https://doi.org/10.35336/VA-1329

INTERATRIAL BLOCK AND ABNORMAL P-WAVE ELECTROCARDIOGRAPHIC PARAMETERS AS NON-INVASIVE PREDICTORS OF ATRIAL FIBRILLATION

T.G.Vaikhanskaya, T.M.Kaptiukh, I.D.Kozlov, A.V.Frolov
State Institution «Republican Scientific and Practical Centre «Cardiology»», Belarus, Minsk, 110b Rose Luxembourg str.

Aim. To identify noninvasive markers of atrial electrical dysfunction and risk of nonvalvular atrial fibrillation (AF) and to develop a predictive mathematical model to estimate the AF risk based on electrocardiographic (ECG) P-wave parameters during sinus rhythm.

Methods. The study included 211 patients with cardiovascular pathology (aged median 62 [52; 71] years, 67.8% male, NYHA heart failure class I-III). All patients (follow-up median 45 [26; 67] months) underwent a complex of studies: 12-lead ECG, echocardiography, 24-hour ECG monitoring. Based on surface ECG data during sinus rhythm, parameters of atrial electrical activation were assessed such as Morphology, Voltage and P waves duration (MVP) according to integral analysis by MVP score.

Results. During 3.7-year period, 44 (20.8%) patients experienced new-onset sustained AF and 12 (5.69%) patients developed ischemic stroke. As a result of ROC analysis and univariate Cox regression, independent predictors of AF were identified: P-wave prolongation in the DII lead, 3rd degree or advanced interatrial block (aIAB), an increase P-wave terminal force in lead V_1 ($PTFV_1$), low-voltage P-wave in the DI lead and calculated level of abnormal P-wave ≥3 points on the MVP score. Data from multivariate Cox proportional hazards regression analysis confirmed the prognostic significance for three independent predictors of AF: aIAB (hazard ratio (HR) 5.92; 95% confidence interval (CI) [2.48-4.12]; p=0.0001); $PTFV_1$ (HR 1.14; 95% CI [1.04-1.24], p=0.003); low-voltage P-wave in lead DI <0.1 mV (HR 1.03; 95% CI [1.02-1.05]; p=0.0001); and as a result a mathematical model was created to predict AF risk (-2LL =258; χ^2 =105; p=0.0001). Predictors such as $PTFV_1$ (HR 1.41; 95% CI [1.17-1.72], p=0.0001) and MVP score of abnormal P-waves (HR 1.85; 95% CI [1.27-1.72] 2.70], p=0.001) were associated with a high risk of stroke according to Cox regression model (-2LL= 62.5; χ^2=38.4; p <0.001).

Conclusion. Complex of ECG markers of atrial electrical dysfunction such as aIAB, $PTFV_1$, level MVP score of abnormal P-wave and low P-wave voltage allows identifying patients at high risk of AF and ischemic stroke.

Key words: advanced interatrial block; P-wave score; risk predictors; atrial fibrillation; stroke; electrocardiography

Conflict of interest: none.
Funding: none.
Received: 31.01.2024 **Revision received:** 07.03.2024 **Accepted:** 28.03.2024
Corresponding author: Tatiyana G. Vaikhanskaya, E-mail: tat_vaikh@mail.ru

T.G.Vaikhanskaya - ORCID ID 0000-0002-2127-8525, I.D.Kozlov - ORCID ID 0009-0002-9247-2904, A.V.Frolov - ORCID ID 0000-0002-7470-6992

For citation: Vaikhanskaya TG, Kaptiukh TM, Kozlov ID, Frolov AV. Interatrial block and abnormal p-wave electrocardiographic parameters as non-invasive predictors of atrial fibrillation. *Journal of Arrhythmology.* 2024;31(2): 24-34. https://doi.org/10.35336/VA-1329.

Atrial fibrillation (AF) is the most common cardiac tachyarrhythmia in the general population (1–2%), the incidence of AF increases with age and reaches 6% in people over 65 years of age. AF is associated with the most common diseases - coronary artery disease (CAD), arterial hypertension (AH), endocrinological diseases, valvular diseases, and heart failure (HF) [1, 2]. In patients with CAD (depending on the type and degree of damage to the coronary arteries), the prevalence of AF ranges from 4.1% to 58%, and the frequency of CAD approaching 65% for individuals with AF. The addition of AF causes exacerbation of symptoms of coronary heart disease and HF, worsens the clinical course, and increases the risk of serious complications - systemic thromboembolism, stroke and cognitive impairment [1-3].

AF is associated with atrial disease, an atriomyopathy characterized by structural and electromechanical changes [3-6]. As a rule, these changes in the atria precede the onset of AF and can be detected by assessing atrial activation both during endocardial mapping and surface electrocardiography (ECG) [7]. P wave parameters on the ECG are reflected the electrical activation of the atria depending on the atrial structure, dimension and electromechanical function, and therefore a number of P wave indicators have been actively studied over the last 10 years as predictors of the occurrence of AF [8-14]. As an example, the authors M. Rasmussen et al. (2020) showed that P wave duration >120 ms, an increase P wave terminal force in V1 (PTFV1) and a deviation of the electrical axis of the P wave to the right were associated with age-dependent manifestation of AF

[14]. Some epidemiological studies have demonstrated the prognostic significance of P wave prolongation and partial and advanced interatrial block as independent predictors of AF [14-18].

Interatrial block (IAB) is one of the most studied ECG phenomena reflecting a conduction delay between the right and left atrium through the Bachmann bundle [18,19]. Atrial abnormalities, such as atrial fibrosis and left atrial (LA) dilatation, lead to abnormal electrophysiology and electrical atrial remodeling with slowing of impulse conduction and these are the electro-anatomical substrate for the occurrence of atrial arrhythmias [17–20]. Structural changes around the Bachmann bundle cause longitudinal dissociation in neighboring muscle fibers and contribute to the formation of the re-entry mechanism for the occurrence of AF. The relationship between IAB and AF was confirmed in numerous studies [13–19]. Experts in the field of electrophysiology, associates of the famous Spanish scientist A. Bayes de Luna, who first presented this phenomenon, proposed a new term in 2015 - "Bayes syndrome" as a separate clinical syndrome which is characterized by a combination of 3rd degree IAB and supraventricular tachyarrhythmias, the most common of which is AF [15, 19-21]. So already in 2018, the results of a meta-analysis were published (16 studies with long-term follow-up of 17.865 patients), which demonstrated a strict relationship between IAB and AF. The authors found that the presence of advanced IAB doubles the risk of AF [22].

Advanced IAB (further in the text a-IAB or third degree) is characterized by retrograde depolarization in the left atrium, which is reflected on the ECG by expansion of the P wave (>120 ms) and biphasic morphology of the P wave in the three inferior ECG leads (II, III, aVF). Partial IAB (further in the text p-IAB or first degree) appears on the surface ECG as an extended positive (mono- or isophasic) P wave lasting ≥120 ms [23].

Table 1.

Clinical characteristics of 211 patients included in the study (ME [LQ; UQ])

Parameter	Patients (n=211)
Age, years	62 [52; 71]
Male, n (%)	143 (67.8)
Body weight, kg	72 [64; 85]
Body mass index, kg/m^2	28 [27; 30]
Diabetes mellitus, n (%)	66 (31.3)
Hypertension, n (%)	118 (55.9)
Chronic obstructive pulmonary disease, n (%)	23 (10.9)
Coronary artery disease, n (%)	121 (57.3)
Hypertrophic non-obstructive cardiomyopathy, n (%)	10 (4.74)
Dilated / restrictive cardiomyopathy, n (%)	7/3 (3.32/1.42)
NYHA III FC heart failure, n (%)	46 (21.8)
Interatrial block (1–3 degrees), n (%)	65 (30.8)
P wave duration in lead II of the ECG, ms	112 [107; 122]
Advanced interatrial block (3rd degree), n (%)	42 (19.9)
P wave amplitude in lead I of the ECG, mV	0.12 [0.10; 0.14]
PR interval duration in lead II of the ECG, ms	176 [156; 200]
P wave amplitude of the negative phase in lead II ECG, mV	0.12 [0.01; 0.17]
P wave amplitude of the positive phase in lead II ECG, mV	0.23 [0.15; 0.28]
P wave amplitude of the negative final phase in lead V1, mV	0.06 [0.01; 0.10]
P wave in duration of the negative phase in lead V1, ms	48 [0.01; 64]
P wave terminal force in lead V1 (PTFV1), ms × mV	3.22 [0.01; 6.43]
P wave evaluation scale (MVP), points	1 [0; 3]
Left ventricular ejection fraction, %	62 [55; 64]
Left atrial diameter (anterior-posterior dimension), mm	40 [36; 44]
HATCH score, points	1 [0; 3]
CHA_2DS_2-VASc score, points	2 [1; 3]
Score HASBLED, points	2 [1; 2]
Implanted electronic devices, n (%)	37 (17.5)
Follow-up, months	45 [26; 67]

Note: HATCH, scoring scale for predicting AF progression: hypertension (1 point), age ≥75 years (1 point), TIA/stroke (1 point), COPD (1 point), HF (2 points); CHA_2DS_2-VASc, thromboembolic risk assessment score; HASBLED, bleeding risk score.

However, studies of the relationship between AF and P wave parameters are limited by certain methodological factors: retrospective analysis, subjectivity in assessing the duration and morphology of the P wave in the absence of unified automatic algorithms for analyzing P waves, and underestimation of the real prevalence of AF due to underdiagnosis of asymptomatic and subclinical variants of AF [7-11].

To assess asymptomatic episodes of AF in a study by F. Kreimer et al. (2021) were examined data from 366 patients with implanted loop recorder. An analysis of independent factors found that advanced IAB and abnormal terminal force P wave in lead V1 were associated with a 5-fold increase in the risk of AF [24].

Thus, intention to investigate was to examine the association of abnormal P wave parameters with occurrence of AF in the analyzed cohort of the patients with cardiovascular pathology, including those with implanted electronic devices (IEDs).

The research aim was to study electrical atrial dysfunction and the prevalence of IAB in patients with cardiovascular diseases (CAD, hypertension,

cardiomyopathy), evaluate non-invasive ECG predictors of the risk of non-valvular AF and create a mathematical model for AF predicting.

METHODS

The study included 211 patients with sinus rhythm and stable cardiovascular disease (CAD, hypertension, cardiomyopathy). Symptoms of HF class II (n=102) and class III (n=46) according to NYHA were detected in 70.1% of the cohort. Electronic pacemakers were implanted in 37 patients (15 dual-chamber DDD and 22 CRT-P devices for resynchronization therapy). Clinical characteristic of the total cohort is presented in Table 1. The follow-up period was median 45 [26; 67] months. When forming a prospective single-center sample representing a "population cross-section" of the most common cardiovascular diseases in people aged ≥50 years, the following criteria for inclusion in the study were used: written informed consent for research; sinus rhythm at the time of inclusion in the study; normal left ventricular ejection fraction (LVEF) or moderate reduced LVEF (≥39%); no previous ablation procedure or valve correction. The criteria for exclusion from studies were the following: a history of stroke, myocardial infarction or coronary artery bypass grafting less than 6 months ago, dementia, primary valvular or congenital heart disease, end-stage heart failure, history of AF or catheter treatment for arrhythmia, poor quality ECG inaccessible for precision measurement of the P wave.

The baseline indices of digital ECG-12 (P amplitude and duration, P wave morphology and PR interval) and echocardiography (Echo) parameters analyzed. Cardiac magnetic resonance imaging (MRI) performed in 183 patients and the late gadolinium enhancement (LGE) pattern adopted as a criterion for myocardial fibrosis. The amplitude-time parameters of the P wave assessed using a 12-channel digital computer system "Intecard-8" (Belarus) according to automatic ECG analysis algorithms. Additional manual correction of P wave marks on the ECG in patients with IEDs was performed by two independent blinded specialists using a zoomed-in scale of ECG complexes and a precision electronic caliper.

The MVP score used for analyzing P wave parameters for an integral assessment of the atrial activity signal on the surface ECG [10], the predictive value of the MVP score has been previously confirmed in several trials studying various population groups [25, 26]. The MVP score (assessment of the Morphology, Voltage and P wave duration) allows to identify a complex of abnormal P wave indices reflecting the degree of atrial electrical remodeling and IAB in points:

- Morphology in the inferior leads (II, III, aVF) scoring with a monophasic P wave <120 ms – 0 points, with a monophasic P wave ≥120 ms – 1 point, with a biphasic P wave ≥120 ms – 2 points;
- Voltage (amplitude) in lead I (for P >0.20 mV – 0 points; for P in the range of 0.10–0.20 mV – 1 point, for P <0.10 mV – 2 points);
- P wave duration (for P <120 ms – 0 points, for P wave duration in the range of 120–140 ms – 1 point, for P >140 ms – 2 points).

ECG classification criteria were used [27, 28] to assess the degree of IAB, classification is presented in Ta-

Table 2.

Classification and criteria for interatrial block (IAB)

Classification of IAB	Degree and type	Pathophysiology	ECG signs
Partial IAB	First	Deceleration of impulse transmission through a Bachmann bundle	P wave ≥ 120 ms, P wave is monophasic in inferior leads (II, III, aVF)
Intermittent IAB	Second	Transient block of impulses along the Bachmann bundle	Alternation of a monophasic P wave ≥120 ms in lead (II, III or aVF) with biphasic (+/−) extended P wave in the same lead
Advanced IAB	Third	Complete permanent block of electrical impulses along the Bachmann bundle with retrograde activation of the left atrium (the impulse spreads downwards to the atrioventricular node and the mouth of the coronary sinus, and then up in the caudal-cranial direction)	P wave is prolongated ≥120 ms with biphasic (+/−) morphology in all inferior leads (II, III and aVF)
Atypical advanced IAB	Type I		P ≥120 ms, P wave in leads III and aVF biphasic (+/−), the terminal component of the P wave in lead II is isoelectric
	Type II		P ≥120 ms, P wave is biphasic in leads III and aVF, the second part of P wave in lead II is biphasic (+/−), therefore, the P wave is triphasic (+ /−/ +)
	Type III		P ≥120 ms, P wave morphology in leads III and aVF is completely negative, but started being isodiphasic, and the P wave in lead II is biphasic (+/−)
	Type IV		P ≥120 ms with 3-phase morphology in leads II, III and aVF
	Type V*		P <120 ms with typical 2-phase morphology (+/-) in all inferior leads (II, III, aVF)

Note: * - with normal P wave duration

ble 2. To differentiate advanced IAB from an atrial ectopic rhythm arising at the level of the crista terminalis, a scrupulously examination of the inferiolateral ECG leads (V5 and V6) was carried for the presence of a positive P wave (a criterion that helps distinguish IAB from ectopic nodal and atrial rhythms). Arrhythmic events assessed over time (twice a year) using surface ECG-12, Holter monitoring (HM) and the pacemaker interrogation procedure (request for specified parameters and statistical data on hardware detection of arrhythmic episodes recorded by the patient's implanted device).

The primary endpoint was the first episode of paroxysmal or persistent AF. The end point (ICD-10 diagnosis code 148) was considered achieved if AF (paroxysmal, persistent and permanent forms) or persistent atrial flutter (AFt) was detected according to ECG and/or HM, with pacemaker interrogation, or with a documented history of AF. Depending on the presence or absence of AF/AFt episodes during the follow-up period, the analyzed total cohort was divided into 2 groups: 1) a group without AF events with sinus rhythm (SR, n=167, including 23 patients with pacemaker) and a group with registered episodes of AF/AFt during the observation period (AF, n=44; including 14 patients with pacemaker).

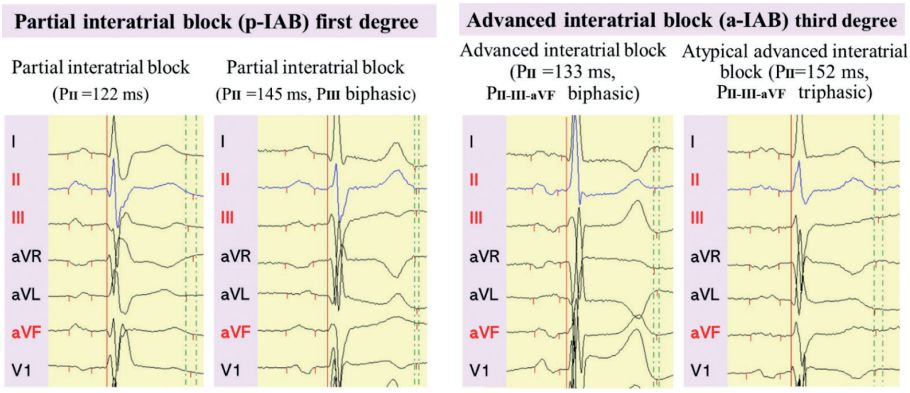


Fig. 1. Variants of abnormal interatrial conduction in patients of the analyzed cohort.

Table 3.

Comparative characteristics of patients depending on achievement of the end point (AF)

	SR group (n=167)	AF group ФП (n=44)	p
Age, years (M±sd)	58.9±14.1	65.3±12.6	0.006
Male, n (%)	117 (70.1)	26 (59.1)	0.166
Hypertension, n (%)	89 (53.3)	29 (65.9)	0.134
Diabetes mellitus, n (%)	49 (29.3)	17 (38.6)	0.237
Dyslipidemia, n (%)	78 (46.7)	16 (36.4)	0.292
Smoking status, n (%)	35 (20.9)	9 (20.4)	0.858
Chronic obstructive pulmonary disease, n (%)	8 (4.8)	15 (34.1)	<0.0001
Echocardiographic parameter			
Left ventricular ejection fraction, %	59.1±9.48	55.9±10.7	0.079
Left atrium volume indexed, ml/m2 (Me [LQ; UQ])	32 [29; 35]	39 [35; 43]	0.006
Left atrium anterior-posterior dimension, mm (M±sd)	39.3±5.16	44.1±6.75	0.011
Electrocardiographic parameter			
P wave duration in lead II, ms (M±sd)	110±9.20	137±23.5	<0.001
Duration of the negative phase of the P wave in lead II, ms (Me [LQ; UQ])	44 [40; 50]	68 [65; 117]	0.001
Duration of the positive phase of the P wave in lead II, ms (Me [LQ; UQ])	39 [33; 52]	38 [30; 49]	0.575
Duration of the negative phase of the P wave in lead V1, ms (M±sd)	33.9±30.5	58.4±31.7	<0.001
P terminal force of negative phase in lead V1 (PTFV1), mV*ms (Me [LQ; UQ])	3.23 [0; 4.45]	5.87 [3.9; 9.98]	0.004
P wave amplitude in lead I, mV (M±sd)	0.14±0.03	0.06±0.03	<0.001
P wave amplitude in lead II, mV (M±sd)	0.24±0.08	0.14±0.04	<0.001
PR interval, ms (M±sd)	176±35.0	203±38.2	<0.001
Partial interatrial block, n (%)	6 (3.59)	17 (38.6)	<0.001
Advanced interatrial block, n (%)	5 (2.99)	37 (84.1)	<0.001
HATCH score, points (Me [LQ; UQ])	1.25 [0; 2.5]	2.5[1.5; 4]	0.001
Score CHA_2DS_2-VASc, points (Me [LQ; UQ])	2 [0.5; 3.25]	3.5 [1.25; 5.25]	0.013
Score MVP, points (Me [LQ; UQ])	0.46 [0; 1.25]	4.5 [3.5; 6]	<0.001

Note here and below: AF, atrial fibrillation, SR, sinus rhythm

Statistical analysis

Statistical data processing was carried out using the IBM SPSS-23.0 program; the critical value of the level of statistical significance when testing null hypotheses was taken equal to 0.05. Quantitative characteristics that do not correspond to the law of normal distribution are presented as median, lower and upper quartiles (Me [LQ; UQ]). For categorical variables, the absolute values (n) of symptom manifestation and the frequency of symptom manifestation as a percentage (%) were calculated. Statistical processing was carried out using the Mann-Whitney test for quantitative indicators, for qualitative indicators - the χ^2 test with Yates correction. Differences between study groups were tested using the median test. Determining the cut-off point corresponding to the optimal predictor value for predicting AF, as well as determining the quality of regression risk models, was carried out using ROC analysis with the construction of ROC curves and assessment of their operational characteristics. Hazard ratio (HR) parameters were calculated using Cox proportional hazards regression model (univariate and multivariate Cox regression).

The study was approved by the local ethics committee and was carried out in accordance with the standards of Good Clinical Practice and the principles of the Declaration of Helsinki. Before inclusion in the study, written informed consent was obtained from all participants.

RESULTS

Initially during the study intact atrial conduction was revealed in 146 (69.2%) patients (if P wave duration <120 ms), and IAB was detected in 65 patients (30.8%), including advanced IAB was recorded in 42 (19.9%) cases. An atypical variant of third degree IAB was identified in 23 (54.8%) of 42 individuals with advanced IAB. The 2nd degree of IAB was recorded in one case. In patients with implanted pacemaker devices, IAB was detected in 16 (43.2%) of 37 patients in native sinus rhythm (in 32.4% - partial IAB, in 10.8% - advanced IAB). Variants of interatrial conduction disturbances are presented in Figure 1.

Episodes of paroxysmal or persistent AF (new onset events) were registered in 44 individuals during the analyzed period; in patients with implanted pacemakers, asymptomatic AF was recorded in 8 (57.1%) of 14 patients with paroxysms of sustained AF. When comparing the initial ECG data, it was found that AF events were significantly more often observed in patients with an extended P wave ≥120 ms (88.6% vs 15.6%; criterion $\chi2=87.2$; $p <0.0001$), in patients with symptomatic HF (III FC vs I-II FC according to NYHA: 38.6% vs 17.4%; $\chi2=9.24$; $p=0.002$) and in persons with chronic obstructive pulmonary disease (COPD): (34.1% vs 4 .8%; $\chi2=30.8$; $p=0.0001$). Descriptive characteristics of patients depending on achievement of the primary end point (AF) are presented in Table 3.

Thus, as a result of comparison of clinical data and markers of electrical atrial dysfunction (abnormal P wave parameters) it was found that patients with newly diagnosed, incl. persistent or asymptomatic AF had baseline more pronounced prolongation of the P wave in the II ECG lead ($p < 0.001$) and a higher initial level of MVP and HATCH scores (HATCH score is risk prediction scale of AF progression). Prolongation of the PR interval and increase of the left atrium diameter were also more common for the group of patients with documented AF ($p <0.05$). In the group of patients with AF events a higher prevalence of advanced

Table 4.

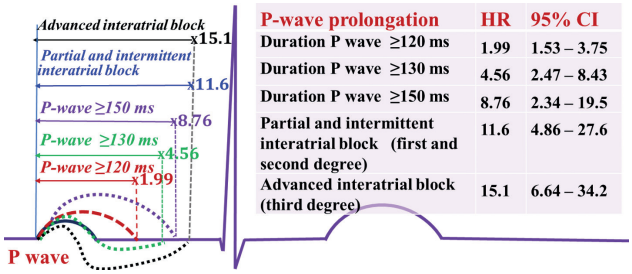
Comparison of categorical parameters in patients with SR and AF events

		SR group (n=167)	AF group (n=44)	χ^2	p
Gender (female – 1, male – 2), n (%)	1	50 (29.9)	18 (40.9)	1.92	0.166
	2	117 (70.1)	26 (59.1)		
Myocardial fibrosis* LV/LA, n (%)	no	119 (85.6)	22 (50.0)	24.0	0.0001
	yes	20 (14.4)	22 (50.0)		
HF (NYHA ≥III FC), n (%)	no	138 (82.6)	27 (61.4)	9.24	0.002
	yes	29 (17.4)	17 (38.6)		
Chronic obstructive pulmonary disease, n (%)	no	159 (95.2)	29 (65.9)	30.8	0.0001
	yes	8 (4.8)	15 (34.1)		
Diabetes mellitus, n (%)	no	118 (70.7)	27 (61.4)	1.40	0.237
	yes	49 (29.3)	17 (38.6)		
P wave duration more than 130 ms, n (%)	no	167 (100)	20 (45.5)	102.8	0.0001
	yes	0	24 (54.5)		
P wave duration more than 150 ms, n (%)	no	167 (100)	35 (79.5)	35.7	0.0001
	yes	0	9 (20.5)		
MVP score ≥3 points, n (%)	no	166 (99.4)	6 (4.2)	170	0.0001
	yes	1 (0.6)	38 (86.4)		
Interatrial block (1–3 degrees), n (%)	no	141 (84.4)	5 (13.6)	87.2	0.0001
	yes	26 (15.6)	39 (88.6)		
Interatrial block third degree (advanced), n (%)	no	162 (97.0)	7 (15.9)	144	0.0001
	yes	5 (3.0)	37 (84.1)		
Death, n (%)	no	166 (99.4)	37 (84.1)	22.4	0.0001
	yes	1 (0.6)	7 (15.9)		
Stroke, n (%)	no	166 (99.4)	33 (75.0)	38.7	0.0001
	yes	1 (0.6)	11 (25.0)		

Note: criteria adjusted for all pairwise comparisons using Bonferroni correction; * - marker of myocardial fibrosis LGE (late gadolinium enhancement) in the left atrium or/and left ventricle was determined during magnetic resonance imaging for 183 out of 211 patients; HF, heart failure.

IAB was observed (Chi-square test with Yates correction χ^2=144; p <0.001), MRI signs of myocardial fibrosis of the LV/LA (LGE: χ^2=24.7; p <0.001) and cardioembolic stroke (χ^2=38.7; p <0.001). Data from the categorical analysis of the compared groups are presented in Table 4.

To select independent variables suitable for constructing a prognostic regression model, ROC analysis was performed using multiple parameters with a significance level of differences p ≤0.001, determined as a result of comparison of two groups by Mann-Whitney-Wilcoxon or Pearson χ^2 tests. The maximum level of sensitivity, specificity and significance was determined for the MVP scale (AUC 0.908: 95% CI 0.895–0.989; p = 0.0001; cut-off point - 3 points; sensitivity 92%, specificity 89%). Prognostically significant P wave prolongation in the II lead ECG was ≥130 ms (AUC 0.878: 95% CI 0.777–0.979; sensitivity 82%, specificity 90%; p=0.0001). Highly significant predictors of AF were identified: low P wave voltage in lead I of the ECG (AUC 0.987: 95% CI 0.975–0.999; cut-off point <0.1 mV; p=0.001; sensitivity 92%, specificity 86%) and abnormal PTFV1 - increased P wave terminal force in lead V1 (AUC 0.873; 95% CI 0.771–0.976; cut-off point >4.75 mV×ms; p=0.001). The asymptotic significance and informative value of the morpho-structural independent risk factors for AF – LV fibrosis (AUC 0.697; 95% CI 0.597–0.796: p=0.001) and LA diameter (AUC 0.696; 95% CI 0.594–0.798: p=0.001) were comparatively less significant.



P-wave prolongation	HR	95% CI
Duration P wave ≥120 ms	1.99	1.53 – 3.75
Duration P wave ≥130 ms	4.56	2.47 – 8.43
Duration P wave ≥150 ms	8.76	2.34 – 19.5
Partial and intermittent interatrial block (first and second degree)	11.6	4.86 – 27.6
Advanced interatrial block (third degree)	15.1	6.64 – 34.2

Fig. 2. Exponential increase in hazard ratio (HR) depending on the degree of interatrial block according to univariate Cox regression model for predicting atrial fibrillation/

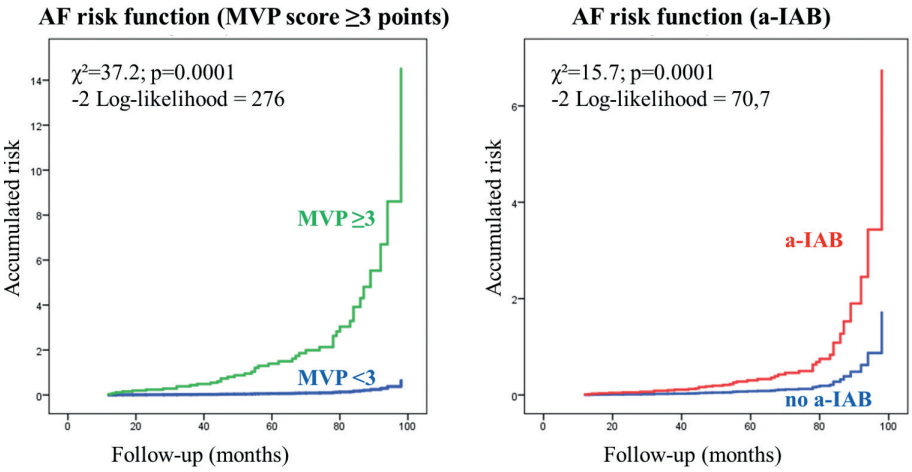


Fig. 3. Graphs demonstrating the dynamics of AF risk functions over time according to univariate proportional hazards models in Cox regression, and reflecting the influence of independent predictors – advanced interatrial block and P-wave abnormality corresponding to the MVP score ≥3 points.

To assess the probable risk of AF a univariate regression analysis of Cox proportional hazards was performed; the regression results are presented in Table 5. Figure 2 shows a schematic representation of the exponential increase in the predicted probability of AF (hazard ratio in the univariate Cox regression model: HR 1.99 → HR 4.56 →HR 15.1) depending on the duration of the P wave and IAB degree.

The most significant predictors influencing the risk AF in a 3.7-year period according to univariate Cox regression were

Table 5.

Results of univariate Cox regression analysis of the primary endpoint

AF predictors	HR (95% CI)	p
P-wave terminal force in lead V1 (PTFV1)	1.21 (1.01-1.25)	<0.001
P wave duration in the lead II ECG	1.01 (1.001-1.021)	0.035
MVP score	1.51 (1.31-1.73)	<0.001
MVP score ≥3 points	17.8 (7.44-42.7)	<0.001
Duration of the negative phase of the P wave in lead V_1	1.02 (1.01-1.03)	0.003
Amplitude of the negative phase of the P wave in lead V_1	25.9 (1.56-50.2)	0.036
P wave amplitude in the lead I ECG	0.011 (0.005-0.027)	0.012
Low P wave voltage in lead I (PI <0.1 mV)	1.02 (1.012-1.029)	<0.001
P wave duration more than 130 ms	4.56 (2.47-8.43)	<0.001
P wave duration more than 150 ms	8.76 (2.34-19.5)	0.003
IAB partial and intermittent (degrees 1–2)	11.6 (4.86-27.6)	<0.001
Advanced IAB (third degree)	15.1 (6.64-34.2)	<0.001
Left atrium dimension	1.11 (1.06-1.16)	0.001

Note here and below: HR, Hazard ratio; CI, confidence interval; IAB, interatrial block

identified factors such as an advanced IAB (HR 15.1; 95% CI 6.64–34.2; p <0.001) and the level of abnormality of the P wave morphological and voltage-time parameters on the MVP score ≥3 points (HR 17.8; 95% CI 7.44–42.7; p <0.001). Age, gender, presence of myocardial fibrosis and LA volume indexed (HR 0.99 [0.91–1.07] p = 0.078) did not confirm their significance according to univariate Cox regression. Graphs of the influence of independent predictors such as advanced IAB and abnormal atrial activation on the MVP score ≥3 points on the dynamics of AF risk functions according to univariate Cox proportional hazards models are presented in Figure 3.

Multivariate Cox regression analysis was performed to develop a predictive mathematical model. The multivariate Cox regression procedure was performed using the step backward Wald method with stepwise exclusion of risk factors identified using univariate Cox analysis. The results of the regression analysis confirmed the high prognostic significance of the independent ECG marker a-IAB for prediction AF events (HR 5.92; 95% CI [2.48–14.12]; p <0.001). A low-voltage P wave (P_I amplitude <0.1 mV) in lead I of the ECG (HR 1.03; 95% CI [1.02–1.04]; p <0.001) and PTFV1 (HR 1.14; 95% CI [1.04–1.24]; p=0.003) were also identified as a significant independent predictor of AF risk. The morphological parameter – anterior-posterior LA dimension (HR 1.11; 95% CI [1.06–1.16]), which demonstrated prognostic significance (p = 0.001) as a result of univariate Cox analysis, did not confirm its predictive characteristics as a result of multivariate regression analysis of Cox proportional hazards (HR 1.07; 95% CI [0.99–1.18], p=0.051). Thus, the multivariate regression model (Table 6) demonstrated high prognostic significance (-2LL=257; $\chi 2$=92.3; p <0.001) and the level of influence of the identified predictors on the risk of AF, determined by the following mathematical equation:
$\lambda(t) = \exp (0.131 \times PTFV_1 + 1.778 \times$ a-IAB [0/1] + $0.032 \times P_{I<0,1\ мВ}$ [0/1]),
where - λ (t) is the risk of AF at each time-point, [0/1] - is the binary character of the presence or absence of a-IAB (0 – presence of a-IAB, 1 – absence of a-IAB) and low voltage of the P wave in the I lead ECG lead (0 – voltage P_I ≥0.1 mV; 1 – P_I <0.1 mV).

In this model, regression coefficients indicate the influence of each predictor on the risk function - with an increase in the value of the predictor by one, if the values of other variables are unchanged, the risk of an event increases by exp (B) times. Thus, the presented mathematical model makes it possible to estimate the risk AF in any observation time interval.

In the analyzed period (median 45 months), cerebral thromboembolic complications were observed in 12 patients (including 11 patients with paroxysmal AF, 5 of them asymptomatic). According to univariate regression analysis of Cox proportional hazards, significant predictors of stroke were identified: age ≥ 69 years, a decrease in the P wave amplitude in ECG lead I, an increase of the terminal negative phase of the P wave in lead V1, and high scores on the MVP scale. Identified risk factors were included in multivariate Cox regression analysis, which confirmed independent associations of atrial electrical dysfunction with stroke; two independent predictors of stroke were identified: abnormal terminal negative phase P wave area in lead V1 – PTFV1 (HR 1.41; 95% CI [1.17–1.72], p <0.001) and high P wave abnormality scores on the scale MVP (HR 1.85; 95% CI [1.27–2.69], p=0.001). The Cox regression results are presented in Table 7. According to the regression model (-2LL=62.5; $\chi 2$=38.4; p <0.001), abnormal negative phase of the P wave in lead V1 (↑PTFV1) and abnormal atrial activation according to morphological and voltage-time assessment of P waves on the MVP scale are associated with an increase in the likelihood of stroke by 58% and 62%, respectively.

DISCUSSION OF FINDINGS

P wave parameters reflect electromechanical and structural disorders in the atria; therefore, in retrospective and prospective studies [5–17] correlations of abnormal P wave parameters with LA dimension and myocardial fibrosis were assessed, and relationships between P wave indices and indicators of atrial strain deformation with rapid atrial rhythm and AF were studied. Thus, the ARIC study found a strong association between abnormal terminal part of the P wave in lead V1 and risk of AF, and associations of a prolonged P wave with an increased risk of AF and cognitive impairment were also identified [29].

The P wave on a surface ECG reflects atrial depolarization – the action potential is spreading from the sinoatrial node in the right atrium (RA) along the conduction pathways and the interatrial Bachmann bundle to the LA. Any disturbances or modifications of the depolarization front are reflected on the ECG in the form of prolongation or deformation of the P wave. Although the P wave reflects activation of both atria, LA depolarization accounts for most of the amplitude and duration of the P component (terminal phase) because the LA has greater mass than the RA.

The presented study revealed an interesting fact - most of the identified independent prognostic ECG markers are associated with prolongation of the final phase of the P wave, an increase in the amplitude of the negative phase of the P wave in lead V1 and a decrease in the amplitude of the P wave <0.1 mV in lead I ECG. It is likely that these parameters are associated with structural remodeling of the atria, which includes both the hypertrophy stage and the dilatation stage. Hypertrophy is usually manifested by an increase P wave voltage, whereas atrial dilatation is manifested by a decrease P wave amplitude. Slowing of atrial activation is characteristic of both hypertrophy and dilatation of the atria. Thus, different types and stages of atrial myocardial remodeling can lead to diametrically different changes in amplitude (increase or decrease), while

Table 7.

Results of multivariate cox regression analysis of stroke predictors

Stroke predictors	B	SE	Wald	p	HR (95% CI) *
$PTFV_1$	0,347	0,099	12,34	0,000	1,414 (1,166-1,716)
MVP score	0,614	0,193	10,13	0,001	1,847 (1,266-2,695)

Note: $PTFV_1$, P wave terminal force in lead V_1; MVP, score of the Morphology, Voltage and P wave duration

electrical activation of the LA will always be prolonged regardless of the type and stage of LA remodeling, which increases the significance and role of the temporal parameters of the P wave and its phase components dependent on the duration of atrial activation in predicting AF. This hypothesis is confirmed by the high prognostic significance of the pattern of complete Bachmann bundle block – advanced IAB according to the results of multivariate Cox regression analysis in the presented study (HR 5.92; 95% CI 2.48-14.12). Structural changes in the Bachmann bundle contribute to the formation of the re-entry mechanism for AF. Our results are consonant with data from two large multicenter studies that confirmed independent associations of a prolonged P wave with a high risk of AF: ARIC (HR 4.07, 95% CI 2.55-6.51) and the Copenhagen ECG study (P ≥130 ms; HR 2.06, 95 % CI 1.89-2.23) [29, 30].

In clinical practice it is convenient to use score and threshold values of parameters to determine the likelihood of developing adverse complications and stratify patients at high risk. As an example, the authors A. Jadidi et al. (2018) found that P wave duration >150 ms determines a high risk of AF recurrence after the pulmonary vein isolation procedure [31]. In 2019 scientists V. Alexander et al. [10] were the first to propose the MVP AF risk score, which included assessment of morphology (M), voltage (V) and P wave duration (P). The MVP score was developed from an analysis of 676 patients (mean age 65 years; 68% male) without previous AF undergoing coronary angiography. Points (0, 1 or 2) were awarded based on analysis of P-wave morphology in the inferior leads ECG (monophasic <120 ms, monophasic ≥120 ms or biphasic ≥120 ms), P voltage in lead I (P >0.20 mV, 0.10–20 mV or P<0.10 mV) and P wave duration (P<120 ms, 120–140 ms or >140 ms). In patients with scores of 5–6 (high risk) and 3–4 points (intermediate risk), the incidence of AF was significantly higher than in those with scores of 0–2 (low risk) [10]. In our study the integral assessment of atrial electrical remodeling according to the MVP score also demonstrated good prognostic significance: with an MVP cut-off point of ≥3 points for the prognosis of AF (as a binary predictor in univariate Cox regression) and for assessing the risk of stroke (as a discrete predictor in multivariate Cox regression). Our data are concordant with the results of a 5-year study by the Malmö Preventive Project (n=983, age 70±5 years, 38% women), in a population-based cohort of elderly people the MVP score (threshold 4 points) was determined to be an independent predictor of AF (adjusted for gender and age: HR 6.17; CI 95% 1.76–21.64) [32]. However, in the Malmö study, the authors M.Baturova et al. (2024) did not find significant associations between increased P duration, PR interval prolongation, abnormal PTFV1 and high risk of AF, that indicates on the limited value of these P wave parameters as universal predictors of AF risk [32], while the variant of advanced IAB was the most common type of IAB in the Swedish cohort and biphasic morphology P waves (in leads III and aVF) showed good predictive value in the univariate Cox model (HR 2.59 CI 95% 1.02–6.58).

Limitations of the study

The presented study has several limitations: 1) the study is a single-center and retrospective cohort study, despite the prospective nature of the observational registry; 2) cohort and observation period are relatively small; 3) it cannot be excluded that some patients with asymptomatic AF could have been missed (in the absence of implantation and analysis of loop recorders). A large cohort with multicenter approach, long-term follow-up, and prospective clinical studies remain relevant to confirm the prognostic value of noninvasive ECG atrial predictors of abnormal amplitude-time parameters of the P wave.

CONCLUSION

Thus, because of this study a complex of ECG markers of atrial electrical dysfunction was identified, such as a-IAB, PTFV1, MVP score and low P wave voltage, which makes it possible to identify patients at high risk of AF and ischemic stroke.

Data from multivariate Cox proportional hazards regression analysis confirmed the independent association of advanced IAB with risk of AF (HR 5.92; 95% CI [2.48–14.12], p <0.001), which means an almost 6-fold increase in the risk of AF with moment of appearance of a new-onset advanced IAB and this corresponds to 85.5% probability of early onset of AF. Based on the data obtained, advanced IAB should be considered as an independent predictor for risk stratification of AF and this predictor should be used in patients with increased thromboembolic risk for a dynamic and more detailed examination to search and identify atrial tachyarrhythmia (Fig. 4).

Analysis of cerebral thromboembolic complications in the cohort showed information value for two predictors: an abnormal increase of the terminal negative phase P wave in lead V1 – PTFV1 (HR 1.41; 95% CI [1.17–1.72], p <0.001) and P wave changes on the scale MVP (HR 1.85; 95% CI [1.27–2.69], p=0.001), corresponding to 58.5% and 65% likelihood chance of earlier stroke in those with atrial electrical dysfunction.

The data obtained indicate the importance of taking into account atrial ECG patterns in clinical practice and dictate necessity to identify patients with abnormal P wave parameters and atrial risk predictors of AF, which is a priority strategy for dynamic monitoring of patients with cardiovascular pathology who have population and comorbid risk factors (obesity, diabetes mellitus, smoking, sleep apnea, obstructive pulmonary disease, etc.) for timely decision-making on the preventive prescription of anticoagulant therapy and choice of treatment tactics.

REFERENCES

1. Hindricks G, Potpara T, Nikolaos Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic Surgery (EACTS). *Eur Heart J.* 2021;42: 373-498. https://doi.org/10.1093/eurheartj/ehaa612.

2. Gopinathannair R., Chen LY., Chung MK., et al. Managing atrial fibrillation in patients with heart failure and reduced ejection fraction: a scientific statement from the American Heart Association. *Circ Arrhythmia Electrophysiol.* 2021;14: e000078. https://doi.org/10.1161/HAE.0000000000000078.

3. Goette A, Kalman JM, Aguinaga L, et al. EHRA/HRS/APHRS/SOLAECE expert consensus on atrial cardiomyopathies: definition, characterization, and clinical implication. *Europace.* 2016;18(10): 1455-1490. https://doi.org/10.1093/europace/euw161.
4. Goldberger JJ, Arora R, Green D, et al. Evaluating the atrial myopathy underlying atrial fibrillation identifying the arrhythmogenic and thrombogenic substrate. *Circulation*. 2015;132: 278-291. https://doi.org/10.1161/circulationaha.115.016795.
5. Rivner H, Mitrani RD, Goldberger JJ. Atrial Myopathy Underlying Atrial Fibrillation. *Arrhythm Electrophysiol Rev.* 2020;9(2): 61-70. https://doi.org/10.15420/aer.2020.13.
6. Vaikhanskaya TG, Kurushko TV, Persianskikh YuA, et al. Atrial cardiomyopathy - a new concept with a long history. *Russian Journal of Cardiology.* 2020;25(11): 143-1583942. (In Russ.) https://doi.org/10.15829/29/1560-4071-2020-3942.
7. Ciuffo L, Bruña V, Martínez-Sellés M, et al. Association between interatrial block, left atrial fibrosis, and mechanical dyssynchrony: electrocardiography-magnetic resonance imaging correlation. *J Cardiovasc Electrophysiol.* 2020;31: 1719-1725. https://doi.org/10.1111/jce.14608.
8. Massó-van Roessel A, Escobar-Robledo LA, Dégano IR, et al. Analysis of the association between electrocardiographic P-wave characteristics and atrial fibrillation in the REGICOR study. *Rev Esp Cardiol.* 2017;70: 841-847. https://doi.org/10.1016/j.rec.2017.02.019.
9. Tiffany Win T, Ambale Venkatesh B, Volpe GJ, et al. Associations of electrocardiographic P-wave characteristics with left atrial function, and diffuse left ventricular fibrosis defined by cardiac magnetic resonance: The PRIMERI Study. *Heart Rhythm.* 2015;12: 155-162. https://doi.org/10.1016/j.hrthm.2014.09.044.
10. Alexander B, Milden J, Hazim B, et al. New electrocardiographic score for the prediction of atrial fibrillation: the MVP ECG risk score (morphology-voltage-P-wave duration). *Ann Noninvasive Electrocardiol*. 2019;24: e12669. https://doi.org/10.1111/anec.12669.
11. Maheshwari A, Norby FL, Soliman EZ, et al. Refining prediction of atrial fibrillation risk in the general population with analysis of P-Wave axis (from the Atherosclerosis Risk in Communities Study). *Am J Cardiol.* 2017;120: 1980-1984. https://doi.org/10.1016/j.amjcard.2017.08.015
12. Rangel MO, O'Neal WT, Soliman EZ. Usefulness of the Electrocardiographic P-Wave Axis as a Predictor of Atrial Fibrillation. *Am J Cardiol.* 2016;117: 100-104. https://doi.org/10.1016/j.amjcard.2015.10.013
13. Vaikhanskaya TG, Kaptsiukh TM, Frolov AV. Atrial electrical dysfunction as an early predictor of atrial fibrillation in patients with heart failure. *Cardiology in Belarus.* 2023;15 (5): 599-617. (In Russ.) https://doi.org/10.34883/PI.2023.15.5.001.
14. Rasmussen MU, Fabricius-Bjerre A, Kumarathurai P, et al. Common source of miscalculation and misclassification of P-wave negativity and P-wave terminal force in lead V1. *J Electrocardiol.* 2019;53: 85-88. https://doi.org/10.1016/j.jelectrocard.2019.01.088.
15. Escobar-Robledo LA, Bayes-de-Luna A, Lupon J. et al. Advanced interatrial block predicts new-onset atrial fibrillation and ischemic stroke in patients with heart failure: The "Bayes' Syndrome-HF" study. *Int J Cardiol.* 2018;271: 174-180. https://doi.org/10.1016/j.ijcard.2018.05.050
16. Skov MW, Ghouse J, Kühl JT, et al. Risk prediction of atrial fibrillation based on electrocardiographic interatrial block. *J Am Heart Assoc.* 2018;7: e008247. https://doi.org/10.1161/JAHA.117.008247
17. Relander A, Hellman T, Vasankari T, et al. Advanced interatrial block predicts ineffective cardioversion of atrial fibrillation: a FinCV2 cohort study. *Ann Med.* 2021;53: 722-729. https://doi.org/10.1080/07853890.2021.1930139.
18. Nielsen JB, Kühl JT, Pietersen A, et al. P-wave duration and the risk of atrial fibrillation: Results from the Copenhagen ECG Study. *Heart Rhythm.* 2015;12: 1887-1895. https://doi.org/10.1016/j.hrthm.2015.04.026.
19. Hernandez-Betancor I, Izquierdo-Gomez MM, Garcia-Niebla J, et al. Bayes syndrome and imaging techniques. *Curr Cardiol Rev.* 2017;13: 263-273. https://doi.org/10.2174/1573403X13666170713122600.
20. Vaikhanskaya TG, Frolov AV. New clinical Bayes syndrome: definitions, epidemiology and clinical significance. *Cardiology in Belarus.* 2022;14(6): 803-813. (In Russ.) https://doi.org/10.34883/PI.2022.14.6.009.
21. Baturova MA, Platonov PG, Medvedev MM. Interatrial block. *Journal of Arrhythmology.* 2019;26(4): 39-46. (In Russ.) https://doi.org/10.35336/VA-2019-4-39-46.
22. Tse G, Wong CW, Gong M. et al. Predictive value of inter-atrial block for new onset or recurrent atrial fibrillation: A systematic review and meta-analysis. *Int J Cardiol.* 2018;250: 152-156.
23. Chen LY, Ribeiro ALP, Platonov PG, et al. P-Wave Parameters and Indices: A Critical Appraisal of Clinical Utility, Challenges, and Future Research - A Consensus Document Endorsed by the International Society of Electrocardiology and the International Society for Holter and Noninvasive Electrocardiology. *Circ Arrhythm Electrophysiol*. 2022;15: e010435. https://doi.org/10.1161/circep.121.010435.
24. Kreimer F, Mügge A, Gotzmann M. How should I treat patients with subclinical atrial fibrillation and atrial high-rate episodes? Current evidence and clinical importance. *Clin Res Cardiol.* 2022;111(9): 994-1009. https://doi.org/10.1007/s00392-022-02000-7.
25. Pay L, Yumurtaş AÇ, Tezen O, et al. Efficiency of MVP ECG Risk Score for Prediction of Long-Term Atrial Fibrillation in Patients with ICD for Heart Failure With Reduced Ejection Fraction. *Korean Circ J.* 2023;53(9): 621-631. https://doi.org/10.4070/kcj.2022.0353
26. Hayıroğlu MI, Çınar T, Selçuk M, et al. The significance of the morphology-voltage-P-wave duration (MVP) ECG score for prediction of in-hospital and long-term atrial fibrillation in ischemic stroke. *Journal of Electrocardiology.* 2021;69: 44-50. https://doi.org/10.1016/j.jelectrocard.2021.09.006.
27. Silvestrini TL, Burak C, Miranda-Arboleda AF, et al. New pattern of atypical advanced interatrial block. *Journal of Electrocardiology.* 2023;81: 66-69. https://doi.org/10.1016/j.jelectrocard.2023.08.001.
28. Bayés-de-Luna A, Fiol-Sala M, Martínez-Sellés M, Baranchuk A. Current ECG Aspects of Interatrial Block.

Hearts. 2021;2(3): 419-432. https://doi.org/10.3390/hearts2030033.
29. Gutierrez A, Norby FL, Maheshwari A, et al. Association of abnormal P-wave indices with dementia and cognitive decline over 25 years: ARIC-NCS (The Atherosclerosis Risk in Communities Neurocognitive Study). *J Am Heart Assoc.* 2019;8: e014553. https://doi.org/10.1161/jaha.119.014553.
30. Nielsen JB, Kühl JT, Pietersen A, et al. P-wave duration and the risk of atrial fibrillation: Results from the Copenhagen ECG Study. *Heart Rhythm.* 2015;12: 1887-1895. https://doi.org/10.1016/j.hrthm.2015.04.026.
31. Jadidi A, Müller-Edenborn B, Chen J, Keyl C, et al. The Duration of the Amplified Sinus-P-Wave Identifies Presence of Left Atrial Low Voltage Substrate and Predicts Outcome After Pulmonary Vein Isolation in Patients with Persistent Atrial Fibrillation. JACC Clin Electrophysiol. 2018;4(4): 531-543. https://doi.org/10.1016/j.jacep.2017.12.001.
32. Baturova MA, Cornefjord G, Carlson J, et al. P-wave characteristics as electrocardiographic markers of atrial abnormality in prediction of incident atrial fibrillation - The Malmö Preventive Project. *Journal of Electrocardiology.* 2024;82125-130. https://doi.org/10.1016/j.jelectrocard.2023.12.003.