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Incidence of bleeding in patients with atrial fibrillation and advanced liver fibrosis on treatment with vitamin K or non-vitamin K antagonist oral anticoagulants

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ABSTRACT

Objectives: To investigate the incidence of bleeding events in atrial fibrillation (AF) patients treated with vitamin K (VKAs) or non-vitamin K antagonist oral anticoagulants (NOACs) screened for the presence of liver fibrosis (LF).
Background: Previous studies provided conflicting results on bleeding risk in AF patients with liver disease on VKAs, and no data on NOACs in this setting are available.
Methods: Post-hoc analysis of a prospective, observational multicentre study including 2330 AF outpatients treated with VKAs ($n = 1297$) or NOACs ($n = 1033$). Liver damage was quantified by the FIB-4 score (>3.25), a validated marker of LF. The primary endpoint was the incidence of any bleeding, according to ISTH classification.
Results: A high FIB-4 was present in 129 (5.5%) patients: 77 (5.9%) on VKA and 52 (5.0%) on NOACs ($p = 0.344$). During follow-up, 357 (15.3%) patients experienced a bleeding: 261 (80 major and 180 minor) with VKAs (7.2%/year), and 96 (40 major and 56 minor) with NOACs (6.4%/year). In VKA-treated patients, but not in those on NOACs, FIB-4 >3.25 was associated with higher major bleeding (14.3% vs. 5.6%, log-rank test $p < 0.001$). Multivariable Cox regression model showed that FIB-4 was associated with major bleeding only in VKA-treated patients (HR: 3.075, 95% CI 1.626–5.818, $p = 0.001$). On multivariable analysis, FIB-4 was not significantly associated with CVEs neither in VKA or NOAC-treated patients.
Conclusion: We found a significant association between LF and major bleedings in AF patients treated with VKA, which was not evident in patients on NOACs.

1. Introduction

Atrial fibrillation (AF) is associated with a high risk of thromboembolic events and mortality [1], and is frequently associated with a number of atherosclerosis risk factors, which confer an increased risk of cardiovascular events (CVEs), such as myocardial infarction (MI) [2,3].

Oral anticoagulants, both vitamin K antagonists (VKAs) and the non-VKA oral anticoagulants (NOACs) that inhibit thrombin or factor Xa, are recommended for thromboprophylaxis in AF [4]. Nevertheless, anticoagulation is associated with an increased risk of bleeding, with an estimated risk of major bleeding of 0.3–0.5% per year for VKAs [5], which is related to various modifiable (i.e. adequate blood pressure control, stable anticoagulation and concomitant drugs) and non-modifiable risk factors (i.e. increasing age and previous cardio- and cerebrovascular events or a first episode of major bleeding) [4].

The coexistence of chronic liver disease (CLD) in AF patients treated with oral anticoagulants is a matter of concern, as the impact of anticoagulation in this particular subset of patients is still unclear. A first issue is related to the definition of CLD, as it includes many different pathological conditions, ranging from simple fatty liver to viral hepatitis

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and liver cirrhosis. Moreover, patients with advanced CLD may have haemostatic abnormalities, which may favour bleeding [6,7].

Thus far, the only available data stem from retrospective studies have only included warfarin-treated AF patients and do not provide information on the severity of liver failure, anticoagulation status (or type) and bleeding [6,8–10]. Also, patients with AF and liver damage have been excluded from recent phase 3 clinical trials with NOACs, based on raised levels of serum transaminases or bilirubin. Hence, it is still difficult to appreciate if patients with AF and liver damage are actually at increased risk of bleeding if treated with oral anticoagulants.

A common feature of advanced CLD is the presence of liver fibrosis (LF), which is associated with an increased risk of death [11]. Among non-invasive markers of LF, the FIB-4 score displayed a good accuracy in detecting the presence of LF, and was associated with increased mortality [12]. The utility of FIB-4 score relies on its ability to identify advanced LF also in patients with nearly normal or only mildly elevated serum liver enzymes, which indeed do not exclude the presence of significant liver disease [13].

We performed a post-hoc analysis of a prospective, observational, multicentre study to evaluate the prevalence of LF, as assessed by high FIB-4, among patients on oral anticoagulation and second, the safety of VKAs and NOACs in AF patients with and without LF.

2. Methods

We performed a post-hoc analysis of prospective multicentre observational cohort study including 2330 AF patients treated with VKAs ($n = 1297$) or NOACs ($n = 1033$). All patients treated with VKAs (warfarin or acenocumarol) were locally monitored in specialized anticoagulation clinics for INR determination and VKA prescription. None of the patients measured INRs at home (i.e. with point of care devices) and time in therapeutic range (TTR) was used to assess the quality of anticoagulation according to the linear interpolation method described by Rosendaal [14]. NOACs were prescribed according to the regulatory Italian Agency of Drugs (AIFA) indications and European Society of Cardiology (ESC) guidelines [4].

Exclusion criteria were: prosthetic heart valves, cardiac revascularization in the previous year, severe cognitive impairment, chronic autoimmune systemic diseases, and active cancer. Patients treated with antiplatelet drugs alone were also excluded. At baseline, information about personal medical history and concomitant medications were collected, and HAS-BLED (the labile INR was scored 0 in NOAC users) and CHA_2DS_2-VASc scores were calculated. Cardiovascular risk factors, such as arterial hypertension [15], type 2 diabetes mellitus [16] and heart failure [17] were defined according to international guidelines. Patients underwent routine laboratory analyses including AST (U/l), ALT (U/l), haemoglobin (g/dl) and platelet count ($\times 10^9$/l).

The presence of significant LF was assessed non-invasively by FIB-4 in all patients; FIB-4 was calculated according Sterling et al. by the formula: age (years) × AST (U/l) / PLT (10^9/l) × ALT (U/l)$^{1/2}$. A value of FIB-4 >3.25 was set as cut-off for LF [18]. FIB-4 has been validated in different settings of CLD, such viral and metabolic liver disease [19,20].

The occurrence of any major or minor bleeding events was the primary endpoint of the study. A detailed classification of bleeding events is reported in ref. [21].

The secondary endpoint was a composite of CVEs including fatal/non-fatal MI or ischaemic stroke, cardiac revascularization (stent placement or coronary artery bypass graft), cardiovascular death, transient ischaemic attack (TIA) and systemic embolism. Definitions of each CVE are reported in ref. [21].

Data on bleedings and CVEs were prospectively collected during follow-up and only the first event was used for the analysis. All patients provided a written informed consent before being included in the study. The study protocol was approved by the local ethical board of Sapienza-University of Rome and was conducted according to the principles of the Declaration of Helsinki.

2.1. Statistical analysis

Categorical variables were reported as counts (percentages). The normal distribution of parameters was assessed by the Kolmogorov–Smirnov test. Continuous variables were expressed as mean ± standard deviation, or median and interquartile range. Independence of categorical variables was tested with the χ^2 test. The Student *t*-test for unpaired samples was used to compare means.

The cumulative incidence of bleedings and CVEs were estimated using a Kaplan–Meier product-limit estimator. Survival curves were formally compared using the log-rank test. Cox proportional hazards analyses were used to calculate the adjusted relative hazard ratio (HR) by each clinical variable. Due to a significant difference in the length of follow-up, a separate survival analysis was performed according to the use of VKAs or NOACs, respectively. Covariates used as candidates for multivariable models included: low TTR (<70%, only for VKA patients), age, sex, current cigarette smoking, arterial hypertension, diabetes, high FIB-4 (>3.25), previous cardiac events, previous cardiovascular events, heart failure, haemoglobin, antiplatelet drugs and statins. The final multivariable model was chosen through forward stepwise selection.

The following considerations provide evidence that our post-hoc analysis is sufficiently powered for formal claims. Using pilot study data we assumed a proportion of 11.5% CLD patients with 5% hazard rate, 5000 patients/year of accrual and 1.5 years of follow-up. Hence, considering our study as a non-inferiority trial for the CLD patients with respect to safety, a hazard ratio limit defining equivalence of 1.25, a type I error rate of 5%, and a total sample size of 1700 guarantee a power of 90% for a one-sided non-inferiority test.

Statistical significance was set at a p value <0.05. All tests were two-tailed and analyses were performed using computer software packages (SPSS-18.0, SPSS Inc.).

3. Results

The cohort was composed of 2330 AF patients, of which 1297 were treated with VKAs and 1033 with NOACs (276 dabigatran, 365 apixaban, 358 rivaroxaban and 34 edoxaban). Characteristics of patients treated with VKAs or NOACs are reported in ref. [21]. Patients treated with NOACs were older, and more likely to have hypertension, heart failure and previous cerebrovascular events. For bleeding events, follow-up of patients treated with VKAs (3622 patient/years) was significantly longer than those treated with NOACs (1508 patients/years) (i.e. 33.5 ± 25.3 vs. 17.5 ± 11.8 months, $p < 0.001$ respectively).

Characteristics of patients experiencing a bleeding event or not are listed in ref. [21]. During follow-up, 357 (15.3%) patients experienced a bleeding event: 120 major and 237 minor bleedings. Of these, 261 (80 major and 181 minor) bleeding events were recorded in patients on VKAs (7.2%/year, 95% CI 6.3–8.1), and 96 (40 major and 56 minor) in NOAC patients (6.4%/year, 95% CI 5.2–7.8). Ref. [21] provides a detailed description of bleeding events in VKAs and NOACs-treated patients.

3.1. FIB-4 and bleeding events

In the whole cohort, 129 (5.5%) patients had a FIB-4 >3.25; characteristics of patients with and without high FIB-4 are listed in Table 1. When compared to those with normal FIB-4, patients with high FIB-4 were older, had higher transaminases, lower haemoglobin and platelet count and similar TTR (Table 1). Overall, 12 (9.3%) patients with high vs. 108 (4.9%) with normal FIB-4 had a major bleeding during follow-up: a descriptive analysis is provided in ref. [21].

Table 1
Clinical characteristics of patients according to the presence of liver fibrosis.

	Liver fibrosis (i.e. FIB-4 > 3.25)		*p* value
	No ($n = 2201$)	Yes ($n = 129$)	
Age (years)	74.4 ± 9.3	78.9 ± 7.5	<0.001
NOAC treatment (vs. VKA) (%)	44.6	40.3	0.363
Women (%)	46.3	39.5	0.146
Current cigarette smokers (%)	13.1	16.4	0.283
Persistent/permanent atrial fibrillation (%)	63.8	68.0	0.388
HAS-BLED score	1.7 ± 0.9	2.1 ± 0.8	<0.001
CHA_2DS_2-VASc score	3.2 ± 1.5	3.4 ± 1.2	0.086
Arterial hypertension (%)	86.1	88.4	0.598
Diabetes mellitus (%)	23.8	19.4	0.286
Heart failure (%)	14.9	13.3	0.702
Previous cerebrovascular events (%)	15.6	12.4	0.381
Previous cardiac events (%)	18.3	16.3	0.639
Anti-platelet drugs (%)	11.1	10.9	0.921
Statins (%)	41.0	40.3	0.927
Time in therapeutic range (%)[a]	60.0 ± 22.4	60.8 ± 21.4	0.737
AST (U/l)	22.2 ± 9.3	39.4 ± 22.5	<0.001
ALT (U/l)	23.6 ± 13.7	30.3 ± 23.0	<0.001
Haemoglobin (g/dl)	13.5 ± 1.6	13.1 ± 1.7	0.009
Platelet count ($*10^9$/l)	231.4 ± 64.9	137.5 ± 37.8	<0.001

[a] Only for VKA-treated patients.

Of 129 patients with LF, 77 (5.9%) were in the VKA group and 52 in the NOAC group (5.0%, $p = 0.344$). A detailed description of bleeding events in patients treated with VKAs or NOACs according to the presence of liver fibrosis is shown in Table 2.

In the VKA group, patients with high FIB-4 had a higher incidence of bleeding compared to those with normal FIB-4 (27.3% vs. 19.7%, log-rank test $p = 0.027$) (Fig. 1, panel 1). This difference was driven by major bleedings (14.3% vs. 5.6%, log-rank test $p < 0.001$) (Fig. 1, panel 2), while a similar rate of minor bleedings was found (13.0% vs. 13.9%, log-rank test $p = 0.778$, not shown). In the NOAC group, patients with and without high FIB-4 had similar rates of bleeding events (5.8% vs. 9.5%, log-rank test $p = 0.374$) (Fig. 1, panel 3), both major (1.9% vs. 4.0%, log-rank test $p = 0.477$) (Fig. 1, panel 4) and minor (3.8% vs. 5.5%, log-rank test $p = 0.571$, not shown).

Multivariable Cox regression models showed that FIB-4 was associated with major bleedings only in VKA-treated patients (HR: 3.075, 95% CI 1.626–5.818, $p = 0.001$, Table 3).

3.2. Cardiovascular events

Follow-up of patients treated with VKAs was 33.6 ± 22.1 months (3632 patients/years), and 18.5 ± 12.1 months for those treated with NOACs (1597 patient/years, $p < 0.001$ respectively). During follow-up, 169 CVEs occurred: 22 fatal/non-fatal ischaemic strokes, 21 TIAs, 31 cardiac revascularizations, 44 cardiovascular deaths, 44 fatal/non-fatal MI, and 7 systemic embolisms. Of these, 136 CVEs were in patients on VKAs (3.7%/year, 95% CI 3.1–4.4) and 33 on NOACs (2.1%/year, 95% CI 1.4–2.9, $p = 0.002$).

In the VKA group [21], patients with high FIB-4 had a higher incidence of CVEs compared to those with normal FIB-4 (2.1% vs. 9.8%, log-rank test $p = 0.005$). In the NOAC group [21], a similar rate of CVEs was observed between the two groups (5.8% vs. 3.0% in patients with and without high FIB-4, log-rank test, $p = 0.279$).

On multivariable analysis, FIB-4 was not significantly associated with CVEs neither in VKA or NOAC-treated patients (Table 3).

Table 2
Bleeding events in patients treated with VKAs or NOACs according to the presence of liver fibrosis.

	VKAs		NOACs	
	FIB-4 >3.25 ($n = 77$)	FIB-4 ≤3.25 ($n = 1220$)	FIB-4 >3.25 ($n = 52$)	FIB-4 ≤3.25 ($n = 981$)
Cerebral/subdural (n)	3	11	1	3
Gastrointestinal (n)	3	7	0	10
Muscular (n)	0	11	0	0
Articular (n)	0	9	0	1
Haematuria (n)	1	7	0	1
Epistaxis with fall in Hb (n)	2	3	0	0
Extended haematoma (n)	0	3	0	1
Respiratory (n)	0	2	0	0
Retroperitoneal (n)	0	2	0	0
Ocular (n)	2	11	0	1
Pericardial (n)	0	1	0	0
Metrorrhagia (n)	0	1	0	0
Decrease of Hb ≥2 g/dl (n)	0	1	0	22
Total (n)	11	69	1	39
Minor bleedings				
Epistaxis (n)	4	52	0	9
Gastrointestinal (n)	0	34	0	18
Conjunctival (n)	1	32	0	2
Haematuria (n)	2	22	1	13
Cutaneous (n)	2	14	1	2
Post-intervention (n)	1	3	0	2
Oral (n)	0	9	0	1
Respiratory (n)	0	2	0	3
Ear (n)	0	2	0	0
Metrorrhagia (n)	0	1	0	0
Decrease of Hb <2 g/dl (n)	0	0	0	4
Total (n)	10	171	2	54

4. Discussion

Our principal finding is that LF, as assessed by the non-invasive marker FIB-4, is associated with an increased risk of major bleedings in AF patients on treatment with VKAs, but does not seem to affect bleeding risk in patients treated with NOACs.

Data regarding the impact of oral anticoagulants in AF patients with advanced LF stem essentially from retrospective studies where diagnosis of liver disease was made by hospital discharge codes. For example, a retrospective study compared the effect of oral anticoagulants in patients with AF and liver cirrhosis treated ($n = 173$) or not ($n = 148$) with warfarin [22]. During follow-up, the two groups experienced similar rates of stroke, while bleeding complications were more frequent in warfarin-treated patients [22]. Due to the lack of an anticoagulated AF group without CLD, it is difficult to appreciate if warfarin-treated patients with CLD were actually at higher risk of bleeding. Consistently with the present study, two other retrospective studies found that in CLD patients with AF, anticoagulation with VKAs increased the risk of major bleeding compared to non-CLD subjects [23]. Other studies have investigated the rate of cerebral haemorrhage in AF patients with liver disease but the results are conflicting and difficult to interpret given the lack of detailed information regarding anticoagulant use during the follow-up, no clear definition of liver disease or missing TTR [6,8,9].

In order to investigate if bleeding complication in VKA-treated AF patients occurs depending upon the entity of liver damage, we analysed bleeding risk according to FIB-4 value, which is a ratio between transaminases and platelet count, and is considered a validated marker of significant liver fibrosis when its value is >3.25 [18]. In our observational study of anticoagulated AF patients, the rate of bleeding complications was 7.2%/year in VKA patients and 6.4%/year in NOAC ones, which is consistent with previous reports [24,25].

We found that VKA-treated AF patients with high FIB-4 had an increased risk of bleeding, indicating that the presence of advanced liver damage would increase the haemorrhagic risk in case of VKA administration. Classically, the increased risk of bleeding in patients with CLD has been attributed to the presence of the so-called "coagulopathy", which would predispose these patients to bleed. Recently, the concept that advanced CLD is associated with impaired clotting activation or platelet dysfunction has been challenged [26], as the relationship between gastrointestinal and intracerebral haemorrhage with indexes of clotting has never been firmly demonstrated [26,27]. Furthermore, while the rate of gastrointestinal bleeding, which is essentially related to hyper-dynamic flux of portal vein, is high in CLD patients, cerebral haemorrhage rate is similar to the general population [27].

In contrast, a hypercoagulable state, which may predispose to thrombosis in the peripheral and portal circulation, has been described in CLD patients [28]. This pro-thrombotic phenotype depends on increased rate of thrombin generation, resulting from an imbalance between factor VIII and the anticoagulant protein C and/or on increased circulating levels of endotoxins, which are known to up-regulate Tissue Factor [29].

These data are in keeping with recent laboratory and clinical evidence to suggest that advanced CLD is more frequently complicated by thrombosis than bleedings [30]. In accordance with this, we found that AF patients with FIB-4 >3.25 on treatment with VKA had a higher incidence of CVEs compared to those with normal FIB-4, confirming an elevated cardiovascular risk in this setting.

Another factor potentially influencing bleeding and CVE rate is the anticoagulation control, as documented by previous reports showing that CLD may influence TTR [31,32]. In our cohort, we did not observe a significant difference in TTR between patients with and without LF, but the validity of TTR, in patients with advanced CLD has been challenged as it may not entirely reflect the anticoagulation quality in these patients [33–36]. As VKAs are essentially metabolized by the liver [37], liver failure changes may negatively affect drug pharmacodynamics and eventually clotting time, that could not be captured by TTR.

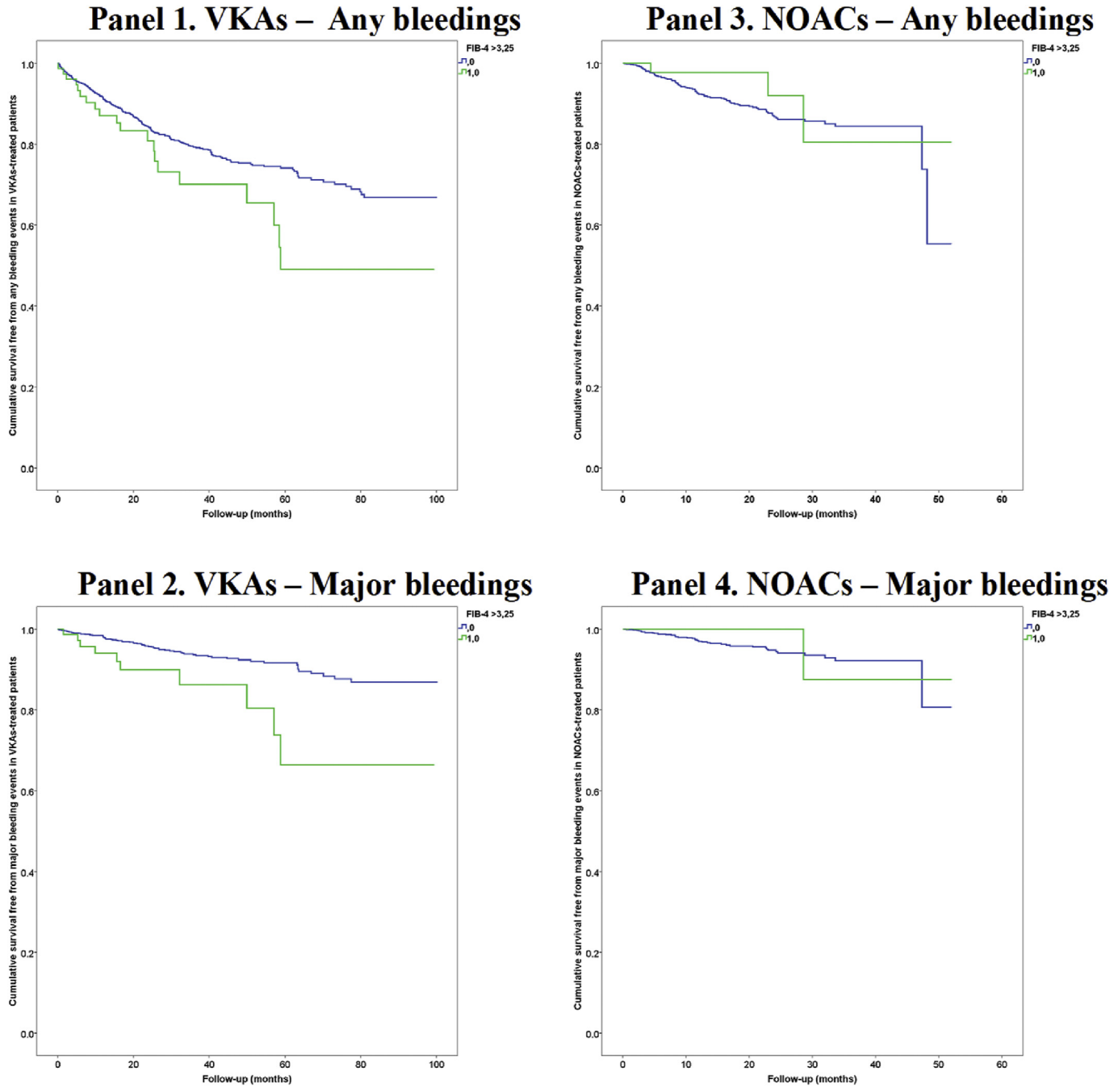

Fig. 1. Kaplan Meier curves for bleedings in patients treated with VKAs (left column, panel 1: any bleedings and panel 2: major bleedings) and NOACs (left column, panel 3: any bleedings and panel 4: major bleedings).

Differently from VKA, there was no difference in the rate of bleeding and CVEs in AF patients with and without LF treated with NOACs. These findings are clinically relevant, considering that AF patients with overt liver disease, such as those with high transaminases, were excluded by interventional trials with NOACs, so that evidence on this specific subgroup of high-risk patients is limited. Hence, this is the first report which analysed the impact of NOACs in AF patients with advanced LF. Our results suggest that a number of patients may be started on NOAC while having an unrecognized significant liver damage. We believe that this is an unmet need to be faced because of the burden of liver-related metabolic disorders such metabolic syndrome and diabetes, which are frequently associated with AF and may favour non-alcoholic fatty liver disease/steatohepatitis [38] and eventually LF [39]. Randomized interventional trials with NOACs in AF patients with advanced LF should be seriously considered.

5. Strengths and limitations

Given the observational design of the study and the small sample size of patients with CLD, the results are to be considered as hypothesis-generating. We used a simple, validated and reproducible marker for LF, which allows identifying AF patients with significant liver damage even in the presence of mildly abnormal levels of serum transaminases. However, despite a good correlation with liver histology findings [40], the FIB-4 score is a surrogate index of LF, which could not fully reflect the degree of liver failure. Another limitation is the inclusion

Table 3
Stepwise multivariable linear regression analysis of factors associated with specified endpoints according to the use of VKA or NOAC.

	p value	Hazard ratio	95% CI	
			Lower	Upper
VKAs — any bleeds				
Age	<0.001	1.033	1.016	1.050
Previous cardiac events	<0.001	1.721	1.288	2.300
Haemoglobin	0.012	1.105	1.022	1.195
VKAs — major bleeds				
FIB-4 >3.25	0.001	3.075	1.626	5.818
Previous cardiac events	0.013	1.903	1.145	3.164
NOACs — any bleeds				
Age	0.035	1.029	1.002	1.056
Diabetes	0.033	0.545	0.312	0.953
Haemoglobin	0.005	0.828	0.726	0.945
NOACs — major bleeds				
Age	0.008	1.065	1.017	1.115
Haemoglobin	<0.001	0.684	0.561	0.834
VKAs — CVEs				
Age	<0.001	1.109	1.079	1.141
Arterial hypertension	0.017	0.553	0.339	0.901
Diabetes	0.002	1.816	1.242	2.656
Previous cerebrovascular events	0.005	1.816	1.199	2.750
Previous cardiac events	<0.001	2.464	1.681	3.614
Smoking	0.001	2.023	1.351	3.029
TTR <70%	0.006	1.765	1.175	2.650
NOACs — CVEs				
Age	0.005	1.078	1.023	1.136
Previous cerebrovascular events	0.004	3.172	1.431	7.034

See Methods for the complete list of covariates.

of only Caucasian patients, thus the generalizability of the results to other ethnic groups is uncertain.

In conclusion, we found a significant association between LF and major bleedings in AF patients treated with VKAs, while this association was not evident in patients receiving NOACs.

Authors' conflict of interests

None related to this manuscript.

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