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Chronic Kidney Disease is a Predictor of Recurrent Bleeding in Patients With Atrial Fibrillation After Resuming Anticoagulant Therapy (based on REGistry of Long-term AnTithrombotic TherApy (REGATA-2)

Aim Patients with atrial fibrillation (AF) at high risk of thromboembolic complications who have had bleeding should strive to resume anticoagulant therapy. Existing traditional scales for assessing the risk of hemorrhagic complications are not highly specific for the risk of recurrent bleeding. Thus, searching is needed for clinical and laboratory predictors to identify patients who require a personalized monitoring regimen. The aim of the study was to assess the incidence rate and predictors of recurrent major and clinically significant bleeding in patients with AF after resumption of the anticoagulant therapy, as well as the contribution of changing the anticoagulant to the treatment safety.

Material and methods Based on a 5-year follow-up of 95 patients with AF who have had major and clinically significant bleeding, the incidence and clinical factors determining the recurrence of hemorrhagic complications were assessed.

Results According to the data of the 5-year follow-up, the recurrence rate of major/clinically significant bleeding was 16.9/100 patient-years. Changing the oral anticoagulant significantly reduced the risk of relapse after clinically significant bleeding and did not affect the risk of recurrence of major bleeding. The predictor for relapse of major/clinically significant bleeding during the therapy resumption was chronic kidney disease with a decrease in creatinine clearance to less than 60 ml/min, which increased the risk of relapse 2.27 times (95% confidence interval: 1.1253–4.6163; p=0.0221).

Conclusion The development of serious bleeding in a patient at high risk of thrombotic complications always requires a reassessment of risk factors and an adequate choice and dosage of the anticoagulant. Development of a unified protocol for the management of AF patients receiving anticoagulants and having a high risk of bleeding is essential and will reduce the risk of adverse outcomes.

Keywords Recurrent bleeding; changing oral anticoagulant; atrial fibrillation; chronic kidney disease

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Introduction

The administration of oral anticoagulants in patients with atrial fibrillation (AF) allowed significantly reducing the incidence of thromboembolic complications but creates a clinical dilemma when a physician has to deal in the daily practice with bleeding events more often than with strokes [1–4]. However, it has been shown that the mortality of AF patients is due to stroke in case of refusal of anticoagulants rather than the recurrence of fatal bleeding [5–7]. This is why the resumption of anticoagulant therapy (ACT) with the best possible correction of risk factors (RFs) is indicated to patients at high risk of developing thrombotic complications and with history of bleeding [1, 2, 8]. There is no unified scale of risk stratification in patients with history of bleeding, since conventional scales of risk assessment (HAS-BLED, ATRIA, HEMORRAGE, ABC) are not specific enough regarding the risk of recurrent hemorrhagic complications [5, 9]. It is relevant to determine clinical and laboratory factors associated with the recurrence of bleeding, which would frame risk stratification for patients resuming ACT.

Objective

Evaluate the frequency and predictors of recurrences of major and clinical relevant bleeding events in AF patients after ACT resumption and the contribution of OAC switch to treatment safety.

Material and Methods

This study is a fragment of the single-center prospective registry REGAT-2 (Registry of prolonged

Antithrombotic Therapy (NCT043447187)) conducted in the Academician Chazov National Medical Research Center (Russian Federation). The protocol of this registry was approved by the Ethics Committee. The eligible AF patients were enrolled from 1998 to 2017. The inclusion criterion was the indication for ACTs: the presence of at least one RF according to CHADS2 (patients included from 1998 to 2011) and CHA2DS2-VASc ≥1 (patients included since 2012). The registry includes a total of 640 patients with AF at high risk of thromboembolism receiving anticoagulants (vitamin K antagonist or direct oral anticoagulant (DOAC)). We have previously described the patient cohort in detail [10, 11]. In accordance with our objective, this fragment of the study included 95 patients who resumed anticoagulants after major or clinical relevant bleeding event as assessed according to the GARFIELD-AF register [12]. Major or clinical relevant bleeding events according to the GARFIELD-AF criteria were also reported in the next 5 years of follow-up.

The baseline clinical characteristics of patients who resumed anticoagulants after the first episode of major (n=44) and clinical relevant bleeding (n=51) are presented in Table 1.

According to the data provided, patients who resumed anticoagulants after major (n=44) or clinical relevant (n=51) bleeding events were at high risk of thromboembolic complications (the median CHA2DS2-VASc score was 4). At the time of bleeding, 82.1% of patients administered warfarin, and every third bleeding event occurred in patients taking an OAC in combination with one or two antiplatelet agents.

The data obtained were processed in Statistica 10.0 and MedCalc 10.0. The incidence of adverse events is expressed as a percentage and a number of events per 100 patient-years. Non-parametric quantitative variables are presented as the medians and the interquartile ranges (Me [25%; 75%]). Survival curves were constructed using the Kaplan-Meier method. The chi-squared test and the Mann-Whitney test were used to evaluate the significance of intergroup differences. The Cox proportional hazard model was used to assess prognostic significance of the variables. The differences were statistically significant at $p < 0.05$.

Table 1. Clinical characteristics of patients with atrial fibrillation who restarted oral anticoagulants after the first episode of major/clinically significant bleeding (n = 95)

Parameter	Value
Age, years	70 [63.5; 74.5]
Male, n (%)	51 (53.7)
Location of the first major or clinically significant bleeding, n (%)	
• Gastrointestinal	31 (32.6)
• Intracranial	2 (2.1)
• Hematuria	18 (18.9)
• Nasal	24 (25.3)
• Other	20 (21.1)
CHA2DS2 VASc score	4 [3; 5]
HAS-BLED, score	3 [3; 4]
History of ischemic stroke/ systemic embolism/TIA, n (%)	25 (26.3)
Chronic heart failure, n (%)	34 (35.8)
Coronary artery disease, n (%)	46 (48.4)
Arterial hypertension, n (%)	55 (84.6)
Diabetes mellitus, n (%)	33 (34.7)
Chronic kidney disease stage ≥3a, n (%)	21 (22.1)
Anticoagulant taken at the time of bleeding	
Warfarin, n (%)	78 (82.1)
DOAC (apixaban, dabigatran or rivaroxaban), n (%)	17 (17.9)
Anticoagulant monotherapy at the time of bleeding, n (%)	64 (67.4)
Combination of an anticoagulant with one or two antiplatelet agents at the time of bleeding, n (%)	31 (32.6)

The data are expressed as the medians and interquartile ranges (Me [Q1; Q3]) unless otherwise specified. TIA, transient ischemic attack; DOAC, direct oral anticoagulant.

Results

Frequency of recurrent bleeding events after anticoagulant resumption within the 5-year follow-up period

According to the 5 year follow-up data, hemorrhagic complications recurred in 34 of 95 patients, which accounted to 16.9/100 patient-years. The incidence of ischemic stroke (IS) in the same patients was 3.3/100 patient-years.

Except for 2 patients with history of clinical relevant bleeding who experienced major bleeding as the second event after treatment resumption, all the rest had the new-onset and recurrent events of the same severity. One major recurrent gastrointestinal bleeding event was fatal.

The median number of days before recurrence of hemorrhagic complications after treatment resumption was 91 [52; 172.5] days, and 64 [37.5; 523.5] days and 127 [90; 151] days before the recurrence of major and clinical relevant bleeding events, respectively.

The Kaplan-Meier curves showed that, according to the 5 year follow-up data, the proportion of patients without recurrent bleeding was 0.59, and the proportion of patients without IS was 0.81 (Figure 1, A). At the same time, the proportion of patients without major bleeding recurrence within 5 years was 0.72, and the proportion of

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patients without clinical relevant bleeding recurrence was 0.49 (Figure 1, B).

Effect of oral anticoagulant switch on the risk of bleeding recurrence

After the first hemorrhagic complication, 59 (62.1%) of 95 patients continued taking the same OAC, the drug was switched in 36 (37.9%) patients: warfarin was replaced with DOAC (n = 32), a DOAC was switched to another DOAC (n = 2), and warfarin was resumed after bleeding in 2 patients with major bleeding associated with the switch of warfarin to a DOAC (Figure 2).

The Kaplan-Meier curves showed that the switch of an OAC did not have a significant effect on the frequency of bleeding recurrence (Figure 3, A). However, a separate assessment showed that the switch of anticoagulants

Figure 1. Percentage of patients without recurrences of all complications (hemorrhagic complications and ischemic stroke (**A**) and separately major and clinical relevant bleeding (**B**) in the follow-up period (Kaplan-Meier curves)

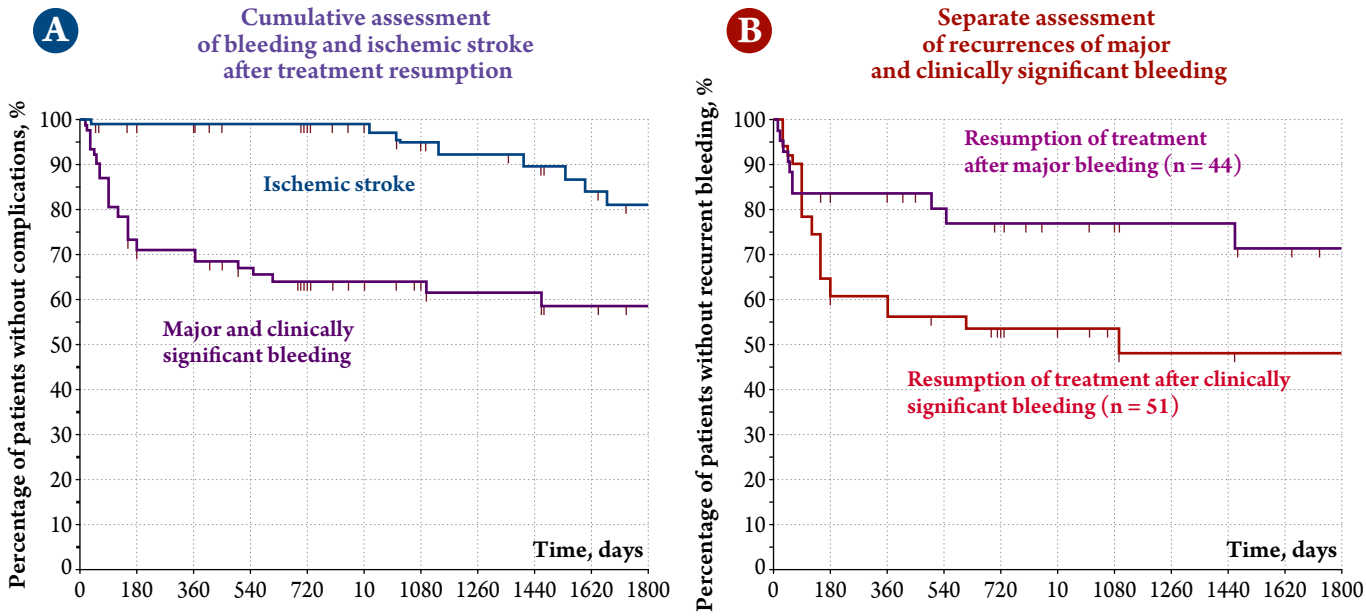
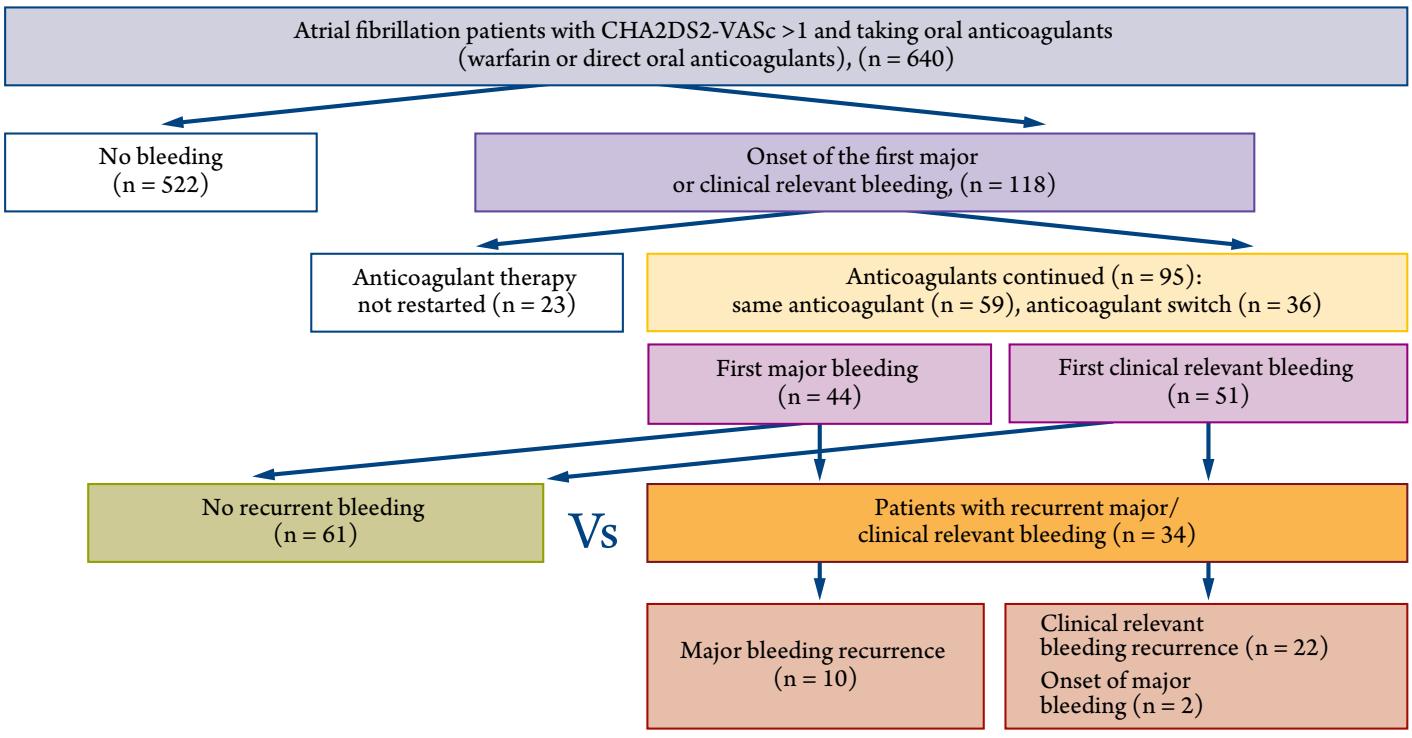


Figure 2. Study design

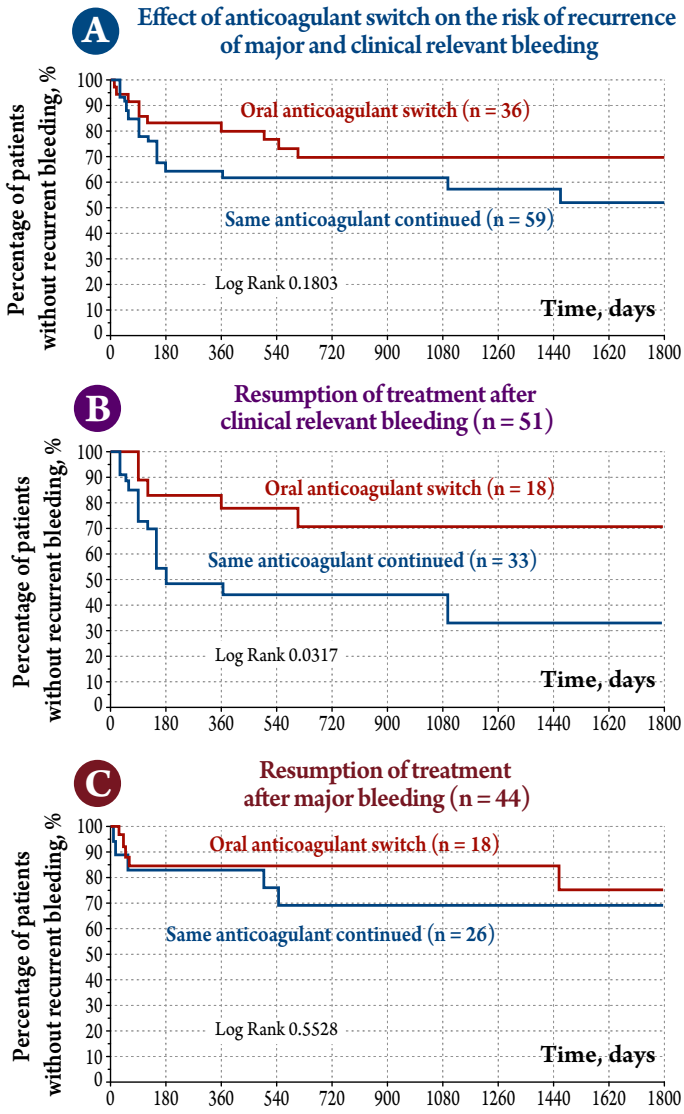


significantly reduced the risk of recurrent clinical relevant bleeding: the proportion of patients who had no recurrent bleeding in the 5 year follow-up period was significantly higher among patients who underwent the drug switch (0.71 vs. 0.33, p=0.0317). In a separate safety assessment of treatment resumption, anticoagulant switch after major hemorrhagic complications did not reduce the risk of bleeding recurrence (Figure 3, B, C).

Determination of clinical factors associated with recurrent bleeding after anticoagulant resumption

Comparison of the indicators of 34 patients with recurrent hemorrhagic complications with a group of 61 patients who had no recurrences in the follow-up period showed no relation between recurrent bleeding and sex, age, and the estimated risk of thromboembolic and hemorrhagic complications (Table 2).

Figure 3. Figure 3. Percentage of patients without recurrence of all hemorrhagic complications (**A**), clinical relevant (**B**) and major (**C**) bleeding in the follow-up period with and without anticoagulant switch (Kaplan-Meier curves)



The incidence of chronic kidney disease (CKD) stage ≥3a was 2 times higher in patients with recurrent bleeding than in patients without recurrent hemorrhagic complications in the follow-up period.

Assessment of the effect of CKD on the risk of recurrent hemorrhagic complications in patients who continue anticoagulants

The Kaplan-Meier curves (Figure 4, A) showed that the proportion of patients who had no recurrent bleeding in the follow-up period was significantly lower among patients with CKD stage ≥3a (0.37 vs. 0.65, log-rank test = 0.0171).

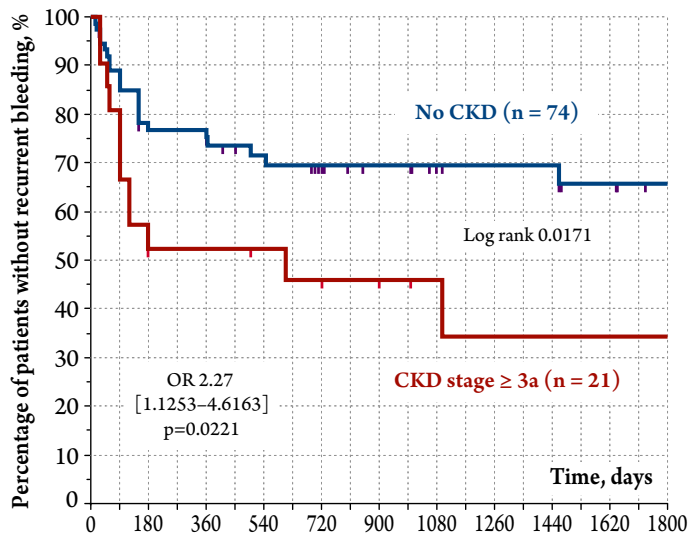
The Cox proportional hazard model revealed that CKD ≥3a was the only predictor of the recurrence of major/clinical relevant bleeding after the OAC resumption; it increased 2.27 times the risk of recurrence (95% confidence interval (CI) 1.1253–4.6163; p=0.0221).

Discussion

Patients with AF and history of bleeding represent a fairly large clinical group in daily medical practice. It has been debated for a long time whether it is reasonable to resume anticoagulant therapy. However, the 2016 consensus document of the European Society of Cardiology working group points out the clinical benefit of resuming anticoagulants after major bleeding if the risk of thrombosis exceeds the risk of bleeding or they are equal [8].

Doctors are undoubtedly beware of recurrent bleeding events, the frequency of which according to our data was 16.9/100 patient-years. However, the priority is given to stroke prevention. Our previous analysis of the 12-month follow-up data of patients with history of major bleeding

Figure 4. Percentage of patients without recurrent major bleeding in the follow-up period who had CKD at the time of bleeding or not (Kaplan-Meier curves)



OR, odds ratio; CKD, chronic kidney disease.

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Table 2. Clinical characteristics of patients with atrial fibrillation with and without recurrent bleeding

Parameter	Patients who experienced recurrent major or clinical relevant bleeding (n = 34)	Patients who had no recurrent bleeding in the follow-up period (n = 61)	p
Male, n (%)	16 (47.1)	35 (57.4)	0.3933
Age, years	70 [63.5; 73]	69 [64; 75]	0.8450
CHA2DS2 VASc score	4 [3; 5]	4 [3; 5]	0.8423
HAS-BLED score	3 [2; 4]	3 [2; 4]	0.7142
History of ischemic stroke/TIA/ systemic embolism, n (%)	9 (26.5)	16 (25)	0.8110
CHF, n (%)	14 (41.2)	20 (32.8)	0.6558
CAD, n (%)	13 (38.2)	33 (51.6)	0.1370
Arterial hypertension, n (%)	26 (76.5)	52 (85.2)	0.4025
Diabetes mellitus, n (%)	12 (35.3)	21 (34.4)	1.0000
Chronic kidney disease stage ≥3a, n (%)	12 (35.3)	9 (14.8)	0.0371
Cognitive decline/dementia, n (%)	14 (41.2)	13 (21.3)	0.0571
Administration of NSAIDs, n (%)	6 (17.6)	4 (6.6)	0.1595
Regular alcohol consumption, n (%)	5 (14.7)	13 (21.3)	0.5867
Continuing need for combined use of an anticoagulant and an antiplatelet agent, n (%)	7 (20.6)	9 (14.8)	0.5694

The data are expressed as the medians and interquartile ranges (Me [Q1; Q3]) unless otherwise specified. TIA, transient ischemic attack; CHF, chronic heart failure; CAD, coronary artery disease; NSAID, non-steroidal anti-inflammatory drug.

[13] showed that 15.8% of patients those who did not resume anticoagulants suffered IS, and the incidence of IS among those who resumed treatment was 2.2%. Analysis of this fragment of the study showed that the 5-year incidence of IS among patients who resumed anticoagulants was 3.3/100 patient-years. These data are consistent with the findings by Sokolova et al. [14], which also demonstrated a low incidence of thrombotic complications in patients who resumed anticoagulants.

In our study, only clinical relevant bleeding decreased after anticoagulant switch, the incidence of major bleeding was comparable in patients who continued using the same drug and switched the anticoagulant. Despite the small number of own findings, this result reflects the current position of the expert community that consists in the fact that the main physician's tasks are to ensure the best possible correction of modifiable RFs and careful monitoring of patients at high risk of recurrent bleeding.

All conventional risk assessment scores contain a history of major bleeding as a scoring parameter, and therefore their diagnostic significance with respect to the risk of recurrent bleeding a priori cannot be high [1, 2, 15–19].

Elderly age and CKD are the most significant non-modifiable RFs of bleeding [1, 2, 15–19]. In our study, age was not associated with the risk of recurrent bleeding, which was likely due to the small sample size.

CKD was the only predictor of recurrent bleeding in our study, including in patients who switched anticoagulants. Kidney pathology is common in patients with AF. CKD increases the risk of thromboembolic and hemorrhagic complications and death [19, 20]. A recent meta-analysis involving about 78 thousand patients with CKD showed better efficacy and safety profile of DOACs compared to vitamin K antagonists [21]. Nevertheless, the choice of a DOAC cannot become the only safety guarantor in real-world practice. The large Japanese registry SAKURA showed that creatinine clearance < 50 mL/min increased 1.83 times the risk of major bleeding with the significance maintained in separate for warfarin and DOACs [22]. Moreover, renal function is a dynamic indicator, which necessitates its regular repeated assessment in all patients receiving DOACs, since all of them are excreted more or less by the kidneys.

The investigation of biomarkers is evidently promising for patient risk stratification. The ARISTOTLE and RE-LY subanalyses confirmed the significance of well-known GDF-15 and high-sensitivity troponin and identified seven new biomarkers associated with the risk of major bleeding [23]. The main limitations of the introduction of biomarkers are little evidence of their sensitivity and specificity, additional difficulties in the calculation and lack of availability for their measurement in real-world clinical practice. Nevertheless, their study is promising, mainly because the clinical RFs of bleeding and stroke are well known, correlated, and therefore are not useful for additional risk stratification in patients with history of bleeding.

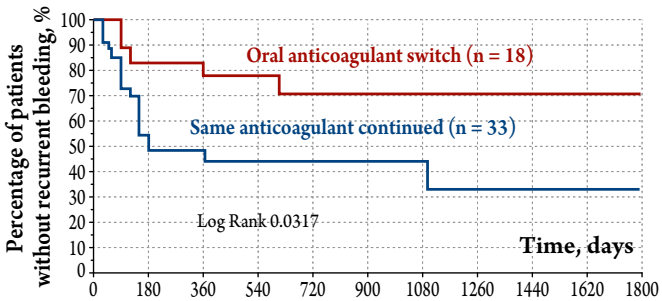
Central illustration

Patients with atrial fibrillation of high thromboembolic risk (n = 95) the administration of anticoagulants after the first episode of major/clinical relevant bleeding took the same anticoagulant (n = 59) or switched the anticoagulant (n = 36)

Five-year follow-up

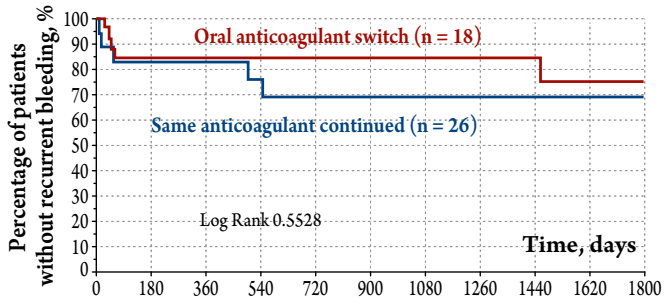
Recurrence rate of major/ clinical relevant bleeding = 16.9/100 patients

Resumption of treatment after clinically significant bleeding (n = 51)



Median time to treatment resumption after bleeding 127 days

Resumption of treatment after major bleeding (n = 44)



Median time to treatment resumption after bleeding 64 days

Chronic kidney disease stage ≥3a is a predictor of the recurrence of major/ clinical relevant bleeding after resumption of anticoagulant therapy OR 2.27 [95% CI 1.1253–4.6163]; p=0.0221

Thus, the onset of serious bleeding always required to reassess the choice, dose of anticoagulant and patient's RFs. The development of a single interdisciplinary protocol for the management of patients receiving anticoagulants and at high risk of bleeding is a solution of practical importance that will reduce the risk of adverse outcomes.

Limitations

The main limitation was the small sample of patients of the single-center prospective registry, who are carefully followed up.

Conclusions

According to the 5 year follow-up data, the recurrence rate of major/clinical relevant bleeding events was 16.9/100 patient-years.

In most cases, the severity and localization of the first and recurrent hemorrhagic complications were the same. One major recurrent gastrointestinal bleeding event was fatal.

The median number of days after anticoagulant resumption before recurrent major bleeding and clinical relevant bleeding events was 64 [37.5; 523.5] days and 127 [90;151] days, respectively.

Anticoagulant switch significantly reduced the risk of recurrent clinical relevant bleeding but did not affect the risk of recurrent major bleeding.

The Cox proportional hazard model showed that chronic kidney disease stage ≥3a was the only predictor of recurrent major/clinical relevant bleeding after the anticoagulant resumption and it increased 2.27 times the risk of recurrence (95% CI 1.1253–4.6163; p=0.0221).

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