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Direct Anticoagulants Versus Vitamin K Antagonists in Patients Aged 80 Years or Older With Atrial Fibrillation in a "Real-world" Nationwide Registry: Insights From the FANTASIIA Study

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Abstract

Objective: To describe major events at follow up in octogenarian patients with atrial fibrillation (AF) according to anticoagulant treatment: direct oral anticoagulants (DOACs) versus vitamin K antagonists (VKAs)
Methods: A total of 578 anticoagulated patients aged 80 years with AF were included in a prospective, observational, multicenter study. Basal features, embolic events (stroke and systemic embolism), severe bleedings, and all-cause mortality at follow up were investigated according to the anticoagulant treatment received.
Results: Mean age was 84.0 + 3.4 years, 56% were women. Direct oral anticoagulants were prescribed to 123 (21.3%) patients. Compared with 455 (78.7%) patients treated with VKAs, those treated with DOACs presented a lower frequency of permanent AF (52.9% vs 61.6%, P = .01), cancer history (4.9% vs 10.9%, P = .046), renal failure (21.1% vs 32.2%, P = .02), and left ventricular dysfunction (2.4% vs 8.0%, P = .03); and higher frequency of previous stroke (26.0% vs 16.6%, P = .02) and previous major bleeding (8.1% vs 3.6%, P = .03). There were no significant differences in Charlson, CHA2DS2VASc, nor HAS-BLED scores. At 3-year follow up, rates of embolic events, severe bleedings, and all-cause death (per 100 patients-year) were similar in both groups (DOACs vs VKAs): 0.34 vs 1.35 (P = .15), 3.45 vs 4.41 (P = .48), and 8.2 vs 11.0 (P = .18), respectively, without significant differences after multivariate analysis (hazard ratio [HR]: 0.25, 95% confidence interval [CI]: 0.03-1.93, P = .19; HR: 0.88, 95% CI: 0.44-1.76, P = .72 and HR: 0.84, 95% CI: 0.53-1.33, P = .46, respectively).
Conclusion: In this "real-world" registry, the differences in major events rates in octogenarians with AF were not statistically significant in those treated with DOACs versus VKAs.
Keywords: direct oral anticoagulants, vitamin K antagonists, atrial fibrillation, octogenarians, FANTASIIA registry.

Introduction

Direct oral anticoagulants (DOACs) have been shown to be non-inferior or superior to vitamin K antagonists (VKAs) regarding embolic events, severe bleeding, and all-cause death rates in patients with atrial fibrillation (AF) in clinical trials[1] as well as in observational studies[2-4]. Subanalysis of randomized clinical trials have shown that the benefits of these therapies are consistent in elderly patients[5-9]. However, there is a paucity of "real-world" data on effectiveness and safety of these drugs, compared to VKAs, in octogenarian patients with AF[10-15]. Moreover, some studies have appointed the possibility of unclear safety in this particularly frail subgroup of patients in conditions of daily clinical practice[16-17]. The FANTASIIA registry (Spanish acronym for Atrial fibrillation: Influence of anticoagulation level and type on stroke and bleeding event incidence) is an observational, national, prospective, multicenter study that included patients aged 18 years or older with AF on anticoagulant treatment. The main objective of the study was to evaluate the incidence of thromboembolic and bleeding events in this population over 3 years, with focus on the use and type of antithrombotic agent, VKAs and DOACs, as well as anticoagulation quality (in those patients prescribed VKAs)[18]. The aim of this study was to describe basal features and major events at follow up in octogenarian patients with AF included in this observational "real-world" registry, according to the use of DOACs versus VKAs.

Methods

The FANTASIIA Registry

Inclusion criteria, procedures, and main results have been previously described[18]. Briefly, patients were consecutively included at 50 outpatient clinics by 100 investigators (81% cardiologists, 11% primary care physicians, and 8% internists) from June 1, 2013, to October 15, 2014. The participant centers, located throughout Spain, were selected by the steering committee, in order to obtain a representative sample of the whole national territory. Only physicians with clinical expertise and a special interest in AF were invited to participate in the study. Inclusion criteria were patients aged 18 years or older diagnosed of AF, who had been receiving anticoagulant therapy for at least 6 months before enrolment (by design, 80% VKAs and 20% DOACs, ie, dabigatran, rivaroxaban, or apixaban). This proportion was established to be representative of DOAC use in Spain at the time of the design of the study. Patients with rheumatic mitral valve disease or valvular prostheses were excluded. Clinical and laboratory information from the patients were collected in an electronic online database. The patients were managed according to the best clinical practice at their physician discretion. The FANTASIIA Registry adhered to the Helsinki recommendations for medical studies, the protocol was approved by all the local ethics committees, and patients granted their written informed consent.

Design of the Study

This is a subanalysis of the main study, focusing in octogenarian patients (those aged ≥80 years). For this analysis, all these patients were selected, and baseline clinical profile and major event rates in follow up were described, comparing patients treated with DOACs with those receiving VKAs. Baseline clinical profile included cardiovascular risk factors, comorbidities, heart disease history, AF data, physical examination, diagnostic procedures, and concomitant treatment at inclusion visit. Data on anticoagulation control in patients treated with VKAs in our series have been previously reported[18,19]. After the first visit, revisions appointments were scheduled after 1, 2, and 3 years, and major events were registered. In case of noshow to a visit, a phone contact was tried or electronic clinical records were consulted. Major events considered were embolic events (ischemic stroke or systemic embolism), severe bleeding (fatal bleeding, symptomatic bleeding in a critical area or organ, or causing a fall in hemoglobin level of ≥20 g/L, or leading to transfusion of ≥2 units of whole

blood or red cells, according to the 2005 International Society of Thrombosis and Haemostasis criteria[20]), and all-cause death.

Statistical Analysis

Quantitative variables were reported as the mean + SD, if normally distributed, or median (interquartile range) otherwise. Adjustment to normal distribution was tested with the Kolmogorov–Smirnov method. Student t test or Mann–Whitney U test (continuous variables) and χ^2 test (qualitative variables) were used for between-group comparisons, as appropriate. Event rates were calculated per 100 patientsyear, and 95% confidence intervals (CIs) are provided. For multivariate analysis, multivariate Cox proportional hazard ratio (HR) models were constructed. In all regression analyses, type of anticoagulant treatment (DOACs/VKAs) was the main exposure of interest and forced to remain in every model. Variables initially included in the models were those univariably related with the main exposure of interest or the events in follow up and those with known prognostic value in literature. The specific variables included were age, sex, diabetes mellitus, arterial hypertension, chronic pulmonary obstructive disease, cancer, renal failure, hepatic dysfunction, heart failure, Charlson comorbidity index, coronary disease, previous stroke, previous severe bleeding, left ventricle dysfunction, dilated cardiomyopathy, AF type, European Heart Rhythm Association functional class, anticoagulant treatment (DOACs/VKAs), and anti-arrhythmics use. Backward stepwise regression was used to select variables in the final adjusted models. The criterion to remain in the model was $P < .1$. The results are presented as HRs with 95% CI. Goodness-of-fit of the models was checked by means of the Grønnesby and Borgan test[21], for which $P > .05$ suggests a reasonably good adjustment. We used SPSS software version 21.0 (SPSS Inc., Chicago, Illinois) DSfor statistical analysis. Significance was defined as $P < .05$.

Results

Patients

A total of 574 patients were included, with a mean age of 84.0 + 3.4 years, 55.8% were women. Vitamin K antagonist was the anticoagulant drug in 451 patients (78.7%) and DOACs in 123 (2.3%). The specific DOAC prescribed at first visit was dabigatran in 57 (46.3%) patients, apixaban in 53 (43.1%) patients, and rivaroxaban in 13 (10.6%) patients. The baseline characteristics of the patients are described in Table 1. More frequent cardiovascular risk factors were hypertension, hypercholesterolemia, and diabetes mellitus. More significant comorbidities were chronic renal failure, cerebrovascular disease, and chronic pulmonary obstructive disease. Structural heart disease was present in nearly half of the patients. Most of them presented permanent AF, were in functional class I or II of the European Heart Rhythm Association (EHRA), and their embolic and bleeding risk was high, as assessed by CHA_2 DS_2-VAS_c and HAS-BLED scores. Diuretics, β-blockers, and statins were the most frequent concomitant drugs prescribed at the first visit.

Comparison Between Basal Features of Patients Receiving DOACs Versus VKAs

Compared to patients treated with VKAs, those who were prescribed DOACs presented a lower prevalence of renal failure, cancer history, dilated cardiomyopathy and permanent AF; and higher frequency of previous stroke and major bleeding (Table 1). Both groups presented similar age, sex, cardiovascular risk factors, and concomitant pharmacologic treatment. There were no significant differences in Charlson, $CHADS_2$, CHA_2 DS_2-VAS_c, nor HAS-BLED scores.

Events in Follow-Up

After up to 3-year follow up (1338 patients-years of observation), 15 patients presented embolic events, 55 patients had severe bleedings, and 139 patients died. The differences in rates of embolic events, severe bleedings, cardiovascular death, all-cause death, and combined events (embolic events/severe bleedings or embolic events/severe bleedings/all-cause death) were not statistically significant between patients prescribed DOAC and those who received VKAs (Figure 1). A detailed description of events and crude and adjusted HRs for treatment group comparisons are shown in Table2.

Predictors of Individual Events

In multivariate analysis, only age and coronary disease independently predicted embolic events; renal failure, previous severe bleeding, and EHRA functional class II were independently associated to severe bleedings; age, diabetes, renal failure, liver dysfunction, heart failure, and EHRA functional class predicted cardiovascular death; and age, female sex, diabetes, chronic obstructive pulmonary disease, renal failure, and EHRA functional class were independently associated with all-cause death (Table 3).

Discussion

The main finding of our study was that the differences in major event rates between DOAC and VKA users in octogenarian patients were not statistically significant, in a prospective, multicenter, observational "real-world" cohort of anticoagulated patients with AF. The main clinical implication is that these findings support that the effectiveness and safety of DOAC are non-inferior to VKAs in octogenarian patients with AF in routine clinical practice.

A high burden of cardiovascular risk factors and comorbidities was observed in our study sample, with a high prevalence of permanent AF and high embolic and bleeding risks. Similar findings have been found in the subgroup analysis of octogenarians in the pivotal clinical trials of DOACs that have reported baseline clinical data for these patients[5,8] or in observational studies of elderly patients with AF[10-15]. However, it is remarkable that only 0.7% of patients were current smokers. Although a decline in the smokers proportion has been observed with age in patients with AF in a clinical trial,5 the rate of currents smokers in patients aged ≥75 years has been reported in the range of 3.8% to 8.5%. [5,12]

The decision to treat each patient with DOACs versus VKAs was made at the discretion of the treating physician, and some basal features of the patients, which were more frequently associated with the use of these drugs in our study, can give us some clues about why the selected drug was one or another. Hence, patients treated with DOACs presented a lower prevalence of renal failure, cancer history, dilated cardiomyopathy, permanent AF, and higher frequency of previous stroke and major bleeding. The quality of anticoagulation control in patients prescribed VKAs in our study[18] was in the range of those described in the control group of the pivotal clinical trials of DOACs[5-9]: The meantime in therapeutic range in our series was 62.2%, without significant differences among age groups[19], versus 56.9% to 69.6% in those trials. So we can anticipate that the outcomes in the group treated with VKAs are in the context of a standard quality of anticoagulation.

Rates of embolic and severe bleeding found in our study are in the range found in the subgroup of octogenarian patients included in the pivotal trials[5,7,8]. So, the embolic event rate ranged from 1.5 to 2.8 (per 100 patients-year) with DOACs and from 1.9 to 2.9 with warfarin. In our study, embolic events rates were 0.3 (95% CI: 0.1-2.4) for DOACs and 1.4 (95% CI: 0.8-2.3) for VKAs. Although mean values are numerically lower in our series, confidence intervals are wide and include the figures observed in the trials. For severe bleeding events, rates observed in this subgroup of patients included in the pivotal trials ranged from 3.6 to 6.2 with DOAC and from 5.4 to 6.2 with warfarin, whereas in our study the figures were 3.5 (95% CI: 1.9-6.4) for DOACs versus 4.4 (95% CI: 3.3-5.9) for VKAs, also consistent with those reported by the trials.

Table 1. Baseline Features of the Study Sample, According to the Anticoagulant Prescribed in First Visit.

Variable	All Patients	Direct Oral Anticoagulants	Vitamin K Antagonists	P Value
Patients, n (%)	574	123 (21.3)	451 (78.7)	
Demographic data				
Age	84.0 + 3.4	83.9 + 3.9	84.0 + 3.4	.82
Female sex (%)	55.8	61.0	54.3	.19
Cardiovascular risk factors and concurrent disease				
Hypertension (%)	84.2	83.7	84.3	.89
Hyperlipidemia (%)	49.0	48.0	49.2	81
Diabetes mellitus (%)	26.8	29.3	26.2	.49
Current smoker (%)	0.7	0	0.9	.30
Renal failure[a] (%)	29.8	21.1	32.2	.02
Chronic obstructive pulmonary disease/sleep obstructive apnea syndrome	18.3	16.3	17.6	.74
Cancer history (%)	9.6	4.9	10.9	.046
Liver dysfunction (%)	1.4	0.8	1.6	.54
Aortic/peripheral artery disease (%)	5.1	6.5	4.7	.41
Previous stroke/transient ischemic attack (%)	18.6	26.0	16.6	.02
Major bleeding in previous 6 months (%)	4.5	8.1	3.6	.03
Charlson comorbidity index	1.2 + 1.1	1.1 + 1.0	1.2 + 1.1	.94
Cardiac history				
Previous structural heart disease	48.8	44.7	49.9	.31
Heart failure (%)	30.3	26.0	31.5	.24
Coronary disease (%)	19.2	16.3	20.0	.36
Previous acute coronary syndrome (%)	14.5	12.2	15.1	.42
Coronary stents (%)	8.7	7.3	9.1	.54
Dilated cardiomyopathy (%)	6.8	2.4	8.0	.03
Hypertrophic cardiomyopathy (%)	1.4	0.8	1.6	.54
Aortic valvular disease (%)	5.9	4.9	6.2	.58
Hypertensive heart disease (%)	20.4	20.3	20.4	.99
Atrial fibrillation–related information				
Permanent atrial fibrillation (%)	59.8	52.9	61.6	.01
EHRA functional class III-IV (%)	13.1	8.9	14.2	.54
$CHADS_2$ score	2.8 + 1.1	2.9 + 1.2	2.8 + 1.1	.19
CHA_2DS_2-VASc score	4.5 + 1.3	4.7 + 1.3	4.5 + 1.3	.07
HAS-BLED score	2.4 + 0.9	2.4 +1.1	2.4 + 0.9	.63
Examination and diagnostic procedures at initial visit				
Heart rate (bpm)	73.6 +14.6	73.2 + 15.5	73.7 + 14.4	.49
Weight (kg)	72.6 + 11.5	71.6 + 10.3	72.9 + 11.8	.42
Height (cm)	161.5 + 8.5	161.4 + 8.8	161.5 + 8.4	.67
Body mass index (kg/m)	27.9 + 4.1	27.5 + 3.7	27.9 + 4.2	.22
Creatinine clearance (mL/min)	55.6 + 16.8	58.7 + 18.1	54.8 + 16.3	.05
Pharmacologic treatment at inclusion visit				
Diuretics (%)	63.9	56.9	65.9	.07
Aldosterone antagonists (%)	13.6	9.8	14.6	.16
Angiotensin-converting enzyme inhibitors (%)	31.5	29.3	32.2	.54
Angiotensin receptor blockers (%)	40.2	40.7	40.1	.92
Statins (%)	52.1	54.5	51.4	.55
Antiplatelet agents (%)	11.0	14.6	10.0	.14
β-blockers (%)	54.0	50.4	55.0	.37
Digoxin (%)	21.3	22.8	20.8	.64
Calcium antagonists (%)	23.5	29.3	22.0	.22
Anti-arrhythmics use (%)	14.5	15.5	14.2	.73

Abbreviation: EHRA, European Heart Rhythm Association.

[a]Renal failure was considered if glomerular filtration rate was lower than 60 mL/min.

In the comparison between DOACs and VKAs, subgroup analyses of pivotal randomized clinical trials have shown, for patients aged ≥75 years, similar results to the rest of the population included[5-9], and outcomes for patients 80 years or older have been reported by most of them[5,7,8]. In general, these older subgroup of patients presented higher rates of embolic and bleeding events, and all-cause mortality than younger patients. Efficacy was similar for dabigatran rivaroxaban, and edoxaban versus warfarin [5,6,8] and better for apixaban[7]. Safety regarding major bleeding was similar for rivaroxaban[6] and low dose dabigatran[5] versus warfarin, higher with apixaban[7] and edoxaban[8], and lower for the high dose of dabigatran[5], supporting the selection of dabigatran 110 mg twice daily for octogenarian patients. Due to the reduced number of patients receiving each DOAC, we have not been able to do an individualized analysis. However, our overall results appear consistent with clinical trial data regarding comparative effectiveness and safety of DOACs versus VKAs[9].

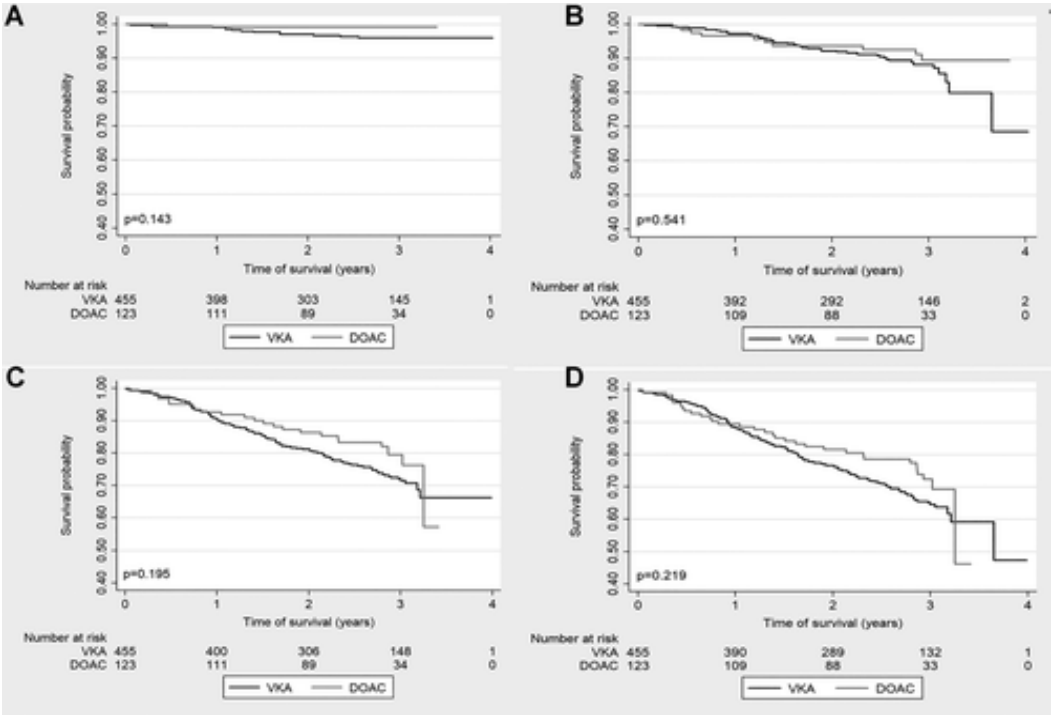

Figure 1. Kaplan–Meier curves for embolic events (A), severe bleedings (B), all-cause mortality (C) and the combined end point of embolic events/severe bleedings/all-cause death (D), according to anticoagulant treatment prescribed at first visit. DOAC indicates direct oral anticoagulant; VKA, vitamin K antagonists

There is some evidence of observational studies on the efficacy and safety of DOACs in elderly patients[10-15]. The designs have been retrospective analysis of administrative databases[10,15]or monocentric prospective[11,12] or retrospective[14] studies, and recently, a prospective, nationwide, multicentric Italian study addressing the specific subgroup of patients aged 80 years or older has been published[13]. However, the results have generally been consistent with those found in our study: Different clinical profile has been reported for elderly patients treated with DOACs versus VKAs[10,12-15], and similar stroke or bleeding risk with both treatments[10,12,13], even for those aged 90 years or older[10], but with benefits for intracranial hemorrhage incidence[10,15]. Rates of embolic events

of 0.9% (95% CI: 0.8-0.9) and major bleeding events of 4.4% (95% CI: 1.7-7.2), similar to those found in our study, have been reported for patients aged 82 ± 6 years with AF treated with DOACs in a monocentric observational prospective study[11]. The Italian multicentric study also found similar figures (1.5% vs 1.3% for embolic events and 3.4% vs 3.7% for severe bleedings in patients receiving DOACs vs VKAs, respectively) in a population of 756 propensity-matched patients with a mean age of 85 ± 3 years, although a benefit in overall survival was observed in this work[13]. Perhaps the larger size of the sample made it possible to detect this difference in mortality that we did not appreciate in our study. Finally, 2 recently published observational retrospective studies [14,15] have reported benefits in overall mortality of DOACs versus VKAs in octogenarian patients, with one of them[14] describing a lower incidence of thromboembolic events and major bleeding, and the other[15], of intracranial hemorrhage and cardiovascular death. Curiously, both of them have been performed in Asian countries, where control of anticoagulation with VKAs has been reported to be suboptimal[22], and this fact could be another possible explanation of the benefit found.

We found that only age and coronary artery disease were associated with embolic events in this sample of anticoagulated patients with AF aged ≥80 years. Previous observational and post hoc analysis of clinical trials including octogenarians[13] and a wider spectrum of age[23,24] have found those variables to be associated with this outcome, as well as other factors, as chronic kidney disease[13], that we have not been able to confirm, possibly due to lack of statistical power. Renal failure, previous severe bleeding, and EHRA functional class II were independently associated with severe bleeding in our study. The first 2 factors have been previously reported as predictors of severe bleeding in anticoagulated patients in the literature[24,25]. As far as we know, EHRA functional class II had not been described as a predictor of bleeding. Finally, age, female sex, diabetes, chronic obstructive pulmonary disease, renal failure, and advanced EHRA functional class were associated with all-cause death, and most of these factors, as well as heart failure and liver dysfunction, with cardiovascular death. Again, although most risk factors had been previously described in the analyses of octogenarians[13] and broader age populations of anticoagulated patients with AF[26,27], this is the first report of advanced EHRA functional class as a strong predictor of allcause mortality in this specific population. Although it is not strange to think that worse symptomatic status can have an adverse prognostic impact, this variable had not been considered in the multivariate analysis of previous studies[13,23,27].

Our study has some strengths. First, the multicenter, nationwide nature of this registry can be representative of the reality of the studied subgroup of patients in our country. Moreover, this is a prospective study with investigators-adjudicated end points, hence overcoming the uncertainties of retrospective administrative databases analysis. On the other hand, main limitations are the limited sample size, which makes it impossible to exclude a significant, albeit small, difference between both treatment groups, and which has precluded an individual drug analysis of results; the absence of patients treated with edoxaban that was not commercially available in Spain during the study period; the selection of physicians with clinical expertise and a special interest in AF to participate in the study, which makes it uncertain if the results might be different had a more general sample of medical doctors been included; the fact that only outpatients were selected, so our results should only be extrapolated very cautiously to frail patients during hospital admissions or cared in hospice facilities; and finally, we must acknowledge that the intergroup differences require consideration. Although we used multivariate analysis to attempt to adjust for these differences, propensity score matching would have been an alternative approach; however, our sample size limits the likely efficacy of this method. Future studies should examine registries with larger sample sizes, including this statistical approach.

Table 2. Rate of Events per 100 Patients/Year According to Anticoagulant Treatment at First Visit

	All Patients	Direct Oral Anticoagulants	Vitamin K Antagonists	P Value	Hazard Ratio (CI 95%)	P Value	Adjusted Hazard Ratio[a] (CI 95%)	P Value	GB statistic P Value
	N/Rate (CI 95%)	N/Rate (CI 95%)	N/Rate (CI 95%)						
Embolic events	15/1.13 (0.68-1.87)	1/0.34 (0.05-2.41)	14/1.35 (0.8-2.28)	.15	0.25 (0.03-1.88)	.18	0.25 (0.03-1.93)	.19	.16
Severe bleeding	55/4.19 (3.22-5.46)	10/3.45 (1.85-6.41)	45/4.41 (3.29-5.9)	.48	0.81 (0.41-1.60)	.54	0.88 (0.44-1.76)	.72	.89
Embolic events/severe bleeding	67/5.19 (4.08-6.59)	11/3.8 (2.11-6.87)	56/5.58 (4.3-7.26)	.24	0.69 (0.36-1.33)	.27	0.74 (0.39-1.43)	.37	.10
Cardiovascular death	59/4.41 (3.42-5.69)	8/2.72 (1.36-5.43)	51/4.89 (3.71-6.43)	.12	0.55 (0.26-1.15)	.11	0.64 (0.30-1.37)	.25	.45
All-cause death	139/10.39 (8.79-12.26)	24/8.15 (5.46-12.16)	115/11.02 (9.18-13.23)	.18	0.75 (0.48-1.16)	.20	0.84 (0.53-1.33)	.46	.36
Embolic events/severe bleeding/all-cause death	175/13.54 (11.68-15.71)	32/11.06 (7.82-15.65)	143/14.26 (12.1-16.8)	.19	0.79 (0.54-1.15)	.22	0.97 (0.65-1.44)	.89	.56

Abbreviations: CI: confidence interval; GB: Grønnesby-Borgan.

[a]Cox proportional hazard method. All models were initially adjusted by age, sex, diabetes mellitus, arterial hypertension, chronic pulmonary obstructive disease, cancer, renal failure, hepatic dysfunction, heart failure, Charlson comorbidity index, coronary disease, previous stroke, previous severe bleeding, left ventricle dysfunction, dilated cardiomyopathy, AF type, European Heart Rhythm Association functional class and anti-arrhythmics use. Backward stepwise regression was used to select variables in the final adjusted models. The criterion to remain in the model was $P < .1$. Variables in the final adjusted models are shown in Table 3.

Table 3. Variables Included in the Final Multivariate Models for Each Event of Interest, Besides Anticoagulant Treatment.

Events and Associated Variables	Hazard Ratio	95% Confidence Interval	P Value
Embolic events			
Age	1.17	1.03-1.32	.02
Coronary disease	3.09	1.09-8.76	.03
Severe bleedings			
Renal failure	2.4	1.4-4.11	.001
Previous severe bleeding	5.11	2.28-11.46	<.001
EHRA functional class II[a]	2.91	1.30-6.52	.009
EHRA functional class III[a]	1.92	0.6-6.14	.27
EHRA functional class IV[a]	0.00		
Embolic events or severe bleedings			
Renal failure	2.19	1.34-3.56	.002
Previous severe bleeding	4.78	2.15-10.66	<.001
EHRA functional class II[a]	2.40	1.21-4.77	.01
EHRA functional class III[a]	1.68	0.60-4.66	.32
EHRA functional class IV[a]	0.00		
Antiarrhythmic treatment	0.38	0.14-1.05	.06
Cardiovascular death			
Age	1.10	1.03-1.18	.007
Diabetes mellitus	2.43	1.43-4.14	.001
Renal failure	2.32	1.37-3.94	.002
Liver dysfunction	.36	1.03-18.45	.046
Heart failure	2.06	1.18-3.6	.01
EHRA functional class II[a]	2.31	0.96-5.54	.06
EHRA functional class III[a]	4.78	1.82-12.58	.002
EHRA functional class IV[a]	0.00		
All-cause death			
Age	1.09	1.04-1.14	<.001
Female sex	0.67	0.47-0.95	.03
Hypertension	1.65	0.94-2.90	.08
Diabetes mellitus	1.59	1.10-2.30	.01
Chronic obstructive pulmonary disease	1.54	1.03-2.31	.04
Renal failure	1.69	1.18-2.40	.004
Previous severe bleeding	1.87	0.93-3.76	.08
Persistent AF[2]	1.09	0.54-2.19	.81
Long-standing persistent AF[b]	2.13	0.95-4.78	.07
Permanent AF[2]	1.62	0.99-2.65	.06
EHRA functional class II[a]	2.19	1.31-3.67	.003
EHRA functional class III[a]	3.91	2.12-7.19	<.001
EHRA functional class IV[a]	18.86	4.13-86.18	<.001
Embolic events, severe bleedings, or all-cause death			
Age	1.08	1.03-1.12	.001
Female sex	0.69	0.51-0.94	.02
Renal failure	1.83	1.34-2.51	<.001
Previous stroke/transient ischemic attack	0.62	0.40-0.96	.03
Charlson index	1.27	1.10-1.47	.001
Previous severe bleeding	2.35	1.32-4.19	.004
EHRA functional class II[a]	1.88	1.22-2.87	.004
EHRA functional class III[a]	3.04	1.79-5.16	<.001
EHRA functional class IV[a]	11.67	2.66-51.14	.001

Abbreviations: AF, atrial fibrillation; EHRA, European Heart Rhythm Association.
[a]Considering EHRA functional class I as reference.
[b]Considering paroxysmal AF as reference.

Conclusion

In this nationwide, “real-world” registry of octogenarian patients with AF, different basal features were found between patients treated with DOACs and those who received VKAs. The differences in major events rates between patients treated with DOACs and VKAs did not reach statistical significance. These results are reassuring in the safety and effectiveness of these drugs in this special population in a daily clinical practice setting.

Author Contributions

Martín Ruiz Ortiz drafted the manuscript, Javier Muñiz performed statistical analysis; both of them and all coauthors made substantial contributions to the concept and design of the work, participated in acquisition and interpretation of data, revised the manuscript for important intellectual content, approved the final version of the manuscript and are able to take public responsibility for the full text of the article.

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