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Patients aged 90 years or older with atrial fibrillation treated with oral anticoagulants: A multicentre observational study

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ABSTRACT

Background: Patients aged 90 years or older are often excluded from or under-represented in clinical trials and cohort studies. The clinical benefit of anticoagulation in nonagenarians with atrial fibrillation (AF) remains undefined.
Objectives: To assess the effectiveness and safety of oral anticoagulants in AF patients aged 90 years or older.
Methods: Non-valvular AF patients aged 90 years or older receiving direct oral anticoagulants (DOACs) or vitamin K antagonists (VKAs) were included in this observational multicentre study. The primary outcome was the composite of ischaemic stroke/transient ischemic attack (TIA) and systemic embolism (SE). Major bleeding (MB), anticoagulant discontinuation and all-cause death were also assessed. Results are reported as sub-distribution hazard ratios (SHR) with 95% CI, taking death as competing risk.
Results: 546 patients were included (301 VKAs retrospective cohort and 245 DOACs prospective cohort; median follow-up 404 days). The rate of ischaemic stroke/TIA/SE was 2.4% patient-year and that of MB 5.5% patient-year. Previous ischaemic stroke/TIA (SHR 3.47; 95% CI 1.54–7.81) and vascular disease (SHR 2.89; 95% CI 1.27–6.60) were independent predictors of ischaemic stroke/TIA/SE. Previous bleeding (SHR 2.53; 95% CI 1.37–4.64) was an independent predictor of MB. The risk of ischaemic stroke/TIA/SE (SHR 0.78, 95% CI 0.30–2.04) or MB (SHR 1.43, 95% CI 0.77–2.65) was not significantly different with DOACs or VKAs.
Conclusions: In AF nonagenarians receiving anticoagulant treatment, the rate of ischaemic stroke/TIA/SE is relatively low with the drawback of a not negligible rate of MB. DOACs seem a reasonable option for prevention of ischaemic stroke/TIA/SE in this setting.

1. Background

Atrial fibrillation (AF) is the most common heart rhythm disorder [1]. The prevalence of AF varies from 0.2% in patients aged <55 years to 11% in patients aged 85 years or older [2]. By aging trends in the global population, the burden of AF is rapidly growing. According to worldwide epidemiological data from the World Health Organization regions, AF is defined as a global epidemic with significant and progressive effects on estimated disability and mortality [3]. Overall, AF patients have a 5-fold higher risk of suffering a stroke than patients without AF [4]. Anticoagulation reduces the risk of stroke by about 60% but this benefit is counterbalanced by an increased risk of bleedings [5]. According to current international guidelines, age over 75 years is by itself associated with a risk for stroke or systemic embolism high enough to recommend anticoagulant treatment [1].

Vitamin K antagonists (VKAs) or direct anticoagulants (DOACs) are the currently recommended anticoagulants in AF patients. However, limited evidence from randomized trials is currently available on the efficacy and safety of either DOACs or VKAs in patients aged 90 years or older. This lack of evidence often leads to de-prescription of anticoagulant agents in these patients. Thus, the overall clinical benefit of antithrombotic treatment as well as the best anticoagulant strategy in AF patients aged 90 years or older remains uncertain.

The aim of the study is to evaluate the effectiveness and safety of oral anticoagulants in patients 90 years or older with non-valvular AF in clinical practice.

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2. Methods

2.1. Patients

In and outpatients with non-valvular AF were eligible for inclusion in the study if a) they were treated with DOACs or VKAs, either as naïve or switchers and b) were aged 90 years or older or they turned 90 years when on DOACs or VKAs (see Fig. 1 in Ref [6]).

DOAC patients were derived from an on-going multicentre prospective Italian registry of AF patients receiving DOACs [7]. In this registry, consecutive AF patients were included at four Italian hospitals since August 2013 when DOACs became available in clinical practice. The choice of the individual DOAC was in charge of the attending physician. Adherence to the criteria of the European Medicines Agency (EMA) for prescription of reduced doses was suggested.

VKAs patients were derived from those referred to the Anticoagulation Clinic of the University Hospital in Perugia. In this group, patient data were retrospectively collected.

Exclusion criteria were refusal of informed consent and valvular AF. AF was defined as 'valvular' if it was related to rheumatic valvular disease (predominantly moderate or severe mitral stenosis) or associated with prosthetic heart valves [1].

Observation started: a) at time of prescription of anticoagulant therapy for patients 90 years old or older naïve to oral anticoagulants or b) since the patient became 90 years old for those already on anticoagulant therapy (see Fig. 1 in Ref [6]).

Patients who switched from VKAs to DOACs or vice versa during the study period remained in the study and crossed over into the new treatment group. Observation ended in case of death or permanent discontinuation of anticoagulant treatment.

The study was approved by the Ethical Committee and/or Institutional Review Boards of the participating centres.

2.2. Study outcome events

The primary outcome was the composite of ischaemic stroke/transient ischemic attack (TIA) and systemic embolism (SE).

The safety outcome was major bleeding (MB).

Secondary endpoints of the study were i) overall mortality and ii) permanent discontinuation.

Bleeding was defined as major according to the ISTH definition, if clinically overt and associated with a decrease in the haemoglobin level of 2.0 g per decilitre or more, transfusion of 2 or more units of red cells, if it was intracranial or retroperitoneal, occurred in another critical site, or contributed to death [8]. Stroke was defined as a focal neurological defect, lasting at least 24 h while TIA as transient episode of neurological dysfunction resulting from focal cerebral ischemia not associated with permanent cerebral infarction. Permanent discontinuation was defined as anticoagulants withdrawal for a period longer than 30 days.

In case of death, the presumed cause was reported as adjudicated by the attending physician. The results of all the available tests used to confirm/exclude bleeding or thromboembolism as the cause of death were reported.

2.3. Data collection

For all included patients the following data were collected: age, gender, comorbidities (hypertension, congestive failure, diabetes, previous stroke, vascular diseases, renal or liver disease, previous bleeding defined according to the CHA_2DS_2-VASc and HAS-BLED score), concomitant medications as non-steroidal anti-inflammatory (NSAIDs) or corticosteroids, type of AF (first diagnosed, paroxysmal and permanent AF), laboratory tests (e.g. creatinine clearance), type and dosage of DOACs and mean time in therapeutic range (TTR) in patients treated with VKAs.

Chronic heart failure and vascular disease were defined according to the CHA_2DS_2-VASc criteria [9]. Renal disease was defined as chronic dialysis or renal transplantation or serum creatinine >2.3 mg/d according to HAS-BLED score definition [10]. Liver disease was defined according to the HAS-BLED criteria [10].

In the DOACs prospective cohort, follow-up visits or telephone contacts were scheduled every 6 months or in case of signs/symptoms of study outcome events.

For VKAs patients, data were retrospectively collected since the start of anticoagulant treatment or when the patient became 90 years of age or older.

2.4. Statistical analysis

Categorical data were reported as frequencies and continuous data as mean ± SD or median (range). Continuous data were compared with Student's *t*-test whereas categorical data were compared with χ^2 test. The reported *p*-values were based on two sided tests. The mean percentage of time spent in the therapeutic range (TTR) was calculated by the method of linear interpolation [11].

Study outcome events were presented either as the total number of first events or as number of events per 100 person-years.

Due to the high mortality of these patients, competing risk analysis taking competing risk by death into account was used to estimate the cumulative incidences and the risks of a) ischaemic stroke/TIA/SE; b) MB; c) permanent discontinuation occurring during the study period. Results were reported as sub-distribution hazard ratios (SHR) and 95% CI.

Variable selection for the multivariable cumulative incidence regression models was performed by the use of the Bayesian information criterion (BIC) [12,13].

In order to manage treatment discontinuation over time, we performed a further competing risk analysis taking into account permanent discontinuation and death as competing risks. Moreover, to reduce 'healthy patient bias' the following sensitivity analyses were performed: i) oral anticoagulant naïve vs. long-term oral anticoagulant users,

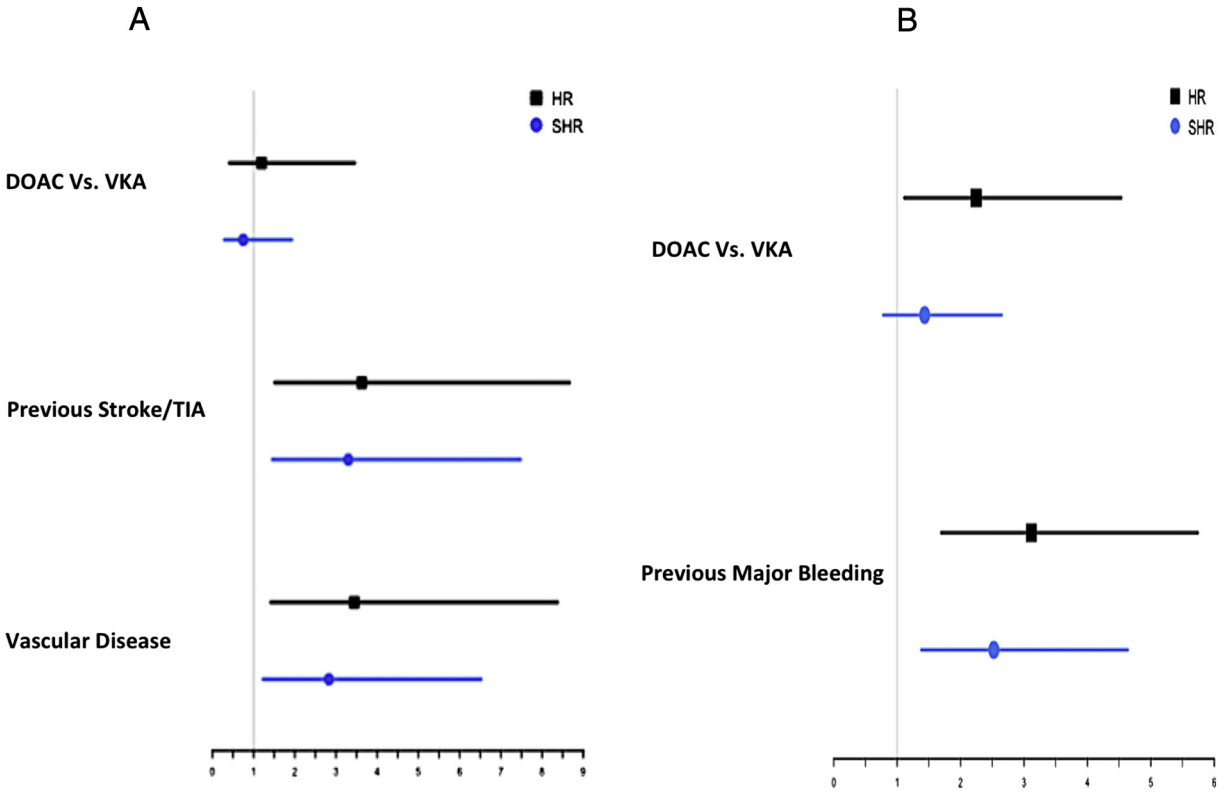

Fig. 1. Hazard ratio and subdistribution hazard ratio of main predictors for ischaemic stroke/TIA/SE (Panel A) and for major bleeding (Panel B).

ii) patients on anticoagulant therapy for <2 years (new users) vs. patients on anticoagulant therapy for >2 years (non new user) [14].

To assess the effect of competing risk analysis in our population, the risks of primary and secondary study outcomes were also calculated by Cox proportional hazards regression models. These results were reported as hazard ratios (HRs) with 95% confidence intervals (CI).

Statistical analysis was performed using R 3.5.0 (https://www.r-project.org, The R Foundation for Statistical Computing) following the methodology described in Scrucca et al. [15].

3. Results

Overall, 559 patients aged 90 or older with non-valvular AF were evaluated for inclusion in the study. After exclusion of 13 VKA retrospective cohort (2.3%) for incomplete baseline and follow-up data, 546 patients were finally included in the study. Mean age was 92 ± 1.9 (range 90–100) and 63.4% of patients were female. Main clinical features of study patients are reported in Table 1. The majority of the patients had permanent AF (63.2%) while 108 had first diagnosed AF (19.8%). Hypertension was the most common comorbidity.

At the time of inclusion in the study, 301 patients were on VKAs (55.1%) and 245 on DOACs (44.9%). Concerning VKA patients, 62 were anticoagulation naïve (20.6%) and the remaining 239 were already on VKAs when they turned 90 years and were included in the study (79.4%) (see Fig. 1 in Ref [6]). The mean TTR was 61 ± 22% (range 5.24–100%).

Among DOAC patients, 128 were anticoagulation naïve (52.2%) and 117 were already on anticoagulant treatment when they turned 90 years and were included in the study (47.8%) (see Fig. 1 in Ref [6]). Before starting DOACs, 36% of patients were on treatment with VKAs.

DOAC patients were younger and had higher prevalence of previous stroke or hypertension compared to VKA patients (Table 1). The mean $CHADS_2$ score was higher in DOAC compared to VKA patients. VKA patients had higher prevalence of renal disease.

Among DOAC patients, 40 received dabigatran, 121 rivaroxaban and 84 apixaban. The majority of patients received the reduced dose of DOACs (81.6%; 39 out of 40 dabigatran patients, 96 out of 121 rivaroxaban patients and 65 out of 84 apixaban patients).

3.1. Study outcome events

During a mean follow-up of 596 ± 539 days (median 404), ischaemic stroke/TIA/SE occurred in 20 patients (2.4% patient-year) and MB in 44 patients (5.5% patient-year) (Table 2). MB was intracranial haemorrhage in 15 patients. All-cause death occurred in 146 patients during the study (17.2% patient-year) (Table 2). Fatal bleeding occurred in nine patients (1.2% patient-year) and fatal ischemic stroke in two patients (0.3% patient-year).

Previous ischaemic stroke or TIA (SHR 3.47; 95% CI 1.54–7.81, $p = .003$) and vascular disease (SHR 2.89; 95% CI 1.27–6.60, $p = .012$) were independent predictors of ischaemic stroke/TIA/SE at multivariable analysis (Table 3; see Fig. 2 in Ref [6]).

Previous bleeding (SHR 2.53; 95% CI 1.37–4.64, p = .003) was the only independent predictor of MB (Table 3, see Fig. 2 in Ref [6]).

Permanent discontinuation occurred in 95 patients (10.1% patient-year) and bleeding was the most common cause of discontinuation (see Table 1 in Ref [6]). Age (SHR 0.79; 95% CI 0.71–0.90, $p < .001$) and anticoagulant therapy naïve (SHR 1.89; 95% CI 1.14–3.15, $p = .014$) were independent predictors of permanent discontinuation at multivariate analysis (see Fig. 3 in Ref [6]).

Being anticoagulant naïve (190 patients) was not associated with different risk in terms of both stroke/TIA/SE (SHR 1.85, 95% 0.55–6.24, $p = .320$) and MB (SHR 1.24, 95% 0.47–3.31, $p = .660$) compared to patients already on anticoagulant (356 patients). Similarly, the risk for ischaemic stroke/TIA/SE (SHR 1.37, 95% 0.51–3.71, $p = .530$) and for MB (SHR 1.62, 95% 0.78–3.36, $p = .200$) was similar between new user patients (245 patients, 44.8%) and that on anticoagulation for >2 years (see Table 2 in Ref [6]).

Table 1
Main baseline clinical features of the overall study population and according to treatment group.

Variable	All patients ($n = 546$)	VKAs patients ($n = 301$)	DOACs patients ($n = 245$)	*P*-value
Age, years	92 ± 1.9	92.4 ± 2.0	91.5 ± 1.8	<0.001
Range	(90–100)	(90–100)	(90–99)	
≥ 95, n (%)	64 (12)	45 (15)	19 (8)	
Female, n (%)	346 (63)	189 (63)	157 (64)	0.789
Type of AF,				
First diagnosis, n (%)	108 (20)	61 (20)	47 (19)	0.871
Paroxysmal, n (%)	93 (17)	39 (13)	54 (22)	0.018
Permanent, n (%)	345 (63)	201 (67)	144 (59)	0.358
Anticoagulation naïve, n (%)	190 (35)	62 (21)	128 (52)	<0.001
BMI (257 pts), Kg/m^2	24.8 ± 4.1	24.7 ± 4.1	24.9 ± 4.1	0.686
Range	(17–44)	(17–36)	(17–44)	
< 24, n (%)	123 (22)	89	34	0.891
≥ 30, n (%)	29 (5)	20	9	0.829
Hypertension, n (%)	464 (85)	246 (82)	218 (89)	0.022
Chronic heart failure, n (%)	199 (36)	120 (40)	79 (32)	0.074
Diabetes mellitus, n (%)	93 (17)	52 (17)	41 (17)	0.909
Previous stroke/TIA, n (%)	155 (28)	68 (22)	87 (35)	0.001
Vascular disease, n (%)	186 (34)	106 (35)	80 (33)	0.586
Previous bleeding, n (%)	202 (37)	102 (34)	100 (41)	0.109
Liver failure, n (%)	22 (4)	16 (5)	6 (2)	0.125
Renal failure, n (%)	38 (7)	33 (11)	5 (2)	<0.001
eGFR (477 pts), ml/min	51.8 ± 22.8	54.0 ± 24.6	49.5 ± 20.1	0.031
Range	(7–145)	(7–143)	(14–145)	
eGFR >60, n (%)	143 (30)	92 (37)	51 (22)	
eGFR 30–59, n (%)	271 (57)	113 (47)	158 (68)	
eGFR <30, n (%)	63 (13)	38 (16)	25 (10)	
$CHADS_2$,	2.86 ± 1.1	2.67 ± 1.1	3.09 ± 1.1	<0.001
Range	(1–6)	(1–5)	(1–5)	
CHA_2DS_2-Vasc,	4.93 ± 1.4	4.82 ± 1.4	5.06 ± 1.4	0.063
Range	(2–9)	(2–9)	(2–9)	
CHA_2DS_2-Vasc = 2–3	85 (16)	57 (19)	28 (11)	
CHA_2DS_2-Vasc = 4	131 (24)	68 (22)	63 (26)	
CHA_2DS_2-Vasc = 5	150 (28)	92 (31)	58 (24)	
CHA_2DS_2-Vasc = 6–9	180 (33)	85 (28)	95 (39)	
HAS-BLED,	2.59 ± 1.1	2.57 ± 1.2	2.60 ± 1.1	0.761
Range	(1–7)	(1–7)	(1–6)	
HAS-BLED = 1	101 (19)	57 (19)	44 (18)	
HAS-BLED = 2	167 (31)	96 (32)	71 (29)	
HAS-BLED = 3	165 (30)	89 (29)	76 (31)	
HAS-BLED = 4–7	113 (20)	60 (20)	53 (22)	

3.2. Study outcome events in VKAs and DOACs patients

During the study period, 14 VKA patients had stroke/TIA/SE (2.3% patient-year) and 27 had a MB (4.2% patient-year) (Table 2). Ischaemic stroke occurred in nine patients, TIA in two patients, SE in three patients. Concerning MBs, seven were intracranial haemorrhages of which four spontaneous and three post-traumatic.

During the study period, six DOAC patients had stroke/TIA/SE (2.4% patient-year) and 17 had MB (6.8% patient-year) (Table 2).

Table 2
Incidence of study outcomes and of all-cause death in the overall study population and according to treatment group.

Outcome event	All patients (n = 546)	VKAs patients (n = 301)	DOACs patients (n = 245)
Follow-up (days)	595.7 ± 539.1 (2–2857)	783.6 ± 632.2 (3–2857)	369.6 ± 257.5 (2−1200)
Ischaemic stroke/TIA/SE, n	20	14	6
(% pts-y)	(2.4)	(2.3)	(2.4)
Major bleeding, n	44	27	17
(% pts-y)	(5.5)	(4.2)	(6.3)
All-cause death, n	146	97	49
(% pts-y)	(17.2)	(15.0)	(19.4)
Permanent discontinuation, n	95	72	23
(% pts-y)	(10.4)	(10.9)	(8.9)

Table 3
Univariable and multivariable analyses for the identification of determinants of study outcome events.

	Univariable analysis			Multivariable analysis		
Variable	SHR	95% CI	P-value	SHR	95% CI	P-value
Ischaemic stroke/TIA and SE						
Age (years)	0.96	0.33–2.31	NS	–	–	–
DOACs	0.87	0.33–2.31	NS	0.78	0.30–2.04	NS
Heart failure	0.72	0.29–1.79	NS	–	–	–
Hypertension	1.49	0.46–4.77	NS	–	–	–
Diabetes	1.95	0.79–4.83	NS	–	–	–
Previous stroke/TIA	3.51	1.55–7.93	0.002	3.47	1.54–7.81	0.002
Vascular disease	3.03	1.31–7.01	0.009	2.89	1.27–6.60	0.012
Female	1.26	0.52–3.07	NS	–	–	–
Renal failure	0.66	0.20–2.15	NS	–	–	–
Previous bleeding	0.89	0.36–2.15	NS	–	–	–
Use of NSAID/ corticosteroids	4.23	1.43–12.4	0.008	3.00	0.99–9.06	0.050
Anticoagulation naïve	0.89	0.34–2.28	NS	–	–	–
Major bleeding						
Age (years)	0.90	0.78–1.04	NS	–	–	–
DOACs	1.56	0.86–2.84	NS	1.43	0.77–2.65	NS
Heart failure	1.11	0.61–2.02	NS	–	–	–
Hypertension	1.86	0.70–4.94	NS	–	–	–
Diabetes	1.13	0.52–2.44	NS	–	–	–
Previous stroke/TIA	0.90	0.46–1.78	NS	–	–	–
Vascular disease	1.30	0.71–2.38	NS	–	–	–
Female	0.75	0.41–1.36	NS	–	–	–
Renal failure	0.66	0.28–1.56	NS	–	–	–
Previous bleeding	2.60	1.44–4.68	0.001	2.53	1.37–4.64	0.002
Use of NSAID/ corticosteroids	1.35	0.41–4.41	NS	–	–	–
Anticoagulation naïve	1.34	0.59–3.02	NS	–	–	–

NSAID = nonsteroidal anti-inflammatory drugs; NS = not significant

Ischaemic stroke and TIA occurred in 3 and 2 patients, respectively. Concerning MBs, spontaneous and post-traumatic intracranial haemorrhage occurred in one and six patients each.

No significant difference was observed between DOAC and VKA treated patients in the risk for ischaemic stroke/TIA/SSE (SHR 0.78, 95% 0.30–2.04, $p = .620$) and for MB (SHR 1.43, 95% 0.77–2.65, $p = .250$) (Figs. 1–2). Rates of fatal ischaemic stroke/TIA/SE or MB were 2.8% and 1.1% patient-year in DOAC and VKA patients, respectively.

During the study period, 49 DOAC patients (19.4% patient-year) and 97 VKA patients (15.0% patient-year) died. Among VKA patients, 72 permanently discontinued treatment (11.1% patient-year) and 38 (12.6%) were shifted to DOACs during the study period.

In DOAC patients, 23 permanently discontinued treatment (9.1% patient-year) and 15 were shifted to a different anticoagulant (12 patients to DOAC and 3 patients to VKAs). The dose of DOAC was reduced in five patients due to worsening in renal function.

Compared to patients on VKAs, those on DOACs had a lower rate of permanent discontinuation (SHR 0.41, 95% CI 0.23–0.74, $p = .003$) (see Fig. 3 in Ref [6]).

Considering both permanent discontinuation and death as competitive risks, no significant difference was observed in terms of ischaemic stroke/TIA/SE (SHR 0.75, 95% CI 0.29–1.93, $p = .550$) and MB (SHR 1.34, 95% CI 0.73–2.41, $p = .340$) between DOACs and VKAs.

Finally, in the sub-group analysis of anticoagulant naïve patients and new users the risks of ischaemic stroke/TIA/SE and that of MB were not significantly different between DOACs and VKAs treated patients (see Table 2 in Ref [6]).

4. Discussion

This study in patients aged 90 years or older with non-valvular AF treated with oral anticoagulants, shows a relatively low rate of ischaemic stroke/TIA/SE with the drawback of a not negligible rate of MB. Patients on DOACs had a numerically higher incidence of bleeding complications and death compared to patients on VKAs but none of these differences was statistically significant.

According to currently available evidence, age over 75 in absence of additional risk factors and of anticoagulant treatment accounts for an estimated annual risk for stroke/SE of about 3.6% [8]. Based on that evidence, current guidelines recommend that AF patients aged 75 or older should receive anticoagulant treatment [16]. However, advanced age is associated with an increased risk for bleeding during anticoagulant treatment [3]. Thus, the clinical benefit of anticoagulant treatment should be balanced against the increase in MB. In AF patients aged 75 years or more, warfarin was shown to reduce the risk of thromboembolic events without an increased risk of bleeding compared with aspirin [17]. In patients aged 85 years or more included in the AVERROES trial, apixaban dramatically reduced the rate of stroke or SE as compared with aspirin with similar rates of MB [18]. In the PREFER-AF registry, oral anticoagulants, mostly warfarin, reduced the risk of thromboembolic events compared with no antithrombotic treatment or antiplatelet therapy in AF patients aged 85 years or more. Similar risk of bleeding was reported on anticoagulants and aspirin treated patients [19]. However, the effectiveness and safety of anticoagulant treatment in patients aged 90 years or older is undefined as these patients are often excluded or substantially under-represented in randomized or cohort studies. Our findings in nonagenarians AF expand previous observations by showing an acceptable rate of ischaemic stroke/SE during anticoagulant treatment at the cost of a not negligible risk for MB. Moreover, a previous ischemic stroke/TIA/SE or a previous MB were associated with an increased risk of thromboembolic events or bleeding, respectively, confirming the relevance of personal medical history in the decision making process of anticoagulant treatment.

As expected, we observed a high rate of death. These findings confirm the peculiar frailty of this population of patients. However, the risks of thromboembolism and MBs were only partially influenced by the competing risk of death (Fig. 1). It should be noted that only about 10% of deaths was deemed to be due to fatal thromboembolic or bleeding events.

In our study, the risk of ischaemic stroke/TIA/SE and MB did not significantly differ between DOAC and VKA patients. The risk for MB was numerically higher with DOACs but not significantly different compared with VKAs. Spontaneous intracranial haemorrhage was less frequent with DOAC-compared to VKA-patients. These results are similar to those of a recent large retrospective study of the National Health Insurance Research Database in Taiwan AF patients aged 90 years or older [20]. This analysis showed that compared with VKAs, DOACs were associated with a lower risk of intracranial bleeding (HR 0.32; 95% CI 0.10–0.97 in competing risk model for mortality), with no difference in risk of ischaemic stroke. Data from randomized controlled studies are scarce in this setting as only 0.5% AF patients in the ARISTOTLE trial and 0.4% AF patients in the RE-LY trial were aged 90 years or older [21,22]. By pooling the results of these studies in the subgroups of patients aged 75 years or more, DOACs were more effective than VKAs (OR 0.65, 95% CI 0.5–0.9) for the prevention of stroke or SE with similar risk of major or clinically relevant bleeding (OR 1.02, 95% CI 0.7–1.4) [23]. Overall, while awaiting for definitive evidence of their efficacy and safety in nonagenarians of AF, DOACs could be considered the agents of choice in these patients on the basis of reported non-inferiority, possible reduction of intracranial bleeding and ease of use. In fact, recent European consensus guidelines recommend the use of oral FXa inhibitors over VKAs in elderly with AF [16].

In our study, the majority of patients on DOACs received the reduced dose. These patients were more often female and slightly older compared to those receiving standard doses of DOACs. This is in line with the recent European consensus guidelines, also taking into account recommendations on dosing and renal function [16]. Notably, none of the fatal bleeding events occurred in patients receiving standard dose of DOACs.

We used a competing risk analysis for the study [24,25]. This approach is not common in clinical research outside the cancer setting. A competing risk is an event whose occurrence precludes the occurrence of the primary event of interest. In our study examining time to ischemic stroke or systemic embolism and time to major bleeding, the cumulative incidence of death due to other causes exceeded that of the study outcome events at each point in time. Based on this evidence, death attributable causes different from ischemic stroke or major bleeding was considered a competing risk. This approach allowed avoiding overestimation of the cumulative incidence of study outcome events in the presence of the competing events [24,25]. By a methodological point of view, the choice of modelling the subdistribution hazard function according to the Fine and Gray method was preferred as it allows to estimate the effect of covariates on the cumulative incidence function for the event of interest [26,27].

A not negligible proportion of patients discontinued anticoagulant treatment during the study. A higher rate of permanent discontinuation was observed in VKAs compared to DOACs patients. However, when considering both permanent discontinuation and death as competing risk, no significant differences were observed between DOACs and VKAs in term of ischaemic stroke/TIA/SE and MB. Physician or patient's decision, high risk of falls and poor adherence were some of the main reasons of discontinuation in VKAs patients. Thanks to their predictable effect without need of monitoring and less food or drugs interaction, DOACs may improve treatment adherence.

This study has some limitations. Data collection followed a prospective design for DOAC patients and a retrospective design for VKA patients. These different approaches could have influenced the accuracy of study outcome assessment. However, our final results are consistent with currently available evidence in the elderly AF patients. In order to deal with potential bias and confounders, several sub-analyses were reported. Comparing anticoagulation naïve vs non-naïve patients, no significant difference was observed in terms of either ischaemic stroke/TIA/SE or MB. Moreover, in order to account different duration of anticoagulation before inclusion in the study, an analysis was performed in new users vs non-new users patients, to deal with possible 'healthy patient bias' [14]. Again, no significant difference was observed in terms of either ischaemic stroke/TIA/SE or MB in new users-patients vs non-new user regardless of type of anticoagulants (VKAs or DOACs). However, some of these analyses may have been influenced by under-power for limited sample size. Moreover, decision for type and dosage of DOAC was in charge of the attending physician. This may lead to generate further bias despite extensive confounder adjustment strategies.

In the context of its limitations due to the non-randomized design, mixed design of the study, absence of patients without anticoagulation as controls, unavailability of information such as Charlson comorbidity Index, our study has some strengths. The prospective data collection of the DOACs arm and the inclusion of an unselected population are some of these. These features allowed to provide a real-life picture of patients with AF aged 90 years or older receiving oral anticoagulant treatment.

In conclusion, our study suggests that oral anticoagulants seem to be safely and effectively administered in AF patients aged 90 years or older. However, further larger studies are needed to validate our results in unselected nonagenarian patients with AF.

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Declarations of interest

None.

References

[1] A.J. Camm, P. Kirchhof, G.Y. Lip, U. Schotten, I. Savelieva, S. Ernst, et al., Guidelines for the management of atrial fibrillation: the task force for the management of atrial fibrillation of the European Society of Cardiology (ESC), Europace 12 (2010) 1360–1420.
[2] A.S. Go, E.M. Hylek, K.A. Phillips, Y. Chang, L.E. Henault, J.V. Selby, et al., Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study, JAMA 285 (2001) 2370–2375.
[3] S.S. Chugh, R. Havmoeller, K. Narayanan, D. Singh, M. Rienstra, E.J. Benjamin, et al., Worldwide epidemiology of atrial fibrillation: a global burden of disease 2010 study, Circulation 129 (2014) 837–847.
[4] P.A. Wolf, R.D. Abbott, W.B. Kannel, Atrial fibrillation as an independent risk factor for stroke: the Framingham study, Stroke 22 (1991) 983–988.
[5] V. Pengo, C. Legnani, F. Noventa, G. Palareti, ISCOAT Study Group (Italian Study on Complications of Oral Anticoagulant Therapy). Oral anticoagulant therapy in patients with nonrheumatic atrial fibrillation and risk of bleeding. A multicenter inception cohort study, Thromb. Haemost. 85 (2001) 418–422.
[6] M. Giustozzi, M.C. Vedovati, M. Verso, L. Scrucca, S. Conti, P. Verdecchia, et al., Data on the use of oral anticoagulants in patients aged 90 years or older with atrial fibrillation, Int. J. Cardiol. Data in Brief (2019).
[7] M. Giustozzi, M.C. Vedovati, P. Verdecchia, L. Pierpaoli, M. Verso, S. Conti, et al., Vitamin K and non-vitamin K antagonist oral anticoagulants for non-valvular atrial fibrillation in real-life, Eur. J. Intern. Med. 33 (2016) 42–46.
[8] S. Schulman, C. Kearon, Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients, J. Thromb. Haemost. 3 (2005) 692–694.
[9] G.Y. Lip, R. Nieuwlaat, R. Pisters, D.A. Lane, H.J. Crijms, Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on Atrial Fibrillation, Chest 137 (2010) 263–272.
[10] R. Pisters, D.A. Lane, R. Nieuwlaat, C.B. de Vos, H.J. Crijns, G.Y. Lip, A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey, Chest 138 (2010) 1093–1100.
[11] F. Rosendaal, S. Cannegieter, F. Van Der Meer, E. Briet, A method to determine the optimal intensity of oral anticoagulant therapy, Thromb. Haemost. 69 (1993) 236–239.
[12] P.C. Austin, D.S. Lee, R.B. D'Agostino, J.P. Fine, Developing points-based risk-scoring systems in the presence of competing risks, Stat. Med. 35 (2016) 4056–4072.
[13] G. Schwartz, Estimating the dimension of a model, Ann. Stat. 6 (1978) 461–464.
[14] M.A. Brookhart, A.R. Patrick, C. Dormuth, et al., Adherence to lipid lowering therapy and the use of preventive health services: an investigation of the healthy user effect, Am. J. Epidemiol. 166 (2007) 348–354.
[15] L. Scrucca, A. Santucci, F. Aversa, Regression modeling of competing risk using R: an in depth guide for clinicians, Bone Marrow Transplant. 45 (2010) 1388–1395.
[16] F. Andreotti, B. Rocca, S. Husted, R.A. Ajjan, J. ten Berg, M. Cattaneo, et al., ESC thrombosis working group. antithrombotic therapy in the elderly: expert position paper of the European Society of Cardiology Working Group on Thrombosis, Eur. Heart J. 36 (2015) 3238–3249.
[17] J. Mant, F.D. Hobbs, K. Fletcher, A. Roalfe, D. Fitzmaurice, G.Y. Lip, et al., Midland Research Practices Network (MidReC). Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the aged study, BAFTA): a randomised controlled trial, Lancet 370 (2007) 493–503.
[18] S.J. Connolly, J. Eikelboom, C. Joyner, H.C. Diener, R. Hart, S. Golitsyn, et al., AVERROES steering committee and investigators. Apixaban in patients with atrial fibrillation, N. Engl. J. Med. 364 (2011) 806–817.
[19] G. Patti, M. Lucerna, L. Pecen, J.M. Siller-Matula, I. Cavallari, P. Kirchhof, et al., Thromboembolic risk, bleeding outcomes and effect of different antithrombotic strategies in very elderly patients with atrial fibrillation: a sub-analysis from the PREFER in AF (PREvention oF Thromboembolic Events-European Registry in Atrial Fibrillation), J. Am. Heart Assoc. 6 (7) (2017) (pii:e005657).
[20] T.F. Chao, C.J. Liu, Y.J. Lin, S.L. Chang, L.W. Lo, Y.F. Hu, et al., Oral anticoagulation in very elderly patients with atrial fibrillation: a nationwide cohort study, Circulation 3 (138) (2018) 37–47.
[21] C.B. Granger, J.H. Alexander, J.J. McMurray, R.D. Lopes, E.M. Hylek, M. Hanna, et al., ARISTOTLE committees and investigators. Apixaban versus warfarin in patients with atrial fibrillation, N. Engl. J. Med. 365 (2011) 981–992.
[22] S.J. Connolly, M.D. Ezekowitz, S. Yusuf, J. Eikelboom, J. Oldgren, A. Parekh, et al., RELY steering committee and investigators. Dabigatran versus warfarin in patients with atrial fibrillation, N. Engl. J. Med. 361 (2009) 1139–1151.
[23] M. Sharma, V.R. Cornelius, J.P. Patel, J.G. Davies, M. Molokhia, Efficacy and harms of direct oral anticoagulants in the elderly for stroke prevention in atrial fibrillation

and secondary prevention of venous thromboembolism: systematic review and meta-analysis, Circulation 132 (2015) 194–204.
[24] B. Lau, S.R. Cole, S.J. Gange, Competing risk regression models for epidemiologic data, Am. J. Epidemiol. 170 (2009) 244–256.
[25] H. Putter, M. Fiocco, R.B. Geskus, Tutorial in biostatistics: competing risks and multi-state models, Stat. Med. 26 (2007) 2389–2430.
[26] J.P. Fine, R.J. Gray, A proportional hazards model for the subdistribution of a competing risk, J. Am. Stat. Assoc. 94 (1999) 496–509.
[27] P.C. Austin, D.S. Lee, J.P. Fine, Introduction to the analysis of survival data in the presence of competing risks, Circulation 133 (2016) 601–609.