ORIGINAL RESEARCH

Bleeding risk with rivaroxaban compared with vitamin K antagonists in patients aged 80 years or older with atrial fibrillation

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ABSTRACT

Objective Direct oral anticoagulants have been evaluated in the general population, but proper evidence for their safe use in the geriatric population is still missing. We compared the bleeding risk of a direct oral anticoagulant (rivaroxaban) and vitamin K antagonists (VKAs) among French geriatric patients with non-valvular atrial fibrillation (AF) aged ≥80 years.

Methods We performed a sequential observational prospective cohort study, using data from 33 geriatric centres. The sample comprised 908 patients newly initiated on VKAs between September 2011 and September 2014 and 995 patients newly initiated on rivaroxaban between September 2014 and September 2017. Patients were followed up for up to 12 months. One-year risks of major, intracerebral, gastrointestinal bleedings, ischaemic stroke and all-cause mortality were compared between rivaroxaban-treated and VKA-treated patients with propensity score matching and Cox models.

Results Major bleeding risk was significantly lower in rivaroxaban-treated patients (7.4/100 patient-years) compared with VKA-treated patients (14.6/100 patient-years) after multivariate adjustment (HR 0.66; 95% CI 0.43 to 0.99) and in the propensity score–matched sample (HR 0.53; 95% CI 0.33 to 0.85). Intracerebral bleeding occurred less frequently in rivaroxaban-treated patients (1.3/100 patient-years) than in VKA-treated patients (4.0/100 patient-years), adjusted HR 0.59 (95% CI 0.24 to 1.44) and in the propensity score–matched sample HR 0.26 (95% CI 0.09 to 0.80). Major lower bleeding risk was largely driven by lower risk of intracerebral bleeding.

Conclusions Our study findings indicate that bleeding risk, largely driven by lower risk of intracerebral bleeding, is lower with rivaroxaban than with VKA in stroke prevention in patients ≥80 years old with non-valvular AF.

INTRODUCTION

Atrial fibrillation (AF) is a disease of the elderly, with increasing prevalence and incidence among older age groups.[1] AF is with age a major risk factor for ischaemic stroke; hence, stroke prevention with oral anticoagulants is the cornerstone for AF management in the elderly. Although in the elderly, the risk of stroke without oral anticoagulation exceeds the bleeding risk on anticoagulation,[2 3] a significant underuse of anticoagulation is observed in older patients with AF essentially due to fear of bleeding.[4]

Direct oral anticoagulants (DOACs) have been proposed as an alternative to vitamin K antagonists (VKAs) for stroke prevention in patients with non-valvular AF.

Randomised controlled trials have demonstrated that DOACs have a more favourable benefit–risk profile than VKAs,[5] and meta-analyses focused on patients >75 years old found that DOACs are more effective than VKAs in stroke prevention, with a significantly lower risk of intracerebral haemorrhage and a similar risk of major bleeding.[6]

Although DOACs have been extensively evaluated in the general population, only 38% of patients enrolled in the four landmark trials of DOACs in non-valvular AF were aged ≥75 years, and only around 15% were >80 years old.[5 7–10] Moreover, elderly patients in randomised clinical trials are usually a selected group who are relatively healthy with few geriatric conditions such as dementia, falls, malnutrition or disability. Consequently, evidence for the efficacy and safety of DOACs in very old and frail patients is still insufficient.[11]

Given the limited evidence on the risks of bleeding with DOACs in individuals 80 years and older, generating evidence supporting the use of DOACs in this specific geriatric population is critical. Accordingly, the purpose of this large sequential observational prospective cohort study was to compare the bleeding risk of rivaroxaban with that of VKAs among patients with non-valvular AF aged ≥80 years in geriatric settings in France.

METHODS

Study design and study population

This was a balanced sequential cohort study using data from 33 geriatric centres across France. Patients were followed up every 3 months for up to

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12 months. The study was conducted under real-life conditions of daily clinical practice and in accordance with the Declaration of Helsinki, the Good Pharmacoepidemiology Practice guidelines, and abided by French laws and regulations. The protocol was approved by the ethics committee of *Ile de France V*. No consent to participate was sought for the subjects in accordance with the French ethics rules because the study was observational and no nominative data were collected.

Study participants

Eligible patients comprised men and women aged 80 years and older, with documented non-valvular AF on ECG or 24-hour Holter monitoring, originating from geriatric settings (hospitals, private practice or nursing homes). Two cohorts of patients were evaluated. One had recently (less than 6 months) initiated VKA and the other rivaroxaban. In order to reduce selection bias, VKA cohort was constituted from September 2011 to September 2014 whereas rivaroxaban cohort was constituted from September 2014 to September 2017. Because rivaroxaban was marketed in France in 2011, prescriptions were more likely to be given to healthier patients for this initial period. Indeed, several observational studies showed that VKAs were more likely used in older comorbid patients whereas DOACs were more likely used in healthier patients.[12] To limit the difference between the two cohorts in terms of comorbidity and age, we decided to include patients in the rivaroxaban group a few years after its marketing in France.

To optimise generalisability of the study findings, exclusion criteria were limited to participation in an interventional clinical trial, and contraindications to VKA or rivaroxaban as described in the summary of product characteristics. All patients were informed about the nature of the study.

Data collection

At baseline, patient and treatment characteristics were collected from the electronic medical record databases of the study centres. These included clinical characteristics, CHA_2DS_2-VASc[13] and HAS-BLED[14] scores, age-adjusted Charlson comorbidity index (ACCI),[15] comprehensive geriatric assessment including cognition (mini-mental state examination (MMSE)),[16] dementia, disability (activities of daily living (ADL)),[17] falls, anaemia according to WHO definition: haemoglobin <130 g/L in men and <120 g/L in women, malnutrition, medications taken and most recent laboratory data (serum creatinine, eGFR (glomerular filtration rate estimated with Cockcroft-Gault formula),[18] haemoglobin, albumin). Labile international normalised ratio (INR) was not included in the HAS-BLED score because it was unavailable in the local centres' databases.

At each 3-month follow-up, all bleeding events, thrombotic events, hospitalisations, anticoagulant discontinuation and deaths were prospectively registered.

Major bleeding was defined according to the International Society on Thrombosis and Haemostasis: clinically overt bleeding associated with any of the following: (1) death; (2) involvement of a critical anatomical site (intracranial, spinal, ocular, pericardial, retroperitoneal, articular or intramuscular with compartment syndrome); (3) drop in haemoglobin concentration ≥2 g/dL; (4) transfusion ≥2 U of whole blood or red blood cells.[19]

Statistical analysis

Baseline characteristics were analysed in the two cohorts in terms of means and SD for continuous variables, and in terms of counts and percentages for categorical variables and compared with t-tests and χ^2, respectively. Missing data were not imputed, and patients were left censored from analysis at the point of loss to follow-up (see online supplemental table 1). Kaplan-Meier curves were drawn for major bleedings, intracerebral and gastrointestinal haemorrhages, and ischaemic strokes in the two cohorts. Cox proportional-hazard models were used to calculate HR and 95% CI for the incidence of bleeding and ischaemic events in rivaroxaban-treated patients as compared with those treated with VKAs. For each comparison, we fit three sets of Cox models: unadjusted (crude); adjusted for age, sex, eGFR and ACCI (model 1); and adjusted for various variables selected based on univariate p values <0.10, including model 1+malnutrition (albumin <35 g/L), anaemia, falls, use of antiplatelets, amiodarone, proton-pump inhibitors (PPIs) and selective serotonin reuptake inhibitors (SSRIs) (model 2). In both adjusted models, dementia was not included as a covariate because it is already taken into account in the ACCI. A sensitivity analysis was performed for major bleedings with adjustment for HAS-BLED with age, sex and Charlson comorbidity index score, even though both scores include some identical variables. Also we performed three logistic regression models with the same adjustment for major bleedings.

The proportional-hazard assumption was checked graphically for all covariates and using Schoenfeld residuals. Log-linearity was also tested for all covariates. Because proportional-hazard assumption was marginally broken in the crude Cox model for ischaemic strokes (p=0.064), we built three logistic regression models with the same adjustment for ischaemic strokes.

A propensity score matching method (GenMatch package in R) was also used to balance patients' characteristics between the two cohorts. The propensity score was calculated on characteristics significantly different regarding haemorrhagic events (ie, age, sex, Charlson comorbidity index, eGFR, haemoglobin, albumin, antiplatelets) (see online supplemental table 2). One participant treated with VKA was matched to one participant treated with rivaroxaban without replacement with a calliper of 0.8 SD in standardised unit. This sample comprised 760 subjects, 380 in the VKA cohort and 380 in the rivaroxaban group. The power to detect a difference similar to that of the overall sample was 73.1%.

The balance of measured covariates between matched rivaroxaban and VKA users was assessed using standardised mean differences that were all ≤0.1 (10%) indicating a negligible difference between the cohorts[20] (online supplemental table 2).

A two-sided p value <0.05 was considered statistically significant. All statistical analyses were performed using R.[21]

RESULTS

Patient characteristics

For the rivaroxaban cohort, 1045 consecutive patients were enrolled. Of these patients, 995 (95.2%) had at least 6 months of follow-up (mean age=86.0 (4.3), including 23% aged 90 years and older) and mean follow-up was 322 (89) days.

For the VKA group, 924 consecutive patients were enrolled from the same 33 geriatric centres across France. Of these patients, 908 (98.2%) had at least 6 months of follow-up (mean age=86.4 (5.2), including 27% aged 90 years and older) and mean follow-up was 286 (117) days.

Compared with VKA-treated patients (see table 1), rivaroxaban-treated patients were slightly younger, more often male and heavier. They had significantly less comorbidity, higher eGFR and were less likely to receive antiplatelets, amiodarone, PPIs and SSRIs. CHA_2DS_2VASc score was similar in the two

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Table 1 Baseline characteristics among rivaroxaban and VKA cohorts

General characteristics, M (SD)	VKA n=908	Rivaroxaban n=995	P value*
Age (years)	86.4 (5.2)	86.0 (4.3)	0.06
Women, % (n)	66.4 (603)	61.1 (608)	0.02
Weight (kg)	64.5 (15.8)	67.2 (14.8)	0.0002
Body mass index (kg/m^2)	24.8 (5.6)	25.1 (4.9)	0.16
Haemorrhagic and thrombotic scores			
CHA_2DS_2VASc (score)	4.58 (1.39)	4.58 (1.39)	0.96
HAS-BLED (score)	2.15 (0.85)	1.99 (0.93)	0.003
Charlson comorbidity index (score)	8.59 (2.65)	6.68 (2.02)	<0.0001
Geriatric parameters			
Dementia, % (n)	55.3 (446)	38.5 (382)	<0.0001
Mini-mental state examination (score)	20.1 (6.8)	21.5 (6.9)	<0.0001
Activity of daily living (score)	2.47 (1.83)	4.42 (1.87)	<0.0001
Falls (more than 2 the previous year), % (n)	47.6 (374)	27.0 (265)	<0.0001
Malnutrition (albumin <35 g/L), % (n)	76.5 (657)	54.7 (465)	<0.0001
Anaemia†, % (n)	64.5 (578)	40.8 (396)	<0.0001
Biological characteristics			
Serum creatinine (µmol/L)	98.7 (59.8)	80.4 (23.1)	<0.0001
eGFR (mL/min)	47.2 (26.0)	53.1 (16.4)	<0.0001
Haemoglobin (g/dL)	11.7 (1.6)	12.6 (1.6)	<0.0001
Treatment, % (n)			
Antiplatelets	16.1 (128)	11.6 (114)	0.007
Amiodarone	19.4 (154)	15.1 (150)	0.02
Proton-pump inhibitors	46.3 (377)	35.0 (348)	<0.0001
Serotonin reuptake inhibitors	30.6 (244)	19.7 (196)	<0.0001

M (SD), mean (standard deviation); % (n), percentage (count).
*T-test or χ^2 test.
†Anaemia according to WHO definition: haemoglobin <130 g/L in men and <120 g/L in women.
eGFR, glomerular filtration rate estimated with Cockcroft-Gault formula; VKA, vitamin K antagonist.

groups. HAS-BLED score was significantly lower in the rivaroxaban group.

In the rivaroxaban cohort, 65% of patients were prescribed rivaroxaban as initial anticoagulant therapy, while 35% switched from VKA. Thirty-six per cent of patients were prescribed 20 mg of rivaroxaban once daily, 63% 15 mg and 1% 10 mg. In patients with a baseline eGFR 30–50 mL/min, 84.5% were prescribed rivaroxaban 15 mg once daily. In patients with a baseline eGFR ≥50 mL/min, rivaroxaban was prescribed 20 mg once daily in 54.6% and 15 mg once daily in 45.4% of patients.

Figure 1 shows the Kaplan-Meier cumulative probability of being free from major, intracerebral and gastrointestinal haemorrhages and from ischaemic strokes in rivaroxaban and VKA cohorts.

Major bleeding

During the 1-year follow-up, major bleeding occurred in 63/995 (6.3%) rivaroxaban-treated patients (7.4 events/100 patient-years) and in 102/908 (11.2%) VKA-treated patients (14.6 events/100 patient-years) (figures 1–3 and table 2).

Major bleeding rate was significantly lower in the rivaroxaban cohort than in the VKA cohort in the crude Cox model (HR (95% CI)), and model 1 (adjusted for age, sex, eGFR and CCI)

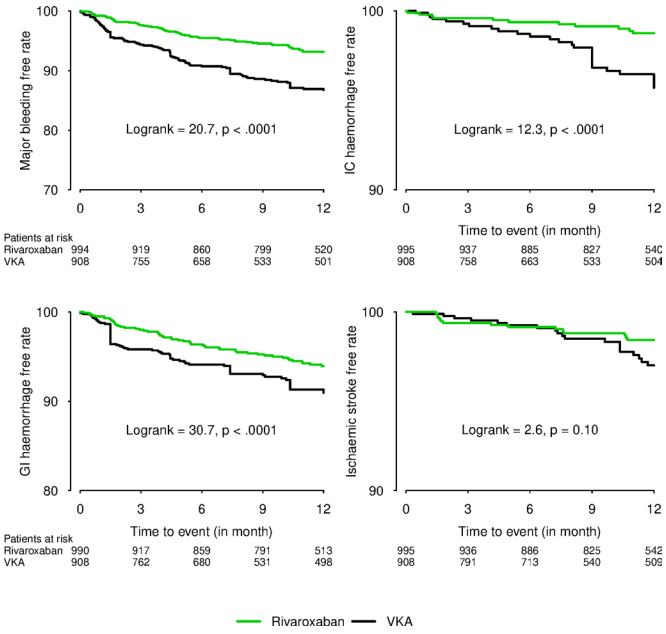

Figure 1 Major bleeding, intracerebral (IC) and gastrointestinal (GI) haemorrhages and ischaemic stroke in vitamin K antagonist (VKA) and rivaroxaban cohorts.

and model 2 (model 1 adjusted for malnutrition, anaemia, falls, antiplatelets, amiodarone, PPI and SSRI use) (HR (95% CI) 0.66 (0.43 to 0.99)).

In the propensity score–matched sample, the difference between rivaroxaban and VKA groups was also significant (HR 0.53 (0.33 to 0.85), p=0.009).

Fatal bleeding occurred in 9/995 (0.9%) rivaroxaban-treated patients (1.0/100 patient-years) and in 21/908 (3.3%) VKA-treated patients (3.0/100 patient-years). Fatal bleedings were significantly different in the two cohorts in the crude Cox model and model 1 (HR 0.42 (0.18 to 0.99), p=0.04), but not in model

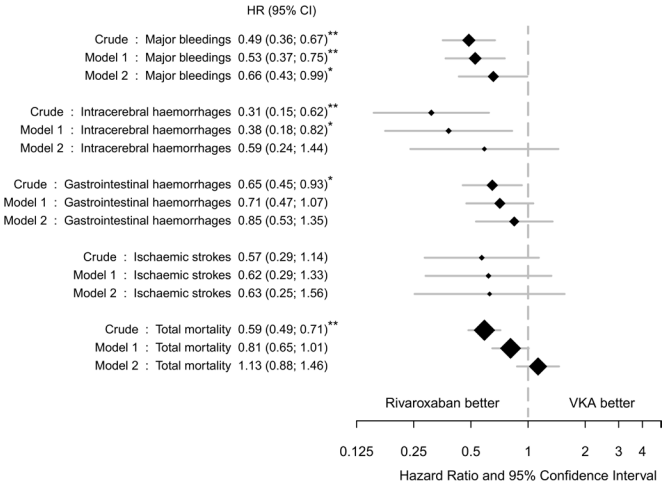

Figure 2 Comparison of rate of events between rivaroxaban and vitamin K antagonist (VKA). Diamonds are sized proportionally to the number of events. Model 1: Cox model adjusted for age, sex, estimated glomerular filtration rate and Charlson comorbidity index. Model 2: model 1+ malnutrition, anaemia, falls, use of antiplatelets, use of amiodarone, proton-pump inhibitors and serotonin reuptake inhibitors. *p<0.05 **p<0.001.

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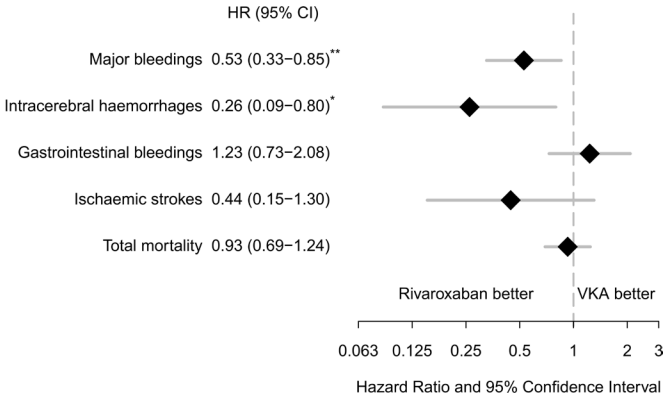

Figure 3 Comparison of rate of events between rivaroxaban and vitamin K antagonist (VKA) in the propensity score–matched sample. *p<0.05 **p<0.01.

2 (HR 0.48 (0.15 to 2.07), p=0.21). Two-thirds (20/30) of the fatal bleeding were related to intracerebral haemorrhages.

In a sensitivity analysis, HAS-BLED score was added in the model with age, sex and Charlson comorbidity index score. Likewise, major bleeding rate was lower in rivaroxaban-treated patients than in VKA-treated patients (HR 0.61 (0.37 to 1.00), p=0.05).

In the three logistic regression models, major bleeding rate was significantly lower in the rivaroxaban cohort than in the VKA cohort (online supplemental table 3).

Intracerebral haemorrhages

Intracerebral haemorrhages occurred in 11/995 (1.1%) rivaroxaban-treated patients (1.3 events/100 patient-years) and 28/908 (3.1%) VKA-treated patients (4.0 events/100 patient-years). Intracerebral haemorrhage rate was significantly lower in rivaroxaban cohort than in VKA cohort in the crude Cox model and model 1 but not in model 2 (table 2 and figures 1–3)

In the propensity score–matched sample, intracerebral haemorrhage rate was significantly lower in the rivaroxaban cohort than in the VKA cohort.

Gastrointestinal haemorrhages

Gastrointestinal haemorrhage occurred in 26/995 (3.0%) in the rivaroxaban cohort (3.0 events/100 patient-years) compared with 34/908 (3.7%) in the VKA cohort (4.9 events/100 patient-years). The difference of gastrointestinal haemorrhage rate was significant in the crude Cox model but not in the adjusted models and in the propensity score–matched sample (table 2 and figures 1–3).

Ischaemic strokes

Ischaemic stroke occurred in 14/995 (1.4%) rivaroxaban-treated patients (1.6 events/100 patient-years), while it occurred in 19/908 (2.1%) patients in the VKA cohort (2.7 events/100 patient-years). The difference between the two cohorts was not significantly different in any of the Cox models or in the propensity score–matched sample (table 2 and figures 1–3).

In all three logistic regression models, ischaemic strokes were not significantly different in the two cohorts.

All-cause mortality

In the rivaroxaban cohort, 178/995 (17.9%) patients (20.3/100 patient-years) died during the follow-up whereas 241/908 (26.5%) patients (34.5/100 patient-years) died in the VKA cohort (table 2 and figures 2 and 3).

The mortality rate was significantly lower among rivaroxaban-treated patients than in VKA-treated patients in the crude Cox model but not in the adjusted models.

Factors associated with major bleedings

In the rivaroxaban cohort, compared with those without a major bleeding (n=932), patients with a major bleeding (n=63) were older, more often male and treated with antiplatelets and amiodarone and had more often anaemia, dementia and lower eGFR; meanwhile, HAS-BLED was not associated with major bleeding events (table 3). When all those variables were simultaneously entered into a multivariate logistic model, age, male sex, lower eGFR and anaemia remained significantly associated with major bleedings (table 4).

In the VKA cohort, compared with those without a major bleeding (n=806), patients with a major bleeding (n=102) were more often male and treated with antiplatelets and PPIs, had more often anaemia and lower eGFR, and had a higher HAS-BLED score (table 3). When all those variables were simultaneously entered into a multivariate logistic model (table 4), male sex and lower eGFR remained significantly associated with major bleedings.

DISCUSSION

To our knowledge, this is the first large observational prospective study in geriatric patients with AF comparing data on bleeding complications between rivaroxaban and VKA.

The 1-year rate of major bleedings was 7.4 per 100 person-years for rivaroxaban, suggesting that major bleeding risk with rivaroxaban is higher in older frail patients than in younger ones. In the ROCKET-AF trial involving patients with AF with a median age of 73 years, major bleeding risk was 3.6 events per 100 patient-years.[8] In the XANTUS study with a mean age of

Table 2 Events during the follow-up period among rivaroxaban and VKA groups

	Rivaroxaban		VKA		
Event	n (%)	/100 person-years	n (%)	/100 person-years	HR (95% CI)
Major bleedings	63 (6.3)	7.4	102 (11.2)	14.6	0.49 (0.36 to 0.67)
Fatal bleedings	9 (0.9)	1.0	21 (3.3)	3.0	0.34 (0.16 to 0.76)
Intracerebral haemorrhages	11 (1.1)	1.3	28 (3.1)	4.0	0.65 (0.45 to 0.93)
Gastrointestinal haemorrhages	26 (3.0)	3.0	34 (3.7)	4.9	0.82 (0.53 to 1.28)
Ischaemic strokes	14 (1.4)	1.6	19 (2.1)	2.7	0.57 (0.29 to 1.14)
All-cause mortality	178 (17.9)	20.3	241 (26.5)	34.5	0.59 (0.49 to 0.72)

n (%), count (percentage); HR (95% CI), hazard ratio (95% confidence interval)

VKA, vitamin K antagonist.

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Table 3 Characteristics of patients with and without major bleeding events among rivaroxaban and VKA cohorts

	Rivaroxaban			Vitamin K antagonist		
	No major bleeding	Major bleeding		No major bleeding	Major bleeding	
General characteristics, M (SD)	n=932	n=63	P value*	n=806	n=102	P value*
Age (years)	85.9 (4.2)	87.5 (4.8)	0.003	86.3 (5.3)	86.7 (5.0)	0.46
Women, % (n)	61.9 (577)	49.2 (31)	0.06	67.4 (543)	58.8 (60)	0.11
Weight (kg)	67.2 (14.9)	65.9 (13.2)	0.49	64.5 (15.9)	64.3 (15.4)	0.89
Height (cm)	164 (29)	164 (8)	0.99	162 (10)	162 (10)	0.75
Body mass index (kg/m^2)	25.2 (5.0)	24.4 (4.0)	0.22	24.8 (5.6)	24.5 (6.1)	0.64
Activity of daily living (score)	4.40 (1.88)	4.69 (1.69)	0.23	2.49 (1.83)	2.32 (1.78)	0.4
Mini-mental state examination (score)	21.4 (7.0)	22.8 (6.6)	0.14	20.1 (6.9)	20.0 (6.6)	0.87
Charlson comorbidity index (score)	6.68 (2.03)	6.66 (1.83)	0.92	8.60 (2.67)	8.52 (2.50)	0.78
Anaemia†, % (n)	39.9 (362)	54.0 (34)	0.04	63.7 (508)	71.4 (70)	0.16
Falls (more than 2 the previous year), % (n)	26.8 (247)	28.6 (18)	0.88	47.2 (329)	51.1 (45)	0.56
Dementia, % (n)	39.1 (364)	28.6 (18)	0.12	55.7 (398)	51.6 (48)	0.52
Biological characteristics						
Serum creatinine (µmol/L)	80.0 (23.0)	86.4 (23.0)	0.03	97.9 (60.9)	105 (50)	0.26
eGFR mL/min	53.5 (16.5)	47.6 (14.7)	0.006	47.9 (26.6)	42.0 (19.1)	0.04
Haemoglobin (g/dL)	12.7 (1.6)	12.0 (1.7)	0.0009	11.7 (1.6)	11.5 (1.5)	0.19
Treatment, % (n)						
Antiplatelets	11.2 (103)	17.5 (11)	0.20	15.0 (106)	25.9 (22)	0.02
Amiodarone	14.6 (136)	22.2 (14)	0.15	20.1 (142)	14.1 (12)	0.24
Proton-pump inhibitors	35.2 (328)	31.7 (20)	0.68	45.3 (330)	54.7 (47)	0.12
Serotonin reuptake inhibitors	19.7 (184)	19.0 (12)	0.99	30.6 (218)	31.0 (26)	0.99
Haemorrhagic and thrombotic scores						
HAS-BLED	1.98 (0.93)	2.12 (0.97)	0.29	2.10 (0.83)	2.67 (0.93)	0.0001
CHA_2DS_2VASc	4.56 (1.41)	4.84 (1.21)	0.18	4.59 (1.40)	4.41 (1.24)	0.32

M (SD), mean (standard deviation); % (n), percentage (count).
*T-test or χ^2 test.
†Anaemia according to WHO definition: haemoglobin <130 g/L in men and <120 g/L in women.
eGFR, glomerular filtration rate estimated with Cockcroft-Gault formula; VKA, vitamin K antagonist.

Table 4 Multivariable analysis of factors associated with major bleedings in the rivaroxaban and VKA cohorts

	HR (95% CI)	P value
Rivaroxaban cohort		
Age (years)	1.07 (1.00 to 1.13)	0.04
Male sex	1.79 (1.06 to 3.01)	0.03
eGFR	0.67 (0.48 to 0.94)	0.02
Anaemia*	1.68 (1.00 to 2.82)	0.05
History of bleeding	1.46 (0.81 to 2.62)	0.21
Dementia	0.66 (0.38 to 1.14)	0.13
Medication		
Antiplatelets	1.55 (0.79 to 3.06)	0.20
Amiodarone	1.64 (0.90 to 3.00)	0.11
Vitamin K antagonist cohort		
Male sex	1.56 (0.97 to 2.49)	0.06
eGFR	0.74 (0.55 to 0.99)	0.04
Anaemia*	1.31 (0.79 to 2.19)	0.30
Medication		
Antiplatelets	1.55 (0.90 to 2.63)	0.11
Proton-pump inhibitor	1.37 (0.87 to 2.17)	0.18

HR (95% CI), hazard ratio (95% confidence interval)
*Anaemia according to WHO definition: haemoglobin <130 g/L in men and <120 g/L in women.
eGFR, glomerular filtration rate estimated with Cockcroft-Gault formula (HR for an increase of 1 SD); VKA, vitamin K antagonist.

71.5 years, major bleeding risk was 2.1 events per 100 patient-years.[22] Meanwhile, our results are consistent with a retrospective study including AF octogenarians showing a rate of 9.0% of bleeding in subjects treated with DOACs.[23] Similarly, our study showed a high rate of major bleeding in the VKA group (14.6 per 100 person-years) consistent with previous studies.[23 24]

The 1-year rate of major bleeding events was significantly lower in the rivaroxaban group than in the VKA group. The difference remained significant even after adjustment for all potentially confounding factors and in a propensity score–matched sample. The difference in major bleedings was largely driven by the difference in intracerebral haemorrhages and also explained the difference in fatal bleedings. In European registries in patients aged ≥75 years, major bleedings were less frequent in patients treated with DOAC than VKAs.[3] Our results are also consistent with a meta-analysis including elderly patients that finds a lower rate of bleedings in the DOAC group compared with VKA[25] but not with others that show similar rates of major bleedings in DOAC and VKA groups.[6 26 27]

There was a lower rate of intracerebral haemorrhages in the rivaroxaban group. The difference remained significant after adjustment in model 1 and in the propensity score matching sample but not in model 2 possibly because of lack of power. However, the HR was still 0.59. In most studies, DOAC is associated with a significantly lower risk of intracerebral haemorrhages in elderly patients (≥75 years old) compared with VKA.[6 28] There are only few studies in patients >80 years old especially with a prospective design. Retrospective data found

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intracerebral haemorrhage rate similar to ours (0.89%/person-years)[29] and lower risk among patients with AF ≥90 years of age.[28]

Major bleedings in patients treated with rivaroxaban were associated with age, male sex, low eGFR and anaemia and interestingly were not associated with geriatric features like falls, dementia, malnutrition and co-medication.

HAS-BLED score was not associated with major bleedings in the rivaroxaban group whereas it was highly significantly related to major bleedings in the VKA group. HAS-BLED was created to predict major bleedings in patients treated with VKA and not with DOAC. This result shows the need for a specific bleeding score for patients treated with DOAC.

There was no difference in gastrointestinal haemorrhages between the two groups in the adjusted models. In randomised studies, gastrointestinal haemorrhages were more frequent with rivaroxaban than with VKA. Our results could be related to a selection bias from investigators: patients with higher risk of gastrointestinal haemorrhage might not have been treated by geriatricians with rivaroxaban.

There was no difference in ischaemic strokes between the two cohorts. This result is consistent with the ROCKET-AF study, especially the sub-analysis in elderly ≥75 years old.[30] However, the number of events was small (19 in the VKA group and 14 in the rivaroxaban group) and a longer follow-up would be necessary to better analyse this outcome.

Our study has some limitations. Despite the time lag between the two including periods, the two cohorts were not totally comparable. As it has already been shown in other studies,[12] patients treated with VKA usually have more comorbidity. To take into account these issues, we adjusted for all potentially confounding factors and also ran the analyses in a propensity score–matched sample. Meanwhile, despite the use of advanced statistical methods to account for differences between cohorts, we cannot make causal inference. No data on INR control in VKA-treated patients were available, lessening the strength of the study. Investigators calculated and entered HAS-BLED and CHA_2DS_2VASc scores directly and variables contained in these scores were not recorded. Lastly, this study only analysed rivaroxaban and not the other DAOCs because apixaban and edoxaban were not yet marketed in France at the time of study inception and dabigatran was not widely used in the geriatric population because of its renal elimination.

The strength of our study lies in its very old population, characterised by high Charlson comorbidity index and geriatric syndromes such as dementia, falls and malnutrition, and which profile is never included in randomised controlled studies. To our knowledge, this is the largest observational prospective study on a geriatric population comparing DOAC and VKA medication in patients with AF. We evaluated cardiologic determinants of bleeding and stroke risks and also comprehensive geriatric assessment that are usually not assessed in randomised and observational studies. Furthermore, the study's prospective design allowed for greater completeness of data and potentially better data quality compared with retrospective designs. Loss to follow-up was low for a prospective study in geriatric patients (7%). Finally, drugs potentially interacting with rivaroxaban and frequently prescribed in elderly patients such as antiplatelets, PPIs, SSRIs and amiodarone were monitored.

This study shows that, compared with VKAs, rivaroxaban use is associated with a lower risk of major bleeding and intracerebral haemorrhage in very old geriatric patients with AF treated in clinical practice. Our findings are consistent with evidence-based data and indicate that rivaroxaban can be used for stroke prevention in geriatric patients with non-valvular AF.

Key messages

What is already known on this subject?

- Direct oral anticoagulants have been proposed as an alternative to vitamin K antagonists (VKAs) for stroke prevention in patients with non-valvular atrial fibrillation (AF). However, proper evidence for their safe use is still missing in the geriatric population with dementia, falls, anaemia, malnutrition and disability.

What might this study add?

- During the 1-year follow-up, major bleeding occurred significantly less often in rivaroxaban-treated patients, 63/995 (6.3%) (7.4 events/100 patient-years), than in VKA-treated patients, 102/908 (11.2%) (14.6 events/100 patient-years). That result was significant in crude model, in adjusted Cox model and in propensity-matched sample.

How might this impact on clinical practice?

- Our study findings indicate that bleeding risk is lower with rivaroxaban than with VKA in stroke prevention in patients ≥80 years old with non-valvular AF.

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Author note SAFIR study group: bleeding risk in elderly Subjects Aged more than 80 years in atrial FIbrillation treated by Rivaroxaban

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