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The DOAC score is associated with elevated growth differentiation factor 15 and 3-nitrotyrosine in atrial fibrillation: prediction of bleeding at one-year follow-up

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Short title: The DOAC score in AF and biomarkers

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INTRODUCTION

Atrial fibrillation (AF) patients on oral anticoagulation are at greater risk of major bleeding. Existing clinical decision-making aids for evaluating the risk of bleeding in AF patients were originally designed for individuals treated with warfarin [1]. The HAS-BLED score has shown limited accuracy in numerous studies and was validated within cohorts of AF patients with a relatively low bleeding risk [2]. In 2023 the DOAC score was developed and validated on AF patients receiving direct oral anticoagulants (DOACs) [3]. This score assessed in randomized controlled trials with dabigatran and apixaban exhibited a stronger predictive performance compared to the HAS-BLED score in predicting bleeding events [3]. Since 2016 there is growing evidence for a predictive role of elevated growth differentiation factor-15 (GDF-15), a stress response protein that is increased in inflammation, oxidative stress, and tissue injury [4]. GDF-15 was found a valuable biomarker that can predict major bleeding in anticoagulated AF patients [4, 5]. To our knowledge, there have been no studies linking the DOAC score with bleeding risk biomarkers in AF. We investigated whether a high DOAC score is related to elevated GDF-15 or circulating biomarkers related to inflammation and prothrombotic state in AF patients and if the DOAC score is associated with bleeding in a 1-year follow-up while on DOAC.

MATERIAL AND METHODS

We studied 245 consecutive AF patients treated with DOACs enrolled during routine visit in the outpatient clinic between June 2020 and December 2021. The study population, exclusion

criteria, and definitions of comorbidities were described previously [6]. AF classification was based on the 2020 European Society of Cardiology guidelines [5]. The study was approved by the ethics committee (1072.6120.186.2020), and all participants provided written informed consent.

The DOAC score was assigned as very low (score 0–3), low (score 4–5), moderate (score 6–7), high (score 8–9), and very high (score 10). Individuals with scores >10 were assigned a score of 10 [3].

Blood samples from antecubital veins were drawn prior to the intake of the morning dose of a DOAC. Routine laboratory investigations were conducted using standard laboratory techniques. Serum GDF-15 levels, matrix metalloproteinase 9, and plasma 3-nitrotyrosine were assayed using ELISAs. Endogenous thrombin potential and fibrin clot properties were assessed as previously [6, 7]. For details see Supplementary material.

Patients were followed up by telephone or clinical visits for a minimum of twice during 12 months. We recorded major, non-major clinically relevant, and minor bleeding [8].

Statistical analysis

Variables were presented as numbers (percentages) or median (interquartile range). The normality of data distribution was assessed using the Shapiro–Wilk test. Differences between two groups were compared using the Wilcoxon test. Categorical variables were compared using Pearson's chi-squared test or Fisher's exact test. Correlation analyses were conducted utilizing Spearman's or Pearson's correlation coefficients, as appropriate. A *P*-value of <0.05 was considered statistically significant. For details see Supplementary material. Statistical analyses were performed with the STATISTICA software (Version 13.3, TIBCO Software, Palo Alto, CA, US).

RESULTS AND DISCUSSION

Among 245 AF patients (40% women) paroxysmal AF was the most prevalent (45.7%; Supplementary material, *Table S1*). The median CHA_2DS_2-VASc score was 3 (2–4), with a maximum value of 9 and HAS-BLED score was 2 (1–2) with a maximum value of 4. The median DOAC score was 4 (interquartile range 2–6; range from 0 to 10; Supplementary material, *Table S2*). As many as 103 patients (42%) were at very low risk of bleeding, 68 (27.7%) at low bleeding risk, 52 (21.2%) at moderate bleeding risk, 9 (3.7%) at high bleeding risk, and 13 (5.3%) at very high bleeding risk. We categorized patients with the DOAC score

above 3 points as a low-to-very high bleeding risk group for further analysis (see Supplementary material).

In the whole group, GDF-15 correlated with age (r = 0.36; *P* <0.001), CHA_2DS_2-VAS score (r = 0.3; *P* <0.001), and HAS-BLED (r = 0.21; *P* = 0.001). The DOAC score correlated positively with GDF-15 (Figure 1) but not with other markers. Patients with low-to-very high bleeding risk were characterized by 45.5% higher GDF-15 level, also after adjustment for age and sex (*P* = 0.02), compared to patients with very low bleeding risk.

In terms of laboratory parameters GDF-15 weakly correlated with CRP (r = 0.23; *P* = 0.001), 3-nitrotyrosine (r = 0.2; *P* = 0.002), and inversely with clot permeability (K_s; r = –0.34; *P* <0.001). Interestingly, patients at low-to-very high bleeding risk had 57% higher 3-nitrotyrosine concentration than the remainder (Supplementary material, *Table S1*). Analysis of fibrin clot properties and thrombin generation showed no differences in relation to the DOAC score (Supplementary material, *Table S1*).

During follow-up none of the patients was lost. Bleeding events were observed in 19 (7.8%) patients, including minor and non-major bleeding in 17 (6.9%) and major bleeding in 2 (0.8%) individuals (Supplementary material, *Table S1*). The median DOAC score for patients who experienced bleeding was 6 compared to 4 for non-bleeding subjects. No difference was observed for the HAS-BLED score (*P* >0.05). The DOAC score with each additional point scored was associated with a 28% higher risk of all bleeding events (OR, 1.28 [95% CI, 1.09–1.53]; *P* = 0.004). With each point in this score, GDF-15 levels rise by 72.4 (95% CI, 43.3–101.5) pg/ml. However, there was no difference between patients with bleeding events during follow-up compared to the remainder in terms of GDF-15 levels (*P* >0.05).

To our knowledge, this study is the first to show that a new 10-point DOAC score for prediction of bleeding in AF patients on DOAC is associated with increased GDF-15, a biomarker known to predict bleeding. This finding provides additional evidence for a predictive value of the DOAC score in a real life setting in contrast to GDF-15 alone or the HAS-BLED score, which indicates that this new system is worth further validation in large registries and could empower decisions about anticoagulation in patients with AF [3]. GDF-15 was also included in biomarker-based bleeding risk scores, such as the ABC-bleeding and ABC-death risk scores [9, 10]. However, calculation of these scores was beyond the scope of this study. Association between GDF-15 and higher bleeding risk might result from increased GDF-15 expression at cellular stress and vulnerability, potentially heightening the risk of bleeding across tissue injury and its inhibitory effects on platelet activation [4]. In our study, we demonstrated that patients with a very-low bleeding risk exhibited lower GDF-15

concentrations compared to the remainders, and further studies to confirm this observation are needed.

The current study shows that 3-nitrotyrosine, reflecting an oxidative stress and myocardial injury [11], is higher among patients with low-to-very high bleeding risk, which is a novel finding. It might be speculated that the association of 3-nitrotyrosine with bleeding risk in AF shares a similar mechanism to that of GDF-15, since both markers are related to cellular stress and vulnerability.

We failed to show associations between the DOAC score and fibrin clot properties. Drabik et al. showed that low K_s in AF patients predicted major bleeds but was not associated with the HAS-BLED score [12]. Similar findings were reported by Janion-Sadowska et al. [13] in AF patients on rivaroxaban. It seems that fibrin-related mechanisms of bleeding reach beyond clinical scoring systems available now, which still cannot predict a large proportion of bleeding AF patients.

Our study has several limitations. First, the group size was limited, but represented typical real-life AF patients [14, 15]. Second, long-term follow-up was only 12 months long and bleeding rates were low. Third, we excluded patients with advanced renal failure, cancer or acute thromboembolism, therefore our findings could not be extrapolated to these patient subsets. In addition, all parameters were assessed only once and changes over time cannot be excluded. We did not assess other biomarkers listed in the European Society of Cardiology guidelines in relation to bleeding risk [5].

Our hypothesis-generating study showed that GDF-15 and possibly 3-nitrotyrosine combined with the DOAC score may improve bleeding risk stratification among patients with AF. However, larger long-term studies are needed to validate this observation.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska.

Article information

Conflict of interest: None declared.

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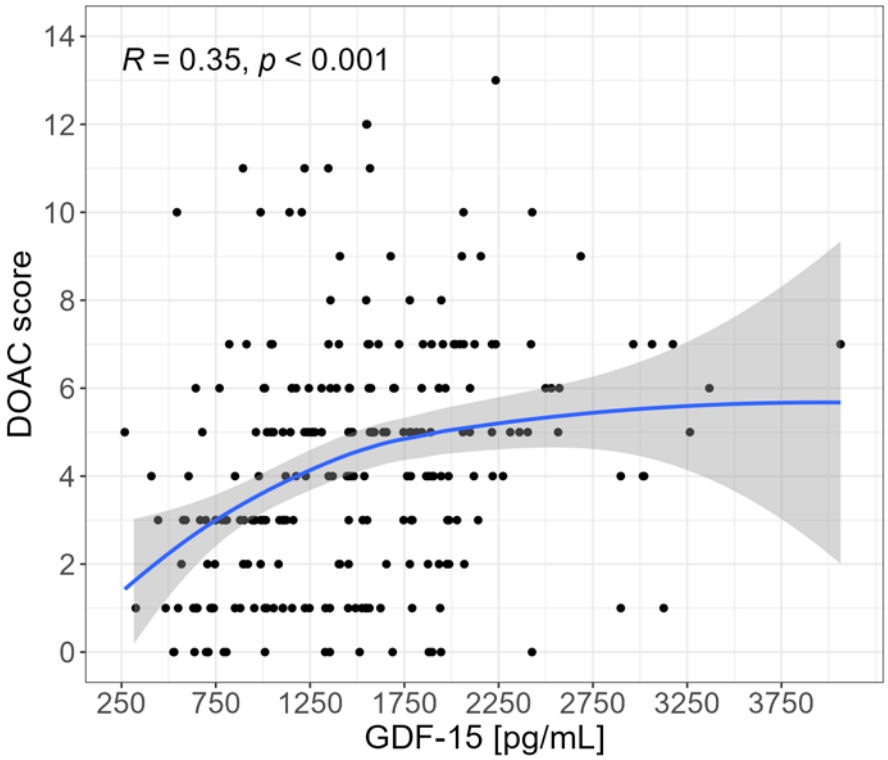

Figure 1. The association between the DOAC score and GDF-15

Abbreviations: DOAC, direct oral anticoagulants; GDF-15, growth differentiation factor-15