Impact of oral anticoagulation on the association between frailty and clinical outcomes in people with atrial fibrillation: Nationwide primary care records on treatment analysis

Dr Chris Wilkinson*[1], Dr Jianhua Wu*[2,3], Professor Andrew Clegg[4,5], Dr Ramesh Nadarajah[2,3], Professor Kenneth Rockwood[6], Dr Oliver Todd[4,5], Professor Chris P Gale[2,3,7]

Affiliations

1. Population Health Sciences Institute, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, UK
2. Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, Leeds, UK
3. Leeds Institute for Data Analytics, University of Leeds, Leeds, UK
4. Academic Unit for Ageing and Stroke Research, Leeds Institute of Health Sciences, University of Leeds, Leeds, UK
5. Bradford Institute for Health Research, Bradford Teaching Hospitals NHS Foundation Trust, Bradford, UK
6. Geriatric Medicine, Dalhousie University, Halifax, Nova Scotia, Canada
7. Department of Cardiology, Leeds Teaching Hospitals NHS Trust, Leeds, UK

* joint first authors

Corresponding author

Dr Jianhua Wu, 6.090a Worsley Building, University of Leeds, Leeds, LS2 9JT, UK

Telephone: +44(0)113 343 3431. Email: J.H.Wu@leeds.ac.uk

Introduction

Atrial fibrillation (AF) is a major risk factor for thromboembolic stroke, which causes substantial morbidity and mortality.[1] Every year in Europe around 800,000 strokes are considered to be related to AF.[2] Although the risk of AF-related stroke is substantially reduced by oral anticoagulation (OAC),[1] the evidence to guide the treatment of people with AF and concomitant frailty is less clear.

Frailty describes a state of vulnerability to adverse outcomes due to failure of homeostatic mechanisms and a reduction in physiological reserves.[3] It is common in older people with AF, and is considered useful in guiding individualised treatment of people with cardiovascular disease.[4-6] In those living with frailty, the balance of risk and benefit associated with OAC may be complex,[7] yet the 2020 European Society of Cardiology Clinical Practice Guideline state that: "Frailty, comorbidities, and increased risk of falls do not outweigh the benefits of OAC given the small absolute risk of bleeding in anticoagulated elderly patients."[8] This statement is not supported by reference to outcomes data for patients with frailty and there is a gap in the evidence concerning the association between frailty and clinical outcomes by OAC prescription for people with AF who are at higher risk of stroke.

To address this, we undertook an open cohort study of primary care data for 89,996 patients with AF, linked to hospital records and national mortality data to quantify rates of all-cause mortality, stroke, severe bleeding, transient ischaemic attack (TIA) and falls; and examined associations between frailty and OAC prescription for these outcomes.

Methods

Setting and participants

We used electronic health records (EHR) data from the Clinical Practice Research Datalink (CPRD) Gold, which includes data from over 19 million patients registered at 394 general practices across the UK.[9] Records were linked by CPRD to hospital admissions data from Hospital Episode Statistics (HES), cause of death data from the UK Office for National Statistics, and to local measures of deprivation (indices of multiple deprivation [IMD] and Townsend score). Clinical diagnoses were identified using ICD-10 and Read codes (appendix 1), which have been shown to have high reported accuracy in UK EHR.[10]

Participants were included in the study if they were aged 18 years or older, received a new diagnosis of non-valvular AF (paroxysmal, persistent or permanent) or atrial flutter, and their CHA_2DS_2-VASc stroke risk score was coded as two or more (which is a commonly used threshold for OAC initiation),[11] between 01.01.1998 and 30.11.2018, and had at least one year of available GP records prior to AF diagnosis (supplementary figure 1). The study start date was the day that their CHA_2DS_2-VASc was coded as two or more.

The primary outcome was a composite of all-cause mortality, ischaemic or unspecified stroke, systemic embolism, major bleeding event that led to hospital admission or death, or any intra-cranial bleeding. Secondary outcomes were all-cause mortality; ischaemic or unspecified stroke; severe bleeding (defined as bleeding that led to hospital admission, death, or any intra-cranial bleeding); TIA; and falls. The date and cause of death was ascertained from linked Office for National Statistics data and was provided as part of the anonymised patient-level dataset. All other outcomes were ascertained from Hospital Episode Statistics and CPRD.

Frailty was ascertained on the study start date using the electronic frailty index (eFI), in which primary care EHR are used to calculate the proportion of deficits (symptoms and signs, abnormal laboratory values, disability, or disease state) from a total of 36 possible deficits. This was then categorised into fit (0-0.12), mild (>0.12-0.24), moderate (>0.24-0.36) or severe (>0.36) frailty.[3] The eFI is recommended by the National Institute for Health and Care Excellence to identify adults with multimorbidity who are at risk of adverse events. When ICD codes were used to calculate eFI, they were mapped from the originally defined CTV3 codes. With the exception of polypharmacy (≥5 prescriptions in preceding 12-months), deficits were identified if they were recorded at any time point in a patient's EHR preceding their inclusion.[3]

Baseline characteristics were reported by frailty category, including patient demographics (age, sex, postcode, IMD, ethnicity, smoking status [ever vs never]), medical history (of stroke or TIA, heart failure, diabetes mellitus, hypertension, peripheral vascular disease [PVD], renal disease, liver disease, previous intracranial or gastrointestinal bleeding). Risk of stroke (CHA_2DS_2-VASc) and bleeding (Anticoagulation and Risk Factors in Atrial Fibrillation study [ATRIA]: anaemia, severe renal disease, age ≥ 75 years, prior haemorrhage, hypertension;[12] and modified HAS-BLED score: one point for hypertension, renal or liver disease, stroke, major bleeding or predisposition to bleeding, age > 65 years, medication use predisposing to bleeding or alcohol misuse. Labile INR was omitted as this is not consistently recorded in the dataset) are reported by frailty category.[8, 13] The most recent OAC agent prescribed (direct oral anticoagulant [DOAC] or vitamin K antagonist [VKA]), and prescription of the following medications after the index date that may influence the choice to prescribe OAC were reported: antiplatelet medications, proton pump inhibitors (PPI), statins, phenytoin, carbamazepine, macrolide antibiotics, non-steroidal anti-inflammatory drugs (NSAID), and corticosteroids.

Statistical analyses

Unadjusted rates of the primary and secondary outcomes were reported, alongside those age-standardised to the 2013 European Standard Population. Patients were censored at death, withdrawal from CPRD (for example moving to a non-CPRD general practice), or study end (30th Nov 2018). Fine-Gray competing risk models were used to estimate the hazard ratio for each outcome with death as a competing risk. After testing assumptions, hazard ratios (HR) with 95% confidence intervals (95% CI) for each outcome were reported by frailty status, adjusted for age, sex, IMD, smoking status, CHA_2DS_2-VASc score, index year, prescription of aspirin and statin, and comorbidities including diabetes, heart failure, myocardial infarction, hypertension and PVD. A random intercept for general practice code was included to account for the clustering effect. The prescription of OAC was included as a time-varying variable accounting for the on/off anticoagulation status for each patient throughout the study period. If an OAC prescription was recorded within the 90-days preceding an outcome event, the patient was categorised as being prescribed OAC. Participants were excluded from the main analysis if they died within 3 months of the index date, to allow sufficient time between diagnosis of AF to allow OAC to be commenced. Cumulative incidence functions were visualised for each clinical outcome, stratified by frailty category and time-varying OAC prescription. Age-standardised incidences were calculated according to European Standard Population by frailty category and OAC prescription, and adjusted to duration of follow up to account for the differing length of follow up for DOAC and VKA. Data were collected on a positive recording basis, whereby the absence of a recorded diagnosis is treated as the absence of that event. Therefore, no formal missing data strategy was employed. Analyses were undertaken using R (version 3.6.3) with statistical significance determined at $p<0.05$.

Role of the funder

The funder had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the article for publication. The researchers are independent of the funders.

Ethics

The protocol for CPRD has been approved by the Independent Scientific Advisory Committee for MHRA Database Research. This study was conducted in accordance with the Declaration of Helsinki and is reported in line with RECORD recommendations. JW had full access to the data and can take responsibility for the integrity of the data and the accuracy of the data analysis. All authors take responsibility for the interpretation of the analyses.

Results

The cohort comprised 89,996 participants. 18,740 (20.8%) were fit and 71,256 (79.2%) were living with frailty (mild: 33,674, moderate 25,686, severe 11,896, table 1). The mean age of participants was 78.3 (SD 9.5, range 18 to 108) years, and 45.5% were male. There were 369,489 person-years of follow-up (median 2.8, IQR 1.2-5.5 years).

With increasing frailty category, participants tended to be older (fit: 76.6, severe frailty: 80.4 years), were more commonly women (fit: 53.5%, severe frailty: 62.1%) and with a history of smoking (fit: 47.8%, severe frailty: 56.9%). The proportion of participants with a history of gastrointestinal bleeding was higher with increasing frailty category (fit: 4.7%, severe frailty: 16.8%) and people living with frailty tended to have higher CHA_2DS_2-VASc and ATRIA scores (table 1).

Overall, 43,228 (48.0%) participants were prescribed OAC during their analytical period. Of these, DOAC was prescribed in 23.9% and VKA in 76.1%. Prescription rates of OAC were higher in patients with increasing frailty (fit: 27.0%, mild frailty: 49.3%, moderate: 55.6%, severe: 61.0%). Prescription rates of anti-platelet medication were also higher with increasing frailty (aspirin: fit 24.3%, severe frailty 64.3%; clopidogrel: fit 3.4%; severe frailty 22.8%), although this was not necessarily concomitant with OAC.

Composite clinical outcomes – standardised to the European populace

The composite clinical outcome occurred in 48,311 (53.7%) people (supplementary table 1). Overall, the prescription of OAC was associated with a reduction in the rates of the composite clinical endpoint. For patients who were not prescribed OAC, the incidence rates (IR, per 100 person-years) of the composite outcomes increased with increasing frailty category (fit: IR 4.8, 95%CI 4.7-4.8; mild frailty: IR 5.9, 95% CI 5.8-6.0; moderate: IR 6.8, 95% CI 6.6-6.9; severe: IR 8.7, 95% CI 8.3-9.0 [table 2]; crude rates are shown in supplementary table 2). However, in those prescribed VKA, the IR of

composite outcomes did not increase consistently with increasing frailty (fit: IR 4.3, 95% CI 3.7-4.9; mild frailty: IR 7.3, 95% CI 6.9-7.8; moderate: IR 5.6, 95% CI 5.4-5.8; severe: IR 8.6, 95% CI 8.1-9.0). In those prescribed DOAC, event rates were lower than those prescribed VKA and those not prescribed OAC in all but the severe frailty category (fit: IR 0.9, 95% CI 0.8-1.0; mild frailty: IR 1.8, 95% CI 1.7-1.9; moderate: IR 1.7, 95% CI 1.6-1.8; severe: 9.5, 95% CI 8.7-10.4).

Composite clinical outcomes – on treatment and adjusted

The cumulative incidence function shows that prescription of OAC was associated with a substantial reduction in the composite clinical outcome (Figure 1).

In models further adjusted for demographics, stroke risk, other medications, cardiovascular comorbidities and accounting for OAC as a time-varying covariate, the prescription of DOAC or VKA were associated with a consistent reduction in composite clinical outcomes across all frailty categories compared with no OAC (table 3). VKA was associated with an average reduction in the composite endpoint of 31% in the fit group (HR 0.69, 95%CI 0.64-0.75), 48% in those with mild frailty (HR 0.52, 95% CI 0.50-0.54), 46% in those with moderate frailty (HR 0.54, 95%CI 0.52-0.56) and 52% in those with severe frailty (HR 0.48, 95%CI 0.45-0.51). DOAC was associated with an average reduction of 58% in the fit group (HR 0.42, 95%CI 0.33-0.53), 43% in those with mild frailty (HR 0.57, 95%CI 0.52-0.63), 43% with moderate frailty (HR 0.57, 95%CI 0.52-0.63) and 42% with severe frailty (HR 0.58, 95%CI 0.52-0.65).

Secondary clinical outcomes

All-cause mortality

There were 44,380 (49.3%) deaths during the follow-up period. Figure 2 shows that for each frailty category, mortality rates were lowest amongst patients prescribed DOAC, then VKA and highest amongst people who were not prescribed OAC (figure 2). Standardised mortality rates were higher with increasing frailty compared to those who were fit (table 2) and were lowest for those that were prescribed DOAC in the fit, mild and moderate frailty groups. In the group with severe frailty, those prescribed DOAC had a higher rate of mortality (IR 8.4, 95%CI 7.6-9.3) than those prescribed VKA and those not prescribed OAC (VKA, IR 4.9, 95%CI 4.7-5.1; no OAC, IR 4.6, 95%CI 4.5-4.6).

The adjusted analyses also show that OAC prescription was associated with a reduction in mortality across all four categories compared with no OAC prescription (HR for VKA vs no OAC: fit 0.70, 95%CI 0.64-0.76; mild frailty 0.48, 95%CI 0.46-0.50; moderate 0.47, 95%CI 0.45-0.49; severe 0.48, 95%CI 0.45-0.51. HR for DOAC vs no OAC: Fit 0.41, 95%CI 0.31-0.53; mild frailty 0.52, 95%CI 0.47-0.58; moderate 0.57, 95%CI 0.52-0.62; severe 0.55, 95%CI 0.49-0.61).

Stroke

Overall, 7,028 (7.8%) participants had a stroke during follow-up, 84.0% (n= 5,896) of which were ischaemic. Prescription of DOAC was associated with a substantially lower risk of stroke than VKA or no OAC prescription (figure 3). Standardised rates tended to be higher with increasing frailty category, and lower in those that were prescribed OAC – but without a consistent benefit of one agent over the other across the frailty categories (table 2). Following adjustment, prescription of VKA or DOAC was associated with a reduction in ischaemic stroke across every frailty category compared with no OAC (HR for VKA vs no OAC: fit 0.46, 95%CI 0.35-0.61; mild frailty 0.44, 0.39-0.50; moderate 0.57, 0.51-0.63; severe 0.50, 0.43-0.58. HR for DOAC vs no OAC: fit 0.49, 0.25-0.95; mild frailty 0.58, 0.43-0.77; moderate 0.43, 0.32-0.59; severe 0.54, 0.39-0.75).

Severe bleeding

Severe bleeding occurred in 6,401 (7.1%) people and was more frequent with increasing frailty (figure 4). The standardised rates of bleeding showed no consistent pattern between agents across the frailty categories (table 2), whereas the adjusted models showed that OAC prescription was associated with a similar bleeding risk than no OAC – except for in the fit group prescribed DOAC, in whom bleeding appeared less common than no OAC (HR for VKA vs no OAC: fit 0.91, 95%CI 0.74-1.11; mild frailty 0.94, 95%CI 0.84-1.04; moderate 1.06, 95%CI 0.97-1.17; severe 1.00, 95%CI 0.88-1.13; HR for DOAC vs no OAC, fit 0.43, 95%CI 0.24-0.77; mild frailty 1.07, 95%CI 0.87-1.32; moderate 0.88, 95%CI 0.71-1.10; severe 1.24, 95%CI 0.97-1.57, table 3).

Transient ischaemic attack

There were 1,785 (2.0%) TIAs, with the lowest event rates observed in people prescribed DOAC (figure 5). Standardised rates increased with frailty (table 2). Following adjustment, the prescription of VKA was associated with a consistent reduction in TIA rate across all frailty categories (HR for VKA vs no OAC: fit 0.43, 95%CI 0.23-0.79; mild frailty 0.59, 95%CI 0.46-0.77; moderate 0.62, 95%CI 0.50-0.77; severe 0.71, 95%CI 0.55-0.92), but the reduction with DOAC was only statistically significant in the group with mild frailty (HR for DOAC vs no OAC: fit 0.32, 95%CI 0.08-1.31; mild frailty 0.51, 95%CI 0.28-0.93; moderate 0.80, 95%CI 0.52-1.24; severe 0.65, 95%CI 0.37-1.13, table 3).

Falls

Overall, 9,931 (11.0%) participants had a fall recorded. Falls were more common with increasing frailty and tended to occur more frequently in patients prescribed VKA than no OAC or DOAC (supplementary figure 2). In the adjusted analyses, on average, those prescribed OAC more commonly had a fall than those not prescribed OAC (HR for VKA vs no OAC: fit 2.53, 95%CI 1.87-3.43; mild frailty 1.49, 95%CI 1.36-1.64; moderate 1.19, 95%CI 1.11-1.28; severe 1.24, 95ECI 1.14-1.34. HR

for DOAC vs no OAC: fit 2.24, 95%CI 1.06-4.76; mild frailty 1.36, 95%CI 1.08-1.70; moderate 1.21, 95%CI 1.02-1.43; severe 1.28, 95%CI 1.06-1.53, table 3).

Discussion

This cohort study included 89,996 participants and used primary care EHR linked to hospital and mortality data to study the on-treatment effects of OAC on clinical outcomes among people with AF according to frailty status. We found that frailty was more commonly associated with adverse clinical outcomes in patients with AF and, although the use of OAC for stroke prophylaxis increased with increasing frailty category, overall the use of OAC was suboptimal. Moreover, we found that the prescription of OAC was associated with a substantial reduction in the composite endpoint of death, stroke, systemic embolism and major bleeding across the frailty spectrum.

The study benefited from a large sample size, a long duration of follow-up, and addresses a topical and important clinical issue. We used a robust, validated and guideline-recommended measure of frailty, and a linked dataset for outcome ascertainment. Nonetheless, we recognise the limitations of our work. We were reliant on the accurate identification and coding of events in a routine dataset, which may not be completely accurate.[14] There have been changes in clinical guidance over the duration of the study follow-up period. Nevertheless, the thresholds used for this study are based upon current UK guidance, and so are applicable to contemporary practice.[11] As we lacked data on treatment adherence, prescription of OAC does not necessarily mean that it was taken, thereby possibly under-estimating strength of association.[15] We estimated frailty when the patient became eligible for prescription of OAC, as this is the key inflection point for clinical decision making, however, frailty is a dynamic phenomenon and patients are likely to have accumulated further deficits over the follow-up period,[3] and coding practices may have changed over time. There was a small difference in the duration of follow-up between groups, although this was accounted for in the primary analysis by standardization and fitting time-varying exposure of OAC prescription. Although adjustment was made for potential confounders, there is likely to be residual unmeasured confounding including confounding by indication. Finally, this was an observational study; therefore, we describe associations and cannot attribute causation or a comparison between treatments.

In the original trials of stroke prophylaxis in AF, each DOAC agent was compared with VKA. Meta-analysis of these trials has shown that overall, DOACs have favourable efficacy and safety profiles compared to warfarin.[16] In a sub-group meta-analysis of older people, there was superior stroke prevention in the DOAC group than the VKA group, and whilst the intracranial haemorrhage rate was lower in patients randomised to a DOAC the overall rate of major bleeding was similar between the two groups.[17]

Our finding that there was a greater reduction in the risk of the composite outcome with VKA compared to DOAC in people with mild, moderate and severe frailty is of interest. Whilst a head-to-head comparison of treatments is not possible in this observational study, this is an important avenue for future work. There are no randomised clinical trials comparing DOAC and VKA specifically for a population with frailty, and of those trials comparing DOAC and VKA the proportion of participants who were frail was limited. For example, only one-fifth of the people recruited into the ENGAGE AF-TIMI 48 trial were living with frailty;[18] this compares with almost four-fifths in this real-world naturalistic study. The recent *post-hoc* analysis of the ENGAGE AF-TIMI 48 trial showed similar efficacy to warfarin across the frailty spectrum, with lower rates of bleeding except in those with severe frailty.[18] Furthermore, observational work suggests that there may be differences in the efficacy and safety between DOAC agents for different degrees of frailty.[19] Although there is a need for randomised evidence to evaluate the safety of efficacy of DOAC compared to VKA in people with frailty, we recognise that a comparative effectiveness trial is unlikely given that conducting a trial in this population may be challenging.

The population burden of AF is growing, as is the proportion of people with AF that are also living with frailty. We have shown that this group of people have poor clinical outcomes, especially if they are not prescribed OAC. Over the 20 year period we found that OAC prescription rates were low, but this will likely be a reflection of the temporal increase of the use of OAC in the UK.[20] Moreover, we

found a positive association between frailty and OAC prescription, which validates previous findings, and may reflect that practitioners are considering the high risk of stroke in people with advancing frailty. Even so, we also show that the risk of severe bleeding is highest in people with frailty, as is the rate of falls. These findings reinforce the importance of minimising bleeding risk through reviewing concomitant therapy associated with bleeding such as NSAIDs and antiplatelet medications,[11] and adopting a multi-disciplinary approach to mitigating falls risk.

Conclusion

In this large, community-based cohort study of people with AF, frailty was associated with adverse clinical outcomes in patients with AF. However, OAC prescription was associated with substantial reductions in the composite endpoint of death, stroke, systemic embolism and major bleeding across the frailty spectrum.

Declarations

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Conflicts of interest

Outside this work, CPG reports personal fees from AstraZeneca, Amgen, Bayer, Boehrinher-Ingelheim, Daiichi Sankyo, Menarini, Oxford University Press, Raisio Group, Vifor Pharma, Wondr Medical, Zydus; grants from Abbott, British Heart Foundation, European Society of Cardiology, Horizon 2020, National Institute for Health Research. KR has received consultancy honoraria from Nutricia, and is co-founder of Ardea Outcomes, which has contracts with Hollister, INmune Bio, LuMind, Novartis, Nutricia, and Takeda.

Data sharing

Data are available through application: www.cprd.com/research-applications. Code-lists for the eFI were obtained from Professor Andrew Clegg, University of Leeds.

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Figure legends

Figure 1: Cumulative incidence function for composite outcome (death, stroke, systemic embolism, gastrointestinal or intracranial haemorrhage) by frailty category and time-varying anticoagulation status (with 95% confidence intervals)

Figure 2: Cumulative incidence function for all-cause death by frailty category and time-varying anticoagulation status (with 95% confidence intervals)

Figure 3: Cumulative incidence function for stroke by frailty category and anticoagulation status (with 95% confidence intervals)

Figure 4: Cumulative incidence function for severe bleeding by frailty category and anticoagulation status (with 95% confidence intervals)

Figure 5: Cumulative incidence function for transient ischaemic attack by frailty category and anticoagulation status

Table 1: Characteristics of participants by frailty status at study entry

	All	Fit	Mild frailty	Moderate frailty	Severe frailty
	89996	**18740**	**33674**	**25686**	**11896**
Demographics, n (%)					
Age, mean (SD)	78.33 (9.50)	76.61 (10.04)	77.63 (9.77)	79.53 (8.89)	80.44 (8.35)
Male	40950 (45.5)	8714 (46.5)	16389 (48.7)	11343 (44.2)	4504 (37.9)
IMD					
1	19500 (21.7)	4451 (23.8)	7498 (22.3)	5276 (20.5)	2275 (19.1)
2	19345 (21.5)	4238 (22.6)	7466 (22.2)	5421 (21.1)	2220 (18.7)
3	20393 (22.7)	4198 (22.4)	7632 (22.7)	5818 (22.7)	2745 (23.1)
4	17000 (18.9)	3380 (18.1)	6244 (18.6)	4977 (19.4)	2399 (20.2)
5	13705 (15.2)	2452 (13.1)	4812 (14.3)	4187 (16.3)	2254 (19.0)
Ethnicity, white	84382 (94.9)	17032 (93.0)	31363 (94.5)	24485 (95.8)	11502 (96.9)
Ever smoked	44203 (54.3)	7303 (47.8)	16791 (54.6)	13666 (56.9)	6443 (56.9)
Medical history					
Previous stroke/TIA	12448 (13.8)	944 (5.0)	4098 (12.2)	4483 (17.5)	2923 (24.6)
Previous stroke	6779 (7.5)	526 (2.8)	2255 (6.7)	2414 (9.4)	1584 (13.3)
Previous TIA	7283 (8.1)	502 (2.7)	2249 (6.7)	2665 (10.4)	1867 (15.7)
Previous MI	10500 (11.7)	889 (4.7)	3332 (9.9)	3810 (14.8)	2469 (20.8)
Heart failure	10899 (12.1)	542 (2.9)	3158 (9.4)	4203 (16.4)	2996 (25.2)
Diabetes	16842 (18.7)	1795 (9.6)	5502 (16.3)	5758 (22.4)	3787 (31.8)
Hypertension	54914 (61.0)	7841 (41.8)	20214 (60.0)	17748 (69.1)	9111 (76.6)
PVD	4353 (4.8)	143 (0.8)	1031 (3.1)	1727 (6.7)	1452 (12.2)
Renal disease	16923 (18.8)	728 (3.9)	5365 (15.9)	6651 (25.9)	4179 (35.1)
Liver disease	283 (0.3)	34 (0.2)	101 (0.3)	111 (0.4)	37 (0.3)
Previous major bleeding					
Intracranial	72 (0.1)	10 (0.1)	18 (0.1)	21 (0.1)	23 (0.2)
Gastrointestinal	8939 (9.9)	879 (4.7)	2906 (8.6)	3161 (12.3)	1993 (16.8)

CHA_2DS_2-VASc					
2	26487 (29.4)	8863 (47.3)	10869 (32.3)	5267 (20.5)	1488 (12.5)
3	30531 (33.9)	7037 (37.6)	12192 (36.2)	8235 (32.1)	3067 (25.8)
4	24034 (26.7)	2525 (13.5)	8542 (25.4)	8641 (33.6)	4326 (36.4)
5	7109 (7.9)	292 (1.6)	1779 (5.3)	2834 (11.0)	2204 (18.5)
6	1520 (1.7)	21 (0.1)	259 (0.8)	599 (2.3)	641 (5.4)
7	267 (0.3)	2 (0.0)	28 (0.1)	102 (0.4)	135 (1.1)
8	45 (0.1)	0 (0.0)	5 (0.0)	8 (0.0)	32 (0.3)
9	3 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.0)
ATRIA score					
<4 - low risk	61727 (68.6)	17003 (90.7)	24531 (72.8)	14969 (58.3)	5224 (43.9)
4 - medium risk	4263 (4.7)	446 (2.4)	1826 (5.4)	1381 (5.4)	610 (5.1)
>4 - high risk	24006 (26.7)	1291 (6.9)	7317 (21.7)	9336 (36.3)	6062 (51.0)
Modified HAS-BLED, mean (SD)	2.73 (0.99)	2.17 (0.83)	2.65 (0.92)	2.98 (0.95)	3.29 (0.98)
Medications					
Oral anticoagulation					
Any OAC	43228 (48.0)	5053 (27.0)	16603 (49.3)	14293 (55.6)	7256 (61.0)
DOAC	10352 (11.5)	1382 (7.4)	3967 (11.8)	3258 (12.7)	1745 (14.7)
Apixaban	4558 (5.1)	580 (3.1)	1722 (5.1)	1472 (5.7)	784 (6.6)
Dabigatran	1122 (1.2)	157 (0.8)	437 (1.3)	341 (1.3)	187 (1.6)
Edoxaban	415 (0.5)	53 (0.3)	182 (0.5)	130 (0.5)	50 (0.4)
Rivaroxaban	5164 (5.7)	677 (3.6)	1932 (5.7)	1620 (6.3)	935 (7.9)
VKA	32876 (36.5)	3671 (19.6)	12636 (37.5)	11058 (43.1)	5511 (46.3)
Warfarin	32809 (36.5)	3660 (19.5)	12613 (37.5)	11035 (43.0)	5501 (46.2)
Acenocoumarol	168 (0.2)	19 (0.1)	55 (0.2)	58 (0.2)	36 (0.3)
Phenindione	57 (0.1)	4 (0.0)	22 (0.1)	20 (0.1)	11 (0.1)
Antiplatelet prescription at any time during follow-up					

Aspirin	43034 (47.8)	4554 (24.3)	15973 (47.4)	14855 (57.8)	7652 (64.3)
Clopidogrel	10547 (11.7)	629 (3.4)	3208 (9.5)	3997 (15.6)	2713 (22.8)
Prasugrel	47 (0.1)	3 (0.0)	19 (0.1)	16 (0.1)	9 (0.1)
Ticagrelor	162 (0.2)	20 (0.1)	59 (0.2)	48 (0.2)	35 (0.3)
Dipyridamole	2692 (3.0)	155 (0.8)	793 (2.4)	1054 (4.1)	690 (5.8)
Other medication at any time during follow-up					
PPI	40884 (45.4)	3493 (18.6)	14371 (42.7)	14740 (57.4)	8280 (69.6)
Statin	40779 (45.3)	3876 (20.7)	15126 (44.9)	14215 (55.3)	7562 (63.6)
Phenytoin	477 (0.5)	51 (0.3)	147 (0.4)	185 (0.7)	94 (0.8)
Carbamazepine	1101 (1.2)	67 (0.4)	345 (1.0)	425 (1.7)	264 (2.2)
Macrolide antibiotics	17411 (19.3)	1084 (5.8)	5370 (15.9)	6618 (25.8)	4339 (36.5)
NSAIDS	16577 (18.4)	1342 (7.2)	5660 (16.8)	5974 (23.3)	3601 (30.3)
Corticosteroids	46895 (52.1)	4085 (21.8)	16880 (50.1)	16853 (65.6)	9077 (76.3)

Abbreviations

ATRIA: one point each for anaemia, severe renal disease, prior haemorrhage, or hypertension. Two points for age ≥75 years. Three points for severe renal disease; CHA_2DS_2-VASc: one point for age 65-74 years, female sex; history of heart failure, hypertension, vascular disease, or diabetes. Two points are allocated for age >75 years, and two points for a history of stroke, transient ischaemic attack or thromboembolism; DOAC: Direct Oral Anticoagulant; modified HAS-BLED: (one point for hypertension, renal or liver disease, stroke, major bleeding or predisposition to bleeding, age > 65 years, medication use predisposing to bleeding or alcohol misuse; MI: myocardial infarction; NSAID: non-steroidal anti-inflammatory drug; PPI: proton pump inhibitor; SD: standard deviation; VKA: vitamin K antagonist

Table 2: Age-standardised incidence rate per 100 person years for composite and secondary outcomes, by frailty status and OAC prescription.

	Incidence rate per 100 person years (95% confidence interval)											
	Fit			Mild frailty			Moderate frailty			Severe frailty		
Outcome	No OAC	VKA	DOAC	No OAC	VKA	DOAC	No OAC	VKA	DOAC	No OAC	VKA	DOAC
Composite	4.8 (4.7- 4.8)	4.3 (3.7- 4.9)	0.9 (0.8- 1.0)	5.9 (5.8- 6.0)	7.3 (6.9- 7.8)	1.8 (1.7- 1.9)	6.8 (6.6- 6.9)	5.6 (5.4- 5.8)	1.7 (1.6- 1.8)	8.7 (8.3- 9.0)	8.6 (8.1- 9.0)	9.5 (8.7-10.4)
Death	3.9 (3.9-4.0)	3.8 (3.2-4.3)	0.7 (0.6-0.8)	4.7 (4.6-4.8)	5.0 (4.7-5.4)	1.1 (1.0-1.2)	5.5 (5.4-5.6)	3.3 (3.2-3.5)	1.3 (1.2-1.4)	4.6 (4.5-4.6)	4.9 (4.7-5.1)	8.4 (7.6-9.3)
Ischaemic stroke	0.4 (0.4-0.4)	0.4 (0.4-0.5)	0.1 (0.1-0.1)	0.6 (0.6-0.6)	0.3 (0.3-0.4)	0.4 (0.4-0.4)	0.8 (0.7-0.8)	0.6 (0.5-0.6)	0.1 (0.1-0.2)	1.0 (0.9-1.0)	0.6 (0.6-0.6)	0.4 (0.3-0.4)
All stroke	0.5 (0.5-0.5)	0.7 (0.6-0.7)	0.1 (0.1-0.1)	0.6 (0.6-0.7)	0.5 (0.5-0.6)	0.5 (0.4-0.5)	0.8 (0.8-0.9)	0.7 (0.7-0.7)	0.2 (0.1-0.3)	1.0 (1.0-1.0)	0.7 (0.7-0.8)	0.4 (0.4-0.4)
Severe bleeding	0.8 (0.8-0.8)	0.6 (0.6-0.6)	0.1 (0.1-0.1)	0.7 (0.7-0.8)	2.5 (2.2-2.8)	0.4 (0.4-0.4)	0.7 (0.7-0.8)	2.1 (2.0-2.2)	0.2 (0.2-0.3)	3.2 (2.9-3.6)	1.3 (1.3-1.3)	0.7 (0.7-0.7)
TIA	0.1 (0.1-0.1)	0.1 (0.1-0.2)	0.0 (0.0-0.0)	0.2 (0.2-0.2)	0.1 (0.1-0.1)	0.1 (0.1-0.1)	0.3 (0.3-0.3)	0.5 (0.5-0.5)	0.1 (0.1-0.1)	0.2 (0.2-0.2)	0.3 (0.3-0.4)	0.3 (0.2-0.3)
Fall	0.3 (0.3-0.4)	0.4 (0.0-1.0)	0.1 (0.1-0.1)	0.6 (0.6-0.6)	1.6 (1.4-1.8)	2.7 (2.3-3.0)	1.8 (1.7-1.8)	2.0 (1.9-2.1)	0.4 (0.4-0.4)	3.2 (3.2-3.3)	3.2 (3.0-3.4)	0.9 (0.8-0.9)

Abbreviations DOAC: direct oral anticoagulant; OAC: oral anticoagulant; TIA: transient ischaemic attack; VKA: vitamin K antagonist

Table 3. The association between oral anticoagulation and outcomes, stratified by frailty category

	Adjusted hazard ratio (95% confidence interval) compared to no anticoagulation (reference), within each frailty category							
	Fit		Mild frailty		Moderate frailty		Severe frailty	
	VKA	DOAC	VKA	DOAC	VKA	DOAC	VKA	DOAC
Composite	0.69 (0.64-0.75)	0.42 (0.33-0.53)	0.52 (0.50-0.54)	0.57 (0.52-0.63)	0.54 (0.52-0.56)	0.57 (0.52-0.63)	0.48 (0.45-0.51)	0.58 (0.52-0.65)
Death	0.70 (0.64-0.76)	0.41 (0.31-0.53)	0.48 (0.46-0.50)	0.52 (0.47-0.58)	0.47 (0.45-0.49)	0.57 (0.52-0.62)	0.39 (0.37-0.42)	0.55 (0.49-0.61)
Ischaemic stroke	0.46 (0.35-0.61)	0.49 (0.25-0.95)	0.44 (0.39-0.50)	0.58 (0.43-0.77)	0.57 (0.51-0.63)	0.43 (0.32-0.59)	0.50 (0.43-0.58)	0.54 (0.39-0.75)
All stroke	0.70 (0.57-0.86)	0.60 (0.35-1.03)	0.58 (0.52-0.64)	0.66 (0.52-0.84)	0.59 (0.53-0.65)	0.47 (0.36-0.61)	0.53 (0.47-0.61)	0.52 (0.39-0.70)
Severe bleeding	0.91 (0.74-1.11)	0.43 (0.24-0.77)	0.94 (0.85-1.04)	1.07 (0.87-1.32)	1.06 (0.97-1.17)	0.88 (0.71-1.10)	1.00 (0.88-1.13)	1.24 (0.97-1.57)
TIA	0.43 (0.23-0.79)	0.32 (0.08-1.31)	0.59 (0.46-0.77)	0.51 (0.28-0.93)	0.62 (0.50-0.77)	0.80 (0.52-1.24)	0.71 (0.55-0.92)	0.65 (0.37-1.13)
Fall	2.53 (1.87-3.43)	2.24 (1.06-4.76)	1.49 (1.36-1.64)	1.36 (1.08-1.70)	1.19 (1.11-1.28)	1.21 (1.02-1.43)	1.24 (1.14-1.34)	1.28 (1.06-1.53)

Each model was performed by frailty status adjusted for age, sex, deprivation index, smoking, CHA_2DS_2-VASc score, medication on aspirin and statin, comorbidities including history of diabetes, heart failure, myocardial infarction, hypertension, peripheral vascular disease and index year. A random intercept for practices was included to account for the clustering effect. The prescription of OAC (including VKA and DOAC) was included as time-varying variables accounting for the on/off anticoagulation status for each patient.

Abbreviations DOAC: direct oral anticoagulant; OAC: oral anticoagulant; TIA: transient ischaemic attack; VKA: vitamin K antagonist

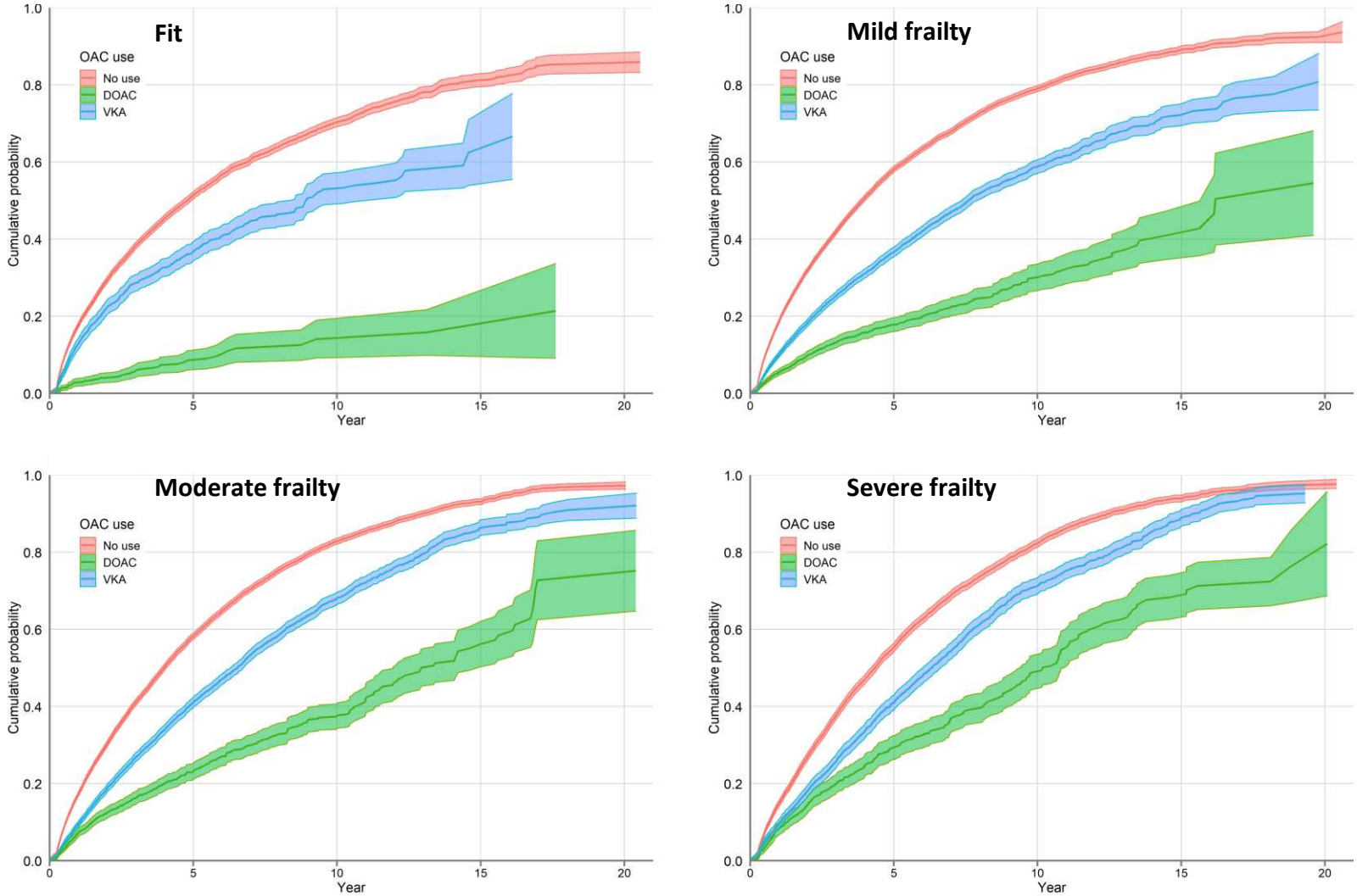


Figure 1: Cumulative incidence function for composite outcome (death, stroke, systemic embolism, gastrointestinal or intracranial haemorrhage) by frailty category and time-varying anticoagulation status (with 95% confidence intervals)

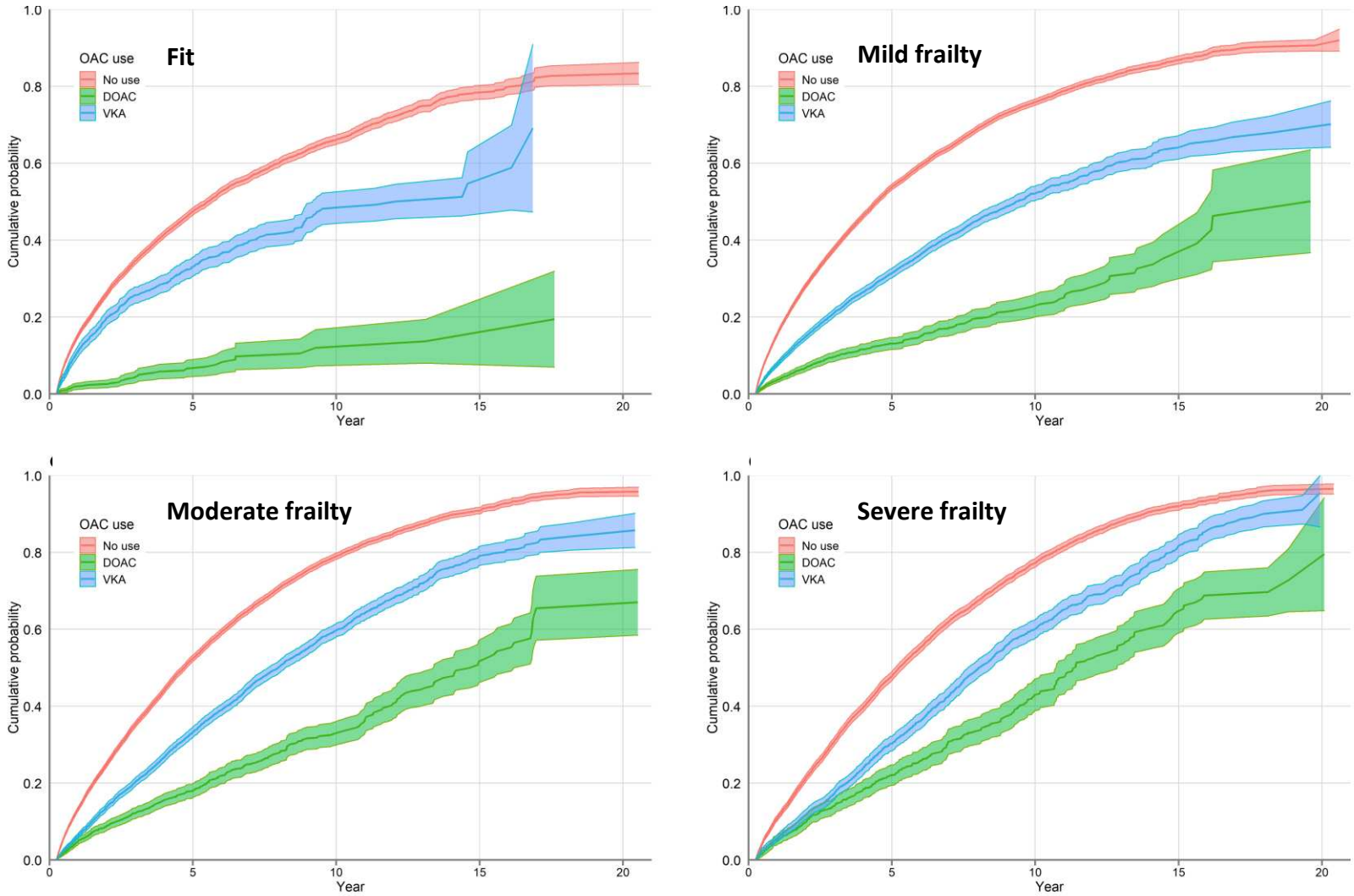


Figure 2: Cumulative incidence function for all-cause death by frailty category and time-varying anticoagulation status (with 95% confidence intervals)

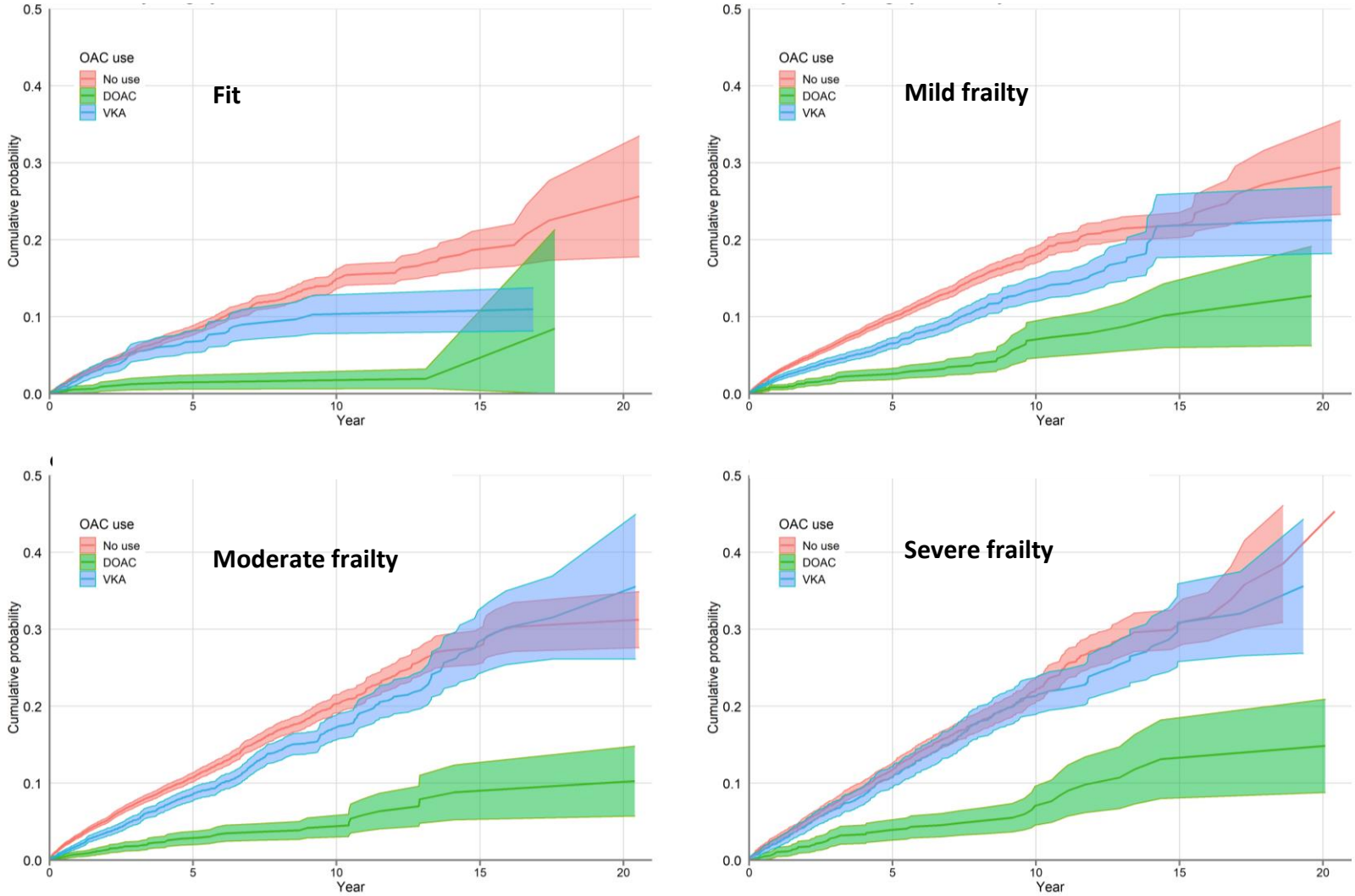


Figure 3: Cumulative incidence function for stroke by frailty category and anticoagulation status (with 95% confidence intervals)

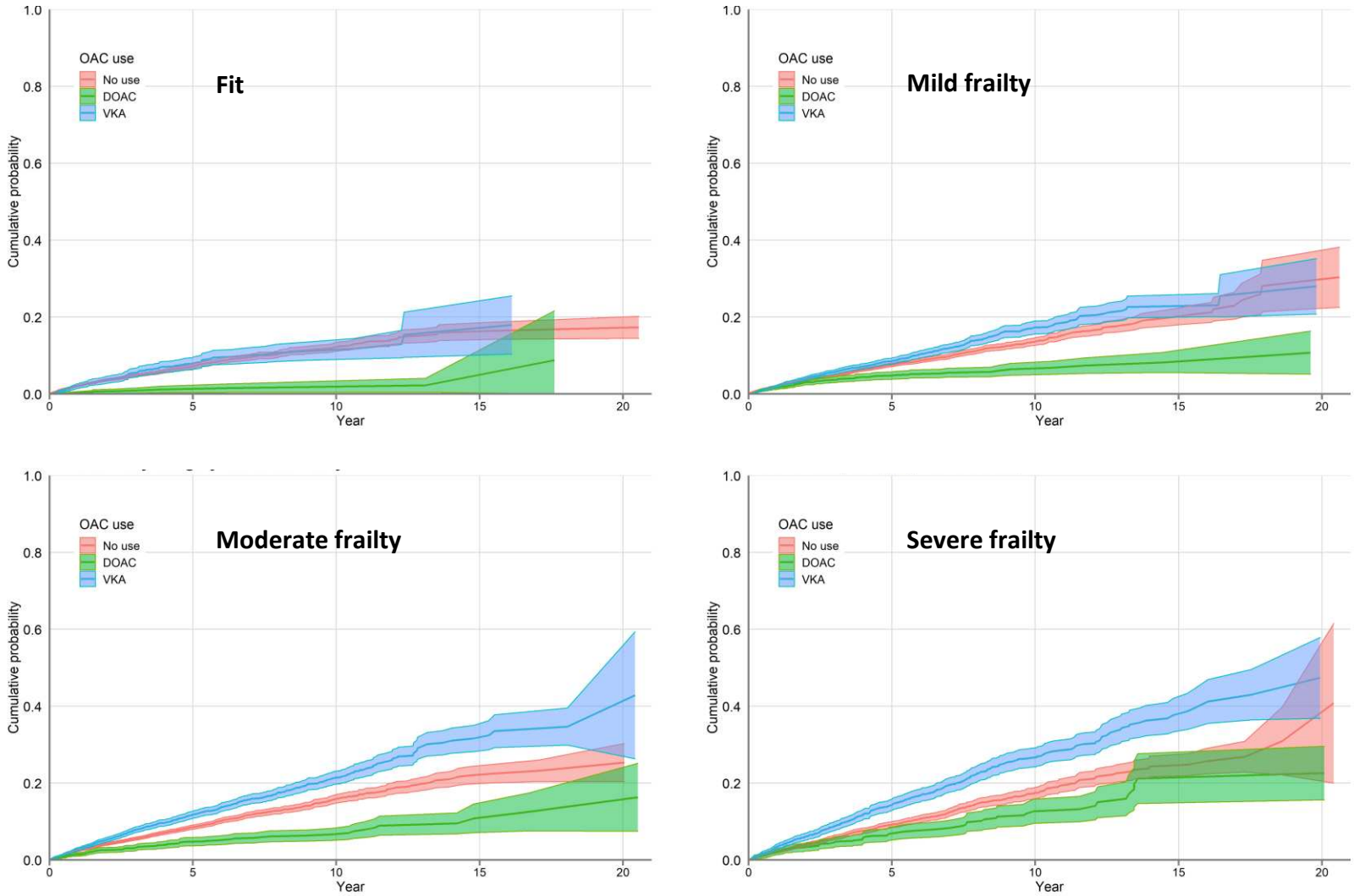


Figure 4: Cumulative incidence function for severe bleeding by frailty category and anticoagulation status (with 95% confidence intervals)

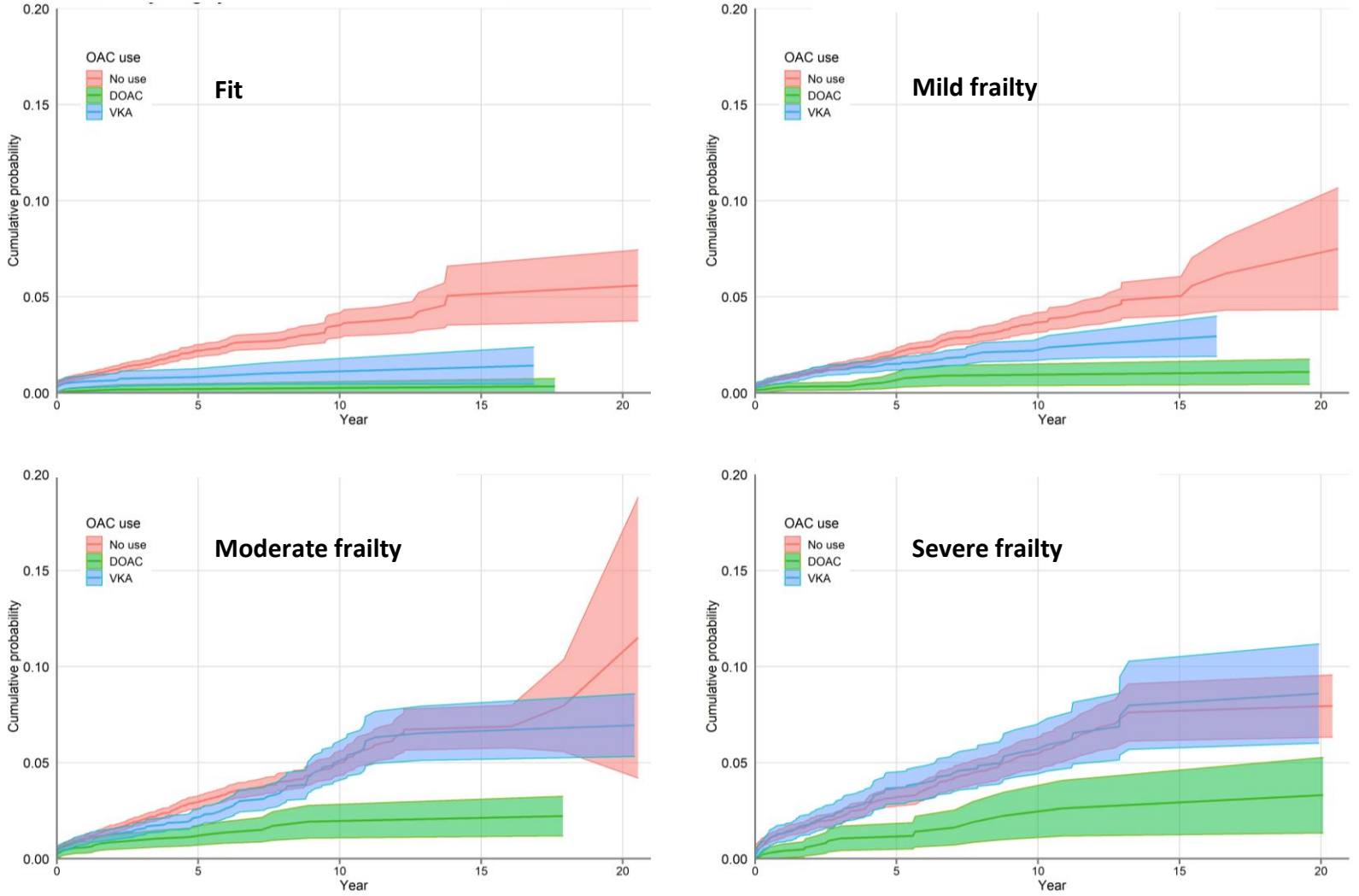


Figure 5: Cumulative incidence function for transient ischaemic attack by frailty category and anticoagulation status

Supplementary data

Appendix 1: ICD-10 and Read codes for outcome diagnoses

Outcome diagnoses	ICD-10	Read code
Stroke	I60* I61* I62* I63* I64* G463 G464 G465 G466 G467	G64z.00 G64..11 G64z.12 G64z200 G64z300 G64z.11 G640.00 G63y000 G63y100 G64z000 G64z400 G641000 G665.00 G640000 G676000 G64z100 Gyu6400 G63..11 Gyu6300 Gyu6G00 G66..11 G66..00 G66..13 G66..12 G667.00 G663.00 G668.00 G664.00 G666.00 662o.00 G681.00 G682.00 G61..00 G61..11 G61..12 G610.00 G611.00 G612.00 G613.00 G614.00 G616.00 G617.00 G618.00 G61X.00 G61X000 G61X100 G61z.00 Gyu6200 Gyu6F00 G601.00 G602.00 G60X.00 7017000 G621.00 G622.00 G623.00 S62..13 S622.00 S623.00 S628.00 S629.00 S629000 S629100 7032000 G620.00 S62..11 S624.00 S624.11 S625.00 S626.00 S62A.00 G62..00 G62z.00 A94y600 S62..00 S62..14 S62z.00 S63..00 S63z.00
Ischaemic/unspecified stroke	I63* I64*	G64z.00 G64..11 G64z.12 G64z200 G64z300 G64z.11 G640.00 G63y000 G63y100 G64z000 G64z400 G641000 G665.00 G640000 G676000 G64z100 Gyu6400 G63..11 Gyu6300 Gyu6G00 G66..11 G66..00 G66..13 G66..12 G667.00 G663.00 G668.00 G664.00 G666.00
Major bleeding	N837 O717 O902 T810 I60 I61 I62 I690 I692 S065 S066 H356 H431 H450 S064 I230 I312 S260 P261 R041 R042 R048 R049 I850 I983 K226 K250 K252 K254 K256 K260 K262 K264 K266 K270 K272	14C8.00 14C9.00 14CA.11 158..00 158Z.00 15A1.00 15A6.00 7421300 7517500 7531400 7H22600 7J01300 7M0U400 SP21.11 SP21.12 SP21100 SP21200 7004200 7004300 7032000 7303000

	K274 K276 K280 K282 K284 K286 K290 K625 K920 K921 K922	7303200 7736000 7D05200 7G2H400 7G31400 7M0G000 7M0G400 F503100 G844.11 K138300 K13y800 K275100 K286000 K286300 K286v00 K31y000 K537.00 K575.00 L345.00 L345.11 L345.12 L345000 L345100 L345z00 L357.00 L357000 L357100 L394600 L443.11 S62A.00 S740100 S750100 S751100 S760100 S760111 S761100 SE...11 SE22300 SE23111 SE33011 SE33200 SE45.11 SE46.00 SE4z.11 SE4z.12 SP21.00 ZA13600 ZA13700 ZA13800 7004100 7008200 7017000 G60..00 G600.00 G601.00 G602.00 G603.00 G604.00 G605.00 G606.00 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 G61X.00 G61z.00 G62..00 G620.00 G621.00 G622.00 G623.00 G62z.00 G680.00 G682.00 Gyu6100 Gyu6200 Gyu6F00 S62..12 S62..13 S620.00 S621.00 S622.00 S623.00 S627.00 S628.00 S629.00 S629000 S629100 S630.12 2BB5.00 2BB8.00 F404500 F424300 F42y.11 F42y100 F42y300 F42y400 F42y500 F436000 F436100 F437200 F4K2800 FyuH400 S624.11 S626.00 793B000 G360.00 G530.00 G53z.11 S714.00 1C6..00 1C62.00 1C6Z.00 7404 7404y00 7404z00 R047.11 172..00 172..12 2DE7.00 H5y0000 R048.00 R063.00 R063000 R063100 R063z00 196B.00 196C.00 1994 1994.11 1995 19E4.12 19E6.00 19E6.11 4737.11 4762 4762.11 479..11 4A23.00 4A23.11 4A5..00 4A5..11 4A51.00 4A5Z.00 7609y11

		7619100 7627200 771H100 G850.00 G852000 J107.00 J10y000 J110100 J110111 J110300 J111100 J111111 J111300 J11y100 J11yy00 J120100 J120300 J121100 J121111 J121300 J12y100 J12y300 J12yy00 J130100 J130300 J131100 J13y100 J13y300 J140100 J14y100 J150000 J573.00 J573.11 J573000 J573011 J573012 J573z00 J68..00 J680.00 J680.11 J681.00 J681.11 J681.12 J681.13 J68z.00 J68z.11 J68z000 J68z100 J68z200 J68zz00
Systemic embolism	I74*	L43..00 G401.12 G401000 L432.00 L43..11 L43z.00 G401100 L43z100 L43zz00 L43z000
TIA	G458 G459	G65..00 F423600 G65..12 G65z.00 G65..13 G65..11 G650.11 G660.00 G662.00 G661.00 G65y.00 G651000 G650.00 G651.00 G653.00 G654.00 Fyu5500
Fall	W00-W19	TC...11 16D..00 TC...00 TCz..00 16D1.00 TC5..00 8Hk1.00 8HTl.00 8O9..00

Appendix 2: Supplementary tables and figures

Supplementary table 1: clinical outcomes by frailty status and OAC prescription

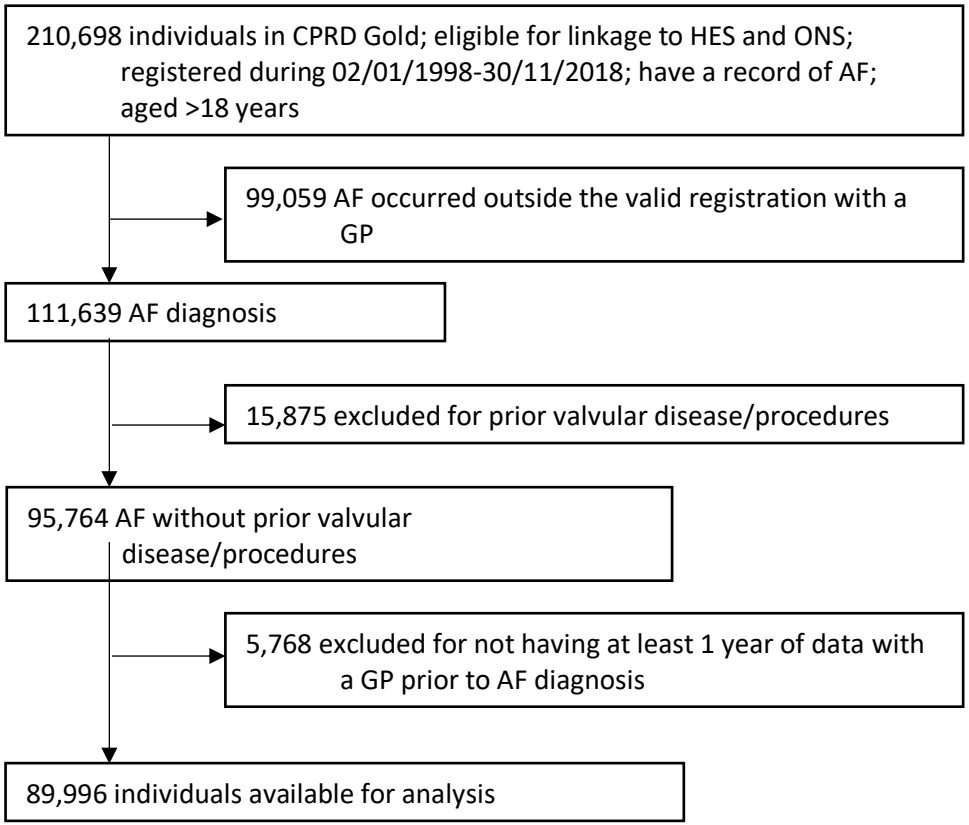
	Number (%) of participants experiencing clinical events during follow-up															
	Fit				Mild frailty				Moderate frailty				Severe frailty			
Outcome	Total	No OAC	VKA	DOAC	Total	No OAC	VKA	DOAC	Total	No OAC	VKA	DOAC	Total	No OAC	VKA	DOAC
Composite	8087 (43.2)	7330 (47.8)	690 (30.8)	67 (5.8)	16968 (50.4)	13567 (59.7)	2940 (37.9)	461 (14.4)	15345 (59.7)	11470 (67.9)	3334 (52.0)	541 (22.7)	7911 (66.5)	5804 (73.0)	1717 (61.5)	390 (33.7)
Death	7483 (39.9)	6830 (44.5)	600 (27.2)	53 (4.5)	15659 (46.5)	12871 (56.3)	2426 (32.2)	362 (11.1)	14031 (54.6)	10901 (63.8)	2627 (43.7)	503 (19.6)	7207 (60.6)	5548 (68.6)	1281 (50.7)	378 (29.5)
Ischaemic stroke	855 (4.6)	792 (5.2)	54 (2.4)	9 (0.8)	1905 (5.7)	1563 (6.8)	290 (3.8)	52 (1.6)	1970 (7.7)	1486 (8.7)	437 (7.2)	47 (1.9)	1166 (9.8)	867 (10.6)	257 (10.1)	42 (3.5)
All stroke	1062 (5.7)	942 (6.1)	106 (4.8)	14 (1.2)	2318 (6.9)	1769 (7.7)	474 (6.2)	75 (2.3)	2296 (8.9)	1658 (9.7)	575 (9.4)	63 (2.6)	1352 (11.4)	962 (11.9)	339 (13.0)	51 (4.2)
Severe bleeding	942 (5.0)	808 (5.3)	122 (5.4)	12 (1.0)	2064 (6.1)	1332 (5.9)	614 (7.9)	118 (3.6)	2118 (8.2)	1238 (7.4)	777 (12.2)	103 (4.1)	1277 (10.7)	709 (9.0)	478 (17.3)	90 (7.2)
TIA	277 (1.5)	256 (1.7)	18 (0.8)	3 (0.3)	509 (1.5)	387 (1.7)	105 (1.4)	17 (0.5)	625 (2.4)	438 (2.6)	156 (2.6)	31 (1.2)	374 (3.1)	257 (3.2)	99 (3.9)	18 (1.4)
Fall	260 (1.4)	183 (1.2)	68 (3.1)	9 (0.8)	2530 (7.5)	1608 (7.1)	828 (10.6)	94 (2.9)	4130 (16.1)	2501 (14.9)	1452 (22.3)	177 (7.3)	3011 (25.3)	1639 (21.3)	1220 (39.8)	152 (13.4)
Abbreviations DOAC: direct oral anticoagulant; OAC: oral anticoagulant; TIA: transient ischaemic attack; VKA: vitamin K antagonist																

Supplementary table 2: Incidence rate per 100 person years for composite and secondary outcomes, by frailty status and OAC prescription.

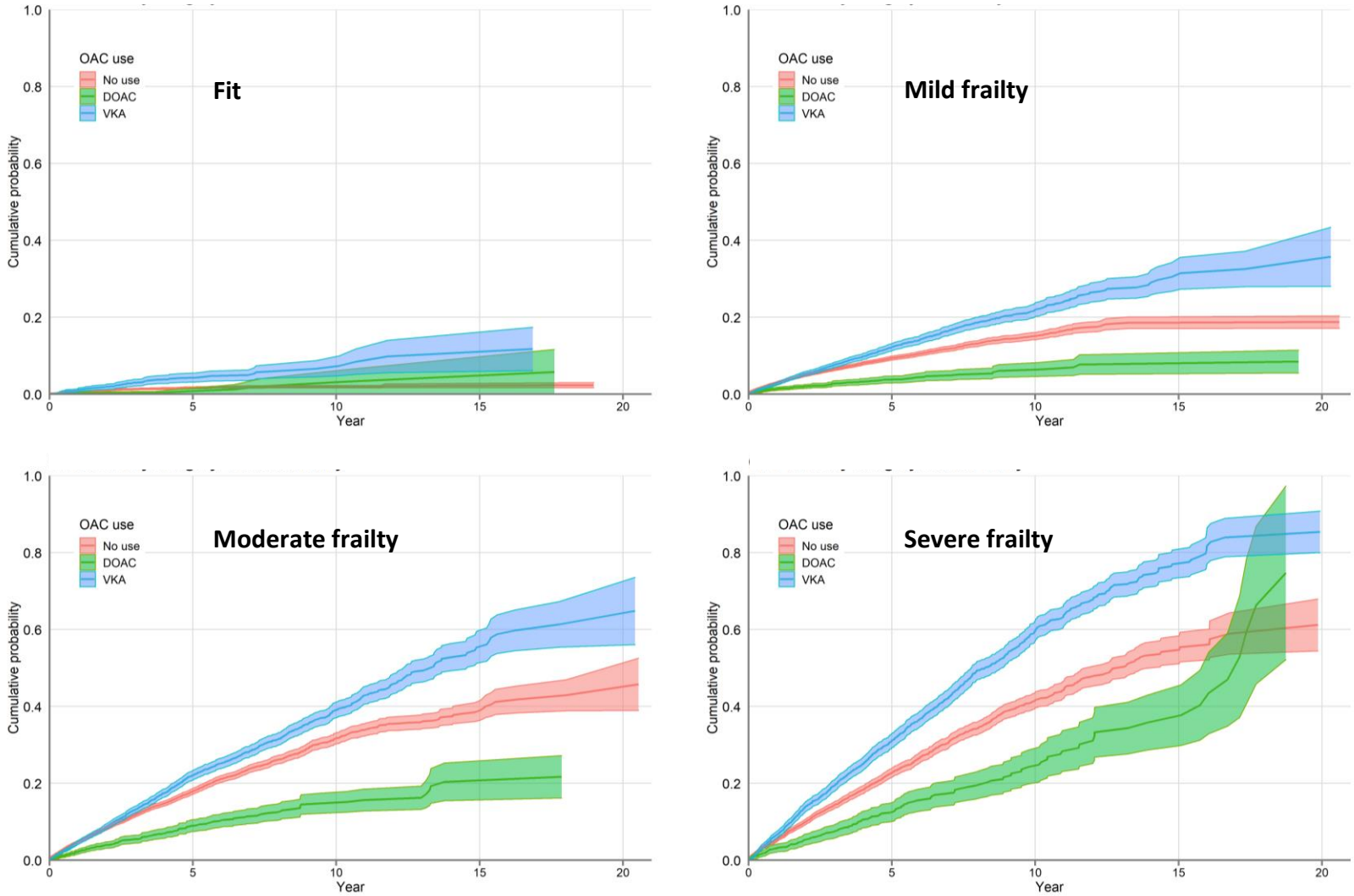
	Incidence rate per 100 person years (95% CI)											
	Fit			Mild frailty			Moderate frailty			Severe frailty		
Outcome	No OAC	VKA	DOAC	No OAC	VKA	DOAC	No OAC	VKA	DOAC	No OAC	VKA	DOAC
Composite	14.3 (14.0-14.7)	9.5 (8.8-10.2)	2.0 (1.5- 2.5)	17.1 (16.8-17.4)	9.2 (8.9- 9.6)	4.2 (3.8- 4.6)	17.7 (17.4-18.0)	11.1 (10.7-11.5)	5.6 (5.1- 6.1)	16.9 (16.5-17.3)	11.9 (11.3-12.4)	7.2 (6.5- 8.0)
Death	12.6 (12.3-12.9)	8.1 (7.5- 8.8)	1.5 (1.1- 1.9)	15.0 (14.8-15.3)	7.5 (7.2- 7.8)	3.1 (2.7- 3.4)	15.1 (14.8-15.4)	8.6 (8.3- 9.0)	4.4 (4.0- 4.8)	14.1 (13.7-14.5)	8.7 (8.2- 9.2)	5.7 (5.1- 6.2)
Ischaemic stroke	1.5 (1.4-1.6)	0.7 (0.5-0.9)	0.3 (0.1-0.4)	1.9 (1.8-2.0)	0.9 (0.8-1.0)	0.5 (0.3-0.6)	2.1 (2.0-2.2)	1.5 (1.3-1.6)	0.5 (0.3-0.6)	2.3 (2.1-2.4)	1.8 (1.6-2.0)	0.7 (0.5-0.9)
All stroke	1.8 (1.7-1.9)	1.5 (1.2-1.7)	0.4 (0.2-0.6)	2.1 (2.0-2.2)	1.5 (1.3-1.6)	0.7 (0.5-0.8)	2.4 (2.3-2.5)	1.9 (1.7-2.1)	0.6 (0.5-0.8)	2.6 (2.4-2.7)	2.4 (2.1-2.6)	0.9 (0.6-1.1)
Severe bleeding	1.5 (1.4-1.6)	1.7 (1.4-2.0)	0.3 (0.2-0.5)	1.6 (1.5-1.7)	1.9 (1.7-2.0)	1.0 (0.8-1.2)	1.8 (1.7-1.9)	2.5 (2.4-2.7)	1.0 (0.8-1.1)	2.0 (1.8-2.1)	3.2 (2.9-3.5)	1.5 (1.2-1.8)
TIA	0.5 (0.4-0.5)	0.2 (0.1-0.4)	0.1 (0.0-0.2)	0.5 (0.4-0.5)	0.3 (0.3-0.4)	0.1 (0.1-0.2)	0.6 (0.6-0.7)	0.5 (0.4-0.6)	0.3 (0.2-0.4)	0.7 (0.6-0.7)	0.7 (0.6-0.8)	0.3 (0.2-0.4)
Fall	0.3 (0.3-0.4)	0.9 (0.7-1.2)	0.3 (0.1-0.4)	2.0 (1.9-2.1)	2.6 (2.4-2.8)	0.8 (0.7-1.0)	4.0 (3.8-4.2)	4.9 (4.7-5.2)	1.8 (1.6-2.1)	5.3 (5.1-5.6)	8.3 (7.8-8.8)	3.0 (2.6-3.5)

Abbreviations DOAC: direct oral anticoagulant; OAC: oral anticoagulant; TIA: transient ischaemic attack; VKA: vitamin K antagonist

Supplementary figure 1: Cohort flow diagram



Abbreviations: AF: atrial fibrillation; CPRD: Clinical Practice Research Database; GP: general practitioner; HES: hospital episode statistics; ONS: Office for National Statistics



Supplementary figure 2: Cumulative incidence function for fall by frailty category and anticoagulation status (with 95% confidence interval)