Prethrombotic State in Young Very Low- Risk Patients With Atrial Fibrillation

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Letters

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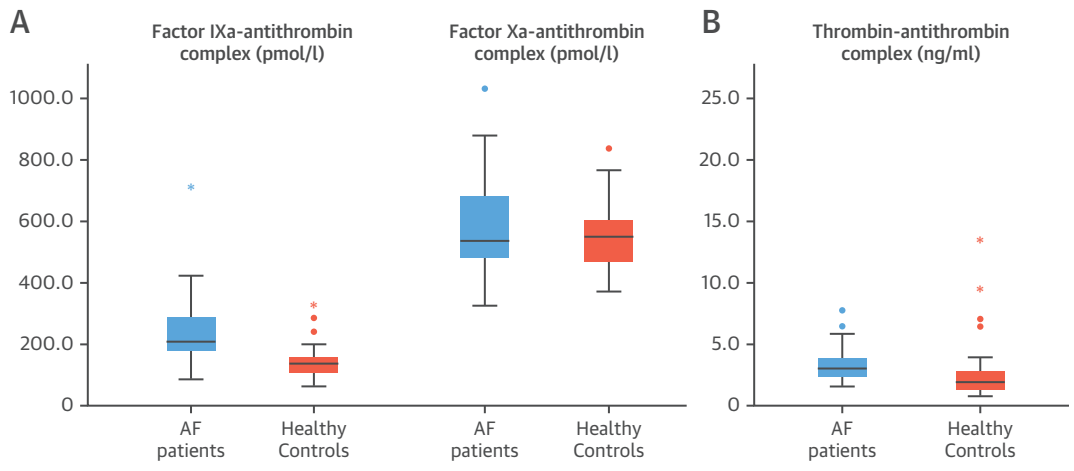
Atrial fibrillation (AF) is associated with thromboembolic complications due to alterations in blood flow, vascular endothelium, and hemostasis (1). Although we have clinical risk assessment scores for stroke risk to identify very-low-risk patients, these prediction rules may misclassify patients as very low risk when their actual risk is much higher (2,3). We hypothesize that elevated markers of hypercoagulability in patients without comorbidities are a manifestation of the underlying disease state of AF, and that they are elevated even in the early stages of the arrhythmia. Therefore, our aim was to assess whether there are differences in coagulation activity between young very-low-risk patients with paroxysmal AF (age of onset <60 years) and healthy control subjects.

The study was performed using data from patients participating in the AF RISK (Identification of a risk profile to guide atrial fibrillation therapy) study (NCT01510210), the Young-AF (Phenotyping young-onset atrial fibrillation patients) study, and the BIOMARKER-AF (Identification of a risk profile to guide atrial fibrillation therapy in patients with AF) study (NCT01510197). All were prospective, observational registries performed at the University Medical Center Groningen. The institutional review board approved the study protocols. All patients gave written informed consent. Control subjects without known comorbidities were recruited at the Department of Internal Medicine and Laboratory for Clinical Thrombosis and Haemostasis, Maastricht University Medical Center.

A total of 44 patients with paroxysmal AF and a CHA_2DS_2-VASc (Congestive Heart failure, Hypertension, Age ≥75 years, Diabetes, previous Stroke, Vascular disease, Age 65 to 74, and female Sex) score

FIGURE 1 Factor IXa-Antithrombin, Factor Xa-Antithrombin, and Thrombin-Antithrombin Complexes in Patients With AF and Healthy Control Subjects



Compared with healthy control subjects, patients with atrial fibrillation (AF) had significantly higher levels of factor IXa-antithrombin complexes ($p < 0.001$). No significant differences were found in factor Xa-antithrombin complexes between AF patients and healthy control subjects ($p = 0.29$) **(A)**. Thrombin-antithrombin levels were normal **(B)**.

of 0 were matched 1:1 with healthy control subjects without AF based on age and sex. All patients were in sinus rhythm at blood sampling, and none of the participants received anticoagulation therapy.

Baseline assessment of the AF patients included a detailed medical history, physical examination, 12-lead electrocardiogram, collection of information on underlying diseases with cardiac ultrasound, conventional and lifestyle-related risk factors for AF, as well as blood samples for biomarker analyses. No information regarding physical examination, electrocardiogram, cardiac ultrasound, lifestyle-related risk factors, and family history was available for the healthy control group.

Selected upstream biomarkers of coagulation activity were factor IXa-antithrombin (factor IXa-AT) and factor Xa-antithrombin (factor Xa-AT) complexes. Factor IXa-AT reflects an early part of the coagulation cascade, immediately prior to factor X and prothrombin conversion. Additionally, thrombin-antithrombin (TAT) complex was measured as marker of downstream coagulation activity. Because trace amounts of thrombin are continuously formed under physiological conditions, complexes of active serine proteases with their natural inhibitor, antithrombin, are detectable in all individuals. TAT levels above 5 ng/ml are considered to be clinically relevant and reflect ongoing coagulation activity.

Mean age was 44 ± 12 years, and 52% of patients were female. Median duration of sinus rhythm at inclusion was 33 days (interquartile range [IQR]: 10 to 75 days). None of the AF patients had hypertension, vascular disease, heart failure, diabetes mellitus, or a previous stroke or transient ischemic attack. Hypercholesterolemia was present in 1 patient, and 1 patient was diagnosed with obstructive sleep apnea syndrome. Two patients had a history of thyroid dysfunction, which was stable at time of inclusion. None of the AF patients used oral anticoagulants, an angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, or calcium-channel blocker. A total of 13 patients used beta-blockers, 1 patient used a statin, 5 patients were treated with a platelet aggregation inhibitor, 4 patients used class 1 antiarrhythmic drugs, and 1 patient was treated with a class 3 antiarrhythmic drug. Mean systolic blood pressure was 123 ± 14 mm Hg, and mean diastolic blood pressure was 79 ± 8 mm Hg. Median body mass index was 26 kg/m^2 (IQR: 22 to 29 kg/m^2). Median left ventricular ejection fraction was 57.5% (IQR: 57.5% to 60.0%), and mean left atrial volume index was 28.1 ± 7.3 ml/m^2.

Factor IXa-AT was higher in AF patients (209.0 pmol/l [IQR: 174.4 to 287.3 pmol/l] vs. 136.3 pmol/l [IQR: 109.6 to 157.3 pmol/l]; $p < 0.001$). No difference was found in factor Xa-AT levels (536.5 pmol/l [IQR: 483.8 to 684.3 pmol/l] vs. 549.3 pmol/l [IQR: 470.1 to 605.1 pmol/l]; $p = 0.29$). TAT levels were normal (3.1 ng/ml [IQR: 2.5 to 4.0 ng/ml] in AF and 2.0 ng/ml [IQR: 1.4 to 3.0 ng/ml] in control subjects) (**Figure 1**).

Mechanisms underlying hypercoagulability in AF and its association with stroke are complex and incompletely unraveled precluding optimal stroke risk prediction (3). Under physiological conditions, ambient levels of coagulation activity are primarily driven by tissue factor/factor VIIa (4). In asymptomatic subjects at risk of thrombosis (e.g., with congenital deficiency in a natural anticoagulant protein, such as protein C), levels of some coagulation activity markers may be elevated without apparent increase in thrombin and/or fibrin formation (4). This so-called prethrombotic state has been postulated to be based on an increased activity of TF-related factor IXa generation, which in absence of activated factor VIII, fails to yield sufficient factor IXa/factor VIIIa complex formation, required to increase factor X conversion and subsequent thrombin generation (5).

Important strengths of our analysis include the careful evaluation of included AF patients. Limitations are the result of the cross-sectional study design retaining conclusions on cause-effect relations. Furthermore, the small sample size causes our data to be insufficient to inform whether comorbidities and structural myocardial alterations influence the hypercoagulable state.

In conclusion, our data suggest that in very-low-risk patients with paroxysmal AF, the elevated factor IXa-AT levels may be interpreted as a first signal of hypercoagulability reflecting a prethrombotic state. Obviously, further research is warranted.

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Prediction of Systemic Septic Embolism in Patients With Left-Sided Infective Endocarditis

Embolic complications (EC) may occur in 10% to 45% of patients with left-sided infective endocarditis (LSIE). These EC mainly affect the central nervous system and therefore worsen prognosis. Two systems have recently been designed for predicting embolic risk in LSIE. We evaluated their prognostic value in a validation cohort with systematic identification of patients with LSIE.

We studied 533 consecutive patients admitted to an academic hospital with a diagnosis of LSIE according to modified Duke criteria between 1990 and 2012 (1). Embolic risk was calculated using 2 scoring systems. The French scheme includes the following covariates with specific coefficients: age; diabetes mellitus; atrial fibrillation; vegetation (< or >10 mm), embolism before antibiotic therapy; and *Staphylococcus aureus* (2). The Italian scoring system assigns 1 point to vegetation ≥13 mm and 1 point to *S. aureus* (3).

Comparisons between groups were made using chi-square tests and the Student *t* test. To identify independent characteristics associated with events during follow-up, a logistic regression model was used. The results were expressed as odds ratios (ORs) and 95% confidence intervals (CIs). We calculated Harrell's c-statistic with 95% CIs as a measure of model performance for each risk scoring system. The c-statistics were compared using the DeLong test. The net reclassification improvement (NRI) was used to compare reclassification by 1 versus the other risk scoring system.

Mean age was 64 ± 15 years, 75% of the patients were male, and 23% had a prosthetic valve. The location of infective endocarditis was aortic in 68% of the patients, and the causative microorganism was *Staphylococcus* in 26%. In the hospital, embolic events occurred in 135 patients (25%), and neurologic complications occurred in 114 patients (21%). The estimations generated with the French score showed a significant association with embolic risk (OR: 1.69; 95% CI: 1.32 to 2.17). The occurrence of EC was better predicted by this system than by chance, although its discrimination was moderate (c-statistic: 0.58; 95% CI: 0.54 to 0.63; p = 0.004). The estimations from the Italian score were also associated with embolic risk: OR: 2.25 (95% CI: 1.67 to 3.04) and c-statistic: 0.60 (95% CI: 0.56 to 0.65; p = 0.0004; p = 0.43 vs. the French score with the 2-tailed DeLong test) (**Figure 1**). When compared with the French score, NRI was significantly improved with the Italian score (NRI: 0.04; p < 0.0001).

The possibility of EC affects treatment options because surgical intervention may be indicated to prevent these events. These EC are relatively early onset phenomena in LSIE, and quantification of the embolic risk at the time of diagnosis may help the therapeutic decision-making process. Our results indicate that approximately 1 in 4 patients had EC after

FIGURE 1 Rate of Embolic Events During Hospital Phase