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ORIGINAL ARTICLE

Impact of frailty on the effectiveness and safety of non-vitamin K antagonist oral anticoagulants (NOACs) in patients with atrial fibrillation: a nationwide cohort study

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Aims Data on non-vitamin K antagonist oral anticoagulants (NOACs) use in patients with atrial fibrillation (AF) and frailty are scarce. Therefore, the impact of frailty on AF-related outcomes and benefit–risk profiles of NOACs in patients with frailty were investigated.

Methods and results AF patients initiating anticoagulation between 2013 and 2019 were included using Belgian nationwide data. Frailty was assessed with the Claims-based Frailty Indicator. Among 254 478 anticoagulated AF patients, 71 638 (28.2%) had frailty. Frailty was associated with higher all-cause mortality risks [adjusted hazard ratio (aHR) 1.48, 95% confidence interval (CI) (1.43–1.54)], but not with thromboembolism or bleeding. Among subjects with frailty (78 080 person-years of follow-up), NOACs were associated with lower risks of stroke or systemic embolism (stroke/SE) [aHR 0.77, 95%CI (0.70–0.86)], all-cause mortality [aHR 0.88, 95%CI (0.84–0.92)], and intracranial bleeding [aHR 0.78, 95%CI (0.66–0.91)], a similar major bleeding risk [aHR 1.01, 95%CI (0.93–1.09)], and higher gastrointestinal bleeding risk [aHR 1.19, 95%CI (1.06–1.33)] compared with VKAs. Major bleeding risks were lower with apixaban [aHR 0.84, 95%CI (0.76–0.93)], similar with edoxaban [aHR 0.91, 95%CI (0.73–1.14)], and higher with dabigatran [aHR 1.16, 95%CI (1.03–1.30)] and rivaroxaban [aHR 1.11, 95%CI (1.02–1.21)] compared with VKAs. Apixaban was associated with lower major bleeding risks compared with dabigatran [aHR 0.72, 95%CI (0.65–0.80)], rivaroxaban [aHR 0.78, 95%CI (0.72–0.84)] and edoxaban [aHR 0.74, 95%CI (0.65–0.84)], but mortality risk was higher compared with dabigatran and edoxaban.

Conclusion Frailty was an independent risk factor of death. Non-vitamin K antagonist oral anticoagulants had better benefit–risk profiles than VKAs in patients with frailty, especially apixaban, followed by edoxaban.

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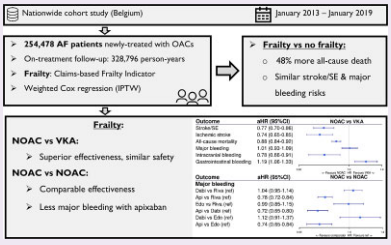
Graphical Abstract

AF: atrial fibrillation; aHR: adjusted hazard ratio; Api: apixaban; CI: confidence interval; Dabi: dabigatran; Edo: edoxaban; IPTW: inverse probability of treatment weighting; NOAC: non-vitamin K antagonist oral anticoagulant; OAC: oral anticoagulant; Ref: reference category; Riva: rivaroxaban; SE: systemic embolism; VKA: vitamin K antagonist.



Keywords Atrial fibrillation • Frailty • Anticoagulant • Thromboembolism • Bleeding • Death

Introduction

Frailty is a complex clinical syndrome associated with reduced resilience to stressor events due to age- and comorbidity-related decline in multiple physiological organ systems.[1–3] The most frequently applied definitions of frailty include the Frailty Phenotype by Fried *et al.*[4] and Frailty Index by Rockwood *et al.*,[5] although other tools such as the Anamnestic Frailty Phenotype[6] have been proposed for clinical practice.[3] Frailty is up to four times more prevalent in patients with atrial fibrillation (AF) as compared with non-AF patients regardless of age.[1,2,7,8] Frailty is also a prognostic factor, as it was found to be an independent risk factor for falls, hospitalizations, and death.[4,9–16] However, it is currently not known whether frailty is also associated or not with an increased risk of thromboembolism or bleeding in AF patients initiating anticoagulation. Prior studies[9–16] rendered conflicting results, but were often limited by small sample sizes, short follow-up durations, heterogeneous frailty measures, inclusion of anticoagulated and non-anticoagulated AF patients, and limited adjustment for confounders (e.g. only age and sex).

Moreover, the use of oral anticoagulants (OACs) in patients with AF and frailty is a matter of concern for physicians, faced with the challenge of balancing the benefits of stroke reduction against the risk of bleeding.[17] Consequently, increased rates of non-initiation, inappropriate underdosing, low therapy adherence, and early discontinuation of non-vitamin K antagonist oral anticoagulants (NOACs) have been observed in patients with AF and frailty.[8–10,16,18–20] Data on the benefit–risk profile of NOACs in patients with frailty is, however, particularly scarce, which was identified as an important research gap.[17] Although randomized controlled trials (RCTs) have demonstrated that NOACs are associated with an at least comparable efficacy and safety compared with vitamin K antagonists (VKAs),[21–24] resulting in a rapid transition of VKAs to NOACs for stroke prevention in AF,[25–27] patients with frailty were largely under-represented in these trials.[17] To the best of our knowledge, only four studies[1,7,12,28] have investigated the effectiveness and safety of individual NOACs compared with VKAs in AF patients with frailty, among which only one study[7] explored outcomes between three different NOACs (i.e. not including edoxaban yet). Consequently, there is an urgent need for a critical appraisal of the benefit–risk profile of all marketed NOACs in patients with frailty to guide physicians in their choice of (N)OAC.

Therefore, in the present study, we aimed to investigate (1) the impact of frailty on clinical outcomes in AF patients initiating anticoagulation, and (2) the long-term comparative effectiveness and safety of dabigatran, rivaroxaban, apixaban, and edoxaban in comparison with VKAs, and between individual NOACs in patients with both AF and frailty.

Methods

Source population

Details on the study methodology have been published before and are provided in the supplemental materials.[19,27,29] In brief, two nationwide databases provided the source population, namely the InterMutualistic Agency (IMA) database and Minimal Hospital Dataset (MHD). The IMA centralizes all claims data from Belgian health insurance funds on reimbursed ambulatory and hospital care, including demographic characteristics, medical procedures, and drug prescription claims, and represents all legal residents in Belgium.[30] The MHD aggregates hospital discharge diagnoses of every hospital admission (hospitalizations, day-care stays, and emergency room contacts), coded in International Classification of Diseases (ICD) codes (ICD-9 up to 2014, ICD-10 from 2015 onwards).[31] Every individual of the study population could be identified in both databases. This study was approved by the Belgian Commission for the Protection of Privacy (approval code IVC/KSZG/20/344).[32] The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline was followed (see Supplementary material online, *Table S1*).[33]

Study population

From 1 January 2013 to 1 January 2019, persons aged ≥45 years with ≥1 year coverage by health insurance funds were included from the IMA database on the first date of filling an OAC prescription (= index date) (Online Appendix *Figure S1*). Non-vitamin K antagonist oral anticoagulant users, namely dabigatran (approved in Belgium since August 2012), rivaroxaban (approved since September 2012), apixaban (approved since September 2013), and edoxaban (approved since October 2016), and VKA users (warfarin, acenocoumarol, and phenprocoumon) were included.[27] Only OAC-naïve subjects were considered, excluding subjects with an OAC prescription filled ≤1 year before the index date. Subjects were not required to have an ICD-coded hospital discharge diagnosis of AF to be included, as this would create selection bias due to limiting the study population to hospitalized AF subjects and excluding AF subjects treated exclusively in primary or ambulatory care.[29,34]

To avoid competing treatment indications for OACs, persons were excluded in case of total hip or knee replacement, or diagnosis of deep vein thrombosis or pulmonary embolism ≤6 months before the index date (see Supplementary material online, *Table S2* and *Figure S1*). Moreover, only AF patients eligible for NOACs and VKAs were examined, excluding subjects with valvular AF (mechanical prosthetic heart valve or moderate/severe mitral stenosis) or end-stage renal disease (chronic kidney disease (CKD) stage V and/or dialysis). Lastly, subjects with two or more prescription claims of different OAC types or doses on the index date, or treated with

NOAC doses not approved for stroke prevention in AF (e.g. rivaroxaban 10 mg) were excluded.

Frailty

Frailty was identified using the validated Johns Hopkins Claims-based Frailty Indicator (CFI),[35] in line with prior research,[1,7] since a clinical frailty assessment based on Fried's Frailty Phenotype[4] or Rockwood's Frailty Index[5] was more difficult using administrative healthcare data (e.g. need for data on grip strength, walking speed…). The CFI was developed to identify explicitly a frail population and might be applied in large datasets for confounding adjustment or risk prediction.[35] This algorithm weighs 21 variables using only administrative claims data, including demographics, cognitive and physical dysfunction, and the Charlson Comorbidity Index (CCI), to classify individuals as frail or not frail in accordance with Fried's Frailty Phenotype (summarized in Supplementary material online, *Table S2*).[1,4,7,35] A cut-off of ≥0.20 (range 0–1) has been shown to truly identify frail patients (specificity 91%).[1,7,35] However, as the CFI does not allow to identify robust and pre-frail subjects (zero or one to two criteria of the Frailty Phenotype,[4] respectively), these patients are categorized as non-frail.[35]

Outcomes

Effectiveness outcomes included stroke or systemic embolism (stroke/SE), ischemic stroke, and all-cause mortality. Safety outcomes included major, intracranial, and gastrointestinal bleeding. Major bleeding was defined as a hospitalized bleeding event in a critical area or organ (e.g. intracranial), fatal bleeding, or bleeding event with a medical procedure code for blood transfusion ≤10 days after admission.[29,36] This definition is adapted from the International Society on Thrombosis and Haemostasis,[37] considering that no data on haemoglobin levels or number of blood transfusion units were available.[36,37] Outcomes were identified using ICD-coded hospital discharge diagnoses and medical procedure codes (see Supplementary material online, *Table S3*).[19] The incident date of outcomes was defined as the date of hospital admission for ICD codes and date of registration for medical procedure codes, whichever occurred first.

Follow-up

Patients were followed from OAC initiation until the first occurrence of the investigated outcome, discontinuation (>60-day gap of drug supply) or switch of treatment, death, emigration, or end of the study period (1 January 2019), whichever came first (on-treatment analysis).[19]

Covariates

Baseline characteristics were assessed on the index date and included age, sex, comorbidities, medication history, and clinical risk scores. Comorbidities were identified with specific ICD-coded diagnoses, medical procedure codes, and/or medication prescription claims ≤1 year before the index date (see Supplementary material online, *Table S2*). Medication history was identified with medication prescription claims, considering recent use ≤6 months before the index date. The CHA_2DS_2-VASc score, modified HAS-BLED score (without the 'labile INR' criterion), and age-adjusted CCI were calculated.[26,38]

Statistical analyses

Mean and standard deviation were presented for continuous variables if normally distributed, whereas median and interquartile range (IQR) if skewed. For categorical variables, number and percentage were described. Crude event rates per outcome were calculated as the total number of events per 100 person-years at risk. Outcomes were compared between AF patients initiating anticoagulation with vs. without frailty using Cox proportional hazard regression models. Additionally, models were adjusted for age and sex (age- and sex-adjusted model); and for age, sex, type of OAC used, baseline comorbidities, and medication history (multivariable adjusted model with covariates described in *Table 1*). Only statistically significant factors using a two-sided *P*-value of <0.05 were retained in the multivariable adjusted model with backward elimination.

Moreover, outcomes were compared between NOACs and VKAs, and between individual NOACs in patients with AF and frailty using stabilized inverse probability of treatment weighting (IPTW). In comparisons with apixaban and edoxaban, the study population was restricted to subjects having initiated treatment from September 2013 and from October 2016 onwards respectively, to avoid violations of the positivity assumption.[39] Propensity scores (PS) were calculated with logistic regression models, including the 39 confounding covariates described in *Table 1* (demographics, comorbidities, medication history, and risk scores), stratified by calendar year. Based on the PS, stabilized weights were calculated and truncated at the 0.5th and 99.5th percentile. Covariate balance before and after weighting was checked using standardized mean differences with a ≥0.1 threshold to indicate imbalance. Weighted Cox proportional hazard regression models were used to calculate adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs). The proportional hazard assumption was assessed using scaled Schoenfeld residuals. A two-sided *P*-value of <0.05 was considered statistically significant. All analyses were performed in R (R version 3.6.0).

Subgroup analyses

As an interaction between frailty and polypharmacy on the risk of death has been demonstrated before,[40] Cox proportional hazard regression models, which compared outcomes between AF patients with vs. without frailty, were additionally stratified by the number of concomitantly used drugs (<5, 5–9 and ≥10 drugs). Moreover, the effectiveness and safety of OACs were also investigated in AF patients with frailty stratified by age (<85 and ≥85 years old).

Sensitivity analyses

Sensitivity analyses were performed to check the robustness of results on the effectiveness and safety of OACs in AF patients with frailty. First, to examine whether estimates were affected by differential censoring between treatment groups (e.g. due to differences in discontinuation or switching rates), analyses were repeated using an intention-to-treat approach, defining the end of follow-up as the first occurrence of an outcome, death, emigration, or end of study period, whichever occurred first. Second, to take competing risks into account, cause-specific aHRs were calculated, treating death as a competing risk. Third, to reduce misclassification bias, only subjects with an ICD-coded hospital discharge diagnosis of AF before or up to 90 days after the index date were investigated.[34] Fourth, the study population was restricted to subjects having initiated treatment between 1 October 2016 and 1 January 2019, when all NOACs were commercially available in Belgium, to avoid time-period bias and account for the shorter follow-up of edoxaban compared with other NOACs. Lastly, although data were lacking on other causes of death, the risk of AF-related mortality was investigated as an exploratory analysis, by only considering deaths occurring within 60 days after an event of thromboembolism, bleeding, or myocardial infarction.[29]

Results

Baseline characteristics

A total of 254 478 newly treated AF patients were included (*Figure 1*). Baseline characteristics of the 71 638 (28.2%) subjects with frailty and 182 840 (71.8%) subjects without frailty are summarized in *Table 1*. Patients with frailty were older (85.7 ± 5.6 vs. 70.8 ± 9.5 years) and more frequently female (66.3% vs. 40.1%), had a higher prevalence of cardiovascular comorbidities, used more drugs concomitantly (8.3 ± 4.6 vs. 6.0 ± 3.9), and had higher CHA_2DS_2-VASc (4.9 ± 1.6 vs. 2.9 ± 1.6) and HAS-BLED scores (3.1 ± 1.3 versus 2.2 ± 1.2) than patients without frailty.

Table 1 Baseline characteristics of OAC-naïve AF patients with and without frailty at baseline

Patient characteristics	No frailty (*n* = 182 840)	Frailty			SMD*	
		Overall frail (*n* = 71 638)	VKA (*n* = 13 524)	NOAC (*n* = 58 114)	Before IPTW	After IPTW
Age (years)	70.8 ± 9.5	85.7 ± 5.6	85.1 ± 6.0	85.9 ± 5.5	0.144	0.027
Female	73 264 (40.1%)	47 510 (66.3%)	8803 (65.1%)	38 707 (66.6%)	0.032	0.012
Follow-up (years)	0.7 [0.2–2.1]	0.6 [0.1–1.6]	0.2 [0.1–1.0]	0.7 [0.2–1.7]	NA	NA
Comorbidities						
Hypertension	110 426 (60.4%)	54 450 (76.0%)	10 406 (76.9%)	44 044 (75.8%)	0.024	0.002
Coronary artery disease	30 493 (16.7%)	17 350 (24.2%)	4128 (30.5%)	13 222 (22.8%)	0.171	0.011
Congestive heart failure	17 253 (9.4%)	22 640 (31.6%)	4698 (34.7%)	17 941 (30.9%)	0.076	0.001
Valvular heart disease	19 585 (10.7%)	16 576 (23.1%)	3600 (26.6%)	12 976 (22.3%)	0.095	0.018
Peripheral artery disease	12 532 (6.9%)	8404 (11.7%)	2089 (15.4%)	6315 (10.9%)	0.116	0.008
Dyslipidemia	104 247 (57.0%)	39 668 (55.4%)	7763 (57.4%)	31 905 (54.9%)	0.050	0.011
Chronic kidney disease	12 467 (6.8%)	17 028 (23.8%)	4311 (31.9%)	12 717 (21.9%)	0.214	0.023
Chronic liver disease	5450 (3.0%)	3007 (4.2%)	704 (5.2%)	2303 (4.0%)	0.039	0.010
Chronic lung disease	19 204 (10.5%)	12 841 (17.9%)	2724 (20.1%)	10 117 (17.4%)	0.056	0.007
Obstructive sleep apnea	7385 (4.0%)	1388 (1.9%)	342 (2.5%)	1046 (1.8%)	0.040	0.010
Cancer	16 399 (9.0%)	8788 (12.3%)	1763 (13.0%)	7025 (12.1%)	0.017	0.022
Upper GI tract disorder**	10 506 (5.7%)	8672 (12.1%)	1966 (14.5%)	6707 (11.5%)	0.074	0.007
Lower GI tract disorder**	11 611 (6.4%)	6045 (8.4%)	1276 (9.4%)	4769 (8.2%)	0.025	0.003
Diabetes mellitus	52 834 (28.9%)	29 869 (41.7%)	6171 (45.6%)	23 698 (40.8%)	0.092	0.066
Anemia	9483 (5.2%)	11 629 (16.2%)	2828 (20.9%)	8801 (15.1%)	0.129	0.017
Thyroid disease	23 156 (12.7%)	13 753 (19.2%)	2845 (21.0%)	10 908 (18.8%)	0.050	0.006
Depression	27 540 (15.1%)	29 696 (41.5%)	6047 (44.7%)	23 649 (40.7%)	0.081	0.026
Dementia	1845 (1.0%)	11 717 (16.4%)	2357 (17.4%)	9359 (16.1%)	0.022	0.015
Parkinson's disease	2087 (1.1%)	5469 (7.6%)	1047 (7.7%)	4422 (7.6%)	0.005	0.003
History of falling	5979 (3.3%)	14 194 (19.8%)	2547 (18.8%)	11 648 (20.0%)	0.049	0.065
Prior stroke/SE	17 430 (9.5%)	17 965 (25.1%)	3519 (26.0%)	14 446 (24.9%)	0.008	0.017
Prior MB/CRNMB	7219 (3.9%)	7060 (9.9%)	1604 (11.9%)	5456 (9.4%)	0.055	0.010
Medication history						
Number of concomitant drugs	6.0 ± 3.9	8.3 ± 4.6	8.9 ± 4.9	8.2 ± 4.5	0.143	0.028
Beta blockers	105 473 (57.7%)	46 344 (64.7%)	8256 (61.0%)	38 088 (65.5%)	0.093	0.016
Verapamil, diltiazem	7091 (3.9%)	2812 (3.9%)	568 (4.2%)	2244 (3.9%)	0.017	0.014
Digoxin	12 723 (7.0%)	9808 (13.7%)	1528 (11.3%)	8280 (14.2%)	0.088	0.004
Class I AAD	19 586 (10.7%)	3715 (5.2%)	511 (3.8%)	3204 (5.5%)	0.082	0.002
Class III AAD	42 953 (23.5%)	18 498 (25.8%)	3308 (24.5%)	15 190 (26.1%)	0.039	0.026
Acetylsalicylic acid	68 253 (37.3%)	31 728 (44.3%)	5896 (43.6%)	25 832 (44.5%)	0.017	0.004
P2Y12 inhibitor	9607 (5.3%)	5074 (7.1%)	1023 (7.6%)	4051 (7.0%)	0.023	0.028
Proton pump inhibitor	66 579 (36.4%)	35 669 (49.8%)	7136 (52.8%)	28 533 (49.1%)	0.073	0.022
NSAID	48 345 (26.4%)	14 637 (20.4%)	2755 (20.4%)	11 882 (20.4%)	0.002	0.022
Oral corticosteroids	34 727 (19.0%)	17 412 (24.3%)	3609 (26.7%)	13 803 (23.8%)	0.068	<0.001
SSRI/SNRI	15 304 (8.4%)	16 023 (22.4%)	3244 (24.0%)	12 779 (22.0%)	0.047	0.026
Clinical risk score						
CHA_2DS_2-VASc score	2.9 ± 1.6	4.9 ± 1.6	5.1 ± 1.7	4.9 ± 1.6	0.089	0.004
HAS-BLED score	2.2 ± 1.2	3.1 ± 1.3	3.3 ± 1.4	3.1 ± 1.2	0.125	0.011
Charlson Comorbidity Index	3.7 ± 2.0	6.0 ± 2.2	6.2 ± 2.4	5.9 ± 2.1	0.080	0.023

Data shown as mean ± standard deviation, median and [interquartile range], or counts and percentages. NOAC users without frailty (25.3% reduced dose) included 20 492 dabigatran, 53 849 rivaroxaban, 43 575 apixaban, and 17 042 edoxaban users; NOAC users with frailty (64.8% reduced dose) included 7652 dabigatran, 20 572 rivaroxaban, 23 350 apixaban, and 6540 edoxaban users. VKA users without frailty included 22 641 acenocoumarol, 13 157 warfarin, and 12 084 phenprocoumon users; VKA users with frailty included 7009 acenocoumarol, 3702 warfarin, and 2813 phenprocoumon users.

* Absolute SMDs illustrated for comparison of NOACs vs. VKAs in patients with frailty before and after stabilized inverse probability of treatment weighting.

** Upper and lower gastrointestinal tract disorders were defined as gastroesophageal reflux disease or peptic ulcer disease; and diverticulosis, angiodysplasia, colorectal polyposis or hemorrhoids, respectively.

AAD: antiarrhythmic drug; AF: atrial fibrillation; CRNMB: clinically relevant non-major bleeding; GI: gastrointestinal; MB: major bleeding; NA: not applicable; NOAC: non-vitamin K antagonist oral anticoagulant; NSAID: non-steroidal anti-inflammatory drug; OAC: oral anticoagulant; SE: systemic embolism; SMD: standardized mean difference; SNRI: serotonin and norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; and VKA: vitamin K antagonist.

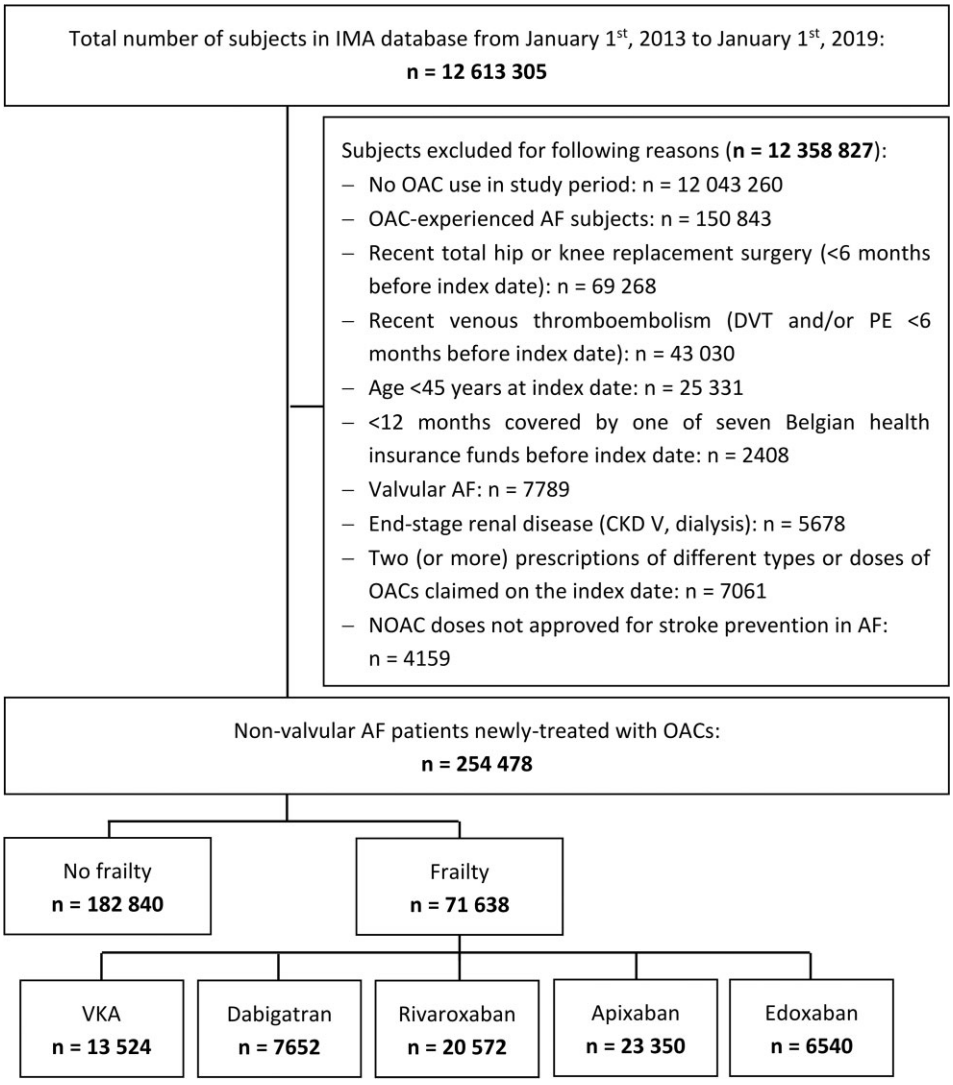


Figure 1 Flowchart of the study population. AF: atrial fibrillation; CKD: chronic kidney disease; DVT: deep vein thrombosis; IMA: InterMutualistic Agency; NOAC: non-vitamin K antagonist oral anticoagulant; OAC: oral anticoagulant; PE: pulmonary embolism; and VKA: vitamin K antagonist.

Among subjects with frailty, the 58 114 NOAC and 13 524 VKA users were on average 85.9 ± 5.5 and 85.1 ± 6.0 years old, concomitantly used 8.2 ± 4.5 and 8.9 ± 4.9 drugs and had a mean CHA_2DS_2-VASc score of 4.9 ± 1.6 and 5.1 ± 1.7 before weighting, respectively (*Table 1*). Baseline characteristics of the 7652 dabigatran, 20 572 rivaroxaban, 23 350 apixaban and 6540 edoxaban users with frailty (reduced dose used in 91.0%, 66.7%, 56.0%, and 59.7% of subjects, respectively) are summarized in Supplementary material online, *Table S4*. After weighting, covariate balance was achieved (*Table 1*, see Supplementary material online, *Figure S2*).

Frailty vs. no frailty

During a median follow-up of 0.6 years (IQR [0.1–1.6]; 78 080 person-years) and 0.7 years (IQR [0.2–2.1]; 250 715 person-years) among anticoagulated patients with and without frailty, respectively, 7380 persons had an event of stroke/SE (event rates 3.60 vs. 1.88 per 100 person-years), 24 853 subjects died (19.53 vs. 3.83 per 100 person-years), and 14 716 had a major bleeding (6.91 vs. 3.95 per 100 person-years) (*Table 2*). Crude, age- and sex-adjusted, and multivariable adjusted HRs of outcomes are summarized in *Table 3*. Before adjustment, the risks of stroke/SE [unadjusted HR 1.80, 95%CI (1.72–1.89)], all-cause mortality [unadjusted HR 4.87, 95%CI (4.75–5.00)], and major bleeding [unadjusted HR 1.66, 95%CI (1.61–1.72)] were higher among AF patients with vs. without frailty, which was consistent after adjusting for age and sex. After multivariable adjustment, frailty was associated with a significantly higher risk of all-cause mortality [aHR 1.48, 95%CI (1.43–1.54)] compared with AF patients without frailty, while the risks of stroke/SE [aHR 1.03, 95%CI (0.96–1.10)] and major bleeding [aHR 1.03, 95%CI (0.98–1.08)] were not significantly different.

Non-vitamin K antagonist oral anticoagulant vs. vitamin K antagonist in patients with frailty

The unadjusted number of events and event rates among subjects with AF and frailty are summarized in *Table 2*. After multivariable

Table 2 The number of events and crude event rates per 100 person-years of outcomes

	No frailty	Frailty						
Outcome	events (per 100 PY)	Overall events (per 100 PY)	VKA events (per 100 PY)	NOAC events (per 100 PY)	Dabigatran events (per 100 PY)	Rivaroxaban events (per 100 PY)	Apixaban events (per 100 PY)	Edoxaban events (per 100 PY)
Effectiveness								
Stroke/SE	4635 (1.88)	2745 (3.60)	493 (4.69)	2252 (3.43)	353 (3.68)	899 (3.35)	848 (3.38)	152 (3.66)
Ischemic stroke	2276 (0.92)	1619 (2.11)	299 (2.81)	1320 (1.99)	243 (2.51)	518 (1.92)	475 (1.87)	84 (2.01)
All-cause mortality	9601 (3.83)	15 252 (19.53)	2512 (23.28)	12 740 (18.93)	1522 (15.38)	4990 (18.21)	5348 (20.74)	880 (20.92)
Safety								
Major bleeding	9543 (3.95)	5173 (6.91)	783 (7.60)	4390 (6.80)	658 (6.95)	1861 (7.12)	1464 (5.88)	407 (10.02)
Intracranial bleeding	2649 (1.07)	1153 (1.49)	209 (1.97)	944 (1.42)	147 (1.51)	389 (1.44)	347 (1.36)	61 (1.46)
Gastrointestinal bleeding	4802 (1.95)	2851 (3.73)	379 (3.57)	2472 (3.75)	395 (4.08)	1074 (4.02)	755 (2.98)	248 (6.01)

NOAC: non-vitamin K antagonist oral anticoagulant; PY: person-year; SE: systemic embolism; and VKA: vitamin K antagonist.

Table 3 Crude, age- and sex-adjusted, and multivariable adjusted hazard ratios with 95% confidence intervals of outcomes compared between anticoagulated AF patients with vs. without frailty using Cox proportional hazard regression models

	Frailty vs. no frailty		
	Crude HR (95%CI)	Age- and sex-adjusted HR (95%CI)*	Multivariable adjusted HR (95%CI)**
Effectiveness			
Stroke/SE	1.80 (1.72–1.89)	1.68 (1.58–1.79)	1.03 (0.96–1.10)
Ischemic stroke	2.15 (2.02–2.29)	1.72 (1.58–1.88)	1.02 (0.93–1.13)
All-cause mortality	4.87 (4.75–5.00)	2.95 (2.85–3.05)	1.48 (1.43–1.54)
Safety			
Major bleeding	1.66 (1.61–1.72)	1.49 (1.43–1.56)	1.03 (0.98–1.08)
Intracranial bleeding	1.30 (1.21–1.39)	1.39 (1.27–1.52)	0.96 (0.87–1.07)
Gastrointestinal bleeding	1.84 (1.76–1.93)	1.49 (1.40–1.59)	1.06 (0.99–1.13)

* Adjusted for age and sex.
** Adjusted for age, sex, OAC type, baseline comorbidities, and medication history with backward elimination.
AF: atrial fibrillation; CI: confidence interval; HR: hazard ratio; OAC: oral anticoagulant; and SE: systemic embolism.

adjustment, NOACs in AF patients with frailty were associated with significantly lower risks of stroke/SE [aHR 0.77, 95%CI (0.70–0.86)], ischemic stroke [aHR 0.74, 95%CI (0.65–0.85)], and all-cause mortality [aHR 0.88, 95%CI (0.84–0.92)] compared with VKAs (see Supplementary material online, *Table S5* and *Figure 2*).

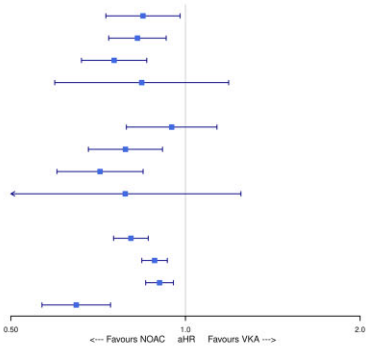
Likewise, dabigatran, rivaroxaban, apixaban, and edoxaban were each associated with significantly lower risks of stroke/SE, ischemic stroke, and all-cause mortality compared with VKAs, although the risks of stroke/SE with edoxaban [aHR 0.84, 95%CI (0.60–1.19)] and risks of ischemic stroke with dabigatran [aHR 0.95, 95%CI (0.79–1.13)] and edoxaban [aHR 0.79, 95%CI (0.50–1.25)] were not significantly different.

In terms of safety, NOACs were associated with a similar risk of major bleeding [aHR 1.01, 95%CI (0.93–1.09)] compared with VKAs, driven by a lower risk of intracranial bleeding [aHR 0.78, 95%CI (0.66–0.91)] but higher risk of gastrointestinal bleeding [aHR 1.19, 95%CI (1.06–1.33)].

Compared with VKAs, the risk of major bleeding was significantly lower with apixaban [aHR 0.84, 95%CI (0.76–0.93)], non-significantly different with edoxaban [aHR 0.91, 95%CI (0.73–1.14)], but significantly higher with dabigatran [aHR 1.16, 95%CI (1.03–1.30)] and rivaroxaban [aHR 1.11, 95%CI (1.02–1.21)]. While trends towards lower risks of intracranial bleeding were observed with other NOACs, only apixaban was associated with a significantly lower risk compared with VKAs [aHR 0.76, 95%CI (0.62–0.93)]. Dabigatran [aHR 1.46, 95%CI (1.25–1.71)] and rivaroxaban [aHR 1.33, 95%CI (1.18–1.50)] were associated with significantly higher risks of gastrointestinal bleeding compared with VKAs, while risks were not significantly different with apixaban [aHR, 95%CI 0.91 (0.79–1.04)] and edoxaban [aHR 1.11, 95%CI (0.82–1.51)].

(A)

Outcome	Comparison	NOAC n	NOAC Events (/100PY)	VKA n	VKA Events (/100PY)	aHR (95%CI)	p-value
Stroke/SE							
	Dabigatran vs.VKA	6009	335 (3.74)	12686	502 (4.67)	0.84 (0.73-0.98)	0.025
	Rivaroxaban vs.VKA	19604	905 (3.45)	12438	475 (4.46)	0.83 (0.74-0.93)	<0.001
	Apixaban vs.VKA	22685	837 (3.38)	9683	368 (4.62)	0.75 (0.66-0.86)	<0.001
	Edoxaban vs.VKA	6294	156 (3.82)	2015	45 (4.62)	0.84 (0.60-1.19)	0.324
Ischemic stroke							
	Dabigatran vs.VKA	6009	227 (2.52)	12686	308 (2.84)	0.95 (0.79-1.13)	0.550
	Rivaroxaban vs.VKA	19604	521 (1.97)	12438	291 (2.71)	0.79 (0.68-0.91)	0.002
	Apixaban vs.VKA	22685	470 (1.88)	9683	224 (2.78)	0.71 (0.60-0.85)	<0.001
	Edoxaban vs.VKA	6294	85 (2.07)	2015	27 (2.74)	0.79 (0.50-1.25)	0.308
All-cause mortality							
	Dabigatran vs.VKA	6009	1583 (17.17)	12686	2435 (22.10)	0.81 (0.75-0.86)	<0.001
	Rivaroxaban vs.VKA	19604	5068 (18.91)	12438	2447 (22.42)	0.88 (0.84-0.93)	<0.001
	Apixaban vs.VKA	22685	5386 (21.20)	9683	1951 (23.89)	0.90 (0.85-0.95)	<0.001
	Edoxaban vs.VKA	6294	901 (21.72)	2015	334 (33.94)	0.65 (0.57-0.74)	<0.001



(B)

Outcome	Comparison	NOAC n	NOAC Events (/100PY)	VKA n	VKA Events (/100PY)	aHR (95%CI)	p-value
Major bleeding							
	Dabigatran vs.VKA	6009	698 (7.93)	12686	763 (7.24)	1.16 (1.03-1.30)	0.012
	Rivaroxaban vs.VKA	19604	1916 (7.51)	12438	751 (7.19)	1.11 (1.02-1.21)	0.020
	Apixaban vs.VKA	22685	1491 (6.09)	9683	582 (7.43)	0.84 (0.76-0.93)	<0.001
	Edoxaban vs.VKA	6294	414 (10.36)	2015	114 (11.95)	0.91 (0.73-1.14)	0.412
Intracranial bleeding							
	Dabigatran vs.VKA	6009	156 (1.72)	12686	212 (1.96)	0.93 (0.74-1.17)	0.517
	Rivaroxaban vs.VKA	19604	399 (1.51)	12438	205 (1.91)	0.85 (0.71-1.01)	0.068
	Apixaban vs.VKA	22685	351 (1.40)	9683	151 (1.88)	0.76 (0.62-0.93)	0.007
	Edoxaban vs.VKA	6294	60 (1.45)	2015	19 (1.97)	0.78 (0.45-1.36)	0.385
Gastrointestinal bleeding							
	Dabigatran vs.VKA	6009	420 (4.66)	12686	365 (3.37)	1.46 (1.25-1.71)	<0.001
	Rivaroxaban vs.VKA	19604	1107 (4.24)	12438	362 (3.38)	1.33 (1.18-1.50)	<0.001
	Apixaban vs.VKA	22685	769 (3.09)	9683	281 (3.50)	0.91 (0.79-1.04)	0.174
	Edoxaban vs.VKA	6294	252 (6.21)	2015	57 (5.86)	1.11 (0.82-1.51)	0.500

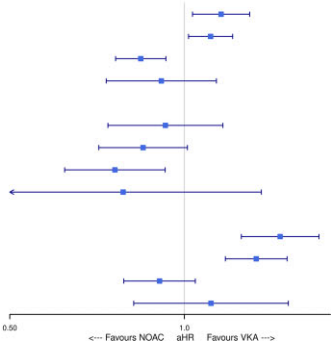


Figure 2 The (A) effectiveness and (B) safety of NOACs vs. VKAs in AF patients with frailty after IPTW. The weighted number of subjects at risk in the pseudopopulation, weighted number of events, weighted event rates per 100 PY, and aHRs with 95%CIs after IPTW are illustrated.
aHR: adjusted hazard ratio; CI: confidence interval; IPTW: inverse probability of treatment weighting; NOAC: non-vitamin K antagonist oral anticoagulant; PY: person-years; Ref: reference category; SE: systemic embolism; VKA: vitamin K antagonist; and vs.: versus.

Comparisons between NOACs in patients with frailty

No significant differences in the risks of stroke/SE and ischemic stroke were observed between individual NOACs in patients with frailty, except for a significantly higher risk of ischemic stroke with dabigatran compared with rivaroxaban [aHR 1.21, 95%CI (1.03–1.42)] (see Supplementary material online, *Table S6* and *Figure 3*). Dabigatran [aHR 0.91, 95%CI (0.86–0.97)] and edoxaban [aHR 0.85, 95%CI (0.77–0.94)] were associated with significantly lower risks of all-cause mortality compared with rivaroxaban, while apixaban was associated with higher mortality risks compared with dabigatran [aHR 1.18, 95%CI (1.10–1.26)] and edoxaban [aHR 1.20, 95%CI (1.11–1.30)]. No significant differences in the risk of death were observed between dabigatran and edoxaban, or apixaban and rivaroxaban.

Apixaban was associated with significantly lower risks of major bleeding in AF patients with frailty compared with dabigatran [aHR 0.72, 95%CI (0.65–0.80)], rivaroxaban [aHR 0.78, 95%CI (0.72–0.84)], and edoxaban [aHR 0.74, 95%CI (0.65–0.84)], driven by significantly lower risks of gastrointestinal bleeding [aHR 0.63, 95%CI (0.55–0.72); aHR 0.68, 95%CI (0.62–0.76); and aHR 0.64, 95%CI (0.54–0.76), respectively]. No significant differences in the risk of major bleeding were observed between other NOACs. The risk of intracranial bleeding was similar between individual NOACs.

Subgroup analyses

Results were consistent on the impact of frailty on clinical outcomes in AF patients stratified by the number of concomitantly used drugs and confidence intervals largely overlapping (e.g. aHR 1.60 (1.45–1.75), aHR 1.46 (1.37–1.55), and aHR 1.33 (1.24–1.42) for the risk of death in AF patients with vs. without frailty using <5, 5–9, and ≥ 10 drugs, respectively) (see Supplementary material online, *Table S7*).

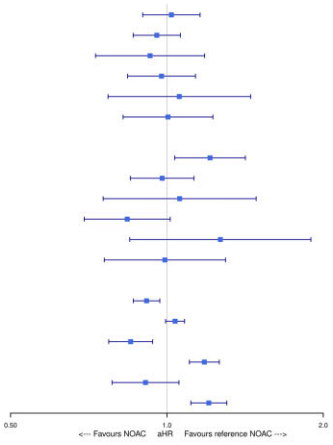
Moreover, comparable trends were observed on the effectiveness and safety of OACs in AF patients with frailty <85 and ≥ 85 years old (see Supplementary material online, *Table S8* and *Figure S3*). However, in AF patient with frailty <85 years old, no significant differences in the risks of major bleeding with dabigatran [aHR 1.02, 95%CI (0.86–1.21)] and rivaroxaban [aHR 1.09, 95%CI (0.96–1.24)] compared with VKAs, and of all-cause mortality with apixaban compared with edoxaban [aHR 1.09, 95%CI (0.95–1.26)] were observed.

Sensitivity analyses

Trends on the benefit–risk profile of NOACs in patients with frailty were consistent with an intention-to-treat approach (mean follow-up of 2.0 $\pm$ 1.6 years; 145 037 person-years) (see Supplementary material online, *Table S9* and *Figure S4*); when treating death as a competing risk (see Supplementary material online, *Table S10* and *Figure S5*); and when restricting the study population to subjects with an ICD-coded hospital discharge diagnosis of AF (n = 45 695)

(A)

Outcome	Comparison	NOAC n	NOAC Events (/100PY)	Reference NOAC n	Reference NOAC Events (/100PY)	aHR (95%CI)	p-value
Stroke/SE							
	Dabigatran vs. Rivaroxaban (ref)	7022	326 (3.52)	20285	920 (3.40)	1.02 (0.90-1.16)	0.760
	Apixaban vs. Rivaroxaban (ref)	22903	813 (3.23)	16211	669 (3.29)	0.96 (0.86-1.06)	0.400
	Edoxaban vs. Rivaroxaban (ref)	6404	151 (3.63)	4864	130 (3.69)	0.93 (0.73-1.18)	0.545
	Apixaban vs. Dabigatran (ref)	23152	856 (3.37)	5411	229 (3.40)	0.98 (0.84-1.14)	0.755
	Dabigatran vs. Edoxaban (ref)	1803	53 (3.76)	6404	155 (3.72)	1.06 (0.77-1.45)	0.734
	Apixaban vs. Edoxaban (ref)	11583	295 (3.69)	6289	155 (3.81)	1.00 (0.82-1.23)	0.963
Ischemic stroke							
	Dabigatran vs. Rivaroxaban (ref)	7022	223 (2.40)	20285	531 (1.95)	1.21 (1.03-1.42)	0.017
	Apixaban vs. Rivaroxaban (ref)	22903	455 (1.79)	16211	365 (1.78)	0.98 (0.85-1.13)	0.768
	Edoxaban vs. Rivaroxaban (ref)	6404	81 (1.95)	4864	62 (1.75)	1.06 (0.75-1.49)	0.744
	Apixaban vs. Dabigatran (ref)	23152	479 (1.86)	5411	149 (2.19)	0.84 (0.69-1.01)	0.070
	Dabigatran vs. Edoxaban (ref)	1803	36 (2.48)	6404	86 (2.06)	1.27 (0.85-1.89)	0.248
	Apixaban vs. Edoxaban (ref)	11583	158 (1.96)	6289	85 (2.08)	0.99 (0.76-1.30)	0.947
All-cause mortality							
	Dabigatran vs. Rivaroxaban (ref)	7022	1566 (16.47)	20285	4929 (17.84)	0.91 (0.86-0.97)	0.003
	Apixaban vs. Rivaroxaban (ref)	22903	5278 (20.45)	16211	3983 (19.21)	1.04 (0.99-1.08)	0.092
	Edoxaban vs. Rivaroxaban (ref)	6404	863 (20.55)	4864	825 (23.11)	0.85 (0.77-0.94)	<0.001
	Apixaban vs. Dabigatran (ref)	23152	5251 (20.16)	5411	1169 (16.91)	1.18 (1.10-1.26)	<0.001
	Dabigatran vs. Edoxaban (ref)	1803	261 (18.10)	6404	864 (20.48)	0.91 (0.78-1.05)	0.210
	Apixaban vs. Edoxaban (ref)	11583	2092 (25.72)	6289	916 (22.23)	1.20 (1.11-1.30)	<0.001



(B)

Outcome	Comparison	NOAC n	NOAC Events (/100PY)	Reference NOAC n	Reference NOAC Events (/100PY)	aHR (95%CI)	p-value
Major bleeding							
	Dabigatran vs. Rivaroxaban (ref)	7022	671 (7.37)	20285	1850 (7.02)	1.04 (0.95-1.14)	0.417
	Apixaban vs. Rivaroxaban (ref)	22903	1466 (5.89)	16211	1457 (7.36)	0.78 (0.72-0.84)	<0.001
	Edoxaban vs. Rivaroxaban (ref)	6404	401 (9.89)	4864	326 (9.46)	0.99 (0.85-1.15)	0.914
	Apixaban vs. Dabigatran (ref)	23152	1456 (5.79)	5411	524 (7.90)	0.72 (0.65-0.80)	<0.001
	Dabigatran vs. Edoxaban (ref)	1803	150 (10.83)	6404	410 (10.06)	1.12 (0.91-1.37)	0.299
	Apixaban vs. Edoxaban (ref)	11583	587 (7.44)	6289	416 (10.44)	0.74 (0.65-0.84)	<0.001
Intracranial bleeding							
	Dabigatran vs. Rivaroxaban (ref)	7022	148 (1.58)	20285	389 (1.43)	1.09 (0.90-1.33)	0.385
	Apixaban vs. Rivaroxaban (ref)	22903	346 (1.35)	16211	282 (1.37)	0.96 (0.82-1.13)	0.604
	Edoxaban vs. Rivaroxaban (ref)	6404	62 (1.49)	4864	60 (1.68)	0.82 (0.57-1.18)	0.284
	Apixaban vs. Dabigatran (ref)	23152	349 (1.35)	5411	112 (1.64)	0.82 (0.65-1.02)	0.074
	Dabigatran vs. Edoxaban (ref)	1803	26 (1.82)	6404	63 (1.50)	1.29 (0.80-2.08)	0.300
	Apixaban vs. Edoxaban (ref)	11583	130 (1.61)	6289	64 (1.56)	1.07 (0.79-1.46)	0.649
Gastrointestinal bleeding							
	Dabigatran vs. Rivaroxaban (ref)	7022	403 (4.33)	20285	1066 (3.95)	1.08 (0.96-1.22)	0.189
	Apixaban vs. Rivaroxaban (ref)	22903	758 (2.99)	16211	860 (4.25)	0.68 (0.62-0.76)	<0.001
	Edoxaban vs. Rivaroxaban (ref)	6404	244 (5.92)	4864	191 (5.46)	1.04 (0.86-1.26)	0.706
	Apixaban vs. Dabigatran (ref)	23152	748 (2.93)	5411	311 (4.60)	0.63 (0.55-0.72)	<0.001
	Dabigatran vs. Edoxaban (ref)	1803	87 (6.18)	6404	250 (6.03)	1.05 (0.80-1.39)	0.706
	Apixaban vs. Edoxaban (ref)	11583	309 (3.85)	6289	249 (6.17)	0.64 (0.54-0.76)	<0.001

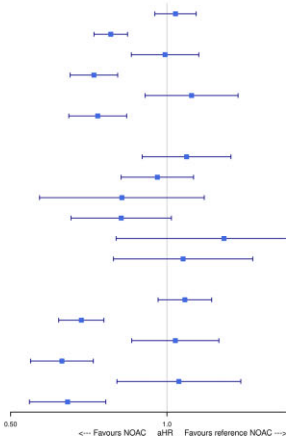


Figure 3 The (A) effectiveness and (B) safety compared between individual NOACs types in AF patients with frailty after IPTW. The weighted number of subjects at risk in the pseudopopulation, weighted number of events, weighted event rates per 100 PY, and aHRs with 95%CIs after IPTW are illustrated.

aHR: adjusted hazard ratio; CI: confidence interval; IPTW: inverse probability of treatment weighting; NOAC: non-vitamin K antagonist oral anticoagulant; PY: person-years; Ref: reference category; SE: systemic embolism; and vs.: versus.

(see Supplementary material online, *Table S11* and *Figure S6*) or to subjects having initiated treatment between October 2016 and January 2019 (n = 27 812) (see Supplementary material online, *Table S12* and *Figure S7*). However, no significant differences in the risks of stroke/SE, ischemic stroke, and intracranial bleeding were observed between individual NOACs and VKAs in the latter analysis. Moreover, NOACs were associated with a significantly lower risk of AF-related mortality compared with VKAs [aHR 0.83, 95%CI (0.74–0.94)], while risks were not significantly different between individual NOACs (see Supplementary material online, *Table S13*).

Discussion

In this nationwide cohort study including more than 250 000 AF patients during 328 796 person-years of on-treatment follow-up, we have demonstrated that frailty, identified in 28% of AF patients initiating anticoagulation, was an independent risk factor for all-cause mortality, but not for thromboembolism or bleeding. Among AF patients with frailty, NOACs were associated with significantly lower risks of stroke/SE and all-cause mortality, and a similar risk of major bleeding compared with VKAs. Despite a comparable effectiveness between individual NOACs, potential differences in safety were identified, with apixaban being associated with the most favourable safety profile across NOACs in patients with frailty due to a lower gastrointestinal bleeding risk, followed by edoxaban. However, the higher observed mortality risk with apixaban compared with dabigatran and edoxaban, warrants caution.

Frailty has been associated with several adverse health outcomes irrespective of AF, including falls, fractures, hospitalizations, cognitive impairment, worsening mobility, and disability in activities of daily living.[4,9,15] As illustrated by the 48% increased risk of all-cause mortality in this study, frailty is also an independent risk factor of death in patients with AF.[9–16] Although confidence intervals were largely overlapping, increased mortality risks seemed somewhat more pronounced in frail AF patients using fewer than five drugs (60% increased risk), which may reflect a subgroup of patients with general undertreatment (e.g. non-ABC-concordant management of AF)[41,42]

or discontinuation of non-essential drugs due to limited life expectancy. Regarding thromboembolic or bleeding risks, results of previous studies were more conflicting, as some studies[10,12,13] did demonstrate higher risks of thromboembolism and/or major bleeding in frail compared with non-frail AF patients, while others did not.[9,11,14–16] Despite higher crude and age- and sex-adjusted risks, frailty was not significantly associated with more thromboembolism or major bleeding after multivariable adjustment in the present study of anticoagulated patients with AF. While the overall vulnerability of AF patients with frailty necessitates close monitoring, previous research suggested that the presence of frailty is no formal contraindication for anticoagulation in AF patients,[16,17] since OAC use in AF patients with frailty has been shown to reduce the risk of thromboembolism and death compared with no OAC use, without significantly increasing the risk of major bleeding.[9–11]

In AF patients with frailty, NOAC use was associated with a 22%, 26%, and 12% reduced risk of stroke/SE, ischemic stroke, and all-cause mortality, respectively, compared with VKAs, while the risk of major bleeding was similar due to a 22% lower risk of intracranial bleeding but 19% higher risk of gastrointestinal bleeding. However, differential safety profiles were observed, as apixaban was associated with a 16% lower risk of major bleeding compared with VKAs, edoxaban with a 9% non-significantly lower risk, while dabigatran and rivaroxaban with a 16% and 11% significantly higher risk, respectively. Likewise, apixaban was associated with lower risks of major and gastrointestinal bleeding compared with dabigatran, rivaroxaban, and edoxaban, while no differences were observed in other comparisons between NOACs.

Similar differences in safety between NOACs, especially regarding the risk of gastrointestinal bleeding, have been demonstrated in the general AF population.[43,44] However, data on NOAC use in AF patients with frailty are scarce, due to the exclusion of patients with an estimated life expectancy of <1–2 years in phase III RCTs.[21–24] To date, only one post-hoc analysis of phase III RCTs, namely the ENGAGE AF-TIMI 48 trial, has been performed on this topic, which demonstrated that edoxaban was associated with a significantly lower risk of major bleeding in patients with mild-moderate frailty and a similar risk in patients with severe frailty compared with warfarin, while no differences in the risks of stroke/SE or death were observed.[12]

In the limited observational data on patients with frailty, NOACs were associated with similar[1] to lower[7,28] risks of stroke/SE and lower[28] risks of death compared with VKAs.[45] Differences in safety were also observed for individual NOACs, as the risk of major bleeding was lower with apixaban,[1,7,28] similar[1,28] to lower[7] with dabigatran, and similar[1,28] to higher[7] with rivaroxaban compared with VKAs. To the best of our knowledge, only one study compared outcomes between NOACs (however not including edoxaban) in frail patients, rendering similar findings as observed in our study, since apixaban was also associated with lower risks of major and gastrointestinal bleeding compared with dabigatran and rivaroxaban.[7] Although results should be considered as hypothesis-generating and interpreted with caution, these findings may help clinicians in choosing to anticoagulate with a NOAC compared with VKAs in AF patients with frailty.

Of note, the risk of ischemic stroke was not significantly different with dabigatran compared with VKAs, which was also observed in prior research.[7,28] However, it should be mentioned that results are likely driven by the predominant use of reduced dose dabigatran (110 mg twice daily) in patients with frailty (91% of patients). In the RE-LY trial, reduced dose dabigatran was indeed associated with similar risks of stroke/SE compared with VKAs, which was not the case with standard dose dabigatran (150 mg twice daily).[21] Moreover, the non-significantly lower risks of stroke/SE and ischemic stroke with edoxaban compared with VKAs may be due to less events during the much shorter follow-up duration of edoxaban users, given that edoxaban has only been approved in Belgium since October 2016. Exemplary, when analyses were restricted to the subgroup of patients having initiated therapy from October 2016 onwards, the risks of stroke/SE and ischemic stroke were no longer significantly lower with other NOACs compared with VKAs due to a lack of power.

Remarkably, significantly higher risks of all-cause mortality were observed with apixaban compared with dabigatran and edoxaban, especially in the oldest AF patients with frailty, while thromboembolic and intracranial bleeding risks were similar, and major and gastrointestinal bleeding risks were lower with apixaban. This may indicate that the higher mortality risks in apixaban users with frailty were driven by higher risks of non-AF-related death and selective prescribing of apixaban to more vulnerable older AF patients with frailty (than dabigatran and edoxaban). Exemplary, no significant differences in the risk of AF-related mortality, defined as deaths occurring within 60 days after an event of thromboembolism, bleeding, or myocardial infarction, were observed between individual NOACs. Moreover, apixaban users were older, had more comorbidities and more polypharmacy than other NOAC users (see Supplementary material online, *Table S4*). Although confounding by indication was minimized using IPTW, any influence of unmeasured confounding (e.g. underweight, sarcopenia, or renal dysfunction) or selective prescribing cannot be excluded. While awaiting more research to replicate these exploratory findings, caution should be warranted given the remarkably high mortality rates in patients with frailty (19.5% per year).

Based on the results of the present study, anticoagulation is recommended in AF patients with frailty and NOACs are still preferred over VKAs. However, physicians should also tackle modifiable bleeding risk factors,[46] initialize fall prevention,[47] optimize therapy adherence,[19] execute a thorough medication review as a part of comprehensive geriatric assessment[48] to switch or discontinue unnecessary, interacting or contraindicated comedication,[46,49,50] and perform an individualized benefit–risk assessment with shared decision making in each AF patient with frailty.[17]

Strengths and limitations

Strengths of this nationwide cohort study include the large sample size, long-term follow-up duration up to 6 years, use of an on-treatment analysis to reduce exposure misclassification, and adjustment for several confounders using stabilized IPTW.

Several limitations should be mentioned. First, coding errors and misclassification bias may be present due to the observational design using healthcare databases. However, by identifying comorbidities based on ICD, medical procedure codes and/or medication prescription claims assessed in ambulatory and hospital care, missing data, and misclassification of characteristics were reduced. Second, frailty was identified with the validated CFI[35] using administrative claims data, but a clinical frailty assessment based on Fried's Frailty Phenotype[4] or Rockwood's Frailty Index[5] was not possible. Moreover, pre-frailty could not be identified. Third, due to the specific inclusion of AF patients initiating anticoagulation, results cannot be extrapolated to AF patients with frailty who do not initiate anticoagulation. Fourth, although we thoroughly adjusted for confounders, there is a risk of unmeasured confounding due to missing lifestyle characteristics (e.g. weight, smoking) and laboratory values (e.g. renal function, INR). In line, (in)appropriate NOAC dosing and time in therapeutic range of VKA users could not be assessed. Moreover, lack of data on residency precluded the possibility to assess differences between counties or hospitals. Fifth, although persons with competing treatment indications were excluded, subjects were not required to have an ICD-coded hospital discharge diagnosis of AF to be included to reduce selection bias.[34] Nevertheless, trends were consistent when specifically investigating subjects with an ICD-coded diagnosis of AF ≤1 year before or ≤90 days after the index date. Sixth, the follow-up duration of edoxaban users was considerably

shorter than other NOACs due to variable approval dates. Nevertheless, effect estimates were consistent when restricting the study population to subjects having initiated treatment since October 2016. Seventh, although the risk of AF-related mortality was explored, data were lacking on other causes of death, which would have been of interest to explore why differences in the risk of all-cause mortality between individual NOACs were observed. Lastly, anticoagulant use was assessed based on dispensing data to account for discontinuation or switch of treatment, not on the patients' actual intake. However, findings were consistent using an intention-to-treat approach.

Conclusion

In conclusion, frailty was an independent risk factor for all-cause mortality in AF patients initiating anticoagulation, but not for thromboembolism or bleeding. Among patients with frailty, NOACs were associated with a superior effectiveness and non-inferior safety compared with VKAs. Although effectiveness was comparable between individual NOACs, safety outcomes differed with apixaban being associated with the most favourable safety profile across NOACs followed by edoxaban, driven by lower risks of gastrointestinal bleeding. However, the potentially increased mortality risk with apixaban compared with dabigatran and edoxaban warrants caution, while awaiting further research.

Supplementary material

Supplementary material is available at *European Heart Journal—Quality of Care and Clinical Outcomes* online.

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Author contributions

M.G. and L.L. contributed to the concept and design of the study. M.G. performed the statistical analysis, interpretation, and writing under the supervision of L.L. M.P., T.D.B., S.S., and L.L. revised the manuscript critically. All authors contributed to the article and approved the final manuscript.

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Conflicts of interests: Outside this manuscript, T.D.B. has served as a chairperson during a lecture for Bayer and Daiichi Sankyo and participated in an expert meeting for Pfizer. Outside this manuscript, L.L. has been consulted as expert for AstraZeneca. Outside this manuscript, M.P. and S.S. have given a lecture sponsored by B.M.S., L.L. a lecture sponsored by Chiesi, and S.S., L.L. and M.G. lectures sponsored by IPSA vzw, a non-profit organization facilitating lifelong learning for health care providers. Neither author has received any fees personally.

Data availability

Requests for the data underlying this article should be directed to the administrators of the InterMutualistic Agency (IMA) database or Minimal Hospital Dataset and are subject to approval.

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