Bleeding tolerance among patients with atrial fibrillation on oral anticoagulation

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Brief summary

Clinical factors are known to affect bleeding tolerance among anticoagulated patients. In atrial fibrillation, minor and major bleeds along with older age decrease the bleeding tolerance. Past thromboembolic events are associated with higher bleeding acceptance. The level of knowledge of atrial fibrillation did not affect the Bleeding Ratio.

Abstract

Background: Oral anticoagulation (OAC) increases the bleeding risk. We investigated how clinical factors and the level of atrial fibrillation (AF) knowledge affect the bleeding acceptance in patients with AF.

Methods: In 173 consecutive anticoagulated outpatients with AF (aged 68.7±10.7 years, 39.3% male), the Bleeding Ratio was assessed based on the declared maximum number of major bleeds the people were willing to endure to avert one stroke. The Jessa AF Knowledge Questionnaire was used to assess the knowledge of AF.

Results: Compared to patients with the high Bleeding Ratio (≥4 accepted bleedings, n=88, 50.9%), subjects with the low Bleeding Ratio (0-3 accepted bleedings, n=85, 49.1%) were older, with longer duration of AF, suffered more commonly from heart failure, and were free of cerebrovascular events. Patients after major bleeding (n=33, 19.1%) and those reporting minor bleeds on anticoagulation (n=77, 44.5%) had lower Bleeding Ratio. The independent predictors of the low Bleeding Ratio were: older age (odds ratio [OR] 2.50, 95% confidence interval [CI] 1.69-3.70), major bleeds on anticoagulation (OR 3.33, 95%CI 1.16-10.0), minor bleeds on anticoagulation (OR 3.45, 95%CI 1.67-7.14) and prior stroke/transient ischemic attack (OR 0.47, 95%CI 0.22-0.99). The level of knowledge of AF did not affect the Bleeding Ratio.

Conclusions: The key determinants of the Bleeding Ratio among anticoagulated AF patients are age, prior thromboembolic and bleeding episodes. The study could support identification of AF patients who need additional effort to increase their acceptance of a life-long OAC therapy.

Introduction

The oral anticoagulant therapy (OAC) with vitamin K antagonists (VKA) or non-vitamin K antagonist oral anticoagulants (NOACs) reduces the risk of thromboembolism in patients with atrial fibrillation (AF) [1,2]. Since VKAs have a narrow therapeutic interval, interfere with several drugs and require routine monitoring of international normalized ratio (INR), NOACs are increasingly used in AF patients providing reduced risk of stroke or systemic thromboembolism by 19% compared with warfarin [3] and the risk of those events on NOAC is 1.12-2.1% per year [4-6]. The Canadian Cardiovascular Society as well as the European Society of Cardiology favors using NOAC over VKA in AF patients initiating OAC [7, 8]. Regular assessment of the bleeding risk during OAC is advised by experts to optimize the management of AF patients [9].

Bleeding is a key adverse event of OAC [10]. The incidence of major bleeding on VKA is estimated at 2-5% per year [10], whereas NOACs show similar or lower annual rates [4-6]. NOACs reduce the intracranial hemorrhage risk by 52% but increase the risk of gastrointestinal bleeding (GI) by 25% compared with warfarin [3]. A number of modifiable and non-modifiable bleeding risk factors affect the real-life bleeding rate in AF patients on OAC. For instance, the use of concomitant antiplatelet agents with VKA or NOAC leads to an increase in bleeding rates by 31% compared to OAC alone [11]. Other modifiable factors are alcohol abuse and high blood pressure [12]. However several bleeding risk factors cannot be modified, including older age, prior stroke, past bleeding events [13], hepatic and renal impairment [12]. AF patients often underuse or discontinue OAC because of its hemorrhagic side effects [14] and lack of disease understanding. The education on AF and OACs is important when it comes to long-term adherence to the therapy [15] and is strongly recommended by experts [16].

LaHaye et al. [17] conducted a survey among AF patients in whom the OAC therapy was considered to determine the Bleeding Ratio defined as the maximum number of major bleeding events they would be ready to withstand to prevent one stroke. On average, the patients initiating OAC were ready to accept 4.4 major bleeds. Factors that increased the number of major bleeds accepted by AF patients were male sex and younger age. Another Canadian study [18] on patients at the high risk of developing AF without previous use of VKA determined bleeding thresholds with a sole purpose of preventing one stroke and showed that 90.2% of those patients were willing to accept 4 or more excess bleeds associated with use of warfarin. Little is known about the bleeding acceptance among AF patients already treated with VKA or NOAC. It is also unclear whether the level of knowledge of AF and its therapy may affect the number of major bleeds accepted by AF patients. The Jessa AF Knowledge Questionnaire (JAKQ) implementation has demonstrated that AF patients have suboptimal knowledge of the disease and its therapy, with a median of correct responses at about 60% [19-21]. It might be hypothesized that the knowledge of AF and OACs has a positive effect on the major bleeding acceptance among AF patients. To our knowledge, there have been no studies on bleeding tolerance performed among AF patients already treated with VKA and NOACs. The aim of the study was to investigate how clinical factors and the level of knowledge of AF and OAC influence the bleeding tolerance in AF patients.

Methods

Patients

The study included patients with documented AF taking VKA or NOAC for at least 1 month. Participants were recruited in an outpatient clinic at John Paul II Hospital in Krakow, Poland, from November 2016 to June 2018. Patients eligible to participate in the study were over 18 years of age and able to give informed consent. The exclusion criteria were as follows: an event of stroke or major bleeding within 3 months before enrollment (n=9), reversible cause of AF mainly thyrotoxicosis (n=5) and persistent bleeding tendency resulting in bleeds unrelated to OAC.

A total of 173 consecutive patients gave informed consent to participate in the study. The local ethical committee issued formal approval for the study which complied with the Declaration of Helsinki.

Demographic and clinical data

We collected basic socio-demographic and clinical data about the arrhythmia (type of AF, time since diagnosis, type of anticoagulation with dose, time since introduction of OAC) and comorbidities. The antiplatelet therapy administration was left at the discretion of the managing physician based on the current indications. All the used definitions of AF type were adapted from our previous paper [22]. Based on medical records, data on cerebrovascular and bleeding events were collected. Stroke was diagnosed as a clinical syndrome comprising rapidly developing clinical signs of focal cerebral dysfunction lasting more than 24 hours. A transient ischemic attack (TIA) was defined as an occurrence of a sudden focal neurological deficit of vascular origin that lasts for less than 24 hours. We defined major bleeding according to the criteria proposed by Schulman et al. [23] as symptomatic bleeding in a critical area or organ, or bleeding causing a fall in hemoglobin level of at least 20 g/l, or leading to transfusion of two or more units of whole blood or red

cells. Minor bleeding was defined as recurrent gingival bleeds or easy bruising resulting in one or more bruises of at least 2.5 cm in diameter present on a day of the study.

Bleeding acceptance

The physician provided participants with standardized verbal information including explanation of the outcomes of a stroke, major, and minor bleeding adopted for the study (see Supplementary material). Additional information was provided by him upon request without any time restrictions. Similarly to LaHaye et al. [17,24] we determined the Bleeding Ratio, which is defined as the maximum number of major bleeds that people were willing to endure to prevent one stroke. The physician inquired the Bleeding Ratio using a specifically designed card containing consecutive numbers from 0 to 12. These numbers were selected based on a pilot survey among 50 AF patients which showed that only one of the inquired individuals chose 0 or a number larger than 12. After selecting the number, patients were asked to consider if they would be able to tolerate one less or one more bleeding. We used the ultimate response as the Bleeding Ratio. Based on the previous report [17], patients were arbitrarily stratified into two groups regarding their declared bleeding acceptance: the high Bleeding Ratio (4 or more) and the low Bleeding Ratio (0-3 major bleedings declared).

Questionnaire

We used (with permission) the JAKQ to assess AF patients' knowledge about the disease, OAC treatment and its side effects as previously described [19]. Briefly, the JAKQ comprised 16 multiple choice questions with only one correct answer. Eight questions were about AF in general, 5 - about the OAC therapy, 3 - about VKA or NOAC depending on the anticoagulant therapy. After the

Bleeding Ratio was established, each participant received the Polish version of the JAKQ from their managing physician. They asked the participant to individually complete the JAKQ.

Statistical analysis

Continuous variables were presented as means (standard deviation [SD]) or median (IQR) as appropriate. The Shapiro-Wilk test was used to determine the normal distribution of variables. Categorical variables were reported as numbers and percentages. The chi-squared test was used to compare categorical variables. The ANOVA, Mann-Whitney U or Kruskal-Wallis tests for continuous variables were conducted to assess the differences between the groups. Multivariate logistic regression analysis was used to determine predictors of the low Bleeding Ratio. Statistical analyses were performed using Statistica13 (StatSoft Inc.) and JMP 14.2 (SAS Institute Inc., Cary, NC, USA). The accepted statistical significance threshold was established as a P-value of <0.05.

Results

Patient characteristics

We studied 173 consecutive outpatients diagnosed with AF aged 68.7 years (SD 10.7, minimum 39 years, maximum 94 years) as shown in Table 1. There were 62 patients (35.8%) who experienced at least one documented thromboembolic event, including 38 (22.0%) with prior TIA and 31 (17.9%) after ischemic stroke. Comparative analysis of the two groups following cerebrovascular ischemic events or free of them (Table 1) indicates that there were no differences in demographic and clinical characteristics. A total of

33 patients (19.1%) had history of major bleeding, including 10 subjects (5.8%) who survived both stroke and major bleeding. Prior major bleeding was associated with older age, female gender, longer time since AF diagnosis, occurrence of heart failure and minor bleeds on anticoagulation (Table 1).

Duration of the OAC therapy was 13.5 (7-23) months. Most of the patients (n=160, 92.5%) were treated with NOAC (Supplementary Table S1). As few as 12 patients (6.9%) were on VKA, warfarin and acenocoumarol, 6 subjects each. One patient received a low-molecular-weight heparin (LMWH) on a long-term basis as stroke prevention. A total of 77 patients (44.5%) reported occurrence of minor bleeds during OAC therapy. Occurrence of minor bleeds was related to heart failure and an prior episode of major bleeding (Table 1). There was no relation between the use of antiplatelet agents and occurrence of bleeds. The VKA users were older and more frequently male compared with patients on NOAC (p=0.014, and p=0.046, respectively). Larger proportions of patients with heart failure, as well as diagnosed with AF and anticoagulated for a longer period of time were observed in the VKA group (Supplementary Table S2).

Bleeding Ratios

A median of the Bleeding Ratio in AF patients was 4 (IQR 2-5, minimum 0, maximum 12; figure 1). As shown in Table 2, subjects with the low Bleeding Ratio (n=85, 49.1%) were older (p<0.001), suffered from AF for a longer period of time (p<0.001) and more commonly had concomitant heart failure (p=0.002) compared with the high Bleeding Ratio group (n=88, 50.9%). There was an inverse correlation between the age and number of accepted possible bleedings (r=-0.52, p<0.001) and time since AF diagnosis (r=-0.34,

p<0.001). The patients with paroxysmal AF declared the highest Bleeding Ratio and the lowest - those with permanent AF (4 [3-6] versus 2 [1-4], p<0.001).

There were no differences between AF patients on VKA versus those on NOAC in terms of the bleeding tolerance (p=0.21; Supplementary table S2). Among NOAC users, patients on dabigatran showed the highest Bleeding Ratio and apixaban users – the lowest (4 [3-7] versus 2 [2-4], p=0.009; Supplementary Table S1). As shown in Supplementary Table S1, patients taking apixaban were the oldest and suffered more commonly from heart failure, diabetes and had more often major bleeding in the past compared with those on dabigatran or rivaroxaban. Surprisingly, patients who switched to NOAC from VKA (n=62, 35.8%) showed lower Bleeding Ratio than the rest of NOAC users (2 [0-10] versus 4 [1-12], p<0.001). Patients on reduced dose had lower Bleeding Ratio compared with those on full dose NOAC (2 [2-4] versus 4 [3-6], p<0.001; Supplementary Table S3).

Stroke or TIA survivors (n=62, 35.8%) were ready to endure more major bleedings related to OAC (range from one to 12 episodes) compared with those free of cerebral thromboembolic events (4 [3-7] versus 3 [2-5], p<0.001). Patients who experienced a major bleeding (n=33, 19.1%) were less tolerant of possible major bleeding complications (2 [1-3] versus 4 [2-5.5], p<0.001). None of those AF patients was ready to accept more than 4 major bleeds to prevent one stroke. After exclusion of 10 patients after both stroke and major bleeding, stroke survivors had still higher Bleeding Ratio compared with those with a history of major bleeding (5 [3-8] versus 3 [2-5], p<0.001).

Regarding current minor bleeding, both patients reporting easy bruising (2 [2-4] versus 4 [3-6]; p<0.001) and those suffering from recurrent gingival bleeds (2 [1.5-4] versus 4 [2-5]; p<0.001, respectively) had lower Bleeding Ratio in comparison with the remaining subjects (Figure 2).

Knowledge of AF patients on OACs

A mean percentage value of correct responses on the JAKQ was 69% (SD 14.5, minimum 4 points, maximum 15 points; Figure 3). Comparison of the high versus low Bleeding Ratio groups showed no difference in the level of knowledge tested with the JAKQ (Supplementary Table S4). However, patients with high Bleeding Ratio had better knowledge of the therapy management in the case of an upcoming operation (73.8% versus 58.3%, p=0.03). Among patients on NOACs, individuals with the high Bleeding Ratio showed better knowledge regarding self-management in the case of a missed dose than those with the low Bleeding Ratio (73.1% versus 54.9%, p=0.02). There were no differences in total scores with regard to demographics, type of anticoagulant, prior thromboembolic events, past major or current minor bleedings.

Predictors of the Bleeding Ratio

Independent predictors of the low Bleeding Ratio were: older age, the occurrence of major or minor bleedings, and no history of prior stroke or TIA (Table 3).

Discussion

This study shows that a history of thromboembolism and bleeding substantially affects the attitude of AF patients on OAC towards the acceptable bleeding risk to avert one major stroke. We found that a prior cerebral thromboembolic event substantially increases the bleeding tolerance, whereas past major bleeding reduces the bleeding acceptance among AF patients during the OAC therapy. Surprisingly, self-reported persistent minor bleeds, which were common in the studied AF patients, had a similar effect on the bleeding tolerance to prior major bleeding, which highlights the clinical relevance of these often neglected adverse events. We also identified age as a predictor of the low Bleeding Ratio. Contrary to our hypothesis, we failed to observe any differences in the level of knowledge of AF and anticoagulation. This suggests that among AF patients with a rather limited knowledge of the disease, the personal experience of life-threatening thromboembolic or bleeding events has a potent impact on their bleeding acceptance. This study highlighted the important factors affecting the willingness of AF patients to accept major bleedings to avoid one stroke during life-long OAC therapy. It might help to guide the education and management of anticoagulated patients at the high risk of adverse events.

From a practical point of view, our key finding is that AF patients already treated with OAC after major bleeding and minor but repeated bleeding incidents, showed a similar Bleeding Ratio with a median of 2. We found that bruises and gingival bleeds experienced on a daily basis seemed to be as deterring as an event of major bleeding in the past. However, the distribution of individual responses regarding the bleeding tolerance was much wider for patients experiencing minor bleeds (minimum 0, maximum

12) than for patients after major bleeding (minimum 1, maximum 4). This observation accounts for substantial differences in patients' opinion regarding side effects and the bleeding tolerance variability within the group.

AF patients often underuse or discontinue the OAC because of its hemorrhagic side effects as it compromises their health-related quality of life [25]. The present study showed that AF patients during the OAC therapy were ready to endure 4 major bleedings on average to prevent one stroke, which is consistent with the study on the bleeding tolerance of hospitalized patients with AF initiating OAC [17]. Not surprisingly, younger patients with AF had higher bleeding acceptance, in part due to lower prevalence of comorbidities and generally lower risk of adverse events. A novel finding was that the longer patients were treated with OACs, the less tolerant they were of major bleedings, which might imply lower persistence of anticoagulation among AF patients. We also found that AF patients who switched from VKA to NOAC were less tolerant of bleeding. It is likely that unstable anticoagulation with VKA led to the change of the class of anticoagulant and decreased the bleeding acceptance. The group of "switchers" should also be intensely educated to improve the adherence to OACs.

The Canadian study [18] on VKA-related bleeding tolerance among the patients with high risk of AF who initiated anticoagulation showed that in this specific group of patients 90% of the subjects were willing to endure 4 or more excess bleedings, whereas in the current study merely 50% of the participants who received OAC for at least a few months were equally tolerant. This suggests that the everyday use of NOAC or VKA reduces bleeding tolerance among AF patients, especially in the elderly. Moreover, our study is the first to evaluate the impact of NOAC on the patients' attitude to the risk of major bleeding to prevent stroke. NOACs appear not to increase the bleeding tolerance in AF patients compared with previous data for patients on VKA.

Among comorbidities, solely heart failure was found to reduce the bleeding acceptance among anticoagulated AF patients. Heart failure was the key comorbidity that increases the stroke risk and significantly affects the patients attitude to the adverse events. A prevalence of heart failure among AF patients is estimated to be 30-35% [26,27], which is similar to the proportion reported by us. It is known that heart failure is often associated with numerous hospital stays and several chronic comorbidities requiring multiple medications [26,27], which might affect the Bleeding Ratio among patients with heart failure. Subsequently the patients need more attention of the treating physician to ensure good adherence to OAC on a long-term basis [28].

Results of the JAKQ in the context of the bleeding acceptance deserve some comments. In the current study participants obtained better results compared to a previous study in which the JAKQ was assessed [20,21] (69.2% versus 62.5%). It may be hypothesized that information provided following the study enrollment (see Supplemental material) had an educational impact on the participants. The level of knowledge of AF and anticoagulation was still unsatisfactory and educational efforts to improve it should be encouraged as recommended [16]. We found no correlation between the total JAKQ score and the Bleeding Ratio as well as a history of major bleeding and thromboembolic events. This finding was unexpected, since one might speculate that better knowledge of AF and its treatment is likely to lead to a larger number of major bleedings accepted to prevent one possible major stroke. Our understanding is that if a general level of knowledge of AF is low without large interindividual differences, the impact of knowledge of the patients' perception was abolished by factors such as age and comorbidities. Even so we observed some differences in knowledge regarding self-management in the case of a missed dose among AF patients on NOACs - those with the high Bleeding Ratio knew what to do if they missed the dose of the anticoagulant more often than the patients with the low Bleeding Ratio. This observation might be

attributed to a relation between the knowledge of the safe management of the OAC therapy and the bleeding acceptance. This study shows that AF patients who know the rules of safe administration of NOACs in emergency situations are more tolerant of the side effects of the OAC therapy.

It has been reported that there is a discrepancy between patients' subjective assessment of the risk and benefits of OAC and the objective estimation made by physicians, as up to 57% of patients underestimate their stroke risk [29] which may account for the fact that some patients on OAC fail to take the drug with the annual cessation rate of 1.54 %/year [30].

There are several study limitations. First, the study design included only outpatients diagnosed with AF, at least three months after stoke or major bleeding. The outpatient setting of the study led to exclusion of patients with or immediately after life-threatening events so the results cannot be extrapolated to such patients. Second, the participants of the study were already diagnosed and treated for AF so their views were affected by previous experience with the OACs as opposed to the patients newly diagnosed with AF. These results were apparently different from previous studies exploring patients at the start of OAC use. Third, patients enrolled to the study were mostly on OAC, what might have biased the results. Finally, the adherence to the OAC therapy was not assessed in the current study, therefore we did not look at the potential associations between the Bleeding Ratio and those issues which should be studied in the future.

Conclusions

We observed that in AF patients, past thromboembolic events were associated with the higher acceptance of possible major bleeding events to prevent one severe stroke whereas the bleeding experienced during the OAC therapy or before its start reduced the perceived tolerance of another bleeding event. We failed to show any impact of the knowledge about AF and OAC on the Bleeding Ratio, which underscores the role of clinical unmodifiable factors on this tolerance during long-term therapy. The current study could help to identify AF patients who require additional educational efforts and doctor's attention to increase the acceptance and approval of a life-long anticoagulant therapy. Further studies are needed to validate our observations in other AF populations.

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stroke and mortality in atrial fibrillation patients. Thromb Haemost 2017;117:1448-54.

Table 1. Characteristics of patients.

	All (n=173)	Stroke or TIA survivors (n=62)	Patients without stroke/TIA (n=111)	P-value	Major bleeding survivors (n=33)	Patients without major bleeding (n=140)	P-value	Patients with minor bleeds (n=77)	Patients without minor bleeds (n=96)	P-value
Age [years]	68.7 ± 10.7	66.9 ± 12.1	69.7 ± 9.8	0.16	75.4 ± 8.8	67.1 ± 10.5	**<0.001**	69.7 ± 10.4	67.9 ± 10.9	0.17
Male, n(%)	68 (39.3)	25 (40.3)	43 (38.7)	0.84	5 (15.2)	63 (45)	**0.002**	27 (35.1)	41 (42.7)	0.31
Type of AF, n(%)										
Paroxysmal	65 (37.6)	26 (41.9)	39 (35.1)	0.67	9 (27.3)	56 (40)	0.07	25 (32.5)	40 (41.7)	0.51
Persistent	61 (35.3)	17 (27.4)	44 (39.6)	0.96	7 (21.2)	54 (38.6)	0.06	25 (32.5)	36 (37.5)	0.79
Permanent	45 (26.0)	19 (30.6)	26 (23.4)	0.75	16 (48.5)	29 (20.7)	0.80	26 (33.8)	19 (19.8)	0.16
Time since AF diagnosis [months]	28.5 (14-63.5)	27 (12-60)	29.5 (14-72)	0.27	60 (34-120)	22 (12-60)	**<0.001**	36 (17-72)	26 (12-60)	0.15

Time since OAC introduction [months]	13.5 (7-23)	14.5 (6-22)	12.5 (8-23)	0.78	10 (6-15)	15 (7-23)	0.06	16 (6-23)	12 (8-20)	0.68
VKA use, n(%)	12 (6.9)	7 (11.3)	5 (4.5)	0.18	2 (6.1)	10 (7.1)	0.11	5 (6.5)	7 (7.3)	0.65
NOAC use, n(%)	160 (92.5)	55 (88.7)	105 (94.6)	0.19	30 (90.9)	130 (92.9)	0.12	72 (93.5)	88 (91.7)	0.65
VKA use before NOAC	74 (42.8)	25 (40.3)	49 (44.1)	0.63	23 (69.7)	51 (36.4)	**<0.001**	39 (50.6)	35 (36.5)	0.06
Aspirin use, n(%)	43 (24.9)	15 (24.2)	28 (25.2)	0.88	7 (21.2)	36 (25.7)	0.75	20 (26.0)	23 (24.0)	0.76
Clopidogrel use, n(%)	10 (5.8)	5 (8.1)	5 (4.5)	0.33	3 (9.1)	7 (5.0)	0.41	7 (9.1)	3 (3.1)	0.09
Comorbidities										
Heart failure, n(%)	63 (36.4)	20 (32.3)	43 (38.7)	0.40	19 (57.6)	44 (31.4)	**0.005**	36 (46.8)	27 (28.1)	**0.011**
Arterial hypertension, n(%)	148 (85.5)	51 (82.3)	97 (87.4)	0.36	29 (87.9)	119 (85.0)	0.80	66 (85.7)	82 (85.4)	0.96
Diabetes mellitus, n(%)	55 (31.8)	18 (29.0)	37 (33.3)	0.56	14 (42.4)	41 (29.3)	0.15	24 (31.2)	31 (32.3)	0.88
Heart valve replacement, n(%)	4 (2.3)	2 (3.2)	2 (1.8)	0.62	1 (3.0)	3 (2.1)	0.58	2 (2.6)	2 (2.1)	0.60
Mitral stenosis, n(%)	9 (5.2)	5 (8.1)	4 (3.6)	0.29	4 (12.1)	5 (3.6)	0.07	4 (5.2)	5 (5.2)	0.64
Previous myocardial infarction,	33 (19.1)	11 (17.7)	22 (19.8)	0.74	8 (24.2)	25 (17.9)	0.46	17 (22.1)	16 (16.7)	0.37

n(%)										
Prior stroke or TIA, n(%)	62 (35.8)	62 (100)	0	-	10 (30.3)	52 (37.1)	0.46	25 (32.5)	37 (38.5)	0.41
Vascular disease, n(%)	38 (22.0)	17 (27.4)	21 (18.9)	0.20	7 (21.2)	31 (22.1)	0.91	17 (22.1)	21 (21.9)	0.97
History of major bleeding, n(%)	33 (19.1)	10 (16.1)	23 (20.7)	0.46	33 (100)	0	-	22 (28.6)	11 (11.5)	**0.004**
Minor bleeds, n(%)	77 (44.5)	25 (40.3)	52 (46.8)	0.41	22 (66.7)	55 (39.3)	**0.004**	77 (100)	0	-
Bleeding Ratio	4 (2-5)	4 (3-7)	3 (2-5)	**<0.001**	2 (1-3)	4 (2-5.5)	**<0.001**	2 (2-4)	4.5 (3-6)	**<0.001**
JAKQ score, %	69.2 ± 14.5	71.9 ± 15.0	67.7 ± 14.1	0.10	67.4 ± 16.0	69.6 ± 14.2	0.54	67.4 ± 14.1	70.6 ± 14.8	0.13

Data reported as number (percentage), mean (standard deviation) or median (interquartile range).

Abbreviations: AF, atrial fibrillation; JAKQ, Jessa AF Knowledge Questionnaire;

NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant; TIA, transient ischemic attack;

VKA, vitamin K antagonist

Table 2. Characteristics of patients depending on the Bleeding Ratio.

	Low Bleeding Ratio (<4) (n=85, 49.1%)	High Bleeding Ratio (≥4) (n=88, 50.9%)	P-value
Age [years]	73.5 ± 9.6	64.1 ± 9.7	**<0.001**
Male, n(%)	32 (37.6)	36 (40.9)	0.66
Type of AF, n(%)			
Paroxysmal	24 (13.9)	41 (23.7)	**0.013**
Persistent	27 (15.6)	34 (19.7)	0.34
Permanent	33 (19.1)	12 (6.9)	**<0.001**
Time since AF diagnosis [months]	40.5 (19-84)	19 (12-48)	**<0.001**
Time since OAC introduction [months]	12 (6-23)	14 (7.5-22.5)	0.47
VKA use, n(%)	77 (90.6)	83 (94.3)	0.83
NOAC use, n(%)	7 (8.2)	5 (5.6)	0.83

VKA use before NOAC, n(%)	49 (57.6)	25 (28.4)	**<0.001**
Aspirin use, n(%)	22 (25.9)	21 (23.9)	0.76
Clopidogrel use, n(%)	5 (5.9)	5 (5.7)	1.000
Comorbidities			
Heart failure, n(%)	41 (48.2)	22 (25.0)	**0.002**
Arterial hypertension, n(%)	69 (81.2)	79 (89.8)	0.11
Diabetes mellitus, n(%)	27 (31.8)	28 (31.8)	0.99
Heart valve replacement, n(%)	2 (2.4)	2 (2.3)	1.00
Mitral stenosis, n(%)	6 (7.1)	3 (3.4)	0.32
Previous myocardial infarction, n(%)	16 (18.8)	17 (19.3)	0.93
Prior stroke or TIA, n(%)	23 (27.1)	39 (44.3)	**0.018**
Vascular disease, n(%)	21 (24.7)	17 (19.3)	0.39
History of major bleeding, n(%)	27 (31.8)	6 (6.8)	**<0.001**

Minor bleeds, n(%)	51 (60.0)	26 (29.4)	**<0.001**
JAKQ score, %	68.0 ± 14.1	70.3 ± 14.9	0.22

Data reported as number (percentage), mean (standard deviation) or median (interquartile range)

Abbreviations: AF, atrial fibrillation; JAKQ, Jessa AF Knowledge Questionnaire;

NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant; TIA, transient ischemic attack;

VKA, vitamin K antagonist

Table 3. Predictors of the low Bleeding Ratio.

Predictors of the low Bleeding Ratio	Univariate analysis OR (95%CI)	Multivariate analysis OR (95% CI)*
Age per 10 years	2.70 (1.87-3.91)	2.50 (1.69-3.70)
Time since AF diagnosis per 10 months	1.14 (1.06-1.22)	-
NOAC use after prior VKA use	3.43 (1.82-6.46)	-
Heart failure	2.80 (1.47-5.32)	-
Major bleedings	6.36 (2.47-16.39)	3.33 (1.16-10.0)
Minor bleedings	3.58 (1.90-6.72)	3.45 (1.67-7.14)
Stroke/TIA	0.47 (0.25-0.88)	0.47 (0.22-0.99)

Abbreviations: CI, confidence interval; OR, odds ratio; TIA, transient ischemic attack; NOAC, non-vitamin K antagonist oral anticoagulants; VKA, vitamin K antagonist

*adjusted for sex

Figure 1. The Bleeding Ratio among stroke or TIA survivors, major bleeding survivors and patients with minor bleedings on anticoagulation.

Abbreviations: TIA, transient ischemic attack

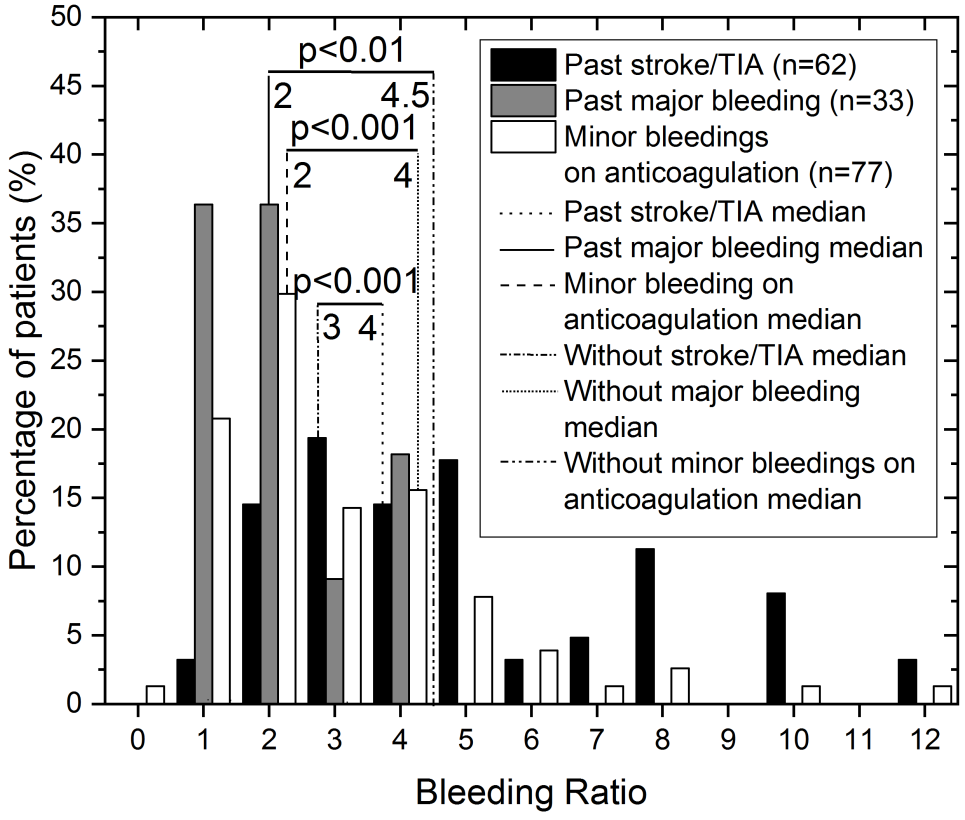
Figure 2. Median of the Bleeding Ratio in the sample group, stroke or TIA survivors, major bleeding survivors and patients with minor bleedings on anticoagulation.

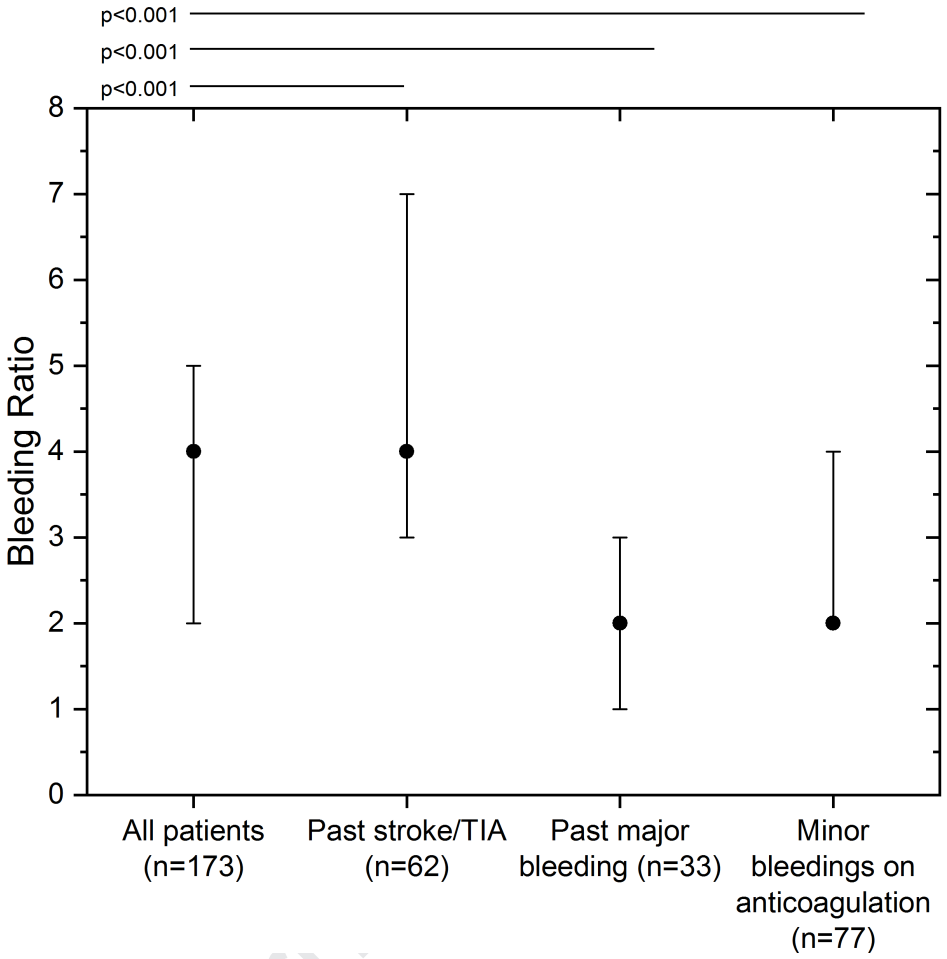
Horizontal bars represent interquartile range of the Bleeding Ratio.

Abbreviations: TIA, transient ischemic attack

Figure 3. Frequency distribution of total scoring to JAKQ questions with regard to the level of the Bleeding Ratio.

Abbreviations: HBR, High Bleeding Ratio; LBR, low Bleeding Ratio


p<0.01
2 4.5
p<0.001
2 4
p<0.001
3 4
Past stroke/TIA (n=62)
Past major bleeding (n=33)
Minor bleedings on anticoagulation (n=77)
Past stroke/TIA median
Past major bleeding median
Minor bleeding on anticoagulation median
Without stroke/TIA median
Without major bleeding median
Without minor bleedings on anticoagulation median
Percentage of patients (%)
Bleeding Ratio
0 5 10 15 20 25 30 35 40 45 50
0 1 2 3 4 5 6 7 8 9 10 11 12


p<0.001
p<0.001
p<0.001
Bleeding Ratio
0
1
2
3
4
5
6
7
8
All patients (n=173)
Past stroke/TIA (n=62)
Past major bleeding (n=33)
Minor bleedings on anticoagulation (n=77)