Journal of the American Heart Association

ORIGINAL RESEARCH

Outcomes and Disease Management in Patients With Atrial Fibrillation ≥80 Years: Data From a Consecutive 11-Year Real-World Registry

Mustafa Yildirim, MD; Barbara Ruth Milles, MD; Hauke Hund; Moritz Biener, MD; Matthias Müller-Hennessen, MD; Norbert Frey, MD; Hugo A. Katus, MD; Evangelos Giannitsis, MD; Christian Salbach, MD

BACKGROUND: As the population ages, atrial fibrillation (AF) prevalence increases, but data on optimal oral anticoagulation (OAC) in patients ≥80 years remain limited. This study tested whether direct OACs offer comparable benefits to vitamin K antagonists in patients ≥80 years with AF presenting to the emergency department.

METHODS: This single-center retrospective all-comer study used data from the Heidelberg Registry of Atrial Fibrillation, including patients with AF presenting to the emergency department of the University Hospital of Heidelberg from June 2009 until March 2020. Data were analyzed by age for outcomes and risk factors for predefined end points.

RESULTS: Patients ≥80 years comprised 32.2% of AF cases. Hazard ratios (HRs) for the primary end point (all-cause mortality, stroke, or myocardial infarction) and secondary end point (including major bleeding) were 3.09 (95% CI, 2.73–3.21) and 2.96 (95% CI, 2.73–3.21) for patients ≥80 years, compared with younger patients. Anticoagulation rates were slightly lower in patients ≥80 years (67.9% versus 70.5%, *P*=0.0070). OAC use, particularly the use of direct OACs, increased over time. Patients ≥80 years without OACs had higher HRs for primary (3.48 [95% CI, 3.07–3.94]) and secondary end points (3.23 [95% CI, 2.86–3.64]) compared with those with OACs. Vitamin K antagonist use was linked to higher HR for stroke or major bleeding events (HR, 1.25 [95% CI, 1.05–1.50]), rising to 1.64 (95% CI, 1.34–2.01) after excluding reduced direct OAC doses.

CONCLUSIONS: Our data highlight patients ≥80 years as an important and vulnerable subpopulation of patients with AF, where evidence for optimal OAC therapy remains conflicting.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT05995561.

Key Words: atrial fibrillation ■ direct oral anticoagulants ■ octogenarians ■ real-world evidence ■ registry ■ vitamin K antagonist

Atrial fibrillation (AF) represents the most prevalent cardiac arrhythmia and manifests in diverse prevalence rates, spanning from 0.1% in individuals younger than 55 years to 17.7% in octogenarians.[1–5] Notably, the population aged 80 years and older is predicted to triple by 2050, signifying a rapid increase compared with patients with AF >65 years.[5] AF, often asymptomatic, harbors substantial risks, elevating the likelihood of stroke, heart failure, renal failure, cognitive decline, and all-cause mortality.[6] Its onset and severity strongly correlate with age and comorbidities, significantly augmenting stroke risk by 5-fold.[7,8]

Correspondence to: Christian Salbach, MD, Medizinische Klinik III, University Hospital Heidelberg, Im Neuenheimer Feld 410, 69120 Heidelberg, Germany. Email: christian.salbach@med.uni-heidelberg.de

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.124.036832

This article was sent to Shaan Khurshid, MD, MPH, Assistant Editor, for review by expert referees, editorial decision, and final disposition.

For Sources of Funding and Disclosures, see page 13.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Patients ≥80 years with atrial fibrillation face higher risks of all-cause mortality, stroke, myocardial infarction, and major bleedings, with a growing trend toward use of direct oral anticoagulants, though no clear outcome advantage over vitamin K antagonists has been found in this group.

What Are the Clinical Implications?

- The lack of a distinct benefit between direct oral anticoagulants and vitamin K antagonists in older patients with atrial fibrillation underscores the need for personalized anticoagulation strategies that balance bleeding risk, frailty, and stroke prevention.

Nonstandard Abbreviations and Acronyms

DOAC	direct oral anticoagulant
HERA-FIB	Heidelberg Registry of Atrial Fibrillation
LCL	lower 95% confidence limit
NOAF	new-onset atrial fibrillation
OAC	oral anticoagulant
VKA	vitamin K antagonist

With advancing age, its prevalence escalates steadily, reaching 10% to 17% beyond 80 years.[3] Conversely age emerges as a pivotal risk factor for AF, established through extensive studies alongside with arterial hypertension, congestive heart failure, diabetes, coronary artery disease, and valvular heart disease.[9,10] An age-associated rise in stroke risk is seen across sexes and spiking beyond 65 and 80 to 89 years, where AF emerges as a predominant contributor to stroke incidence.[5,8,11–15] Moreover, age is considered a crucial factor in determining CHA_2DS_2VASc and HASBLED scores, indicative for increased thromboembolic and bleeding risks, respectively.[16] Despite the efficacy and safety advantages for stroke prevention of direct oral anticoagulants (DOACs) over vitamin K antagonists (VKAs) in nonvalvular AF, their utility in octogenarians remains unclear due to their underrepresentation in pivotal trials.[5,6,17–28] There is an ongoing debate whether DOACs may not offer as many advantages in older patients compared with VKAs, which warrants careful evaluation. Given the potential differences in outcomes between these anticoagulation strategies in older populations, our study aims to test the hypothesis that DOACs do not provide as much benefit as VKA antagonists in patients aged 80 years and older. Thus, the objectives of this study are (1) to offer a comprehensive overview of prevalence, outcomes, and risk factors in patients ≥80 years presenting in the setting of an emergency department (ED); and (2) to evaluate the use of VKA versus DOAC treatment regimens, while specifically investigating whether DOACs are less beneficial compared with VKAs in this high-risk older population.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design and Definitions

The present study uses data from the single-center retrospective all-comer HERA-FIB (Heidelberg Registry of Atrial Fibrillation) study. Design, rationale, and baseline characteristics of HERA-FIB as well as inclusion and exclusion criteria were described previously.[29] This study was approved by the local ethics committee of the University of Heidelberg. Owing the retrospective design of the study, informed consent was waived by local ethics committee. The study was conducted according to ethical principles stated in the Declaration of Helsinki (2008). Patient identifiable data were pseudonymized to ensure data confidentiality and were not passed to third parties. This study is registered at ClinicalTrials.gov, identifier: NCT05995561.

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria for HERA-FIB were previously described in detail.[29] Inclusion criteria were age ≥18 years and diagnosis of AF either as primary reason for admission or as a comorbidity. Exclusion criteria were nonavailability of at least 1 hs-cTnT (highly sensitive cardiac troponin T) value and lost to follow-up for all-cause mortality. Data were adjusted for repeated visits. Patients with missing data were censored from respective analyses. For this subanalysis, patients were stratified based on age at presentation and OAC regimens at discharge. Figure 1 illustrates the flow diagram of included and excluded patients.

Definitions

In this study, the term “octogenarian” is used to describe patients aged ≥80 years. AF with uncontrolled heart rate was diagnosed if the heart rate upon admission exceeded 110 bpm. New-onset AF (NOAF) was defined as AF not previously diagnosed, and non-NOAF encompassed patients with paroxysmal,

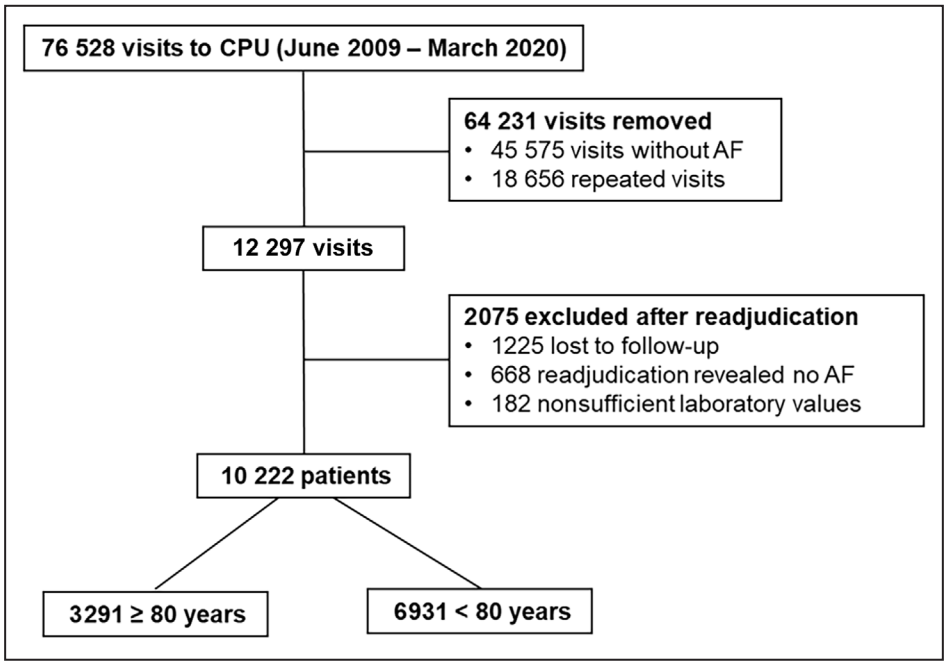

Figure 1. Flow chart for included and excluded patients in the HERA-FIB substudy.
AF indicates atrial fibrillation; CPU, chest-pain unit; and HERA-FIB, Heidelberg Registry of Atrial Fibrillation.

persistent, or permanent AF, as well as those in sinus rhythm with a history of AF. Non-NOAF was classified as paroxysmal, per European Society of Cardiology guidelines, when conversion to sinus rhythm occurred spontaneously within 7 days of presumed onset.[6,30] Upon successful termination using cardioversion (either pharmacological or electrical) or sustained AF for >7 days, AF type was classified as persistent. Valvular AF was defined as patients with AF with mechanical prosthetic heart valve(s) or moderate to severe mitral stenosis.[31] Left ventricular ejection fraction (LVEF) was categorized according to the guidelines recommended by the American Society of Echocardiography and the European Association of Cardiovascular Imaging.[32] Noninvasive rhythm control strategy was defined as electrical or pharmacological cardioversion.

End Point Definitions and Follow-Up

In this study, our primary 3-point end point included all-cause mortality, myocardial infarction (MI), or stroke, and our secondary 4-point end point incorporated major bleedings according to International Society of Thrombosis and Hemostasis bleeding criteria.[33] To minimize lost-to-follow-up, a sequential follow-up method was used, as outlined previously.[29] In order to differentiate between ischemic and bleeding risks, strokes were defined excluding hemorrhagic stroke, and hemorrhagic strokes were categorized as International Society of Thrombosis and Hemostasis major bleeding events.[29]

Statistical Analysis

Data were processed as mean±SD, medians (25th, 75th percentiles, interquartile range), Kaplan–Meier estimates, counts, or percentages. Continuous variables were tested for normal distribution using the Kolmogorov–Smirnov test. Groups were compared by chi-square test or Fisher's exact test for categorical variables, and unpaired Student's *t* test or Wilcoxon rank-sum test for continuous variables. Kaplan–Meier analyses were performed and groups were compared using the log-rank test. To assess the impact of potential unmeasured confounders, the *E*-value was calculated according to the method described by VanderWeele et al,[34] using the R package "EValue" by Mathur et al.[35] When the *E*-value exceeded the observed hazard ratio (HR) or the lower 95% confidence limits (LCL), it indicated that only a confounder with a strong association with both the exposure and outcome could have explained away the observed association. This analysis strengthened the inference that the observed association was unlikely to be entirely due to unmeasured confounding. *P* for interaction was calculated using a Cox regression model. Sensitivity analyses were conducted to specifically compare the effects of apixaban and rivaroxaban in patients aged ≥80 years, using a Cox proportional hazards model adjusted for relevant covariates. To address violations of the proportional hazards assumption, we applied a time-dependent Cox regression model, incorporating an interaction term between each nonproportional

covariate and log (time+1).[36] Proportional hazards assumptions were verified using Schoenfeld residuals, and Martingale residuals were used to evaluate nonlinearity in continuous covariates.[36–38] Restricted cubic splines (degrees of freedom=5) were also applied to model the nonlinear relationship for serum creatinine.[39] Deviance residuals were assessed to detect influential observations, and sensitivity analyses were performed excluding identified outliers to evaluate their impact on model stability.[40,41] A 2-tailed *P* value of <0.05 was considered to indicate statistical significance. All statistical analyses were carried out using the R software (version 4.3.0, R Foundation for Statistical Computing, Vienna, Austria) and MedCalc 20.111 (MedCalc Software bvba, Ostend, Belgium).

RESULTS

The HERA-FIB study included a total of 10 222 patients with AF, of whom 3291 (32.2%) were aged ≥80 years. A breakdown by age decades is depicted in Figure S1. The majority of patients with AF were 70 to 79 years (35.4%) or 60 to 69 years (27.5%), respectively. Among all participants, 3629 (52.4%) had paroxysmal AF, with a lower proportion observed in those aged ≥80 years (1426 patients; 43.3%). In contrast, persistent AF was present in 1266 patients (18.3%) <80 years, compared with 396 patients (12.0%) aged ≥80 years. A total of 227 (2.2%) patients presented with valvular AF, including 176 (2.5%) <80 years and 51 (1.5%) ≥80 years. Herein, 39 (1.2%) patients ≥80 years presented with a mechanical valve, and 151 (2.2%) patients <80 years presented with a mechanical valve. Baseline characteristics for patients aged ≥80 years, compared with those <80 years, are detailed in Table 1, revealing significant differences. Among patients aged ≥80 years, the most prevalent risk factors were arterial hypertension (90.2%), prior coronary artery disease (47.8%), and diabetes (21.3%). Notably, compared with younger patients, the older group exhibited significantly higher levels of hs-cTnT, serum creatinine, CRP (C-reactive protein), and NT-proBNP (N-terminal pro-B-type natriuretic peptide). Anticoagulation regimens for patients aged ≥80 years are presented in Table 2, showing a high use rate of VKA and the highest use rate of rivaroxaban among DOACs.

Outcomes in Patients ≥80 Years

During a median follow-up of 23 months (interquartile range, 12–35), 40.8% of patients aged ≥80 years experienced the primary end point comprising all-cause mortality, stroke, or MI. When evaluating the secondary end point, which additionally included International Society of Thrombosis and Hemostasis major bleeding events, 44.1% of patients aged ≥80 years reached the

Table 1. Baseline Characteristics Stratified by Age: ≥80 Years Versus <80 Years

Variables	Patients<80 y	Patients≥80 y	*P* value*
Age, y, median (IQR)	70 (62–75)	84 (82–88)	<0.0001
Sex, male, n (%$_{all}$)	4392 (63.4)	1565 (47.6)	<0.0001
Body mass index, kg/m^2, median (IQR)	27.4 (24.4–31.3) n=4412	25.6 (23.3–28.4) n=1975	<0.0001
Heart rate at admission, bpm, median (IQR)	93 (75–122) n=6929	84 (70–107) n=3290	<0.0001
Bp$_{systolic}$, median (IQR)	145 (130–159) n=6889	149 (132–165) n=3281	<0.0001
Bp$_{diastolic}$, median (IQR)	86 (76–98) n=6887	83 (72–94) n=3280	<0.0001
Arterial hypertension, n (%$_{all}$)	5467 (78.9)	2969 (90.2)	<0.0001
Diabetes, n (%$_{all}$)	1341 (19.3)	702 (21.3)	0.0192
History of coronary artery disease, n (%$_{all}$)	2840 (41.0)	1574 (47.8)	<0.0001
History of coronary artery bypass graft, n (%$_{all}$)	604 (8.7)	338 (10.3)	0.0111
History of myocardial infarction, n (%$_{all}$)	1062 (15.3)	610 (18.5)	<0.0001
CHA_2DS_2VASc-score, median (IQR)	3 (2–5)	5 (4–6)	<0.0001
ORBIT risk-score, median (IQR)	1 (0–3)	3 (2–4)	<0.0001
Valvular AF, n (%$_{all}$)	176 (2.5)	51 (1.5)	0.0015
Initially diagnosed AF, n (%$_{all}$)	2040 (29.4)	718 (21.8)	<0.0001
Rhythm control strategy in initially diagnosed AF, n (%$_{all}$)*	548 (26.9)	131 (18.2)	<0.0001
Electrical cardioversion, n (%$_{all}$)	471 (85.9)	105 (80.2)	0.0969
Left ventricular ejection fraction (n=6083)			
Normal, n (%$_{all}$)	1950 (48.4)	934 (45.4)	0.0306
Mildly abnormal, n (%$_{all}$)	759 (18.8)	456 (22.2)	0.0306
Moderate abnormal, n (%$_{all}$)	677 (16.8)	379 (18.5)	0.1084
Severely abnormal, n (%$_{all}$)	643 (16.0)	285 (13.9)	0.0326
Highly sensitive cardiac troponin T, ng/L, median (IQR)	15 (8–29)	28 (17–51)	<0.0001
Hemoglobin, g/dL, median (IQR)	13.7 (12.2–14.9)	12.5 (11.1–13.6)	<0.0001
Serum creatinine, mg/dL, median (IQR)	0.95 (0.79–1.20)	1.09 (0.86–1.47)	<0.0001
C-reactive protein, mg/L, median (IQR)	5 (2–17) n=6906	10 (3–31) n=3274	<0.0001
N-terminal pro-B-type natriuretic peptide, ng/L, median (IQR)	2412 (882–6030) n=2786	4987 (2208–11 022) n=1654	<0.0001

(*Continued*)

Table 1. Continued

Variables	Patients<80 y	Patients≥80 y	*P* value*
International normalized ratio, median, (IQR)	1.12 (1.02–1.57)	1.19 (1.06–1.83)	<0.0001

AF indicates atrial fibrillation; bp, blood pressure; IQR, interquartile range; and ORBIT, Outcomes Registry for Better Informed Treatment of Atrial Fibrillation.

*Rhythm control strategy included patients with either electrical or pharmacological cardioversion.

end point. All-cause mortality occurred in 36% of patients, stroke in 4.0%, MI in 5.8%, and a major bleeding event in 8.0%. Kaplan–Meier analyses for the primary and secondary end points are depicted in Figure 2. The HRs for patients aged ≥80 years were 3.09 (95% CI, 2.84–3.36, *P*<0.0001) for the primary end point and 2.96 (95% CI, 2.73–3.21; *P*<0.0001) for the secondary end point, as shown in Table 3. The corresponding *E*-values were 3.75 and 3.62 for the HRs and 3.5 and 3.39 for the LCL, respectively. Even after adjusting for sex, diabetes, arterial hypertension, creatinine, prior coronary artery disease, prior peripheral artery disease (PAD), prior MI, and NOAF, age ≥80 years remained an independent predictor of the primary and secondary end point with adjusted HRs (aHR) of 2.55 (95% CI, 2.36–2.76; *P*<0.001), and 2.44 (95% CI, 2.27–2.63; *P*<0.0001), respectively. The *E*-values for these adjusted HRs were 3.21 and 3.09, with LCL *E*-values of 3.01 and 2.91. The Cox regression analysis identified diabetes, serum creatinine, prior PAD, and prior MI as significant predictors of adverse outcomes for the primary composite end point. Due to observed nonlinearity in serum creatinine as evidenced by Martingale residuals, we used restricted cubic splines with 5 degrees of freedom to better model its relationship with the outcomes. Due to proportional hazards violations for diabetes, PAD, and prior MI, a time-dependent Cox regression model was used. In this model, diabetes (aHR, 1.07; *P*<0.0001), prior PAD (aHR, 1.08; *P*<0.0001), and prior MI (aHR, 1.05; *P*<0.0001) maintained a significant association with increased risk over time. For the secondary composite end point, the time-dependent model showed that arterial hypertension (aHR, 1.03; *P*=0.005), diabetes (aHR, 1.07; *P*<0.0001), prior PAD (aHR, 1.07; *P*<0.0001), and prior MI (aHR, 1.04; *P*=0.0001) were all significantly associated with increased risk over time. These findings underscore the persistent impact of diabetes, prior PAD, and prior MI on adverse outcomes in older patients with AF, emphasizing the role of time-varying effects and the nonlinear relationship of serum creatinine (Table S1). Furthermore, an interaction between age ≥80 years and NOAF or non-NOAF as well as the secondary end point and all-cause mortality could be detected (Table S2). In a subanalysis of 6083 (59.5%) patients with AF where data on LVEF were available, a Cox proportional hazard regression model on predictive variables for the primary and secondary end point revealed that age ≥80 years, diabetes, arterial hypertension, NOAF, prior PAD, prior MI, and estimated glomerular filtration rate <60 mL/min as well as moderately and severely abnormal LVEF were independently associated with the primary and secondary end point (Tables S3 and S4).

Table 2. Anticoagulation Regimens in Patients≥80 y

OAC regimens	Patients ≥80 y
Any OAC regimen, n ($\%_{all}$)	2235 (67.9)
Vitamin K antagonist, n ($\%_{all}$)	949 (42.5)
Rivaroxaban, n ($\%_{all}$)	682 (30.5)
Dabigatran, n ($\%_{all}$)	101 (4.5)
Apixaban, n ($\%_{all}$)	389 (17.4)
Edoxaban, n ($\%_{all}$)	114 (5.1)

OAC indicates oral anticoagulation.

OAC Regimens in Patients ≥80 Years

Among patients with AF aged ≥80 years, 67.7% (2235) received an oral anticoagulation regimen at discharge, with 42.5% (949) on VKA and 57.5% (1286) on DOAC (Table 2). Reduced DOAC dosage was applied in 767 (34.3%) of these patients. Rivaroxaban (30.5%) and apixaban (17.4%) were the most commonly prescribed DOACs throughout the study period. Despite having a higher CHA_2DS_2VASc-score (median 5; interquartile range, 4–6), those aged ≥80 years were less frequently anticoagulated compared with younger patients (70.5% versus 67.9%, *P*=0.0070). Among patients with AF ≥80 years, use of VKA declined within time, whereas use of full- and reduced-dose DOACs in patients ≥80 years increased (Figure 3). Patients ≥80 years without any oral anticoagulation regimen showed higher HRs for the primary (HR, 3.48 [95% CI, 3.07–3.94]; *P*<0.0001) and the secondary end point (HR, 3.23 [95% CI, 2.86–3.64]; *P*<0.0001). The corresponding *E*-values were 4.11 and 3.89 for the HRs and 3.73 and 3.52 for the LCLs, respectively. For patients ≥80 years with oral anticoagulation, there were no significant differences concerning the end point parameters such as the primary, the secondary, and all separate outcome parameters classified by VKA versus DOAC regimens (Table 4). However, patients <80 years on VKA regimens showed an HR of 1.45 (95% CI, 1.25–1.68; *P*<0.0001) for the primary and an HR of 1.45 (95% CI, 1.26–1.67; *P*<0.0001) for the secondary end point favoring a DOAC therapy within these patients. The corresponding *E*-values were 1.91 for both HRs and 1.61 and 1.63 for the LCLs, respectively. When separated by outcomes, patients <80 years showed significantly higher HRs for all-cause mortality, major bleeding, and MI for VKA versus DOAC

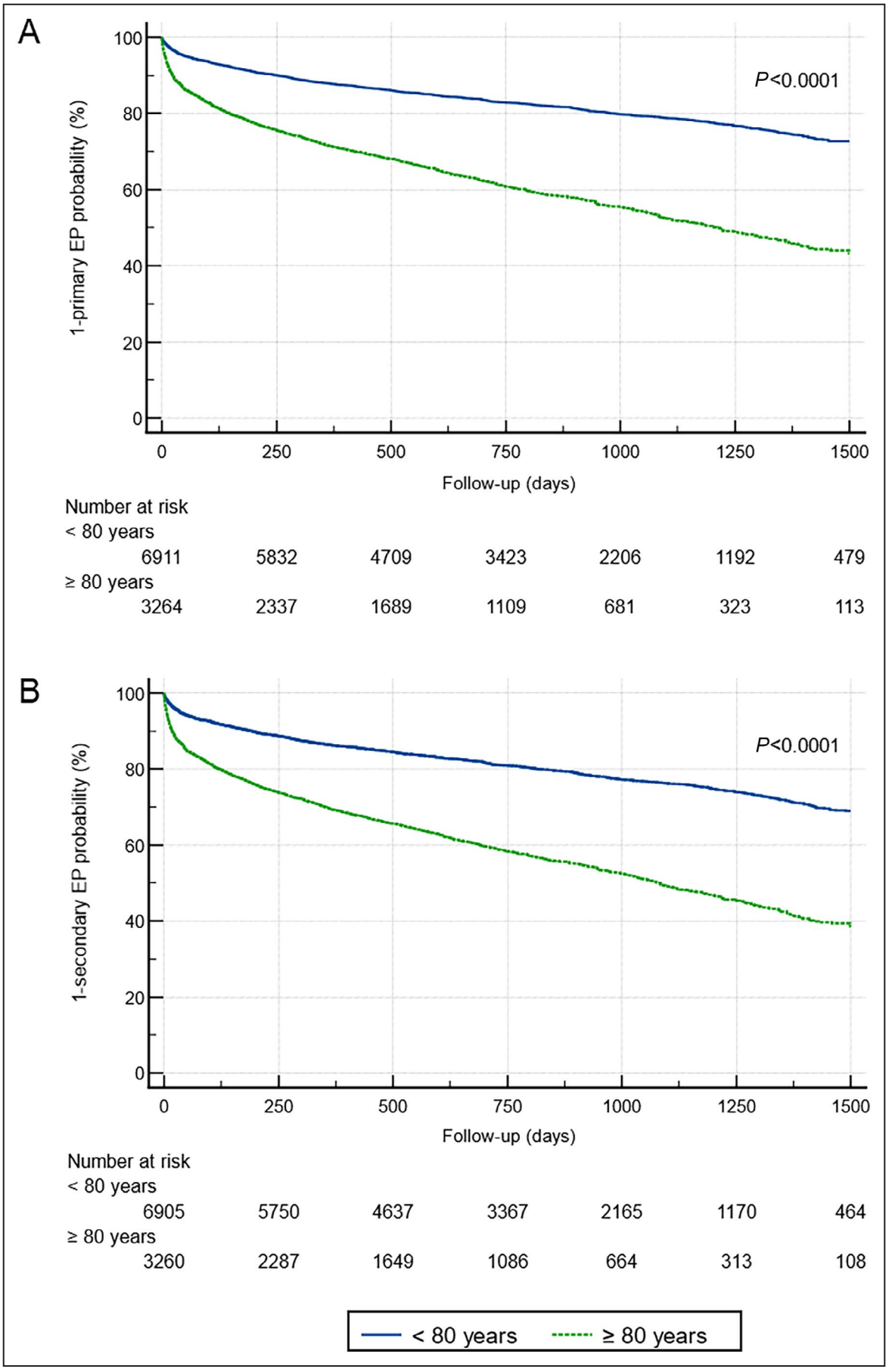
A
1-primary EP probability (%)
100
80
60
40
20
0
P<0.0001
0
250
500
750
1000
1250
1500
Follow-up (days)
Number at risk
< 80 years
6911 5832 4709 3423 2206 1192 479
≥ 80 years
3264 2337 1689 1109 681 323 113
B
1-secondary EP probability (%)
100
80
60
40
20
0
P<0.0001
0
250
500
750
1000
1250
1500
Follow-up (days)
Number at risk
< 80 years
6905 5750 4637 3367 2165 1170 464
≥ 80 years
3260 2287 1649 1086 664 313 108
< 80 years
≥ 80 years

Figure 2. Kaplan–Meier analysis of primary (A) and secondary (B) end point shows higher HRs for patients ≥80 years.
A, Kaplan–Meier curve illustrating the probability of the primary end point (all-cause mortality, stroke, or myocardial infarction) over time for patients aged ≥80 years (green dashed line) compared with those <80 years (blue solid line). Patients ≥80 years demonstrate a significantly higher risk, as reflected by the steep decline in end point-free survival (P<0.0001). **B**, Kaplan–Meier curve illustrating the probability of the secondary end point (primary end point plus major bleeding events) over time for patients aged ≥80 years (green dashed line) compared with those <80 years (blue solid line). The results again highlight a significantly increased risk in the ≥80 years group, with a greater cumulative incidence of events (P<0.0001). EP indicates end point; and HR, hazard ratio.

containing anticoagulation regimens. Regardless of age, we observed an HR of 1.25 (95% CI, 1.05–1.50; P=0.0130) favoring DOAC therapy for stroke or major bleeding events (P for interaction=0.0645; E-value$_{HR}$, 1.61; E-value$_{LCL}$, 1.22). When stratified by age categories, the benefits of DOACs versus VKA for stroke or major bleeding events declined as age increased, with the highest benefits observed in young and middle-aged patients (Figure 4A). This trend was consistent after removing cases who had received reduced doses of DOACs (Figure 4B). In a subanalysis of patients with AF ≥80 years receiving an OAC regimen, patients with NOAF and moderate abnormal LVEF showed higher HRs for VKA therapy compared with DOAC therapy, favoring a DOAC therapy within this patient cohort (Table 5). Additionally, among patients aged ≥80 years, both apixaban (HR, 0.67 [95% CI, 0.56–0.80]; P<0.001; E-value$_{HR}$, 1.98) and rivaroxaban (HR, 0.54 [95% CI, 0.47–0.63]; P<0.001; E-value$_{HR}$, 2.42) were associated with a significantly lower hazard of the composite end point compared with patients without any oral anticoagulation. However, the direct comparison between apixaban and rivaroxaban concerning the primary end point did not show a statistically significant difference (P=0.155), indicating that both DOACs provide similar protective effects in this age group. HRs split for the individual components of major bleeding events or stroke events are depicted in Figures S2 and S3, with and without the inclusion of patients receiving reduced doses of DOACs.

Noninvasive Rhythm Control in Patients ≥80 Years

In patients aged ≥80 years, 718 (21.8%) were classified as NOAF, whereas among those <80 years, 2040 (29.4%) presented with NOAF. Among individuals ≥80 years and NOAF, 131 (18.2%) were treated with a noninvasive rhythm control strategy, whereas 548 (26.9%) of those <80 years received this strategy. Comparing patients aged >80 years with NOAF and noninvasive rhythm control strategy against those without a rhythm control strategy showed no disparity concerning the primary end point (HR, 0.89 [95% CI, 0.65–1.19]; P=0.4038; E-value$_{HR}$, 1.39) (Figure 5). However, data on primary ablation strategies for patients with AF aged ≥80 years with NOAF in our ED were available only from March 2013 to March 2020, and only 3 patients (0.6%) received such treatment. Given this limited sample size, a meaningful statistical subgroup analysis was not feasible.

DISCUSSION

This study uses data from the HERA-FIB study, comprising 10 222 patients with AF presenting in an ED setting, to investigate outcomes and characteristics in patients aged ≥80 years and to evaluate the benefit of the VKA versus DOAC treatment regimens in patients ≥80 years. Notably, octogenarians and other older patients accounted for 32.2% of the study population,

Table 3. Event Rates and Hazard Ratios for Outcomes in Patients Aged ≥80 Years Compared With Younger Patients

Variables	<80 y	≥80 y	P value	HR (95% CI) for ≥80 y	P value
Primary EP*	1297 (18.7)	1342 (40.8)	<0.0001	3.09 (2.84–3.36)	<0.0001
Secondary EP†	1463 (21.1)	1450 (44.6)	<0.0001	2.96 (2.73–3.21)	<0.0001
All-cause mortality	987 (14.2)	1186 (36.0)	<0.0001	3.63 (3.31–3.99)	<0.0001
Stroke	185 (3.0) n=6164	102 (4.0) n=2558	0.0188	1.68 (1.29–2.19)	0.0001
Major bleeding	309 (5.0) n=6157	205 (8.0) n=2568	<0.0001	2.08 (1.70–2.53)	<0.0001
Myocardial infarction	234 (3.8) n=6148	148 (5.8) n=2556	<0.0001	2.06 (1.63–2.60)	<0.0001

EP indicates end point; and HR, hazard ratio.
*The primary EP consisted of all-cause mortality, myocardial infarction, and stroke.
†The secondary EP consisted of all-cause mortality, myocardial infarction, stroke, and major bleedings.

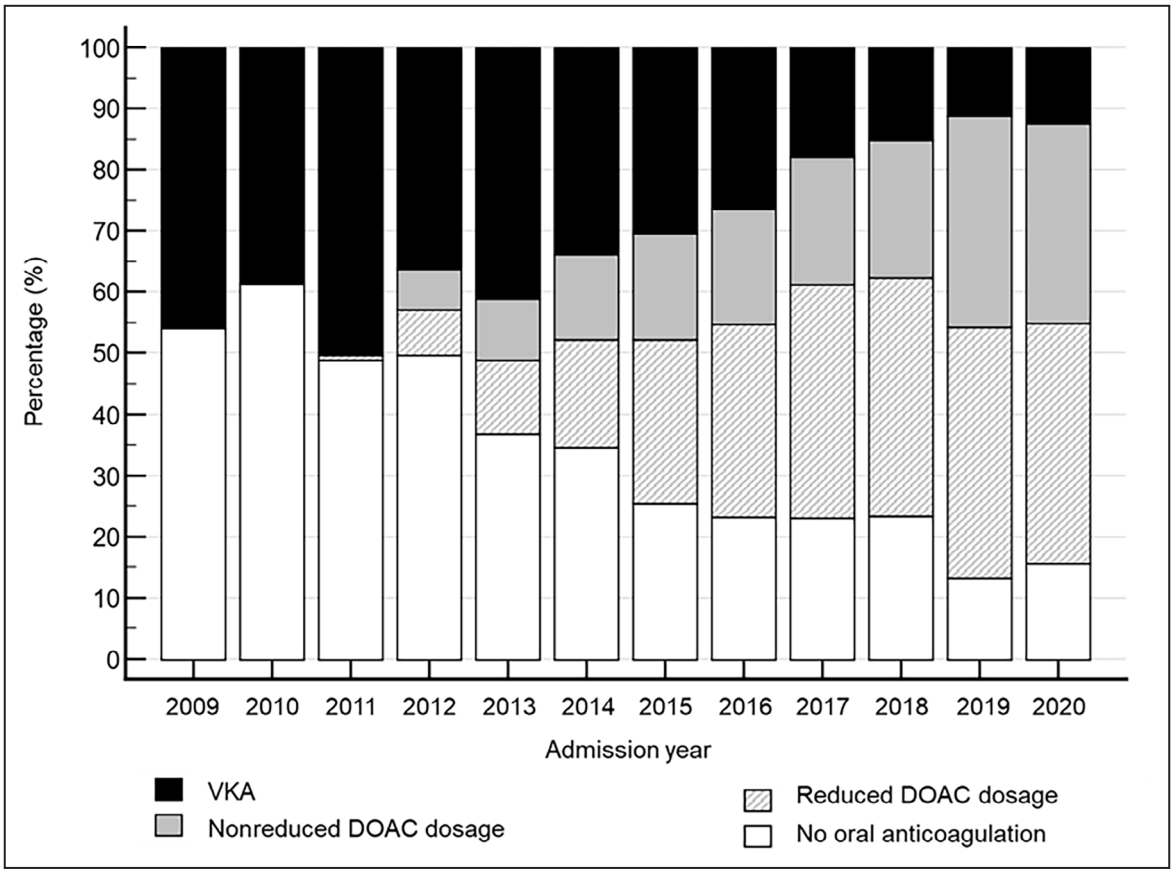

Figure 3. OAC use in patients ≥80 years stratified by no oral anticoagulation, VKA, and DOAC (reduced vs non-reduced dosage) within admission years.
DOAC indicates direct oral anticoagulant; OAC, oral anticoagulant; and VKA, vitamin K antagonist.

reflecting the increasing prevalence of AF with advancing age and highlighting the critical need for optimized management strategies in this patient cohort. In our study, we identified 3 key findings:

First, the observed HRs for primary and secondary end points in patients aged ≥80 years underscore the increased susceptibility of this demographic to adverse outcomes. With 40.8% experiencing the primary end point, including all-cause mortality, stroke, or MI, and 44.6% encountering the secondary end point, inclusive of major bleeding events, the vulnerability of this older subgroup to a range of adverse events is evident. Notably, diabetes, elevated creatinine levels, prior PAD, and MI emerged as significant predictors of adverse outcomes for both primary and secondary end point, with aHRs ranging from 1.03 to 1.28, respectively. To address nonlinearity in the relationship between serum creatinine and outcomes, restricted cubic splines were used, capturing the complex effect of creatinine levels on adverse outcomes. Additionally, a time-dependent analysis revealed that the impact of these comorbidities evolved over time, with diabetes, PAD, and MI

Table 4. Hazard Ratios for Outcomes in Patients ≥80 Years and <80 Years for Patients With Oral Anticoagulation VKA Versus DOAC Regimens

Variables	HR (95% CI) for patients ≥80 y and VKA vs DOAC	*P* value	HR (95% CI) for patients <80 y and VKA vs DOAC	*P* value
Primary EP	1.05 (0.91–1.22)	0.4968	1.45 (1.25–1.68)	<0.0001
Secondary EP	1.04 (0.90–1.20)	0.6031	1.45 (1.26–1.67)	<0.0001
All-cause mortality	1.04 (0.88–1.22)	0.6714	1.44 (1.20–1.73)	0.0001
Stroke	1.00 (0.61–1.65)	0.9880	1.23 (0.86–1.75)	0.2508
Major bleeding	1.20 (0.85–1.70)	0.3014	1.62 (1.23–2.15)	0.0007
Myocardial infarction	1.35 (0.89–2.05)	0.1560	1.41 (1.01–1.97)	0.0456

DOAC indicates direct oral anticoagulant; EP, end pont; HR, hazard ratio; and VKA, vitamin K antagonist.

consistently contributing to elevated risk. In contrast, arterial hypertension showed a significant time-varying effect only for the secondary end point (HR, 1.03; *P*=0.005), indicating its distinct influence on long-term bleeding risk. The substantial proportion of all-cause mortality (36%) highlights the critical impact of mortality in the management of AF among older patients. The corresponding *E*-values for these HRs, ranging from 2.62 to 4.11, indicate that any unmeasured confounder would need to have a very strong effect to negate the observed associations, reinforcing the robustness of our findings and making it unlikely that unmeasured confounders fully explain our results.

Second, the study observed a notable transition from VKAs to DOACs, particularly rivaroxaban (30.5%) and apixaban (17.4%). Among patients ≥80 years, 67.9% received oral anticoagulation, with 57.5% receiving a DOAC and 42.5% receiving a VKA therapy. Notably, rivaroxaban was the most commonly used DOAC, and reduced DOAC dosages were applied in 34.3% of patients ≥80 years. Over time, VKA use declined, whereas DOAC use, both full and reduced dose, increased in older patients. Our observations are consistent with findings by Joosten et al,[28] highlighting a considerable proportion of older patients with AF continuing VKA therapy despite the availability

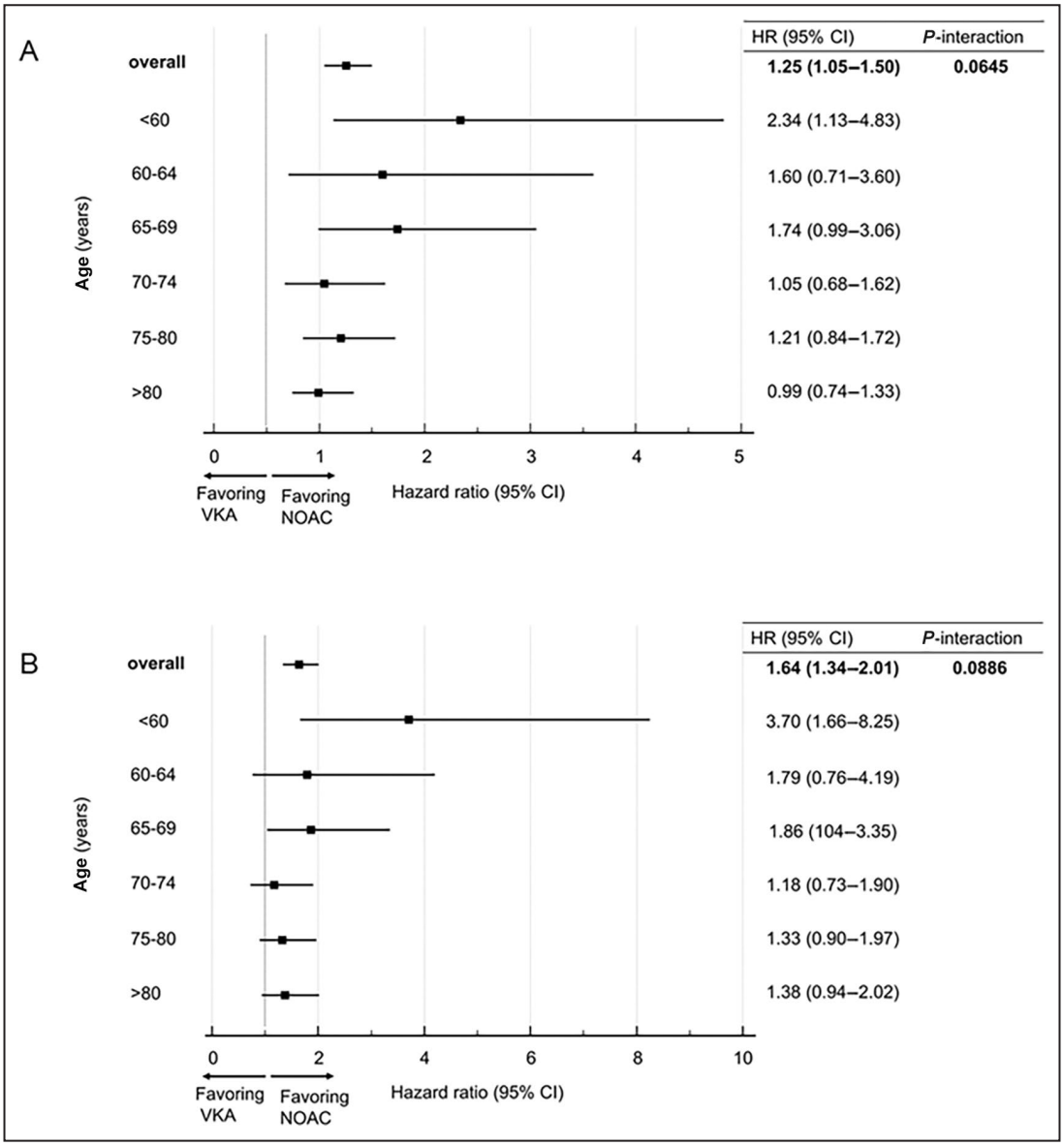

Figure 4. Overall benefit of DOAC therapy compared with VKA: hazard ratios for stroke or major bleeding events in the whole cohort (A) and a cohort after exclusion of patients receiving reduced DOAC dosage (B) across age categories.

DOAC indicates direct oral anticoagulant; HR, hazard ratio; NOAC, non-vitamin K antagonist; and VKA, vitamin K antagonist.

Table 5. Subanalysis for Patients ≥80 Years With AF With Oral Anticoagulation Regarding DOAC Versus VKA and the Primary and Secondary End Point.

	$HR_{primary\ EP}$ (95% CI)	*P* interaction	$HR_{secondary\ EP}$ (95% CI)	*P* interaction
Sex, female		0.7954		0.6788
VKA	0.96 (0.78–1.19)		0.96 (0.79–1.18)	
DOAC	1.04 (0.84–1.29)		1.04 (0.85–1.27)	
Estimated glomerular filtration rate ≤60 mL/min		0.0030		0.0052
VKA	1.06 (0.87–1.28)		1.05 (0.88–1.26)	
DOAC	0.95 (0.78–1.14)		0.95 (0.80–1.14)	
Diabetes		0.0597		0.0364
VKA	0.95 (0.68–1.33)		0.95 (0.69–1.29)	
DOAC	1.05 (0.75–1.46)		1.06 (0.77–1.45)	
Arterial hypertension		0.5190		0.6503
VKA	1.07 (0.92–1.26)		1.06 (0.92–1.23)	
DOAC	0.93 (0.80–1.09)		0.94 (0.81–1.09)	
Previous coronary artery disease		0.9560		0.8517
VKA	1.17 (0.95–1.45)		1.14 (0.94–1.39)	
DOAC	0.85 (069–1.05)		0.88 (0.72–1.07)	
Previous peripheral artery disease		0.3422		0.6122
VKA	1.35 (0.87–2.10)		1.40 (0.92–2.15)	
DOAC	0.74 (0.48–1.15)		0.71 (0.47–1.09)	
Previous myocardial infarction		0.1376		0.2085
VKA	1.13 (0.82–1.57)		1.09 (0.80–1.50)	
DOAC	0.88 (0.64–1.23)		0.92 (0.67–1.26)	
Previous coronary artery bypass graft		0.4355		0.3490
VKA	0.71 (0.47–1.08)		1.33 (0.90–1.96)	
DOAC	1.40 (0.93–2.12)		0.75 (0.51–1.11)	
Normal LVEF		0.7366		0.5657
VKA	0.94 (0.71–1.26)		0.88 (0.67–1.15)	
DOAC	1.06 (0.80–1.42)		1.14 (0.87–1.49)	
Mildly abnormal LVEF		0.8631		0.9314
VKA	0.93 (0.63–1.37)		1.01 (0.70–1.45)	
DOAC	1.08 (0.73–1.59)		0.99 (0.69–1.43)	
Moderate abnormal LVEF		0.5885		0.6677
VKA	1.63 (1.09–2.42)		1.50 (1.03–2.19)	
DOAC	0.62 (0.41–0.92)		0.67 (0.46–0.97)	
Severely abnormal LVEF		0.0924		0.1065
VKA	0.99 (0.62–1.59)		1.02 (0.65–1.60)	
DOAC	1.01 (0.63–1.62)		0.98 (0.62–1.53)	
New-onset atrial fibrillation		0.0051		0.0141
VKA	1.55 (1.05–2.29)		1.48 (1.03–2.12)	
DOAC	0.65 (0.43–0.95)		0.68 (0.47–0.97)	

DOAC indicates direct oral anticoagulant; EP, end point; HR, hazard ratio; LVEF, left ventricular ejection fraction; and VKA, vitamin K antagonist.

of DOAC regimens. This continued reliance on VKA, often seen in frail patients managed primarily in outpatient settings, underscores the clinical complexities and tailored considerations required for anticoagulation management in older patients.

Third, our study observed no significant differences in the predefined outcome parameters between VKA and DOAC strategies among patients aged ≥80 years, prompting reconsideration of the optimal OAC approach in this subgroup. Although DOAC therapy showed favorable HR profile for stroke and major bleeding events, evidence regarding the effectiveness and safety of DOAC regimens in older patients with AF remains limited. The percentage of patients ≥75 years

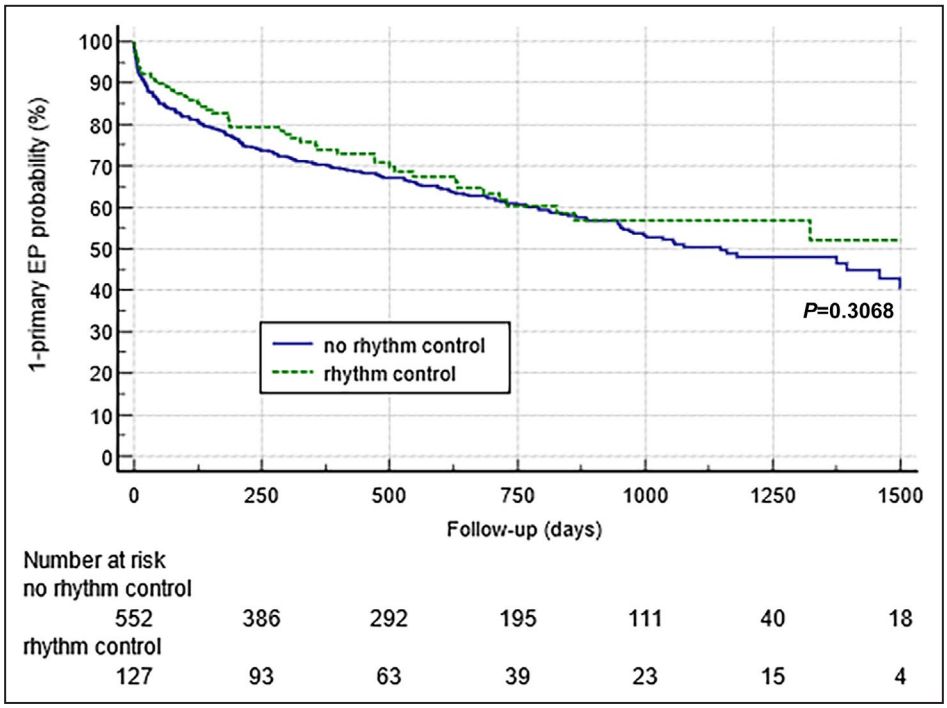

Figure 5. Kaplan–Meier analysis for comparison of rhythm vs no rhythm control strategy in patients with first diagnosed AF aged ≥80 years.
AF indicates atrial fibrillation; and EP, end point.

included in randomized clinical trials is substantially limited, ranging from 31% in ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation)[42] to 44% in ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation).[43] Most evidence is derived from subgroup analyses or meta-analyses from representative randomized clinical trials.[17–20] However, it is noteworthy that older patients included in randomized clinical trials tend to exhibit relatively better health profiles, fewer comorbidities, and improved physical function compared with older adults in the general population.[28] Thus, comparing our trial in the setting of an ED with these previous studies poses challenges due to the limited representation of frail older patients in the 4 pivotal DOAC trials.[5,6,17–28] These patients were often excluded because of high anticipated bleeding risks or were overlooked by physicians, leading to underrepresentation of older patients with AF in current clinical trials. Moreover, prior analyses primarily assessed frailty through comorbidities and polypharmacy, overlooking broader aspects inherent in the clinical syndrome. Our findings additionally indicate that among patients aged ≥80 years, both apixaban (HR, 0.67; $P<0.001$) and rivaroxaban (HR, 0.54; $P<0.001$) were significantly associated with a lower hazard of the primary composite end point compared with patients without an oral anticoagulation. However, the direct comparison between apixaban and rivaroxaban did not show a statistically significant difference ($P=0.155$), suggesting that both DOACs provide similar protective effects in this age group. This reinforces the evidence that DOACs are effective alternatives to no anticoagulation in older patients with AF, despite the known frailty and comorbid conditions that characterize this population. However, the lack of significant differences between DOAC and VKA strategies in our study suggests that specific characteristics of the older population, such as increased frailty, multiple comorbidities, and polypharmacy, may limit the relative benefit of DOACs over VKAs in this age group. These factors can influence both the pharmacokinetics and safety profile of DOACs, potentially reducing their effectiveness compared with VKAs. This highlights the need for a more personalized anticoagulation approach in patients aged ≥80 years, taking into consideration individual bleeding risks and overall health status.

Real-world studies providing data on the effectiveness and safety of DOACs in older patients with AF remain scarce.[27,44–48] These investigations often grapple with limitations such as limited statistical power due to low event rates and small cohort sizes. This scarcity in real-world evidence emphasizes the need for more comprehensive studies focusing on the specific nuances and challenges faced by this older demographic in actual clinical practice. A real-world study consisting of 11 760 patients showed that older patients with AF

are often not adequately treated with OACs, despite their high risk of stroke. Additionally, it demonstrated that patients on warfarin with time in therapeutic range ≥60% had a lower stroke incidence compared with those with time in therapeutic range <60%, whereas those on high-dose DOACs had a higher net clinical benefit with lower intracranial hemorrhage rates.[49]

Comparative analyses with the COMBINE-AF (Collaboration between Multiple Institutions to Better Investigate Non-Vitamin K Antagonist Oral Anticoagulant Use in Atrial Fibrillation) study and observations from ROCKET-AF, ARISTOTLE, and ENGAGE AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation—Thrombolysis in Myocardial Infarction 48) provide valuable contextual insights.[17,42,43,50] The COMBINE-AF consortium, which amalgamated individual patient data from major DOAC trials, encompassed a substantial cohort (n=71 683) and consistently highlighted a notable reduction in major or clinically significant nonmajor bleeding risk associated with DOAC treatment across various age groups.[50] These findings underscore the consistent advantage over warfarin, particularly in terms of efficacy in standard-dose DOACs, which surpassed VKAs, especially among VKA-naïve individuals. This analysis also unraveled age-related patterns, revealing that with both standard and reduced-dose DOAC treatments, increased age correlated with higher HRs for major bleeding events.[50] Noteworthy, interactions between polypharmacy and major bleeding were observed in the ROCKET-AF and ARISTOTLE trials, suggesting a diminishing edge of DOACs over VKAs in terms of safety outcomes in cases of higher medication use.[42,43] Similarly, findings from the ENGAGE AF-TIMI 48 trial portrayed a consistent decrease in bleeding incidents with edoxaban compared with warfarin across different levels of frailty, except in the most severe frailty spectrum where statistical significance was lacking for reduced bleeding with edoxaban.[17] These insights hint at a possible attenuation of DOAC advantages over VKAs, particularly in older and more complex trial participants, echoing our studies discovery of escalated bleeding risk when transitioning from VKAs to DOACs in an even older and frailer patient cohort. Notably, although DOACs exhibited favorable outcomes in bleeding risk compared with warfarin in several studies, the impact in older and frailer populations remained nuanced, possibly due to variations in frailty and polypharmacy. Observational studies corroborated our findings regarding the impact of aging and frailty on outcomes in real-world patients with AF receiving VKA or DOAC. However, frailty remains a complex factor to study due to residual confounding bias in observational studies.[28,51]

Furthermore, reduced LVEF was identified as a significant factor contributing to poor outcomes in older patients with AF, emphasizing the need for comprehensive cardiac assessment. Specifically, patients aged ≥80 years with NOAF and moderate LVEF abnormalities showed higher hazard ratios for VKA therapy compared with DOACs, indicating a preference for DOACs in this group. The coexistence of heart failure and AF significantly elevates the risk of cardiovascular morbidity and mortality, as highlighted by several studies showing that AF in patients with reduced LVEF further increases cardiovascular risk.[52–56] The SwedeHF (Swedish Heart Failure Registry) study also reported increased risks of death, heart failure hospitalization, and stroke or transient ischemic attack across all ranges of LVEF.[57] These observations underscore the need for personalized treatment approaches that address both anticoagulation and cardiac dysfunction to better manage the elevated risk of adverse cardiovascular events.

Finally, our findings on AF management in patients aged ≥80 years, who represent 21.8% of initial diagnoses, reveal notable differences in rhythm control strategy use compared with those <80 years, who account for 29.4% of cases. Specifically, among those ≥80 years with initial AF, 18.2% underwent noninvasive rhythm control, contrasting with 26.9% of individuals <80 years. However, comparison analysis showed no significant differences in primary end point between patients aged ≥80 years with initial AF receiving noninvasive rhythm control strategy with those who did not. These results add to the debate on AF management strategies, where empirical evidence contrasts with the traditional preference for rhythm control over rate control. The subanalysis of the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) trial[58] revealed lower all-cause mortality and hospitalization rates in the rate-controlled group aged 70 to 80 years, contrasting conventional expectations. Similarly, the REPOSI (Registro Politerapie SIMI [Società Italiana di Medicina Interna]) study's[59] ancillary analysis found no significant differences in cardiovascular and all-cause mortality between older patients managed using rate and rhythm control strategies, despite disparate patient profiles. These conflicting findings, alongside the preference for rate control strategies in real-world scenarios, underscore the ongoing discussion on the optimal approach in older patients, which must consider both health outcomes and quality of life. Whereas some studies suggest rate control is more cost effective,[60] other research points to better outcomes and improvements in health-related quality of life with rhythm control.[61,62]

Strengths and Limitations

The study benefits from the robust data set provided by HERA-FIB, which includes 10 222 consecutive, unselected patients with AF over an 11-year recruitment

period. The large sample size, particularly with a focus on patients aged ≥80 years, allows for meaningful examination of outcomes and treatment patterns in this older cohort. The longitudinal design, with a median follow-up of 23 months, enables a detailed analysis of disease progression and therapeutic responses, offering valuable insights into AF management among older patients.

However, the study has several limitations. Its retrospective, single-center design may introduce biases, limiting the generalizability of the findings. Additionally, the retrospective nature of the study precluded the collection of data on time in therapeutic range ≥70% for VKA therapy, limiting meaningful analysis of time in therapeutic range and outcomes in VKA-treated patients. Due to the ED setting and local standards for rhythm control, which did not routinely include primary ablation for patients aged ≥80 years, meaningful numbers for ablation in patients with NOAF in this age group could not be provided. This limitation prevented a meaningful analysis of ablation strategies offered to patients aged ≥80 years. Additionally, no data were available on device therapies or their success/failure rates in the rhythm control strategy analysis for patients aged ≥80 years with NOAF, precluding a meaningful analysis of these factors.

Furthermore, the lack of independently adjudicated end points may affect the precision of reported event rates, and the evolving treatment practices over the study period could influence both treatment patterns and outcomes, warranting cautious interpretation of the results. Our study included patients who were tolerant of VKA treatment, which may have influenced the reporting of bleeding complications after switching to DOACs. The choice of DOAC was determined by treating physicians, potentially affecting outcomes. The absence of significant differences between DOAC and VKA groups may be due to the low number of end point events and the selection bias inherent in a nonrandomized study design. Although the study was not powered to demonstrate differences in isolated clinical outcomes, it provides important insights into anticoagulation strategies in frail, older patients, suggesting that careful consideration is needed when deciding between continuing VKA or switching to a DOAC in this population.

CONCLUSIONS

In conclusion, this study from the HERA-FIB registry highlights the significant risk burden among octogenarians with AF, as shown by higher HRs for primary and secondary end points. The shifting landscape of OAC therapy, particularly the rise in DOAC use, emphasizes the evolving nature of treatment strategies. Our findings suggest no significant difference in outcomes between DOAC and VKA strategies in patients aged ≥80 years, emphasizing the need for individualized treatment approaches based on patient characteristics such as frailty, comorbidities, and polypharmacy. Clinicians should be mindful of these factors when choosing anticoagulation strategies, given the nuanced benefits observed between DOACs and VKAs in this high-risk group. Although these findings provide valuable insights into the real-world management of older patients with AF, the retrospective and single-center nature of the study necessitates cautious interpretation. Future prospective, multicenter studies are needed to validate these findings and further refine therapeutic approaches for this increasingly important, yet understudied, population.

ARTICLE INFORMATION

Received June 18, 2024; accepted December 31, 2024.

Affiliation

Department of Internal Medicine III, Cardiology, University Hospital of Heidelberg, Heidelberg, Germany.

Acknowledgments

We acknowledge Heidi Deigentasch and Amelie Werner for technical assistance.

Sources of Funding

The study was supported by a research grant from Daiichi Sankyo and Bayer diagnostics. The sponsor had no influence on the study concept, data collection, or interpretation. For the publication fee, we acknowledge financial support by Heidelberg University.

Disclosures

Dr Müller-Hennessen received research funding from BRAHMS, Thermo Fisher Scientific, and Roche Diagnostics. Dr Biener received research support from AstraZeneca outside the submitted work. Dr Giannitsis received honoraria for lectures from Roche Diagnostics, AstraZeneca, Bayer, Daiichi-Sankyo, and Lilly Eli Deutschland. He serves as a consultant for Roche Diagnostics, BRAHMS, Thermo Fisher Scientific, Boehringer Ingelheim and has received research funding from BRAHMS Thermo Fisher Scientific, Roche Diagnostics, Bayer Vital, and Daiichi Sankyo. Dr Frey has received speaker honoraria from Daiichi Sankyo, Astra Zeneca, Boehringer Ingelheim, and Bayer Vital. He serves as a consultant for CMS. Dr Milles received research funding from Daiichi Sankyo. The remaining authors have no disclosures to report.

Supplemental Material

Tables S1–S4
Figures S1–S3

REFERENCES

1. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, Singer DE. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study. *JAMA*. 2001;285:2370–2375. doi: 10.1001/jama.285.18.2370
2. Sardar P, Chatterjee S, Chaudhari S, Lip GY. New oral anticoagulants in elderly adults: evidence from a meta-analysis of randomized trials. *J Am Geriatr Soc*. 2014;62:857–864. doi: 10.1111/jgs.12799
3. Zoni-Berisso M, Lercari F, Carazza T, Domenicucci S. Epidemiology of atrial fibrillation: European perspective. *Clin Epidemiol*. 2014;6:213–220. doi: 10.2147/CLEP.S47385

4. Barrios V, Calderon A, Escobar C, de la Figuera M; Primary Care Group in the Clinical Cardiology Section of the Spanish Society of C. Patients with atrial fibrillation in a primary care setting: Val-FAAP study. *Rev Esp Cardiol (Engl ed)*. 2012;65:47–53. doi: 10.1016/j.recesp.2011.08.008
5. Bonanad C, Garcia-Blas S, Torres Llergo J, Fernandez-Olmo R, Diez-Villanueva P, Ariza-Sole A, Martinez-Selles M, Raposeiras S, Ayesta A, Bertomeu-Gonzalez V, et al. Direct oral anticoagulants versus warfarin in octogenarians with nonvalvular atrial fibrillation: a systematic review and meta-analysis. *J Clin Med*. 2021;10:5268. doi: 10.3390/jcm10225268
6. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomstrom-Lundqvist C, Boriani G, Castella M, Dan GA, Dilaveris PE, et al. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): the task force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J*. 2021;42:373–498. doi: 10.1093/eurheartj/ehaa612
7. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham study. *Stroke*. 1991;22:983–988. doi: 10.1161/01.str.22.8.983
8. Zathar Z, Karunatilleke A, Fawzy AM, Lip GYH. Atrial fibrillation in older people: concepts and controversies. *Front Med (Lausanne)*. 2019;6:175. doi: 10.3389/fmed.2019.00175
9. Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham heart study. *JAMA*. 1994;271:840–844. doi: 10.1001/jama.1994.03510350050036
10. Kannel WB, Abbott RD, Savage DD, McNamara PM. Epidemiologic features of chronic atrial fibrillation: the Framingham study. *N Engl J Med*. 1982;306:1018–1022. doi: 10.1056/NEJM198204293061703
11. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation: a major contributor to stroke in the elderly. The Framingham study. *Arch Intern Med*. 1987;147:1561–1564. doi: 10.1001/archinte.1987.00370090041008
12. Flegel KM, Hanley J. Risk factors for stroke and other embolic events in patients with nonrheumatic atrial fibrillation. *Stroke*. 1989;20:1000–1004. doi: 10.1161/01.str.20.8.1000
13. van Latum JC, Koudstaal PJ, Venables GS, van Gijn J, Kappelle LJ, Algra A. Predictors of major vascular events in patients with a transient ischemic attack or minor ischemic stroke and with nonrheumatic atrial fibrillation. European Atrial Fibrillation Trial (EAFT) study group. *Stroke*. 1995;26:801–806. doi: 10.1161/01.str.26.5.801
14. Yuan Z, Bowlin S, Einstadter D, Cebul RD, Conners AR Jr, Rimm AA. Atrial fibrillation as a risk factor for stroke: a retrospective cohort study of hospitalized Medicare beneficiaries. *Am J Public Health*. 1998;88:395–400. doi: 10.2105/ajph.88.3.395
15. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA*. 2001;285:2864–2870. doi: 10.1001/jama.285.22.2864
16. Wang N, Shen NN, Wu Y, Zhang C, Pan MM, Qian Y, Gu ZC. Comparison of effectiveness and safety of direct oral anticoagulants versus vitamin-k antagonists in elderly patients with atrial fibrillation: a systematic review and cost-effectiveness analysis protocol. *Ann Transl Med*. 2020;8:391. doi: 10.21037/atm.2020.02.109
17. Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, Waldo AL, Ezekowitz MD, Weitz JI, Spinar J, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013;369:2093–2104. doi: 10.1056/NEJMoa1310907
18. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361:1139–1151. doi: 10.1056/NEJMoa0905561
19. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365:981–992. doi: 10.1056/NEJMoa1107039
20. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365:883–891. doi: 10.1056/NEJMoa1009638
21. Steffel J, Collins R, Antz M, Cornu P, Desteghe L, Haeusler KG, Oldgren J, Reinecke H, Roldan-Schilling V, Rowell N, et al. 2021 European Heart Rhythm Association practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *Europace*. 2021;23:1612–1676. doi: 10.1093/europace/euab065
22. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC Jr, Ellinor PT, Ezekowitz MD, Field ME, Furie KL, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines and the Heart Rhythm Society in collaboration with the Society of Thoracic Surgeons. *Circulation*. 2019;140:e125–e151. doi: 10.1161/CIR.0000000000000665
23. Okumura K, Akao M, Yoshida T, Kawata M, Okazaki O, Akashi S, Eshima K, Tanizawa K, Fukuzawa M, Hayashi T, et al. Low-dose edoxaban in very elderly patients with atrial fibrillation. *N Engl J Med*. 2020;383:1735–1745. doi: 10.1056/NEJMoa2012883
24. Halvorsen S, Atar D, Yang H, De Caterina R, Erol C, Garcia D, Granger CB, Hanna M, Held C, Husted S, et al. Efficacy and safety of apixaban compared with warfarin according to age for stroke prevention in atrial fibrillation: observations from the ARISTOTLE trial. *Eur Heart J*. 2014;35:1864–1872. doi: 10.1093/eurheartj/ehu046
25. Ng KH, Shestakovska O, Connolly SJ, Eikelboom JW, Avezum A, Diaz R, Lanas F, Yusuf S, Hart RG. Efficacy and safety of apixaban compared with aspirin in the elderly: a subgroup analysis from the AVERROES trial. *Age Ageing*. 2016;45:77–83. doi: 10.1093/ageing/afv156
26. Eikelboom JW, Wallentin L, Connolly SJ, Ezekowitz M, Healey JS, Oldgren J, Yang S, Alings M, Kaatz S, Hohnloser SH, et al. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial. *Circulation*. 2011;123:2363–2372. doi: 10.1161/CIRCULATIONAHA.110.004747
27. Halperin JL, Hankey GJ, Wojdyla DM, Piccini JP, Lokhnygina Y, Patel MR, Breithardt G, Singer DE, Becker RC, Hacke W, et al. Efficacy and safety of rivaroxaban compared with warfarin among elderly patients with nonvalvular atrial fibrillation in the Rivaroxaban Once Daily, Oral, Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF). *Circulation*. 2014;130:138–146. doi: 10.1161/CIRCULATIONAHA.113.005008
28. Joosten LPT, van Doorn S, van de Ven PM, Kohlen BTG, Nierman MC, Koek HL, Hemels MEW, Huisman MV, Kruip M, Faber LM, et al. Safety of switching from a vitamin K antagonist to a non-vitamin K antagonist oral anticoagulant in frail older patients with atrial fibrillation: results of the FRAIL-AF randomized controlled trial. *Circulation*. 2023;149:279–289. doi: 10.1161/CIRCULATIONAHA.123.066485
29. Salbach C, Yildirim M, Hund H, Biener M, Muller-Hennessen M, Frey N, Katus HA, Giannitsis E, Milles BR. Design, rationale and initial findings from HERA-FIB on 10 222 patients with atrial fibrillation presenting to an emergency department over an 11-year period. *J Am Heart Assoc*. 2024;13:e033396. doi: 10.1161/JAHA.123.033396
30. Van Gelder IC, Rienstra M, Bunting KV, Casado-Arroyo R, Caso V, Crijns H, De Potter TJR, Dwight J, Guasti L, Hanke T, et al. ESC guidelines for the management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2024;2024:3314–3414. doi: 10.1093/eurheartj/ehae176
31. Lip GYH, Collet JP, Caterina R, Fauchier L, Lane DA, Larsen TB, Marin F, Morais J, Narasimhan C, Olshansky B, et al. Antithrombotic therapy in atrial fibrillation associated with valvular heart disease: a joint consensus document from the European Heart Rhythm Association (EHRA) and European Society of Cardiology Working Group on Thrombosis, endorsed by the ESC Working Group on Valvular Heart Disease, Cardiac Arrhythmia Society of Southern Africa (CASSA), Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS), South African Heart (SA Heart) Association and Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLEACE). *Europace*. 2017;19:1757–1758. doi: 10.1093/europace/eux240
32. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015;28:1–39.e14. doi: 10.1016/j.echo.2014.10.003
33. Schulman S, Angeras U, Bergqvist D, Eriksson B, Lassen MR, Fisher W; Subcommittee on control of anticoagulation of the S, Standardization

Committee of the International Society on T, Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. *J Thromb Haemost*. 2010;8:202–204. doi: 10.1111/j.1538-7836.2009.03678.x
34. VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. *Ann Intern Med*. 2017;167:268–274. doi: 10.7326/M16-2607
35. Mathur MB, Ding P, Riddell CA, VanderWeele TJ. Web site and R package for computing E-values. *Epidemiology*. 2018;29:e45–e47. doi: 10.1097/EDE.0000000000000864
36. Zhang Z, Reinikainen J, Adeleke KA, Pieterse ME, Groothuis-Oudshoorn CGM. Time-varying covariates and coefficients in cox regression models. *Ann Transl Med*. 2018;6:121. doi: 10.21037/atm.2018.02.12
37. Grambsch PM, Therneau TM, Fleming TR. Diagnostic plots to reveal functional form for covariates in multiplicative intensity models. *Biometrics*. 1995;51:1469–1482. doi: 10.2307/2533277
38. Borgan O, Zhang Y. Using cumulative sums of martingale residuals for model checking in nested case-control studies. *Biometrics*. 2015;71:696–703. doi: 10.1111/biom.12308
39. Lusa L, Ahlin C. Restricted cubic splines for modelling periodic data. *PLoS One*. 2020;15:e0241364. doi: 10.1371/journal.pone.0241364
40. Halabi S, Dutta S, Wu Y, Liu A. Score and deviance residuals based on the full likelihood approach in survival analysis. *Pharm Stat*. 2020;19:940–954. doi: 10.1002/pst.2047
41. Farrington CP. Residuals for proportional hazards models with interval-censored survival data. *Biometrics*. 2000;56:473–482. doi: 10.1111/j.0006-341x.2000.00473.x
42. Guimaraes PO, Pokorney SD, Lopes RD, Wojdyla DM, Gersh BJ, Giczewska A, Carnicelli A, Lewis BS, Hanna M, Wallentin L, et al. Efficacy and safety of apixaban vs warfarin in patients with atrial fibrillation and prior bioprosthetic valve replacement or valve repair: insights from the ARISTOTLE trial. *Clin Cardiol*. 2019;42:568–571. doi: 10.1002/clc.23178
43. Bansilal S, Bloomgarden Z, Halperin JL, Hellkamp AS, Lokhnygina Y, Patel MR, Becker RC, Breithardt G, Hacke W, Hankey GJ, et al. Efficacy and safety of rivaroxaban in patients with diabetes and nonvalvular atrial fibrillation: the Rivaroxaban Once-Daily, Oral, Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF trial). *Am Heart J*. 2015;170:675–682. doi: 10.1016/j.ahj.2015.07.006
44. Rutherford OW, Jonasson C, Ghanima W, Soderdahl F, Halvorsen S. Effectiveness and safety of oral anticoagulants in elderly patients with atrial fibrillation. *Heart*. 2022;108:345–352. doi: 10.1136/heartjnl-2020-318753
45. Kwon S, Lee SR, Choi EK, Lee E, Jung JH, Han KD, Cha MJ, Oh S, Lip GYH. Non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation and prior gastrointestinal bleeding. *Stroke*. 2021;52:511–520. doi: 10.1161/STROKEAHA.120.030761
46. Chan N, Sager PT, Lawrence J, Ortel T, Reilly P, Berkowitz S, Kubitza D, Eikelboom J, Florian J, Stockbridge N, et al. Is there a role for pharmacokinetic/pharmacodynamic-guided dosing for novel oral anticoagulants? *Am Heart J*. 2018;199:59–67. doi: 10.1016/j.ahj.2017.10.002
47. Graham DJ, Baro E, Zhang R, Liao J, Wernecke M, Reichman ME, Hu M, Illoh O, Wei Y, Goulding MR, et al. Comparative stroke, bleeding, and mortality risks in older medicare patients treated with Oral anticoagulants for nonvalvular atrial fibrillation. *Am J Med*. 2019;132:596–604. doi: 10.1016/j.amjmed.2018.12.023
48. Forslund T, Wettermark B, Andersen M, Hjemdahl P. Stroke and bleeding with non-vitamin K antagonist oral anticoagulant or warfarin treatment in patients with non-valvular atrial fibrillation: a population-based cohort study. *Europace*. 2018;20:420–428. doi: 10.1093/europace/euw416
49. Alnsasra H, Haim M, Senderey AB, Reges O, Leventer-Roberts M, Arnson Y, Leibowitz M, Hoshen M, Avgil-Tsadok M. Net clinical benefit of anticoagulant treatments in elderly patients with nonvalvular atrial fibrillation: experience from the real world. *Heart Rhythm*. 2019;16:31–37. doi: 10.1016/j.hrthm.2018.08.016
50. Carnicelli AP, Hong H, Giugliano RP, Connolly SJ, Eikelboom J, Patel MR, Wallentin L, Morrow DA, Wojdyla D, Hua K, et al. Individual patient data from the pivotal randomized controlled trials of non-vitamin K antagonist Oral anticoagulants in patients with atrial fibrillation (COMBINE AF): design and rationale: from the COMBINE AF (a collaboration between multiple institutions to better investigate non-vitamin K antagonist oral anticoagulant use in atrial fibrillation) Investigators. *Am Heart J*. 2021;233:48–58. doi: 10.1016/j.ahj.2020.12.002
51. Menichelli D, Del Sole F, Di Rocco A, Farcomeni A, Vestri A, Violi F, Pignatelli P, Lip GYH, Pastori D. Real-world safety and efficacy of direct oral anticoagulants in atrial fibrillation: a systematic review and meta-analysis of 605 771 patients. *Eur Heart J Cardiovasc Pharmacother*. 2021;7:f11–f19. doi: 10.1093/ehjcvp/pvab002
52. Mamas MA, Caldwell JC, Chacko S, Garratt CJ, Fath-Ordoubadi F, Neyses L. A meta-analysis of the prognostic significance of atrial fibrillation in chronic heart failure. *Eur J Heart Fail*. 2009;11:676–683. doi: 10.1093/eurjhf/hfp085
53. Linssen GC, Rienstra M, Jaarsma T, Voors AA, van Gelder IC, Hillege HL, van Veldhuisen DJ. Clinical and prognostic effects of atrial fibrillation in heart failure patients with reduced and preserved left ventricular ejection fraction. *Eur J Heart Fail*. 2011;13:1111–1120. doi: 10.1093/eurjhf/hfr066
54. Banerjee A, Taillandier S, Olesen JB, Lane DA, Lallemand B, Lip GY, Fauchier L. Ejection fraction and outcomes in patients with atrial fibrillation and heart failure: the Loire Valley atrial fibrillation project. *Eur J Heart Fail*. 2012;14:295–301. doi: 10.1093/eurjhf/hfs005
55. Cheng M, Lu X, Huang J, Zhang J, Zhang S, Gu D. The prognostic significance of atrial fibrillation in heart failure with a preserved and reduced left ventricular function: insights from a meta-analysis. *Eur J Heart Fail*. 2014;16:1317–1322. doi: 10.1002/ejhf.187
56. Li SJ, Sartipy U, Lund LH, Dahlstrom U, Adiels M, Petzold M, Fu M. Prognostic significance of resting heart rate and use of beta-blockers in atrial fibrillation and sinus rhythm in patients with heart failure and reduced ejection fraction: findings from the Swedish Heart Failure Registry. *Circ Heart Fail*. 2015;8:871–879. doi: 10.1161/CIRCHEARTFAILURE.115.002285
57. Sartipy U, Dahlstrom U, Fu M, Lund LH. Atrial fibrillation in heart failure with preserved, mid-range, and reduced ejection fraction. *JACC Heart Fail*. 2017;5:565–574. doi: 10.1016/j.jchf.2017.05.001
58. Shariff N, Desai RV, Patel K, Ahmed MI, Fonarow GC, Rich MW, Aban IB, Banach M, Love TE, White M, et al. Rate-control versus rhythm-control strategies and outcomes in septuagenarians with atrial fibrillation. *Am J Med*. 2013;126:887–893. doi: 10.1016/j.amjmed.2013.04.021
59. Paciullo F, Proietti M, Bianconi V, Nobili A, Pirro M, Mannucci PM, Lip GYH, Lupattelli G, Investigators R. Choice and outcomes of rate control versus rhythm control in elderly patients with atrial fibrillation: a report from the REPOSI study. *Drugs Aging*. 2018;35:365–373. doi: 10.1007/s40266-018-0532-8
60. Perez A, Touchette DR, DiDomenico RJ, Stamos TD, Walton SM. Comparison of rate control versus rhythm control for management of atrial fibrillation in patients with coexisting heart failure: a cost-effectiveness analysis. *Pharmacotherapy*. 2011;31:552–565. doi: 10.1592/phco.31.6.552
61. Tsadok MA, Jackevicius CA, Essebag V, Eisenberg MJ, Rahme E, Humphries KH, Tu JV, Behlouli H, Pilote L. Rhythm versus rate control therapy and subsequent stroke or transient ischemic attack in patients with atrial fibrillation. *Circulation*. 2012;126:2680–2687. doi: 10.1161/CIRCULATIONAHA.112.092494
62. Ha AC, Breithardt G, Camm AJ, Crijns HJ, Fitzmaurice GM, Kowey PR, Le Heuzey JY, Naditch-Brule L, Prystowsky EN, Schwartz PJ, et al. Health-related quality of life in patients with atrial fibrillation treated with rhythm control versus rate control: insights from a prospective international registry (Registry on Cardiac Rhythm Disorders Assessing the Control of Atrial Fibrillation: RECORD-AF). *Circ Cardiovasc Qual Outcomes*. 2014;7:896–904. doi: 10.1161/HCQ.0000000000000011