Safety and Effectiveness of Direct Oral Anticoagulants Versus Warfarin in People with Atrial Fibrillation and Dementia

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Running title: DOACs versus warfarin in AF and dementia

Character summary

DOACs compared to warfarin were associated with similar risks of ischemic stroke, stroke/transient ischemic attack/systemic embolism or other bleeding, and reduced risk of intracranial bleeding; but increased risk of death and gastrointestinal bleeding.

Author contributions

LF, JI and ICKW developed the study concept and design. All authors were involved in acquisition, analysis or interpretation of data. LF drafted the manuscript with input from all authors. All authors were involved in the critical revision of the manuscript for important intellectual content. PD, JI, JSB and ICKW were involved in the study supervision. All authors have read and approved the final manuscript.

Conflicts of interest

IW has received research grants from Hong Kong Research Grant Council, Pfizer, BMS and Bayer in the research of anticoagulant use in patients with AF. KKL has received grant support relating to use of anticoagulants from Pfizer and Boehringer Ingelheim and served on the Advisory Board Committee of Boehringer Ingelheim regarding use of dabigatran. KM has received personal fee from IQVIA Ltd not related to this study. Other authors report no conflicts of interest in this work.

ABSTRACT

Objective: To determine risks of embolic events, bleeding and mortality with direct oral anticoagulants (DOACs) versus warfarin in people with atrial fibrillation (AF) and dementia.

Design: New-user retrospective cohort study using The Health Improvement Network database.

Setting and participants: A population-based sample comprising people with AF and dementia prescribed DOACs or warfarin from August 2011 to September 2017.

Methods: Risk of ischemic stroke, ischemic stroke/transient ischemic attack/systemic embolism (IS/TIA/SE), all-cause mortality, intracranial bleeding (ICB), gastrointestinal bleeding (GIB) and other bleeding were compared for DOACs versus warfarin using propensity score-adjusted Poisson regression. Incidence rate ratios (IRRs) and absolute risk differences (ARDs) were calculated.

Results: Overall, 2399 people with AF and dementia, initiated DOACs (42%) or warfarin (58%). Before propensity score adjustment, patients who initiated DOACs were older and had more comorbidities. After adjustment, DOAC initiators demonstrated similar risks of IS/TIA/SE, IS alone and other bleeding, but reduced ICB risk (IRR, 95% CI, 0.27, 0.08 to 0.86; ARD, 95% CI, -5.2, -6.5 to -1.0 per 1000 person-years) compared to warfarin. Increased risk of GIB (IRR, 95% CI, 2.11, 1.30 to 3.42; ARD, 95% CI, 14.8, 4.0 to 32.4 per 1000 person-years) and all-cause mortality (IRR, 95% CI, 2.06, 1.60 to 2.65; ARD, 95% CI, 53.0, 30.2 to 82.8 per 1000 person-years) were observed in DOAC initiators compared to warfarin.

Conclusion and implications: Among people with AF and dementia, initiating treatment with DOACs compared to warfarin was associated with similar risks of IS/TIA/SE, IS alone and other bleeding. DOAC treated patients demonstrated reduced ICB risk, but increased GIB and all-cause mortality risks. We cannot exclude the possible impact of residual confounding from channelling of DOACs towards older and sicker people, particularly for the outcome of all-cause mortality. Further safety data are urgently needed to confirm findings.

INTRODUCTION

Atrial fibrillation (AF) and dementia predominately affect older adults.[1,2] Compared to the general population with AF, people with AF and dementia have twice the risk of stroke,[3] and 12-47% increased death risk.[4,5] Underutilisation of stroke prophylaxis in people with dementia may contribute to increased stroke and mortality.[6-8] Dementia alone is not an absolute contraindication to stroke prevention; however meta-analyses of 21 studies demonstrate people with AF and dementia have 52% lower odds of receiving warfarin compared to those without dementia.[9] Data from the Swedish Dementia Registry show that only 26% of AF patients are treated with warfarin at the time of dementia diagnosis, yet warfarin is associated with a 24% reduced risk of ischaemic stroke (IS) and a 16% reduced death risk compared to no oral anticoagulation (OAC).[10] Underutilisation may be attributable to concern about an increased bleeding risk in people with dementia. A meta-analysis demonstrated 41% increased risk of intracranial bleeding (ICB) in people with dementia,[11] possibly due to high prevalence of cerebral amyloid angiopathy in this population.[11,12]

Landmark trials of dabigatran, rivaroxaban, apixaban and edoxaban compared with warfarin demonstrated at least equal effectiveness to warfarin for cerebral and systemic embolism prevention, with a reduced risk of ICB.[13-16] However, the landmark trials did not include representative samples of people with dementia.[17,18] American Academy of Neurology guidelines highlight the need for safety data for stroke prevention in people with AF and moderate-to-severe dementia.[19] To our knowledge, no studies have investigated the safety and effectiveness of direct oral anticoagulants (DOACs) compared with warfarin for stroke prevention in people with AF and dementia. The objective of this population-based study was to determine the risks of embolic events, bleeding and mortality with DOACs compared to warfarin in people with AF and dementia.

METHODS

Data source

Data were extracted from The Health Improvement Network (THIN) database. THIN is a nationwide database of electronic primary care records for 15 million individuals (>3 million active patients) from 744 United Kingdom (UK) general practices. THIN includes a 6% representative sample of the UK population.[20] THIN data include patient characteristics, diagnoses, prescriptions, consultations and investigations. Diagnoses, procedures and services were coded using the Read classification system[21] and medications using Multilex codes.[22]

THIN database has been used extensively for pharmacoepidemiological research, including stroke and dementia studies,[23-26] has been validated,[25] and data quality is periodically evaluated. This study was approved by THIN Scientific Review Committee (18THIN033).

Study design and study participants

We conducted a new-user retrospective cohort study. Patients aged ≥18 years first diagnosed with AF (Read codes, Supplemental Table S1) between 1 August 2011 and 26 September 2017 were selected. The index date was the first prescription of dabigatran, rivaroxaban, apixaban, edoxaban or warfarin following AF diagnosis. Patients with <12 months of medical history prior to the index date were excluded. We also excluded patients with valvular heart disease, hyperthyroidism, without dementia, patients who died during their first AF episode and those not prescribed OACs (Figure 1). We used a new-user design and excluded patients who received DOACs or warfarin within 180 days prior to the index date.[27] Dementia was defined as a Read code for dementia, included as a diagnosis or symptom, or a prescription for an anti-dementia medication (memantine, donepezil, rivastigmine or galantamine) prior to or on the index date (Supplemental Table S1).[28,29] Patients with all forms of cognitive impairment or dementia were eligible, including mild cognitive impairment, Alzheimer's disease, vascular dementia, mixed dementias, frontotemporal dementia and Lewy Body dementia (Supplemental Table S2). Study analyses and reporting followed the Strengthening the Reporting of Observational Studies in Epidemiology guideline.[30]

Exposure to oral anticoagulants

DOACs available in the UK between August 2011 and September 2017 (dabigatran, rivaroxaban, apixaban or edoxaban) were grouped and compared with warfarin. Continuous exposure was defined as starting from the first prescription for an OAC after AF diagnosis (index date) until treatment discontinuation or switch. For DOACs, prescription dates, quantity supplied, and dosing frequency were used to determine treatment duration and discontinuation. A gap of >3 days for DOACs between prescription refills (expected end date of last prescription and start date of a subsequent prescription) was considered treatment discontinuation. Warfarin discontinuation was defined as a gap >37 days in either prescription refills or international normalised ratio (INR) testing. We used 3-day and 37-day gaps for DOACs and warfarin, respectively, as 90% of all treatment gaps from our cohort were less than 3 days for DOACs and 37 days for warfarin. This is consistent with research investigating patient persistence to OAC[31] and previous observational studies using 3-60 day treatment gaps.[32-34] Regular dose

DOACs included dabigatran 150mg twice daily, rivaroxaban 20mg daily, apixaban 5mg twice daily and edoxaban 60mg daily. Low-dose DOACs included dabigatran 110mg and 75mg twice daily, rivaroxaban 15mg daily, apixaban 2.5mg twice daily and edoxaban 30mg daily.

Effectiveness and Safety Outcomes

Effectiveness outcomes included ischaemic stroke (IS), IS/transient ischaemic attack (TIA)/systemic embolism (SE) and all-cause mortality. Safety outcomes included non-traumatic intracranial bleeding (ICB) (including subarachnoid, intracerebral or subdural haemorrhage), gastrointestinal bleeding (GIB) and other bleeding (anaemia, urinary tract bleeding, respiratory bleeding, bleeding in eye and haemopericardium). Outcomes were defined using Read codes (Supplemental Table S1). Validation of IS has been undertaken in THIN which demonstrated a positive predictive value between 76 to 86%.[35] Further, an 82% confirmation rate for ICB has been reported (91% for subarachnoid haemorrhage and 73% for ICB).[36] Patients were followed up from the index date until study end (26 September 2017), outcome occurrence, death, OAC switch, treatment discontinuation, last date of data collection or departure from general practice, whichever occurred first.

Comorbidities, concomitant medication use and risk scores

Concomitant medication use was identified from medications prescribed up to 180 days before or on the index date. Data on chronic comorbidities recorded before the index date were extracted, and used to compute the Charlson Comorbidity Index (CCI).[37] Smoking status information from the most recent date prior to the index date was extracted. Patients with missing smoking status (0.25%) were categorized as non-smokers based on a smoking validation study in THIN.[38] Stroke risk was estimated with $CHA_2DS_2\text{-}VAS_C$ scores[39] and major bleeding risk with HAS-BLED scores.[40]

Statistical analysis

Propensity scores (PS) with inverse probability of treatment weights (IPTW) analysis was used to address confounding.[41] IPTWs were derived to estimate population average treatment effects.[41] IPTWs were created for each individual; as such individuals on DOACs were given a weight of 1/PS and warfarin users a weight of 1/(1-PS). PS were estimated by logistic regression; the dependent variable was DOAC exposure (yes/no). Covariates were measured at baseline and included: age (continuous); gender; IS, TIA or SE; major (ICB or GIB) bleeding; other bleeding (anaemia, urinary tract bleeding, respiratory bleeding, eye bleeding

and haemopericardium); vascular disease (myocardial infarction or peripheral vascular disease); congestive cardiac failure; moderate to advanced chronic kidney disease; hypertension; diabetes, smoking status; baseline medication use (≤180 days prior to index date): angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, calcium channel blockers, beta-blockers, aspirin or clopidogrel, loop diuretics, non-steroidal anti-inflammatory drugs, statins, proton pump inhibitors, histamine-2 receptor antagonists, selective serotonin reuptake inhibitors, anti-dementia medications; and CHA_2DS_2-VASc, HAS-BLED and CCI scores.

Standardized differences were used to assess differences in baseline characteristics between treatment groups. A threshold of 0.1 was considered negligible.[42] Weighted distributions for DOAC and warfarin groups were graphically inspected for substantial overlap.[41] Individuals treated contrary to prediction (PS above 97.5[th] percentile for warfarin and below 2.5[th] percentile for DOACs) were trimmed for the main analysis to reduce residual confounding.[43]

Baseline characteristics were presented as numbers, percentages, means (standard deviations), or medians (interquartile ranges). Crude event rates were estimated using the number of events divided by person time, expressed as rates per 1000 person-years. Cause-specific outcome risks between DOAC and warfarin users were compared using Poisson regression. Results were expressed using incidence rate ratios (IRRs) with 95% confidence intervals (CIs). Adjusted absolute risk differences (ARD) were estimated by I × (adjusted IRR–1), where I was the weighted incidence rate among warfarin users).[44,45] A two-sided P-value of <0.05 was considered statistically significant. Statistical analyses were independently conducted by LF and WL for quality assurance. Data preparation and analyses were undertaken using SAS v9.4 (SAS Institute, Inc, Cary, NC, USA).

Sensitivity and subgroup analyses

Sensitivity analyses were conducted to test robustness of results. First, the maximum allowable treatment gap was extended to 14 days for DOACs and 53 days for warfarin to investigate the impact of potential misclassification of exposure time on outcomes (95% of patients with this medication gap).[31] Second, a sensitivity analysis for the full, untrimmed cohort was conducted. Third, subgroup analyses of individual DOACs, apixaban and rivaroxaban, were compared with warfarin. PS models were re-run for apixaban or rivaroxaban versus warfarin in subgroup analyses. Dabigatran or edoxaban versus warfarin were not analysed separately due to insufficient users. Fourth, we conducted a sensitivity analysis using the Fine-Gray Cox

regression model that accounts for competing risk of death by calculating the subdistribution hazard ratios of all outcomes. Fifth, we confirmed all primary outcome results using the PS stratification approach (number of strata=5). Sixth, an analysis of reduced dose DOACs versus warfarin was undertaken. Finally, we conducted a post-hoc sensitivity analysis for the outcome of all-cause mortality. We included additional covariates in the PS model including all cancers, chronic obstructive pulmonary disease and ischemic heart disease based on mortality trends from Public Health England.[46]

RESULTS

There were 2399 people with AF and dementia (80% Alzheimer's dementia) who initiated DOACs (42%) or warfarin (58%). Median age was 82 (IQR 78-87) years and 54% were female. The overall anticoagulation rate was 44%. The distribution of OACs was: warfarin (n=1386, 58%), rivaroxaban (n=503, 21%), apixaban (n=428, 18%), dabigatran (n=77, 3%), and edoxaban (n=5, 0.2%). More people were initiated on DOACs compared to warfarin from 2015 onwards (Supplemental Figure S1).

Table 1 outlines baseline characteristics of patients initiating DOACs versus warfarin, before weighting and trimming. After IPTW adjustment and trimming, these characteristics were well balanced with standardized differences <0.1 for all covariates. Prior to weighting, DOAC users were older, had a higher prevalence of prior stroke/TIA or SE, higher chronic comorbidity burden, higher prevalence of anti-dementia medication use, but a lower prevalence of chronic kidney disease and congestive cardiac failure compared with warfarin users (Table 1).

During 1978 person-years of on-treatment follow up, there were 53 IS and 35 TIA or SE observed. Results for Poisson regression analysis after IPTW demonstrated no difference in embolic risk (IS/TIA/SE: IRR, 95% CI; 0.91, 0.67 to 1.25; ARD, 95% CI per 1000 person-years, -4.0, -15.4 to 11.5) or IS alone (IRR, 95% CI; 1.16, 0.78 to 1.73; ARD, 95% CI per 1000 person-years, 4.0, -5.5 to 18.1) between DOAC and warfarin initiators (Table 2/Figure 2).

Overall, 12 patients developed ICB (0.5%), 43 developed GIB (1.8%) and 57 other bleeding (2.4%). Poisson regression yielded a significantly lower ICB risk with DOAC treatment (IRR, 95% CI, 0.27, 0.08 to 0.86; ARD, 95% CI per 1000 person-years, -5.2, -6.5 to -1.0). DOAC use was associated with significantly increased GIB risk (IRR, 95% CI; 2.11, 1.30 to 3.42; ARD, 95% CI per 1000 person-years 14.8, 4.0 to 32.4). No differences in other bleeding risk were observed between DOAC and warfarin users (IRR, 95% CI; 0.87, 0.59 to 1.28; ARD, 95% CI per 1000 person-years -4.1, -12.6 to 8.4) (Table 2/Figure 2).

Crude rates of all-cause mortality were higher for DOAC initiators compared to warfarin, 121.5 (DOAC) versus 49.9 (warfarin) per 1000 person-years. All-cause mortality risk was significantly increased in DOAC initiators (IRR, 95% CI; 2.06, 1.60 to 2.65; ARD, 95% CI per 1000 person-years, 53.0, 30.2 to 82.2) (Table 2/Figure 2).

Several sensitivity analyses were performed. Consistent with primary analysis, DOAC users were at increased risk of all-cause death (IRR, 95% CI, 1.87, 1.52 to 2.31), but had reduced

ICB risk (IRR, 95% CI, 0.35, 0.14 to 0.93) when treatment gaps were increased. However, IS risk was higher (IRR, 95% CI; 1.62, 1.12 to 2.34) in DOAC users compared with warfarin (a shift from no difference in primary analysis) and no difference in GIB risk was observed (IRR, 95% CI; 1.42, 0.96 to 2.10), a shift from increased risk in DOAC users in primary analysis, when treatment gaps were increased. No differences from primary results were observed when data for the full, untrimmed cohort were analysed. Subgroup analyses of apixaban or rivaroxaban versus warfarin were consistent with primary outcome results for DOACs versus warfarin, except that no difference was observed for ICB risk for apixaban or rivaroxaban versus warfarin (Supplemental Table S5, Figures S2 and S3). Results of Fine-Gray Cox regression accounting for competing risk of death did not change from primary results for any outcome (Supplemental Table S3). Further, all outcome results remained the same when the PS stratification approach was used, except for ICB, of which the confidence intervals became wider and included one (IRR, 95% CI; 0.47, 0.08-1.97) (Supplemental Table S3). On comparison of reduced dose DOACs versus warfarin, an association of a reduced risk of IS/TIA/SE was observed in low dose DOAC users compared with warfarin (IRR, 95% CI, 0.62, 0.40 to 0.94).When additional covariates were included in the PS model evaluating the outcome of all-cause mortality, no significant change from the primary analysis was observed (IRR, 95% CI, 2.04, 1.59 to 2.61).

DISCUSSION

This population-based study demonstrated people with AF and dementia initiated on DOACs had a similar risk of IS/TIA/SE, IS alone or other bleeding, lower risk of ICB, but a higher risk of all-cause mortality and GIB, compared to warfarin users. Results for subgroup analyses of apixaban or rivaroxaban versus warfarin were consistent with DOAC versus warfarin comparisons. Results were robust to almost all sensitivity analyses, which used different treatment gaps, data for the full untrimmed cohort, Fine-Gray Cox regression to account for competing risk of death, an analysis of reduced dose DOACs versus warfarin and a post-hoc analysis for all-cause mortality. When outcomes were re-analysed using an alternate PS modelling approach (stratification), results were similar to the main analysis, except for ICB risk, of which the effect size remained similar, but the confidence intervals widened. This is most likely due to the small number of ICB events and a reduction in statistical power after stratification of the data.

Our study fills an important evidence gap. Due to the lack of safety data, current clinical practice guidelines do not provide comprehensive OAC prescribing information in AF and dementia.[5,19,47] Compared to those without dementia, people with AF and dementia are often older, frailer, have higher rates of multi-morbidity and multiple medication use, which may alter the effect of anticoagulation. Our data show increasing use of DOACs in favour of warfarin from 2015 onwards. The 44% anticoagulation rate among people with dementia in our study was within rates of 14% to 64% reported in previous studies.[9] Our study participants, who were selected based on the presence of dementia, demonstrated differences in baseline characteristics to study samples selected for landmark DOAC trials, including higher rates of prior stroke/TIA or SE than the ARISTOTLE trial,[15] but lower rates than the ROCKET-AF trial,[16] and increased use of aspirin and/or clopidogrel. The ability to study older participants with comorbidities, particularly dementia, is challenging, due to increased risks of unanticipated toxicity[48] and enrolment difficulties.[18] This study provides comparative safety and effectiveness data in an older, frailer population with dementia, which will help to inform anticoagulant decision making in AF and dementia.

We found similar risks of embolic events or IS alone between DOAC and warfarin initiators, and for apixaban or rivaroxaban versus warfarin. Our findings for apixaban versus warfarin in people with dementia differ to ARISTOTLE trial results which demonstrated reduced IS risk and uncertain stroke type in apixaban versus warfarin in the general population,[15] but are in-

line with results from Danish routine care which showed no difference in IS rates between apixaban and warfarin.[49] Our results for similar IS risk with rivaroxaban are in-line with the ROCKET-AF trial which showed non-inferiority of rivaroxaban compared to warfarin for stroke or systemic embolism.[16] People with dementia prescribed rivaroxaban in our study were older than ROCKET-AF participants but had lower rates of prior embolic events (27% versus 55% in ROCKET-AF). Further, apixaban and rivaroxaban users in our study comprised patients treated with lower (54% apixaban, 27% rivaroxaban) and standard- doses of apixaban or rivaroxaban, whereas ARISTOTLE and ROCKET-AF investigated standard doses only.[16] Other high-risk sub-populations, for example, patients with chronic kidney disease, are also commonly prescribed lower DOAC doses in routine care,[34] which could account for the different stroke risks and comparative efficacy observed outside of trial settings. We conducted a sensitivity analysis of low-dose DOACs versus warfarin. This analysis indicated a significant association of a reduced risk of IS/TIA/SE with DOAC treatment. However, given the low numbers of DOAC users compared to warfarin in this analysis (476 versus 1386), results should be viewed with caution as they could arise due to chance alone. Further, our data yielded significantly reduced ICB risk for DOACs versus warfarin, consistent with DOAC trials.[13-16] It has been demonstrated that older people, especially those with Alzheimer's disease, are at increased risk of developing cerebral amyloid angiopathy, which is an established risk factor for intracerebral haemorrhage.[11,12] Impacts of this risk factor for ICB in this high-risk subpopulation, in which there are few data for comparison, is unknown. Nonetheless, increased safety of DOACs compared to warfarin in this high-risk subpopulation for intracranial haemorrhage is promising, however results should be interpreted cautiously due to low numbers.

A statistically significant increased GIB risk was found with DOAC treatment compared to warfarin in this study. This finding is contrary to a meta-analysis, which demonstrated no difference in GIB for DOACs versus warfarin.[50] Our subgroup analyses also demonstrated increased GIB risk for apixaban or rivaroxaban compared to warfarin. Our results differ to the ARISTOTLE trial, which demonstrated reduced GIB risk,[15] but are consistent with the ROCKET-AF trial which showed increased GIB risk with rivaroxaban.[16] Rate of gastric acid suppression was similar between DOAC and warfarin initiators in our study cohort (~50%) but was much higher than reported in ARISTOTLE (18%).[15] Increased use of gastric acid suppression may be due to higher prevalence of GIB risk factors among our cohort. Further,

concurrent use of antiplatelet drugs was double that of trial populations (~60% versus ~33% in ARISTOTLE trial[15]), which substantially adds to GIB risk.

Increased mortality risk with DOACs compared to warfarin observed in our study could reflect altered anticoagulation in people with dementia. However, despite propensity score adjustment, we cannot exclude the possibility that these results arise through channelling of DOACs to older, sicker individuals. Selective prescribing of DOACs in relation to patient characteristics was observed and is consistent with other studies.[49] DOAC initiators were older, more frequently used anti-dementia medications, demonstrated increased prevalence of prior IS/TIA/SE and had a higher chronic comorbidity burden compared to warfarin users. Nonetheless, our results showing increased mortality risk with DOAC treatment are in-line with other UK data, which demonstrated increased all-cause mortality risk in rivaroxaban users and also in patients prescribed lower apixaban doses.[34] It is possible that patients treated with warfarin, who require regular INR monitoring, have higher levels of healthcare interaction leading to better management of medication and health issues. Indeed, prior research has demonstrated well-managed warfarin treatment is associated with lower complication rates and mortality than pivotal DOAC trial data.[51] We suggest that the results for all-cause mortality should be interpreted cautiously, until further data are available. A post-hoc sensitivity analysis that included additional covariates in the PS model relating to causes of death in the UK[46] did not significantly alter results. Ultimately, it may only be possible to address all-cause mortality risk through a prospective randomised study.

Strengths and limitations

A strength of this study was availability of representative clinical data for 2399 people with AF and dementia. We used inverse probability of treatment weighting to account for selective prescribing of anticoagulants based on patients' characteristics. While the IPTW approach can balance baseline risks of DOAC and warfarin groups, it cannot fully account for increased competing risk of death which may limit observed follow-up time during which an outcome of interest could occur. Given this, we conducted a Fine-Gray Cox regression to account for competing risk of death. The results were similar to the main analysis which demonstrated that competing risk of death was unlikely to have a major impact in this study. Moreover, we cannot completely rule out misclassification of dementia, however validation of dementia diagnosis in UK primary care has demonstrated high coding accuracy,[28,52] which suggests misclassification is unlikely to be a significant limitation. Study limitations include wide

confidence intervals for some outcome rates. Further, results only apply to the anticoagulated population; people with AF and dementia not prescribed anticoagulants were likely to have been sicker, older, or have different end-of-life goals. We compared any DOAC versus warfarin in primary analyses and apixaban and rivaroxaban separately to warfarin in subgroup analyses. Few users of dabigatran and edoxaban excluded further subgroup analyses. Our results suggest apixaban and rivaroxaban may have different effects and head-to-head DOAC comparisons among people with dementia are required. OAC adherence is an important determinant of adverse events. Anti-dementia medication use was different for DOAC initiators compared to warfarin initiators (22% vs 8%). The rate of anti-dementia medication use among the DOAC group is within the range for the overall population of dementia in the UK (15-36%), but is lower than this range for warfarin users.[53] We adjusted for this in PS modelling, however we there are no data in a dementia specific population to understand representativeness. We were unable to measure adherence, nor time in therapeutic range for warfarin, this could impact results. As with all observational studies there remains the possibility of confounding for unmeasured parameters.

CONCLUSION and IMPLICATIONS

People with AF and dementia initiated on DOACs demonstrated a reduced risk of ICB, similar risks of embolic events and other bleeding, but an increased risk of all-cause mortality and GIB, compared to warfarin users. It is unclear to what extent this finding reflects altered effects of anticoagulation in people with dementia or results from residential confounding arising from channelling of DOACs to older and frailer individuals. More studies are urgently needed to understand safety and effectiveness of DOACs in people with dementia, including a large prospective trial of DOACs versus warfarin and direct head-to-head DOAC comparisons.

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Table 1. Baseline characteristics before inverse probability of treatment weighting, according to treatment

	DOACs N=1013	Warfarin N=1386	Absolute standardized difference	
			BEFORE IPTW	AFTER IPTW and trimming
Age (years) Median (IQR)	84 (79-88)	81 (77-86)	0.35	0.01
Female, n (%)	563 (56)	737 (53)	0.05	0.00
Comorbidities at baseline, n (%)				
Congestive heart failure	117 (12)	210 (15)	0.11	0.01
Hypertension	672 (66)	967 (70)	0.07	0.03
Diabetes	232 (23)	301 (22)	0.03	0.02
Prior stroke/TIA/SE	305 (30)	351 (25)	0.11	0.01
Vascular disease	203 (20)	266 (19)	0.02	0.01
Chronic kidney disease	99 (10)	243 (18)	0.23	0.00
History of major bleeding	158 (16)	184 (13)	0.07	0.01
History of other bleeding	133 (13)	159 (11)	0.05	0.02
Current smoker	56 (6)	91 (7)	0.04	0.01
Medication use, n (%)				
NSAIDs	85 (8)	142 (10)	0.06	0.02
Aspirin and/or clopidogrel	617 (61)	835 (60)	0.01	0.00
Beta-blockers	600 (59)	840 (61)	0.03	0.02
Calcium channel blockers	342 (34)	508 (37)	0.06	0.01
Loop diuretics	301 (30)	468 (34)	0.09	0.01
Statins	607 (60)	843 (61)	0.02	0.02
ACEI/A2RB	134 (13)	217 (16)	0.07	0.01
PPIs	457 (45)	613 (44)	0.02	0.01
Histamine type-2 receptor antagonists	57 (6)	63 (5)	0.05	0.00
SSRIs	141 (14)	172 (12)	0.04	0.02
Anti-dementia medications	224 (22)	114 (8)	0.39	0.02
$CHA_2DS_2\text{-}VASc$[1]			0.09	0.01
Median (IQR)	4 (3-5)	4 (3-5)	--	--

0-1	18 (2)	31 (2)	--	--
2-3	308 (30)	462 (33)	--	--
≥4	687 (68)	893 (65)	--	--
HAS-BLED[2]			0.05	0.01
Median (IQR)	3 (2-4)	3 (2-4)	--	--
≥3	728 (72)	964 (70)	--	--
Charlson Comorbidity Index			0.26	0.00
Median (IQR)	7 (5-8)	6 (5-7)	--	--
Low dose DOAC, n (%)	479 (47)	N/A	--	--

IPTW = inverse probability of treatment weighting; other bleeding includes: anaemia, urinary tract bleeding, respiratory bleeding, bleeding in the eye, and haemopericardium; major bleeding includes intracranial bleeding and gastrointestinal bleeding; TIA = transient ischemic attack; SE = systemic embolism; ACEI/A2RB = angiotensin-converting enzyme inhibitor/angiotensin-2 receptor blocker; NSAIDs = non-steroidal anti-inflammatory drugs; SSRIs = selective serotonin reuptake inhibitors; Anti-dementia medications include: memantine, donepezil, rivastigmine or galantamine; Trimming = propensity scores above 97.5th percentile for patients treated with warfarin and below 2.5th percentile for patients treated with DOACs were trimmed; Absolute standardized difference is the mean difference in DOAC group versus warfarin group divided by the pooled standard deviation. A standardized difference ≤ 0.1 indicates a negligible difference in covariates between treatment groups.

[1]CHA$_2$DS$_2$-VASc indicates patients with congestive cardiac failure, hypertension, age ≥75 years (doubled), diabetes mellitus, age 65 to 74 years, prior stroke or TIA or SE (doubled), vascular disease, and gender category (women). CHA$_2$DS$_2$-VASc score ranges from 0 to 9 (higher score indicates a higher risk for stroke).

[2]HAS-BLED indicates patients with hypertension, renal disease, liver disease, prior stroke, prior major bleeding, age > 65 years, medications that predispose to bleeding (NSAIDs, aspirin, clopidogrel), alcohol use (labile INR not included). HAS-BLED score ranges from 0 to 8 (as labile INR not included in calculation), a higher score indicates a higher risk for bleeding.

Table 2. Crude event rates and absolute risk differences in outcome events with direct oral anticoagulants versus warfarin

|	Crude event rates (number of events) per 1000 person-years[x]		Absolute risk difference per 1000 person-years (95% CI)*
	DOACs N = 1013	**Warfarin** N = 1386	**DOACs Vs warfarin**
EFFECTIVENESS OUTCOMES			
Ischemic stroke, TIA or SE	39.4 (33)	48.2 (55)	-4.0 (-15.4 to 11.5)
Ischemic stroke	24.9 (21)	27.7 (32)	4.0 (-5.5 to 18.1)
All-cause mortality	121.5 (104)	49.9 (59)	53.0 (30.2 to 82.2)
SAFETY OUTCOMES			
Intracranial bleeding	3.5 (3)	7.6 (9)	-5.2 (-6.5 to -1.0)
GI bleeding	33.2 (28)	12.8 (15)	14.8 (4.0 to 32.4)
Other bleeding	28.7 (24)	28.8 (33)	-4.1 (-12.6 to 8.4)
[X] Event rates = events divided by person time expressed per 1000 person-years * After inverse probability of treatment weighting Other bleeding includes: anaemia, urinary tract bleeding, respiratory bleeding, bleeding in the eye and haemopericardium; TIA = transient ischaemic attack; SE = systemic embolism			
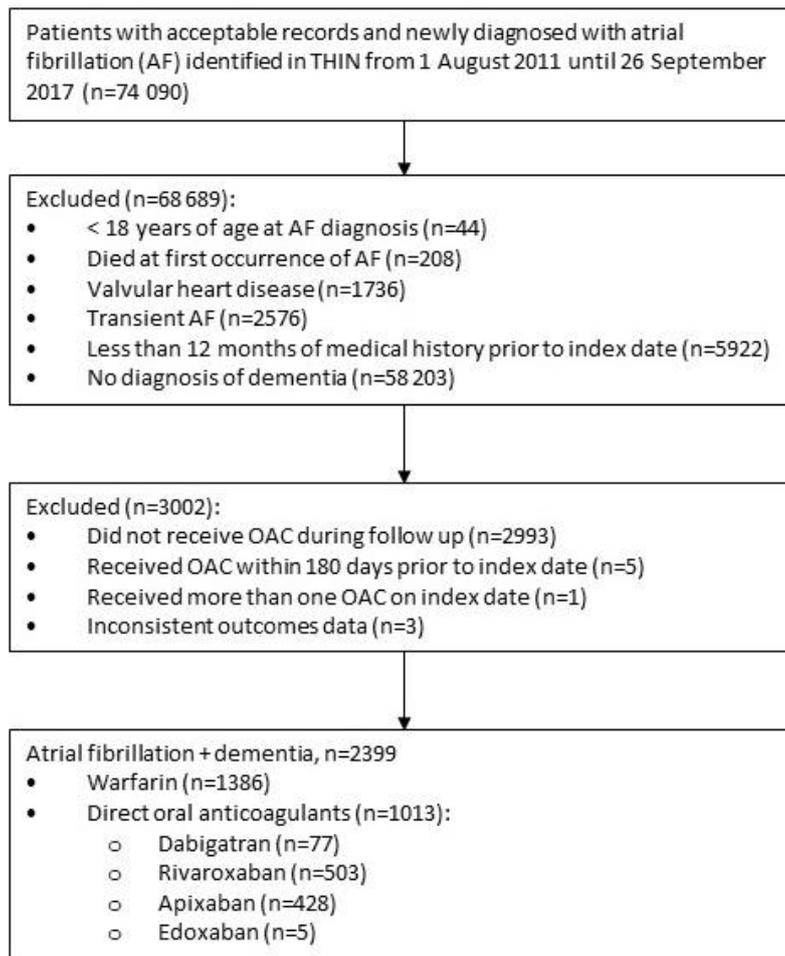
Figure 1. Selection of the study sample from The Health Improvement Network database. OAC = oral anticoagulation

Figure 2. Forest plot depicting incidence rate ratios and 95% confidence intervals of inverse probability of treatment weighted cohort comparisons for direct oral anticoagulants versus warfarin

Outcome	Incidence Rate Ratio (95% CI)	Incidence_Rate_Ratio	P_value
Ischemic stroke, TIA or SE		0.91 (0.67 to 1.25)	p=0.5685
Ischemic stroke		1.16 (0.78 to 1.73)	p=0.4672
All cause mortality		2.06 (1.60 to 2.65)	p<0.0001
Intracranial bleeding		0.27 (0.08 to 0.86)	p=0.0152
Gastrointestinal bleeding		2.11 (1.30 to 3.42)	p=0.0025
Other bleeding		0.87 (0.59 to 1.28)	p=0.4663

← Favors DOACs   Favors warfarin →

0.5   1   1.5   2.5 3.5
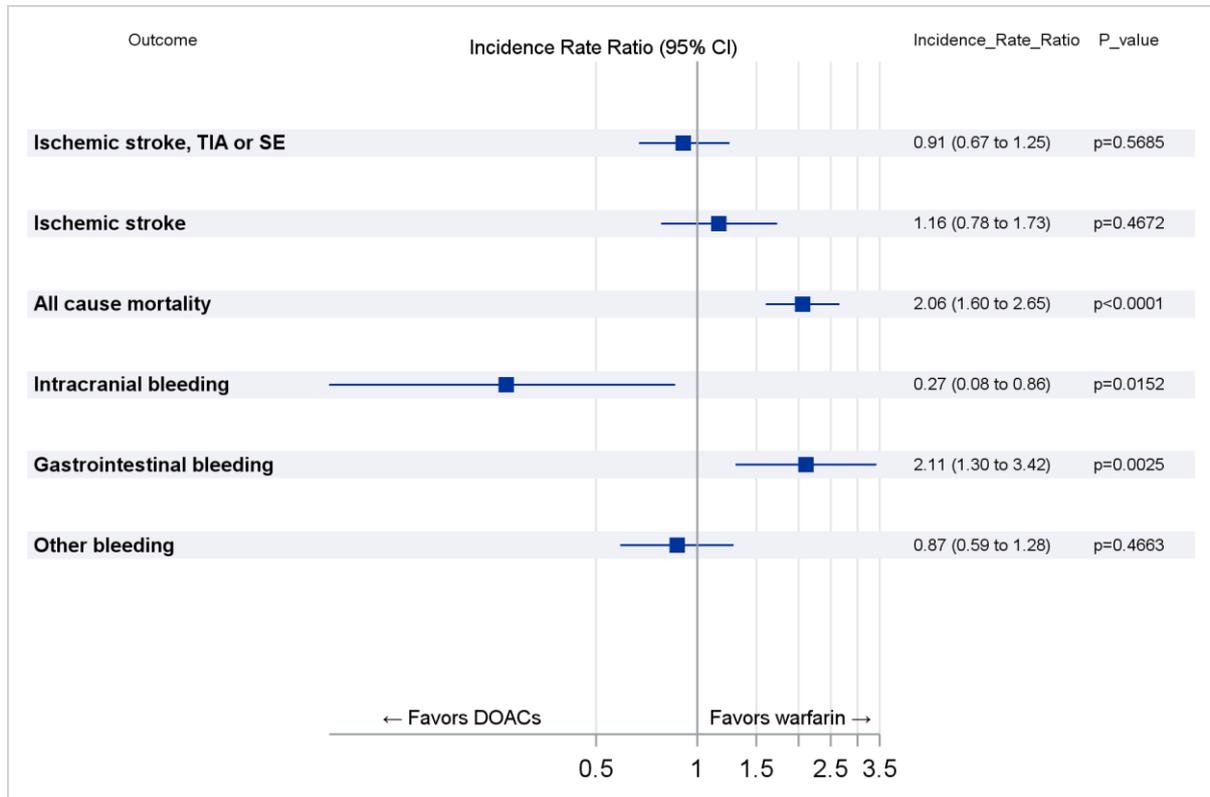
SUPPLEMENTARY DATA

TABLES

Table S1. Read codes, Multilex codes and Anatomical Therapeutic Chemical (ATC) codes for atrial fibrillation, dementia, warfarin, direct oral anticoagulants and outcomes

Table S2. Types of dementia stratified by OAC treatment

Table S3. Sensitivity analyses for DOACs compared to warfarin: hazard ratios or incidence rate ratios with 95% confidence intervals and p-values for increased treatment gap (DOACs = 14 days; warfarin = 53 days), the full untrimmed cohort, reduced dose DOACs Vs warfarin, results using propensity score stratification approach, Fine-Gray Sub distribution hazards Cox regression (for competing risk of death) and all-cause mortality (additional covariates included in propensity score model). Warfarin served as the reference group.

Table S4. Baseline characteristics before inverse probability of treatment weighting and trimming for the subgroup analysis for apixaban or rivaroxaban versus warfarin

Table S5. Crude outcome event rates and absolute risk differences comparing inverse probability of treatment weighted new user cohorts of apixaban or rivaroxaban compared with warfarin

FIGURES

Figure S1. Number of patients starting anticoagulants by study year

Figure S2. Forest plot showing incidence rate ratios and 95% confidence intervals of inverse probability of treatment weighted cohort comparisons for apixaban versus warfarin

Figure S3. Forest plot showing incidence rate ratios and 95% confidence intervals of inverse probability of treatment weighted cohort comparisons for rivaroxaban versus warfarin

Table S1. Read codes, Multilex codes and ATC codes for atrial fibrillation, dementia, warfarin, direct oral anticoagulants and outcomes

Condition	Read Codes	Multilex and ATC codes
Atrial fibrillation	G573.00, G573000, G573200, G573300, G573400, G573500, G573700, G573z00	
Dementia	**Alzheimer's dementia:** Eu00.00, Eu00000, Eu00011, Eu00012, Eu00013, Eu00100, Eu00111, Eu00112, Eu00113, Eu00200, Eu00z00, Eu00z11, F110.00, F110000, F110100, Fyu3000, 66h..00, 6AB..00, 9Ou..00, 9Ou1.00, 9Ou2.00, 9Ou3.00, 9Ou4.00, 9Ou5.00, 9hD..00, 9hD0.00, 9hD1.00, ZS7C500, 1461 **Vascular dementia:** E004.00, E004.11, E004000, E004100, E004200, E004300, E004z00, Eu01.00, Eu01.11, Eu01000, Eu01100, Eu01111, Eu01200, Eu01300, Eu01y00, Eu01z00 **Frontotemporal dementia**: Eu02000, F111.00, F118.00, F113000, Eu02300, F11x900 **Lewy body dementia:** Eu02500, F116.00 **Other dementia: (includes mixed dementia and dementia with identifiable causes other than Alzheimer's, vascular, frontotemporal or Lewy body):** E012.00, E012.11, E02y100, Eu02.00, Eu02100, Eu02200, Eu02400, Eu02y00, Eu10711, Eu02z00, Eu02z11, Eu02z13, Eu02z14, Eu02z16, Eu04100, E00..11, E00..12, E000.00, E001.00, E001000, E001100, E001200, E001300, E001z00, E002.00, E002000, E002100, E002z00, E003.00, E041.00	**ATC:** N06DA **Multilex:** 22950978, 22954978, 32207978, 53097979, 54761979, 54762979, 54763979, 56115979, 58735979, 58737979, 9248979, 59249979, 60403979,61227979, 70165978, 70167978, 70168978, 70169978, 70170978, 70481978, 70484978, 75982978, 75983978, 78073978, 78074978, 78075978, 78583979, 81180998, 81181998, 81182998, 82960978, 83186978, 83488978, 83489978, 83491978, 83567998, 83569998, 83573998, 83574998, 83736978, 83737978, 84086978, 84087978, 84304998, 84305998, 84306998, 84307998, 84615978, 85088998, 85089998, 85090998, 85091998, 85165978, 86814998, 86815998, 86816998, 86817998, 86818998, 86819998, 88277998, 88483996, 88483997, 88483998, 88928998, 88984997, 88984998, 88986997, 88986998, 90702996, 90702997, 90702998, 90705998, 91099998, 91100998, 91605990, 92090998, 92091998, 92301998, 92457998, 92579996, 92579997, 92579998, 97471996, 97471997, 97471998, 98131998, 29567978, 32208978, 32209978, 55685978, 79695978, 83564998, 70166978, 63677979, 72827978
Ischemic stroke	G64..00, G64..11, G64..12, G64..13, G640.00, G640000, G641.00, G641.11, G641000, G64z.00, G64z.11, G64z.12, G64z000, G64z100, G64z111, G64z200, G64z300, G64z400, G66..00, G66..11, G66..12, G66..13, G660.00, G661.00, G662.00, G663.00, G664.00, G665.00, G666.00, G667.00, G668.00, G669.00, G676.00, G676000, G6W..00, G6X..00, G650.00, G650.11, G651.00, G651000, G652.00, G653.00, G654.00, G656.00, G657.00, G65y.00, G65z.00, G65z000, G65z100, G65zz00, Gyu6300, Gyu6400, Gyu6500, Gyu6600, Gyu6G00, G63y000, G63y100	
Transient ischemic attack	G65..00, G65..11, G65..12, G65..13, G650.00, G650.11, G651.00, G651000, G652.00, G653.00, G654.00, G656.00, G657.00, G65y.00, G65z.00, G65z000, G65z100, G65zz00, Fyu5500, ZV12D00	

Systemic embolism	G74..00, G74..11, G74..12, G74..13, G740.00, G740.11, G740.12, G740.13, G740.14, G741.00, G742.00, G742000, G742100, G742200, G742300, G742400, G742500, G742600, G742700, G742800, G742900, G742A00, G742B00, G742z00, G743.00, G74y.00, G74y000, G74y100, G74y200, G74y300, G74y500, G74y600, G74y700, G74y800, G74y900, G74yz00, G74z.00, G650.11, G651.00, G651000, G652.00, G653.00, G654.00, G656.00, G657.00, G65y.00, G65z.00, G65z000, G65z100, G65zz00, Gyu6300, Gyu6400, Gyu6500, Gyu6600, Gyu6G00, G63y000, G63y100	
Intracranial bleeding (non-traumatic)	G60..00, G600.00, G601.00, G602.00, G603.00, G604.00, G605.00, G606.00, G60X.00, G60z.00, G61..00, G61..11, G61..12, G610.00, G611.00, G612.00, G613.00, G614.00, G615.00, G616.00, G617.00, G618.00, G619.00, G61X.00, G61X000, G61X100, G61z.00, G62..00, G620.00, G621.00, G622.00, G623.00, G62z.00, Gyu6000, Gyu6100, Gyu6200	
Gastrointestinal bleeding	J10y000, J110100, J110111, J110300, J111100, J111111, J111300, J11y100, J11y300, J11yy00, J120100, J120300, J121100, J121111, J121300, J12y100, J12y300, J12yy00, J130100, J130300, J131100, J131300, J13y100, J13y300, J13yy00, J140100, J140300, J141100, J141300, J14y100, J14y300, J14yy00, J150000, J56y000, J573.00, J573.11, J573000, J573011, J573012, J573100, J573z00, J68..00, J680.00, J680.11, J681.00, J681.11, J681.12, J681.13, J68z.00, J68z.11, J68z000, J68z100, J68z200, J68zz00, G850.00, G852000	
Other bleeding (anaemia, urinary tract bleeding, respiratory bleeding, bleeding in the eye and haemopericardium)	**Anaemia:** D000.12, D211.00 **Urinary tract bleeding:** K0A2.00, K197.00 **Respiratory bleeding:** R047.00, R047.11, R048.00, R063.00, R063000, R063100, R063z00, S702.00, S703.00, S704.00, S705.00, S707.00, S708.00, S70z.00, Ryu0200, Ryu0700 **Bleeding in the eye:** F436.00, F436000, F436100, F436z00, F42y.11, F42y000, F42y100, F42y300, F42y400, F42y500, F4K2800 **Haemopericardium:** G530.00	
Direct oral anticoagulants (DOACs)	N/A	**ATC:** B01AF01, B01AF02, B01AE07, B01AF03 **Multilex:** 59453978, 59454978, 60767979, 60768979, 60769979, 60770979, 80953998, 80954998, 80955998, 80956998, 83418998, 83425998, 81214998, 81215998 83971998, 83972998, 83973998 83974998, 46894978, 46895978 46896978, 46897978, 46899978, 53246979, 53247979, 81167998 81168998
Warfarin	N/A	**ATC:** B01AA03

		Multilex: 30534978, 30538978, 66290979, 66298979, 79057979, 79061979, 83976998, 83977998, 84565998, 86425998, 90048979, 90049979, 95741992, 52818979, 58667979, 61036979, 62209979, 79051979, 81727998, 82804978, 83005998, 85529998, 88944998, 92245998, 93227990, 93532990, 94878990, 94879990, 95232990, 95514990, 95617996, 95617997, 95617998, 95630990, 96161990, 96162990, 96163990, 96308988, 96308990, 96318988, 96318989, 96318990, 97089988, 97089989, 97089990, 97688979, 97690979, 97694979, 97696979,97700979, 97701979, 97702979, 97711988, 97711989, 97711990, 97941988, 97941989, 97941990, 98014988, 98014989, 98014990, 98031988, 98031989, 98031990, 98289996, 98289997, 98289998, 98906996, 98906997, 98906998, 99034988, 99034989, 99034990, 99035990, 99331988, 99331989, 99331990

Table S2. Types of dementia stratified by treatment

Treatment	Dementia type (N= 2399)				
	Alzheimer's dementia N=1926	Vascular dementia N=272	Frontotemporal dementia N=8	Lewy body dementia N=9	Other dementias N=184
Warfarin, n (%)	1103 (57)	163 (60)	4 (50)	7 (78)	109 (59)
DOACs, n (%)	823 (43)	109 (40)	4 (50)	2 (22)	75 (41)
Dabigatran	65 (3)	6 (2)	0	0	6 (3)
Rivaroxaban	423 (22)	51 (19)	2 (25)	2 (22)	25 (13)
Apixaban	332 (17)	52 (19)	2 (25)	0	42 (23)
Edoxaban	3 (0.15)	0	0	0	2 (1)

Table S3. Sensitivity analyses for DOACs compared to warfarin: hazard ratios or incidence rate ratios with 95% confidence intervals for increased treatment gap (DOACs = 14 days; warfarin = 53 days), the full untrimmed cohort, results using propensity score stratification approach, reduced dose DOACs Vs warfarin, Fine-Gray subdistribution hazards Cox regression (for competing risk of death) and all-cause mortality (additional covariates included in propensity score model).. Warfarin served as the reference group.

	DOACs V Warfarin					
	Increased treatment gap **IRR (95% CI), p-value**	**Full, untrimmed cohort** **IRR (95% CI), p-value**	**Propensity-score stratification approach[1];** **IRR (95% CI), p-value**	**Reduced dose DOACs Vs warfarin (n=479 DOACs; n=1386 warfarin);** **IRR (95% CI), p-value**	**Fine-Gray sub distribution hazards Cox regression;** **HR (95% CI), p-value**	**Sensitivity analysis for the outcome of all-cause mortality[3];** **IRR (95% CI), p-value**
EFFECTIVENESS OUTCOMES						
Ischemic stroke, TIA or systemic embolism	1.21 (0.92-1.61), p=0.1810	0.83 (0.62-1.11), p=0.2003	0.81 (0.50-1.29), p=0.4054	0.62 (0.40-0.94), p=0.0239	0.96 (0.70-1.32), p=0.8121	--
Ischemic stroke	1.62 (1.12-2.34), p=0.0107	0.88 (0.61-1.29), p=0.5370	0.93 (0.50-1.70), p=0.9084	0.71 (0.41-1.23), p=0.2261	1.24 (0.83-1.86), p=0.2868	--
All-cause mortality	1.87 (1.52-2.31), p<0.0001	1.76 (1.42-2.22), p<0.0001	2.00 (1.42-2.86), p<0.0001	1.71 (1.28-2.29), p=0.0003	--	2.04 (1.59-2.61), p<0.0001
SAFETY OUTCOMES						
Intracranial bleeding	0.35 (0.14-0.93), p=0.0343	0.34 (0.12-0.94), p=0.0260	0.47 (0.08-1.97), p=0.4110	N/A[2]	0.28 (0.08-0.91), p=0.0338	--
GI bleeding	1.42 (0.96-2.10), p=0.0794	2.32 (1.45-3.70), p=0.0002	2.42 (1.22-4.97), p=0.0097	2.15 (1.16-4.00), p=0.0155	2.06 (0.29-3.32), p=0.0027	--
Other bleeding	0.96 (0.68-1.37), p=0.8565	0.74 (0.51-1.07), p=0.1100	0.88 (0.49-1.56), p=0.7455	0.70 (0.43-1.14), p=0.1522	0.88 (0.59-1.30), p=0.5151	--

HR = Hazard Ratio; IRR = incidence rate ratio; CI = confidence interval; other bleeding = anaemia, urinary tract bleeding, respiratory bleeding, bleeding in the eye and haemopericardium;

[1]All outcomes were re-analysed using the propensity-score stratification approach (number of strata = 5)

[2]Not applicable, as insufficient numbers did not allow for calculation of IRR

[3]Additional covariates were included in this sensitivity analysis, including: cancer, chronic obstructive pulmonary disease and ischemic heart disease.

Table S4. Baseline characteristics before IPTW and trimming for the subgroup analysis for apixaban or rivaroxaban versus warfarin

	Apixaban N=428	Rivaroxaban N=503	Warfarin N=1386	Absolute standardized difference (Apixaban Vs Warfarin)		Absolute standardized difference (Rivaroxaban Vs Warfarin)	
				BEFORE IPTW	AFTER IPTW and trimming	BEFORE IPTW	AFTER IPTW and trimming
Age (years) Median (IQR)	84 (79-88)	84 (79-88)	81 (77-86)	0.35	0.04	0.34	0.02
Female, n (%)	230 (54)	289 (43)	737 (53)	0.01	0.05	0.07	0.03
Comorbidities at baseline, n (%)							
Congestive heart failure	65 (15)	43 (9)	210 (15)	0.00	0.02	0.21	0.07
Hypertension	289 (68)	320 (64)	967 (70)	0.05	0.01	0.13	0.03
Diabetes	101 (24)	116 (23)	301 (22)	0.04	0.01	0.03	0.04
Prior stroke/TIA/SE	351 (25)	141 (28)	351 (25)	0.16	0.01	0.06	0.01
Vascular disease	104 (24)	92 (18)	266 (19)	0.12	0.04	0.02	0.02
Chronic kidney disease	42 (10)	46 (9)	243 (18)	0.23	0.07	0.25	0.00
History of major bleeding	60 (14)	74 (15)	184 (13)	0.02	0.02	0.04	0.01
History of other bleeding	57 (13)	63 (13)	159 (11)	0.06	0.01	0.03	0.00
Current smoker	29 (7)	23 (5)	91 (7)	0.01	0.03	0.09	0.01
Medication use, n (%)							
NSAIDs	35 (8)	45 (2)	142 (10)	0.07	0.01	0.04	0.01
Aspirin and/or clopidogrel	261 (61)	297 (59)	835 (60)	0.02	0.00	0.02	0.02
Beta-blockers	262 (61)	286 (57)	840 (61)	0.01	0.01	0.08	0.00
Calcium channel blockers	134 (31)	175 (35)	508 (37)	0.11	0.04	0.04	0.02
Loop diuretics	136 (32)	145 (29)	468 (34)	0.04	0.01	0.11	0.02
Statins	276 (64)	279 (55)	843 (61)	0.08	0.01	0.11	0.00
ACEI/A2RB	65 (15)	217 (16)	217 (16)	0.01	0.01	0.11	0.03

PPIs	194 (45)	226 (45)	613 (44)	0.02	0.02	0.01	0.00
Histamine type-2 receptor antagonists	28 (7)	27 (5)	63 (5)	0.09	0.05	0.04	0.02
SSRIs	56 (13)	73 (15)	172 (12)	0.02	0.02	0.06	0.00
Anti-dementia medications	103 (6)	105 (6)	114 (6)	0.44	0.00	0.36	0.03
CHA$_2$DS$_2$-VASc				0.17	0.01	0.03	0.02
Median (IQR)	3 (2-4)	4 (3-5)	4 (3-5)	--	--	--	--
0-1	7 (2)	10 (2)	31 (2)	--	--	--	--
2-3	116 (27)	174 (34)	462 (33)	--	--	--	--
≥4	305 (71)	319 (63)	893 (65)	--	--	--	--
HAS-BLED				0.08	0.02	0.02	0.01
Median (IQR)	4 (3-5)	3 (2-4)	3 (2-4)	--	--	--	--
≥3	307 (72)	347 (68)	964 (70)	--	--	--	--
Charlson Comorbidity Index				0.30	0.02	0.21	0.01
Median (IQR)	7 (5-8)	6 (5-8)	6 (5-7)	--	--	--	--
Reduced dose DOAC, n (%)	230 (54)	179 (36)	N/A	--	--	--	--

IPTW = inverse probability of treatment weighting; other bleeding includes anaemia, urinary tract bleeding, respiratory bleeding, bleeding in the eye and haemopericardium; major bleeding includes intracranial bleeding and gastrointestinal bleeding; TIA = transient ischemic attack; SE = systemic embolism; ACEI/A2RB = angiotensin-converting enzyme inhibitor/angiotensin-2 receptor blocker; NSAIDs = non-steroidal anti-inflammatory drugs; SSRIs = selective serotonin reuptake inhibitors; Anti-dementia medications include: memantine, donepezil, rivastigmine or galantamine; Trimming = propensity scores above 97.5th percentile for patients treated with warfarin and below 2.5th percentile for patients treated with DOACs were trimmed; Absolute standardized difference is the mean difference in DOAC group versus warfarin group divided by the pooled standard deviation. A standardized difference ≤ 0.1 indicates a negligible difference in covariates between treatment groups.

Table S5. Crude outcome event rates and absolute risk differences comparing inverse probability of treatment weighted new user cohorts of apixaban or rivaroxaban compared with warfarin

	Crude event rates (number of events) per 1000 person-years[x]			Absolute risk difference per 1000 person-years (95% CI)*	
	Apixaban N = 428	Rivaroxaban N = 503	Warfarin N = 1386	Apixaban Vs Warfarin	Rivaroxaban Vs Warfarin
EFFECTIVENESS OUTCOMES					
Ischemic stroke, TIA or systemic embolism	49.3 (16)	39.3 (17)	48.2 (55)	-0.3 (-14.5 to 19.8)	-10.0 (-20.6 to 5.3)
Ischemic stroke	30.6 (10)	25.1 (11)	27.7 (32)	-2.4 (-11.9 to 12.8)	1.0 (-8.4 to 15.7)
All-cause mortality	143.6 (48)	115.2 (51)	49.9 (59)	50.1 (24.5 to 84.6)	44.3 (21.2 to 74.8)
SAFETY OUTCOMES					
Intracranial bleeding	6.0 (2)	2.3 (1)	7.6 (9)	-2.7 (-5.4 to 5.1)	N/A
Gastrointestinal bleeding	30.3 (10)	32.2 (14)	12.8 (15)	16.4 (3.6 to 39.1)	15.1 (3.3 to 35.2)
Other bleeding	24.4 (8)	32.3 (14)	28.8 (33)	-11.8 (-19.1 to 0.5)	0.9 (-9.4 to 16.6)
[x] Event rates = events divided by person time expressed per 1000 person-years * After inverse probability of treatment weighting Other bleeding includes: anaemia, urinary tract bleeding, respiratory bleeding, bleeding in the eye and haemopericardium; TIA = transient ischaemic attack; SE = systemic embolism N/A as n=1 intracranial bleed in rivaroxaban group prior to IPTW adjustment and n=0 after IPTW adjustment; which did not allow for calculation of ARD					

Figure S1. Number of patients starting anticoagulants by study year

Number of patients starting anticoagulants by study year
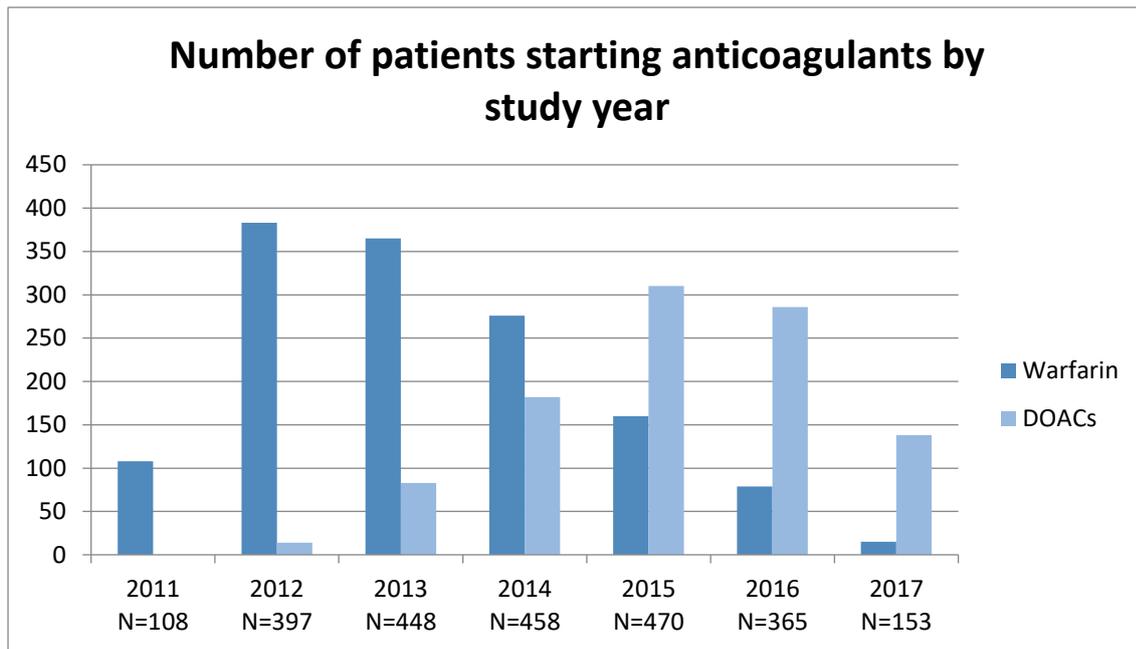
**Data for 2011 starts from August and data from 2017 concludes in September.

Figure S2. Forest plot showing incidence rate ratios and 95% confidence intervals of inverse probability of treatment weighted cohort comparisons for apixaban versus warfarin
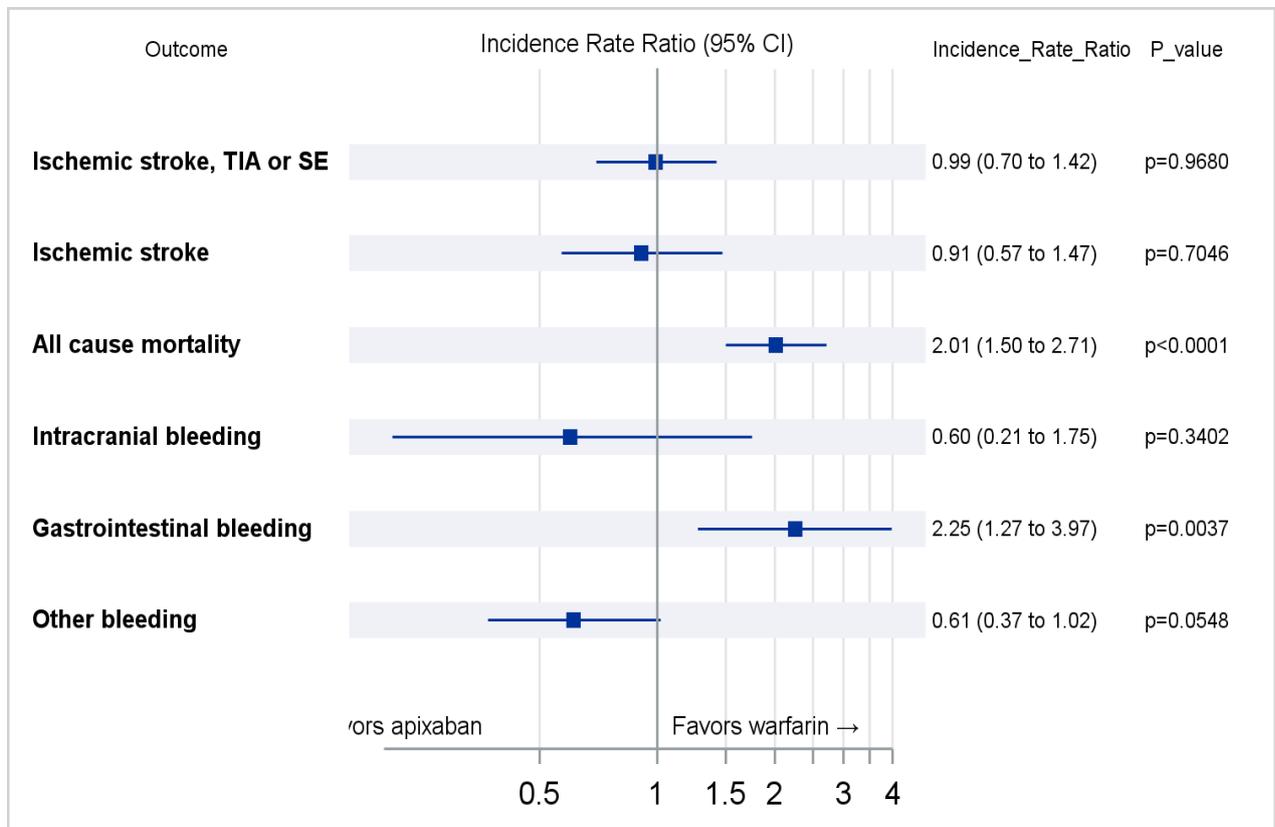
Figure S3. Forest plot showing incidence rate ratios and 95% confidence intervals of inverse probability of treatment weighted cohort comparisons for rivaroxaban versus warfarin

N/A as n=1 intracranial bleed in rivaroxaban group prior to IPTW adjustment and n=0 after IPTW adjustment; which did not allow for calculation of IRR