SHORT COMMUNICATION

The ORBIT bleeding score is associated with lysis and permeability of fibrin clots

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Introduction Clinical schemas largely based on age and comorbidities, in particular the CHA_2DS_2-VASc and HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly [>65 years], drugs/alcohol concomitantly) scores, have been reported to predict thromboembolism or bleeding, respectively, in patients with atrial fibrillation (AF). However, current European Society of Cardiology guidelines do not recommend any preferred scoring system to predict major bleeding but rather suggest identifying and correcting modifiable bleeding risk factors.[1] Several biomarkers have been investigated,[2] and currently some of them may be incorporated into bleeding risk assessment.[3]

Fibrin constitutes a key protein component of thrombi causing ischemic stroke.[4] It has been shown that formation of compact clot networks, evidenced by low fibrin clot permeability, is an independent predictor of both thromboembolic events and major bleedings in patients with atrial fibrillation (AF) on oral anticoagulation. Moreover, low permeability and HAS-BLED score of at least 3 had a predictive value for major bleeds.[5] Similar observations have been made for patients on rivaroxaban.[6] Clot lysis has been found to be prolonged in patients with AF without any impact of CHA_2DS_2-VASc and HAS-BLED scores.[7] It remains unclear whether fibrin-related prothrombotic biomarker(s) added to a scoring system based on clinical risk factors can result in more accurate risk assessment across different AF populations.[8]

In this preliminary report, we investigated whether clinical bleeding risk scores are associated with plasma fibrin clot properties and thrombin generation in patients with AF.

Methods We studied 100 patients with documented nonvalvular AF, derived from the cohort described in detail elsewhere.[9] Briefly, the exclusion criteria were: current anticoagulation, myocardial infarction or venous thromboembolism within the preceding 3 months, malignancy, acute infection, kidney failure requiring dialysis, and liver cirrhosis. ORBIT (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly [>65 years], drugs/alcohol concomitantly),[10] HEMORR$_2$HAGES (hepatic or renal disease, ethanol abuse, malignancy, older [aged >75], reduced platelet count, rebleeding risk, hypertension [uncontrolled], anemia, genetic CYP 2C9 polymorphisms, excessive fall risk, stroke/TIA history),[11] HAS-BLED,[12] and modified HAS-BLED[13] scores were used to evaluate bleeding risk. The study protocol was approved by the University Ethics Committee.

Standard assay techniques were used in routine laboratory investigations. N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels were measured using an immunoassay (Roche Diagnostics, Mannheim, Germany). We determined plasma tissue-type plasminogen activator antigen (tPA, Diagnostica Stago, Asnières-sur-Seine, France), plasminogen activator inhibitor-1 antigen (PAI-1, American Diagnostica, Stamford, Connecticut, United States), thrombin-activatable fibrinolysis inhibitor (Chromogenix, Lexington, Massachusetts, United States), and von Willebrand factor antigen (Diagnostica Stago). Chromogenic

TABLE 1 Patient characteristics according to bleeding risk scores

Variable	ORBIT				HEMORR₂HAGES				HAS-BLED			Modified HAS-BLED		
	Low risk (0–2) (n = 73)	Moderate risk (3) (n = 14)	High risk (≥4) (n = 13)	P value	Low risk (0–1) (n = 58)	Moderate risk (2–3) (n = 35)	High risk (≥4) (n = 7)	P value	Low risk (0–2) (n = 67)	High risk (≥3) (n = 33)	P value	Low risk (0–2) (n = 42)	High risk (≥3) (n = 58)	P value
Age, y	69 (62–74)	74 (68–77)	73 (73–75)[a]	0.007	68 (63–73)	74 (70–77)[a]	74 (73–76)[a]	0.004	68 (62–75)	73 (70–74)	0.02	64 (60–71)	73 (70–76)	<0.001
Women	27 (37.0)	8 (57.2)	6 (46.2)	0.34	20 (34.5)	18 (51.4)	3 (42.9)	0.27	24 (35.8)	17 (51.5)	0.13	10 (23.8)	31 (53.5)	0.003
BMI, kg/m²	30 (27–34)	29 (27–30)	28 (26–30)	0.38	30 (26–34)	28 (26–34)	27 (24–30)	0.18	29 (26–32)	29 (26–35)	0.38	29 (26–33)	29 (27–34)	0.50
Arterial hypertension	58 (79.5)	11 (78.6)	11 (84.6)	0.90	44 (75.9)	29 (82.9)	7 (100.0)	0.28	53 (79.1)	27 (81.8)	0.75	28 (66.7)	52 (89.7)	0.005
Uncontrolled hypertension	13 (17.8)	0 (0.0)	3 (23.1)	0.19	3 (5.2)	10 (28.6)	3 (42.9)[a]	0.002	6 (9.0)	10 (30.3)	0.006	7 (16.7)	9 (15.5)	0.87
Previous stroke	5 (6.9)	2 (14.3)	0 (0.0)	0.34	1 (1.7)	5 (14.3)[a]	1 (14.3)	0.052	1 (1.5)	6 (18.1)	0.005	0 (0.0)	7 (12.1)	0.02
CKD stage 3	11 (15.1)	6 (42.9)[a]	7 (53.9)[a]	0.002	14 (24.1)	7 (20.0)	3 (42.9)	0.43	14 (20.9)	10 (30.3)	0.30	4 (9.5)	20 (34.5)	0.003
Previous severe bleeding	4 (5.5)	2 (14.3)	6 (46.2)[a]	<0.001	0 (0.0)	7 (20.0)[a]	5 (71.4)[a]	<0.001	2 (3.0)	10 (30.3)	<0.001	1 (2.4)	11 (19.0)	0.01
Anemia	1 (1.4)	5 (35.7)	10 (76.9)[a]	<0.001	2 (3.5)	8 (22.9)[a]	6 (85.7)[a]	<0.001	2 (3.0)	14 (42.4)	<0.001	0 (0.0)	16 (27.6)	<0.001
Antiplatelets	32 (43.8)	8 (57.1)[a]	11 (84.6)[a]	0.02	23 (39.7)	22 (62.9)[a]	6 (85.7)[a]	0.02	30 (44.8)	21 (63.6)	0.07	12 (28.6)	39 (67.2)	0.001
Labile INR	18 (24.6)	3 (21.4)	6 (46.2)	0.24	13 (22.40)	10 (28.6)	4 (57.1)	0.14	10 (14.9)	17 (51.5)	0.001	5 (11.9)	22 (37.9)	0.006
CLT, min	101.7 (89–118)	93 (84–101)	80 (78–92)[a]	0.015	99 (86–118)	98 (84–103)	92 (8–116)	0.65	99 (85–114)	99 (84–107)	0.69	100 (85–118)	97 (84–106)	0.37
Kₛ, cm²×10⁻⁹, mean (SD)	6.5 (0.7)	7.3 (0.9)[a]	7.0 (0.8)[a]	<0.001	6.6 (0.8)	6.6 (0.8)	6.9 (0.8)	0.74	6.6 (0.8)	6.8 (0.90)	0.40	6.7 (0.7)	6.6 (0.8)	0.55

Data are presented as number (percentage) or median (interquartile range) unless otherwise indicated.

a   P <0.05 vs low risk

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; CLT, clot lysis time; HAS-BLED, hypertension, abnormal renal / liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly (>65 years), drugs / alcohol concomitantly; HEMORR₂HAGES, hepatic or renal disease, ethanol abuse, malignancy, older (aged >75), reduced platelet count, rebleeding risk, hypertension (uncontrolled), anemia, genetic CYP2C9 polymorphisms, excessive fall risk, stroke / TIA history; INR, international normalized ratio; ORBIT, older (aged >74), reduced hemoglobin / hematocrit / history of anemia, bleeding history, insufficient kidney function, treatment with antiplatelets

assays were used to measure α2-antiplasmin and plasminogen (Diagnostica Stago). Fibrinogen was determined using the Clauss assay. Calibrated automated thrombography (Thrombinoscope BV, Maastricht, the Netherlands) was used to measure endogenous thrombin potential as described.[9] Fibrin clot permeability was measured using a pressure-driven system as described previously.[9] A permeation coefficient (Ks), which indicates the pore size in the fiber network (higher values indicate looser fibrin structure), was calculated.

Clot lysis time (CLT) was defined as the time required for change from the midpoint of the clear-to-maximum-turbid transition, to the final plateau phase at 405 nm, induced by 32 ng/ml tPA (Boehringer Ingelheim, Ingelheim, Germany).[5] All measurements were performed by technicians blinded to the sample status (inter-and intra-assay coefficients of variation <7%).

Statistical analysis Data were presented as mean (SD) or median (interquartile range [IQR]), as appropriate. Normality was checked using the Shapiro–Wilk test. The t test or the Mann–Whitney test were used to test differences between 2 groups as appropriate. Means between the 3 groups were compared by 1-way analysis of variance followed by the Tukey post-hoc test. Medians were analyzed by the Kruskal–Wallis test followed by the test for multiple comparisons of mean rank. Correlations were assessed by the Pearson or Spearman test, as appropriate. Categorical variables were analyzed using the χ^2 test or the Fisher exact tests. A P value of less than 0.05 was considered significant. Statistical analyses were performed using STATISTICA version 13 (Statsoft Inc, Tulsa, Oklahoma, United States).

Results The data of patients with AF are presented in TABLE 1 and in Supplementary material, TABLE 1. The mean (SD) ORBIT, HEMORR$_2$HAGES, HAS-BLED, and modified HAS-BLED scores were 1.78 (1.48), 1.43 (1.14), 2.07 (1.12), and 2.70 (1.16), respectively. A high bleeding risk defined as ORBIT score of at least 4, HEMORR$_2$HAGES score of at least 4, HAS-BLED score of at least 3, and modified HAS-BLED score of at least 3 was found in 13%, 7%, 33%, and 58% patients, respectively.

Patients with ORBIT bleeding score of at least 4 were older, had higher prevalence of chronic kidney disease stage 3, anemia, previous serious bleeding, and use of antiplatelets. This high-risk group had 20.8% shorter CLT (median [IQR], 80 [78–92] min vs 101 [89–118] min; $P = 0.027$), compared with those with ORBIT bleeding score of 0 to 2. There was no difference between CLT in the group with ORBIT bleeding score 3 and at least 4 ($P = 0.28$). K$_s$ was 7.7% and 12.3%

higher in patients with ORBIT bleeding score of at least 4 and 3 compared with ORBIT bleeding score of 0 to 2 (mean [SD], 7.0 [0.8] cm^2×10^{-9} vs 7.3 [0.9] cm^2×10^{-9} vs 6.5 [0.7] cm^2×10^{-9}; $P = 0.002$ and $P = 0.048$, respectively).

No associations of CLT and K$_s$ with HEMORR$_2$HAGES and HAS-BLED and modified HAS-BLED scores were observed in patients with AF.

Multiple linear regression adjusted for age, body mass index, and fibrinogen showed that ORBIT bleeding score (β = −0.17), PAI-1 (β = 0.31), tPA (β = 0.18), and NT-proBNP (β = 0.42) were the independent predictors of CLT ($R^2 = 0.40$) in the whole group. In the multiple regression model, ORBIT bleeding score (β = 0.22), PAI-1 (β = −0.35) and plasminogen (β = 0.22) were the independent predictors of K$_s$ ($R^2 = 0.29$) in the study group.

Discussion This study demonstrates that the 5-element ORBIT bleeding score which has been reported to have better ability to predict major bleeding in patients with AF as compared with HAS-BLED and ATRIA risk scores,[10,14] is associated with enhanced fibrinolysis and looser clot structure, which renders it prone to fragmentation. This finding extends our previous studies regarding plasma fibrin clot density and lysability in patients with AF.[4,5] We did not observe any association between bleeding risk assessed by ORBIT, HEMORR$_2$HAGES, HAS-BLED, modified HAS-BLED scores and thrombin generation, fibrinolytic proteins, and NT-proBNP. We observed that the highest ORBIT bleeding score was associated with impaired kidney function and use of aspirin or clopidogrel that have been reported to unfavorably alter fibrin structure and function and also predispose to bleeding.[4,9] The exact mechanisms underlying these observations remain to be established. Our study supports the concept of a complex clinical and biomarker-based approach in the bleeding risk assessment in patients with AF regarding moderate prediction using schemas based only on age and comorbidities.[5,15]

Our study has several limitations. The size of the study was limited especially in subgroup analyses. All laboratory measurements were determined once and changes over time cannot be excluded. Two biomarkers, GDF-15 and troponin, were not measured in the whole group and were not analyzed. Finally, statistical associations reported here do not necessarily indicate a direct cause-effect relationship. We did not collect follow-up data, therefore, the actual bleeding rate in this group is unknown.

This hypothesis-generating report suggests that tendency to form looser and more lysable fibrin clots can be observed in patients with high bleeding risk assessed by ORBIT score. Further studies are needed to corroborate these results.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/kardiologiapolska.

ARTICLE INFORMATION

CONFLICT OF INTEREST None declared.

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