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Net Clinical Benefit of Non-Vitamin K Antagonist vs Vitamin K Antagonist Anticoagulants in Elderly Patients with Atrial Fibrillation

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ABSTRACT

BACKGROUND: The risks of thromboembolic and hemorrhagic events in patients with atrial fibrillation both increase with age; therefore, net clinical benefit analyses of anticoagulant treatments in the elderly population are crucial to guide treatment. We evaluated the 1-year clinical outcomes with non-vitamin-K antagonist and vitamin K antagonist oral anticoagulants (NOACs vs VKAs) in elderly (≥75 years) patients with atrial fibrillation in a prospective registry setting.

METHODS: Data on 3825 elderly patients were pooled from the PREFER in AF and PREFER in AF PROLONGATION registries. The primary outcome was the incidence of the net composite endpoint, including major bleeding and ischemic cardiovascular events on NOACs (n = 1556) compared with VKAs (n = 2269).

RESULTS: The rates of the net composite endpoint were 6.6%/year with NOACs vs 9.1%/year with VKAs (odds ratio [OR] 0.71; 95% confidence interval [CI], 0.51-0.99; $P = .042$). NOAC therapy was associated with a lower rate of major bleeding compared with VKA use (OR 0.58; 95% CI, 0.38-0.90; $P = .013$). Ischemic events were nominally reduced too (OR 0.71; 95% CI, 0.51-1.00; $P = .050$). Major bleeding with NOACs was numerically lower in higher-risk patients with low body mass index (BMI; OR 0.50; 95% CI, 0.22-1.12; $P = .07$) or with age ≥85 years (OR 0.44; 95% CI, 0.13-1.49; $P = .17$).

CONCLUSIONS: Our real-world data indicate that, compared with VKAs, NOAC use is associated with a better net clinical benefit in elderly patients with atrial fibrillation, primarily due to lower rates of major bleeding. Major bleeding with NOACs was numerically lower also in higher-risk patients with low BMI or age ≥85 years.

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KEYWORDS: Atrial fibrillation; Cardiovascular events; Elderly; Major bleeding; Net clinical benefit; NOACs; VKAs

SEE RELATED COMMENTARY, p. 671.

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INTRODUCTION

The prevalence of atrial fibrillation increases with age, and advancing age predisposes to a higher risk of thromboembolic events in patients with this arrhythmia.[1] The progressive aging of the population calls for the need of effective treatment strategies in older populations with atrial fibrillation.[2] The Birmingham Atrial Fibrillation Treatment of the Aged Study trial demonstrated that, compared with aspirin, warfarin use in elderly patients (aged ≥75 years) reduces atrial fibrillation-related thromboembolic complications without significantly increasing the bleeding risk.[3] Recent observational data confirmed that even in a very elderly population (aged ≥85 years) with atrial fibrillation, the benefit of oral anticoagulant (OAC) therapy on thromboembolic events outweighs the hemorrhagic risk.[3,4]

CLINICAL SIGNIFICANCE

- Compared with vitamin K antagonists, non-vitamin K antagonist oral anticoagulant (NOAC) use is associated with a better net clinical benefit in elderly patients with atrial fibrillation.
- This benefit was primarily due to lower rates of major bleeding.
- Major bleeding with NOACs was numerically lower also in higher-risk patients with low body mass index or age ≥85 years.

Despite this evidence, vitamin K antagonists (VKAs) are underused in elderly patients with atrial fibrillation,[5,6] mainly because of safety concerns related to a higher bleeding risk. In randomized trials, the benefit of the newer anticoagulants (non-vitamin K antagonist oral anticoagulants [NOACs]) vs warfarin was apparent regardless of age and maintained in elderly patients.[7] However, concerns on the utilization of NOACs in older patients may exist due to the high prevalence of comorbid conditions, potentially influencing the clinical effects of these agents.[8] Thus, more evidence on NOAC utilization and outcomes in older populations with atrial fibrillation should be welcome to date, where no extensive real-world data are currently available. Moreover, an assessment of the net clinical benefit with different anticoagulant approaches appears crucial in elderly patients with atrial fibrillation, especially in those at higher bleeding risk.

We therefore extracted data on elderly patients (aged ≥75 years) with atrial fibrillation from 2 large, real-world, prospective, European registries, and compared the net clinical outcome with NOACs vs VKAs over 1-year follow-up.

METHODS

Patient Population and Study Design

Individual patient data were obtained from the Prevention of thromboembolic events—European Registry in Atrial Fibrillation (PREFER in AF)[9] and the Prevention of thromboembolic events—European Registry in Atrial Fibrillation PROLONGATION (PREFER in AF PROLONGATION). These registries pooled data from 9 countries (PREFER in AF and PREFER in AF PROLONGATION: Austria, France, Germany, Italy, Spain, Switzerland and the United Kingdom; PREFER in AF PROLONGATION also: Belgium and The Netherlands). PREFER in AF included 7228 patients in 461 centers from January 2012 to January 2014 and PREFER in AF PROLONGATION a total of 4195 patients in 257 institutions from June 2014 to June 2016. PREFER in AF enrolled patients regardless of antithrombotic treatment prior to the wide adoption of the NOACs in Europe (93% of patients on OAC received VKAs and 7% received NOACs); PREFER in AF PROLONGATION, conversely, included only patients on NOACs. In both registries there were no explicit clinical exclusion criteria. Patients received a clinical evaluation at the time of enrollment and at 1-year follow-up. On-site verification of source data was performed at approximately 5% of the sites, randomly selected; this verification provided results consistent with the overall findings. The registries were sponsored by Daiichi Sankyo Europe GmbH (Munich, Germany).

For the purpose of this study, patients not receiving OAC were excluded. The focus was primarily on elderly patients (aged ≥75 years) with atrial fibrillation who were given VKA or NOAC therapy. Patients were included regardless of the type of VKA or NOAC.

Endpoints and Definitions

The primary endpoint was a comparison, among elderly patients, of the net composite endpoint, including both major bleeding and ischemic cardiovascular events (acute coronary syndrome, coronary revascularization, stroke, transient ischemic attack [TIA], systemic embolic event), with NOACs vs VKAs.

Definitions. *Major bleeding:* fatal bleeding or bleeding into a critical organ or clinically relevant bleeding with hemoglobin decrease ≥2 g/dL, consistent with the definition from the International Society on Thrombosis and Haemostasis.[10]

Stroke: abrupt onset of a focal neurologic deficit lasting >24 hours.

TIA: focal neurologic deficit lasting <24 hours.

Systemic embolic event: abrupt arterial insufficiency with documentation of an arterial occlusion; venous thromboembolism and pulmonary embolism were also included in this outcome measure.

Acute coronary syndrome: unstable angina or non-ST-segment elevation myocardial infarction or ST-segment elevation myocardial infarction. These were classified according to the definitions available, respectively, at the time of conduct of the 2 studies.[11,12]

Coronary revascularization: percutaneous coronary intervention or coronary artery bypass surgery for either stable angina or acute coronary syndrome.

Statistics

Continuous variables were reported using either the mean and standard deviation or the median and lower and upper quartiles, as appropriate. Discrete variables were indicated as frequency counts and percentages (n, %). Baseline characteristics between the 2 treatment groups (NOACs vs VKAs) were compared by the chi-squared test for discrete variables and the Wilcoxon rank-sum test for continuous variables.

Odds ratios (OR) and their confidence intervals between patients with and without events were calculated according to the type of OAC (NOACs vs VKAs) by logistic regression, where outcome events were the dependent variables and NOAC treatment Yes/No was the independent variable. We used the covariate adjustment method for the propensity analysis and the propensity score adjustment for all logistic regression models. Specific details on the covariate adjustment process are reported as Supplementary Material on Statistical Analyses (available online). Baseline demographic/clinical characteristics reported in the Case Report Form (n = 44) were initially used as inputs of the stepwise procedure. A total of 20 variables were then selected via a stepwise procedure into the propensity score and the derived propensity score was added to all models as additional adjusting factor. Multivariate models were adjusted for the propensity score and for the following variables: CHA_2DS_2-VASc score, chronic renal failure, left atrial dilatation, chronic obstructive pulmonary disease, and concomitant antiplatelet therapy. As a sensitivity analysis, the' inverse probability of treatment weight method (IPTW) was calculated, based on the inverse of the propensity score, where the propensity score was derived as predictor of NOAC treatment vs VKA treatment.

The weighted net clinical benefit with NOACs vs VKAs was also evaluated, as previously described.[13,14] The 1-year incidence of both ischemic and bleeding events was adjusted for the estimated mortality of each event type. We first calculated the crude incidence rate per 100 patient/years for each type of adverse event with the 2 anticoagulant strategies, and then the net clinical benefit was defined as the weighted sum of these rates in the NOACs minus the weighted sum of these rates in the VKAs group. The lower the value of the result in this calculation, the higher the net clinical benefit of NOACs vs VKAs was assumed to be.

All statistical analyses were performed using the SAS version 9.3 software (SAS Institute Inc., Cary, NC), with a 2-tailed significance value set at .05.

RESULTS

From the pooled populations of the 2 studies (n = 11,423), a total of 3825 elderly patients (aged ≥75 years) represented the object of this investigation (2269 patients on VKAs and 1556 on NOACs). Mean follow-up duration was 12 ± 2 months. A flow diagram showing how the final study population was derived is reported in the **Supplementary Figure** (available online). The **Supplementary Table** (available online) indicates the main characteristics of those 3825 patients included in this analysis vs elderly patients excluded due to lack of follow-up evaluation, definitive OAC interruption, or cross-over from an NOAC to a VKA or vice versa. Overall, we judged the uneven distribution of risk factors in the 2 groups as globally balanced, and therefore not likely to influence the results. The main baseline demographic and clinical characteristics of the 2 treatment groups (NOACs vs VKAs) are indicated in **Table 1**.

Clinical Outcome in Patients Receiving NOACs vs VKAs

The incidence of the net composite endpoint, including major bleeding and ischemic cardiovascular events, was significantly lower in patients receiving NOACs (6.6 per 100 patients/year) compared with those receiving VKAs (9.1 per 100 patients/year), with an adjusted OR of 0.71 (95% confidence interval [CI], 0.51−0.99; $P = .042$) (**Figure 1**). **Table 2** reports the absolute number of patients with events in the 2 groups as to the net composite endpoint and its individual components. Regarding these components, NOAC use was associated with a 42% lower incidence of major bleeding (2.7 vs 3.8 per 100 patients/year with VKAs; adjusted OR 0.58; 95% CI, 0.38-0.90; $P = .013$), mainly nongastrointestinal. Gastrointestinal hemorrhages were not increased in the NOACs group (adjusted OR 0.78; 95% CI, 0.50-1.21; $P = .26$). There were also nominally fewer ischemic cardiovascular events (4.1 vs 5.8 per 100 patients/year; adjusted OR 0.71; 95% CI, 0.51-1.00; $P = .050$), driven by a lower occurrence of cardiac events (acute coronary syndrome or coronary revascularization: adjusted OR 0.63; 95% CI, 0.42-0.97; $P = .045$), without clear differences in other vascular complications (stroke, TIA, or systemic embolic event: adjusted OR 0.84, 95% CI, 0.53-1.34; $P = .45$) (**Figure 1**).

The results on the net clinical outcome were also analyzed according to concomitant antiplatelet therapy. The benefit of NOACs was observed regardless of the use of antiplatelet drugs (patients without antiplatelet treatment: adjusted OR 0.62; 95% CI, 0.45-0.86; $P = .0043$; patients on antiplatelet treatment: adjusted OR 0.75; 95% CI, 0.39-1.42; $P = .38$) (P for interaction = .96). We also performed an exploratory analysis on the net composite endpoint with different NOACs vs VKAs; adjusted ORs were 0.73 (95% CI, 0.46-1.15) for dabigatran, 0.58 (95% CI, 0.40-0.86) for rivaroxaban, and 0.73 (95% CI, 0.45-1.20) for apixaban, without significant interaction (P for interaction = .32), but such analysis is admittedly affected by the low number of patients (**Figure 2**).

The net clinical outcome was also explored in very elderly patients (aged ≥85 years, n = 658). Here the

Table 1 Distribution of Demographic and Clinical Characteristics in Elderly Patients (Age ≥75 Years) Receiving NOACs or VKAs

Variable	NOACs (n = 1556)	VKAs (n = 2269)	*P* Value
Age (years)	80.5 ± 4.2	80.3 ± 4.1	.23
Female sex	752 (48)	1,061 (47)	.22
BMI (kg/m^2)	27.0 ± 4.1	27.1 ± 4.4	.72
Systemic hypertension	1256 (81)	1805 (80)	.48
sBP*	134.92 ± 15.96	132.96 ± 16.50	.0003
dBP*	77.66 ± 9.70	76.75 ± 10.01	.0129
Congestive heart failure*	424 (27)	776 (35)	< .0001
CHA_2DS_2-VASc*	4.34 ± 1.31	4.51 ± 1.39	.0010
HAS-BLED*	2.26 ± 0.98	2.38 ± 1.02	.0013
EHRA score*	2.45 ± 0.91	2.71 ± 0.89	< .0001
Left ventricular ejection fraction*	58.7 ± 9.9	56.2 ± 11.7	< .0001
Prior TIA/stroke/thromboembolism	303 (20)	434 (19)	.93
Vascular disease*	256 (18)	575 (27)	< .0001
Chronic renal failure *	410 (27)	426 (19)	< .0001
Creatinine clearance (mL/min)*	50.48 ± 15.92	42.23 ± 14.12	< .0001
Left atrial dilatation (diameter >40 mm)*	847 (64)	1469 (78)	< .0001
Chronic obstructive pulmonary disease*	163 (11)	299 (13)	.0101
Hepatic disease	17 (1.1)	34 (1.5)	.2745
Concomitant antiarrhythmic drugs*	799 (51)	1304 (57)	.0002
Antiplatelet therapy	213 (14)	274 (12)	.1415
Type of VKA			
Warfarin	–	964 (43)	NA
Other	–	1305 (57)	NA
Type of NOAC			
Dabigatran	428 (27)	–	NA
Rivaroxaban	772 (50)	–	NA
Apixaban	356 (23)	–	NA

BMI = body mass index; CHA_2DS_2-VASc = Congestive heart failure, Hypertension, Age 75 years, Diabetes mellitus, prior Stroke, TIA, or thromboembolism, Vascular disease, Age 65-74 years, Sex category; dBP = diastolic blood pressure; EHRA = European Heart Rhythm Association; HAS-BLED = Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile international normalized ratio, Elderly, Drugs or alcohol; NOAC = non-vitamin K antagonist oral anticoagulant; sBP = systolic blood pressure; TIA = transient ischemic attack; VKA = vitamin K antagonist.

*Items differing significantly (P < .05) between the NOAC and the VKA groups.Values are given as n (%) or mean ± SD.

distribution of the baseline characteristics in the 2 treatment groups (NOACs vs VKAs) (**Table 3**) was similar to that of the overall elderly population. The clinical benefit of NOAC therapy was maintained in the subgroup aged ≥85 years, where the incidence of the net composite endpoint with NOACs was not significantly lower, due to the reduced number of patients and events (8.5 vs 9.4 per 100 patients/year with VKAs, adjusted OR 0.65; 95% CI, 0.33−1.28; *P* = .21). In the subgroup of patients aged ≥85 years there was a trend toward decreased major bleeding with NOAC use, but this was not significant, potentially due to the low number of patients and events (adjusted OR 0.44; 95% CI, 0.13-1.49; *P* = .17) (**Figure 3**). There was no difference in major bleeding reduction by NOACs in patients aged ≥85 years compared with those aged <85 years (*P* for interaction = 0.50). In patients aged 75-84 years, the adjusted OR for the net composite endpoint was 0.71 (95% CI, 0.52-0.98; *P* = .043) in favor of NOACs.

We also investigated the weighted net clinical benefit. In patients aged ≥75 years, the net clinical benefit, adjusted for the estimated mortality of each event type, tended to favor NOACs, but this did not achieve statistical significance (−1.74%; 95% CI, −4.26-0.08%; *P* = .055). Consistent results were found in the subgroup with age ≥85 years (−0.71%; 95% CI, −3.63-2.21; *P* = .39), without difference vs patients with age <85 years (*P* for interaction = 0.74).

The risk of major hemorrhages was then evaluated as a function of body mass index (BMI). The effect on hemorrhagic outcome was maintained in patients with BMI in the first quartile (<24.7 kg/m^2; n = 1103), where, compared with VKA use, NOAC utilization confirmed a lower occurrence of major bleeding (adjusted OR 0.50; 95% CI, 0.22-1.12; *P* = .07) (**Figure 3**). ORs for major bleeding were 0.55 (95% CI, 0.19-1.51; *P* = .24) in the second quartile, 1.09 (95% CI, 0.42-2.86; *P* = .92) in the third quartile, and 0.29 (95% CI, 0.09-0.96; *P* = .043) in the fourth quartile. There was no difference when evaluating the risk of hemorrhage across BMI categories (*P* for interaction = 0.67).

All the above-mentioned analyses on clinical outcomes with NOACs vs VKAs were then performed by the IPTW method; analyses with IPTW confirmed the results obtained by the covariate adjustment method (see Supplementary Material on Statistical Analyses, available online). To clarify

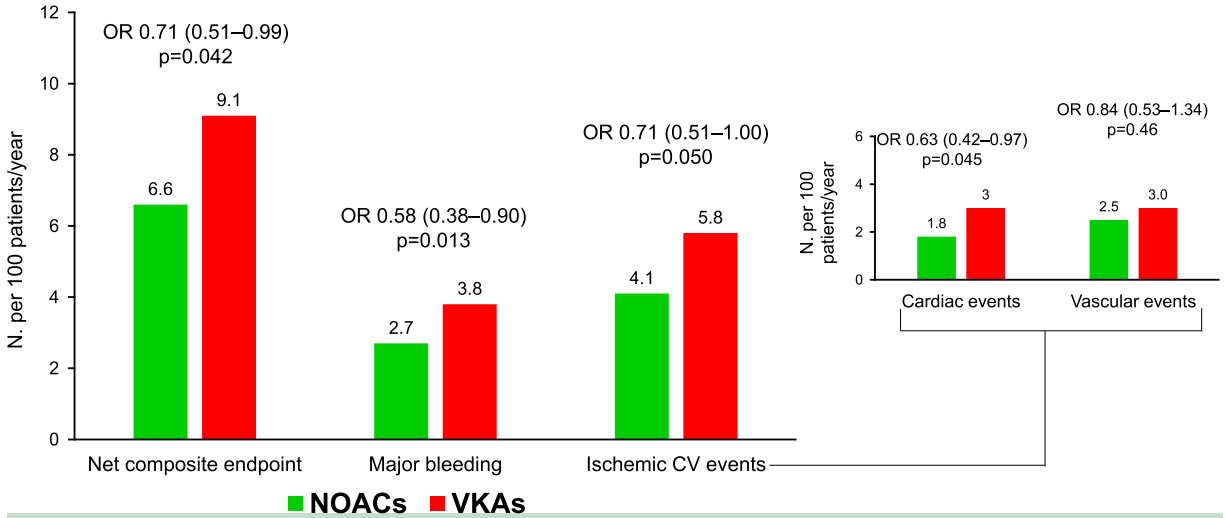

Figure 1 Incidence and related adjusted odds ratios (OR) for the net composite endpoint* and its individual components in patients receiving NOACs or VKAs. CV = cardiovascular; NOACs = non-vitamin K antagonist oral anticoagulants; VKAs = vitamin K antagonists.
*The net composite endpoint included major bleeding and ischemic cardiovascular events (cardiac events [acute coronary syndrome, coronary revascularization] + vascular events [stroke, transient ischemic attack, systemic embolic events]).

a possible confounding issue due to different countries involved in the 2 registries, we also performed an additional sensitivity analysis whereby patients from the 2 countries not included in both registries (Belgium and The Netherlands, n = 99 − 2.6% of patients) were excluded. In this sensitivity analysis, results were consistent with the overall analysis (see Supplementary Material on Statistical Analyses).

DISCUSSION

The present analysis from 2 real-world European registries indicated that, among elderly patients with atrial fibrillation, NOAC use was associated with improved net clinical benefit compared with VKAs. This was mainly driven by lower rates of major bleeding, but was also accompanied by a nominally lower rate of ischemic events, especially cardiac events. The better safety outcome with NOACs was maintained in patients with more advanced age and in those with low BMI.

Although there is now already a robust indication for OAC in the prevention of atrial fibrillation-related thromboembolic events in older populations, the real-world penetration of anticoagulation in this setting of patients is low.[5,6] This is due to an over-representation of VKA limitations in older populations, including drug −drug interactions, unsatisfactory time in therapeutic range, low adherence and perceived bleeding risk related to the propensity of falling, reduced body weight, and impaired renal function.[5,6,15] Thus, there is an urgent need for the implementation of stroke prevention strategies alternative to VKAs to balance ischemic protection and hemorrhagic risk in older populations.

NOACs are now available in clinical practice. A pooled analysis of phase III studies on NOACs in patients with

Table 2 Number of Elderly Patients (%) with Events at 1-Year Follow-Up in the 2 Groups for the Primary Net Composite Endpoint and its Individual Components

	NOACs n = 1556	VKAs n = 2269
Primary net composite endpoint	99 (6.6)	207 (9.1)
Major bleeding	40 (2.7)	85 (3.8)
Vascular events (Stroke/TIA/systemic embolism)	37 (2.5)	67 (3.0)
Stroke	14 (0.9)	21 (0.9)
TIA	20 (1.3)	36 (1.6)
Systemic embolism	5 (0.3)	13 (0.6)
Cardiac events (ACS, coronary revascularization)	27 (1.8)	69 (3.0)
ACS	20 (1.3)	37 (1.6)
Coronary revascularization	19 (1.2)	47 (2.1)

ACS = acute coronary syndrome; NOACs = non-vitamin K antagonist oral anticoagulants; TIA = transient ischemic attack; VKAs = vitamin K antagonists.

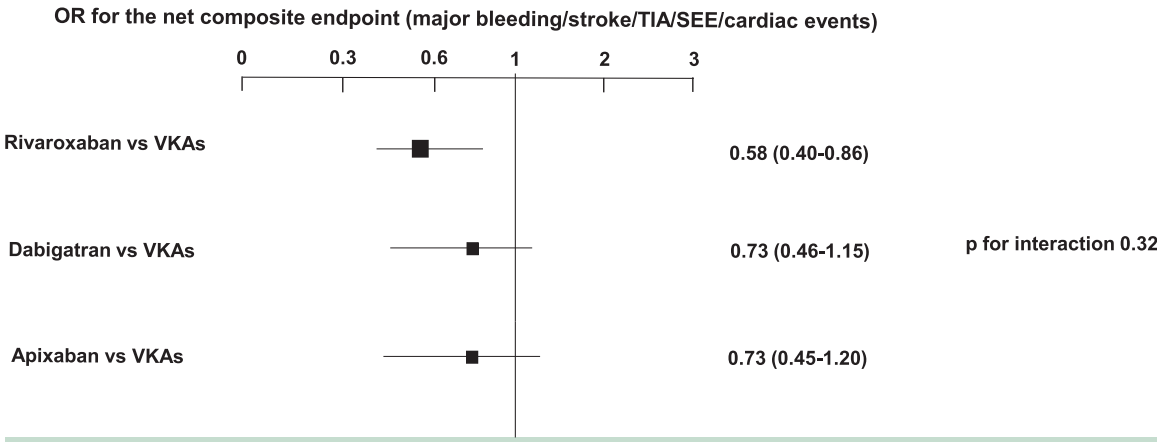

Figure 2 Analysis on the net composite endpoint with different NOACs vs VKAs. NOACs = non-vitamin K antagonist oral anticoagulants; OR = odds ratio; SEE = systemic embolic events; TIA = transient ischemic attack; VKAs = vitamin K antagonists.

atrial fibrillation found no interaction between clinical benefit of these agents vs warfarin and age.[7,16-19] Moreover, in a meta-analysis on elderly patients with atrial fibrillation, NOACs were more effective than conventional therapy in preventing thromboembolic events, without bleeding excess.[20] However, available data on NOACs in older

Table 3 Distribution of Demographic and Clinical Characteristics in Very Elderly Patients (Age ≥85 Years) Receiving NOACs or VKAs

Variable	NOACs (n = 296)	VKAs (n = 362)	*P* Value
Age (years)	87.3 ± 2.2	87.2 ± 2.4	.21
Female sex	173 (58)	197 (54)	.30
BMI (kg/m^2)	26.1 ± 3.9	25.6 ± 3.9	.19
Systemic hypertension	244 (83)	282 (79)	.23
sBP*	136.13 ± 15.73	133.17 ± 17.75	.0231
dBP	76.67 ± 9.31	75.30 ± 10.44	.1444
Congestive heart failure*	86 (29)	156 (44)	< .001
CHA_2DS_2-VASc	4.58 ± 1.34	4.72 ± 1.45	.22
HAS-BLED	2.53 ± 1.01	2.40 ± 1.04	.14
EHRA score*	2.59 ± 0.90	2.84 ± 0.88	< .001
Left ventricular ejection fraction*	58.4 ± 10.0	56.0 ± 12.4	.020
Prior TIA/stroke/thromboembolism	76 (26)	79 (22)	.26
Vascular disease*	50 (19)	103 (30)	.001
Chronic renal failure*	106 (36)	85 (24)	< .001
Creatinine clearance*	42.79 ± 13.16	36.09 ± 11.52	.0023
Left atrial dilatation (diameter >40 mm)*	169 (68)	242 (81)	< .001
Chronic obstructive pulmonary disease*	28 (10)	54 (15)	.033
Hepatic disease	3 (1.0)	6 (1.7)	.4748
Concomitant antiarrhythmic drugs	160 (54)	192 (53)	.7950
Antiplatelet therapy	49 (17)	47 (13)	.1968
Type of VKA			
Warfarin	—	150 (41)	NA
Other	—	212 (59)	NA
Type of NOAC			
Dabigatran	76 (26)	—	NA
Rivaroxaban	138 (46)	—	NA
Apixaban	82 (28)	—	NA

Values are given as n (%) or mean ± SD.

BMI = body mass index; CHA2DS2-VASc = Congestive heart failure, Hypertension, Age 75 years, Diabetes mellitus, prior Stroke, TIA, or thromboembolism, Vascular disease, Age 65-74 years, Sex category; dBP = diastolic blood pressure; EHRA = European Heart Rhythm Association; HAS-BLED = Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile international normalized ratio, Elderly, Drugs or alcohol; NOAC = non-vitamin K antagonist oral anticoagulant; sBP = systolic blood pressure; TIA = transient ischemic attack; VKA = vitamin K antagonist.

*Items significantly differing between the 2 populations investigated.

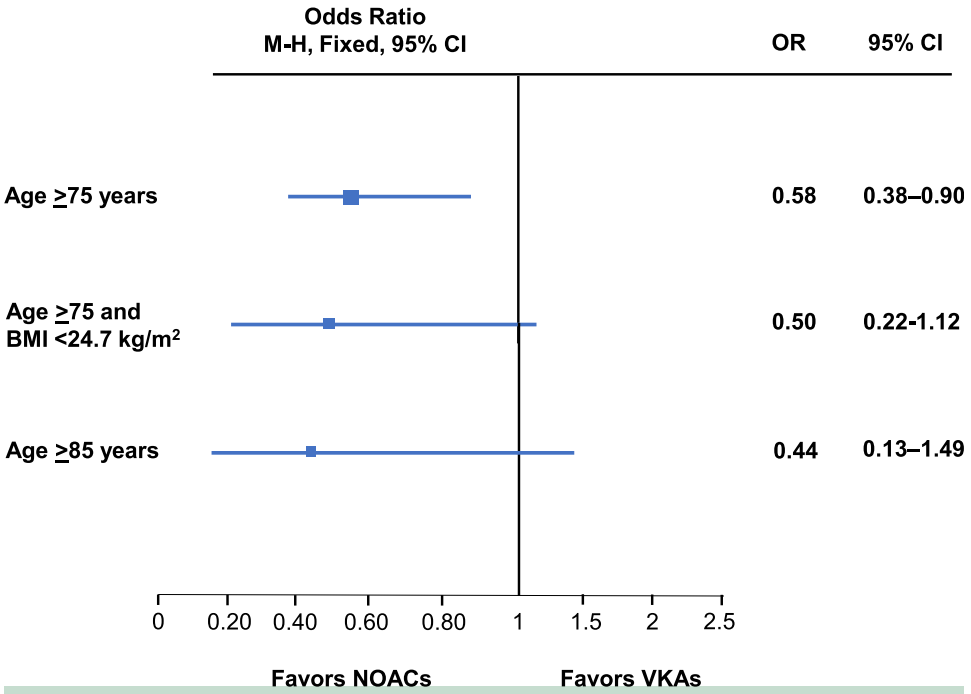

Figure 3 Odds ratios (OR) for major bleeding with NOACs vs VKAs in elderly patients (aged ≥75 years), elderly patients with BMI <24.7 kg/m^2, and very elderly patients (aged ≥85 years). BMI = body mass index; NOACs = non-vitamin K antagonist oral anticoagulants; VKAs = vitamin K antagonists.

populations with atrial fibrillation are essentially derived from subgroup analyses of randomized studies that, although often prespecified, have included low numbers of patients. Moreover, various conditions at high prevalence in older populations may impact on the efficacy, and mainly on the safety of NOACs, for example, hypoalbuminemia, fluctuations of renal function, low body weight, and propensity to gastrointestinal bleeding. Thus, real-world data on the topic are needed. A small observational study showed low event rates with NOACs in elderly patients switched from other antithrombotic treatments.[21] Indeed, real-world evidence focused on the net clinical outcome of NOAC utilization in advancing age populations is relevant to address current concerns and better define the specific role of such agents in this expanding setting of patients. The analysis here presented is consistent with this need.

The present study pooled data from 2 multicenter, real-world registries (PREFER in AF and PREFER in AF PROLONGATION) and evaluated the net clinical benefit at 1 year with NOACs vs VKAs in elderly patients with atrial fibrillation. NOAC use led to a significantly lower incidence of the net composite endpoint, including major bleeding and cardiovascular events, compared with VKAs. This was primarily driven by a 42% lower rate of major bleeding. Consistent results were observed in the analysis on the weighted net clinical benefit, adjusted for the estimated mortality of each adverse event type. NOACs were prescribed at the time of the PREFER in AF registries to less-sick patients. Our results on outcome with the 2 anticoagulant approaches needed, therefore, to be adjusted for possible confounders, although the nonrandomized nature of the source data preclude absolute certainty on conclusions to be derived from this approach. Of note, this better safety of NOACs was regardless of concomitant antiplatelet therapy; the higher bleeding risk carried by the concomitant antiplatelet therapy and the high prevalence of the association OAC plus antiplatelet treatment underscored the need to limit this combination therapy to situations where it is really needed.[22] Elderly patients are at higher risk of gastrointestinal bleeding, and in randomized trials an increased incidence of gastrointestinal bleeding was observed with rivaroxaban, high-dose dabigatran, and high-dose edoxaban vs warfarin.[19,23] Importantly, no excess of gastrointestinal hemorrhages in elderly patients receiving the newer anticoagulants has emerged from our analysis. Our findings are in line with recent real-world data from Taiwan indicating that NOACs use in patients aged ≥90 years was associated with lower rates of intracranial hemorrhage and similar stroke rates as warfarin.[24]

In the NOAC group we also observed a significantly lower occurrence of ischemic cardiovascular complications, mainly cardiac events. Although our analysis was adjusted for available variables that could potentially influence the risk of cardiovascular events, this finding may still be due to confounders not captured by the risk variables collected in the registries. Of note, in the ROCKET-AF trial the rates of

cardiac events were lower in patients assigned to rivaroxaban compared with warfarin,[25] consistent with our findings. The apparently better coronary protection with NOACs in our study is intriguing, but has to be taken with a word of caution and would merit confirmation.

We also evaluated the clinical outcome with the 2 anticoagulant strategies in subgroups at even higher bleeding risk, such as elderly patients with concomitant low BMI and very elderly patients (aged ≥85 years). The improved safety outcome with NOACs was maintained also in patients with the lowest BMI, where the occurrence of major bleeding with the newer agents was 50% lower. Moreover, we found that very elderly patients, when receiving NOACs instead of VKAs, had a 56% relative reduction of major bleeding.

Our study has strengths and limitations. Both registries were prospective investigations on atrial fibrillation patients receiving a complete baseline assessment and a planned follow-up visit at 1 year, with accurate evaluation of treatments and endpoints. Channeling bias or bias in patient enrollment and treatment decision cannot be excluded, although recruitment of consecutive patients at each center was mandatory. No specific information on adherence and persistence with therapy was available, although compliance was assessed during follow-up visits and those few patients who had definitely stopped OAC were excluded. No data on international normalized ratio (INR) control in VKA-treated patients were available. However, INR control was assessed by collecting the last 3 INR measurements prior to enrollment; these pre-enrollment, repeated, INR detections may be inadequate due to the large INR variability over time, although these measurements were reported to be a reliable proxy for the time in therapeutic range.[26] An adequate INR control (ie, at least 2 of 3 INR values in the therapeutic range) was demonstrated in 72% of the overall population. Only cardiology institutions participated in the registries, and therefore, very frail patients (ie, residents in nursing homes with multiple comorbidities and major functional disabilities) were not included. Moreover, no outcome data on patients receiving edoxaban may be obtained. Finally, our results were adjusted for possible confounding variables, but residual confounding cannot be excluded; nevertheless, an estimation of the impact of a potential unmeasured confounder on the outcome measures suggests that it is unlikely such a confounder alone could have driven the results.

In conclusion, our study shows that, compared with VKAs, NOAC use is associated with a lower incidence of major bleeding in elderly patients with atrial fibrillation. Protection from cardiovascular events was also more prominent with the NOACs, with the safety benefits providing the greatest contribution to the improved net clinical outcome observed in the NOAC group. Moreover, NOAC utilization overcomes intrinsic limitations of VKAs that are highly prevalent in older populations. Thus, logical considerations and evidence-based data both make NOACs the anticoagulant drugs of choice in elderly patients, here achieving the best net clinical benefit.

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Authorship: All investigators contributing to the study are listed as authors. All listed auhtors contributed to the study. In particular: GP: designed the study; performed the interpretation of the results; drafted the paper. LP: performed the analysis; reviewed the paper ML: contributed to data collection. KH, MR, GR, JSM, FR, PK and RDC: provided critical revision of the paper for important intellectual content.

SUPPLEMENTARY MATERIAL

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.amjmed.2018.12.036.

DETAILS ON THE COVARIATE ADJUSTMENT PROCESS

The following baseline demographic/clinical characteristics reported in the Case Report Form (n = 44) were initially used as inputs of the stepwise procedure:

1	AF type
2	Maximum EHRA score
3	Antiarrhythmic drug
4	Vascular disease
5	Chronic renal insufficiency
6	Left atrial dilatation
7	Previous other ischemic-thromboembolic event
8	Arterial hypertension
9	HAS-BLED score
10	Age
11	Cardioversion
12	Previous ischemic stroke
13	Previous ischemic stroke/TIA/other thromboembolic event
14	Previous TIA
15	Reduced left ventricular function
16	Heart failure
17	Antiplatelet drug
18	Dyslipidemia
19	Coronary heart disease (CHD) OR Peripheral artery disease (PAD) OR myocardial infarction (MI)
20	Systolic blood pressure
21	Diastolic blood pressure
22	Gender
23	Ablation (pulmonary vein isolation)
24	Previous myocardial infarction
25	Chronic hepatic disease
26	Diabetes mellitus
27	Obesity (BMI >30)
28	BMI
29	Chronic obstructive pulmonary disease
30	Current smoker
31	Previous smoker
32	Any smoking (current or previous)
33	Hyperthyroidism
34	Heart valve dysfunction
35	Coronary heart disease (CHD)
36	Chronic heart insufficiency
37	Reduced left ventricular function
38	Peripheral artery disease (PAD)
39	Left ventricular ejection fraction
40	Current heart rhythm
41	CHA_2DS_2-VASc score
42	$CHADS_2$ score
43	Alcohol abuse
44	Weight

Of course, not all those 44 baseline characteristics were selected via stepwise procedure into the propensity score (PS). The following 20 variables were selected via a stepwise procedure into the PS:

Summary of Stepwise Selection							
	Effect						
Step	Entered	Removed	DF	Number In	Score Chi-Squared	Wald Chi-Squared	Pr > ChiSq
1	AF type		3	1		218.9979	< .0001
2	Maximum EHRA score		1	2		103.2338	< .0001
3	Antiarrhythmic drug		1	3		46.6609	< .0001
4	Vascular disease		1	4		48.1339	< .0001
5	Chronic renal insufficiency		1	5		50.9278	< .0001
6	Left atrial dilatation		1	6		38.6998	< .0001
7	Previous other ischemic-thromboembolic event		1	7		33.7989	< .0001
8	Arterial hypertension		1	8		18.5104	< .0001
9	HAS-BLED score		1	9		37.1147	< .0001
10	Age		1	10		19.8497	< .0001
11	Cardioversion		1	11		14.6368	.0001
12	Previous ischemic stroke		1	12		8.8477	.0029
13	Previous ischemic stroke/TIA/other thromboembolic event		1	13		10.7021	.0011
14	Previous TIA		1	14		23.7044	< .0001
15	Reduced left ventricular function		1	15		7.8787	.0050
16	Heart failure		1	16		14.2966	.0002
17	Antiplatelet drug		1	17		7.7806	.0053
18	Dyslipidaemia		1	18		4.9385	.0263
19	Coronary heart disease (CHD) OR Peripheral artery disease (PAD) or myocardial infarction (MI)		1	19		5.2008	.0226
20	Systolic blood pressure		1	20		5.2559	.0219

The PS (conditional probability of being assigned to a NOAC vs being assigned to VKA at an observed set of covariates) was the following:

PROPENSITY SCORE (PS), estimating NOAC treatment vs VKA treatment probability =

+ AF type (Paroxysmal 0, Persistent -0.3147, Long-standing persistent -1.1332, Permanent -0.9997)
+ Maximum EHRA score −0.3264
+ Antiarrhythmic drug −0.3626
+ Vascular disease −0.6972
+ Chronic renal failure 0.9145
+ Left atrial dilatation −0.4547
+ Previous other ischemic-thromboembolic event 1.1345
+ Arterial hypertension 0.5108
+ HAS-BLED score −0.3542
+ Age 0.0133
+ Cardioversion −0.2551
+ Previous ischemic stroke 1.2111
+ Previous ischemic stroke/TIA/other thromboembolic event −1.1653
+ Previous TIA 0.8340
+ Reduced left ventricular function −0.5613
+ Heart failure 0.4150
+ Antiplatelet therapy 0.3093
+ Dyslipidemia −0.1603
+ Coronary heart disease (CHD) or peripheral arterial disease (PAD) or myocardial infarction (MI) 0.2643
+ Systolic blood pressure 0.00426

The probability to be treated by NOACs was PS_prob=1/[1+exp(−PSscore)]. The abovementioned derived PS was added to all models as additional adjusting factor. Multivariate models were not adjusted for all 44 baseline characteristics or for those 20 baseline characteristics selected into the PS.

Based on a combination of medical reasons and statistical analyses of all possible confounding effects from all baseline characteristics, the following variable were selected as adjusting factors: CHA_2DS_2-VASc score, chronic renal failure, left atrial dilatation, chronic obstructive pulmonary disease, concomitant antiplatelet therapy. Interaction of each of these parameters with treatment effect (NOACs vs VKAs) was assessed, but none interaction was significant or remarkable.

Regression adjustment was done using PROC LOGISTIC, where the treatment effect (NOACs vs VKAs) for the abovementioned covariates was included into the model: *PROC LOGISTIC data=AF_registries; Class trt (REF=' VKAs') renal_failure (REF=' No') left_atrial_dilat (REF=' No') COPD (REF=' No') antiplatelets (REF=' No'); Model FU_outcome (event='Yes') = trt CHADSVASc*

renal_failure left_atrial_dilat COPD antiplatelets / link=-logit rsquare; run.

Multivariate models were adjusted for the PS and for the following variables: CHA_2DS_2-VASc score, chronic renal failure, left atrial dilatation, chronic obstructive pulmonary disease and concomitant antiplatelet therapy. Thus, after adding the PS into adjustment factors, the real coefficient of each adjustment factor is a sum of its coefficient at the PS and its coefficient as additional adjusting factor.

INVERSE PROBABILITY OF TREATMENT WEIGHTING ANALYSIS

The inverse probability of treatment weight (IPTW) was calculated as the inverse of the propensity score (PS) (*Hogan, J.W., Lancaster, T. 2004. "Instrumental variable and propensity weighting for causal inference from longitudinal observational studies". Statistical Methods in Medical Research 13: 17-48*), according to the propensity PS_prob to be on NOACs vs VKAs. For those patients who were not on NAOCs, the PS would be 1- PS_prob and the PS weight would be the inverse of 1- PS_prob. According to the abovementioned paper (Hogan JW, et al):

- If trt=' NOACs' then PS_weight=1/ PS_prob;
- If trt=' VKAs' then PS_weight=1/(1- PS_prob);

This PS-weighted logistic linear regression model using PROC LOGISTIC procedure was then fitted to compare NOACs use on the outcome events vs VKAs use effect:

proc logistic data=AF_registries; Class trt (REF=' VKAs'); Model FU_outcome (event='Yes') = trt / expb link=logit rsquare; Weight PS_weight; run

Results of the IPTW analysis:

IPTW Odds Ratio Estimates — NOACs vs VKAs

	Point Estimate	95% Wald Confidence Limits		*P* Value
Net composite endpoint (age ≥75 years)	0.727	0.595	0.889	.0019
Major bleeding (age ≥75 years)	0.772	0.576	1.034	.0824
Ischemic cardiovascular events (age ≥75 years)	0.892	0.759	1.048	.1630
Ischemic cardiac events (age ≥75 years)	0.896	0.581	1.383	.6211
Ischemic vascular events (age ≥75 years)	0.859	0.727	1.015	.0742
Gastro-intestinal bleeding (age ≥75 years)	0.730	0.479	1.113	.1435
Net composite endpoint (age ≥75 years) in patients not receiving antiplatelet therapy	0.734	0.587	0.917	.0065
Net composite endpoint (age ≥75 years) in patients receiving antiplatelet therapy	0.683	0.430	1.085	.1063
Net composite endpoint (age ≥85 years)	0.376	0.216	0.656	.0006
Major bleeding (age ≥85 years)	0.249	0.085	0.726	.0109
Major bleeding (age ≥75 years in the first BMI quartile)	0.700	0.413	1.187	.1853
Major bleeding (age ≥75 years in the second BMI quartile)	0.429	0.225	0.819	.0103
Major bleeding (age ≥75 years in the third BMI quartile)	1.353	0.806	2.271	.1248
Major bleeding (age ≥75 years in the fourth BMI quartile)	0.545	0.300	0.991	.0465
Net composite endpoint (age ≥75 years, rivaroxaban vs VKAs)	0.663	0.517	0.851	.0012
Net composite endpoint (age ≥75 years, dabigatran vs VKAs)	0.873	0.659	1.156	.3441
Net composite endpoint (age ≥75 years, apixaban vs VKAs)	0.738	0.529	1.030	.0744
Weighted net clinical benefit (age ≥75 years)				.0367
Weighted net clinical benefit (age ≥85 years)				.0669

Additional sensitivity analysis on 3726 patients, whereby patients from countries not included in both registries were excluded (Belgium and The Netherlands, n = 99 patients).

Covariate Adjustment: Odds Ratio Estimates — NOACs (n = 1457) vs VKAs (n = 2269)				
	Point Estimate	95% Wald Confidence Limits		*P* Value
Net composite endpoint (age ≥75 years)	0.66	0.50	0.89	.006
Major bleeding (age ≥75 years)	0.51	0.32	0.81	.004
Ischemic cardiovascular events (age ≥75 years)	0.72	0.51	1.00	.050
Ischemic cardiac events (age ≥75 years)	0.64	0.32	1.29	.212
Ischemic vascular events (age ≥75 years)	0.67	0.52	0.86	.002
Gastro-intestinal bleeding (age ≥75 years)	0.50	0.25	0.98	.043
Net composite endpoint (age ≥75 years) in patients not receiving antiplatelet therapy	0.66	0.48	0.91	.012
Net composite endpoint (age ≥75 years) in patients receiving antiplatelet therapy	0.69	0.36	1.36	.285
Net composite endpoint (age ≥85 years)	0.67	0.34	1.32	.246
Major bleeding (age ≥85 years)	0.55	0.19	1.58	.228
Major bleeding (age ≥75 years in the first BMI quartile)	0.43	0.18	1.04	.062
Major bleeding (age ≥75 years in the second BMI quartile)	0.43	0.17	1.12	.085
Major bleeding (age ≥75 years in the third BMI quartile)	1.30	0.44	3.82	.635
Major bleeding (age ≥75 years in the fourth BMI quartile)	0.46	0.18	1.23	.122
Weighted net clinical benefit (age ≥75 years)				.049
Weighted net clinical benefit (age ≥85 years)				.488

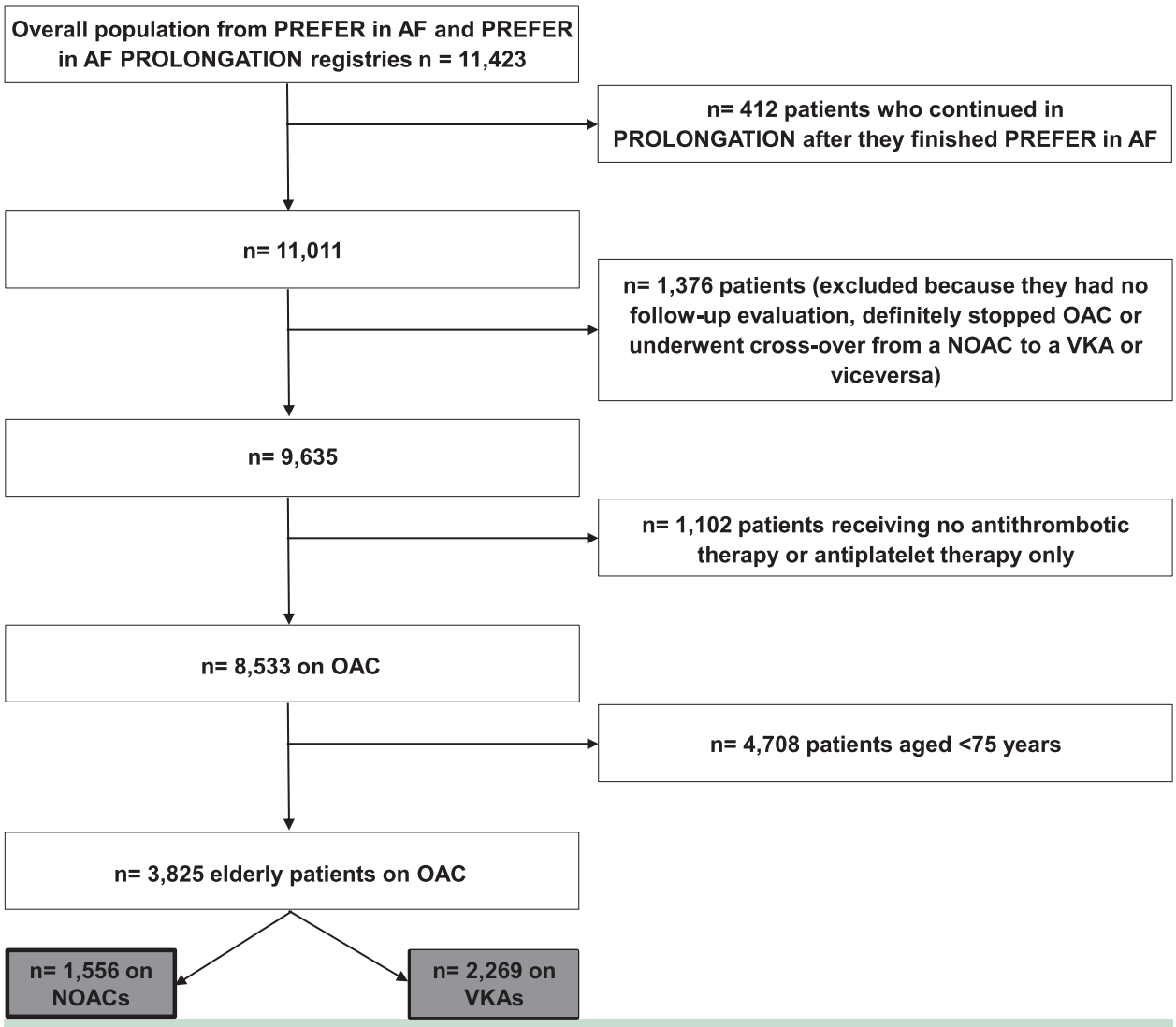
Supplementary Table Demographic and Clinical Characteristics of Elderly Patients Included in the Study vs Elderly Patients Excluded from the Analysis

Variable	Patients Included (n = 3852)	Patients Excluded (n = 1079)	*P* Value
Age (years)	80.4 ± 4.1	81.1 ± 4.4	< .0001
Female sex	1813 (47)	560 (52)	.0082
BMI (kg/m^2)	27.1 ± 4.3	27.0 ± 4.4	.2582
Systemic hypertension	3061 (80)	862 (81)	.8349
sBP	133.68 ± 16.34	133.29 ± 18.29	.1444
dBP	77.07 ± 9.91	76.81 ± 10.72	.4667
Congestive heart failure	1200 (32)	298 (29)	.0468
CHA_2DS_2-VASc	4.44 ± 1.36	4.44 ± 1.35	.7961
HAS-BLED	2.34 ± 1.01	2.53 ± 0.98	< .0001
EHRA Score	2.61 ± 0.91	2.67 ± 0.90	.0544
Left ventricular ejection fraction	57.2 ± 11.1	56.7 ± 11.0	.0824
Prior TIA/stroke/thromboembolism	737 (19)	161 (15)	.0021
Vascular disease	831 (24)	226 (25)	.5097
Chronic renal failure	836 (22)	235 (22)	.9538
Left atrial dilatation (diameter >40 mm)	2316 (72)	603 (65)	< .0001
Chronic obstructive pulmonary disease	462 (12)	150 (14)	.0729

Values are given as n (%) or mean ± SD.

BMI = body mass index; CHA2DS2-VASc = Congestive heart failure, Hypertension, Age 75 years, Diabetes mellitus, prior Stroke, TIA, or thromboembolism, Vascular disease, Age 65-74 years, Sex category; dBP = diastolic blood pressure; EHRA = European Heart Rhythm Association; HAS-BLED = Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile international normalized ratio, Elderly, Drugs or alcohol; sBP = systolic blood pressure; TIA = transient ischemic attack.

*Items differing significantly ($P < .05$).



Supplementary Figure Flow diagram showing how the final study population was derived from the 2 registries. NOACs = non-vitamin K antagonist oral anticoagulants; OAC = oral anticoagulant therapy; VKAs = vitamin K antagonists.