
    - <18 years of age on index date
    - <12 months' registration with a GP prior to the index date
    - ≥1 prescription record for DOACs in the 12 months prior to the index date (i.e., prevalent users)
    - ≥1 diagnosis code for the study outcomes of interest (stroke, MI, TIA, major bleeding events) on index date or any time prior
    - ≥1 diagnosis code for the following conditions on index date or any time prior:
        - Angina
        - Congenital heart disease
    - Missing age
    - Missing gender

8.2.2. Study Periods

The study observation period spans July 1, 2013 through December 31, 2020, consisting of a drug indexing, baseline and follow-up periods (Figure 8.1). The drug indexing period will be used to ascertain DOACs initiation (index date). Baseline period is defined as 12 months prior to and including the index date. The follow-up period will include all available time after study index date. Patients will be followed in an “intention to treat” (ITT) approach from their index date until the end of follow-up period or the occurrence of the following events, whichever occurs first:

- First occurrence of the study outcomes of interest
- Death
- End of patient data
- End of patient registration with GP.

In addition, patients meeting the selection criteria will be followed in an “as-treated” approach from their index date until the end of the study follow-up period or the occurrence of the following events, whichever occurs first:

- First occurrence of the study outcomes of interest.
- Death
- End of patient data.
- End of patient registration with GP.
- Termination of exposure, crossover of exposure group, or addition of another DOAC.

Termination of exposure in the as-treated analysis is defined as having a gap exceeding 30 days (grace period) between the end of a prescription, based on its start date and duration, and the start of the next prescription, or if no additional prescription occurs. The termination date is defined as the prescription end date plus a 30-day risk window.

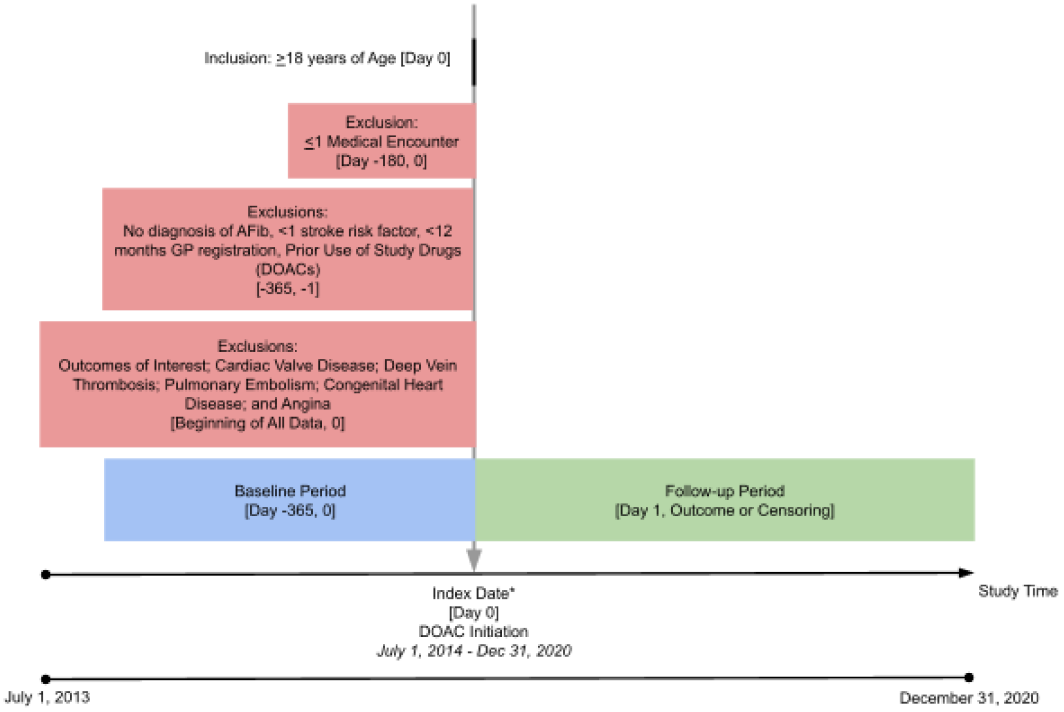

Figure 8.1 Study Design Diagram

8.3. Variables

The following sections describe the study exposures, outcomes, and covariates (including patient demographics, clinical characteristics, comorbidities, and concomitant medications).

8.3.1. Exposures

DOACs of interest will include apixaban, rivaroxaban, edoxaban, and dabigatran. Exposures will be defined by corresponding ATC codes: B01AF02; B01AF01; B01AF03; and B01AE07, respectively. Initiators of DOACs are defined as new users of DOACs with no record of prescription for any DOAC during 12 months before index date.

Only a single index date is allowed per patient; if a patient qualifies as a new user of an exposure group multiple times, the patient will enter the cohort on the first qualifying exposure date. Patients with exposure to more than one DOAC on the index date will be excluded. Duration of treatment is calculated from the provided days supplied/duration data field. Fields with 0 are assumed to be 1 day. A grace period of 30 days between refills and risk window of 30 days after the last refill is used to define persistence.The operationalized definition of exposure will be recorded in the STaRT RWE template and is available on request.

8.3.1.1. Primary Exposure Groups

- *Exposure Group 1:* Initiators of apixaban
- *Exposure Group 2:* Initiators of rivaroxaban

8.3.1.2. Secondary Exposure Groups

The following independent Exposure Groups will be created:

- *Exposure Group 3:* Initiators of edoxaban
- *Exposure Group 4:* Initiators of dabigatran
- *Exposure Group 5:* Initiators of rivaroxaban, edoxaban, and dabigatran
- *Exposure Group 6:* Initiators of apixaban, edoxaban, and dabigatran
- *Exposure Group 7:* Initiators of apixaban, rivaroxaban, and dabigatran
- *Exposure Group 8:* Initiators of apixaban, rivaroxaban, and edoxaban

8.3.1.3. Primary Comparison

- *Primary Comparison:* initiators of apixaban vs initiators of rivaroxaban (i.e., *Exposure Group 1* vs *Exposure Group 2*)

8.3.1.4. Secondary Comparisons

- *Secondary Comparison 1:* initiators of apixaban vs initiators of edoxaban (i.e., *Exposure Group 1* vs *Exposure Group 3*)
- *Secondary Comparison 2:* initiators of apixaban vs initiators of dabigatran (i.e., *Exposure Group 1* vs *Exposure Group 4*)
- *Secondary Comparison 3:* initiators of apixaban vs initiators of other DOACs class (i.e., *Exposure Group 1* vs *Exposure Group 5*)
- *Secondary Comparison 4:* initiators of rivaroxaban vs initiators of edoxaban (i.e., *Exposure Group 2* vs *Exposure Group 3*)
- *Secondary Comparison 5:* initiators of rivaroxaban vs initiators of dabigatran (i.e., *Exposure Group 2* vs *Exposure Group 4*)
- *Secondary Comparison 6:* initiators of rivaroxaban vs initiators of other DOACs class (i.e., *Exposure Group 2* vs *Exposure Group 6*)
-
- *Secondary Comparison 7:* Initiators of edoxaban vs initiators of other DOACs class (i.e., *Exposure Group 3* vs *Exposure Group 7*)
- *Secondary Comparison 8:* initiators of dabigatran vs initiators of other DOACs class (i.e., *Exposure Group 4* vs *Exposure Group 8*)

8.3.2. Outcomes

The primary outcome is ischemic or hemorrhagic stroke. Secondary outcomes include the occurrence of all-cause mortality, myocardial infarction, transient ischemic attacks, major bleeding events, and major adverse cardiovascular events (MACE). Major bleeding is defined as a composite outcome of major intracranial (including hemorrhagic stroke), gastrointestinal, and urogenital bleeds. MACE outcomes will be a composite endpoint of angina, myocardial infarction, and stroke.

Outcomes of interest will be measured during the study follow-up period, and defined by corresponding Read Medical Codes and ICD-10 diagnosis codes at the primary care setting. The operational definitions of each outcome will be recorded in the STaRT-RWE template and are available on request.

8.3.3. Covariates

Patient demographics, clinical characteristics, comorbidities, and concomitant medications will be measured during baseline period and index date, and identified by Read Medical Codes,

ICD-10 diagnosis codes, and medication ATC codes for corresponding covariates. These covariates include cohort entry year, age, sex, socioeconomic indicators (e.g., marital status), and selected components of CHA_2DS_2 VASc stroke risk score[27,28] (heart failure, hypertension, and diabetes), and ORBIT-AF bleeding risk score in AFib patients[29,30] (heart failure, renal impairment, hepatic impairment; osteoporosis/hip fractures, anemia, antiplatelet therapy, aspirin therapy, NSAIDs therapy, and smoking and alcohol drinking history [if available]).

Additional comorbidities and concomitant medications deemed to be associated with the primary and secondary outcomes of interest will be included in the analyses. All covariates will be determined based on the literature and clinical knowledge. The operational definitions of each covariate will be recorded in the STaRT-RWE template and are available on request.

9. Data Analysis

Data analyses will be performed in a stepwise approach involving three distinct sequential phases (Figure 9.1): *Exploratory Phase* (data explorations will be done in advance to inform key design decisions), *Diagnostic Phase* (requirements that must be met prior to viewing study outcomes, e.g. covariate balance), and *Inferential Phase* (comparative analyses).

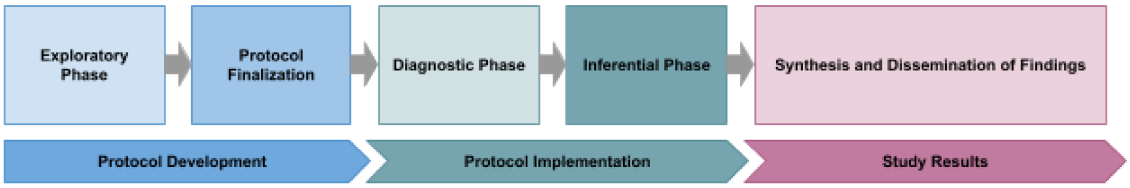

Figure 9.1 Data Analysis Phases

In the *Exploratory Phase*, the study implementation team completed explorations related to the patient selection criteria, exposure groups, and outcome definitions that informed the development of the study protocol.

For the *Diagnostic Phase*, the checklist in Table 9.1 must be satisfactorily completed prior to beginning the implementation of the *Inferential Phase*. As such, the relationship between the exposure and outcome of interest will not be described or evaluated in the analytic dataset until the study implementation team reaches consensus that the diagnostic criteria are satisfied.

Table 9.1 Diagnostic Checklist to Complete Prior to Progression to the Inferential Phase

Diagnostic Criteria	Description
Confirm adequate sample size	Adequate sample size will be defined as the minimum sample size required to achieve 80% power to detect a HR of ≥0.80 for the primary outcome of stroke under the assumptions of 1:1 matching ratio of the primary comparators (apixaban vs. rivaroxaban); a false-positive rate α=0.05; a 1-sided test; and a background stroke incidence rate of 47 events per 100,000 person-years in patients with AFib[31] Note: If adequate sample size is not reached (i.e., minimum HR

	that we can detect is <0.80), it will not solely prohibit us from moving on to interferential analysis. NICE would typically use treatment effect estimates to parameterise economic models and as long as the uncertainty in estimates is quantified, it can be accounted for in decision-making. In addition, a recent article[32] deprioritized the importance of power calculations for observational studies, noteing that observational analyses with imprecise effect estimates should be completed as small studies can be pooled to provide a more precise effect estimate. Therefore, this analysis is informative even if the sample size is insufficient to detect a HR ≥0.80 with 80% power.
Confirm positivity of variables	Propensity score distributions will be visually inspected, and overlap in all areas of the propensity score distributions will be confirmed. Other approaches, such as propensity score weighting, will be explored to achieve covariate balance in case propensity score matching is insufficient.
Confirm baseline confounder balance	The distributions of all potential confounders will be confirmed to be balanced for each comparison of interest. Covariate balance will be defined as ASD ≤0.10. Although covariates with balance prior to propensity score matching may be removed from the propensity score model, balance of these covariates will still be confirmed after matching. Covariates with small residual imbalance (defined as 0.10 ≤ ASD ≤ 0.15) may be deemed balanced if the covariate does not predict the outcome among the referent group (defined as ASD <0.10 when comparing the risk of the outcome in those with the covariate vs. those without it) Evaluation of imbalance in outcome prediction will only be conducted once at the end of the diagnostic phase if all other diagnostic criteria are met.
Confirm models are not overfit	All models must contain ≥12 exposed patients per covariate
Confirm persistence of treatment	Initiators of DOACs stay on treatment for a substantial amount of time after starting treatment. The definition of “substantial persistence” will be finalized during the diagnostic phase and will be data driven. If substantial crossover or censoring is observed, appropriate methods to account for these censoring issues will be applied in the comparative analyses. Preliminary analyses show patients treated with DOACs in the database have a median follow-up of 2.3 years (IQR, 1.0-3.9). In clinical trials, the median duration of treatment was 1.5 years.

Unless otherwise specified, results will be provided as descriptive statistics with categorical variables reported using frequency distributions, and continuous variables reported using means, standard deviations, medians, minimums, maximums, 25th percentiles and 75th

percentiles. For inferential statistics, both crude and covariate adjusted analyses will be reported for study outcomes.

Among patients in each of the exposure groups, the incidence rates and 95% confidence intervals (CI) of stroke and secondary outcomes will be calculated for each of the mutually exclusive comparison groups, along with the number of events, total number of individuals, and accrued person-time. Incidence rates will be calculated as the number of incident outcomes of interest within the follow-up period divided by the total person-time at-risk, and reported as rate per 1,000 person-years.

In each comparison cohort, multivariable logistic regression will be used to estimate the probability of a patient's initiation of the exposure given baseline covariates and cohort entry year (i.e., the propensity score). Propensity score matching between exposure groups will be performed using 1:1 nearest neighbor matching without replacement with a maximum matching caliper of 0.01. In addition to graphical depictions of propensity score distributions, the absolute standardized differences (ASD) in proportions and means of baseline characteristics will be estimated to examine comparability of exposure groups. Covariates with ASD ≤0.10 are considered balanced between comparator groups.[33] Covariates with small imbalances 0.10 ≤ ASD ≤ 0.15) may be deemed balanced if the covariate does not predict the outcome among the referent group.

Cox proportional hazards regression (outcomes model) will be used to estimate hazard ratios (HR) and 95% CI for each outcome after propensity score matching. The incidence of stroke and secondary outcomes will be compared between individual DOACs in primary and secondary comparisons as mutually exclusive cohorts.

Subgroup analyses that will be considered include DOACs initiators with prior warfarin use; age (<75 and ≥75 years); concomitant aspirin use; CHA_2DS_2 VASc score (0-1, 2-3, and ≥4), and selected comorbid conditions, e.g. diabetes, heart failure, and BMI status (<30 and ≥30 kg/m²).

Sensitivity analyses will be performed to assess the impact of varying the study period on study findings by limiting analyses on data up to February 28, 2020 to account for potential impact of COVID-19 pandemic on healthcare utilization.

Additionally, high-dimensional propensity score (HdPS) analysis will be used as a sensitivity analysis to estimate the association between treatment with DOACs and the primary outcome of stroke. The HdPS approach is a 7-step algorithm that empirically identifies a pool of covariates from different data dimensions based on their prevalence, and then selects a subset of the covariates for inclusion in a propensity score model based on their potential to bias the exposure-outcome association.[30]

Missing values will be reported as missing, and no imputation will be undertaken. All data analysis will be conducted using Aetion Evidence Platform® (2021), software for real-world data analysis. Aetion, Inc. https://www.aetion.com.

10. Limitations of the Research Methods

This study will be based on secondary use data from EHR with inherent limitations, including misclassification. For example, a patient may not necessarily use a medication that they have received a prescription for; however, this is less likely in the case of medications for chronic conditions like cardiovascular diseases. Additionally, while it is possible to identify study

outcomes of interest in the THIN® database, misclassification of the outcome is possible, as the presence of a diagnosis in medical records does not necessarily indicate a true presence of disease; however, the outcomes of interest are included in the Quality and Outcome Framework (QOF)[34] which rewards and incentivizes GPs in England for quality care and coding of diagnoses. In addition, validated algorithms from previously published real-world studies will be used to define study variables of interest.

An incident user design will be applied to reduce biases that can impact non-randomized studies, especially when using EHR.[35] An ITT analysis will be used because it has the advantage of eliminating certain types of biases by preserving the prognostic balance obtained through the propensity score matching and maintaining sample size;[36,37] however, ITT analysis is sometimes considered to be “too conservative” and has the possibility of exposure misclassification.[35,36] Additionally, “as-treated” approach will be used that will censor individuals upon discontinuation of index treatment or treatment crossover. However, limitations of an “as-treated” analysis include the possibility of introducing certain biases including differential and informative censoring, or time-dependent confounding biases.[36,37]

Finally, while the THIN® database contains substantial information for inclusion/exclusion criteria and confounder control, medical conditions or a family history of medical conditions are only ascertainable where established diagnoses and procedures for those conditions exist. Additionally, some key covariates may not be available (unmeasured or imperfectly measured confounders), e.g. alcohol and smoking histories are not routinely recorded. Residual confounding by unmeasured variables will likely be present; however, efforts will be made to incorporate all potential confounding variables into the propensity score analysis to minimize impacts from unmeasured confounding, including the application of HdPS sensitivity analysis. Compared to conventional confounding adjustment methods, HdPS algorithm improves confounding control in situations when the variables are weak confounders that are weakly associated with exposure and themselves are associated with unmeasured confounders.[38]

11. Quality Control

The study data to be used for the proposed analysis will be connected to the Aetion Evidence Platform (AEP), which will be used to perform all the analyses. The AEP is a data-handling technology, which allows for the analysis of large patient claims, EHR, and other transactional datasets by indexing patient data into a form that can be queried by an internal patient variable language. Data is minimally transformed at the point of connection to the AEP, thus the original format of the THIN® data is preserved. At the point of data connection to the platform some discard rules are applied. Patient events are excluded if there are no dates associated with them, or if the start date of the event is preceded by the end date of the event (e.g. discharge date precedes admission date for an inpatient event). Aetion IDs are assigned to THIN® patient IDs and a crosswalk file is kept as a protected file available upon request to authorized parties. The patient data is individual level patient data and will be analyzed within the AEP. Aggregated results will be exported from the platform in the form of tables.

THIN® data are loaded into the AEP after minimal processing into patient longitudinal timelines to enable representation of the original data and without any data loss. The following data checks are performed during the data connection process:

- Events are required to have a valid start date.
- Record counts are cross-checked for validation and compared to the original data counts.

- Enrollment information is processed and checked, and all fields and sample records are checked to ensure validity.

The process is implemented via a double-programming, rule-based approach that is flexible, automated, and scalable so that it can be reproduced when data is updated. Data processed through the data connector (coded by the Aetion Data Engineering team) are compared against data transformed independently to reproduce the data connector logic (coded by the Aetion Data Science team). Checks are performed first on a subset of data, then on the full data. This process ensures that customers are working with a scientifically valid data product when they perform analyses on the data using the AEP. Statistical analyses will be conducted using the validated AEP.

The Aetion Science Team will build measures for cohort inclusion/exclusion criteria, outcomes and covariates. All measures created, cohorts developed, statistical analyses implemented, and tables populated will undergo quality control review by at least one additional analyst or scientist under the supervision of the Senior Scientist. Quality control methods include checks for the validity and logical content of codes and checks for missing values and variables. In order to control for potential inconsistencies and errors, all variables will be tabulated. In addition, the distribution of values for each variable, including potential outliers, will be examined. This protocol will be strictly followed in the study implementation. However, variable definitions may undergo modification if determined to be scientifically sensible. All changes to this protocol will be documented in protocol amendments.

12. Protection of Human Subjects

This study will be conducted in accordance with applicable laws and regulations of the country where the study is being conducted, as appropriate. This observational, non-interventional study does not affect the treatment of the patients. The study is conducted in accordance with ethical principles that are consistent with the Declaration of Helsinki, International Conference on Harmonisation (ICH) Good Clinical Practice (GCP), Good Pharmacoepidemiology Practice (GPP), and the applicable legislation on non-interventional studies and/or observational studies.

The study concept was approved by the THIN® Scientific Review Committee on July 6, 2021.

13. Management and Reporting of Adverse Events/Adverse Reactions

This is a non-interventional study using only structured secondary data, and attribution of adverse reactions/adverse events to specific exposure is not possible, and therefore no individual case safety report (ICSR) reporting is required. During the course of observational research using existing secondary databases, the proposed study will use structured data fields only and will not involve chart review or validation to obtain additional information on the adverse events other than the study outcomes of interest.

14. Plans for Disseminating and Communicating Study Results

This study protocol will be registered in the ENCePP EU PAS Register[39] prior to the implementation of the diagnostic phase. In addition, study findings will be disseminated as manuscript(s) in peer-reviewed journals and/or as conference abstract presentations at international professional conferences.

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Aetion Measure Appendix

Administrative Information (STaRT-RWE Table 1)	
Protocol Title	UK
Primary Objective	Estimate the incidence rates and evaluate the association of nonfatal stroke (ischemic or hemorrhagic) for patients nonvalvular AFib who initiated apixaban compared to rivaroxaban
Secondary	apixaban compared to edoxaban, dabigatran, and DOAs class
Secondary I	transient ischemic attack (TIA), major bleeding events, and major adverse cardiovascular events (MACE) for patie

Registration		
Registration Identifier	**Date**	**Registration Site**
45074	1/10/2022	EU PASS register

Version	
Version Number	**Version Date**
V1	10/22/21

Protocol Contributors		
Name	**Role**	**Affiliation**
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Funding	
Grant Identifier	**Source**
-	This research was conducted as part of a Research Collaboration Agreement with NICE.

Data Use Agreement (DUA)		
DUA Identifier	**Data Provider**	**Data Provider Contact for DUA**
-	Cegedim	Shelley Jessop

Human Subjects/Ethics Approval

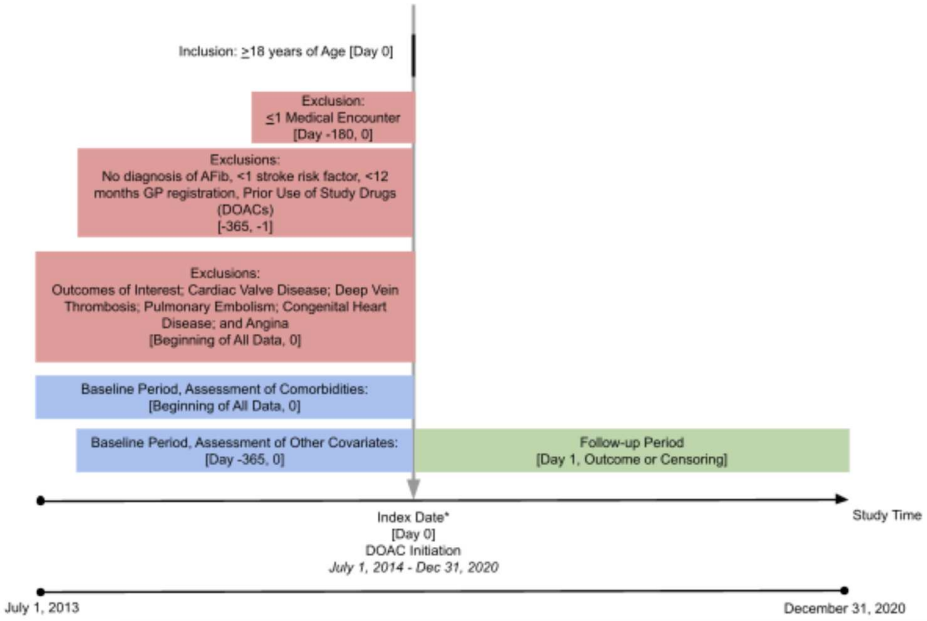
observational, non-interventional study does not affect the treatment of the patients. The study is conducted in accordance with ethical principles that are

This Measure Appendix is based largely on the STaRT-RWE templates proposed by Wang et. al., 2020.

Research Question Overview

fibrillation (AFib) in the UK. Individual DOAs of interest include apixaban, rivaroxaban, edoxaban, and dabigatran.

Study Design Diagram (STaRT-RWE Figure 1)



Measure Appendix Version History (STaRT-RWE Table 2)			
Version Number	**Version Date**	**Change Log**	**Rationale for Changes**
1	1/3/2022	N/A	N/A

Data Source Details (STaRT-RWE Table 3)	
calendar time range of data available for pre-index assessment windows and post-index follow up (study period). The data source nam	
	Data Source 1
Data Source Name	The Health Improvement Network (THIN) Database (A prioritary database from Cegedim)
Study Period	July 1, 2013 - December 31, 2020
Eligible Cohort Entry Period	July 1, 2014 - December 31, 2020
Data Extraction Date / Version	July 30, 2021
Data Sampling / Extraction Criteria	As part of the study application and data access process, Cegedim applied limited inclusion/exclusion criteria to extract the data set used in the analysis. See Cohort tab for more details.
Type(s) of Data	EHR
Data Linkage	N/A
Data Conversion	N/A
Software to Create Study Population	Aetion Evidence Platform

Index

Study Population							Implementation						
Abbreviation	Name	Corresponding Study Objective	Index Date Description	Number of Entries	Type of Entry	Washout Window	Care Settings (Events)	Code Type	Code Position	Incident With Respect to...	Pre-Specified	Varied for Sensitivity	Source
Apixaban	Incident Users of apixaban	Primary	initiation of apixaban during July 1, 2014 through December 31, 2020	Single	Incident	Day -365 to Day -1	Perscriptions	Product ATC code	N/A	Incident users with respect to exposure and all other DOACs	Yes	No	ATC index;reviewed by Pharmacist
Rivaroxaban	Incident users of rivaroxaban	Primary	initiation of apixaban during July 1, 2014 through December 31, 2020	Single	Incident	Day -365 to Day -1	Perscriptions	Product ATC code	N/A	Incident users with respect to exposure and all other DOACs	Yes	No	ATC index;reviewed by Pharmacist
Dabigatran	Incident users of dabogatran	Secondary	initiation of apixaban during July 1, 2014 through December 31, 2020	Single	Incident	Day -365 to Day -1	Perscriptions	Product ATC code	N/A	Incident users with respect to exposure and all other DOACs	Yes	No	ATC index;reviewed by Pharmacist
Edoxaban	Incident users of edoxaban	Secondary	initiation of apixaban during July 1, 2014 through December 31, 2020	Single	Incident	Day -365 to Day -1	Perscriptions	Product ATC code	N/A	Incident users with respect to exposure and all other DOACs	Yes	No	ATC index;reviewed by Pharmacist
DOAC other than Apixaban	incident users of Rivaroxaban, Edoxaban, or Dabigatran	Secondary	initiation of apixaban during July 1, 2014 through December 31, 2020	Single	Incident	Day -365 to Day -1	Perscriptions	Product ATC code	N/A	Incident users with respect to exposure and all other DOACs	Yes	No	ATC index;reviewed by Pharmacist
DOAC other than Rivaroxaban	incident users of Apixaban, Edoxaban, or Dabigatran	Secondary	initiation of apixaban during July 1, 2014 through December 31, 2020	Single	Incident	Day -365 to Day -1	Perscriptions	Product ATC code	N/A	Incident users with respect to exposure and all other DOACs	Yes	No	ATC index;reviewed by Pharmacist
DOAC other than Edoxaban	incident users Apixaban, Rivaroxaban, or Dabigatran	Secondary	initiation of apixaban during July 1, 2014 through December 31, 2020	Single	Incident	Day -365 to Day -1	Perscriptions	Product ATC code	N/A	Incident users with respect to exposure and all other DOACs	Yes	No	ATC index;reviewed by Pharmacist
DOAC other than Dabigatran	Incident users of Apixaban, Rivaroxaban, or Edoxaban	Secondary	initiation of apixaban during July 1, 2014 through December 31, 2020	Single	Incident	Day -365 to Day -1	Perscriptions	Product ATC code	N/A	Incident users with respect to exposure and all other DOACs	Yes	No	ATC index;reviewed by Pharmacist

The criterion that define the date of entry to the cohort(s) is specified in this section. There should be one row for each unique definition of a study population entry. If the study is descriptive, there may only be one row filled out. An active comparator study may have 2 rows, one for the exposure of interest and one for the comparator.

Check the pre-specified box if the exclusion criterion was specified before beginning data analyses, check the varied for sensitivity box if it was modified as part of sensitivity analyses. Specify the source of algorithms to define study entry criteria.

Cohort

				Implementation							
Criterion (Measure)	**Criterion Details**(Measure Details)	**Order Applied**	**Applied by**	**Assessment Window**	**Care Settings**(Events)	**Code Type**	**Code Position**	**Notes**	**Pre-Specified**	**Varied for Sensitivity**	**Source**
Initiators of DOAC	Prescription for DOAs of interest. Washout for prior use described below.	Before selection of cohort entry	Cegedim/THIN	**Day 0**	Primary care/General practice	Product ATC codes	N/A	B01AF01 B01AF02 B01AF03 B01AE07	Yes	No	https://www.whocc.no/atc_ddd_index/ and Reviewed by pharmacist
Age	18+ on index date	Before selection of cohort entry	Cegedim/THIN	**Day 0**	N/A	N/A	N/A	N/A	Yes	No	N/A
Diagnosis of Afib	≥1 diagnosis code for AFib on index date or 12 months prior	Before selection of cohort entry	Cegedim/THIN	**[-365, 0]**	Primary care/General practice	READ Codes	N/A	INUK.3272.00 INUK.3273.00 INUK.3274.00 INUK.7936A00 INUK.G570.00 INUK.G570000 INUK.G573.00 INUK.G573000 INUK.G573100 INUK.G573200 INUK.G573z00 INUK.14AN.00 INUK.212R.00 INUK.662S.00 INUK.6A9..00 INUK.9hF..00 INUK.9hF1.00 INUK.9Os..00 INUK.9Os0.00 INUK.9Os1.00 INUK.9Os2.00 INUK.9Os3.00 INUK.9Os4.00 INUK.G573300	Yes	No	Ruigomez, 2019
≥ 1 risk factor for stroke other than Afib	≥1risk factor for stroke other than AFib on index date or in 12 months prior defined by $CHADS_2$ score (CHA_2DS_2 VASc) >1 for men and >2 for women	Before selection of cohort entry	Cegedim/THIN	**[-365, 0]**	N/A	READ Codes	N/A	Based on the CHA2DS2 score and its cooresponding READ codes - INUK.38DE.00, INUK.38DE.11, INUK.38DE000	Yes	No	Cegedim/THIN
GP registration	Registered with a GP for ≥12 months prior t the index date	Before selection of cohort entry	Cegedim/THIN	**[-365,0]**	N/A	READ Codes	N/A		Yes	No	Cegedim/THIN
≥ 1 medical encounter	≥1 medical encounter in the 180 days prior t index date	Before selection of cohort entry	Cegedim/THIN	**[-180,0]**	N/A	READ Codes	N/A		Yes	No	Cegedim/THIN
Previous diognoses	≥ diagnosis code for the following conditions on index date or any time prior: Angina Cardiac valve disease (mitral stenosis, valvular replacement) Congenital heart disease Deep vein thrombosis Pulmonary embolism	Before selection of cohort entry	Cegedim/THIN	**[-∞, 0]**	Primary care/General practice	READ Codes	N/A	Mitral Stenosis, Valvular Relpacement, Pulmonary Embolism, DVT	Yes	No	Ruigomez, 2019
Washout period	≥1 prescription record for any DOAC in the months prior to the index date (i.e., prevalen users)	Before selection of cohort entry	Aetion	**[-365,0]**	Primary care/General practice	Product ATC codes	N/A	New user design	Yes	No	Reviewed by pharmacist
Prior outcomes	≥1 diagnosis code for the study outcomes o interest (stroke, MI, TIA, major bleeding events) on index date or any time prior	Before selection of cohort entry	Aetion	**[-∞, 0]**	Primary care/General practice	READ and ICD10 codes	Any	Prior stroke, MI, TIA, major bleeding event, angina from the Diognosti and First Diognosis tables	Yes	No	

Covariate Drugs

Characteristic(Measure)	Details(Measure Definition)	Type of Variable	Assessment Window	Implementation: Care Settings (Events)	Implementation: Code Type	Implementation: Code Position	Implementation: Notes	Implementation: Pre-Specified?	Implementation: Varied for Sensitivity?
Antianemic preparations	B03*, B03X*	Binary	[-365, 0]	N/A	*ATC codes*	N/A		Yes	No
Antiarrhythmics	C01B*	Binary	[-365, 0]	N/A	*ATC codes*	N/A		Yes	No
Antihyperglycemics (other than Insulins)	A10BJ*, A10BX04, A10BX10, A10BX13, A10BX14, A10AE54, A10AE56, A10BX07, A10BH*, A10BD07, A10BD08, A10BD09, A10BD10, A10BD11, A10BD12, A10BD13, A10BD18, A10BD22, A10BD25, A10BD19, A10BD21, A10BD24, A10BD15, A10BD16, A10BD19, A10BD20, A10BD21, A10BD23, A10BD24, A10BD25, A10BK*, A10BX09, A10BX11, A10BX12, A10B, A10BA*, A10BB A10BC* A10BD*, A10BF*, A10BG*, A10BX*	Binary	[-365, 0]	N/A	*ATC codes*	N/A		Yes	No
Antihypertensives	C09A*, C09B*, C09C*, C09D*, C09XA*, C08 C07AA, C07AA01, C07AA02, C07AA03, C07AA05, C07AA06, C07AA07, C07AA12, C07AA14, C07AA15, C07AA16, C07AA17, C07AA19, C07AA23, C07AA27, C07AA57, C07AB, C07AB01, C07AB02, C07AB03, C07AB04, C07AB05, C07AB06, C07AB07, C07AB08, C07AB09, C07AB10, C07AB11, C07AB12, C07AB13, C07AB14, C07AB52, C07AB57, C07AG, C07AG01, C07AG02, C07B, C07BA, C07BA02, C07BA05, C07BA(C07BA07, C07BA12, C07BA68, C07BB, C07BB02, C07BB03, C07BB04, C07BB06, C07BB07, C07BB12, C07BB52, C07BG, C07BG01, C07C, C07CA, C07CA02, C07CA03, C07CA17, C07CA23, C07CB, C07CB02, C07CB03, C07CB53, C07CG, C07CG01, C07D, C07DA, C07DA06, C07DE C07DB01, C07E, C07EA, C07EB, C07F, C07FA, C07FA05, C07FB, C07FB02, C07FB03, C07FB07, C07FB12, C07FB13, C07FX, C07FX01, C07FX02, C07FX03, C07FX04, C07FX05, C07FX06	Binary	[-365, 0]	N/A	*ATC codes*	N/A		Yes	No
Antineoplastics	L01*, L02*	Binary	[-365, 0]	N/A	*ATC codes*	N/A		Yes	No
Antiplatelets (excluding Aspirin)	B01AC, B01AC01, B01AC02, B01AC03, B01AC04, B01AC05, B01AC07, B01AC08, B01AC09, B01AC10, B01AC11, B01AC13, B01AC15, B01AC16, B01AC17, B01AC18, B01AC19, B01AC21, B01AC22, B01AC23, B01AC24, B01AC25, B01AC26, B01AC27, B01AC30	Binary	[-365, 0]	N/A	*ATC codes*	N/A		Yes	No
Antipsychotics (Excluding BZD)	N05A*	Binary	[-365, 0]	N/A	*ATC codes*	N/A		Yes	No
Aspirin	B01AC06, B01AC56, N02BA01	Binary	[-365, 0]	N/A	*ATC codes*	N/A		Yes	No
Benzodiazepines (BZD)	N03AE01, N05BA*, N05CF*, N05CD*	Binary	[-365, 0]	N/A	*ATC codes*	N/A		Yes	No
Bisphosphonates and other agents affecting bone structure	M05BA*, M05BB*, M05BC*, M05BX*	Binary	[-365, 0]	N/A	*ATC codes*	N/A		Yes	No

Cardiac Stimulants	C01AA*, C01CA*, C01CE*	Binary	**[-365, 0]**	N/A	*ATC codes*	N/A		Yes	No
GI Protective Agents	A02A*, A02BA*, A02BC*, A02BD*, A02BB01 A02BB02	Binary	**[-365, 0]**	N/A	*ATC codes*	N/A		Yes	No
Insulin	A10A*	Binary	**[-365, 0]**	N/A	*ATC codes*	N/A		Yes	No
Lipid Lowering Agents	C10AA*, C10BA*, C10BX*, C10AB*	Binary	**[-365, 0]**	N/A	*ATC codes*	N/A		Yes	No
Nitrates Cardiac Vasodilators	C01DA*	Binary	**[-365, 0]**	N/A	*ATC codes*	N/A		Yes	No
NSAIDs (Excluding Aspirin & APAP)	M01A*	Binary	**[-365, 0]**	N/A	*ATC codes*	N/A		Yes	No
Opioid Analgesics	N02A*	Binary	**[-365, 0]**	N/A	*ATC codes*	N/A		Yes	No
Other Antidepressants (Excluding SSRI)	N06A, N06AA*, N06AF*, N06AG*, N06AX*	Binary	**[-365, 0]**	N/A	*ATC codes*	N/A		Yes	No
Other Antiepileptics (Excluding BZD)	N03AA*, N03AB*, N03AC*, N03AD*, N03AF N03AG*, N03AX*	Binary	**[-365, 0]**	N/A	*ATC codes*	N/A		Yes	No
SSRI	N06AB*	Binary	**[-365, 0]**	N/A	*ATC codes*	N/A		Yes	No
Systemic Antibiotics	P02*, J01*, J02*, D01B*, P01B*, J04*, P01A P01C*	Binary	**[-365, 0]**	N/A	*ATC codes*	N/A		Yes	No
Systemic Antivirals	J05*	Binary	**[-365, 0]**	N/A	*ATC codes*	N/A		Yes	No
Systemic Corticosteroids	H02A*, H02B*	Binary	**[-365, 0]**	N/A	*ATC codes*	N/A		Yes	No
Vaccines and Immunoglobulins	J06*, J07*	Binary	**[-365, 0]**	N/A	*ATC codes*	N/A		Yes	No
Warfarin	B01AA03	Binary	**[-365, 0]**	N/A	*ATC codes*	N/A		Yes	No

STaRT-RWE Instructions:

Define the covariate conceptually, with accompanying details as necessary. Specify which planned analyses adjust for the covariate, and how it is specified in the analysis (e.g., continuous, categorical, binary). D assessment window relative to the index date (day 0), whether there are restrictions on care setting or diagnosis position in the algorithm, and which study populations defined in Table 3B the covariate is measur Specify the source of algorithms to define covariates.

Check the pre-specified box if the covariate was specified before beginning data analyses, check the varied for sensitivity box if it was modified as part of sensitivity analyses. Specify the source of algorithms to d covariates.

Covariate Conditions

			Implementation							
Characteristic(Measure)	**Type of Variable**	**Assessment Window**	**Care Settings** (Events)	**Code Type**	**Code Position**	**Notes**	**Pre-Specified?**	**Varied for Sensitivity?**	**Included in Quality Framework?**	**Included in PS model?**
Acute Kidney Injury	Binary	**[-∞, 0]**	GP	*ICD10 and READ codes*	First Diognosis or Diognostics		Yes	No	No	Yes
Anemia	Binary	**[-∞, 0]**	GP	*ICD10 and READ codes*	First Diognosis or Diognostics		Yes	No	No	Yes
Asthma or COPD	Binary	**[-∞, 0]**	GP	*ICD10 and READ codes*	First Diognosis or Diognostics		Yes	No	Yes	Yes
Chronic Kidney Disease	Binary	**[-∞, 0]**	GP	*ICD10 and READ codes*	First Diognosis or Diognostics		Yes	No	No	Yes
Dementia	Binary	**[-∞, 0]**	GP	*ICD10 and READ codes*	First Diognosis or Diognostics		Yes	No	Yes	Yes
Diabetes Mellitus	Binary	**[-∞, 0]**	GP	*ICD10 and READ codes*	First Diognosis or Diognostics		Yes	No	Yes	Yes
Heart Failure	Binary	**[-∞, 0]**	GP	*ICD10 and READ codes*	First Diognosis or Diognostics		Yes	No	Yes	Yes
Hypertension	Binary	**[-∞, 0]**	GP	*ICD10 and READ codes*	First Diognosis or Diognostics		Yes	No	Yes	Yes
Malignant Neoplasms	Binary	**[-∞, 0]**	GP	*ICD10 and READ codes*	First Diognosis or Diognostics		Yes	No	No	Yes
Non Major Bleeding	Binary	**[-∞, 0]**	GP	*ICD10 and READ codes*	First Diognosis or Diognostics		Yes	No	No	Yes
Osteoporosis/Hip Fractures	Binary	**[-∞, 0]**	GP	*ICD10 and READ codes*	First Diognosis or Diognostics		Yes	No	Yes	Yes
CHA2DS2 VASc score	Categorical	**[-∞, 0]**	GP	*ICD10 and READ codes for diagnoses, ATC codes for use of antihypertensives*	First Diognosis or Diognostics	- Age: +1 if age 65-74, +2 if age ≥75 years - Gender: +1 if female - Heart failure: +1 if any history - Stroke:, TIA, or thromboembolism +1 if any history - Vascular disease (MI, PAD, aortic plaque): +1 if any history - Diabetes mellitus: +1 if any history - Hypertension or use of antihypertensives: +1 if any history See "Code List Catalog" for definitions	Yes	No	Yes	Yes

Follow Up				
Follow Up Begins				
			Pre-Specified?	**Varied for Sensitivity?**
Begins	Day 1		Yes	No
Follow Up Ends				
Ends	**Select All That Apply**	**Specify Details**	**Pre-Specified?**	**Varied for Sensitivity?**
Date of Outcome	√	Primary analysis (ITT) and AT sensitivity analysis	Yes	No
Date of Death	√	Primary analysis (ITT) and AT sensitivity analysis	Yes	No
End of patient data	√	Primary analysis (ITT) and AT sensitivity analysis	Yes	No
End of registration with GP	√	Primary analysis (ITT) and AT sensitivity analysis	Yes	No
Crossover of exposure group o addition of drug from other exposure group	√	AT sensitviity analysis only	Yes	Yes
Termination of exposure	√	AT sensitviity analysis only. Defined allowing a 30-day grace period and 30-day risk window.	Yes	Yes

STaRT-RWE Instructions:

Specify when follow up begins relative to the index date (day 0) and select each criterion that is used to end follow up.

Check the pre-specified box if the outcome parameters were specified before beginning data analyses, check the varied for sensitivity box if the parameters were modified as part of sensitivity analyses.

Outcomes

Outcome Name (Measure)	Outcome Measurement Characteristics(Measure Definition)	Primary Outcome?	Type of Outcome	Washout Window	Implementation: Care Settings (Events)	Implementation: Code Type	Implementation: Code Position	Implementation: Notes	Implementation: Pre-Specified?	Implementation: Varied for Sensitivity?	Citations
Stroke (Ischemic or hemorrhagic)	See Code List Catelog tab	Yes	Incident	[-∞, 0]	Primary care/General practice	READ & ICD-10	Any	From Diognostics table	Yes	No	Rannikmäe K, Ngoh K, Bush K, Al-Shahi Salma R, Doubal F, Flaig R, Henshall DE, Hutchison A Nolan J, Osborne S, Samarasekera N, Schnier C, Whiteley W, Wilkinson T, Wilson K, Woodfield R, Zhang Q, Allen N, Sudlow CLM. Accuracy of identifying incident stroke cases from linked health care data in UK Biobank. Neurology. 2020 Aug 11;95(6):e697-e707. doi: 10.1212/WNL.0000000000009924. Epub 2020 2. PMID: 32616677; PMCID: PMC7455356.
All-cause mortality	State Code = "D - Dead"	No	Incident	[-∞, 0]	Primary care/General practice	N/A	N/A		Yes	No	
Myocardial infarction	See Code List Catelog tab	No	Incident	[-∞, 0]	Primary care/General practice	READ & ICD-10	Any	From Diognostics table	Yes	No	Arana A, Margulis AV, Varas-Lorenzo C, Bui C Gilsenan A, McQuay LJ, Reynolds M, Rebordos C, Franks B, de Vogel S, Appenteng K, Perez-Gutthann S. Validation of cardiovascular outcomes and risk factors in the Clinical Practic Research Datalink in the United Kingdom. Pharmacoepidemiol Drug Saf. 2021 Feb;30(2):237-247. doi: 10.1002/pds.5150. Epu 2020 Oct 28. PMID: 33091194; PMCID: PMC7821285. Metcalfe A, Neudam A, Forde S, et al. Case definitions for acute myocardial infarction in administrative databases and their impact on in hospital mortality rates. Health Serv Res. 2013;48(1):290-318. doi:10.1111/j.1475-6773.2012.01440.x
Transient ischemic attack	See Code List Catelog tab	No	Incident	[-∞, 0]	Primary care/General practice	READ & ICD-10	Any	From Diognostics table	Yes	No	Andrade SE, Harrold LR, Tjia J, et al. A systematic review of validated methods for identifying cerebrovascular accident or transien ischemic attack using administrative data. Pharmacoepidemiol Drug Saf. 2012;21 Suppl 1(Suppl 1):100-128. doi:10.1002/pds.2312
Major bleeding events	Defined as a composite outcome of major intracranial (including hemorrhagic stroke), gastrointestinal, and urogenital bleeds; see code lists.	No	Incident	[-∞, 0]	Primary care/General practice	READ & ICD-10	Any	From Diognostics table	Yes	No	Pasea L, Chung SC, Pujades-Rodriguez M, et a Bleeding in cardiac patients prescribed antithrombotic drugs: electronic health record phenotyping algorithms, incidence, trends and prognosis. BMC Med. 2019;17(1):206. Publishe 2019 Nov 20. doi:10.1186/s12916-019-1438-y
Composite angina / MI / stroke (AMS)	Composite endpoint of angina, myocardial infarction, and stroke.; see code lists.	No	Incident	[-∞, 0]	Primary care/General practice	READ & ICD-10	Any	From Diognostics table	Yes	No	

Analysis Plan Specification										
	Primary Objective	**Secondary Objective I**	**Secondary Objective II**	**Secondary Objective III**	**Secondary Objective IV**	**Secondary Objective V**	**Secondary Objective VI**	**Secondary Objective VII**	**Secondary Objective VIII**	**Secondary Objective IX**
Hypothesis	Null hypothesis HR=1	Null hypothesis HR=1	Null hypothesis HR=1	Null hypothesis HR=1	Null hypothesis HR=1	Null hypothesis HR=1	Null hypothesis HR=1	Null hypothesis HR=1	Null hypothesis HR=1	Null hypothesis HR=1
Study Populations	Initiators of apixaban Initiators of rivaroxaban	Initiators of apixaban Initiators of edoxaban	Initiators of apixaban Initiators of dabigatran	Initiators of apixaban Initiators of rivaroxaban, edoxaban, and dabigatran	Initiators of rivaroxaban Initiators of edoxaban	Initiators of rivaroxaban Initiators of dabigatran	Initiators of rivaroxaban Initiators of apixaban, edoxaban, and dabigatran	Initiators of edoxaban Initiators of dabigatran	Initiators of edoxaban Initiators of apixaban, rivaroxaban, and dabigatran	Initiators of dabigatran Initiators of apixaban, rivaroxaban, and edoxaban
Outcome	Incidence of stroke									
Software										
Model(s)	comparisons as mutually exclusive cohorts.									
Confounding Adjustment Method (check all that apply and provide details where specified)										
Bivariate										
Multivariate	√									
Propensity Score Matching (Specif matching algorithm, ratio, and calipe	√; Propensity score matching between exposure groups will be performed using 1:1 nearest neighbor matching without replacement with a maximum matching caliper of 0.01									
Propensity Score Weighting (specif formula, weighting, and truncatio decisions)										
Propensity Score Stratification (specif strata definitions										
Other (Specify details	√; High-demensional propensity score analysis will be used as sensativity analysis									
Missing Data Method (select all that apply)										
Missing Indicators	√									
Complete Case										
Last Value Carried Forward										
Multiple Imputation (specify variables)										
Other (Specify Details										
Subgroup Analysis	DOACs initiators with prior warfarin use; age (<65, 65-74, and >75 years); concomitant aspirin use; CHADS$_2$ score (1, 2, and >3), and selected comorbid conditions, e.g. diabetes, heart failure, and BMI status (<30 and >30 kg/m²).									

Sensitivity Analyses (SA)				
Sensitivity Analysis	**What is the parameter being varied? (Be clear what is changing from)**	**Why? (What do you expect to learn?)**	**Strengths of the Sensitivity Analysis compared to the Primary?**	**Weaknesses of the Sensitivity Analysi compared to the Primary?**
As-treated follow-up	Primary (ITT) analysis does not censor on treatment discontinuation or crossover. This is changed to censoring on discontinuation or crossover.	ITT and AT analyses are subject to different biases (exposu misclassification versus potential for informative censoring). Running both can test influance of these effects and help bo the range of plausible effect estimates.	Avoids misclassification of time following discontinuation of crossover as expose time.	Estimates may be biased if discontinuatio and crossover are driven by symptoms o perceive lack of efficacy.
Limiting analysis up to February 28, 2020**[Note, this was not completed due to sample size issues]**	End of data is truncated to Feb 28th, 2020 instead of De 31, 2020.	With the COVID -19 pandemic starting in March 2020, there a possibility that patients' care pathways were interupted. This could impact results.	Eliminates the possibiity of confounding by COVID-19, e.g. if COVID results in temporal trends in outcomes, and there are temporal trends in drug choice.	Reduced follow-up time and power
high-dimensional propensity score (HdPS) analysis		A difference in estimates between the hdPS and PS analys could indicate the presence of uncontrolled confounding in t PS analysis.	May reduce confounding by identifying confounders and proxies missed in user-specified PS model	there is a slight risk of including instrume like variables in a hdPS model, introducin bias

This Measure Appendix is based largely on the START-RWE templates proposed by Wang et. al., 2020.

Inclusion or Exclusion for primary comparison of apixabar v. rivaroxaban	Criterion (Measure)	Order of Application	TOTAL Excluded Patients	TOTAL Remaining Patients
All patients initiating DOACs between 01-07-2013 through 12-3 2020	N/A	N/A	N/A	124,106
Excluded due to age ≤18 at index	Age	1	50	124,056
Excluded due to no diagnosis of non-valvular Afib in 12 months prior to index	Non-valvular Afib	2	77,747	46,309
Excluded due to CHA2DS2 VASc <1 for men and <2 for wome	CHA2DS2 VASc score	3	30,613	15,696
Excluded due to <12 months prior registration wth GP and <1 medical encounter in 6mo prior to index	GP registration	4	952	14,744
Excluded due to any prior diagnosis of cardiac valve disease (mitral stenosis, valvular replacement, deep vein thrombosis, o pulmonary embolism)	Cardiac valve disease	5	753	13,991
Excluded due to history of a DOAC prescription in the 365 days prior to a qualifying DOAC initiation	DOAC	6	7255	6,736
Excluded due to history of stroke, MI, TIA, major bleeding even angina, or congenital heart disease at any point prior to index d	Stroke, MI, TIA, major bleeding ever angina, congenital heart disease	7	1019	5,717
Excluded due to censoring prior to the start of follow-up		8	62	5,655
Not included in propensity score matching for inferential analyses		9	1977	3,678

Inclusion or Exclusion for primary comparison of apixabar v. DOACs	Criterion (Measure)	Order of Application	TOTAL Excluded Patients	TOTAL Remaining Patients
All patients initiating DOACs between 01-07-2013 through 12-3 2020	N/A	N/A	N/A	124,106
Excluded due to age ≤18 at index	Age	1	50	124,056
Excluded due to no diagnosis of non-valvular Afib in 12 months prior to index	Non-valvular Afib	2	77,747	46,309
Excluded due to CHA2DS2 VASc <1 for men and <2 for wome	CHA2DS2 VASc score	3	30,613	15,696
Excluded due to <12 months prior registration wth GP and <1 medical encounter in 6mo prior to index	GP registration	4	952	14,744
Excluded due to any prior diagnosis of cardiac valve disease (mitral stenosis, valvular replacement, deep vein thrombosis, o pulmonary embolism)	Cardiac valve disease	5	753	13,991
Excluded due to history of a DOAC prescription in the 365 days prior to a qualifying DOAC initiation	DOAC	6	7255	6,736
Excluded due to history of stroke, MI, TIA, major bleeding even angina, or congenital heart disease at any point prior to index d	Stroke, MI, TIA, major bleeding ever angina, congenital heart disease	7	1019	5,717
Excluded due to censoring prior to the start of follow-up		8	62	5,655

Not included in propensity score matching for inferential analyses		9	1,103	4,552
Inclusion or Exclusion for primary comparison of rivaroxiban v. DOACs	**Criterion** (Measure)	**Order of Application**	**TOTAL Excluded Patients**	**Remaining Patients**
All patients initiating DOACs between 01-07-2013 through 12-3 2020	N/A	N/A	N/A	124,106
Excluded due to age ≤18 at index	Age	1	50	124,056
Excluded due to no diagnosis of non-valvular Afib in 12 months prior to index	Non-valvular Afib	2	77,747	46,309
Excluded due to CHA2DS2 VASc <1 for men and <2 for wome	CHA2DS2 VASc score	3	30,613	15,696
Excluded due to <12 months prior registration wth GP and <1 medical encounter in 6mo prior to index	GP registration	4	952	14,744
Excluded due to any prior diagnosis of cardiac valve disease (mitral stenosis, valvular replacement, deep vein thrombosis, o pulmonary embolism)	Cardiac valve disease	5	753	13,991
Excluded due to history of a DOAC prescription in the 365 days prior to a qualifying DOAC initiation	DOAC	6	7255	6,736
Excluded due to history of stroke, MI, TIA, major bleeding even angina, or congenital heart disease at any point prior to index d	Stroke, MI, TIA, major bleeding ever angina, congenital heart disease	7	1019	5,717
Excluded due to censoring prior to the start of follow-up		8	62	5,655
Not included in propensity score matching for inferential analyses		9	1,685	3,970

Software	R

Sample Size & Power Calculations for primary comparison (apixaban vs. rivoraxiban)			
Population Assumptions	**Analysis**	**Range**	**Source for Estimated Parameters**
Assuming 1:1 PS matching with 1,851 patients per group and an unstratified stroke risk of 27.15/1,000 patients	Minimum detectable HR with 80% power using intent to treat follow-up	Minimum detectable HR with 80% power = 0.57	Feasibility analysis
Assuming 1:1 PS matching with 1,851 patients per group and an unstratified stroke risk of 16.17/1,000 patients	Minimum detectable HR with 80% power using as treate follow-up	Minimum detectable HR with 80% power = 0.48	Feasibility analysis

Sample Size & Power Calculations for primary comparison (apixaban vs. other DOACs)			
Population Assumptions	**Analysis**	**Range**	**Source for Estimated Parameters**
Assuming 1:1 PS matching with 2,305 patients per group and an unstratified stroke risk of 16.63/1,000 patients	Minimum detectable HR with 80% power using intent to treat follow-up	Minimum detectable HR with 80% power = 0.60	Feasibility analysis

Sample Size & Power Calculations for primary comparison (rivoraxiban vs. other DOACs)			
Population Assumptions	**Analysis**	**Range**	**Source for Estimated Parameters**
Assuming 1:1 PS matching with a total of 2,023 patients per group and an unstratified stroke risk of 27.41/1,000 patients	Minimum detectable HR with 80% power using intent to treat follow-up	Minimum detectable HR with 80% power = 0.58	Feasibility analysis

Measure	ATC Codes	Source
DOCA exposure (ATC Codes)		
rivaroxaban	B01AF02	
dibigatran	B01AF01	
apixaban	B01AF03	
edoxaban	B01AE07	
Covariate Drugs (ATC Codes)		
Antianemic preparations	B03*, B03X*	
Antiarrhythmics	C01B*	
Antihyperglycemics (other than Insulins)	A10BJ*, A10BX04, A10BX10, A10BX13, A10BX14, A10AE54, A10AE56, A10BX07, A10BH*, A10BD07, A10BD08, A10BD09,	
Antihypertensives	C09A*, C09B*, C09C*, C09D*, C09XA*, C08*, C07AA, C07AA01, C07AA02, C07AA03, C07AA05, C07AA06, C07AA07, C07A	
Antineoplastics	L01*, L02*	
Antiplatelets (excluding Aspirin)	B01AC, B01AC01, B01AC02, B01AC03, B01AC04, B01AC05, B01AC07, B01AC08, B01AC09, B01AC10, B01AC11, B01AC1	
Antipsychotics (Excluding BZD)	N05A*	
Aspirin	B01AC06, B01AC56, N02BA01	
Benzodiazepines (BZD)	N03AE01, N05BA*, N05CF*, N05CD*	
Bisphosphonates and other agents affecting bone structure	M05BA*, M05BB*, M05BC*, M05BX*	
Cardiac Stimulants	C01AA*, C01CA*, C01CE*	
GI Protective Agents	A02A*, A02BA*, A02BC*, A02BD*, A02BB01, A02BB02	
Insulin	A10A*	
Lipid Lowering Agents	C10AA*, C10BA*, C10BX*, C10AB*	
Nitrates Cardiac Vasodilators	C01DA*	
NSAIDs (Excluding Aspirin & APAP)	M01A*	
Opioid Analgesics	N02A*	
Other Antidepressants (Excluding SSRI)	N06A, N06AA*, N06AF*, N06AG*, N06AX*	
Other Antiepileptics (Excluding BZD)	N03AA*, N03AB*, N03AC*, N03AD*, N03AF*, N03AG*, N03AX*	
SSRI	N06AB*	
Systemic Antibiotics	P02*, J01*, J02*, D01B*, P01B*, J04*, P01A*, P01C*	
Systemic Antivirals	J05*	
Systemic Corticosteroids	H02A*, H02B*	
Vaccines and Immunoglobulins	J06*, J07*	
Warfarin	B01AA03	

Measure	READ Codes	ICD10 codes	READ Code Source	ICD10 Code Source
Chort Inclusion/Exclusion Criteria				
Atrial Fibrillation	INUK.3272.00 ECG: ATRIAL FIBRILLATION INUK.3273.00	N/A	Ruigómez A, Vora P, Balabanova Y, et al. Discontinuation of non-Vitamin K antagoni oral anticoagulants in patients with non-valvular atrial fibrillation: a population-base cohort study using primary care data from The Health Improvement Network in the U [published correction appears in BMJ Ope 2020 Apr 16;10(4):e031342corr1]. BMJ Open. 2019;9(10):e031342. Published 201 Oct 18. doi:10.1136/bmjopen-2019-03134	N/A
Mitral Stenosis	INUK.G110.00 Mitral stenosis INUK.G110.11 Rheumatic n	N/A	Ruigómez A, Vora P, Balabanova Y, et al. Discontinuation of non-Vitamin K antagoni oral anticoagulants in patients with non-valvular atrial fibrillation: a population-base cohort study using primary care data from The Health Improvement Network in the U [published correction appears in BMJ Ope 2020 Apr 16;10(4):e031342corr1]. BMJ Open. 2019;9(10):e031342. Published 201 Oct 18. doi:10.1136/bmjopen-2019-03134	N/A

Valvular Replacement	INUK.7910.12 Replacement of mitral valve INUK.7910000	N/A	Ruigómez A, Vora P, Balabanova Y, et al. Discontinuation of non-Vitamin K antagoni oral anticoagulants in patients with non- valvular atrial fibrillation: a population-base cohort study using primary care data from The Health Improvement Network in the U [published correction appears in BMJ Ope 2020 Apr 16;10(4):e031342corr1]. BMJ Open. 2019;9(10):e031342. Published 201 Oct 18. doi:10.1136/bmjopen-2019-03134	N/A
Pulmonary Embolism	INUK.G401100 Recurrent pulmonary embolism INUK.G40100	N/A	Ruigómez A, Vora P, Balabanova Y, et al. Discontinuation of non-Vitamin K antagoni oral anticoagulants in patients with non- valvular atrial fibrillation: a population-base cohort study using primary care data from The Health Improvement Network in the U [published correction appears in BMJ Ope 2020 Apr 16;10(4):e031342corr1]. BMJ Open. 2019;9(10):e031342. Published 201 Oct 18. doi:10.1136/bmjopen-2019-03134	N/A
Deep Vein Thrombosis	INUK.G801.11 Deep vein thrombosis INUK.G801.12 Deep	N/A	Ruigómez A, Vora P, Balabanova Y, et al. Discontinuation of non-Vitamin K antagoni oral anticoagulants in patients with non- valvular atrial fibrillation: a population-base cohort study using primary care data from The Health Improvement Network in the U [published correction appears in BMJ Ope 2020 Apr 16;10(4):e031342corr1]. BMJ Open. 2019;9(10):e031342. Published 201 Oct 18. doi:10.1136/bmjopen-2019-03134	N/A
Exclusion criteria and outcomes				
Stroke (Ischemic and Hemorrhagic)	INUK.G60..00, INUK.G600.00, INUK.G601.00, INUK.G602.00, INUK.G603.00, INUK.G604.00, INUK.G605.00, INUK.G606.00, INUK.G60X.00, INUK.G60z.00, INUK.G61..00, INUK.G61..11, INUK.G61..12, INUK.G610.00, INUK.G611.00, INUK.G612.00, INUK.G613.00, INUK.G614.00, INUK.G615.00, INUK.G616.00, INUK.G617.00, INUK.G618.00, INUK.G619.00, INUK.G61X.00, INUK.G61X000, INUK.G61X100, INUK.G61z.00, INUK.G63y000, INUK.G63y100, INUK.G64..00, INUK.G64..11, INUK.G64..12, INUK.G64..13, INUK.G640.00, INUK.G640000, INUK.G641.00, INUK.G641.11, INUK.G641000, INUK.G64z.00, INUK.G64z.11, INUK.G64z.12, INUK.G64z000, INUK.G64z100, INUK.G64z111, INUK.G64z200, INUK.G64z300, INUK.G64z400, INUK.G66..00, INUK.G66..11, INUK.G66..12, INUK.G66..13, INUK.G667.00, INUK.G668.00, INUK.G676000, INUK.G6W..00, INUK.G6X..00, INUK.Gyu6000, INUK.Gyu6100, INUK.Gyu6200, INUK.Gyu6300, INUK.Gyu6E00, INUK.Gyu6F00, INUK.Gyu6G00	I60*, I61*, I63*	Rannikmäe K, Ngoh K, Bush K, Al-Shahi Salman R, Doubal F, Flaig R, Henshall DE Hutchison A, Nolan J, Osborne S, Samarasekera N, Schnier C, Whiteley W, Wilkinson T, Wilson K, Woodfield R, Zhan Q, Allen N, Sudlow CLM. Accuracy of identifying incident stroke cases from linke health care data in UK Biobank. Neurology 2020 Aug 11;95(6):e697-e707. doi: 10.1212/WNL.0000000000009924. Epub 2020 Jul 2. PMID: 32616677; PMCID: PMC7455356.	Rannikmäe K, Ngoh K, Bush K, Al-Shahi Salman R, Doubal F, Flaig R, Henshall DE Hutchison A, Nolan J, Osborne S, Samarasekera N, Schnier C, Whiteley W, Wilkinson T, Wilson K, Woodfield R, Zhan Q, Allen N, Sudlow CLM. Accuracy of identifying incident stroke cases from linke health care data in UK Biobank. Neurology 2020 Aug 11;95(6):e697-e707. doi: 10.1212/WNL.0000000000009924. Epub 2020 Jul 2. PMID: 32616677; PMCID: PMC7455356.

Myocardial Infarction	INUK.3235.00, INUK.G30..12, INUK.G30..13, INUK.G30..14, INUK.G30..16, INUK.G301.00, INUK.G301z00, INUK.G302.00, INUK.G305.00, INUK.G306.00, INUK.G307.00, INUK.G307100, INUK.G308.00, INUK.G30A.00, INUK.G30X.00, INUK.G30y100, INUK.G30yz00, INUK.G30z.00, INUK.G31y100, INUK.G35..00, INUK.G351.00, INUK.G363.00, INUK.G365.00, INUK.G501.00, INUK.G5y6.00, INUK.Gyu3100, INUK.Gyu3400, INUK.3233.00, INUK.3234.00, INUK.3236.00, INUK.323Z.00, INUK.G30..00, INUK.G30..11, INUK.G30..15, INUK.G30..17, INUK.G300.00, INUK.G301000, INUK.G301100, INUK.G303.00, INUK.G304.00, INUK.G307000, INUK.G309.00, INUK.G30B.00, INUK.G30X000, INUK.G30y.00, INUK.G30y000, INUK.G30y200, INUK.G350.00, INUK.G353.00, INUK.G35X.00, INUK.G36..00, INUK.G360.00, INUK.G361.00, INUK.G362.00, INUK.G364.00, INUK.G366.00, INUK.Gyu3500, INUK.Gyu3600	I21*, I22*	Arana A, Margulis AV, Varas-Lorenzo C, Bui CL, Gilsenan A, McQuay LJ, Reynolds M, Rebordosa C, Franks B, de Vogel S, Appenteng K, Perez-Gutthann S. Validatio of cardiovascular outcomes and risk factor in the Clinical Practice Research Datalink in the United Kingdom. Pharmacoepidemio Drug Saf. 2021 Feb;30(2):237-247. doi: 10.1002/pds.5150. Epub 2020 Oct 28. PM 33091194; PMCID: PMC7821285.	Metcalfe A, Neudam A, Forde S, et al. Cas definitions for acute myocardial infarction i administrative databases and their impact on in-hospital mortality rates. Health Serv Res. 2013;48(1):290-318. doi:10.1111/j.14 6773.2012.01440.x
TIA	Fyu5500 [X]Other transient cerebral ischaemic attacks + related syndromes G65..00 Transient cerebral ischaemia G65..11 Drop attack G65..12 Transient ischaemic attack G65..13 Vertebro-basilar insufficiency G650.00 Basilar artery syndrome G650.11 Insufficiency - basilar artery G651.00 Vertebral artery syndrome G651000 Vertebro-basilar artery syndrome G652.00 Subclavian steal syndrome G653.00 Carotid artery syndrome hemispheric G654.00 Multiple and bilateral precerebral artery syndromes G656.00 Vertebrobasilar insufficiency G657.00 Carotid territory transient ischaemic attack G65y.00 Other transient cerebral ischaemia G65z.00 Transient cerebral ischaemia NOS G65z000 Impending cerebral ischaemia G65z100 Intermittent cerebral ischaemia G65zz00 Transient cerebral ischaemia NOS	G45.x*	Moran GM, Calvert M, Feltham MG, Ryan R, Marshall T. A retrospective cohort study to investigate fatigue, psychological or cognitive impairment after TIA: protocol paper. BMJ Open. 2015;5(4):e008149. Published 2015 May 3. doi:10.1136/bmjop 2015-008149	Andrade SE, Harrold LR, Tjia J, et al. A systematic review of validated methods fo identifying cerebrovascular accident or transient ischemic attack using administrative data. Pharmacoepidemiol Drug Saf. 2012;21 Suppl 1(Suppl 1):100-128. doi:10.1002/pds.2312
Intracranial Hemorrhage	INUK.G60..00, INUK.G600.00, INUK.G603.00, INUK.G604.00, INUK.G605.00, INUK.G606.00, INUK.G61..00, INUK.G610.00, INUK.G613.00, INUK.G614.00, INUK.G615.00, INUK.G616.00, INUK.G617.00, INUK.G61X100, INUK.G620.00, INUK.Gyu6100, INUK.Gyu6F00, INUK.G601.00, INUK.G602.00, INUK.G60z.00, INUK.G611.00, INUK.G612.00, INUK.G618.00, INUK.G61X.00, INUK.G61X000, INUK.G621.00, INUK.G623.00, INUK.G62z.00, INUK.Gyu6200, INUK.S626.00	I60.0, I60.1, I60.11, I60.12, I60.2, I60.21, I60.30, I60.32, I6 I60.8, I61, I61.1, I61.4, I61.5, I61.8, I62, I62.0, I62.01, I62.1 I60.00, I60.01, I60.02, I60.10, I60.20, I60.22, I60.3, I60.31, I60.4, I60.5, I60.50, I60.51, I60.52, I60.6, I60.9, I61.0, I61.2 I61.3, I61.6, I61.9, I62.00, I62.02, I62.03, I62.9, S06.4	Pasea L, Chung SC, Pujades-Rodriguez M et al. Bleeding in cardiac patients prescribe antithrombotic drugs: electronic health record phenotyping algorithms, incidence, trends and prognosis. BMC Med. 2019;17(1):206. Published 2019 Nov 20. doi:10.1186/s12916-019-1438-y	Pasea L, Chung SC, Pujades-Rodriguez M et al. Bleeding in cardiac patients prescribe antithrombotic drugs: electronic health record phenotyping algorithms, incidence, trends and prognosis. BMC Med. 2019;17(1):206. Published 2019 Nov 20. doi:10.1186/s12916-019-1438-y
Gastrointestinal Hemorrhage	INUK.196B.00, INUK.19E6.00, INUK.4737.11, INUK.4A23.00, INUK.4A23.11, INUK.4A5..00, INUK.4A5..11, INUK.4A51.00, INUK.G850.00, INUK.J110100, INUK.J110300, INUK.J111111, INUK.J121111, INUK.J121300, INUK.J12y300, INUK.J12yy00, INUK.J130300, INUK.J140100, INUK.J150000, INUK.J573.00, INUK.J573000, INUK.J68..00, INUK.J680.00, INUK.J680.11, INUK.J681.00, INUK.J681.11, INUK.J681.12, INUK.J681.13, INUK.J68z000, INUK.J68z100, INUK.SE22300, INUK.196C.00, INUK.19E4.12, INUK.19E6.11, INUK.479..11, INUK.4A5Z.00, INUK.7619100, INUK.G852000, INUK.J10y000, INUK.J110111, INUK.J111100, INUK.J111300, INUK.J11y100, INUK.J11yy00, INUK.J120100, INUK.J120300, INUK.J121100, INUK.J12y100, INUK.J130100, INUK.J131100, INUK.J13y100, INUK.J13y300, INUK.J14y100, INUK.J510900, INUK.J573011, INUK.J573012, INUK.J573100, INUK.J573z00, INUK.J68z.00, INUK.J68z.11, INUK.J68z200, INUK.J68zz00, INUK.SE23111, INUK.1994.00, INUK.1994.11, INUK.1995.00, INUK.4762.00, INUK.4762.11	I85.01, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K K29.01, K62.5, K66.1, K92.0, K92.2, K92.1	Pasea L, Chung SC, Pujades-Rodriguez M et al. Bleeding in cardiac patients prescribe antithrombotic drugs: electronic health record phenotyping algorithms, incidence, trends and prognosis. BMC Med. 2019;17(1):206. Published 2019 Nov 20. doi:10.1186/s12916-019-1438-y	Pasea L, Chung SC, Pujades-Rodriguez M et al. Bleeding in cardiac patients prescribe antithrombotic drugs: electronic health record phenotyping algorithms, incidence, trends and prognosis. BMC Med. 2019;17(1):206. Published 2019 Nov 20. doi:10.1186/s12916-019-1438-y

Urogenital Hemorrhage	INUK.1A45.00, INUK.K167.00, INUK.K197.00, INUK.K197000, INUK.K197300, INUK.K19y411, INUK.K221100, INUK.K275200, INUK.K56y100, INUK.K575.00, INUK.K59yy00, INUK.K5E0.00, INUK.K5Ez.00, INUK.K16y200, INUK.K197100, INUK.K197400, INUK.K19y400, INUK.K275100, INUK.K286100, INUK.K286400, INUK.K286v00, INUK.K286w00, INUK.K537.00, INUK.K55y300, INUK.K566.00, INUK.K59yx00, INUK.K5E..00, INUK.K5E1.00, INUK.K5E2.00, INUK.Kyu9D00, INUK.1584.00	N02, N02.0, N02.1, N02.2, N02.3, N02.4, N02.5, N02.6, N02.7, N02.8, N02.9, N02.A, N93, N93.0, N93.1, N93.8, N93.9, R31, R31.0, R31.1, R31.2, R31.21, R31.29, R31.9, N42.1, N83.6, N83.7, N85.7, N89.7, N92.1, N95.0	Pasea L, Chung SC, Pujades-Rodriguez M et al. Bleeding in cardiac patients prescribed antithrombotic drugs: electronic health record phenotyping algorithms, incidence, trends and prognosis. BMC Med. 2019;17(1):206. Published 2019 Nov 20. doi:10.1186/s12916-019-1438-y	Pasea L, Chung SC, Pujades-Rodriguez M et al. Bleeding in cardiac patients prescribed antithrombotic drugs: electronic health record phenotyping algorithms, incidence, trends and prognosis. BMC Med. 2019;17(1):206. Published 2019 Nov 20. doi:10.1186/s12916-019-1438-y
Major Bleeding Events	*See "Intracranial Hemorrhage", "Gastrointestinal Hemorrhage", and "Major Bleeding Events" above*	*See "Intracranial Hemorrhage", "Gastrointestinal Hemorrhage", and "Major Bleeding Events" above*		
Angina	INUK.G311.11, INUK.G311.13, INUK.G311.14, INUK.G311100, INUK.G311200, INUK.G311300, INUK.G311400, INUK.G33..00, INUK.G330.00, INUK.G330000, INUK.G330z00, INUK.G331.00, INUK.G331.11, INUK.G33z.00, INUK.G33z300, INUK.G33z500, INUK.G33z600, INUK.G33z700, INUK.G33zz00, INUK.Gyu3000	I20.0, I20.1, I20.8, I20.9, I25.110, I25.700, I25.710, I25.750 I25.760, I25.790, I20, I23.7, I25.720, I25.730		
Covariate Conditions				
Acute Kidney Injury	INUK.K04..12, INUK.14D8.00, INUK.K04C.00, INUK.K04D.00, INUK.K04E.00, INUK.K04..00, INUK.K04..11, INUK.K043000, INUK.K043100, INUK.K043200, INUK.K043300, INUK.K043400, INUK.K044.00, INUK.K045.00, INUK.K046.00, INUK.K046000, INUK.K046100, INUK.K047.00, INUK.K048.00, INUK.K049.00, INUK.K04A.00, INUK.K04B.00, INUK.K04y.00, INUK.K04z.00, INUK.Kyu2000, INUK.SK08.00	N17*		Tomlinson, L.A., Riding, A.M., Payne, R.A. et al. The accuracy of diagnostic coding for acute kidney injury in England – a single centre study. BMC Nephrol 14, 58 (2013). https://doi.org/10.1186/1471-2369-14-58
Anemia	INUK.1453.00, INUK.1454.00, INUK.2C2..00, INUK.B937000, INUK.B937200, INUK.B937300, INUK.B937600, INUK.B937700, INUK.B937800, INUK.BBmA.00, INUK.BBmL.00, INUK.D0…11, INUK.D0…12, INUK.D00..12, INUK.D000.00, INUK.D000.11, INUK.D00y.00, INUK.D00yz00, INUK.D00z.00, INUK.D00zz00, INUK.D01..00, INUK.D010.11, INUK.D011.11, INUK.D011z00, INUK.D012000, INUK.D012111, INUK.D012500, INUK.D013000, INUK.D013z00, INUK.D014z00, INUK.D01y.00, INUK.D01y011, INUK.D01y012, INUK.D01yy00, INUK.D01z.11, INUK.D01z000, INUK.D0y..00, INUK.D102000, INUK.D102200, INUK.D102y00, INUK.D102z00, INUK.D103.00, INUK.D103000, INUK.D103100, INUK.D104.12, INUK.D106.00, INUK.D106100, INUK.D106300, INUK.D106400, INUK.D106z00, INUK.D10yz00, INUK.D11..00, INUK.D110.00, INUK.D110000, INUK.D110100, INUK.D110200, INUK.D110400, INUK.D111.00, INUK.D111000, INUK.D111100, INUK.D111400, INUK.D111500, INUK.D111y00, INUK.D111z00, INUK.D112z12, INUK.D1y..00, INUK.D1z..00, INUK.D200.00, INUK.D200011, INUK.D200100, INUK.D201.11, INUK.D201000, INUK.D201100, INUK.D201111, INUK.D201200, INUK.D201300, INUK.D201311, INUK.D201700, INUK.D201z00, INUK.D204.00, INUK.D20z.00, INUK.D21..00, INUK.D210100, INUK.D210300, INUK.D210400, INUK.D211.00, INUK.D212.00, INUK.D213.00, INUK.D215.00, INUK.D21y.00, INUK.D21y000, INUK.D21y011, INUK.D21z.00, INUK.D21z.12, INUK.D21z.13, INUK.D2z..00, INUK.D41yz11, INUK.Dyu0.00, INUK.Dyu0000, INUK.Dyu0100, INUK.Dyu0200, INUK.Dyu0300, INUK.Dyu0400, INUK.Dyu1.00, INUK.Dyu1000, INUK.Dyu1400, INUK.Dyu1700, INUK.Dyu2100, INUK.Dyu2200, INUK.Dyu2400, INUK.F381500, INUK.145..11, INUK.1451.00, INUK.1452.00, INUK.1458.00, INUK.2C2Z.00, INUK.B937100, INUK.B937X00, INUK.BBMA.00, INUK.ByuHC00, INUK.D0…00, INUK.D00..00, INUK.D00..11, INUK.D000.12, INUK.D001.00, INUK.D00y100, INUK.D00z000, INUK.D00z100, INUK.D00z200, INUK.D01..11, INUK.D010.00, INUK.D010.12, INUK.D011.00, INUK.D011000, INUK.D011013, INUK.D011100, INUK.D011X00, INUK.D012.00, INUK.D012.11, INUK.D012100, INUK.D012112, INUK.D012200, INUK.D012300, INUK.D012400, INUK.D012z00, INUK.D013.00, INUK.D014.00, INUK.D014000,	D50.0, D50.1, D50.8, D50.9, D51.0, D51.1, D51.2, D51.3, D51.8, D51.9, D52.0, D52.1, D52.8, D52.9, D53.0, D53.1, D53.2, D53.8, D53.9, D55.0, D55.1, D55.2, D55.3, D55.8, D55.9, D56.0, D56.1, D56.2, D56.3, D56.4, D56.5, D56.8, D56.9, D58.0, D58.1, D58.2, D58.8, D58.9, D59.0, D59.1, D59.2, D59.3, D59.4, D59.5, D59.6, D59.8, D59.9, D60.0, D60.1, D60.8, D60.9, D61.01, D61.09, D61.1, D61.2, D61. D61.810, D61.811, D61.818, D61.82, D61.89, D61.9, D63 D63.1, D63.8, D64.0, D64.1, D64.2, D64.3, D64.4, D64.89 D64.9, D57.00, D57.01, D57.02, D57.1, D57.20, D57.211, D57.212, D57.219, D57.3, D57.40, D57.411, D57.412, D57.419, D57.80, D57.811, D57.812, D57.819		CCS 0059, Deficiency and other anemia CCS 0061, Sickle cell anemia Elixhauser A, Steiner C, Palmer L. Clinical Classifications Software (CCS), 2018. U.S Agency for Healthcare Research and Quality. Available https://www.hcup-us.ahrq.gov/tools_software.jsp

Asthma or COPD	INUK.173d.00, INUK.1780.00, INUK.1781.00, INUK.1782.00, INUK.1783.00, INUK.1785.00, INUK.1786.00, INUK.1787.00, INUK.178A.00, INUK.178B.00, INUK.663N000, INUK.663N100, INUK.663O000, INUK.663P.00, INUK.663P100, INUK.663U.00, INUK.663V000, INUK.663V200, INUK.663V300, INUK.663e100, INUK.663j.00, INUK.663n.00, INUK.663r.00, INUK.663s.00, INUK.663t.00, INUK.663w.00, INUK.663x.00, INUK.66Ys.00, INUK.H312000, INUK.H33..00, INUK.H330.00, INUK.H330.11, INUK.H330.14, INUK.H330011, INUK.H331.00, INUK.H331.11, INUK.H331111, INUK.H335.00, INUK.H33z011, INUK.H33z200, INUK.H33zz00, INUK.H33zz12, INUK.H35y600, INUK.H35y700, INUK.14B4.00, INUK.1784.00, INUK.1788.00, INUK.1789.00, INUK.1O2..00, INUK.663J.00, INUK.663N.00, INUK.663N200, INUK.663P000, INUK.663P200, INUK.663R.00, INUK.663S.00, INUK.663T.00, INUK.663V100, INUK.663W.00, INUK.663X.00, INUK.663e000, INUK.663f.00, INUK.663p.00, INUK.663u.00, INUK.66YS.00, INUK.8H2P.00, INUK.H33..11, INUK.H330.12, INUK.H330.13, INUK.H330111, INUK.H330z00, INUK.H331z00, INUK.H332.00, INUK.H333.00, INUK.H334.00, INUK.H33z.00, INUK.H33z100, INUK.H33z111, INUK.H33zz11, INUK.H47y000, INUK.173c.00, INUK.66YQ.00, INUK.66Yq.00, INUK.173A.00, INUK.663H.00, INUK.663O.00, INUK.663Q.00, INUK.663V.00, INUK.663h.00, INUK.663o.00, INUK.663q.00, INUK.663v.00, INUK.66YP.00, INUK.66YR.00, INUK.66Yp.00, INUK.66Yr.00, INUK.H330000, INUK.H330100, INUK.H331000, INUK.H331100, INUK.H33z000, INUK.66YG.00, INUK.66YH.00, INUK.H3…00, INUK.H310.00, INUK.H310z00, INUK.H311100, INUK.H311z00, INUK.H312.00, INUK.H312100, INUK.H313.00, INUK.H31y.00, INUK.H31yz00, INUK.H32..00, INUK.H320300, INUK.H320z00, INUK.H32y111, INUK.H32y200, INUK.H32yz00, INUK.H32z.00, INUK.H37..00, INUK.H39..00, INUK.H3B..00, INUK.H3y..11, INUK.H581.00, INUK.Hyu3000, INUK.J650200, INUK.K101400, INUK.14B3.12, INUK.66Yg.00, INUK.66Yh.00, INUK.H31..00, INUK.H311.00, INUK.H311000, INUK.H312z00, INUK.H31z.00, INUK.H320.00, INUK.H320000, INUK.H320100, INUK.H320200, INUK.H321.00, INUK.H322.00, INUK.H32y.00, INUK.H32y000, INUK.H32y100, INUK.H36..00, INUK.H38..00, INUK.H3z..11,	J45*, J46*, J82.83, J41*, J42*, J43*, J44*		Khakban A, FitzGerald JM, Tavakoli H, Lynd L, Ehteshami-Afshar S, Sadatsafavi Extent, trends, and determinants of controller/reliever balance in mild asthma: 14-year population-based study. Respir Res. 2019;20(1):44. Published 2019 Feb 2 doi:10.1186/s12931-019-1007-0
Chronic Kidney Disease	INUK.K05..13, INUK.K05..00, INUK.D215000, INUK.K0E..00, INUK.Kyu2100, INUK.1Z1..00, INUK.1Z10.00, INUK.1Z11.00, INUK.1Z12.00, INUK.1Z13.00, INUK.1Z14.00, INUK.1Z15.00, INUK.1Z16.00, INUK.1Z17.00, INUK.1Z18.00, INUK.1Z19.00, INUK.1Z1A.00, INUK.1Z1B.00, INUK.1Z1C.00, INUK.1Z1D.00, INUK.1Z1E.00, INUK.1Z1F.00, INUK.1Z1G.00, INUK.1Z1H.00, INUK.1Z1J.00, INUK.1Z1K.00, INUK.1Z1L.00, INUK.K051.00, INUK.K052.00, INUK.K053.00, INUK.K054.00, INUK.K055.00, INUK.1Z17.11, INUK.1Z18.11, INUK.1Z19.11, INUK.1Z1A.11, INUK.1Z1B.11, INUK.1Z1C.11, INUK.1Z1D.11, INUK.1Z1E.11, INUK.1Z1F.11, INUK.1Z1G.11, INUK.1Z1H.11, INUK.1Z1J.11, INUK.1Z1K.11, INUK.1Z1L.11, INUK.1Z1M.00, INUK.1Z1N.00, INUK.1Z1P.00, INUK.1Z1Q.00, INUK.1Z1R.00, INUK.1Z1S.00, INUK.1Z1T.00, INUK.1Z1V.00, INUK.1Z1W.00, INUK.1Z1X.00, INUK.1Z1Y.00, INUK.1Z1Z.00, INUK.1Z1a.00, INUK.1Z1b.00, INUK.1Z1c.00, INUK.1Z1d.00, INUK.1Z1e.00, INUK.1Z1f.00, INUK.66i..00, INUK.6AA..00, INUK.8L50.00, INUK.D215.00, INUK.G22..11, INUK.K05..11, INUK.K06..00, INUK.K06..11, INUK.K060.00, INUK.K08..00, INUK.K08z.00, INUK.K0D..00, INUK.SP08300	N18, N18.1, N18.2, N18.3, N18.30, N18.31, N18.32, N18.4 N18.5, N18.9	Denburg MR, Haynes K, Shults J, Lewis JD, Leonard MB. Validation of The Health Improvement Network (THIN) database fo epidemiologic studies of chronic kidney disease. Pharmacoepidemiol Drug Saf. 2011;20(11):1138-1149. doi:10.1002/pds.2203	

Dementia	INUK.1461.00, INUK.E001000, INUK.E001100, INUK.E001200, INUK.E001z00, INUK.E002.00, INUK.E002100, INUK.E004.00, INUK.E004.11, INUK.E004000, INUK.E004200, INUK.E004300, INUK.E004z00, INUK.E012.00, INUK.E012.11, INUK.E02y100, INUK.E041.00, INUK.Eu00200, INUK.Eu00z11, INUK.Eu01.00, INUK.Eu01100, INUK.Eu01111, INUK.Eu02.00, INUK.Eu02000, INUK.Eu02100, INUK.Eu02300, INUK.Eu02500, INUK.Eu02y00, INUK.Eu02z11, INUK.Eu02z13, INUK.Eu02z16, INUK.Eu04100, INUK.Eu84311, INUK.E00..11, INUK.E00..12, INUK.E000.00, INUK.E001.00, INUK.E001300, INUK.E002000, INUK.E002z00, INUK.E003.00, INUK.E004100, INUK.Eu00.00, INUK.Eu00000, INUK.Eu00011, INUK.Eu00012, INUK.Eu00100, INUK.Eu00112, INUK.Eu00113, INUK.Eu00z00, INUK.Eu01.11, INUK.Eu01000, INUK.Eu01200, INUK.Eu01300, INUK.Eu01y00, INUK.Eu01z00, INUK.Eu02200, INUK.Eu02400, INUK.Eu02z00, INUK.Eu02z14, INUK.Eu10711, INUK.F118100	F01, F01.5, F01.50, F01.51, F02, F02.8, F02.80, F02.81, F F03.9, F03.90, F03.91, G31.0, G31.09, G31.83		Quan H, Li B, Saunders LD, et al. Assessi validity of ICD-9-CM and ICD-10 administrative data in recording clinical conditions in a unique dually coded database. Health Serv Res. 2008;43(4):14 1441. doi:10.1111/j.1475-6773.2007.0082
Diabetes Mellitus	INUK.C100.00, INUK.C100100, INUK.C101.00, INUK.C101000, INUK.C101y00, INUK.C101z00, INUK.C102.00, INUK.C102100, INUK.C103.00, INUK.C103000, INUK.C103y00, INUK.C103z00, INUK.C104100, INUK.C104z00, INUK.C105.00, INUK.C105000, INUK.C105100, INUK.C105y00, INUK.C105z00, INUK.C106.12, INUK.C106.13, INUK.C107.00, INUK.C107.11, INUK.C107100, INUK.C108.00, INUK.C108.11, INUK.C108011, INUK.C108012, INUK.C108312, INUK.C108412, INUK.C108500, INUK.C108700, INUK.C108711, INUK.C108712, INUK.C108800, INUK.C108811, INUK.C108900, INUK.C108911, INUK.C108A11, INUK.C108D00, INUK.C108E11, INUK.C108E12, INUK.C108F00, INUK.C108F11, INUK.C108F12, INUK.C108G11, INUK.C108G12, INUK.C108H00, INUK.C108H11, INUK.C108H12, INUK.C109.00, INUK.C109.13, INUK.C109000, INUK.C109011, INUK.C109012, INUK.C109200, INUK.C109211, INUK.C109212, INUK.C109312, INUK.C109400, INUK.C109411, INUK.C109412, INUK.C109511, INUK.C109512, INUK.C109611, INUK.C109900, INUK.C109911, INUK.C109A00, INUK.C109A11, INUK.C109C11, INUK.C109D11, INUK.C109E11, INUK.C109E12, INUK.C109F11, INUK.C109F12, INUK.C109G00, INUK.C109G12, INUK.C109H12, INUK.C109J00, INUK.C109J11, INUK.C109J12, INUK.C10C.00, INUK.C10D.00, INUK.C10D.11, INUK.C10E.12, INUK.C10E000, INUK.C10E012, INUK.C10E200, INUK.C10E211, INUK.C10E300, INUK.C10E411, INUK.C10E511, INUK.C10E611, INUK.C10E700, INUK.C10E711, INUK.C10E712, INUK.C10E800, INUK.C10E900, INUK.C10E911, INUK.C10E912, INUK.C10EA12, INUK.C10EB00, INUK.C10EB11, INUK.C10EB12, INUK.C10EC00, INUK.C10ED11, INUK.C10EE00, INUK.C10EE11, INUK.C10EF12, INUK.C10EH11, INUK.C10EH12, INUK.C10EJ11, INUK.C10EL11, INUK.C10EM00, INUK.C10EM11, INUK.C10EN11 INUK.C10EP00, INUK.C10EP11, INUK.C10EQ00, INUK.C10F.11, INUK.C10F000, INUK.C10F011, INUK.C10F111, INUK.C10F311, INUK.C10F411, INUK.C10F500, INUK.C10F511, INUK.C10F711, INUK.C10F900, INUK.C10FA00, INUK.C10FA11, INUK.C10FB00, INUK.C10FB11, INUK.C10FC00, INUK.C10FD00, INUK.C10FD11, INUK.C10FF00, INUK.C10FF11, INUK.C10FJ11, INUK.C10FK00, INUK.C10FK11, INUK.C10FL11, INUK.C10FM00, INUK.C10FN11, INUK.C10FP00, INUK.C10FP11, INUK.C10FQ00, INUK.C10FQ11,	E10, E10.1, E10.10, E10.11, E10.2, E10.21, E10.22, E10.3 E10.3, E10.31, E10.311, E10.319, E10.32, E10.321, E10.3 E10.3212, E10.3213, E10.3219, E10.329, E10.3291, E10. E10.3293, E10.3299, E10.33, E10.331, E10.3311, E10.33 E10.3313, E10.3319, E10.339, E10.3391, E10.3392, E10. E10.3399, E10.34, E10.341, E10.3411, E10.3412, E10.34 E10.3419, E10.349, E10.3491, E10.3492, E10.3493, E10. E10.35, E10.351, E10.3511, E10.3512, E10.3513, E10.35 E10.352, E10.3521, E10.3522, E10.3523, E10.3529, E10. E10.3531, E10.3532, E10.3533, E10.3539, E10.354, E10. E10.3542, E10.3543, E10.3549, E10.355, E10.3551, E10. E10.3553, E10.3559, E10.359, E10.3591, E10.3592, E10. E10.3599, E10.36, E10.37, E10.37X1, E10.37X2, E10.37X E10.37X9, E10.39, E10.4, E10.40, E10.41, E10.42, E10.4 E10.44, E10.49, E10.5, E10.51, E10.52, E10.59, E10.6, E10.61, E10.610, E10.618, E10.62, E10.620, E10.621, E10.622, E10.628, E10.63, E10.630, E10.638, E10.64, E10.641, E10.649, E10.65, E10.69, E10.8, E10.9, E11, E1 E11.00, E11.01, E11.1, E11.10, E11.11, E11.2, E11.21, E11.22, E11.29, E11.3, E11.31, E11.311, E11.319, E11.32 E11.321, E11.3211, E11.3212, E11.3213, E11.3219, E11. E11.3291, E11.3292, E11.3293, E11.3299, E11.33, E11.3 E11.3311, E11.3312, E11.3313, E11.3319, E11.339, E11. E11.3392, E11.3393, E11.3399, E11.34, E11.341, E11.34 E11.3412, E11.3413, E11.3419, E11.349, E11.3491, E11. E11.3493, E11.3499, E11.35, E11.351, E11.3511, E11.35 E11.3513, E11.3519, E11.352, E11.3521, E11.3522, E11. E11.3529, E11.353, E11.3531, E11.3532, E11.3533, E11. E11.354, E11.3541, E11.3542, E11.3543, E11.3549, E11. E11.3551, E11.3552, E11.3553, E11.3559, E11.359, E11. E11.3592, E11.3593, E11.3599, E11.36, E11.37, E11.37X E11.37X2, E11.37X3, E11.37X9, E11.39, E11.4, E11.40, E11.41, E11.42, E11.43, E11.44, E11.49, E11.5, E11.51, E11.52, E11.59, E11.6, E11.61, E11.610, E11.618, E11.62 E11.620, E11.621, E11.622, E11.628, E11.63, E11.630, E11.638, E11.64, E11.641, E11.649, E11.65, E11.69, E11 E11.9, E13*		Chi GC, Li X, Tartof SY, Slezak JM, Koebnick C, Lawrence JM. Validity of ICD- 10-CM codes for determination of diabetes type for persons with youth-onset type 1 a type 2 diabetes. BMJ Open Diabetes Res Care. 2019;7(1):e000547. Published 2019 Feb 16. doi:10.1136/bmjdrc-2018-000547

Heart Failure	INUK.G58..00, INUK.1O1..00, INUK.G580.00, INUK.G580.12, INUK.G580000, INUK.G580100, INUK.G580400, INUK.G582.00, INUK.G583.00, INUK.G583.11, INUK.G583.12, INUK.G585.00, INUK.G58z.00, INUK.G5y4z00, INUK.SP11111, INUK.G58..11, INUK.G580.11, INUK.G580200, INUK.G580300, INUK.G58z.12, INUK.L09y200, INUK.Q48y100, INUK.G232.00, INUK.G1yz100, INUK.G580.13, INUK.G580.14, INUK.G581.00, INUK.G581000, INUK.G584.00	I50*		Frolova N, Bakal JA, McAlister FA, Rowe BH, Quan H, Kaul P, Ezekowitz JA. Assessing the use of international classification of diseases-10th revision codes from the emergency department for the identification of acute heart failure. JACC Heart Fail. 2015 May;3(5):386-391. doi: 10.1016/j.jchf.2014.11.010. PMID: 25951759. Delekta J, Hansen SM, AlZuhairi KS, Bork CS, Joensen AM. The validity of the diagnosis of heart failure (I50.0-I50.9) in th Danish National Patient Register. Dan Me J. 2018 Apr;65(4):A5470. PMID: 2961992
Hypertension	INUK.G2…11, INUK.G2…00, INUK.G2…11, INUK.G20..00, INUK.G20..12, INUK.G200.00, INUK.G203.00, INUK.G20z.00, INUK.G21..00, INUK.G211.00, INUK.G211000, INUK.G211100, INUK.G211z00, INUK.G21z000, INUK.G21z011, INUK.G21z100, INUK.G22..00, INUK.G220.00, INUK.G222.00, INUK.G232.00, INUK.G240z00, INUK.G241.00, INUK.G24z.00, INUK.G26..11, INUK.G27..00, INUK.G28..00, INUK.G2y..00, INUK.G41y000, INUK.G41y100, INUK.Gyu2.00, INUK.Gyu2000, INUK.Gyu2100, INUK.J17B.00, INUK.G201.00, INUK.G202.00, INUK.G20z.11, INUK.G210.00, INUK.G210000, INUK.G210100, INUK.G210z00, INUK.G21z.00, INUK.G21zz00, INUK.G221.00, INUK.G22z.00, INUK.G22z.11, INUK.G23..00, INUK.G230.00, INUK.G231.00, INUK.G233.00, INUK.G23z.00, INUK.G24..00, INUK.G240.00, INUK.G240000, INUK.G241000, INUK.G241z00, INUK.G244.00, INUK.G24z000, INUK.G24z100, INUK.G24zz00, INUK.G25..00, INUK.G25..11, INUK.G26..00, INUK.G2z..00, INUK.G410.00, INUK.G672.11, INUK.G8y3.00, INUK.J623.00	I10*, I11*, I12*, I13*, I15*	Peng M, Chen G, Kaplan GG, Lix LM, Drummond N, Lucyk K, Garies S, Lowerison M, Weibe S, Quan H. Methods defining hypertension in electronic medica records: validation against national survey data. J Public Health (Oxf). 2016 Sep;38(3):e392-e399. doi: 10.1093/pubmed/fdv155. Epub 2015 Nov PMID: 26547088; PMCID: PMC5072168.	Tu K, Campbell NR, Chen ZL, Cauch-Dudek KJ, McAlister FA. Accuracy of administrative databases in identifying patients with hypertension. Open Med. 2007;1(1):e18-e26. Published 2007 Apr 1

Malignant Neoplasms	INUK.142E.00, INUK.142F.00, INUK.142G.00, INUK.B0...11, INUK.B00..00, INUK.B00..11, INUK.B000100, INUK.B000z00, INUK.B002.00, INUK.B002000, INUK.B003100, INUK.B003300, INUK.B004100, INUK.B006.00, INUK.B007.00, INUK.B00zz00, INUK.B010.00, INUK.B010000, INUK.B010z00, INUK.B011000, INUK.B011100, INUK.B012.00, INUK.B015.00, INUK.B01y.00, INUK.B02..00, INUK.B022.00, INUK.B03..00, INUK.B030.00, INUK.B031.00, INUK.B03y.00, INUK.B04y.00, INUK.B04z.00, INUK.B05..00, INUK.B050.11, INUK.B051z00, INUK.B053.00, INUK.B054.00, INUK.B055.00, INUK.B055100, INUK.B055z00, INUK.B05y.00, INUK.B05z000, INUK.B06..00, INUK.B060.00, INUK.B060100, INUK.B060z00, INUK.B062.00, INUK.B062000, INUK.B062300, INUK.B064000, INUK.B065.00, INUK.B066.00, INUK.B06y.00, INUK.B06yz00, INUK.B06z.00, INUK.B071100, INUK.B071z00, INUK.B072000, INUK.B072100, INUK.B074.00, INUK.B07y.00, INUK.B07z.00, INUK.B08..00, INUK.B0z1.00, INUK.B1...00, INUK.B10..00, INUK.B100.00, INUK.B101.00, INUK.B102.00, INUK.B104.00, INUK.B105.00, INUK.B106.00, INUK.B10y.00, INUK.B10z.00, INUK.B110.00, INUK.B110000, INUK.B110z00, INUK.B111000, INUK.B111100, INUK.B111z00, INUK.B112.00, INUK.B113.00, INUK.B11y.00, INUK.B11y100, INUK.B11yz00, INUK.B124.00, INUK.B12y.00, INUK.B13..00, INUK.B130.00, INUK.B131.00, INUK.B132.00, INUK.B136.00, INUK.B13y.00, INUK.B13z.00, INUK.B140.00, INUK.B142.00, INUK.B142000, INUK.B143.00, INUK.B14z.00, INUK.B15..00, INUK.B150.00, INUK.B150z00, INUK.B151000, INUK.B151z00, INUK.B160.00, INUK.B161100, INUK.B161300, INUK.B161z00, INUK.B16y.00, INUK.B17..00, INUK.B170.00, INUK.B171.00, INUK.B173.00, INUK.B175.00, INUK.B180.00, INUK.B180100, INUK.B180200, INUK.B180z00, INUK.B18y.00, INUK.B18y300, INUK.B18y600, INUK.B18yz00, INUK.B18z.00, INUK.B1z0.00, INUK.B1z1.00, INUK.B1zy.00, INUK.B200000, INUK.B200200, INUK.B200300, INUK.B200z00, INUK.B201000, INUK.B201100, INUK.B201200, INUK.B203.00, INUK.B206.00, INUK.B210.00, INUK.B213.00, INUK.B213000, INUK.B213100, INUK.B213300, INUK.B215.00, INUK.B21y.00, INUK.B22..00, INUK.B220.00, INUK.B220000, INUK.B220100, INUK.B221.00, INUK.B221000,	C00, C00.0, C00.1, C00.2, C00.3, C00.4, C00.5, C00.6, C00.8, C00.9, C01, C02, C02.0, C02.1, C02.2, C02.3, C02 C02.8, C02.9, C03, C03.0, C03.1, C03.9, C04, C04.0, C04 C04.8, C04.9, C05, C05.0, C05.1, C05.2, C05.8, C05.9, C C06.0, C06.1, C06.2, C06.8, C06.80, C06.89, C06.9, C07, C08, C08.0, C08.1, C08.9, C09, C09.0, C09.1, C09.8, C09 C10, C10.0, C10.1, C10.2, C10.3, C10.4, C10.8, C10.9, C C11.0, C11.1, C11.2, C11.3, C11.8, C11.9, I82.C11, C12, I82.C12, C13, C13.0, C13.1, C13.2, C13.8, C13.9, I82.C13 C14, C14.0, C14.2, C14.8, C15, C15.3, C15.4, C15.5, C15 C15.9, C16, C16.0, C16.1, C16.2, C16.3, C16.4, C16.5, C16.6, C16.8, C16.9, C17, C17.0, C17.1, C17.2, C17.3, C17.8, C17.9, C18, C18.0, C18.1, C18.2, C18.3, C18.4, C18.5, C18.6, C18.7, C18.8, C18.9, C19, I82.C19, C20, C C21.0, C21.1, C21.2, C21.8, I82.C21, C22, C22.0, C22.1, C22.2, C22.3, C22.4, C22.7, C22.8, C22.9, I82.C22, C23, I82.C23, C24, C24.0, C24.1, C24.8, C24.9, C25, C25.0, C25.1, C25.2, C25.3, C25.4, C25.7, C25.8, C25.9, C26, C26.0, C26.1, C26.9, C30, C30.0, C30.1, C31, C31.0, C31 C31.2, C31.3, C31.8, C31.9, C32, C32.0, C32.1, C32.2, C32.3, C32.8, C32.9, C33, C34, C34.0, C34.00, C34.01, C34.02, C34.1, C34.10, C34.11, C34.12, C34.2, C34.3, C34.30, C34.31, C34.32, C34.8, C34.80, C34.81, C34.82, C34.9, C34.90, C34.91, C34.92, C37, C38, C38.0, C38.1, C38.2, C38.3, C38.4, C38.8, C39, C39.0, C39.9, C40, C40 C40.00, C40.01, C40.02, C40.1, C40.10, C40.11, C40.12, C40.2, C40.20, C40.21, C40.22, C40.3, C40.30, C40.31, C40.32, C40.8, C40.80, C40.81, C40.82, C40.9, C40.90, C40.91, C40.92, C41, C41.0, C41.1, C41.2, C41.3, C41.4, C41.9, C43, C43.0, C43.1, C43.10, C43.11, C43.111, C43.112, C43.12, C43.121, C43.122, C43.2, C43.20, C43 C43.22, C43.3, C43.30, C43.31, C43.39, C43.4, C43.5, C43.51, C43.52, C43.59, C43.6, C43.60, C43.61, C43.62, C43.7, C43.70, C43.71, C43.72, C43.8, C43.9, C44, C44.0 C44.00, C44.01, C44.02, C44.09, C44.1, C44.10, C44.101 C44.102, C44.1021, C44.1022, C44.109, C44.1091, C44.1092, C44.11, C44.111, C44.112, C44.1121, C44.112		
Non Major Bleeding	INUK.14c..00, INUK.14c..11, INUK.16R..00, INUK.1928.00, INUK.1C6..00, INUK.1C6..11, INUK.2BB5.00, INUK.2BB8.00, INUK.2D25.00, INUK.F42y.11, INUK.F42y100, INUK.F42y500, INUK.F436000, INUK.F436100, INUK.F4C7200, INUK.F4K7.00, INUK.FyuH400, INUK.N091.00, INUK.N091000, INUK.N091100, INUK.N091200, INUK.N091500, INUK.N091600, INUK.N091611, INUK.N091711, INUK.N091800, INUK.N091900, INUK.N091B00, INUK.N091C00, INUK.N091K00, INUK.N091L00, INUK.N091M00, INUK.N091N00, INUK.N091Q00, INUK.N091R00, INUK.N091S00, INUK.N091T00, INUK.N091z00, INUK.R048.00, INUK.R063000, INUK.R063100, INUK.Ryu0200, INUK.14C..00, INUK.14C..11, INUK.1C62.00, INUK.1C6Z.00, INUK.2556.00, INUK.2DE7.00, INUK.F42y300, INUK.F42y400, INUK.F436.00, INUK.F436z00, INUK.F4C7100, INUK.F4Ey000, INUK.F4G3200, INUK.F4H4100, INUK.F4K2800, INUK.J017200, INUK.N091211, INUK.N091300, INUK.N091311, INUK.N091400, INUK.N091511, INUK.N091700, INUK.N091A00, INUK.N091D00, INUK.N091E00, INUK.N091F00, INUK.N091G00, INUK.N091H00, INUK.N091J00, INUK.N091P00, INUK.N091U00, INUK.N091V00, INUK.R047.00, INUK.Ryu0700	R04, R04.1, R04.2, R04.8, R04.81, R04.89, R04.9, H35.6, H35.60, H35.61, H35.62, H35.63, H43.1, H43.10, H43.11, H43.12, H43.13, M25.0, M25.00, M25.01, M25.011, M25.0 M25.019, M25.02, M25.021, M25.022, M25.029, M25.03, M25.031, M25.032, M25.039, M25.04, M25.041, M25.042 M25.049, M25.05, M25.051, M25.052, M25.059, M25.06, M25.061, M25.062, M25.069, M25.07, M25.071, M25.072 M25.073, M25.074, M25.075, M25.076, M25.08, R04.0		

Osteoporosis/Hip Fractures	INUK.14G6.00, INUK.14G9.00, INUK.N330100, INUK.N330200, INUK.N330300, INUK.N330400, INUK.N330500, INUK.N330600, INUK.N330900, INUK.N330A00, INUK.N330B00, INUK.N331400, INUK.N331500, INUK.N331A00, INUK.N331B00, INUK.N331K00, INUK.N331M00, INUK.N331M11, INUK.NyuB000, INUK.NyuB100, INUK.NyuB800, INUK.S30y.11, INUK.14G7.00, INUK.14G8.00, INUK.14GA.00, INUK.14GB.00, INUK.N330.00, INUK.N330000, INUK.N330700, INUK.N330800, INUK.N330C00, INUK.N330D00, INUK.N330z00, INUK.N331.14, INUK.N331200, INUK.N331300, INUK.N331600, INUK.N331800, INUK.N331900, INUK.N331H00, INUK.N331J00, INUK.N331L00, INUK.N374600, INUK.NyuB200, INUK.S30..11	M80, M80.0, M80.00, M80.00XA, M80.00XD, M80.00XG, M80.00XK, M80.00XP, M80.00XS, M80.01, M80.011, M80.011A, M80.011D, M80.011G, M80.011K, M80.011P, M80.011S, M80.012, M80.012A, M80.012D, M80.012G, M80.012K, M80.012P, M80.012S, M80.019, M80.019A, M80.019D, M80.019G, M80.019K, M80.019P, M80.019S, M80.02, M80.021, M80.021A, M80.021D, M80.021G, M80.021K, M80.021P, M80.021S, M80.022, M80.022A, M80.022D, M80.022G, M80.022K, M80.022P, M80.022S, M80.029, M80.029A, M80.029D, M80.029G, M80.029K, M80.029P, M80.029S, M80.03, M80.031, M80.031A, M80.031D, M80.031G, M80.031K, M80.031P, M80.031S, M80.032, M80.032A, M80.032D, M80.032G, M80.032K, M80.032P, M80.032S, M80.039, M80.039A, M80.039D, M80.039G, M80.039K, M80.039P, M80.039S, M80.04, M80.041, M80.041A, M80.041D, M80.041G, M80.041K, M80.041P, M80.041S, M80.042, M80.042A, M80.042D, M80.042G, M80.042K, M80.042P, M80.042S, M80.049, M80.049A, M80.049D, M80.049G, M80.049K, M80.049P, M80.049S, M80.05, M80.051, M80.051A, M80.051D, M80.051G, M80.051K, M80.051P, M80.051S, M80.052, M80.052A, M80.052D, M80.052G, M80.052K, M80.052P, M80.052S, M80.059, M80.059A, M80.059D, M80.059G, M80.059K, M80.059P, M80.059S, M80.06, M80.061, M80.061A, M80.061D, M80.061G, M80.061K, M80.061P, M80.061S, M80.062, M80.062A, M80.062D, M80.062G, M80.062K, M80.062P, M80.062S, M80.069, M80.069A, M80.069D, M80.069G, M80.069K, M80.069P, M80.069S, M80.07, M80.071, M80.071A, M80.071D, M80.071G, M80.071K, M80.071P, M80.071S, M80.072, M80.072A, M80.072D, M80.072G, M80.072K, M80.072P, M80.072S, M80.079, M80.079A, M80.079D, M80.079G, M80.079K, M80.079P, M80.079S, M80.08, M80.08XA, M80.08XD, M80.08XG, M80.08XK, M80.08XP, M80.08XS, M80.0A, M80.0AXA, M80.0AXD, M80.0AXG, M80.0AXK, M80.0AX M80.0AXS, M80.8, M80.80, M80.80XA, M80.80XD, M80.80XG, M80.80XK, M80.80XP, M80.80XS, M80.81,		
CHA2DS2 VASc score component: heart failure	*See "Heart Failure" above*	*See "Heart Failure" above*		
CHA2DS2 VASc score component: thromboembolism	INUK.G401.00, INUK.G401.12, INUK.G401000, INUK.G401100, INUK.G402.00, INUK.G80..00, INUK.G800.12, INUK.G800300, INUK.G800400, INUK.G801.00, INUK.G801.11, INUK.G801.12, INUK.G801.13, INUK.G801500, INUK.G801600, INUK.G801700, INUK.G801800, INUK.G801900, INUK.G801A00, INUK.G801B00, INUK.G801C00, INUK.G801D00, INUK.G801E00, INUK.G801F00, INUK.G801G00, INUK.G801H00, INUK.G801J00, INUK.G801z00, INUK.G802.00, INUK.G802000, INUK.G80y.00, INUK.G80y.11, INUK.G80y400, INUK.G80y500, INUK.G80y600, INUK.G80y700, INUK.G80y800, INUK.G80yz00, INUK.G80z.00, INUK.G80z100, INUK.G80zz00, INUK.G82..00, INUK.L096400, INUK.L414.00, INUK.L414.11, INUK.L414.12, INUK.14A8.12, INUK.14A8100, INUK.SP12200, INUK.ZV12800, INUK.ZV12811, INUK.ZV12900, INUK.L413.00, INUK.L413.11, INUK.L413000, INUK.L413100, INUK.L413200, INUK.L413z00	I26.01, I26.92, I26.99, I82.402, I82.403, I82.409, I82.492, I82.499, I82.4Y1, I82.4Y2, I82.4Y3, I82.4Z9, I82.502, I82.5 I82.5Y2, I82.5Y9, I82.5Z1, I82.5Z2, I82.621, I82.721, I82.7 I82.729, I26.02, I26.09, I26.90, I82.491, I82.493, I82.4Y9, I82.4Z1, I82.4Z2, I82.4Z3, I82.501, I82.503, I82.509, I82.5 I82.593, I82.599, I82.5Y1, I82.5Y3, I82.5Z3, I82.5Z9, I82.6 I82.623, I82.629, I82.723	Ruigómez A, Brobert G, Vora P, García Rodríguez LA. Validation of venous thromboembolism diagnoses in patients receiving rivaroxaban or warfarin in The Health Improvement Network. Pharmacoepidemiol Drug Saf. 2021;30(2):229-236. doi:10.1002/pds.514	
CHA2DS2 VASc score component: stroke, TIA, or thromboembolism	*See "Stroke (Ischemic and Hemorrhagic)", "TIA", and "CHA2DS2 VASc score component: thromboembolism" above*	*See "Stroke (Ischemic and Hemorrhagic)", "TIA", and "CHA2DS2 VASc score component: thromboembolism" above*		

CHA2DS2 VASc score component: PAD	INUK.G73..00, INUK.G73..11, INUK.G73..12, INUK.G73..13, INUK.G734.00, INUK.G73y.00, INUK.G73z.00, INUK.G73z000, INUK.G73z011, INUK.G73z012, INUK.G73zz00, INUK.Gyu7400	I70.208, I70.209, I70.212, I70.22, I70.222, I70.223, I70.228 I70.229, I70.231, I70.234, I70.238, I70.239, I70.24, I70.241 I70.242, I70.249, I70.25, I70.262, I70.268, I70.269, I70.292 I70.293, I70.298, I70.299, I70.3, I70.301, I70.302, I70.308, I70.311, I70.312, I70.313, I70.319, I70.321, I70.322, I70.32 I70.33, I70.332, I70.333, I70.334, I70.338, I70.339, I70.34, I70.349, I70.36, I70.362, I70.368, I70.391, I70.398, I70.399 I70.40, I70.401, I70.402, I70.413, I70.419, I70.42, I70.422, I70.428, I70.43, I70.432, I70.433, I70.434, I70.44, I70.442, I70.443, I70.445, I70.449, I70.461, I70.462, I70.463, I70.46 I70.491, I70.498, I70.499, I70.5, I70.50, I70.501, I70.509, I70.51, I70.518, I70.519, I70.52, I70.521, I70.523, I70.53, I70.531, I70.532, I70.533, I70.535, I70.538, I70.539, I70.54 I70.55, I70.56, I70.561, I70.562, I70.568, I70.59, I70.591, I70.593, I70.6, I70.601, I70.608, I70.609, I70.61, I70.611, I70.613, I70.62, I70.623, I70.628, I70.629, I70.633, I70.638 I70.641, I70.642, I70.643, I70.645, I70.649, I70.66, I70.662 I70.692, I70.693, I70.699, I70.7, I70.701, I70.702, I70.703, I70.711, I70.713, I70.718, I70.72, I70.721, I70.733, I70.734 I70.735, I70.741, I70.743, I70.745, I70.749, I70.761, I70.76 I70.763, I70.768, I70.769, I70.792, I70.793, I73.9, I70.2, I7 I70.201, I70.202, I70.203, I70.21, I70.211, I70.213, I70.218 I70.219, I70.221, I70.23, I70.232, I70.233, I70.235, I70.243 I70.244, I70.245, I70.248, I70.26, I70.261, I70.263, I70.29, I70.291, I70.30, I70.303, I70.309, I70.31, I70.318, I70.32, I70.323, I70.329, I70.331, I70.335, I70.341, I70.342, I70.34 I70.344, I70.345, I70.348, I70.35, I70.361, I70.363, I70.369 I70.39, I70.392, I70.393, I70.4, I70.403, I70.408, I70.409, I70.41, I70.411, I70.412, I70.418, I70.421, I70.423, I70.429 I70.431, I70.435, I70.438, I70.439, I70.441, I70.444, I70.44 I70.45, I70.46, I70.468, I70.49, I70.492, I70.493, I70.502, I70.503, I70.508, I70.511, I70.512, I70.513, I70.522, I70.52 I70.529, I70.534, I70.54, I70.541, I70.542, I70.543, I70.545 I70.548, I70.549, I70.563, I70.569, I70.592, I70.598, I70.59 I70.60, I70.602, I70.603, I70.612, I70.618, I70.619, I70.62 I70.622, I70.63, I70.631, I70.632, I70.634, I70.635, I70.639 I70.64, I70.644, I70.648, I70.65, I70.661, I70.663, I70.668,	Quality Outcomes Framework V38	Colantonio LD, Shannon ED, Orroth KK, Zaha R, Jackson EA, Rosenson RS, Exter J, Mues KE, Muntner P. Ischemic Event Rates in Very-High-Risk Adults. J Am Coll Cardiol. 2019 Nov 19;74(20):2496-2507. d 10.1016/j.jacc.2019.09.025. PMID: 31727288.
CHA2DS2 VASc score component: aortic plaque	INUK.G700.00	I70.0		Tischer Ts, Schneider R, Lauschke J, et a Prevalence of atrial fibrillation in patients with high CHADS2- and CHA2DS2VASc-scores: anticoagulate or monitor high-risk patients?. Pacing Clin Electrophysiol. 2014;37(12):1651-1657. doi:10.1111/pace.12470
CHA2DS2 VASc score component: vascular disease (MI, PAD, or aortic plaque)	*See "Myocardial infarction", "CHA2DS2 VASc score component: PAD", and "CHA2DS2 VASc score component: aortic plaque" abov*	*See "Myocardial infarction", "CHA2DS2 VASc score component: PAD", and "CHA2DS2 VASc score componen aortic plaque" above*		
CHA2DS2 VASc score component: diabetes mellitus	*See "Diabetes Mellitus" above*	*See "Diabetes Mellitus" above*		
CHA2DS2 VASc score component: hypertension, includin use of antihypertensives	*See "Hypertension" and "Antihypertensives" above*	*See "Hypertension" and "Antihypertensives" above*		

Supplemental Table 1. Baseline characteristics of patients with nonvalvular atrial fibrillation newly initiating a DOAC, before and after propensity score matching: characteristics not included in propensity score models due to high missingness assessed in the year prior to and including index date

	Patient characteristics before propensity score matching				Patient characteristics after propensity score matching								
	Apixaban	Rivaroxaban	Edoxaban	Dabigatran	Apixaban	Rivaroxaban	ASD	Apixaban	Other DOACs	ASD	Rivaroxaban	Other DOACs	ASD
Number of patients	2,801	2,221	398	261	1,839	1,839		2,276	2,276		1,985	1,985	
Patient characteristics, evaluated as the last value observed in the one year prior to index date													
Marital status							0.222			0.128			0.289
Married; n (%)	32 (1.1%)	21 (0.9%)	8 (2.0%)	1 (0.4%)	21 (1.1%)	18 (1.0%)		28 (1.2%)	28 (1.2%)		19 (1.0%)	26 (1.3%)	
Unmarried; n (%)	13 (0.5%)	11 (0.5%)	3 (0.8%)	0 (0.0%)	8 (0.4%)	11 (0.6%)		9 (0.4%)	12 (0.5%)		11 (0.6%)	8 (0.4%)	
Missing; n (%)	2,756 (98.4%)	2,189 (98.6%)	387 (97.2%)	260 (99.6%)	1,810 (98.4%)	1,810 (98.4%)		2,239 (98.4%)	2,236 (98.2%)		1,955 (98.5%)	1,951 (98.3%)	
Cigarettes per day							0.216			0.150			0.163
mean (sd)	10.50 (5.98)	12.22 (8.33)	12.25 (8.28)	11.15 (5.98)	10.51 (6.01)	12.00 (7.71)		10.34 (6.05)	11.38 (7.72)		12.17 (8.10)	10.99 (6.27)	
median [IQR]	10.00 [5.75, 15.00]	10.00 [5.00, 16.25]	10.00 [6.50, 15.00]	10.00 [6.00, 17.50]	10.00 [5.50, 15.00]	10.00 [5.00, 15.00]		10.00 [5.75, 15.00]	10.00 [5.00, 15.00]		10.00 [5.00, 20.00]	10.00 [6.00, 15.00]	
Missing; n (%)	2,695 (96.2%)	2,127 (95.8%)	382 (96.0%)	248 (95.0%)	1,774 (96.5%)	1,764 (95.9%)		2,190 (96.2%)	2,181 (95.8%)		1,907 (96.1%)	1,913 (96.4%)	
Glasses per day*							0.076			0.043			0.128
mean (sd)	40,314.49 (901,176.02)	14.69 (15.77)	75,469.73 (3,379,675.36)	20.22 (35.00)	58,421.88 (1,084,888.39)	15.00 (16.19)		46,984.77 (972,895.01)	99,476.87 (1,413,606.11)		14.70 (15.95)	62,906.26 (1,806,540.38)	
median [IQR]	10.00 [2.00, 18.00]	10.00 [4.00, 20.00]	12.00 [5.00, 20.25]	10.00 [2.00, 21.50]	10.00 [2.00, 20.00]	10.00 [4.00, 20.00]		10.00 [2.00, 18.00]	10.00 [4.00, 21.00]		10.00 [4.00, 20.00]	10.00 [3.00, 20.00]	
Missing; n (%)	2,301 (82.1%)	1,822 (82.0%)	328 (82.4%)	212 (81.2%)	1,494 (81.2%)	1,504 (81.8%)		1,847 (81.2%)	1,871 (82.2%)		1,626 (81.9%)	1,614 (81.3%)	
BMI (kg/m2)							0.083			0.045			0.074
mean (sd)	29.20 (6.24)	29.86 (6.51)	28.81 (6.28)	29.83 (6.34)	29.23 (6.29)	29.75 (6.42)		29.21 (6.24)	29.49 (6.43)		29.78 (6.48)	29.30 (6.46)	
median [IQR]	28.30 [24.70, 32.60]	28.90 [25.30, 33.40]	27.80 [24.50, 32.23]	29.20 [25.40, 32.90]	28.30 [24.70, 32.40]	28.80 [25.30, 33.40]		28.40 [24.78, 32.60]	28.55 [25.08, 33.00]		28.80 [25.20, 33.40]	28.50 [24.80, 32.60]	
Missing; n (%)	970 (34.6%)	846 (38.1%)	104 (26.1%)	98 (37.5%)	672 (36.5%)	702 (38.2%)		790 (34.7%)	830 (36.5%)		765 (38.5%)	708 (35.7%)	
HbA1c (mmol/mol)							0.066			0.076			0.075
mean (sd)	46.53 (15.17)	48.59 (16.25)	46.69 (14.76)	46.92 (13.99)	46.87 (16.39)	47.94 (16.05)		46.41 (15.13)	47.58 (15.65)		48.34 (16.04)	47.12 (16.24)	
median [IQR]	44.00 [39.00, 52.00]	45.00 [39.00, 54.00]	43.00 [39.00, 52.25]	44.00 [40.00, 52.00]	44.00 [39.00, 53.00]	44.00 [39.00, 53.00]		44.00 [39.00, 52.00]	44.00 [39.00, 53.00]		45.00 [39.00, 54.00]	44.00 [39.00, 53.00]	
Missing; n (%)	1,544 (55.1%)	1,235 (55.6%)	252 (63.3%)	150 (57.5%)	1,025 (55.7%)	1,034 (56.2%)		1,262 (55.4%)	1,299 (57.1%)		1,104 (55.6%)	1,110 (55.9%)	
INR							0.036			0.021			0.044
mean (sd)	4.77 (13.57)	3.77 (8.53)	8.34 (19.23)	2.01 (0.81)	4.33 (12.41)	3.94 (9.40)		4.71 (13.54)	4.44 (11.17)		3.94 (9.07)	4.42 (12.60)	
median [IQR]	2.40 [1.80, 2.80]	2.30 [1.80, 2.90]	2.40 [2.00, 3.20]	2.00 [1.40, 2.38]	2.40 [1.80, 2.80]	2.30 [1.80, 2.90]		2.40 [1.80, 2.80]	2.30 [1.80, 2.90]		2.30 [1.80, 2.90]	2.30 [1.80, 2.75]	
Missing; n (%)	2,464 (88.0%)	1,880 (84.6%)	349 (87.7%)	225 (86.2%)	1,606 (87.3%)	1,575 (85.6%)		1,982 (87.1%)	1,952 (85.8%)		1,685 (84.9%)	1,708 (86.0%)	
GFR (ml/min/1.73 m2)							0.135			0.131			0.145
mean (sd)	61.04 (16.17)	63.66 (15.95)	62.25 (15.62)	64.86 (15.23)	61.49 (16.24)	63.67 (16.01)		61.21 (16.17)	63.30 (15.79)		63.72 (15.97)	61.39 (16.30)	
median [IQR]	61.00 [50.00, 73.00]	64.00 [52.00, 76.00]	60.00 [52.00, 76.00]	65.00 [54.00, 79.00]	61.00 [50.00, 74.00]	64.00 [52.00, 76.00]		61.00 [50.00, 74.00]	64.00 [52.00, 76.00]		64.00 [52.00, 76.00]	60.40 [50.00, 74.00]	
Missing; n (%)	1,052 (37.6%)	870 (39.2%)	190 (47.7%)	94 (36.0%)	736 (40.0%)	714 (38.8%)		879 (38.6%)	909 (39.9%)		781 (39.3%)	786 (39.6%)	
CrCl (ml/min)							0.029			0.017			0.066
mean (sd)	63.93 (22.40)	65.75 (19.46)	56.73 (21.52)	71.84 (4.95)	66.81 (21.09)	66.22 (19.78)		63.89 (21.95)	64.24 (20.10)		65.75 (19.46)	67.14 (22.51)	
median [IQR]	63.00 [48.00, 81.50]	65.00 [52.50, 77.25]	50.00 [40.00, 65.00]	71.00 [68.25, 75.84]	64.50 [49.43, 82.25]	66.35 [51.50, 77.75]		62.50 [48.75, 81.25]	63.50 [47.50, 77.25]		65.00 [52.50, 77.25]	66.50 [46.50, 85.11]	
Missing; n (%)	2,700 (96.4%)	2,175 (97.9%)	383 (96.2%)	256 (98.1%)	1,793 (97.5%)	1,795 (97.6%)		2,194 (96.4%)	2,214 (97.3%)		1,939 (97.7%)	1,943 (97.9%)	
Apixaban and rivaroxaban dosage, evaluated on the index date; n (%)**													
Apixaban 2.5mg	761 (27.2%)	-	-	-	512 (27.8%)	-	-	622 (27.3%)	-		-	499 (25.1%)	
Apixaban 5mg	2,063 (73.7%)	-	-	-	1,342 (73.0%)	-		1,674 (73.6%)	-		-	1,161 (58.5%)	
Rivaroxaban 2.5mg	-	14 (0.6%)	-	-	-	9 (0.5%)		-	9 (0.4%)		12 (0.6%)	-	
Rivaroxaban 10mg	-	18 (0.8%)	-	-	-	15 (0.8%)		-	11 (0.5%)		14 (0.7%)	-	
Rivaroxaban 15mg	-	409 (18.4%)	-	-	-	341 (18.5%)		-	329 (14.5%)		370 (18.6%)	-	
Rivaroxaban 20mg	-	1,793 (80.7%)	-	-	-	1,484 (80.7%)		-	1,368 (60.1%)		1,600 (80.6%)	-	
Edoxaban 15mg	-	-	2 (0.5%)	-	-	-		-	2 (0.1%)		-	1 (0.1%)	
Edoxaban 30mg	-	-	108 (27.1%)	-	-	-		-	103 (4.5%)		-	34 (1.7%)	
Edoxaban 60mg	-	-	295 (74.1%)	-	-	-		-	282 (12.4%)		-	91 (4.6%)	
Dabigatran 75mg	-	-	-	16 (6.1%)	-	-		-	14 (0.6%)		-	16 (0.8%)	
Dabigatran 110mg	-	-	-	123 (47.1%)	-	-		-	91 (4.0%)		-	102 (5.1%)	
Dabigatran 150mg	-	-	-	125 (47.9%)	-	-		-	88 (3.9%)		-	97 (4.9%)	

Characteristics assessed in the year prior to and including index date.

SD = standard deviation; IQR = interquartile range; DOAC = direct oral anticoagulants; ASD = absolute standardized difference.

* Values reported reflect all available data without modification or cleaning.

** Patients with prescriptions for multiple dosages are reported as having all dosages observed

Supplemental Table 2. Per-protocol analysis using a 365d baseline period for all characteristics: Baseline characteristics of patients with nonvalvular atrial fibrillation newly initiating a DOAC, before and after propensity score matching

	Patient characteristics before propensity score matching				Patient characteristics after propensity score matching								
	Apixaban	Rivaroxaban	Edoxaban	Dabigatran	Apixaban	Rivaroxaban	ASD	Apixaban	Other DOACs	ASD	Rivaroxaban	Other DOACs	ASD
Number of patients	2,801	2,221	398	261	1,840	1,840		2,301	2,301		2,023	2,023	
Year of Cohort Entry Date							0.034			0.017			0.038
2014	76 (2.7%)	138 (6.2%)	0 (0.0%)	32 (12.3%)	76 (4.1%)	81 (4.4%)		76 (3.3%)	78 (3.4%)		116 (5.7%)	108 (5.3%)	
2015	365 (13.0%)	548 (24.7%)	0 (0.0%)	81 (31.0%)	357 (19.4%)	359 (19.5%)		362 (15.7%)	372 (16.2%)		441 (21.8%)	436 (21.6%)	
2016	571 (20.4%)	646 (29.1%)	11 (2.8%)	77 (29.5%)	532 (28.9%)	523 (28.4%)		555 (24.1%)	550 (23.9%)		582 (28.8%)	596 (29.5%)	
2017	546 (19.5%)	383 (17.2%)	20 (5.0%)	42 (16.1%)	388 (21.1%)	374 (20.3%)		427 (18.6%)	423 (18.4%)		379 (18.7%)	392 (19.4%)	
2018	530 (18.9%)	257 (11.6%)	115 (28.9%)	21 (8.0%)	242 (13.2%)	256 (13.9%)		393 (17.1%)	385 (16.7%)		257 (12.7%)	250 (12.4%)	
2019	423 (15.1%)	143 (6.4%)	129 (32.4%)	5 (1.9%)	145 (7.9%)	142 (7.7%)		263 (11.4%)	268 (11.6%)		142 (7.0%)	146 (7.2%)	
2020	290 (10.4%)	106 (4.8%)	123 (30.9%)	3 (1.1%)	100 (5.4%)	105 (5.7%)		225 (9.8%)	225 (9.8%)		106 (5.2%)	95 (4.7%)	
Age (years)							0.053			0.038			0.038
mean (sd)	77.35 (8.54)	76.71 (8.62)	77.11 (8.35)	76.23 (8.56)	77.34 (8.60)	76.89 (8.26)		77.14 (8.63)	76.82 (8.39)		76.84 (8.53)	77.17 (8.72)	
median [IQR]	78 [72, 83]	77 [71, 83]	78 [72, 83]	77 [70, 82]	78 [71, 83]	77 [71, 83]		77 [71, 83]	77 [71, 83]		77 [71, 83]	78 [71, 83]	
Age categories (years)							0.021			0.003			0.019
< 55	30 (1.1%)	34 (1.5%)	5 (1.3%)	4 (1.5%)	18 (1.0%)	17 (0.9%)		26 (1.1%)	26 (1.1%)		30 (1.5%)	26 (1.3%)	
55 - 64	131 (4.7%)	120 (5.4%)	18 (4.5%)	13 (5.0%)	96 (5.2%)	92 (5.0%)		116 (5.0%)	117 (5.1%)		99 (4.9%)	100 (4.9%)	
65 - 74	808 (28.8%)	634 (28.5%)	120 (30.2%)	83 (31.8%)	514 (27.9%)	530 (28.8%)		686 (29.8%)	683 (29.7%)		577 (28.5%)	585 (28.9%)	
>= 75	1,832 (65.4%)	1,433 (64.5%)	255 (64.1%)	161 (61.7%)	1,212 (65.9%)	1,201 (65.3%)		1,473 (64.0%)	1,475 (64.1%)		1,317 (65.1%)	1,312 (64.9%)	
Gender							0.003			0.006			0.013
Female	1,070 (38.2%)	785 (35.3%)	158 (39.7%)	81 (31.0%)	661 (35.9%)	664 (36.1%)		864 (37.5%)	857 (37.2%)		730 (36.1%)	717 (35.4%)	
Male	1,731 (61.8%)	1,436 (64.7%)	240 (60.3%)	180 (69.0%)	1,179 (64.1%)	1,176 (63.9%)		1,437 (62.5%)	1,444 (62.8%)		1,293 (63.9%)	1,306 (64.6%)	
Non-Major Bleeding Events	31 (1.1%)	32 (1.4%)	6 (1.5%)	6 (2.3%)	20 (1.1%)	22 (1.2%)	0.010	27 (1.2%)	23 (1.0%)	0.017	29 (1.4%)	23 (1.1%)	0.026
Anemia	79 (2.8%)	63 (2.8%)	5 (1.3%)	9 (3.4%)	52 (2.8%)	50 (2.7%)	0.007	55 (2.4%)	58 (2.5%)	0.008	53 (2.6%)	51 (2.5%)	0.006
Diabetes Mellitus	104 (3.7%)	98 (4.4%)	7 (1.8%)	11 (4.2%)	76 (4.1%)	69 (3.8%)	0.020	85 (3.7%)	89 (3.9%)	0.009	83 (4.1%)	86 (4.3%)	0.007
Hypertension	165 (5.9%)	132 (5.9%)	22 (5.5%)	18 (6.9%)	106 (5.8%)	99 (5.4%)	0.017	138 (6.0%)	131 (5.7%)	0.013	117 (5.8%)	126 (6.2%)	0.019
Heart Failure	208 (7.4%)	161 (7.2%)	19 (4.8%)	13 (5.0%)	126 (6.8%)	119 (6.5%)	0.015	149 (6.5%)	155 (6.7%)	0.010	139 (6.9%)	135 (6.7%)	0.008
Osteoporosis and Hip Fractures	32 (1.1%)	23 (1.0%)	9 (2.3%)	5 (1.9%)	16 (0.9%)	20 (1.1%)	0.022	30 (1.3%)	28 (1.2%)	0.008	23 (1.1%)	18 (0.9%)	0.025
Malignant Neoplasms	111 (4.0%)	77 (3.5%)	17 (4.3%)	12 (4.6%)	73 (4.0%)	63 (3.4%)	0.029	85 (3.7%)	86 (3.7%)	0.002	74 (3.7%)	72 (3.6%)	0.005
Acute Kidney Injury	49 (1.7%)	30 (1.4%)	3 (0.8%)	2 (0.8%)	24 (1.3%)	25 (1.4%)	0.005	31 (1.3%)	33 (1.4%)	0.007	28 (1.4%)	33 (1.6%)	0.020
Chronic Kidney Disease	80 (2.9%)	80 (3.6%)	9 (2.3%)	6 (2.3%)	59 (3.2%)	59 (3.2%)	0.000	73 (3.2%)	70 (3.0%)	0.008	69 (3.4%)	64 (3.2%)	0.014
Asthma and COPD	145 (5.2%)	135 (6.1%)	17 (4.3%)	10 (3.8%)	108 (5.9%)	109 (5.9%)	0.002	125 (5.4%)	123 (5.3%)	0.004	110 (5.4%)	116 (5.7%)	0.013
Dementia	34 (1.2%)	23 (1.0%)	1 (0.3%)	2 (0.8%)	19 (1.0%)	20 (1.1%)	0.005	23 (1.0%)	25 (1.1%)	0.009	22 (1.1%)	21 (1.0%)	0.005
Aspirin	824 (29.4%)	709 (31.9%)	89 (22.4%)	93 (35.6%)	569 (30.9%)	569 (30.9%)	0.000	653 (28.4%)	684 (29.7%)	0.030	643 (31.8%)	628 (31.0%)	0.016
Antiplatelets (other than aspirin)	164 (5.9%)	123 (5.5%)	18 (4.5%)	16 (6.1%)	99 (5.4%)	110 (6.0%)	0.026	130 (5.6%)	127 (5.5%)	0.006	115 (5.7%)	114 (5.6%)	0.002
Warfarin	391 (14.0%)	397 (17.9%)	53 (13.3%)	41 (15.7%)	292 (15.9%)	294 (16.0%)	0.003	350 (15.2%)	344 (15.0%)	0.007	328 (16.2%)	322 (15.9%)	0.008
Antianemic Preparations	519 (18.5%)	334 (15.0%)	49 (12.3%)	33 (12.6%)	276 (15.0%)	294 (16.0%)	0.027	369 (16.0%)	365 (15.9%)	0.005	307 (15.2%)	298 (14.7%)	0.012
NSAIDs	340 (12.1%)	275 (12.4%)	50 (12.6%)	42 (16.1%)	237 (12.9%)	236 (12.8%)	0.002	288 (12.5%)	286 (12.4%)	0.003	261 (12.9%)	250 (12.4%)	0.016
Opioids	862 (30.8%)	640 (28.8%)	113 (28.4%)	73 (28.0%)	532 (28.9%)	534 (29.0%)	0.002	666 (28.9%)	670 (29.1%)	0.004	596 (29.5%)	585 (28.9%)	0.012
SSRIs	240 (8.6%)	181 (8.1%)	36 (9.0%)	17 (6.5%)	147 (8.0%)	157 (8.5%)	0.020	194 (8.4%)	195 (8.5%)	0.002	164 (8.1%)	161 (8.0%)	0.005
Antidepressants (other than SSRIs)	301 (10.7%)	235 (10.6%)	36 (9.0%)	26 (10.0%)	193 (10.5%)	199 (10.8%)	0.011	238 (10.3%)	236 (10.3%)	0.003	214 (10.6%)	207 (10.2%)	0.011
Antiepileptics	210 (7.5%)	150 (6.8%)	25 (6.3%)	19 (7.3%)	124 (6.7%)	127 (6.9%)	0.006	154 (6.7%)	163 (7.1%)	0.015	142 (7.0%)	138 (6.8%)	0.008
Antipsychotics	141 (5.0%)	92 (4.1%)	20 (5.0%)	12 (4.6%)	80 (4.3%)	82 (4.5%)	0.005	109 (4.7%)	103 (4.5%)	0.012	91 (4.5%)	87 (4.3%)	0.010
Benzodiazepines	256 (9.1%)	182 (8.2%)	43 (10.8%)	23 (8.8%)	162 (8.8%)	154 (8.4%)	0.016	196 (8.5%)	201 (8.7%)	0.008	170 (8.4%)	173 (8.6%)	0.005
Lipid Lowering Drugs	1,539 (54.9%)	1,199 (54.0%)	191 (48.0%)	138 (52.9%)	1,012 (55.0%)	998 (54.2%)	0.015	1,216 (52.8%)	1,254 (54.5%)	0.033	1,089 (53.8%)	1,092 (54.0%)	0.003
Insulin	91 (3.2%)	80 (3.6%)	9 (2.3%)	5 (1.9%)	57 (3.1%)	61 (3.3%)	0.012	70 (3.0%)	73 (3.2%)	0.008	61 (3.0%)	67 (3.3%)	0.017
Antihyperglycemics other than Insulins	525 (18.7%)	466 (21.0%)	51 (12.8%)	54 (20.7%)	363 (19.7%)	372 (20.2%)	0.012	421 (18.3%)	446 (19.4%)	0.028	406 (20.1%)	396 (19.6%)	0.012
Antihypertensives	2,611 (93.2%)	2,079 (93.6%)	366 (92.0%)	242 (92.7%)	1,723 (93.6%)	1,718 (93.4%)	0.011	2,141 (93.0%)	2,151 (93.5%)	0.017	1,889 (93.4%)	1,901 (94.0%)	0.024
Antiarrhythmics	94 (3.4%)	91 (4.1%)	10 (2.5%)	10 (3.8%)	67 (3.6%)	70 (3.8%)	0.009	79 (3.4%)	80 (3.5%)	0.002	81 (4.0%)	75 (3.7%)	0.015
Nitrates Cardiac Vasodilators	130 (4.6%)	99 (4.5%)	21 (5.3%)	9 (3.4%)	79 (4.3%)	81 (4.4%)	0.005	105 (4.6%)	105 (4.6%)	0.000	95 (4.7%)	100 (4.9%)	0.012
Cardiac Stimulants	347 (12.4%)	272 (12.2%)	30 (7.5%)	17 (6.5%)	236 (12.8%)	229 (12.4%)	0.011	271 (11.8%)	263 (11.4%)	0.011	237 (11.7%)	235 (11.6%)	0.003
Gastrointestinal Protective Agents	1,214 (43.3%)	893 (40.2%)	173 (43.5%)	106 (40.6%)	752 (40.9%)	761 (41.4%)	0.010	952 (41.4%)	955 (41.5%)	0.003	830 (41.0%)	802 (39.6%)	0.028

Bisphosphonates and Other Agents Affecting Bone Structure	228 (8.1%)	171 (7.7%)	32 (8.0%)	15 (5.7%)	135 (7.3%)	138 (7.5%)	0.006	192 (8.3%)	188 (8.2%)	0.006	166 (8.2%)	151 (7.5%)	0.028
Systemic Corticosteroids	442 (15.8%)	345 (15.5%)	53 (13.3%)	37 (14.2%)	272 (14.8%)	271 (14.7%)	0.002	353 (15.3%)	358 (15.6%)	0.006	308 (15.2%)	307 (15.2%)	0.001
Antineoplastics	140 (5.0%)	99 (4.5%)	21 (5.3%)	13 (5.0%)	81 (4.4%)	88 (4.8%)	0.018	111 (4.8%)	113 (4.9%)	0.004	93 (4.6%)	90 (4.4%)	0.007
Systemic Antibiotics	1,357 (48.4%)	1,075 (48.4%)	177 (44.5%)	119 (45.6%)	872 (47.4%)	867 (47.1%)	0.005	1,084 (47.1%)	1,097 (47.7%)	0.011	969 (47.9%)	961 (47.5%)	0.008
Systemic Antivirals	31 (1.1%)	32 (1.4%)	3 (0.8%)	3 (1.1%)	22 (1.2%)	22 (1.2%)	0.000	29 (1.3%)	26 (1.1%)	0.012	26 (1.3%)	26 (1.3%)	0.000
Vaccines and Immunoglobulins	137 (4.9%)	204 (9.2%)	11 (2.8%)	24 (9.2%)	119 (6.5%)	131 (7.1%)	0.026	133 (5.8%)	134 (5.8%)	0.002	157 (7.8%)	138 (6.8%)	0.036
CHA2DS2 VASc score										0.013			0.045
0	93 (3.3%)	79 (3.6%)	16 (4.0%)	13 (5.0%)	64 (3.5%)	64 (3.5%)	0.047	83 (3.6%)	80 (3.5%)		74 (3.7%)	73 (3.6%)	
1	518 (18.5%)	442 (19.9%)	79 (19.8%)	57 (21.8%)	347 (18.9%)	354 (19.2%)		452 (19.6%)	459 (19.9%)		392 (19.4%)	379 (18.7%)	
2	1,174 (41.9%)	949 (42.7%)	165 (41.5%)	112 (42.9%)	794 (43.2%)	802 (43.6%)		962 (41.8%)	964 (41.9%)		861 (42.6%)	892 (44.1%)	
3	868 (31.0%)	631 (28.4%)	119 (29.9%)	63 (24.1%)	542 (29.5%)	529 (28.7%)		684 (29.7%)	682 (29.6%)		587 (29.0%)	572 (28.3%)	
4	133 (4.7%)	99 (4.5%)	18 (4.5%)	14 (5.4%)	79 (4.3%)	82 (4.5%)		108 (4.7%)	104 (4.5%)		95 (4.7%)	93 (4.6%)	
5	14 (0.5%)	20 (0.9%)	1 (0.3%)	2 (0.8%)	13 (0.7%)	9 (0.5%)		12 (0.5%)	12 (0.5%)		13 (0.6%)	14 (0.7%)	
6	1 (0.0%)	1 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)		0 (0.0%)	0 (0.0%)		1 (0.0%)	0 (0.0%)	
7	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	
8	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	
9	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	

Characteristics reported as N (%) unless otherwise specified.

SD = standard deviation; IQR = interquartile range; DOAC = direct oral anticoagulants; ASD = absolute standardized difference.

Supplemental Table 3. Per-protocol analysis using a 365d baseline period for all characteristics: Hazard ratio of stroke and secondary outcomes among patients with nonvalvular atrial fibrillation newly initiating DOACs after propensity score matching

	Patients	Events	Rate per 1,000 PY	Patients	Events	Rate per 1,000 PY	Hazard Ratio
Apixaban vs rivaroxaban: primary and secondary outcomes							
Outcome	Apixaban			Rivaroxaban			aHR (95% CI)
Stroke, ITT	1,840	53	11.77	1,840	56	13.00	0.89 (0.61, 1.30)
Stroke, AT	1,840	30	9.26	1,840	32	11.00	0.87 (0.53, 1.43)
All-cause mortality, ITT*	1,846	276	59.46	1,846	264	61.37	0.96 (0.81, 1.14)
Myocardial infarction (MI), ITT	1,840	22	4.84	1,840	25	6.00	0.84 (0.47, 1.48)
Transient ischemic attack	1,840	32	7.08	1,840	29	7.00	1.06 (0.64, 1.76)
Major bleeding event, ITT	1,840	117	26.70	1,840	189	48.00	0.57 (0.46, 0.72)
Composite angina/MI/stroke	1,840	92	20.82	1,840	98	24.00	0.89 (0.67, 1.18)
Apixaban vs rivaroxaban: primary outcome (stroke) among subgroups, ITT							
Subgroup	Apixaban			Rivaroxaban			aHR (95% CI)
Age <75 years	631	12	7.17	631	12	8.00	0.93 (0.42, 2.06)
Age ≥75 years	1,195	37	13.29	1,195	39	15.00	0.89 (0.57, 1.40)
Concomitant aspirin use	400	12	11.54	400	9	9.00	1.24 (0.52, 2.94)
No concomitant aspirin use	1,416	41	12.09	1,416	36	11.00	1.08 (0.69, 1.69)
Prior warfarin use	271	8	12.79	271	10	17.00	0.73 (0.29, 1.86)
No prior warfarin use	1,528	43	11.48	1,528	37	11.00	1.09 (0.70, 1.69)
With diabetes	44	0	0.00	44	2	20.00	<0.001 (<0.001, >999)
Without diabetes	1,771	55	12.70	1,771	50	12.00	1.02 (0.70, 1.50)
With heart failure	83	1	5.72	83	2	11.00	0.49 (0.04, 5.38)
Without heart failure	1,740	47	10.81	1,740	50	13.00	0.87 (0.58, 1.30)
CHA2DS2 VASc 0-1	403	12	11.05	403	7	7.00	1.54 (0.61, 3.93)
CHA2DS2 VASc 2-3	1,334	38	11.74	1,334	36	12.00	0.99 (0.62, 1.56)
CHA2DS2 VASc 4+	61	2	15.19	61	0	0.00	>999 (<0.001, >999)
Analysis of secondary comparisons: primary outcome (stroke), ITT							
Outcome	Apixaban			DOACs other than apixaban			aHR (95% CI)
Stroke	2,301	64	12.41	2,301	65	13.00	0.95 (0.67, 1.34)
Outcome	Rivaroxaban			DOACs other than rivaroxaban			aHR (95% CI)
Stroke	2,023	54	11.47	2,023	58	12.00	0.99 (0.68, 1.43)

PY = person-years; aHR = adjusted hazard ratio; CI = confidence interval; PS = propensity score; ITT = intent-to-treat; AT = as-treated

PS model accounts for age, gender, CHA2DS2 VASc score, year of treatment initiation, and the following diagnoses and treatments in baseline: non-major bleeding events, anemia, diabetes, hypertension, heart failure, osteoporosis/hip fracture, malignant neoplasm, acute kidney injury, chronic kidney disease, asthma/copd, dementia, aspirin, antiplatelets other than aspirin, warfarin, antiameric preparations, NSAIDs, opioids, SSRIs, antidepressants other than SSRIs, antiepileptics, antipsychotics, benzodiazepines, lipid

In analysis of stroke, MI, TIA, major bleeding events, and AMS, patients were followed until occurrence of outcome, death, end of patient registration, or end of study period (12/2020).

* In analysis of all cause mortality, patients were followed until occurrence of outcome (death), end of study period (12/2020), or the later date of end of patient registration and any recorded death within 90 days of end of patient registration. Propensity score matched sample size for analysis of all cause mortality differs from sample size in analysis of other outcomes because of differences in censoring criteria which impact a small number of patients' eligibility for inclusion in analysis at the start of follow-up.
DOACs comprised apixaban, rivaroxaban, edoxaban, dabigatran

Supplemental Table 4: Length of follow-up and censoring reasons for the primary comparison (stroke, ITT and AT analyses) and secondary comparisons (stroke, ITT analyses) after PS-matching

	Apixaban vs rivaroxaban (ITT)		Apixaban vs rivaroxaban (AT)		Apixaban vs other DOACs (ITT)		Rivaroxaban vs other DOACs (ITT)	
Exposure group	Apixavan	Rivaroxaban	Apixavan	Rivaroxaban	Apixaban	Other DOACs	Rivaroxaban	Other DOACs
Numer of patients	1,839	1,839	1,839	1,839	2,276	2,276	1,985	1,985
Follow-up time, days								
mean (sd)	891.39 (604.23)	839.10 (580.42)	647.66 (535.75)	574.74 (510.77)	829.15 (586.35)	770.05 (553.42)	844.22 (588.55)	894.75 (611.26)
median [IQR]	845 [340, 1,368]	779 [322, 1,284]	506 [197, 1,001]	412 [170, 855]	742 [298, 1,259]	681 [296, 1,170]	784 [318, 1,296]	828 [343, 1,399]
Censor reason								
Death	40 (2.2%)	26 (1.4%)	24 (1.3%)	18 (1.0%)	44 (1.9%)	28 (1.2%)	29 (1.5%)	42 (2.1%)
End of patient registration	943 (51%)	1,074 (58%)	630 (34%)	662 (36%)	1,081 (47%)	1,227 (54%)	1,187 (60%)	1,066 (54%)
End of study period (12/2020)	800 (44%)	682 (37%)	448 (24%)	367 (20%)	1,086 (48%)	953 (42%)	710 (36%)	812 (41%)
Outcome (stroke)	56 (3.0%)	57 (3.1%)	33 (1.8%)	32 (1.7%)	65 (2.9%)	68 (3.0%)	59 (3.0%)	65 (3.3%)
End of index DOAC	-	-	615 (33%)	562 (31%)	-	-	-	-
Start of DOAC from other comparator group	-	-	43 (2.3%)	119 (6.5%)	-	-	-	-
Start of another DOAC (dabigatran, edoxaban)	-	-	46 (2.5%)	79 (4.3%)	-	-	-	-

DOAC = direct oral anticoagulant; ITT = intent-to-treat; AT = as-treated; PS = propensity score.

Apixaban was compared with other DOACs which included rivaroxaban, edoxaban, and dabigatran; rivaroxaban was compared with other DOACs which included apixaban, edoxaban, and dabigatran.