CLINICAL RESEARCH STUDY

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Clinical Outcomes in Older Patients with Atrial Fibrillation: Insights from the GARFIELD-AF Registry

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ABSTRACT

BACKGROUND: Oral anticoagulants (OAC) are underutilized in older patients with atrial fibrillation, despite proven clinical benefits. Our objective was to investigate baseline characteristics, treatment patterns, and impact of anticoagulation upon clinical outcomes with respect to age.

METHODS: Adults with newly diagnosed atrial fibrillation were recruited into the prospective observational registry, GARFIELD-AF, and followed up for 24 months. Adjusted hazard ratios (HR) were obtained via Cox proportional-hazards models with applied weights, to quantify the association of age with clinical outcomes. Comparative effectiveness of OAC vs No OAC and non-vitamin K oral anticoagulants (NOAC) vs vitamin K antagonists (VKA) were assessed using a propensity score with an overlap weighting scheme.

RESULTS: Of 52,018 patients, 32.6% were 65-74 years of age, 29.3% were 75-84 years, and 7.9% were ≥85 years. OAC treatment was associated with a numerical reduction in all-cause mortality among those aged 65-74 years (HR; 95% confidence interval) (0.86; 0.69-1.06) and aged 75-84 years (0.89; 0.75-1.05) and a significant reduction in patients ≥85 years (0.77; 0.63-0.95) vs no OAC. Similarly, OACs were associated with a decrease in stroke: 65-74 (0.51; 0.35-0.76) and ≥85 years (0.58; 0.34-0.99) and a numerical decrease in 75-84 years (0.84; 0.59-1.18). No increase in major bleeding was observed in patients aged ≥85 treated with OACs. Compared with VKA, NOACs were associated with a significant reduction in all-cause mortality in patients aged <65 and 65-74, with numerical reductions in those aged 75-84 and ≥85 years.

CONCLUSIONS: Older patients using OACs saw lower all-cause mortality and stroke risk; NOACs had less mortality and major bleeding compared with VKAs.

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INTRODUCTION

Atrial fibrillation is the most common sustained arrhythmia encountered in adults; it is often a marker for underlying heart and vascular disease. However, atrial fibrillation itself contributes to adverse outcomes by increasing the risk of stroke, diminishing cardiac performance, and exposing symptomatic patients to therapies that also have risks, such as antiarrhythmic medications and ablation.[1]

Older age is a major risk factor for developing atrial fibrillation and its sequelae such as stroke or systemic embolism, heart failure,[2] acute coronary syndrome,[3] and an increased risk of death.[4] The reported prevalence of atrial fibrillation is at least 10% among those older than age 80 years.[5] For those aged 75-79, the cumulative incidence of mortality over 5 years following the onset of atrial fibrillation is about 40%. The 5-year mortality incidence increases to 84% in those 90 years of age or older. The 3 leading causes of death are heart failure, stroke, and gastrointestinal bleeding.[6]

During the 30-year span from 1990 through 2019, the estimated prevalence of atrial fibrillation doubled globally to 59.7 million.[7] In a Danish cohort study of 146,377 atrial fibrillation patients, the median age was 74 years.[8] In the Framingham Heart study, the lifetime risk of atrial fibrillation was 1 in 3 in individuals with at least one cardiovascular risk factor.[9]

The present study investigates patient characteristics, clinical outcomes, anticoagulation use and dose, and their effect on clinical outcomes in the old (75-84 years) and very old (≥85 years) with atrial fibrillation who were enrolled in the Global Anticoagulant Registry in the Field−Atrial Fibrillation (GARFIELD-AF).

CLINICAL SIGNIFICANCE

- Oral anticoagulants (OACs) are underutilized in patients aged ≥85 years.
- OAC treatment in this patient group showed mortality and stroke reductions.
- No increase in major bleeding was observed in anticoagulated ≥85 patients compared with <85 years of age.
- With OACs, patients aged ≥85 years benefitted from lower mortality and stroke, with no increase in major bleeding in comparison with no OAC.

METHODS

Study Design and Participants

In GARFIELD-AF, the major inclusion criteria were atrial fibrillation diagnosed within 6 weeks prior to enrollment, at least one risk factor (determined by the investigator) for stroke, and age >18 years.[10] Investigator sites were selected randomly and represented the different care settings in each participating country. Patients were enrolled prospectively and consecutively into 5 separate cohorts and followed for 24 months. The main analysis was conducted in patients enrolled at 1318 sites in 35 countries between March 2010 and August 2016 (cohorts 1-5). A subset of patients enrolled from April 2013 to August 2016 (cohorts 3-5), coinciding with the growing availability of non-vitamin K oral anticoagulants (NOACs), was considered eligible for inclusion in the analysis on comparative effectiveness for different anticoagulation strategies. Patients with a CHA_2DS_2-VASc (Congestive heart failure/left ventricular ejection fraction <40%, Hypertension, Age (≥75 years), Diabetes mellitus, Stroke/transient ischemic attack/thromboembolism history, Vascular disease, Age (65-74 years), female sex) <2 (excluding sex) or with vitamin K antagonist (VKA) use prior to enrollment were excluded from this latter analysis. Data were extracted from the study database in June 2019.

Ethics

The study was approved by independent ethics committees and each relevant locality and hospital-based institutional review board. The registry was conducted in accordance with the principles of the Declaration of Helsinki, local regulatory requirements, and the International Conference on Harmonization−Good Pharmacoepidemiological and Clinical Practice guidelines. Written informed consent was obtained from all participants.

Definitions and Outcomes

Patients were stratified by age into 4 groups: <65 years, 65-74 years, 75-84 years, and ≥85 years.

Clinical endpoints included all-cause, cardiovascular, and non-cardiovascular mortality, non-hemorrhagic stroke/systemic embolism, major bleeding, acute coronary syndrome, and heart failure at 2-year follow-up.

Statistical Analysis

Baseline characteristics and cardiovascular outcomes were analyzed in the full cohort of GARFIELD-AF patients, according to age group. Continuous baseline variables were expressed as mean (± standard deviation) or median (interquartile range), and categorical variables as frequency and percentage. Occurrence of clinical outcomes was described using the number of events, event rate per 100 person-years, and 95% confidence intervals (CI). Person-year rates were estimated using a Poisson model. Only the first occurrence of each event was considered.

Comparative analyses were performed in patients who had a CHA_2DS_2-VASc ≥2 for males, ≥3 for females, No prior history of VKA treatment prior to enrollment, and with available baseline treatment and follow-up information. Outcomes for mortality, stroke, bleeding, acute coronary syndrome, and heart failure for 2 years in patients aged 65- 74, 75-84, and ≥85 years vs younger patients (<65 years) were evaluated using unadjusted and adjusted Cox proportional hazards models. Hazard ratios are presented with their corresponding 95% CIs. The ROBINS-I (Risk Of Bias In Non-randomized Studies − of Interventions) tool was applied to assess the risk of bias.[11]

Hazard ratios for oral anticoagulants (OAC) vs no OAC use and for NOAC vs VKA were obtained using a Cox proportional hazards model with a propensity method of overlap weighting to balance covariates.[12] Covariates evaluated in the weighting scheme included demographic factors, medical history, and other characteristics (Supplementary Figure). Treatment was defined as the first treatment received at the time of enrollment, approximating "intention-to-treat." The risk of stroke was investigator-defined and not specified. Bleeding risk was defined based on the ISTH (International Society for Thrombosis and Hemostasis) criteria. Treatments were compared within subsets of age categories across the cohorts, in this post hoc analysis. Patients with missing values were not removed from the study. Multiple imputation was applied in the comparative effectiveness analyses, combining results from 5 imputed datasets. Data analysis was carried out under the auspices of the Thrombosis Research Institute using SAS Enterprise Guide 8.3. (SAS Institute Inc., Cary, NC).

RESULTS

Baseline Demographics

A total of 52,018 newly diagnosed atrial fibrillation participants were enrolled in GARFIELD-AF, most within 2 weeks of the diagnosis of atrial fibrillation. Of these, 15,691 (30.2%) were aged <65 years, 16,946 (32.6%) were 65-74 years, 15,252 (29.3%) were 75-84 years, and 4129 (7.9%) were ≥85 years of age at the time of enrollment (Figure 1). All qualifying patients with available follow-up were used to describe baseline characteristics and major cardiovascular outcomes. This constituted the main analysis. We also performed a further selection, to enable appropriate treatment comparisons across age groups. A total of 25,538/52,018 who were eligible for OACs qualified for the treatment comparison analysis. Among the patients eligible for OACs, 18,373/25,538 received OACs, while 7165/25,538 did not receive OAC (Figure 1).

Baseline characteristics stratified by age are provided in the Table. Patients <75 years of age were more often male (<65 years: 68.2%, 65-74 years: 56.3%), and those ≥75 years were more often female (75-84 years: 52.9%, ≥85 years: 61.2%). The proportion of Caucasians increased

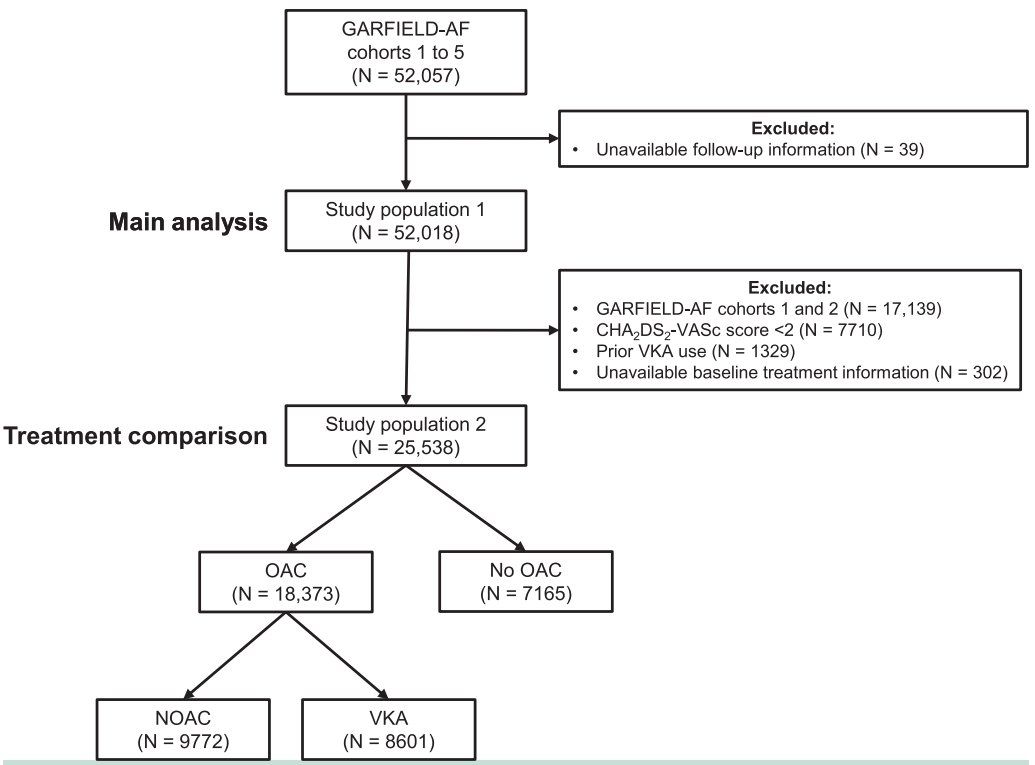

Figure 1 Flowchart for the selection of the study population.

Table Baseline Characteristics by Age Group (N = 52,018)

Variable	Age Group, Years			
	Age <65 (n = 15,691)	Age 65-74 (n = 16,946)	Age 75-84 (n = 15,252)	Age ≥85 (n = 4129)
Sex, n (%)				
Male	10,698 (68.2)	9544 (56.3)	7187 (47.1)	1602 (38.8)
Female	4993 (31.8)	7402 (43.7)	8065 (52.9)	2526 (61.2)
Age, median (Q1; Q3), years	58.0 (52.0; 62.0)	70.0 (67.0; 72.0)	79.0 (77.0; 81.0)	87.0 (86.0; 89.0)
Ethnicity, n (%)				
Caucasian	8818 (57.2)	10,442 (63.0)	9943 (67.3)	2794 (69.9)
Hispanic/Latino	918 (6.0)	1091 (6.6)	1099 (7.4)	285 (7.1)
Asian	5198 (33.7)	4710 (28.4)	3501 (23.7)	867 (21.7)
Afro-Caribbean/Mixed/Other	472 (3.1)	321 (1.9)	227 (1.5)	51 (1.3)
Body mass index, median (Q1; Q3), kg/m^2	27.7 (24.6; 32.0)	27.1 (24.2; 31.0)	26.3 (23.5; 29.7)	24.8 (22.2; 27.9)
Body mass index group, kg/m^2, n (%)				
<18.5	127 (1.0)	195 (1.5)	273 (2.3)	172 (5.7)
18.5-24.9	3488 (27.6)	4010 (30.3)	4196 (36.0)	1404 (46.2)
25.0-29.9	4584 (36.3)	4992 (37.7)	4454 (38.2)	1014 (33.3)
≥30.0	4437 (35.1)	4049 (30.6)	2729 (23.4)	451 (14.8)
Systolic blood pressure, median (Q1; Q3), mm Hg	130.0 (120.0; 142.0)	131.0 (120.0; 145.0)	133.0 (120.0; 145.0)	132.0 (120.0; 145.0)
Diastolic blood pressure, median (Q1; Q3), mm Hg	80.0 (72.0; 90.0)	80.0 (70.0; 88.0)	80.0 (70.0; 85.0)	78.0 (69.5; 84.0)
Pulse, median (Q1; Q3), beats per minute	85.0 (72.0; 108.0)	84.0 (70.0; 105.0)	83.0 (70.0; 102.0)	84.0 (70.0; 104.0)
Type of atrial fibrillation, n (%)				
Permanent	1430 (9.1)	2076 (12.3)	2371 (15.5)	753 (18.2)
Persistent	2396 (15.3)	2616 (15.4)	2175 (14.3)	566 (13.7)
Paroxysmal	4683 (29.9)	4734 (27.9)	3878 (25.4)	1009 (24.4)
New onset (unclassified)	7179 (45.8)	7518 (44.4)	6827 (44.8)	1801 (43.6)
Care setting specialty at diagnosis, n (%)				
Internal Medicine/Neurology/Geriatrics	2760 (17.6)	3384 (20.0)	3308 (21.7)	991 (24.0)
Cardiology	11,215 (71.5)	11,141 (65.8)	9452 (62.0)	2365 (57.3)
Primary care/general practice	1713 (10.9)	2419 (14.3)	2491 (16.3)	773 (18.7)
Care setting location at diagnosis, n (%)				
Hospital	10,149 (64.7)	9722 (57.4)	8405 (55.1)	2059 (49.9)
Office/Anticoagulation clinic/thrombosis center	3720 (23.7)	5361 (31.6)	5242 (34.4)	1595 (38.6)
Emergency department	1818 (11.6)	1861 (11.0)	1604 (10.5)	475 (11.5)
Medical history, n (%)				
Heart failure	3612 (23.0)	3566 (21.0)	3397 (22.3)	1164 (28.2)
Acute coronary syndromes	1334 (8.5)	1846 (10.9)	1848 (12.2)	505 (12.3)
Vascular disease	3164 (20.3)	4305 (25.6)	4239 (28.0)	1107 (27.0)
Carotid occlusive disease	232 (1.5)	464 (2.8)	646 (4.3)	196 (4.8)
Pulmonary embolism/deep vein thrombosis	253 (1.6)	453 (2.7)	496 (3.3)	153 (3.7)
Prior stroke/TIA/SE	1135 (7.3)	1838 (10.9)	2165 (14.3)	701 (17.1)
Prior bleeding	273 (1.7)	411 (2.4)	448 (2.9)	183 (4.5)
Hypertension	11,008 (70.5)	13,216 (78.2)	12,134 (79.7)	3246 (78.7)
Hypercholesterolemia	5767 (38.3)	7303 (44.5)	6377 (42.9)	1508 (37.5)
Diabetes	3205 (20.4)	4190 (24.7)	3385 (22.2)	762 (18.5)
Cirrhosis	100 (0.6)	117 (0.7)	65 (0.4)	11 (0.3)
Moderate to severe CKD	611 (4.0)	1315 (8.0)	2389 (16.2)	1039 (26.2)
Dementia	23 (0.1)	111 (0.7)	346 (2.3)	284 (6.9)
Heavy alcohol consumption, n (%)	562 (4.1)	317 (2.2)	132 (1.0)	17 (0.5)
Current smoker, n (%)	2958 (20.4)	1512 (9.8)	659 (4.8)	73 (2.0)
Treatment at baseline, n (%)				
NOAC ± AP	3609 (23.3)	4868 (29.1)	4399 (29.3)	1236 (30.2)
VKA ± AP	5429 (35.1)	6906 (41.3)	6409 (42.7)	1439 (35.2)
AP only	3876 (25.1)	3252 (19.5)	2722 (18.1)	911 (22.3)

Table (*Continued*)

Variable	Age Group, Years			
	Age <65 (n = 15,691)	Age 65-74 (n = 16,946)	Age 75-84 (n = 15,252)	Age ≥85 (n = 4129)
None	2549 (16.5)	1688 (10.1)	1496 (10.0)	507 (12.4)
Antiplatelet treatment, n (%)	5854 (37.9)	5833 (34.9)	5015 (33.4)	1401 (34.2)
CHA_2DS_2-VASc score, mean ± SD	1.8 ± 1.2	3.2 ± 1.2	4.4 ± 1.3	4.5 ± 1.3
HAS-BLED score, mean ± SD*	0.6 ± 0.7	1.7 ± 0.7	1.8 ± 0.8	1.9 ± 0.8

AP = antiplatelet; CHA_2DS_2-VASc = Congestive heart failure/left ventricular ejection fraction <40%, Hypertension, Age ≥75 y, Diabetes mellitus, Stroke/transient ischemic attack/thromboembolism history, Vascular disease, Age 65-74 y, female sex; CKD = chronic kidney disease; HAS-BLED = Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio [INR], Elderly (age >65 years), Drugs/alcohol concomitantly; NOAC = non-vitamin K oral anticoagulant; SE = systemic embolism; TIA = transient ischemic attack; VKA = vitamin K antagonist.

*The risk factor 'Labile INRs' is not included in the HAS-BLED score as it is not collected at baseline. As a result, the maximum HAS-BLED score at baseline is 8 points (not 9)

with increasing age. In contrast, the proportion of Asians decreased with increasing age.

Median body mass index decreased with age. Of those <65 years of age, 35% had a body mass index of ≥30 kg/m^2, compared with 15% of those at least 85 years of age.

New-onset (unclassified) atrial fibrillation was the most common form of atrial fibrillation in all age groups. However, permanent atrial fibrillation increased with age, from 9.1% in the <65 to 18.2% in the ≥85 group, and paroxysmal atrial fibrillation decreased from 29.9% to 24.4%, respectively.

Common medical comorbidities in all 4 age groups were: hypertension, hypercholesterolemia, heart failure, vascular disease, and diabetes. Chronic kidney disease, prior stroke, and major bleeding were also common in those aged ≥85 years. Incidence of pulmonary embolism and deep vein thrombosis was low (1.6%-3.7%) across the age groups.

The mean ± SD CHA_2DS_2-VASc scores increased with age: <65 years: 1.8 ± 1.2, 65-74 years: 3.2 ± 1.2, 75-84 years: 4.4 ± 1.3, and ≥85 years: 4.5 ± 1.3. Similarly, the mean HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (age >65 years), Drugs/alcohol concomitantly) score increased with age: <65 years: 0.6 ± 0.7, 65-74 years: 1.7 ± 0.7, 75-84 years: 1.8 ± 0.8, and ≥85 years: 1.9 ± 0.8.

Oral Anticoagulation Treatment

Among the 40,416 patients eligible for anticoagulation (ie, CHA_2DS_2-VASc score of at least 2, excluding female sex as a risk factor) 33,890 (84%) were ≥65 years. Anticoagulation use was less frequently prescribed in patients aged <65 and ≥85, compared with patients between 65 and 84 years of age. Those <65 had the highest use of antiplatelet agents alone (26.2%) and the lowest rate of receiving neither anticoagulant nor antiplatelet agents (8.5%) (Figure 2A). The use of anticoagulants overall and antiplatelet agents changed little across age groups within the subgroup of 25,538 patients enrolled during the era of NOAC therapy (Figure 2B).

In the treatment comparison group, 18,373/25,538 received anticoagulation at baseline (9772 NOACs and 8601 VKAs) (Figure 1). The proportion of non-anticoagulated patients was higher among very old (≥85; 32%) and young (<65; 34%) patients, with a lower proportion observed among patients 65-74 and 75-84 groups (26%). VKA

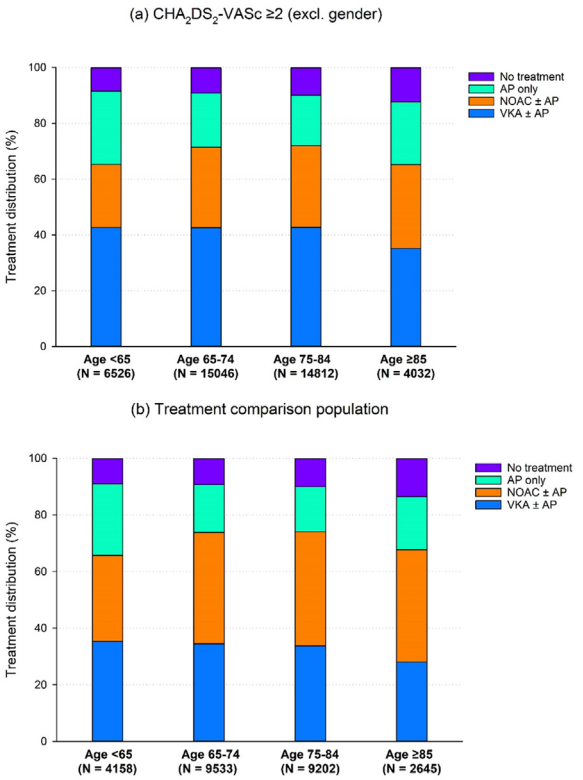

Figure 2 Baseline treatment distribution by age group in (**A**) all patients with available CHA_2DS_2-VASc (Congestive heart failure/left ventricular ejection fraction <40%, Hypertension, Age ≥75 y, Diabetes mellitus, Stroke/transient ischemic attack/thromboembolism history, Vascular disease, Age 65-74 y, female sex) score ≥2 (excl. gender) (n = 40,416) and (**B**) the subset of patients eligible for the OAC analysis (n = 25,538).

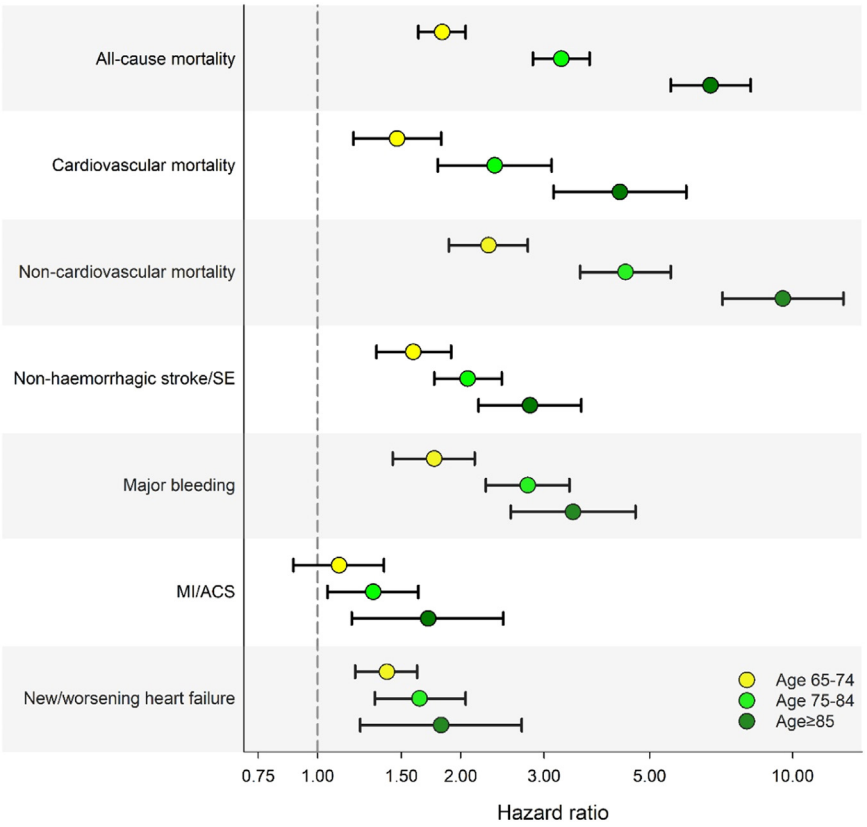

Figure 3 Adjusted* hazard ratios for selected outcomes through 2 years of follow-up by age group (ref.: age <65 years).
*Hazard ratios adjusted by sex, ethnicity, type of AF, heart failure, vascular disease, hypertension, prior stroke/TIA/SE, prior bleeding, diabetes, moderate-to-severe CKD, and baseline anticoagulation. AF = atrial fibrillation; CKD = chronic kidney disease; SE = systemic embolism, TIA = transient ischemic attack.

treatment was less common among the ≥85 years group (28%) compared with younger age groups (35.3% for <65 years, 34.5% for 65-74 years, and 33.8% for 75-84 years, respectively) (Figure 2B).

Major Adverse Clinical Outcomes

Major adverse clinical outcomes within 24 months of follow-up are presented for all 4 age strata in the Supplementary Table 1 (N = 52,018). Compared with patients <65 years (the reference group), the hazard ratios (HR) for all-cause, cardiovascular, and non-cardiovascular mortality, non-hemorrhagic stroke or systemic embolism, major bleeding, myocardial infarction/acute coronary syndrome, and new or worsening heart failure increased as the age stratum increased (Figure 3).

Impact of Anticoagulation Therapy on Outcomes at 24 Months

The number of events and the event rate for the 25,538 patients in the treatment comparison set are reported in Supplementary Table 2.

In patients aged ≥85 years, we observed a decreased risk of all-cause mortality (HR 0.77; 95% CI, 0.63-0.95) and non-hemorrhagic stroke/systemic embolism (SE; HR 0.58; 95% CI, 0.34-0.99) with OACs, with no evidence of an increased risk in major bleeding (HR 0.97; 95% CI, 0.56-1.68). In patients of all age groups combined, we observed a reduction in all-cause mortality (HR 0.82; 95% CI, 0.74-0.91), non-hemorrhagic stroke/SE (HR 0.69; 95% CI, 0.56-0.86), and an increase in major bleeding (HR 1.40; 95% CI, 1.11-1.78) compared with those who did not receive OACs (Figure 4A).

The occurrence of clinical outcomes for the 18,373 patients receiving either NOACs or VKAs is reported in Supplementary Table 3. Among patients aged ≥85 years who were anticoagulated, those receiving NOACs had a numerically lower risk of all-cause mortality and major bleeding, although the estimates were not statistically significant. In all age groups combined, NOACs were associated with a reduction in all-cause mortality (HR 0.79; 95% CI, 0.70-0.90) and major bleeding (HR 0.77; 95% CI, 0.61-0.98) compared with those receiving VKAs (Figure 4B).

There was no significant interaction between baseline treatment and age group (Supplementary Table 4). The

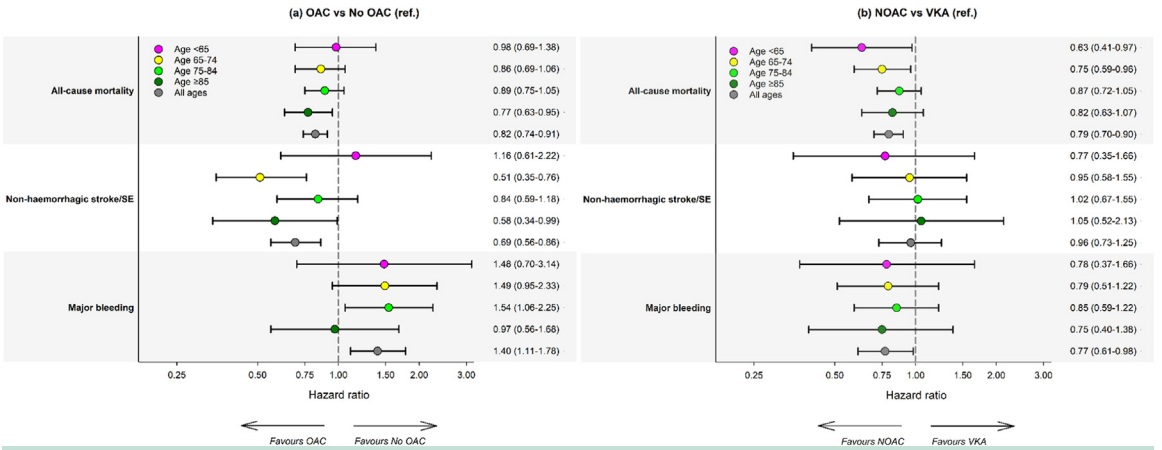

Figure 4 Adjusted* hazard ratios of (**A**) OAC vs No OAC (ref.) and (**B**) NOAC vs VKA (ref.) for selected outcomes at 2 years of follow-up by treatment at baseline within age groups.
*Obtained using an overlap-weighted Cox model. Variables included in the weighting scheme are: country and cohort enrollment, sex, age, ethnicity, type of atrial fibrillation, care setting specialty and location, congestive heart failure, acute coronary syndromes, vascular disease, carotid occlusive disease, prior stroke/TIA/SE, prior bleeding, VTE, hypertension, hypercholesterolemia, diabetes, cirrhosis, moderate to severe CKD, dementia, hyperthyroidism, hypothyroidism, current smoking, heavy alcohol consumption, BMI, heart rate, systolic and diastolic blood pressure at diagnosis, and baseline antiplatelet use.
BMI = body mass index; CKD = chronic kidney disease; NOAC = non-vitamin K oral anticoagulant; OAC = oral anticoagulant; SE = systemic embolism; TIA = transient ischemic attack; VTE = venous thromboembolism.

time within the therapeutic range among patients who received VKA at baseline was: <65 years: 56.5%; 65-74 years: 56.1%; 75-84 years: 56.0%; and ≥85 years: 55.5% (data not shown).

When comparing NOAC vs no OAC and VKA vs no OAC (Supplementary Table 5), the benefits of NOAC were observed, especially for all-cause mortality in ages ≥65 years. These benefits were not evident in patients receiving VKA.

Distribution of Full-Dose or Low-Dose NOACs

Drug labels, summaries of product characteristics, and guidelines based on clinical trial results have been established for standard dosing and reduced NOAC dosing (Supplementary Table 6). The distribution of anticoagulant treatment prescribed at baseline in age groups <85 years and ≥85 years is reported in Supplementary Table 7. The proportion of patients treated with apixaban is higher in patients ≥85 years compared with younger patients (43.3% vs 31.5%), while the proportion of dabigatran-treated patients among the ≥85 years is lower compared with younger patients (13.8% vs 21.7%). The distribution of NOAC-treated patients receiving standard vs reduced NOAC dosing is presented in Supplementary Table 8. As age increased, patients were more likely to receive a non-recommended low NOAC dose. At ≥85 years, 48.9% received non-recommended low dosing of NOAC, and 45.9% received recommended dosing. In contrast, among those <65 years, 17.0% received non-recommended low NOAC dosing, whereas 79.8% received recommended dosing. In patients receiving non-recommended high dose of NOAC, there was an overall trend toward higher bleeding risk. In patients ≥85 years, who received a non-recommended high dose, we observed higher major bleeding rate compared with patients <85 years who received non-recommended high dose (HR 7.25; 95% CI, 3.02-17.41) vs HR 1.34; 95% CI, 0.64-2.81) (Supplementary Table 9). No differences in stroke occurrence were observed, however, for non-recommended low NOAC dose as compared with the recommended dose among either the <85 years or ≥85 years old atrial fibrillation patients. We observed a higher proportion of patients on non-recommended NOAC low-dosing among patients with a HAS-BLED score of 4 or higher compared with patients with HAS-BLED score of 0 or 1 (38.0% vs 26.7%, respectively; Supplementary Table 10).

Finally, we examined the factors associated with withholding of OACs in the very old (≥85 years). The main patient-related risk factors associated with an increased likelihood of not receiving OAC among older patients were: non-white ethnicity, history of bleeding, vascular disease, and dementia. Enrollment in an early GARFIELD-AF cohort (ie, atrial fibrillation diagnosis occurred in early 2010s) and a non-cardiology care setting at atrial fibrillation diagnosis were also associated with increasing likelihood of not receiving OAC. When compared with patients aged <85, no significant differences were observed in the factors associated with withholding OAC (Supplementary Tables 11-14).

DISCUSSION

In this large observational study, OACs showed reduction in the risk of death and stroke in atrial fibrillation patients aged >65 years, with no evidence of increase in the risk of bleeding. This finding underscores that OACs appear safe in old and very old atrial fibrillation patients who would normally not receive appropriate dosing due to concerns of frailty and bleeding risk.

American atrial fibrillation guidelines[13] do not recommend utilizing a specific bleeding risk score. European atrial fibrillation guidelines recommend using the HAS-BLED score,[14] and the National Institute for Health and Care Excellence (NICE) guidelines prefer the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT) bleeding risk score.[15] All sets of guidelines emphasize that a high bleeding risk score should not discourage the use of OAC.[6] Instead, high bleeding risk scores should be used to identify and change modifiable risk factors for bleeding.

Among patients of ≥85 years in the PREvention oF Thromboembolic Events−European Registry (PREFER) in atrial fibrillation registry, the thromboembolic event rate was 6.3% per year on no anticoagulant vs 4.3% per year on anticoagulation. The risk of stroke increased with age more than the risk of bleeding, and the absolute benefit of anticoagulation was highest in the patients ≥85 years.[16]

Despite these findings, it is likely that some health care providers continue to remain hesitant to prescribe anticoagulation to patients aged ≥75 due to frailty, falling history, or comorbidities such as chronic kidney disease. To obviate this dilemma, one approach is to prescribe an ultra-low dose of anticoagulant, such as a daily dose of 15 mg of edoxaban (25% of the standard dose). In a Japanese placebo-controlled trial of patients aged ≥80 years, the annualized rate of stroke or systemic embolism was 2.3% in the edoxaban 15 mg group vs 6.7% in the placebo group.[17] In GARFIELD-AF, the highest-risk patients were most likely to receive non-recommended low dose rather than recommended dose of NOACs.[18] However, this approach warrants further study before it can be recommended.

In this study, major bleeding event rates were similar between the oldest group (≥85 years) of patients receiving NOAC non-recommended low dose and the recommended dose. However, a high major bleeding rate was observed among those who received a non-recommended high dose. These are crude estimates based on low number of events; interpretation requires caution because of limitations related to the observational design. Older patients constitute a high bleeding risk group, which has been traditionally underrepresented in pivotal clinical trials of NOACs. Previous studies in patients with high bleeding risk have shown similar results.[19]

Limitations and Strengths

The limitations of this study include underrepresentation of several races and ethnicities, such as Hispanic and Afro-Caribbean. Further, as with any observational study, there may have been confounders that were unrecognized or under-weighted/over-weighted in multivariable analyses, such as dosing regimen and patient adherence to prescribed anticoagulants. In addition, the patient follow-up period was limited to 2 years. Finally, the available data were limited to the information in the registry, hence, beyond dementia which is reported, we were unable to delve further into other age-associated comorbidities and geriatric syndromes such as cognitive function, frailty, functional limitations, and falls. Social determinants of health could have also played a role in the access to OACs. However, this information was not recorded in the GARFIELD-AF registry.

This paper also has important strengths. GARFIELD-AF is the largest international prospective registry in atrial fibrillation, with extensive quality control, including manual audits of 20% of the raw data.

CONCLUSIONS

This study helps alleviate concerns regarding prescribing oral anticoagulants for atrial fibrillation patients aged ≥75 years. Oral anticoagulants, as prescribed in everyday practice to this patient group, may reduce all-cause mortality and stroke with no significant increase in major bleeding, as compared with no anticoagulants. The results from this study would help inform the physician community in providing effective anticoagulation to older atrial fibrillation patients.

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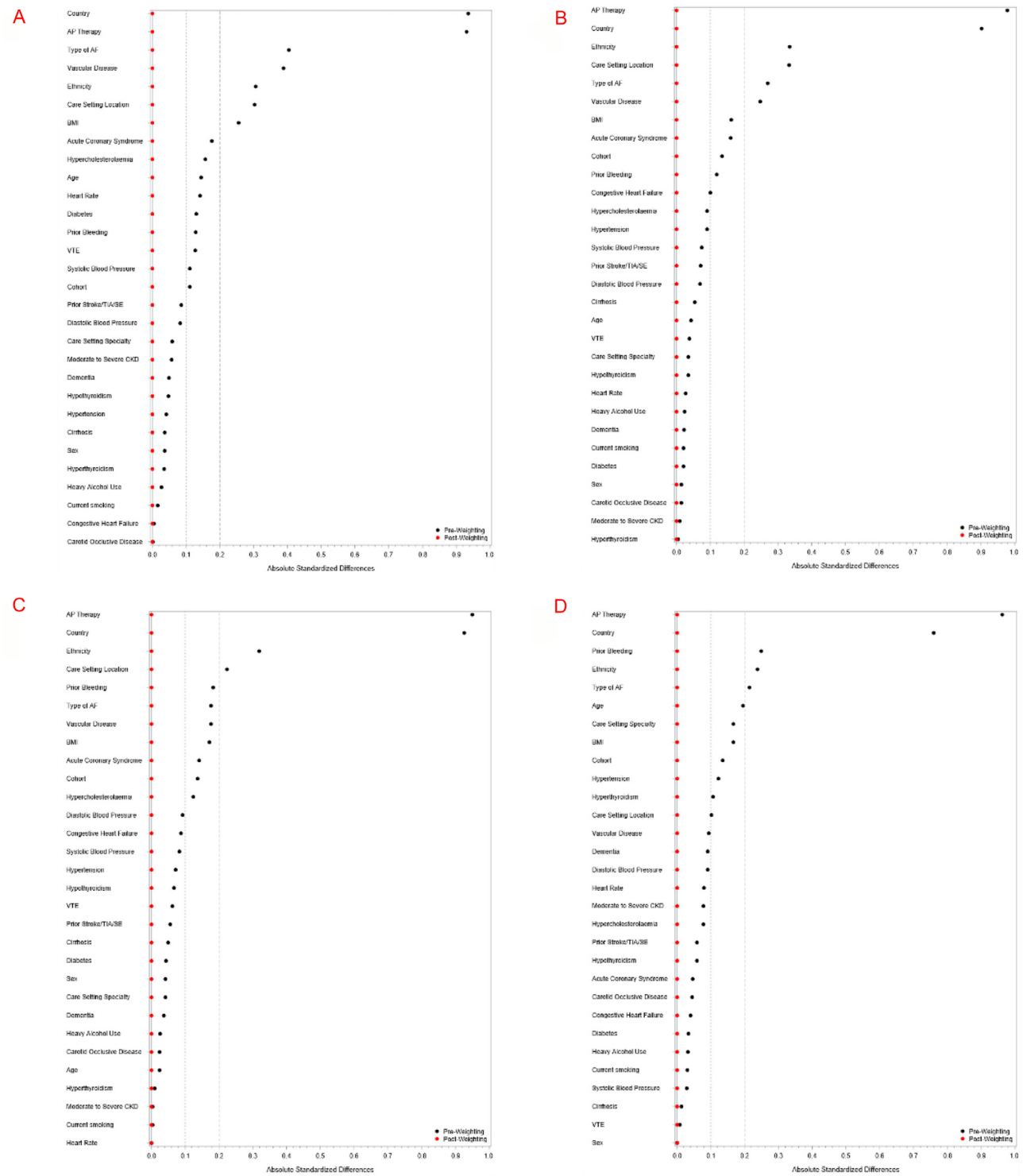
SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found in the online version at doi 10.1016/j.amjmed.2023.10.027.



Supplementary Figure Balance of variables associated with oral anticoagulation (OAC) treatment (ref.: No OAC) prior to and after propensity score weighting among patients (**A**) <65 years; (**B**) 65-74 years; (**C**) 75-84 years (**D**) ≥85 years. AF = atrial fibrillation; AP = antiplatelet; BMI = body mass index; CKD = chronic kidney disease; VTE = venous thromboembolism.

Supplementary Table 1 Event Rates (per 100 Person-Years), Unadjusted and Adjusted* Hazard Ratios for Selected Outcomes Through 2 Years of Follow-Up By All Age Groups (N = 52,018)

Outcomes Age Group	Events	Rate (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
All-cause mortality				
<65	459	1.54 (1.40-1.68)	1 (ref.)	1 (ref.)
65-74	895	2.80 (2.62-2.99)	1.82 (1.61-2.07)	1.83 (1.63-2.05)
75-84	1493	5.33 (5.07-5.61)	3.46 (2.89-4.13)	3.26 (2.84-3.74)
≥85	861	12.24 (11.45-13.08)	7.89 (6.22-10.00)	6.72 (5.54-8.16)
Cardiovascular mortality				
<65	197	0.66 (0.57-0.76)	1 (ref.)	1 (ref.)
65-74	326	1.02 (0.92-1.14)	1.55 (1.23-1.94)	1.47 (1.19-1.82)
75-84	519	1.85 (1.70-2.02)	2.80 (2.02-3.86)	2.36 (1.79-3.11)
≥85	278	3.95 (3.51-4.44)	5.89 (3.97-8.75)	4.33 (3.14-5.97)
Non-cardiovascular mortality				
<65	142	0.48 (0.40-0.56)	1 (ref.)	1 (ref.)
65-74	334	1.05 (0.94-1.16)	2.20 (1.78-2.72)	2.29 (1.89-2.77)
75-84	598	2.13 (1.97-2.31)	4.48 (3.52-5.71)	4.45 (3.57-5.54)
≥85	354	5.03 (4.53-5.58)	10.51 (7.89-14.00)	9.54 (7.12-12.79)
Non-hemorrhagic stroke/SE				
<65	167	0.56 (0.48-0.65)	1 (ref.)	1 (ref.)
65-74	294	0.93 (0.83-1.04)	1.65 (1.37-1.98)	1.59 (1.33-1.91)
75-84	366	1.32 (1.19-1.46)	2.33 (1.94-2.80)	2.07 (1.76-2.44)
≥85	139	2.00 (1.69-2.36)	3.50 (2.61-4.71)	2.80 (2.18-3.59)
Major bleeding				
<65	131	0.44 (0.37-0.52)	1 (ref.)	1 (ref.)
65-74	273	0.86 (0.76-0.97)	1.95 (1.59-2.39)	1.76 (1.44-2.14)
75-84	405	1.46 (1.33-1.61)	3.30 (2.67-4.07)	2.77 (2.26-3.39)
≥85	133	1.92 (1.62-2.28)	4.27 (3.17-5.76)	3.45 (2.55-4.67)
MI/ACS				
<65	148	0.50 (0.42-0.58)	1 (ref.)	1 (ref.)
65-74	186	0.59 (0.51-0.68)	1.17 (0.93-1.49)	1.11 (0.89-1.38)
75-84	206	0.74 (0.65-0.85)	1.48 (1.17-1.85)	1.31 (1.05-1.63)
≥85	71	1.01 (0.80-1.28)	1.99 (1.36-2.92)	1.71 (1.18-2.46)
New/worsening heart failure				
<65	170	0.57 (0.49-0.67)	1 (ref.)	1 (ref.)
65-74	262	0.83 (0.73-0.93)	1.44 (1.22-1.70)	1.40 (1.20-1.62)
75-84	297	1.07 (0.96-1.20)	1.85 (1.44 (2.38)	1.64 (1.32-2.05)
≥85	95	1.37 (1.12-1.67)	2.31 (1.46-3.66)	1.82 (1.23-2.69)

ACS = acute coronary syndrome; AF = atrial fibrillation; CI = confidence interval; CKD = chronic kidney disease; HR = hazard ratio; MI = myocardial infarction; SE = systemic embolism; TIA = transient ischemic attack.

*Hazard ratio adjusted by sex, ethnicity, type of AF, heart failure, vascular disease, hypertension, prior stroke/TIA/SE, prior bleeding, diabetes, moderate-to-severe CKD and baseline anticoagulation.

Supplementary Table 2 Event Rates (Per 100 Person-Years) Through 2 Years of Follow-Up By Age Group and Treatment (N = 25,538)

Age Group, Years Outcome	OAC (n = 18,373)		No OAC (n = 7165)	
	Events	Rate (95% CI)	Events	Rate (95% CI)
Age <65				
All-cause mortality	132	2.52 (2.12-2.99)	66	2.42 (1.90-3.07)
Non-hemorrhagic stroke/SE	40	0.77 (0.56-1.05)	17	0.63 (0.39-1.01)
Major bleeding	38	0.73 (0.53-1.00)	11	0.40 (0.22-0.73)
Age 65-74				
All-cause mortality	362	2.69 (2.42-2.99)	168	3.58 (3.08-4.16)
Non-hemorrhagic stroke/SE	88	0.66 (0.53-0.81)	55	1.18 (0.91-1.54)
Major bleeding	126	0.94 (0.79-1.12)	28	0.60 (0.41-0.87)
Age 75-84				
All-cause mortality	619	4.85 (4.48-5.24)	290	6.72 (5.99-7.54)
Non-hemorrhagic stroke/SE	126	0.99 (0.83-1.18)	66	1.55 (1.22-1.97)
Major bleeding	183	1.45 (1.26-1.68)	41	0.96 (0.71-1.30)
Age ≥85				
All-cause mortality	329	10.36 (9.30-11.54)	214	15.36 (13.43-17.56)
Non-hemorrhagic stroke/SE	47	1.50 (1.12-1.99)	34	2.47 (1.77-3.46)
Major bleeding	60	1.92 (1.49-2.47)	26	1.89 (1.29-2.78)

CI = confidence interval; OAC = oral anticoagulant; SE = systemic embolism.

Supplementary Table 3 Event Rates (Per 100 Person-Years) Through Two Years of Follow-Up By Age Group and OAC Treatment (N = 18,373)

Age Group, Years Outcome	NOAC (n = 9772)		VKA (n = 8601)	
	Events	Rate (95% CI)	Events	Rate (95% CI)
Age <65				
All-cause mortality	40	1.63 (1.19-2.22)	92	3.31 (2.70-4.06)
Non-hemorrhagic stroke/SE	14	0.57 (0.34-0.97)	26	0.94 (0.64-1.38)
Major bleeding	15	0.61 (0.37-1.02)	23	0.83 (0.55-1.25)
Age 65-74				
All-cause mortality	142	1.95 (1.66-2.30)	220	3.55 (3.11-4.05)
Non-hemorrhagic stroke/SE	41	0.57 (0.42-0.77)	47	0.76 (0.57-1.01)
Major bleeding	50	0.69 (0.52-0.91)	76	1.24 (0.99-1.55)
Age 75-84				
All-cause mortality	303	4.32 (3.86-4.83)	316	5.49 (4.92-6.13)
Non-hemorrhagic stroke/SE	64	0.92 (0.72-1.17)	62	1.09 (0.85-1.39)
Major bleeding	86	1.24 (1.00-1.53)	97	1.71 (1.40-2.09)
Age ≥85				
All-cause mortality	184	9.74 (8.43-11.25)	145	11.28 (9.58-13.27)
Non-hemorrhagic stroke/SE	28	1.49 (1.03-2.16)	19	1.50 (0.95-2.34)
Major bleeding	29	1.56 (1.08-2.24)	31	2.46 (1.73-3.50)

CI = confidence interval; NOAC = non-vitamin K oral anticoagulant; SE = systemic embolism; VKA = vitamin K antagonist.

Supplementary Table 4 *P* Values for Interaction Between Baseline Treatment and Age Group

Outcome	OAC vs No OAC*	NOAC vs VKA†
All-cause mortality	.1429	.1363
Non-hemorrhagic stroke/SE	.1812	.7981
Major bleeding	.7611	.5686

OAC = oral anticoagulant; VKA = vitamin K antagonist.
*Models, Figure 4A.
†Models, Figure 4B.

Supplementary Table 5 Adjusted* Hazard Ratios of NOAC vs No OAC (Ref.) and VKA vs No OAC (Ref.) for Selected Outcomes at Two Years of Follow-Up By Age Group

Age Group, Years Outcome	NOAC vs No OAC (ref.) HR (95% CI)	VKA vs No OAC (ref.) HR (95% CI)
Age <65		
All-cause mortality	0.74 (0.44-1.24)	1.05 (0.72-1.53)
Non-hemorrhagic stroke/SE	1.02 (0.44-2.36)	1.42 (0.68-2.97)
Major bleeding	1.57 (0.61-4.08)	2.00 (0.84-4.77)
Age 65-74		
All-cause mortality	0.67 (0.51-0.89)	0.97 (0.77-1.23)
Non-hemorrhagic stroke/SE	0.51 (0.31-0.83)	0.55 (0.35-0.87)
Major bleeding	1.00 (0.57-1.73)	2.10 (1.28-3.47)
Age 75-84		
All-cause mortality	0.73 (0.59-0.89)	1.00 (0.83-1.20)
Non-hemorrhagic stroke/SE	0.70 (0.46-1.07)	0.85 (0.56-1.27)
Major bleeding	1.12 (0.71-1.76)	1.90 (1.24-2.91)
Age ≥85		
All-cause mortality	0.69 (0.54-0.89)	0.86 (0.66-1.12)
Non-hemorrhagic stroke/SE	0.59 (0.32-1.11)	0.58 (0.29-1.13)
Major bleeding	0.97 (0.51-1.86)	1.06 (0.55-2.06)
All ages		
All-cause mortality	0.67 (0.59-0.77)	0.93 (0.82-1.04)
Non-hemorrhagic stroke/SE	0.63 (0.48-0.82)	0.74 (0.57-0.96)
Major bleeding	1.03 (0.77-1.37)	1.79 (1.37-2.34)

CI = confidence interval; CKD = chronic kidney disease; HR = hazard ratio; NOAC = non-vitamin K oral anticoagulant; OAC = oral anticoagulant; SE = systemic embolism; TIA = transient ischemic attack; VKA = vitamin K antagonist.
*Obtained using an overlap-weighted Cox model. Variables included in the weighting scheme are: country and cohort enrollment, sex, age, ethnicity, type of atrial fibrillation, care setting specialty and location, congestive heart failure, acute coronary syndromes, vascular disease, carotid occlusive disease, prior stroke/TIA/SE, prior bleeding, venous thromboembolism, hypertension, hypercholesterolemia, diabetes, cirrhosis, moderate to severe CKD, dementia, hyperthyroidism, hypothyroidism, current smoking, heavy alcohol consumption, body mass index, heart rate, systolic and diastolic blood pressure at diagnosis, and baseline antiplatelet use.

Supplementary Table 6 Description of Criteria Applied for Recommended Dosing According to NOAC and NOAC Guideline

NOAC Prescribed at Baseline	Guideline Considered	Criteria Applied for Recommended Dosing
Rivaroxaban	EMA/FDA	• 20 mg once daily if CKD stage: None, I, II • 15 mg once daily if CKD stage: III, IV
	Japanese	• 15 mg once daily if CKD stage: None, I, II • 10 mg once daily if CKD stage: III, IV
Apixaban	EMA/FDA/Japanese	• 5 mg twice daily if <2 of the following: ○ CKD stage: III ○ Age ≥80 y ○ Weight ≤60 Kg • 2.5 mg twice daily if ≥2 of the following: ○ CKD stage: III ○ Age ≥80 y ○ Weight ≤60 Kg *or* if CKD stage: IV
Dabigatran	EMA	• 150 mg twice daily if: ○ CKD stage: None, I, II *and* ○ Age <75 y *and* ○ HAS-BLED <2 • 150 or 110 mg twice daily if: ○ CKD stage: III *or* ○ 75≤ age <80 *or* ○ HAS-BLED ≥2 • 110 mg twice daily if: ○ CKD stage: None, I, II, III *and* ○ Age ≥80 y
	FDA	• 150 mg twice daily if CKD stage: None, I, II, III • 75 mg twice daily if CKD stage: IV
	Japanese	• 150 or 110 mg twice daily if CKD stage: None, I, II • 110 mg twice daily if CKD stage: III
Edoxaban	EMA/FDA	• 60 mg once daily if CKD stage: None, I, II • 30 mg once daily if CKD stage: III, IV
	Japanese	• 60 mg once daily if: ○ CKD stage: None, I, II *or* ○ CKD stage: III *and* weight ≥60 • 30 mg once daily if: ○ CKD stage: III *and* weight <60 • 15 mg once daily if CKD stage: IV

CKD = chronic kidney disease; EMA = European Medicines Agency; FDA = US Food and Drug Administration; HAS-BLED = Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (age >65 years), Drugs/alcohol concomitantly; NOAC = non-vitamin K oral anticoagulant; OAC = oral anticoagulant.

Concomitant Antiplatelet (AP) therapy

Only considering OAC-treated patients who meet the inclusion criteria for the comparative effectiveness analysis.

Among OAC-treated patients <85 years old, 3669 (22.1) were on concomitant AP therapy.

Among OAC-treated patients ≥85 years old, 288 (16.1) were on concomitant AP therapy.

Supplementary Table 7 Distribution of NOAC Treatment by NOAC Prescribed at Baseline and Age Group

NOAC	Age <85	Age ≥85	Overall
Rivaroxaban	3320 (44.1)	350 (38.6)	3670 (43.5)
Apixaban	2372 (31.5)	392 (43.3)	2764 (32.8)
Edoxaban	200 (2.7)	39 (4.3)	239 (2.8)
Dabigatran	1635 (21.7)	125 (13.8)	1760 (20.9)

NOAC = non-vitamin K oral anticoagulant.

For this analysis, only NOAC-treated patients meeting the criteria for the comparative effectiveness analyses were selected, with the additional restriction of available NOAC dosing information. The population for this analysis thus consists of 8433 patients.

Supplementary Table 8 Distribution of NOAC Recommended Dosing by Age Group

Dosing Appropriateness	Age Group, Years n (%)			
	Age <65 (n = 1046)	Age 65-74 (n = 3174)	Age 75-84 (n = 3087)	Age ≥85 (n = 865)
Non-recommended low dosing	178 (17.0)	594 (18.7)	962 (31.2)	423 (48.9)
Recommended dosing	835 (79.8)	2483 (78.2)	1980 (64.1)	397 (45.9)
Non-recommended high dosing	33 (3.2)	97 (3.1)	145 (4.7)	45 (5.2)

CKD = chronic kidney disease; NOAC = non-vitamin K oral anticoagulant.

For this analysis, only NOAC-treated patients meeting the criteria for the comparative effectiveness analyses were selected, with the additional restriction of available NOAC dosing information and available criteria to determine recommended dosing (eg, CKD information). The population for this analysis thus consists of 8172 patients

Supplementary Table 9 Major Bleeding and Non-Hemorrhagic Stroke/SE Event Rates (per 100 Person-Years) at 2 Years Follow-Up for NOAC-Treated Patients with Available Dosing and CKD Information (N = 8172) by Age Group and NOAC Dosing Appropriateness

Age Group, Years NOAC Dosing Appropriateness	Clinical Outcomes			
	Major Bleeding		Non-Hemorrhagic Stroke/SE	
	Events	Rate (95% CI)	Events	Rate (95% CI)
Age <85				
Non-recommended low dosing	24	0.73 (0.49-1.09)	17	0.52 (0.32-0.83)
Recommended dosing	94	0.92 (0.76-1.13)	74	0.73 (0.58-0.91)
Non-recommended high dosing	7	1.34 (0.64-2.81)	6	1.15 (0.52-2.56)
Age ≥85				
Non-recommended low dosing	9	1.20 (0.62-2.30)	10	1.32 (0.71-2.46)
Recommended dosing	10	1.41 (0.76-2.63)	8	1.13 (0.56-2.26)
Non-recommended high dosing	5	7.25 (3.02-17.41)	2	2.75 (0.69-11.01)

CI = confidence interval; CKD = chronic kidney disease; NOAC = non-vitamin K oral anticoagulant; SE = systemic embolism.

Supplementary Table 10 Distribution of NOAC Recommended Dosing by HAS-BLED Score

Dosing Appropriateness	HAS-BLED Score, n (%)		
	0-1 (n = 3914)	2-3 (n = 2583)	4+ (n = 79)
Non-recommended low dosing	1044 (26.7)	674 (26.1)	30 (38.0)
Recommended dosing	2810 (71.8)	1718 (66.5)	37 (46.8)
Non-recommended high dosing	60 (1.5)	191 (7.4)	12 (15.2)

CKD = chronic kidney disease; HAS-BLED = Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (age >65 years), Drugs/alcohol concomitantly; NOAC = non-vitamin K oral anticoagulant.

For this analysis, only NOAC-treated patients meeting the criteria for the comparative effectiveness analyses were selected, with the additional restriction of available NOAC dosing information and available criteria to determine recommended dosing (eg, CKD information). Patients with unavailable HAS-BLED score were also excluded. The population for this analysis thus consists of 6576 patients.

Supplementary Table 11 Factors Associated with Withholding of OAC in Patients at High Risk of Stroke (CHA_2DS_2-VASc ≥2 excl. sex) by Age Group

Variable	Age <85 Y		Age ≥85 Y	
	OR (95% CI)	Wald Chi-Square − DF	OR (95% CI)	Wald Chi-Square − DF
Cohort (ref.: Cohort 1)		438		82
Cohort 2	0.84 (0.78-0.92)		0.68 (0.54-0.87)	
Cohort 3	0.64 (0.59-0.69)		0.50 (0.39-0.64)	
Cohort 4	0.51 (0.46-0.55)		0.43 (0.33-0.55)	
Cohort 5	0.52 (0.48-0.56)		0.36 (0.29-0.46)	
Care setting specialty (ref.: Cardiology)		338		76
Internal Medicine/Neurology/Geriatrics	1.28 (1.21-1.36)		1.59 (1.34-1.89)	
Primary Care/GP	1.97 (1.83-2.12)		2.36 (1.93-2.90)	
Race/Ethnicity (ref.: White)		692		61
Asian	2.17 (2.05-2.30)		1.86 (1.54-2.24)	
Hispanic/Latino	1.59 (1.44-1.74)		1.90 (1.47-2.47)	
Black/Mixed/Other	1.33 (1.13-1.57)		1.45 (1.25-1.69)	
History of bleeding	2.68 (2.34-3.06)	210	3.16 (2.31-4.33)	50
Age (1-year increase)	0.98 (0.97-0.99)	66	1.08 (1.05-1.10)	36
Paroxysmal/Unclassified AF (ref.: Permanent/Persistent)	1.71 (1.62-1.81)	374	1.45 (1.25-1.69)	23
Vascular disease	1.75 (1.67-1.84)	484	1.41 (1.21-1.64)	18
Moderate to severe CKD	0.90 (0.83-0.97)	7	0.79 (0.67-0.92)	8
Prior stroke/TIA/SE	0.72 (0.67-0.77)	86	0.76 (0.63-0.91)	8
BMI (1 kg/m^2 increase)	0.99 (0.98-0.99)	40	0.98 (0.96-0.99)	8
Care setting location (ref.: Hospital)		170		7
Emergency department	0.87 (0.81-0.94)		0.86 (0.69-1.08)	
Office/AC clinic/Thrombosis center	0.68 (0.64-0.72)		0.80 (0.68-0.94)	
Dementia	1.45 (1.18-1.77)	12	1.41 (1.09-1.83)	6
VTE	0.57 (0.49-0.67)	43	0.72 (0.49-1.04)	2

AC = anticoagulation; AF = atrial fibrillation; BMI = body mass index; CHA_2DS_2-VASc = Congestive heart failure/left ventricular ejection fraction <40%, Hypertension, Age ≥75 y, Diabetes mellitus, Stroke/transient ischemic attack/thromboembolism history, Vascular disease, Age 65-74 y, female sex; CI = confidence interval; CKD = chronic kidney disease; DF = degrees of freedom; GP = general practitioner; OAC = oral anticoagulant; OR = odds ratio; SE = systemic embolism; TIA = transient ischemic attack; VTE = venous thromboembolism.

ORs >1 indicate the variable is associated with an increased likelihood of withholding OAC. ORs <1 indicate the variable is associated with a decreased likelihood of withholding OAC. Wald Chi-square − DF indicates the relative significance of each variable.

Supplementary Table 12 *P* Values for Interaction Between OAC Treatment and Selected Demographics/Risk Factors/Risk Score for Non-Hemorrhagic Stroke/SE and Major Bleeding Within 2-Year Follow-Up Among Patients Age ≥85

Demographic/Risk Factor/Risk Score	*P* Value for Interaction for Non-Hemorrhagic Stroke/SE	*P* Value for Interaction for Major Bleeding
Sex	.5161	.2378
Race/Ethnicity	.1978	.4445
Type of AF	.3240	.8362
Heart failure	.1610	.3181
Diabetes	.1622	.0623
History of bleeding	.2977	.1359
Hypertension	.3925	.6724
Vascular disease	.1112	.1250
Moderate to severe CKD	.2977	.1754
Prior stroke/TIA/SE	.4621	.1067
Obesity (BMI >30 kg/m^2)	.1113	.1214
Current smoking	.1221	.2130
Heavy alcohol consumption	.1988	.1580
CHA_2DS_2-VASc score	.7084	.2216
HAS-BLED score	.1430	.8079

AF = atrial fibrillation; BMI = body mass index; CHA_2DS_2-VASc = Congestive heart failure/left ventricular ejection fraction <40%, Hypertension, Age ≥75 y, Diabetes mellitus, Stroke/transient ischemic attack/thromboembolism history, Vascular disease, Age 65-74 y, female sex; CKD = chronic kidney disease; HAS-BLED = Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (age >65 years), Drugs/alcohol concomitantly; SE = systemic embolism; TIA = transient ischemic attack.

Supplementary Table 13 Frequency and Proportion of Patients Who Received Oral Anticoagulation (OAC) at Baseline Among Patients ≥85 Years by Country

Country	Baseline OAC n (%)
Argentina	32 (43.8)
Australia	52 (60.5)
Austria	33 (67.4)
Belgium	118 (81.9)
Brazil	33 (48.5)
Canada	89 (65.4)
Chile	67 (76.1)
China	16 (21.6)
Czech Republic	52 (54.2)
Denmark	41 (71.9)
Egypt	7 (100.0)
Finland	15 (68.2)
France	254 (74.1)
Germany	194 (61.0)
Hungary	45 (77.6)
India	16 (31.4)
Italy	211 (84.1)
Japan	407 (72.3)
South Korea	29 (46.0)
Mexico	61 (51.3)
Netherlands	83 (90.2)
Norway	14 (100.0)
Poland	67 (61.5)
Russia	32 (57.2)
Singapore	4 (23.5)
South Africa	22 (53.7)
Spain	209 (65.1)
Sweden	67 (71.3)
Switzerland	9 (90.0)
Thailand	35 (47.3)
Turkey	20 (76.9)
Ukraine	4 (30.8)
United Arab Emirates	11 (55.0)
United Kingdom	291 (60.6)
United States	35 (58.3)

Supplementary Table 14 Frequency and Proportion of Patients Who Received Oral Anticoagulation (OAC) at Baseline Among Patients Aged ≥85 Years by Region

Region	Baseline OAC n (%)
Europe	1759 (68.9)
North America	124 (63.3)
Latin America	193 (55.5)
Asia	507 (60.2)
Other countries	92 (59.7)

APPENDIX

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