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Low atrial fibrillatory rate is associated with spontaneous conversion of recent onset atrial fibrillation.

Short title: Atrial fibrillatory rate and spontaneous conversion

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ABSTRACT:

Background: Atrial fibrillatory rate (AFR) is considered a non-invasive index of atrial remodeling. Low AFR has been associated with favorable outcome of interventions in patients with persistent atrial fibrillation (AF). However, AFR has never been studied in unselected patients with short duration of AF, prone to regain sinus rhythm (SR) spontaneously.

Objective: The aim of the study was to assess if AFR can predict spontaneous conversion in patients with recent-onset AF.

Methods: Files of consecutive patients with AF<48 h seeking emergency room care during a twelve-month period were screened (n=225). Patients with thyroid illness, acute ischemic heart disease (IHD) or acute congestive heart failure, significant valvular heart disease, congenital heart disease, history of cardiac surgery or catheter ablation, or on class I/III antiarrhythmics were excluded. AFR was obtained by QRST-cancellation and time-frequency analysis of ECG at admission.

Results: The study population comprised 148 patients (age 64±13 yrs., 52 men), of whom 48 converted to SR within 18 h. Those converting spontaneously comprised more women, had a higher prevalence of first-ever AF episode, IHD and a lower AFR. The multivariate analysis revealed: AFR<350 fpm (Odds ratio (OR) 3.7, 95% confidence interval (CI) 1.3-10.5, P=0.016), IHD (OR 5.7, 95%CI 1.5-22.4, P=0.012) and first-ever AF episode (OR 4.1, 95%CI 1.3-13.0, P=0.015) as independent predictors of spontaneous conversion.

Conclusion: A low AFR was predictive of spontaneous conversion in patients with recent-onset AF. Along with first-ever AF episode and IHD, AFR can be used in assessing likelihood of spontaneous conversion, if proven in prospective studies.

Keywords: Atrial fibrillation – Atrial fibrillatory rate – First-ever atrial fibrillation episode – Ischemic heart disease - Recent-onset atrial fibrillation - Spontaneous conversion - Time-frequency analysis

What's new?

- Largest real-life population investigated regarding predictors of spontaneous conversion of recent onset atrial fibrillation.
- ECG-based marker of atrial electrical remodeling, i.e. atrial fibrillatory rate, predicts spontaneous conversion of recent onset atrial fibrillation.
- Along with a low atrial fibrillatory rate, presence of ischemic heart disease and first-ever episode of atrial fibrillation are proved to be independent predictors of spontaneous conversion within 18 h.

Introduction:

In patients with atrial fibrillation (AF) lasting less than 48 hours (h), treatment strategy generally aims to restore sinus rhythm (SR). The duration of spontaneously terminating AF-episodes varies from patient to patient and from episode to episode. Some studies have suggested that approximately 50% of patients with AF of less than 24 h duration will convert spontaneously within the 24-h period (1, 2). Consistent with the concept that “AF begets AF” (3), many studies have demonstrated that a shorter duration of AF is predictive of spontaneous conversion (4-6). Many studies have explored other clinical parameters to predict spontaneous conversion, e.g. the age (4, 7, 8), the left atrial (LA) size (4, 5, 7-10), and heart failure (4, 5, 7, 10), however the results are inconclusive.

The precise pathophysiological mechanism for self-termination of AF has not been fully resolved, and no clinical parameters have yet been proved helpful in assessing the likelihood of spontaneous conversion. From a clinical point of view, the timing for implementing strategies to restore SR by either pharmacological or electrical cardioversion remains a challenge.

Non-invasive assessment of AF substrate complexity in order to estimate the inter-individual degree of atrial electrophysiological alterations and hence predict outcome in patients with AF, has been studied in several studies reviewed recently by Schotten et al. (11). Atrial fibrillatory rate (AFR) has been associated with atrial refractoriness, and is regarded as a non-invasive index of atrial remodeling (12-17). Several studies have tested AFR as a predictor of outcome in patients with persistent AF, showing an association between low AFR and favorable outcome of cardioversion (13, 18, 19) and catheter ablation (20, 21). The predictive value of AFR in identifying patients prone to convert to SR spontaneously has been examined in few previously published studies, showing a lower AFR in self-terminating AF episodes (22-24). These studies involved a

comparatively small patient sample, making their findings difficult to relate to a broader patient population and apply in a clinical context. AFR has never been studied in an unselected population with short duration of AF episodes, prone to regain SR spontaneously. The aim of this study was to assess if AFR is useful in predicting spontaneous conversion in patients with recent-onset AF, and thus valuable in providing necessary information for clinical decision-making.

Methods:

Study population:

Study design:

A retrospective register-based analysis.

Inclusion and exclusion criteria:

Inclusion criteria were episodes of paroxysmal AF of less than 48 h, a known symptom onset, and AF verified by ECG at admission.

Exclusion criteria were determined based on potential confounders capable of implicating the results, and were: (1) treatment with class I and/or III antiarrhythmic drugs at admission or during the period leading to conversion; (2) thyroid illness; (3) significant valvular heart disease; (4) congenital heart disease; (5) acute ischemic heart disease (IHD) or acute congestive heart failure (CHF); and (6) history of cardiac surgery or catheter ablation.

Subject identification:

Files of patients discharged from Skåne University Hospital (Lund, Sweden) during a twelve-month period between 1st January 2009 and 31st December 2009 with the diagnosis of I48 (ICD-10) were systematically assessed.

Medical records were reviewed for the presence of inclusion and exclusion criteria at time of admission to the emergency room (ER) and for assessment of time-to-SR based on the timing of symptom onset and return to SR, either spontaneous or by DC-cardioversion. The most recent conventional transthoracic echocardiography was reviewed for quantification of LA-diameter and left ventricular ejection fraction (LVEF). The study was approved by the local Ethics Committee.

Data acquisition and processing:

A standard 12-lead ECG recorded at admission in digital format was extracted from the hospital ECG database and processed off-line. AFR was estimated using *AFRtracker* software (CardioLund Research AB, Lund, Sweden) from lead V1 on the 10-s long digital 12-lead ECG.

The ECG signals were pre-processed, including baseline filtering, beat detection and cross-correlation-based beat classification. Spatiotemporal QRST cancellation, in which an amplitude and morphology adjusted average beat is subtracted from each beat in the signal, was then employed (14). Individual beat averages were used for beats belonging to different beat classes. The resulting residual ECG containing mainly the atrial activity was analyzed using sequential atrial signal characterization (25) which performs time-frequency analysis using overlapping windows of short duration (2.56 s long, 1 window per second) in order to provide second-by-second trends of the atrial fibrillation rate. With this method, the signal structure of each window is continuously analyzed by means of its harmonic frequency pattern in order to assure that the corresponding signal contains an oscillatory atrial signal (26).

Statistical analysis:

All continuous variables are expressed as mean \pm one standard deviation unless stated otherwise. Comparison between samples was performed using the Student's *t*-test or the Mann-Whitney U test. Kaplan-Meier curves with log rank statistics were used to analyze time to spontaneous conversion in relation to baseline AFR.

A multivariate regression analysis was performed based on significant variables from the univariate analysis, step-by-step excluding the variable with the highest non-significant P-value. Statistically significant continuous variables were dichotomized using median values in order to be implemented as categorical variables in multivariate analysis. The multivariable odds ratios (OR) and their corresponding 95% confidence intervals (CI) were calculated. Pearson's test was used to evaluate the correlation between AFR and clinical covariates. All statistical analyzes were performed using IBM SPSS Statistics, version 19.0.0 (SPSS, Chicago, Illinois). All tests were two-sided, and a P-value < 0.05 was considered statistically significant.

Results:

Data availability and study population:

Of 841 patients with I48 as the diagnosis code at admission, 225 patients met the inclusion criteria.

Seventy-seven patients were excluded due to exclusion criteria; out of these 77, 22 patients had more than one exclusion criterion. The patient selection process is shown in Figure 1.

The study population comprised 148 patients (age 64 ± 13 years, 81 men). Forty-two patients experienced their first-ever episode of AF. In 51% of the patients, there were no

other significant comorbidities. SR was restored by external DC-cardioversion in 74 patients; 69 patients converted spontaneously, and in 5 patients cardioversion was not attempted.

Compared to the 148 patients included in the study, the 77 patients with one or more exclusion criterion were younger (60 ± 15 vs. 64 ± 13 years, $P = 0.037$), had a lower prevalence of first-ever episode of arrhythmia (8% vs. 29%, $P = 0.001$), and a higher proportion was medicated with warfarin (48% vs. 22%, $P < 0.001$). No differences were observed in regard to gender or comorbidities.

AFR and spontaneous conversion:

Mean AFR at admission was 352 ± 57 fibrillations per minute (fpm) (median 350 fpm, range 191 - 490 fpm).

In a Kaplan-Meier analysis, patients with an AFR below the population median (AFR < 350 fpm) appeared to have a greater preponderance to spontaneous restoration to SR compared with those with a higher AFR (Figure 2, $P = 0.017$).

Predictors of spontaneous conversion to sinus rhythm:

Predictors of early spontaneous conversion were assessed in a subgroup of patients who did not undergo a cardioversion attempt within the first 18 h of symptom onset ($n = 105$, age 65 ± 13 years, 53 men, mean AFR 351 ± 59 fpm). The 18 h cut-off was selected retrospectively in order to achieve reasonable equally-sized patient groups, and in order to set a clinically relevant time range for predicting spontaneous conversion.

No significant differences in age, gender, time from AF onset to ECG, prevalence of first-ever AF episode, treatment with beta-blockers for rate control at admission or AFR were

observed between patients included in the analysis and patients who underwent cardioversion during the first 18 h and were excluded for that reason (n=43, age 61 ± 12 years, 28 men; mean AFR 354 ± 53 fpm).

Patient characteristics and measured parameters are presented in Table 1.

Patients spontaneously converting to SR within 18 h comprised more women, had a higher prevalence of first-ever AF episode as well as IHD and lower AFR, compared with patients who did not spontaneously convert to SR within the first 18 h.

In the multivariate analysis, three parameters proved to be independent predictors of spontaneous conversion within 18 h: AFR < 350 fpm, presence of IHD, and first-ever episode of AF. The results of the univariate and multivariate logistic regression models are shown in Table 2.

The incidence of spontaneous conversion differed based on the number of independent predictors present (Figure 3). All patients with all three predictors present converted to SR spontaneously, whereas only 14% of patients with no positive predictors present converted spontaneously within the first 18 h of symptom onset.

Clinical covariates of AFR in recent onset atrial fibrillation:

There was a negative correlation between AFR and age ($R = -0.411$, $P < 0.001$), patients with an age above the population median (age > 65 years) having a mean AFR of 329 ± 50 fpm, compared to 376 ± 55 fpm in patients younger than 65 years. Female patients had a lower AFR than male patients (333 ± 53 vs. 367 ± 56 fpm, $P = 0.001$).

There was no correlation between AFR and LA-diameter. The presence of hypertension or treatment with beta-blockers were not shown to be related to AFR, whereas IHD history was associated with a low AFR (324 ± 51 vs. 358 ± 57 fpm, $P = 0.015$).

Furthermore, AFR was significantly higher in patients with a first-ever episode of AF (376 ± 64 vs. 345 ± 53 fpm, $P = 0.012$).

Discussion:

Main findings:

In the present study, we demonstrate that a low AFR is associated with a higher likelihood of spontaneous conversion. Furthermore, $AFR < 350$ fpm adds significant value along with the presence of IHD and first-ever episode of AF in identifying those patients most likely to convert spontaneously within 18 h, thus suggesting that DC-cardioversion in patients with a high likelihood of spontaneous conversion can be postponed while priority for cardioversion should be given to those who are unlikely to convert spontaneously.

AFR as predictor of clinical outcome:

In the present study, AFR was revealed as one of the important electrophysiological parameters determining AF sustenance and termination. Clinically it has been shown that AF responds better to antiarrhythmic drugs and cardioversion at low fibrillatory rates (27). Furthermore, Holmqvist et al. revealed that the most prominent predictive effect of fibrillatory rate was found in those with short AF duration (less than 30 days), prone to maintain SR post-cardioversion (18).

The predictive value of AFR in identifying patients prone to convert to SR spontaneously has been examined in few previously published studies. The relation between AFR and the duration of AF paroxysms was first reported by Bollmann et al. in a limited

population of 11 patients with paroxysmal AF, in whom low AFR was associated with shorter duration of AF paroxysms (22). However, the findings of Bollmann et al. are difficult to apply in a clinical context since the mean AF episode duration in that study was 115 min, while vast majority of patients with AF at ER arrival have had much longer symptom duration.

In another study of 30 Holter-ECG recordings derived from the Physionet database of patients with paroxysmal AF, a low AFR was useful for identifying patients with spontaneously terminating AF with high accuracy (23).

Similarly, based on data from the Physionet database, Chiarugi et al. used 50 case-dataset to achieve significant discrimination between non-terminating and terminating AF, showing that the dominant atrial frequency together with heart rate were good predictors of paroxysmal AF termination (90% accuracy) (24). However, both of these studies were based on data from the Physionet database, designed to measure ECG characterization, with no clinical data available for the patient sample, making the results hard to compare with other studies and to relate to a broad patient population.

In another recent clinical study by Husser et al. on 25 patients with new-onset AF, sensitivity and specificity for predicting AF termination were strongly related to AFR. In this study, AF terminated within 24 h in 7 patients. Multivariate analysis revealed AFR to be the only independent predictor of AF termination that showed 89% sensitivity and 71% specificity for AFR of 355 fpm (28), which is in remarkable agreement with the cut-off of AFR < 350 fpm identified in our study. However, this study involved a rather small patient population with a median AF duration of 8 days who are less prone to spontaneous conversion and are managed differently from patients seeking care for AF lasting several hours (such as patients included in our analysis).

Well aware of limitations of a retrospective study, our study nevertheless involves largest patient sample reported to date.

Determinants of AFR:

First, an inverse correlation between AFR and age was observed, consistent with previous studies (28-31). This finding has been explained by electrophysiological changes of aging atria (32), and structural atrial abnormalities found in the eighth decade (33, 34). Platonov et al. has, however, recently reported that the extent of structural changes in the atrial wall was not associated with age, but was significantly correlated with AF presence and persistency (35), suggesting that age-related structural alterations are not the only parameter determining AFR.

Secondly, we observed gender differences in AFR. This has been evaluated previously, but with inconclusive results (30, 31, 36). As far as we know, it has not been proven whether low AFR in women can be explained by hormonal effects on atrial electrophysiology, heart size or other factors.

No association between IHD or beta-blocker treatment and AFR was seen in the study by Bollmann et al. (31). In the study by Holmqvist et al., a higher AFR was observed in patients on beta-blockers (18), which is in contrast to our findings, as well as to earlier findings of lower AFR associated with beta-blocker therapy (37, 38).

Finally, as atrial refractoriness shortens as AF persists, AFR may accelerate at initiation of AF episodes, which may affect the interpretation of AFR estimated early after AF onset. Some reports indicate that the AFR increase is over within the first 5 min during self-terminating short AF-paroxysms (22, 39). However, during persistent AF relevant in the context of cardioversion, AFR increase continues during the initial three to four hours as shown recently using implantable loop ECG recordings (40). These

observations indicate the reach of a plateau after several hours elapse, and the necessity of analyzing AFR beyond the initial hours from onset. In our population, 87% of AFR readings were based on ECG's past 3 hours from symptom onset, and therefore can be considered to represent the stable phase of the arrhythmia.

Other clinical predictors of spontaneous conversion:

IHD and spontaneous conversion:

To the best of our knowledge, no previous study has revealed any relation between IHD and duration of AF-episodes.

The pathophysiological role of atrial ischemia in the genesis of AF, in terms of presence of a significant stenosis in the proximal right coronary artery and the circumflex artery prior to the take-off of the atrial branches was investigated recently in patients with stable coronary artery disease and AF showing no significant difference in the allocation of coronary artery stenosis (41). However, these findings do not exclude the pathophysiological role of coronary microvascular disease with ischemia inducing metabolic stress.

Although the precise pathophysiology of AF development in patients with IHD is currently unknown, it is possible that IHD correlate with atrial structural alterations and thus exhibit unique behavior. The finding of a lower baseline AFR in patients with IHD supports this theory. Notably, multivariate analysis revealed both IHD history and low AFR as independent predictors of spontaneous AF termination.

Another possible explanation is that the patients seek ER care earlier due to more severe symptoms associated with AF due to IHD than those without IHD who are less likely to have chest pain as an AF-associated symptom and thus less likely to seek ER care.

First-ever episode of AF and spontaneous conversion:

An unexpected finding in our study was that even though first-ever AF was predictive of spontaneous conversion, AFR was significantly higher in patients experiencing their first-ever AF episode than in patients with recurrent AF. One explanation of the higher AFR in first-ever episodes of AF can be the lack of structural remodeling, i.e. atrial fibrosis, that would have resulted in slowing of the atrial fibrillatory process (42). In our population, the majority (85%) of patients experiencing their first-ever AF episode had absence of structural heart disease, so-called "lone AF," which supports this explanation. Another possible explanation is the involvement of rapidly firing foci within the pulmonary veins as a trigger of lone AF, that may result in a higher fibrillatory rate (43). However, it is important to note that these findings are based on a small sub-group (n = 42) and that the natural course and temporal variability of AFR in a first-ever episode of AF is currently unknown.

Study limitations:

Being a retrospective study, data was derived from medical records and ECG recordings, with no possibility of collecting additional measurements. Patients had to be excluded from the study due to missing data, such as unavailability of ECG verification of AF.

Almost one-third of the patients included in the study underwent external DC-cardioversion within 18 h and could not be included in the analysis of predictors of spontaneous conversion. It is possible, however, that some of these patients would have converted spontaneously if DC-cardioversion had not been attempted. However, there was no significant difference in age, gender and AFR between patients who underwent DC-cardioversion within 18 h and the population selected for sub-groups analysis,

suggesting that exclusion of these patients do not affect the generalizability of our findings.

Finally, time-frequency analysis was performed using AFRtracker system default settings and therefore only involved analysis of ECG signal from lead V1 containing the most prominent atrial fibrillatory waves and shown to reflect fibrillatory frequency recorded in the right atrium (12, 21). Using ECG signals from other leads might have provided additional information about atrial fibrillatory process but would be of limited value without endocardial validation that was not possible in our study.

Conclusion:

In patients with recent-onset AF, a low AFR predicts early spontaneous conversion and can, along with first-ever AF episode and IHD, be used for identification of patients in whom spontaneous conversion is likely to occur. The proposed stratification scheme may help avoiding the risk associated with active interventions, however further prospective studies are needed to validate AFR's role as a predictor of spontaneous conversion.

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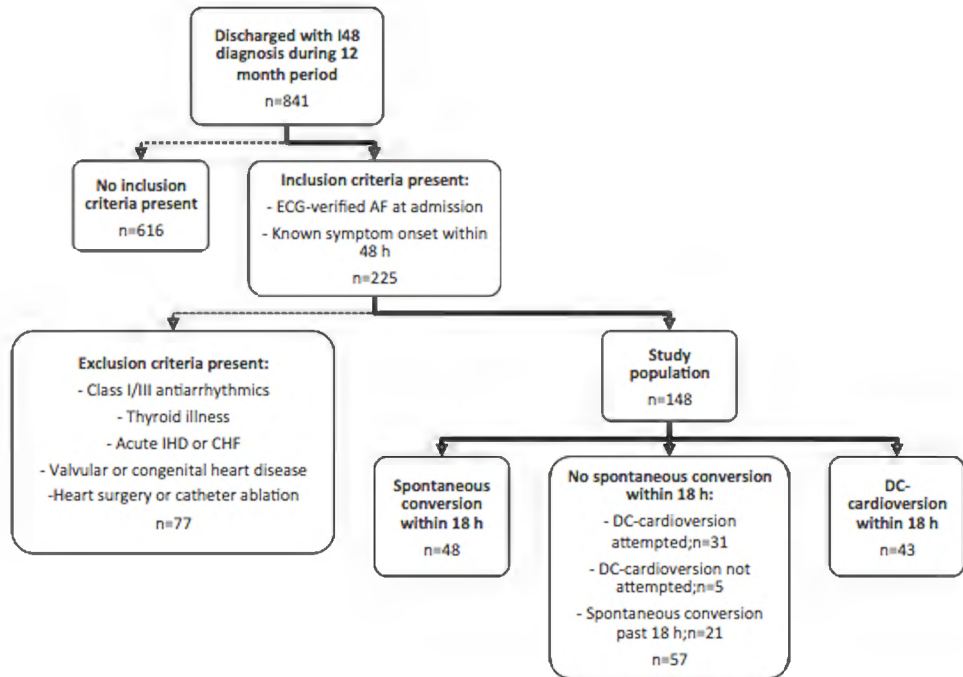
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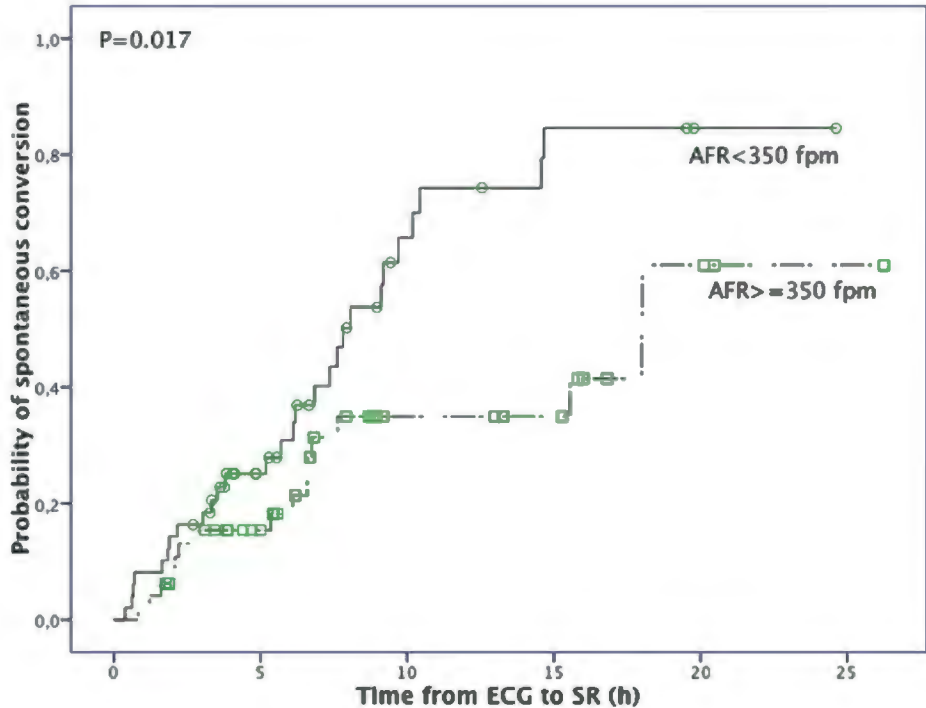
Figure legends

Figure 1: Flow chart illustrating the patient selection process.

Figure 2: Atrial fibrillatory rate (AFR) and spontaneous conversion in patients with recent onset of AF. Kaplan-Meier curve analysis of time from ECG to SR in regard to AFR, with 350 fibrillations per minute (fpm) as a cut-off. Patients who restored SR by external cardioversion were censored (empty green circles and squares).

Figure 3: The incidence of spontaneous conversion within 18 h and no spontaneous conversion within 18 h, based on numbers of independent predictors (IHD, first-ever AF episode, AFR < 350 fpm) present.





No spontaneous conversion < 18 h

Spontaneous conversion < 18 h

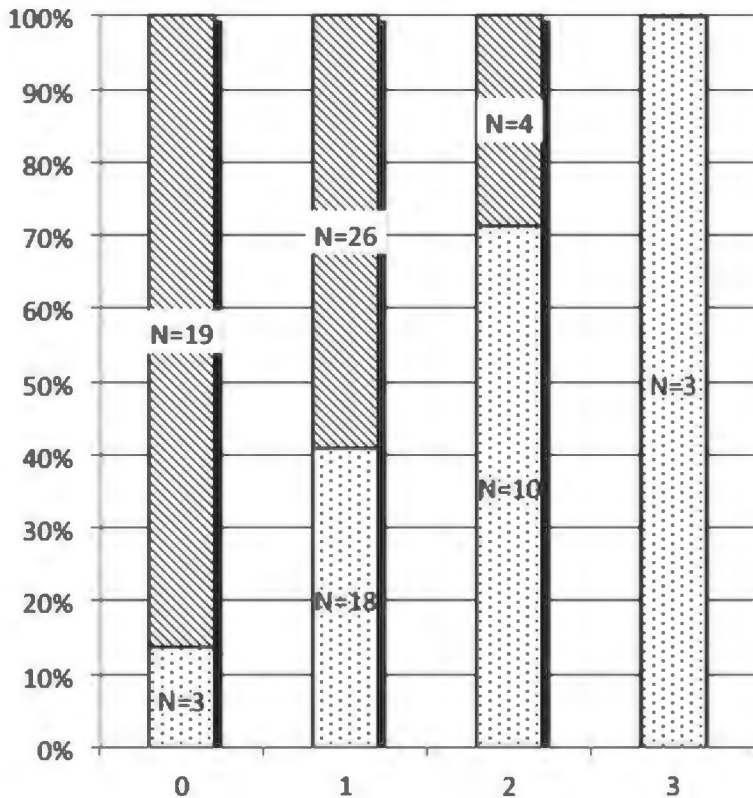


Table 1: Clinical characteristics of patients admitted to emergency room with AF duration not exceeding 48 hours. Patients who received DC-cardioversion within the first 18 hours (n = 43) were excluded from assessment of spontaneous conversion rate.

	Study population (n=148)	Spontaneous conversion < 18h (n=48)	No spontaneous conversion < 18 h (n=57)	P-value
Characteristics:				
Age, yrs	64±13	68±12	63±14	Ns
Gender, female	45%	63%	39%	0.015
Heart rate	117±30	117±29	107±24	Ns
BP syst, mmHg	136±22	137±22	138±21	Ns
BP diast, mmHg	83±14	83±16	83±15	Ns
Comorbidites:				
Hypertension	40%	50%	47%	Ns
CHF	1%	4%	0%	Ns
IHD	15%	25%	9%	0.025
Diabetes	12%	10%	18%	Ns
Stroke	6%	8%	7%	Ns
Medications on admission:				
Aspirin	32%	29%	33%	Ns
Warfarin	22%	21%	23%	Ns
β-blockers	61%	53%	68%	Ns
Ca-blockers	1%	0%	0%	Ns
Digoxin	5%	11%	5%	Ns
Rate control treatment at admission:				
β-blockers	53%	44%	60%	Ns
Echocardiographic parameters:				
LA-diameter, cm	4.21± 0.6	4.25±0.7	4.24±0.7	Ns
Normal LVEF	70%	97	95	Ns
Diastolic dysfunction	48%	46	39	Ns
AFR, fpm	352±57	332±55	364±58	0.012
First-ever AF episode	28%	46%	22%	0.011

AF: atrial fibrillation; AFR: atrial fibrillatory rate; BP: blood pressure; CHF: congestive heart failure; IHD: ischemic heart disease; LA: Left atrial; LVEF: Left ventricular ejection fraction.

Table 2: Results of the univariate and multivariate analysis of predictors of spontaneous conversion within 18 h.

	Univariate			Multivariate		
	OR	95% CI	P-value	OR	95% CI	P-value
Gender	2.7	1.2-5.8	0.016	---	---	---
IHD	3.5	1.1-10.7	0.031	5.7	1.5-22.4	0.012
First-ever AF episode	3.0	1.3-7.1	0.012	4.1	1.3-13.0	0.015
AFR<350 fpm	2.7	1.1-6.6	0.025	3.7	1.3-10.5	0.016

AF: atrial fibrillation; AFR: atrial fibrillatory rate; IHD: ischemic heart disease