CHA_2DS_2-VASc score and fibrinogen concentration in patients with atrial fibrillation

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Abstract

Background. Assessment of thromboembolic risk is crucial in choosing appropriate treatment in atrial fibrillation (AF). Current guidelines recommend basing the decision on the CHA_2DS_2-VASc score. However, the score is based only on clinical parameters and therefore its relationship with laboratory-assessed coagulation status might not always be objective.

Objectives. The aim of this study was to assess if the CHA_2DS_2-VASc score is associated with blood parameters in AF patients.

Material and methods. Patients with continuous AF prequalified for catheter ablation were enrolled into the study and had CHA_2DS_2-VASc calculated and blood taken for coagulation parameters.

Results. The study population comprised of 266 patients (65.0% males; age 57.6 ±10.1 years). Patients were divided into those with CHA_2DS_2-VASc score 0, and those with ≥1 points, respectively requiring and not requiring anticoagulation treatment. The group with CHA_2DS_2-VASc = 0 (12% of patients) compared to those with CHA_2DS_2-VASc ≥ 1 had a significantly lower fibrinogen concentration (285.6 ±82.0 vs 322.6 ±76.4 mg/dL; $p = 0.02$). Partial thromboplastin time was not significantly different between groups ($p > 0.05$). Differences were noticed in parameters concerning red blood cells. Lower risk patients had a lower red blood cell count (4.9 ±0.4 vs 5.1 ±6.0 10^6/μL); $p = 0.03$), higher hemoglobin concentration (14.9 ±1.0 vs 14.3 ±1.4 g/dL; $p = 0.04$), and higher hematocrit (43.5 ±2.6 vs 41.7 ±4.7%; $p = 0.001$). It was observed that along with the increase in CHA_2DS_2-VASc score mean fibrinogen concentration increased (p-value for trend = 0.04).

Conclusions. In summary, a higher CHA_2DS_2-VASc score is independently associated with an increase in fibrinogen concentration. Further research is needed to assess the value of fibrinogen in thromboembolic risk assessment.

Key words: fibrinogen, atrial fibrillation, thromboembolic risk, CHA_2DS_2-VASc score

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Introduction

Atrial fibrillation (AF) is one of the most common types of cardiac arrhythmia. The current estimate of the prevalence of AF in the developed world is approx. 1.5–2% of the general population, but the part of the population affected by AF is steadily increasing.[1,2] For people 40 years of age and older, a lifetime risk for developing of AF is approx. 25%.[3] The presence of arrhythmia is associated with an increased long-term risk of heart failure, pulmonary embolism and stroke, and all-cause mortality.[1,4,5] It is estimated that approx. 1/5 of all strokes are attributable to AF; further, the risk of pulmonary embolism is assessed to be 80% higher in those with AF compared with those without the arrhythmia.[5,6] It explains why the management of AF focuses on preventing thromboembolism, regarding equally relevant to managing heart rate/rhythm.[7]

Current guidelines recommend estimating thromboembolic risk individually for every patient and planning the anticoagulant treatment according to the risk.[1] Both current recommended prognostic scores $CHADS_2$ and CHA_2DS_2-VASc are based on basic and easy to obtain clinical data, including the presence of congestive heart failure, hypertension, diabetes mellitus or vascular disease, age, sex, and history of stroke. Point values obtained in the scores inform us about approximately how high the annual stroke risk is and, in consequence, about indications for anticoagulant treatment.[8,9] However, current scores do not include laboratory parameters, while biomarkers of inflammation, coagulation or myocardial injury may help refine the risk estimated by the scores.

Proposed mechanisms linking inflammation and the pro-thrombotic state in AF include endothelial activation, increased platelet activation and increased expression of fibrinogen.[10] Increased levels of plasma fibrinogen are associated with an increased risk of ischemic heart disease and stroke, and may promote disease by increasing fibrin formation and platelet aggregation.[11]

The aim of this study was to assess if the CHA_2DS_2-VASc score currently used for thromboembolic risk assessment is associated with laboratory parameters in AF patients.

Material and methods

Study population

The study was designed and performed in accordance with the Declaration of Helsinki, and the study protocol was approved by the University Ethics Committee. Continuous patients with confirmed diagnosis of AF, prequalified for catheter ablation by means of pulmonary vein isolation (PVI), were prospectively enrolled into the study between 2011 and 2013. Written informed consent for study participation was obtained from every enrolled patient. Lack of consent prior to the enrollment or later resulted in exclusion from the study. Also, patients with myocardial infarction or decompensation of heart failure within 6 months prior to study entry and with estimated life expectancy less than 6 months were excluded from the cohort. The criteria for inclusion were as follows: age 18–75 years, persistent AF defined in accordance with the definitions of the European Society of Cardiology,[1] and qualification for ablation of AF made prior to the study initiation. After applying the criteria, the study included 266 patients.

Diagnosis of atrial fibrillation and qualification for ablation

Diagnosis of AF was based on the European Society of Cardiology Guidelines.[1,12] Diagnosis of arrhythmia was confirmed when 12-lead ECG or 24-hour ECG Holter monitoring documented at least 1 episode of AF defined as 30 s or more of irregular ventricular response with fibrillation wave and without P-waves. Every case was verified individually by 2 expert cardiologists. Figure 1 shows samples of ECG tracing of patients' AF. All patients included in the study were qualified for AF ablation prior to enrollment in the study by qualified specialist according to ECG guidelines criteria.[1,12] Briefly, qualified patients had symptomatic AF and symptomatic recurrences of AF on antiarrhythmic drug therapy, or ablation was considered as an alternative to antiarrhythmic drug therapy, considering patient choice, benefit and risk ratio.

Assessment of thromboembolic risk

According to the current scoring guidelines, all patients were assessed with $CHADS_2$ and CHA_2DS_2-VASc scores.[1] In the $CHADS_2$ score, 1 point was assigned for the history of congestive heart failure, arterial hypertension, age ≥75 years, and diabetes mellitus, while 2 points for the history of stroke or transient ischemic attack (TIA). In the CHA_2DS_2-VASc score, 1 point was assigned for each of the following: the history of congestive heart failure, arterial hypertension, diabetes mellitus, vascular disease, age between 65 and 74 years and female sex, whereas 2 points were given for age ≥75 years and history of the stroke or TIA or thromboembolism. All patients were interviewed for the presence of abovementioned factors, history and conditions or taking drugs applicable or de novo diagnosis.

Biochemical measurements

From each patient, a 10 mL blood sample for coagulation parameters and blood morphology assessment was drawn in vacuum tubes with sodium citrate after 12 h of fasting. The samples were immediately centrifuged for 20 min at 2,000 g. The plasma was aliquoted and stored at –70°C until analyzed. Plasma fibrinogen levels were measured

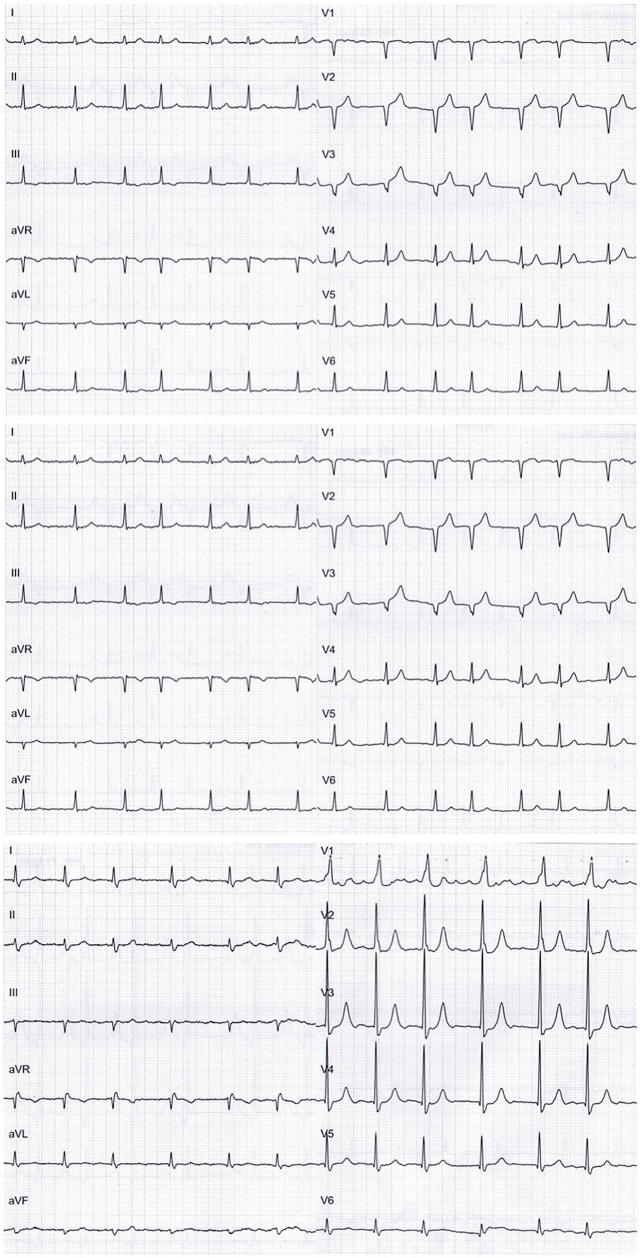

Fig. 1. Samples of atrial fibrillation ECG recorded in the study population

according to the von Clauss method, which is indirect, based on the thrombin clotting time.[13] The assay was performed according to recommendations of the manufacturer. The assay was calibrated against human plasma standard. Other laboratory parameters were obtained and assessed with regard to applicable laboratory methods and current guidelines.

Statistical analysis

Continuous data is presented as the mean ± standard deviation (SD) and was compared using the Mann–Whitney test or Student's t-test. Categorical variables were compared using either the χ^2 or Fisher's exact tests. A p-value of less than 0.05 was considered statistically significant, whereas the confidence intervals (CI) were 95%. Statistical processing of data was made using SPSS v. 21 software (IBM Corp., Armonk, USA).

Results

The study population comprised of 266 continuous patients; 35.0% were females. Mean age of the study population was 57.6 ±10.1 years. Arterial hypertension was present in 198 (74%) patients and diabetes mellitus in 27 (10.2%) patients. Twenty-nine patients (10.9%) suffered from vascular disease and 4 (1.5%) were afflicted with heart failure. Twenty-four patients (9%) had a history of stroke or TIA. The population characteristics and details of the patients' blood test results are presented in Table 1.

According to the current European guidelines, patients were divided into those with CHA_2DS_2-VASc score 0

Table 1. Baseline characteristics of the study population

Parameter	Value
ALT [U/L]	43.2 ±25.0
AST [U/L]	35.0 ±18.5
APTT [s]	35.0 ±8.8
Fibrinogen [mg/dL]	318.7 ±77.7
Glucose [mg/dL]	99.8 ±21.2
Protrombin time [s]	17.4 ±11.0
Creatinine [mg/dL]	1.0 ±0.4
Urea [mg/dL]	39.7 ±10.4
White blood cells [10^3/μL]	7.3 ±1.7
Red blood cells [10^6/μL]	5.1 ±5.6
Hemoglobin [g/dL]	14.4 ±1.3
Hematocrite [%]	42.0 ±4.5
MCV [fl]	89.0 ±5.8
MCH [pg]	31.5 ±14.2
MCHC [g/dL]	34.2 ±1.1
Platelets [10^3/μL]	219.9 ±45.2
Potassium [mmol/L]	4.5 ±0.4
Sodium [mmol/L]	141.4 ±2.7
TSH [μIU/mL]	2.1 ±2.3
CHA_2DS_2-VASc score components	
Chronic heart failure	4 (1.5%)
Hypertension	198 (74%)
Diabetes mellitus	27 (10.2%)
Female	97 (36.5%)
History of stroke or thromboembolism	24 (9.0%)
Vascular disease	29 (10.9%)

ALT – alanine transaminase; AST – aspartate transaminase; INR – international normalized ratio; MCV – mean corpuscular volume; MCH – mean corpuscular hemoglobin; MCHC – mean corpuscular hemoglobin concentration; TSH – thyroid-stimulating hormone. Values are presented as mean ± standard deviation (SD) or n (%).

(31 patients) and those with ≥1 points (235 patients), respectively requiring and not requiring anticoagulation treatment. Analysis of blood parameters revealed that the group with CHA_2DS_2-VASc = 0 (12% of patients) compared to those with CHA_2DS_2-VASc ≥1 had a significantly lower fibrinogen concentration (285.6 ±82.0 vs 322.6 ±76.4 mg/dL; p = 0.02) and shorter prothrombin time (13.6 vs 17.9 s; p = 0.01). Partial thromboplastin time and platelet count were not significantly different between the groups (p > 0.05). Differences were noticed also in the parameters concerning red blood cells. Patients with lower thromboembolic risk had a lower red blood cell count (4.9± 0.4 vs 5.1 ±0.6 10^6/μL; p = 0.03), higher hemoglobin (14.9 ±1.0 vs 14.3 ±1.4 g/dL; p = 0.04) and higher hematocrit (43.5 ±2.6 vs 41.7 ±4.7%; p = 0.001) (Table 2). No differences were seen also in transaminase enzymes, renal parameters, thyroid-stimulating hormone, glucose, as well as potassium and sodium level.

After dividing patients into 6 categories associated with results in CHA_2DS_2-VASc score: CHA_2DS_2-VASc = 0, CHA_2DS_2-VASc = 1, CHA_2DS_2-VASc = 2, CHA_2DS_2-VASc = 3, CHA_2DS_2-VASc = 4, and CHA_2DS_2-VASc ≥5, we observed that along with the increase in CHA_2DS_2-VASc scores, mean fibrinogen concentration inreased (285.6 ±82.1 vs 307.6 ±82.6 vs 327.8 ±74.5 vs 332.9 ±58.6 vs 339.5 ±64.1 vs 349.3 ±77.1 mg/dL; p-value for trend = 0.04) (Fig. 2). On the other hand, patients with higher thromboembolic risk had lower mean hemoglobin concentrations (14.9 ±1.0 vs 14.8 ±1.2 vs 14.1 ±1.3 vs 14.0 ±1.3 vs 13.7 ±1.7 vs 13.9 ±1.2 g/dL; p-value for trend ≤0.001) (Fig. 3). It has not been demonstrated that platelet count depends on the CHA_2DS_2-VASc score (Table 3).

Discussion

Our study has revealed that fibrinogen concentration is associated with CHA_2DS_2-VASc score results. It has been observed that patients with different scores also have different results in the fibrinogen level. The more points

Table 2. Characteristics of patients with CHA_2DS_2-VASc = 0 vs CHA_2DS_2-VASc ≥ 1

Parameter	CHA_2DS_2-VASc = 0 (n = 31)	CHA_2DS_2-VASc ≥1 (n = 235)	p-value
ALT [U/L]	37.3 ±15.7	44.0 ±26.0	0.36
AST [U/L]	34.7 ±9.2	35.0 ±8.9	0.81
APTT [s]	30.9 ±13.5	35.6 ±19.1	0.14
Fibrinogen [mg/dL]	285.6 ±82.1	322.6 ±76.4	**0.02**
Glucose [mg/dL]	93.0 ±12.4	100.8 ±22.0	0.05
Protrombin time [s]	13.6 ±9.0	17.9 ±11.2	**0.01**
Creatinine [mg/dL]	1.0 ±0.2	1.0 ±0.4	0.75
Urea [mg/dL]	39.0 ±8.3	39.7 ±10.7	0.66
White blood cells [10^3/μL]	7.3 ±1.6	7.3 ±1.8	0.90
Red blood cells [10^6/μL]	4.9 ±0.4	5.1 ±6.0	**0.03**
Hemoglobin [g/dL]	15.0 ±1.0	14.3 ±1.4	**0.02**
Hematocrite [%]	43.5 ±2.6	41.7 ±4.7	**0.01**
MCV [fl]	89.6 ±4.2	88.9 ±6.0	0.77
MCH [pg]	31.0 ±1.6	31.6 ±15.2	0.35
MCHC [g/dL]	34.4 ±1.0	34.2 ±1.1	0.36
Platelets [10^3/μL]	223.0 ±37.7	219.8 ±46.1	0.59
Potassium [mmol/L]	4.6 ±0.3	4.5 ±0.4	0.17
Sodium [mmol/L]	141.0 ±2.5	141.4 ±2.8	0.10
TSH [μIU/mL]	2.5 ±2.6	2.1 ±2.3	0.32
CHA_2DS_2-VASc score components			
Chronic heart failure	0 (0.0%)	4 (1.7%)	0.61
Hypertension	0 (0.0%)	198 (84.0%)	**<0.0001**
Diabetes mellitus	0 (0.0%)	27 (11.5%)	**0.03**
Female sex	0 (0.0%)	97 (41.3%)	**<0.0001**
History of stroke of thromboembolic disease	0 (0.0%)	24 (10.2%)	**0.04**
Vascular disease	0 (0.0%)	29 (12.3%)	**0.03**

ALT – alanine transaminase; AST – aspartate transaminase; INR – international normalized ratio; MCV – mean corpuscular volume; MCH – mean corpuscular hemoglobin; MCHC – mean corpuscular hemoglobin concentration; TSH – thyroid-stimulating hormone; values are presented as mean ± standard deviation (SD) or n (%); p-values in bold indicate statistical significance (p < 0.05).

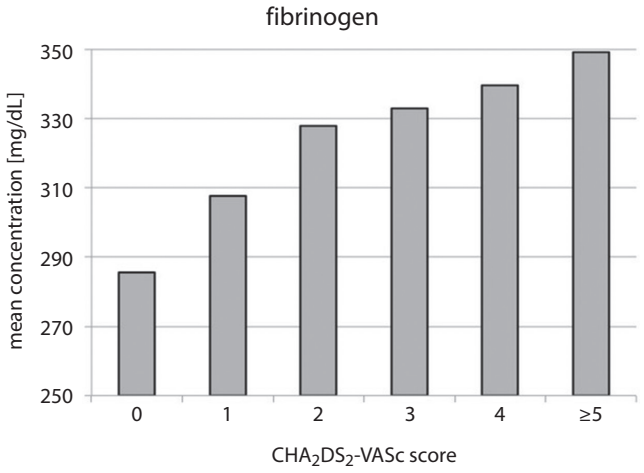

Fig. 2. Comparison of mean concentration of fibrinogen in different thromboembolic risk strata, according to CHA_2DS_2-VASc score

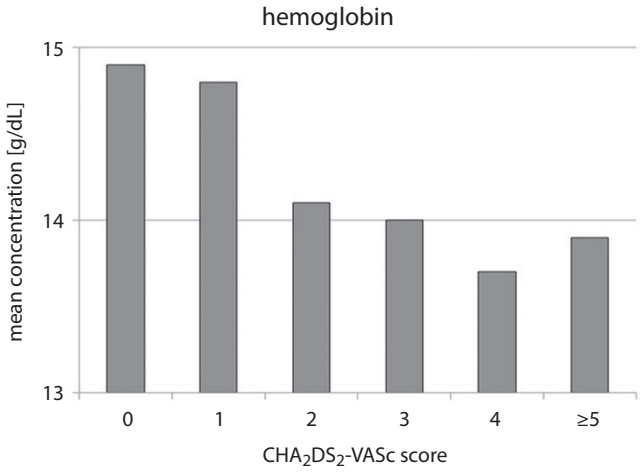

Fig. 3. Comparison of mean concentration of hemoglobin in different thromboembolic risk strata, according to CHA_2DS_2-VASc score

in the CHA_2DS_2-VASc score, the higher fibrinogen concentration, which independently proves its clinical utility, especially in a relatively young population assigned to pulmonary vein isolation. To the best of our knowledge, this particular association has not been thoroughly investigated thus far, although the relationship of hemostatic plasma parameters and risk of stroke has been proved.[26,27,34]

The CHA_2DS_2-VASc score is a simple scheme to assess cardiovascular risk among patients with AF and the legitimacy of using anticoagulation treatment. It includes clinical parameters that are all proven to be independent predictors of a pro-thrombotic state. The score is an independent predictor of mortality.[1,14] The CHA_2DS_2-VASc score is used in order to plan anticoagulation therapy. If a patient gets 0 points, no anticoagulant is needed; otherwise, the treatment should be introduced.[1]

The CHA_2DS_2-VASc score is seen to predict the thromboembolic and stroke risk in different patient populations.[15] Nevertheless, it is based only on clinical parameters and does not include biochemical and even some clinical data.[16–20] In the current study, we showed that despite its flaws, the CHA_2DS_2-VASc score has a direct reflection in altered coagulation parameters. One of the most important biochemical factors of stroke is fibrinogen concentration.

Fibrinogen is one of the plasma proteins which is converted to fibrin by thrombin and then forms a clot. Fibrinogen is synthesized in the liver by hepatocytes and then is secreted into circulation; therefore, it plays an important role in platelet aggregation. It is also a biomarker of inflammation.[21,22]

It has been proved that higher concentration of fibrinogen is associated with risk of cardiovascular disease.[22,23] Appiah et al. in the ARIC study have examined patients between 1993 and 1995 in order to assess the relationship between fibrinogen and cardiovascular disease endpoint. Results showed that the fibrinogen concentration correlates positively with heart failure, peripheral artery disease and cardiovascular deaths. In their opinion, fibrinogen leads to atherosclerosis by inducing inflammation.[24]

Fibrinogen concentration is said to be an important factor of stroke episodes among patients with cardiovascular disease.[25] Fibrinogen concentration is strongly associated with thromboembolic risk. Furthermore, increased hemostatic markers have been observed in AF patients; however, the mechanism taking part in the pathogenesis of AF is multifactorial.[26,27]

Tables 3. Comparison of selected laboratory results in different thromboembolic risk strata, according to CHA_2DS_2-VASc score

Parameters	CHA_2DS_2-VASc = 0 (n = 31)	CHA_2DS_2-VASc = 1 (n = 104)	CHA_2DS_2-VASc = 2 (n = 56)	CHA_2DS_2-VASc = 3 (n = 42)	CHA_2DS_2-VASc = 4 (n = 13)	CHA_2DS_2-VASc ≥ 5 (n = 20)	p-value for trend
Fibrinogen [mg/dL]	285.6 ±82.1	307.6 ±82.6	327.8 ±74.5	332.9 ±58.6	339.5 ±64.1	349.3 ±77.1	**0.04**
Protrombin time [s]	13.7 ±9.2	16.5 ±10.0	16.5 ±10.2	17.5 ±7.6	20.4 ±16.3	26.6 ±16.6	0.29
Hematocrite [%]	43.4 ±2.6	42.7 ±5.5	41.4 ±3.7	41.2 ±4.1	39.9 ±4.2	40.9 ±3.2	0.08
Hemoglobin [g/dL]	14.9 ±1.0	14.8 ±1.2	14.1 ±1.3	14.0 ±1.3	13.7 ±1.7	13.9 ±1.2	**<0.001**
Creatinine [mg/dL]	1.0 ±0.2	1.0 ±0.2	0.9 ±0.2	1.1 ±0.8	1.0 ±0.2	1.0 ±0.4	0.40
MCV [fl]	89.7 ±4.3	88.7 ±7.6	88.4 ±4.3	89.0 ±4.1	90.8 ±4.0	89.4 ±6.0	0.79
Platelets [10^3/μL]	222.3 ±38.2	214.1 ±45.7	226.4 ±50.0	224.0 ±52.3	208.4 ±33.0	225.5 ±30.4	0.46

MCV – mean corpuscular volume. Values are presented as mean ± standard deviation (SD) or n (%); p-values in bold indicate statistical significance ($p < 0.05$).

Recently, several blood biomarkers have been identified to be helpful in diagnosis, outcomes and prognosis of AF, e.g., d-dimer, which is strongly related to fibrinogen concentration. It has been said that blood biomarkers can play an important role in predicting the development of AF and its complications (especially stroke episodes). Unfortunately, fibrinogen concentration has not been included as one of the parameters of risk-assessment scores.[28] Moreover, specific treatment can promote coagulation disturbance.[29]

It has not been discovered yet how AF contributes to thromboembolism and stroke episodes. Several hypotheses of thrombogenesis in AF patients have been published. The most probable mechanism is associated with Virchow's triad for thrombogenesis, inflammation factors, growth factors, and anatomical abnormalities, which contribute to hypercoagulable state in this arrhythmia.[30] A recent meta-analysis showed that the levels of coagulation, fibrinolytic and endothelial markers are significantly higher in AF patients than in patients with sinus rhythm.[31] However, the level to which this elevation is important and associated with prognosis has not been assessed yet. Moreover, the concentration seems not to be affected by anticoagulation treatment.[32] Assessment of the role of fibrinogen in AF patients is also important in light of recent findings, showing that fibrinogen concentration can be predictive of other cardiovascular disease, including coronary artery disease severity.[23,33]

Another parameter that was associated with higher thromboembolic risk in the CHA_2DS_2-VASc score is lower hemoglobin concentration and lower hematocrit. This phenomenon may be associated with the fact that, due to the overlapping factors, a higher CHA_2DS_2-VASc score is usually observed in patients with higher HAS-BLED. This may be associated with elevated bleeding risk, also subclinical, resulting in lower hemoglobin concentration and lower hematocrit.[34]

We suggest the implementation of fibrinogen concentration as an additional laboratory parameter to clinical variables in the CHA_2DS_2-VASc score. Still, this relationship requires further research.

A major limitation of this study is that laboratory parameters were assessed with relation to the risk scores only. An exploration of long-term follow-up with clinical endpoints (stroke, peripheral embolism, death) would be much more valuable.

Conclusions

Higher CHA_2DS_2-VASc score is independently associated with increased fibrinogen concentration. This finding may be a link between CHA_2DS_2-VASc and thromboembolic complications. Further research is necessary to assess if fibrinogen – an easy to obtain laboratory parameter – can add additional value to CHA_2DS_2-VASc as a predictor of higher thromboembolic risk.

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