CLINICAL STUDY

Concentration of apelin inversely correlates with atrial fibrillation burden

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ABSTRACT

AIM: Asymptomatic atrial fibrillation (AF) detection and pulmonary veins isolation (PVI) outcome prediction remain challenging. Our aim was to study the association between apelin and paroxysmal AF in patients undergoing radiofrequency catheter PVI.

METHODS: Sixty-three consecutive patients (55 ± 8years, 12 females) with paroxysmal AF without a structural heart disease and implanted ECG loop recorders undergoing PVI and healthy control group of 34 persons (41 ± 9.5years, 21 females) were included. Apelin plasmatic concentrations were measured before and three months after PVI. AF burden was continually assessed for three years.

RESULTS: Apelin was significantly decreased in AF patients compared to the healthy controls (0.79 ± 0.09 vs 0.98 ± 0.06 ng/ml; p < 0.00001). Apelin plasmatic concentration of 0.89 ng/ml had 94 % specificity and 89 % sensitivity for AF prediction with the area under the curve (AUC) of 0.96. After propensity matching to sex, age and comorbidities, apelin concentration was significantly lower in AF group (0.78 ± 0.1 vs 0.99 ± 0.06 ng/ml; p < 0.0001; AUC: 0.97). There was a significant inverse correlation between apelin concentration and AF burden both before and after PVI (Rho = –0.22; p = 0.05) and (Rho = –0.51; p = 0.006), respectively. There was no significant association between pre-PVI apelin and PVI long-term outcome.

CONCLUSION: In patients without a structural heart disease apelin showed a significant specificity and sensitivity for AF prediction and inversely correlated with AF burden *(Tab. 3, Fig. 3, Ref. 34)*. Text in PDF *www.elis.sk*

KEY WORDS: atrial fibrillation, catheter ablation, apelin, biomarkers.

Introduction

Atrial fibrillation (AF) is one of the most common heart conditions affecting approximately 3 % of adult population over 20 years with even greater prevalence among older patients and patients with chronic conditions. It is an independent risk factor associated with a higher risk of stroke (1), increased mortality twice-fold in women and 1.5-fold in men (2). One of the main challenges is AF detection since it can be asymptomatic and diagnostic capacity of standard ECG monitoring is limited (3, 4).

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Identification of pulmonary vein ectopy as a trigger of AF (Haïssaguerre et al, 1998) became the corner-stone for rhythm control using pulmonary vein isolation (PVI) via catheter ablation (5). Preservation of sinus rhythm with catheter ablation has been reported in up to 70 % patients with paroxysmal and 50 % with persistent AF, so the proportion of patients with AF recurrence still remains relatively high (6). Several protective and risk factors were identified (e.g. AF type, left atrial dimensions, presence of structural heart disease, hypertension or obstructive sleep apnea) (7).

A plasma biomarker capable of detecting AF and predicting outcome of PVI would be a turning point in the management of these patients (35, 36).

Apelin is an endogenous peptide produced in adipose tissue and heart chambers, especially in atria. It acts as a ligand for G-protein coupled APJ receptor. The Apelin-APJ system has a wide range of effects on cardiovascular system affecting for example vasomotor tone, cardiac contractility, heart rate and fibrosis via renin-angiotensin system and thus preventing electrical and structural remodelling of the atria (8, 9). We hypothesized that its concentration is associated with the presence of AF and that it predicts PVI success.

The objective of this study was to evaluate the relationship between apelin plasma concentration and atrial fibrillation. First,

to compare the apelin concentration between patients with AF and healthy controls. Second, to assess the correlation between apelin concentration and AF burden in patients undergoing PVI. Third, to analyse apelin concentrations in plasma before and after the PVI and fourth, to investigate the apelin´s ability to predict long-term PVI outcome.

Methods

Study population

The study was designed as a prospective single centre cohort study. Study group included patients with symptomatic, drug refractory, paroxysmal AF and implanted loop recorders indicated for PVI, who were consecutively recruited in the National Cardiovascular Institute.

The inclusion criteria were: Age 18 or higher; planned PVI; implanted implantable loop recorder (ILR) at least two months before PVI; symptomatic and drug refractory, paroxysmal AF (characterized by spontaneous or medical termination within seven days of onset) documented prior to ILR implantation; continuous, effective oral anticoagulation at least one month prior to the PVI; antiarrhythmic therapy with beta blocker and amiodarone at least three months before the procedure; ability and willingness of the patients to provide a written informed consent for the study. The exclusion criteria were: patients with a history of clinically significant supraventricular or ventricular arrhythmia other than AF; diabetes mellitus or impaired fasting plasma glucose (fasting plasma glucose > 5.6 mmol/l); stable coronary artery disease; acute coronary syndrome; signs and symptoms of heart failure not related to AF; reduced left ventricular ejection fraction (< 50 %); chronic inflammatory disease; chronic kidney disease; uncontrolled hyperthyroidism; smoking; ongoing acute inflammatory disease; anticipating major cardiac surgery within the course of this study; previous catheter ablation; an implanted pacemaker or implantable cardioverter defibrillator (ICD).

Healthy control group consisted of random blood donors. Atrial fibrillation was excluded based on the history and 12-lead ECG at the time of enrolment. The study was approved by the ethical committee of the National Cardiovascular Institute and a written informed consent was obtained from all of the patients.

Radiofrequency catheter ablation with pulmonary veins isolation

All the patients remained on their original antiarrhythmic therapy. Effective oral anticoagulation (INR 2–3) was administered to all the patients. Transesophageal echocardiography for exclusion of left atrial (LA) thrombus was performed immediately prior to PVI. All patients underwent a contrast CT scan for a documentation of individual LA anatomy.

A complete electrophysiological study was performed before PVI to exclude any arrhythmia other than AF. During the PVI procedure one 6Fr quadripolar diagnostic catheter (Supreme™, SJM, USA) was inserted via the right femoral vein to the His bundle area. A 6Fr decapolar diagnostic catheter (Response™, SJM, USA) was positioned in the coronary sinus via the right

jugular vein. Fluoroscopically guided double transseptal puncture was performed with a Brockenbrough needle (BK1) inserted via the right femoral vein through an 8.5 Fr long sheath (SL1, SJM, USA) continuously flushed with heparinized normal saline. Two fixed curve sheaths or deflectable transseptal sheaths (AGILIS, SJM, USA) were used for entering the LA and for stabilizing the circumferential mapping catheter (Lasso, Biosence-Webster, USA), and irrigated-tip ablation catheter (NaviStar Thermocool, Biosence-Webster, USA or Therapy Cool Path, SJM, USA) in the LA. In the cases with a complex LA anatomy, intracardiac echocardiography was performed to guide the procedure. During the entire procedure, the activated clotting time (ACT) was measured each 20 min and maintained above 300 s.

Surface ECGs and bipolar endocardial electrograms were monitored continuously and stored in a computer-based digital amplifier/recording system (Prucka, GE, USA or AXIOM Sensis, Siemens, Germany). The procedure was performed with a conscious sedation, with addition of midazolam, propofol or fentanyl in the case of further pain during the ablation (ABL).

An electroanatomic mapping system (CARTO, Biosense-Webster or NavX, SJM) generated a three-dimensional map to support the creation and validation of radiofrequency (RF) lesions during PVI. Ablation consisted of PV isolation only, creating circular lines of conduction block around each PV ostium. Radiofrequency pulses were delivered through a Stockert (Biosense-Webster, USA) or IBI Therapy (Irvine Biomedical, Inc.) generator using irrigated-tip catheter in a temperature-controlled mode limited to 43 °C using a maximal power of 40W and an irrigation rate up to 20 ml/min in LA. PV isolation was confirmed by the abolition or dissociation of the local PV potentials on the circumferential mapping catheter placed in an ostial position of each PV. PV disconnection that persisted during AF more than 30 minutes after the last RF application had to be confirmed in sinus rhythm, too.

Implantable loop recorder

This method was described in our previous study (10).

Data collection and biochemical analysis

In the study group, baseline clinical data from the patients were collected one day before scheduled PVI. Information about the AF burden was downloaded from the ILR immediately after the procedure and then 3, 6, 9, 20 and 30 months after the PVI with explantation of the device at the end of follow-up. All the patients received a prespecified antiarrhythmic therapy with beta blocker and amiodarone three months after PVI. Peripheral fasting blood was taken in the morning into K3EDTA tubes immediately before the procedure and on follow-up three months after.

In the control group, baseline clinical data and fasting blood samples were collected at the time of blood donation, similarly as in the study group.

The blood was centrifuged at 2700 g for five minutes and the obtained plasma samples were stored at −20 °C. The apelin-12 concentration was measured using a commercially available ELISA kit (Phoenix Pharmaceutical, Karlsruhe, Germany) in plasma samples.

Fifty microliters of plasma samples were used for measurement according to the protocol of the manufacturer.

PVI outcome definition

The definition of the long-term PVI success was based on AF burden and asymptomatic AF after PVI.

In terms of AF burden, the cut-off limit of 0.5 % was used as previously suggested (11, 12). The long-term AF burden success was defined as AF burden < 0.5 % during the whole follow-up, excluding the three-month blanking period. Based on the AF burden success, the patients were divided into optimal responders and non-responders.

In terms of the asymptomatic AF, a long-term alternative success was defined according to the Expert consensus statement on the catheter and surgical ablation of atrial fibrillation (13) as a freedom from symptomatic AF/atrial flutter/atrial tachycardia after discontinuation of antiarrhythmic therapy as assessed from the end of the three-month blanking period to the end of the follow-up. Based on the alternative success, patients were divided into the clinical responders and non-responders.

Statistical methods

Continuous variables are presented as the means and standard deviations, whereas categorical variables are presented as percentages. Normality of data was tested using a Shapiro-Wilk test. Paired or unpaired Student t-test and Mann-Whitney test were used to compare continuous variables as appropriate. Spearman's rank correlation was used to test the relationship between variables with non-normal distribution. Receiver operating characteristic (ROC) curves together with the respective values of sensitivity, specificity and accuracy at various cut-off levels of the selected parameter were calculated to evaluate the diagnostic performance. The effect of explanatory variables on various outcomes was evaluated using a logistic regression analysis. The estimates are presented together with the 95% confidence interval (CI). $p < 0.05$ was considered statistically significant. Data were analyzed using StatsDirect statistical software version 3.2.10 (http://www.statsdirect.com) and RStudio 1.2.5033 (RStudio Team (2019). RStudio: Integrated Development for R. RStudio, Inc., Boston, MA URL http://www.rstudio.com/.)

Results

Our study was composed of two groups. The healthy control group (n = 34) included 13 males and 21 females with the mean age of 41 (ranging from 21 to 61, SD ± 9.5). Patients in this group had no medical history of cardiovascular diseases.

AF group was composed of 63 patients with paroxysmal atrial fibrillation, 51 males and 12 females. The mean age was 55 (ranging from 36 to 77, SD ± 8.3). Arterial hypertension was present in 46 patients (73 %) and five patients (7.9 %) suffered from prior stroke (Tab. 1).

The average time of continuous ECG monitoring before PVI was 177 ± 131 days and after PVI was 1063 ± 271 days, respectively.

Difference in the baseline apelin concentration between the patients with AF and healthy control

There was a significant difference in the baseline apelin concentrations between patients with AF and healthy control group (0.79 ± 0.09 vs 0.98 ± 0.06 ng/ml; CI: –0.22 to –0.16, p < 0.001). Based on the ROC analysis, the apelin plasmatic concentration of 0.89 ng/ml had 94 % specificity and 89 % sensitivity for the prediction of atrial fibrillation (AUC 96.2 %, CI: 92.2–100 %) (Fig. 1).

Multivariate analysis, after adjustment for age, gender, AF duration before PVI, arterial hypertension and stroke showed that all factors except for stroke were statistically significant for diagnosing AF (Tab. 2).

After propensity matching to sex, age, and comorbidities, apelin concentrations were significantly higher in the healthy group in comparison to patients' group (0.99 ± 0.06 ng/ml vs 0.78 ± 0.1 ng/ml, CI: –0.29 to –0.14, p < 0.001) (Tab. 3). Subsequent ROC analysis for propensity matched groups showed almost identical results. Apelin concentration of 0.86 ng/ml in plasma had 100 % specificity and 83 % sensitivity for the prediction of atrial fibrillation (AUC 97.2 %, CI: 92.03–100 %) (Fig. 2).

Correlation between apelin and LA, left ventricular end diastolic diameter (LVEDD) and AF history

There was a statistically significant inverse correlation between the apelin concentrations with corresponding LA diameter (r = –0.31, p = 0.02), LVEDD (r = –0.29, p = 0.026) and history of AF (r = –0.29, p = 0.035) (Fig. 3).

Correlation between apelin and AF burden

There was a statistically significant inverse correlation between the apelin concentration and AF burden both before and after PVI (Rho = –0.22, p = 0.05, CI = –0.45 to 0.05) and (Rho = –0.52, CI = –0.77 to –0.13, p = 0.006) respectively.

Correlation between the pre-PVI apelin concentration and post-PVI AF burden

There was no statistically significant correlation between the pre-PVI apelin levels and total AF burden excluding blanking period – the first three months after PVI (Rho = –0.08, CI = –0.34 to 0.19, p = 0.28).

Tab. 1. Baseline characteristics of the patients with AF.

Baseline characteristics of AF group	Total (n=63)
Age (years)	55±8
Female gender, no. (%)	12 (19.04 %)
BMI (kg/m²)	28.5±4.16
AF history before PVI (years)	5.98±4.47
LA size at PVI (mm)	44.32±4.5
LVEDD at PVI (mm)	51.86±3.41
Arterial hypertension, no. (%)	46 (73 %)
Stroke, no. (%)	5 (7.9 %)

Data are presented as the mean ± standard deviation or n (%). BMI – body mass index; AF – atrial fibrillation; PVI – pulmonary vein isolation; LA – left atrium; LVEDD – left ventricular end diastolic diameter
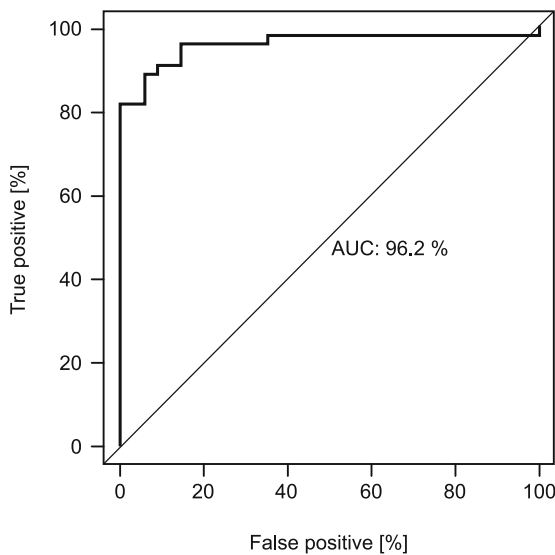
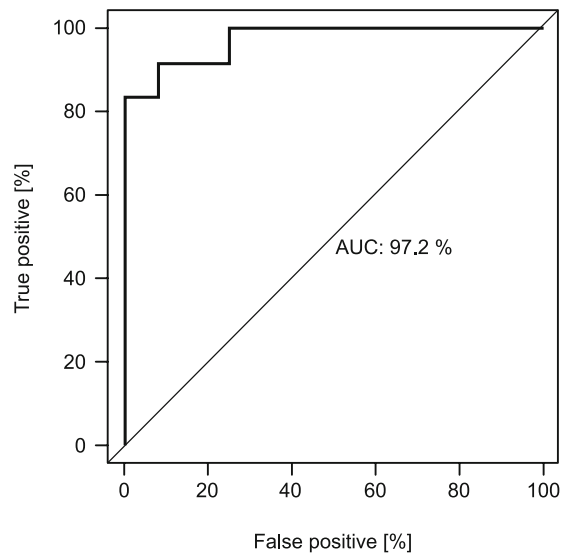**Fig. 1. Receiver operating characteristic plot for apelin levels.**

Fig. 2. Receiver operating characteristic plot for apelin levels (propensity matched groups).

Difference in the pre-PVI apelin concentration between clinical responders and non-responders.

There was no statistically significant difference between clinical responders and non-responders in pre-PVI apelin levels (CI = –0.03 to 0.07, p = 0.53).

Difference in pre-PVI apelin concentration between optimal responders and non-responders.

There was no statistically significant difference between optimal responders and non-responders in pre-PVI apelin levels (CI = –0.03 to 0.07, p = 0.45).

Tab. 2. Multivariate analysis.

	Odds Ratio	(95% confidence interval)	p
Age	1.01	1.005 to 1.016	<0.001
Male gender	1.23	1.101 to 1.363	<0.001
AF history before PVI	1.02	1.002 to 1.029	0.03
Arterial hypertension	1.29	1.138 to 1.468	<0.001
Stroke	1.08	0.872 to 1.328	0.495
Apelin level	0.24	0.138 to 0.429	<0.001

AF – atrial fibrillation; PVI – pulmonary vein isolation

Tab. 3. Propensity matched groups.

	Healthy control	AF group	p
Age (years)	47±8,5	50±6	N/A
Female gender, no. (%)	2 (16.67 %)	2 (16.67%)	N/A
Arterial hypertension, no. (%)	0 (0 %)	0 (0 %)	N/A
Stroke, no. (%)	0 (0 %)	0 (0 %)	N/A
Apelin level [ng/ml]	0.99±0.06	0.78±0.1	< 0.001

Data are presented as mean ± standard deviation or n (%)

Difference in pre-PVI and post-PVI apelin concentration

There was no statistically significant difference between pre-PVI and three months post-PVI apelin levels (CI = –0.05 to 0.02, p = 0.28).

Discussion

This research follows and builds on previous findings from our small pilot study, with the goal to better clarify the role of apelin in the management of AF patients (14). To our knowledge this is the first study related to apelin and AF taking an advantage of data acquired from the patients with implantable loop-recorders and long-term follow-up.

This study identified apelin as a potential biomarker for the prediction of AF in the patients without structural heart disease. In our study, apelin showed a high specificity and sensitivity in detecting AF with AUC over 96 % when comparing the patients with AF and the healthy control group. These results are promising even when compared to other biomarkers (e.g. troponin or NT-proBNP). These results were also supported by the propensity-matched groups. Furthermore, apelin concentrations significantly correlated inversely with AF burden prior to PVI and on follow-up, suggesting that apelin also reflects the amount of atrial fibrillation.

Apelin is an endogenous peptide expressed in many tissues, endothelium and human plasma and acts as a ligand for G-protein coupled APJ receptor. The Apelin-APJ system has a wide range of effects on cardiovascular system and has been studied as a potential candidate for the treatment of heart failure and prevention of postischemic ischemia-reperfusion (I/R) injury, apoptosis, fibrosis and cardiac remodelling (11). Many processes that are linked and studied in the relation to atrial fibrillation (e.g. inflam-
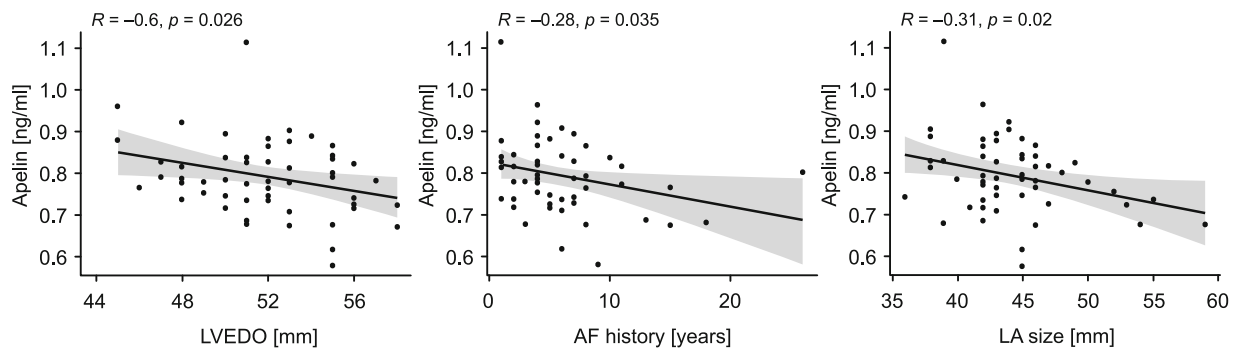
Fig. 3. Correlations between apelin levels and LVEDD, AF history and LA size. LVEDD – left ventricular end diastolic diameter; AF – atrial fibrillation; LA – left atrium.

mation (15), oxidative stress (16) or atrial fibrosis (17)) are directly or indirectly affected by apelin. Renin-angiotensin-aldosterone signalling pathway is known to be associated with the process of atrial remodelling (18) and fibrosis seen in AF. Apelin is the second catalytic substrate for angiotensin converting enzyme (ACE) 2 and functions as an inotrope, vasodilator and cardiovascular (19) peptide. To some extent it is also counter-regulated by the angiotensinogen (20). The role of oxidative stress in pathogenesis and perpetuation of atrial fibrillation has been thoroughly investigated and demonstrated in several studies (9, 16, 21). There is also evidence, based on in vitro animal models, that apelin shortens the duration of action potential in atrial myocytes via effect on multiple ionic channels (22). This relationship between apelin and AF is observed in two studies, which showed that apelin levels were significantly lower in patients with lone AF compared to the patients without AF (23). The outcomes of our study were consistent with these results.

Decreased apelin concentrations in AF could be caused by chronically increased atrial stretch induced by the increased LA pressure typical for AF (24, 25). However, patients in our group had paroxysmal AF, which opens a new hypothesis that LA pressure in the patients with AF is increased even in sinus rhythm. In our study, apelin levels also statistically significantly correlated inversely with left atrial (LA) size, left ventricular diastolic diameter and duration of AF, which might be indirect markers of chronically increased LA stretch. According to our knowledge, this was not studied before, but research from Sramko et al. suggested that an increased left atrial pressure in the patients with AF regardless if measured in sinus rhythm was associated with an extensive LA arrhythmogenic substrate (26). Whether patients with paroxysmal AF have chronically increased LA pressure even in sinus rhythm and therefore decreased apelin concentrations merits further research.

Only patients without structural heart disease were included in our study. Other cardiac pathologies affect circulating apelin as well. Apelin levels have been shown to be lower in patients with significant coronary atherosclerosis (27), left ventricular hypertrophy (28) or severe aortic stenosis (29). Assessment of

apelin levels in the context of heart failure appears to be more complex. Some studies reported decreased, unaltered or even increased plasma levels compared to the control subjects (30, 31). Chen et al demonstrated increased plasma concentrations in patients with mild to moderate heart failure, followed by a decline with the transition from moderate to severe chronic failure (32). The use of apelin for diagnosing AF can therefore be problematic in patients with other cardiac pathologies, especially with heart failure and would require further thorough investigation. Conversely, in patients with lone AF, its diagnostic potential appears to be significant.

Apelin in our study was not able to predict PVI results contrary to the study by Wang YZ et al from 2018 (33) and there was also no significant difference between the apelin levels pre-PVI and post-PVI. This could be caused due to a limited sample size, but also different PVI outcome definition and a longer follow up in our study. One of the problems with studying and analysing the outcomes of PVI for AF is dichotomizing the patients into those responding and not responding to the therapy. Previous studies and our own experience showed several difficulties in accurately identifying these patients (14, 34). Using a continuous variable of AF burden, as used in this study, instead of dichotomous division to responders and non-responders offers a better insight into this problem and allows a more precise analysis of the relationship between apelin and atrial fibrillation. Based on our results, apelin was not shown to be a biomarker that could be used in clinical practice for the predicting PVI outcome, but for detecting or screening of AF in high-risk patients, e.g. in patients after an embolic stroke of undetermined source (ESUS). AF is often asymptomatic and standard 12-lead ECG, 24h or even 48h Holter monitoring does not provide a sufficient detection rate (3, 4). Furthermore, there is also evidence that subclinical asymptomatic AF is associated with a higher risk of stroke (1). Plasmatic biomarker capable of diagnosing or identifying high-risk of AF would be of remarkable clinical interest. Further research will show if apelin would be suitable for this role.

Learning points

- Plasmatic concentration of apelin is decreased in the patients with AF without structural heart diseases.
- Plasmatic concentration of apelin inversely correlated with AF burden.
- Apelin could be used as a plasmatic biomarker of AF in the future.

Study limitations

Our study had several limitations. Our study population included uncomplicated patients with either lone AF or AF with arterial hypertension. Therefore, the findings of our study cannot be generalized to the entire AF population. The healthy control group included younger patients without arterial hypertension and the necessary propensity matching led to a substantial reduction of compared populations.

Conclusion

Our results suggest that apelin might be a promising biomarker for detecting a high probability of presence of substrate for arterial fibrillation. Its significance is also supported by an inverse correlation with AF burden. Combining this plasma biomarker with clinical characteristics might lead to an improved prediction of AF of AF-prone patients. Additional research on different independent cohorts of patients with AF is however needed to confirm and further investigate our findings.

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