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Nonsustained Atrial Fibrillation in Ischemic Stroke Patients and Stroke-Free Controls From the Perspective of Stroke Pathophysiology

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Background—Short-lasting (<30 s), nonsustained episodes of atrial fibrillation (NS-AF) are considered a risk factor for future development of paroxysmal or persistent AF. Nonetheless, their causal role in stroke pathogenesis is currently unknown. In this study we determined the frequency of NS-AF, together with the associated clinical and imaging features, in stroke-free controls and ischemic stroke patients.

Methods and Results—A total of 332 controls, ≥ 50 years of age and no prior history of stroke or AF, were evaluated with 24-hour Holter monitoring for the presence of <30-s-long AF episodes. The demographic and cardiovascular features of this cohort, together with imaging finding on magnetic resonance imaging, were compared to a consecutive series of ≥ 50 -year-old ischemic stroke patients without AF ($n=498$). The prevalence of NS-AF was significantly higher among ischemic stroke patients in comparison to controls (37% versus 27%; $P=0.002$). In multivariable analyses, after adjustment for demographic and cardiovascular risk factors, patients with ischemic stroke were more likely to harbor NS-AF episodes (odds ratio 1.43; 95% CI 1.01–2.02; $P=0.041$). The association between ischemic stroke and NS-AF weakened when the analyses were restricted to cryptogenic stroke patients (odds ratio 1.31; 95% CI 0.82–2.08). No significant association was observed between the presence of chronic cortical infarcts and NS-AF.

Conclusions—Our study shows a higher prevalence of NS-AF episodes in ischemic stroke patients in comparison to controls. Nonetheless, the lack of a stronger association with cryptogenic strokes and absence of a relationship with chronic cortical infarcts brings into question the causal influence of NS-AF in the ischemic stroke setting. (*J Am Heart Assoc.* 2016;5:e004021 doi: 10.1161/JAHA.116.004021)

Key Words: atrium • cerebral infarction • embolism • fibrillation • imaging

The influence of the duration of atrial fibrillation (AF) episodes on stroke pathophysiology has become the focus of attention over the past few years, possibly as a reflection of the wide availability and choice of inpatient and outpatient cardiac rhythm monitoring tools. Traditionally, paroxysmal AF—defined as ≥ 30 s-long duration of AF episodes—is considered to harbor a similar risk of ischemic stroke in comparison to persistent AF, and thereby is approached in an analogous fashion during risk stratification

and treatment algorithms.¹ However, recently published studies performed in large patient cohorts has cast doubt regarding the validity of this assumption.^{2–4} Pooled analyses of nonanticoagulated patients in ACTIVE-A and AVERROES trials have shown significant differences in annual embolic event rates between patients with persistent AF and paroxysmal AF (3.0% versus 2.1%), despite similar CHA₂DS₂-VASc scores.² Furthermore, these rates were still lower than the rate observed in the permanent AF group (4.2%). A similar trend with respect to lower risk of embolic events in the setting of paroxysmal AF is also present among anticoagulated patients according to the results of ROCKET-AF and ARISTOTLE trials.^{3,4}

A relevant discussion in this perspective is whether much shorter periods of AF (<30 s) should be considered as a risk factor for stroke, similar to their longer-lasting counterparts. These brief and nonsustained atrial high-rate episodes have been shown to predict future conversion to persistent AF, and therefore are considered to be pathophysiologically related arrhythmias.^{5,6} However, their direct contribution to ischemic stroke pathogenesis is still unknown. A previous analysis

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limited to ischemic stroke patients has shown that these nonsustained AF episodes are observed quite frequently in this setting, yet the associated clinicoradiologic features did not entirely resemble those of patients with paroxysmal or persistent AF.⁷ More importantly, its prevalence was not different between cryptogenic and noncryptogenic stroke patients, bringing into question the direct role of nonsustained AF as the culprit pathology in stroke etiology. As an additional step to shed some light on this uncertainty, in this study we determined the prevalence of nonsustained AF in stroke-free controls and compared it to a consecutive series of ischemic stroke patients. Furthermore, by additional analyses focusing on stroke etiology and imaging features, we tried to gather clues that might suggest a causal influence of this arrhythmia in the setting of ischemic stroke.

Methods

Study Sample

Ischemic stroke population

A consecutive series of patients admitted to a tertiary care hospital with a diagnosis of ischemic stroke between the period of 2010 and 2015 comprised the ischemic stroke population. The analyses were restricted to patients (1) ≥ 50 years of age, (2) with no previous history of AF, (3) with no observed episodes of AF lasting ≥ 30 s during ECG or inpatient cardiac monitoring throughout the admission period, and (4) who underwent 24-hour Holter ECG monitoring as part of the routine stroke work-up in the stroke service of the Neurology Department.

Control cohort

The control group was recruited via printed and electronic flyers distributed across Hacettepe University and its affiliated hospitals. The following prerequisites were asked from the volunteers in order to be included in the current study: (1) age ≥ 50 years, (2) absence of a previous diagnosis of stroke, (3) absence of a previous diagnosis of chronic neurodegenerative disease, and (4) absence of a previous diagnosis of AF. Transthoracic echocardiography and 24-hour Holter ECG monitoring was performed in all subjects in the control cohort. In addition, a subset of them underwent cranial magnetic resonance imaging (MRI), as detailed below.

Data Collection and Interpretation

The study was approved by the local institutional review board. Informed consent was obtained from the control group, whereas this was waived in ischemic stroke patients. Baseline demographic and clinical information (age, sex, history of

hypertension, diabetes mellitus, coronary heart disease, hyperlipidemia, and smoking) were collected in both study populations. All this information was extracted from the prospectively collected departmental stroke database for the ischemic stroke patients, while the relevant information was obtained by face-to-face interview in the control cohort. Stroke etiology, according to the Causative Classification of Stroke (CCS) system, was additionally determined in ischemic stroke patients by stroke specialists with ≥ 10 years of experience.⁸

The 24-hour Holter monitoring was performed via 3-channel recordings with standard settings (Lifecard CF, Spacelabs Healthcare, WA; ELA Spiderview, ELA Medical, Sorin Group, Paris, France). All the recordings from both groups were evaluated for the presence of <30 -s-long or ≥ 30 -s-long AF episodes by an experienced cardiologist blinded to characteristics of the participants. Supraventricular runs with >3 beats, lasting <30 s with absolutely irregular RR interval and no distinct p-waves were considered as nonsustained AF. Self-terminating episodes with similar morphological characteristics and lasting ≥ 30 s were defined as paroxysmal AF.

Echocardiographic examination was performed with patients in the left lateral decubitus position by using a state-of-the-art echocardiographic ultrasound system (GE Vivid E9, Vingmed Ultrasound, Horten, Norway) with a 3.5-MHz transducer. Parasternal long- and short-axis views and apical views were used as standard imaging windows. Left atrial dimension, left ventricle end-systolic and end-diastolic dimensions, and left ventricular diastolic septal and posterior wall thickness were evaluated in the parasternal long-axis view. Left ventricular ejection fraction was calculated by using the modified Simpson method. During echocardiography, a single-lead ECG was recorded simultaneously. M-mode measurements and conventional Doppler echocardiographic examinations were calculated according to the criteria proposed by the American Society of Echocardiography.⁹ All echocardiographic images included at least 3 consecutive beats and were analyzed by an experienced cardiologist who was blind to participants' clinical status.

A subset of control cohort underwent MRI by a 1.5-T scanner (Magnetom TIM, Symphony, Siemens, Erlangen, Germany). Axial images with a 5-mm-slice thickness and no interslice gap were obtained from T2-weighted (W) turbo spin echo (SE) (repetition time [TR]/echo time [TE]; 3900/100 ms), fluid-attenuated inversion recovery (TR/TE/TI; 8900/100/2000 ms), and T1-weighted SE (TR/TE; 550/15 ms) sequences and these images were used to evaluate the presence or absence of chronic cortical infarcts. Single-shot echo planar diffusion-weighted imaging, applied at 3 b values with a maximum of 1000 s/mm² and a TR/TE of 5100/137 ms, were used to rule out acute ischemic lesions in this cohort.

Statistical Analyses

Categorical variables are expressed as n (%) and continuous variables as median (interquartile range). Groupwise comparisons were performed by χ^2 test for categorical variables and Mann–Whitney *U* test for continuous variables. Logistic regression models with the dependent variable being presence or absence of nonsustained AF was performed to evaluate multivariable associations of this arrhythmia. A backward regression algorithm (with a $P < 0.10$ used as retention threshold) was used to prevent overfitting related to independent variables introduced into the model, which was composed of all the demographic and clinical variables collected. Echocardiographic parameters were not included in the model because of the close interplay of these variables with AF and uncertainty regarding the direction of the cause–effect relationship between them. Cryptogenic and noncryptogenic strokes were exclusively introduced into the models in analyses focusing on the relationship between cryptogenic stroke and nonsustained AF, while chronic cortical infarcts constituted the dependent variable in the model evaluating the association of chronic cortical infarcts and nonsustained AF in the control group. A $P < 0.05$ was considered statistically significant. SPSS version 16.0 was used for statistical analyses.

Results

Study Sample

A total of 1245 patients with a diagnosis of stroke and ≥ 50 years of age were admitted during the study period. Out of these, 274 (22%) had an established diagnosis of paroxysmal or persistent AF, and an additional 135 (11%) were newly diagnosed with AF during their admission either by 12-lead resting ECG or inpatient cardiac monitoring. Of the remaining 836 patients, those 498 patients who were evaluated by 24-hour Holter monitoring comprised the ischemic stroke population. The control group consisted of 332 cases without prior history of stroke or AF. Baseline characteristics of the overall study population are shown in Table 1. Expectedly, patients with ischemic stroke had a higher vascular risk factor burden and abnormal echocardiographic features in comparison to controls.

Prevalence and Predictors of Nonsustained AF

A new diagnosis of AF lasting < 30 s and ≥ 30 s was established in 37.1% and 3.6% of ischemic stroke patients, respectively. The corresponding figures were 26.6% and 1.5% in the control group (Figure 1).

The distribution of demographic and clinical features with respect to presence or absence of nonsustained AF is

Table 1. Baseline Characteristics of the Study Population

	Control Group (n=332)	Ischemic Stroke Patients (n=498)	P Value
Age, y	63 (56–70)	68 (61–75)	<0.001
Female sex	196 (59%)	188 (38%)	<0.001
Hypertension	173 (52%)	392 (79%)	<0.001
Diabetes mellitus	65 (20%)	183 (37%)	<0.001
Coronary artery disease	67 (20%)	177 (36%)	<0.001
Hyperlipidemia	164 (49%)	274 (55%)	0.112
Smoking	59 (18%)	120 (24%)	0.030
Ejection fraction, %	64 (60–65)	61 (55–65)	<0.001
Left atrial diameter, cm	3.4 (3.2–3.7)	3.7 (3.3–4.0)	<0.001

Continuous variables are expressed as median (interquartile range).

summarized in Table 2. Aging was one of the most critical factors closely related to nonsustained AF ($P < 0.001$; Figure 2). Other features that were found to be positively associated with this arrhythmia in univariate analyses included female sex ($P = 0.037$) and history of hypertension ($P = 0.001$). On echocardiography, patients with nonsustained AF had significantly enlarged left atrial size (left atrial diameter 3.7 [3.4–4.0] cm versus 3.5 [3.2–3.8] cm; $P < 0.001$), but similar left ventricular ejection fractions ($P = 0.459$) when compared to patients without any arrhythmia. In multivariable analyses, after adjustment for demographic and cardiovascular risk factors, patients with ischemic stroke were more likely to harbor nonsustained AF episodes in comparison to controls (odds ratio 1.43; 95% CI 1.01–2.02; $P = 0.041$) (Table 3).

Interplay Between Cryptogenic Stroke and Nonsustained AF

The ischemic stroke patient group consisted of 155 patients with cryptogenic stroke and 325 patients with noncryptogenic stroke. Nonsustained AF was observed in 40% ($n = 62$) of cryptogenic cases and 36% ($n = 116$) of noncryptogenic stroke patients ($P = 0.361$) (Table 4). When the aforementioned multivariable model was repeated separately for both groups, the association between nonsustained AF and ischemic stroke was found to be nonsignificantly stronger among noncryptogenic strokes (odds ratio 1.46; 95% CI 1.01–2.13) in comparison to cryptogenic stroke (odds ratio 1.31; 95% CI 0.82–2.08) patients.

Chronic cortical infarcts and nonsustained AF

In the control group, a total of 283 patients had additionally undergone a cranial MRI study, and 13 (5%) of them were

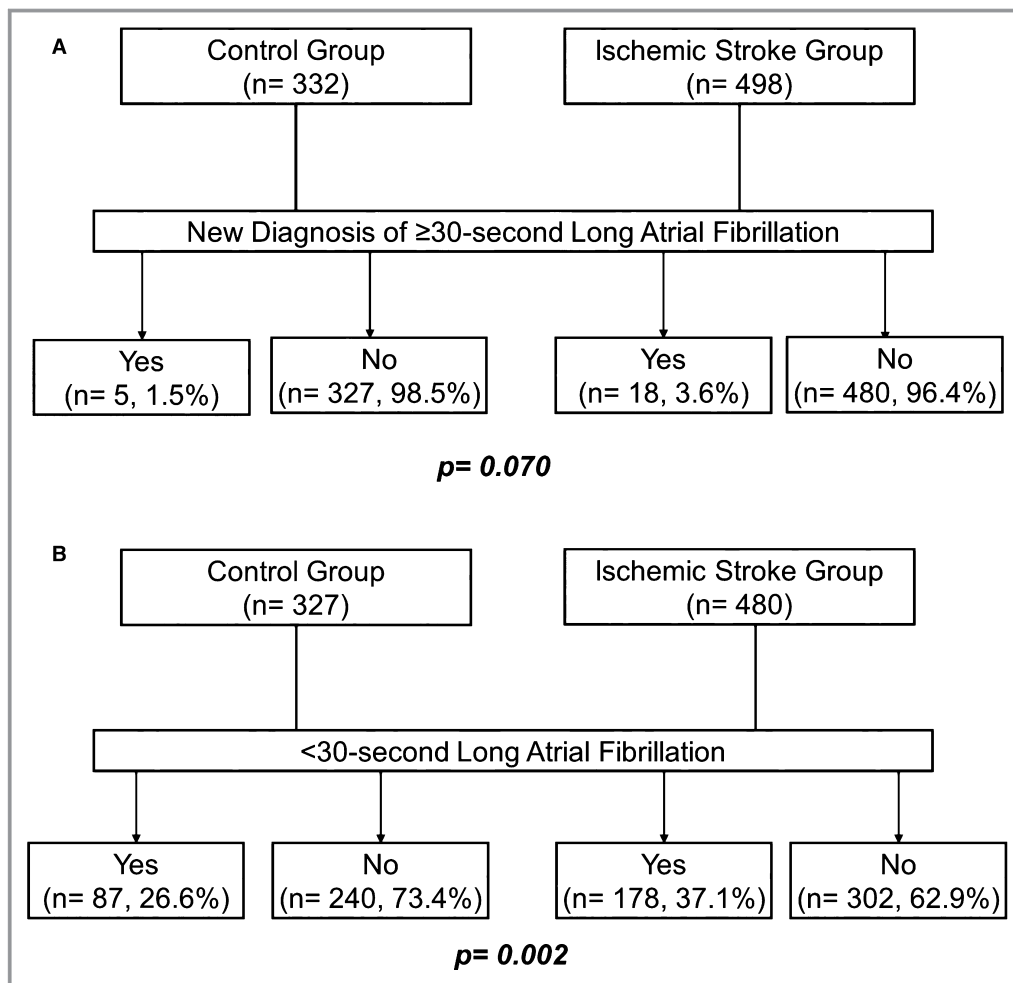


Figure 1. Prevalence of ≥ 30 -s-long (A) and < 30 -s-long (B) atrial fibrillation episodes in ischemic stroke patients and controls.

found to have chronic cortical infarcts. None had any evidence of acute ischemic lesions on diffusion-weighted imaging. The odds of having chronic cortical infarcts were nonsignificantly higher among cases with nonsustained AF (odds ratio 2.31, 95% CI 0.75–7.11; $P=0.143$). However, the trend for this association was abolished after adjustment for vascular risk factors, with age ($P=0.010$) and history of coronary artery disease ($P=0.010$) remaining as the only significant factors associated with chronic cortical infarcts.

Discussion

Our study has 2 important and clinically relevant findings. First, < 30 -s-long AF episodes were relatively more common among ischemic stroke patients when compared to a cohort of stroke-free controls. This positive association between ischemic stroke and nonsustained AF remains significant after adjustment for other relevant factors such as age and vascular risk factors. On the other hand, as the second major

conclusion of our study, we were unable to detect clues that might suggest a causative influence of < 30 -s-long AF on pathogenesis of ischemic stroke; the link between the 2 phenomena was not stronger for cryptogenic strokes, and chronic, silent cortical infarcts were not more frequently encountered on MRIs of cases with nonsustained AF.

The critical duration of AF that leads to formation of a thrombotic milieu in the heart and thereby causes embolic complications including ischemic stroke is unknown. Although atrial stunning following short paroxysms of AF is considered to be related to changes in cellular metabolism, longer-lasting episodes of AF may induce further changes causing a more persistent atrial contractile dysfunction.¹⁰ It has been previously demonstrated that AF episodes lasting less than 20 minutes do not result in significant left atrial mechanical dysfunction.¹¹ On the other hand, studies performed in patients with pacemakers or implantable cardioverter-defibrillators have shown discordant results regarding the minimum duration of atrial tachyarrhythmias related to embolic

Table 2. Comparison of Clinical Features Among Cases With and Without Nonsustained AF

	Cases With <30-S-Long Atrial Fibrillation (n=265)	Cases Without <30-S-Long Atrial Fibrillation (n=542)	P Value
Age, y	70 (64–76)	63 (56–70)	<0.001
Female sex	136 (51%)	236 (44%)	0.037
Hypertension	199 (75%)	345 (64%)	0.001
Diabetes mellitus	75 (28%)	163 (30%)	0.604
Coronary artery disease	83 (31%)	154 (28%)	0.394
Hyperlipidemia	131 (49%)	295 (54%)	0.182
Smoking	52 (20%)	126 (23%)	0.244

Continuous variables are expressed as median (interquartile range). AF indicates atrial fibrillation.

complications with a range extending between 5 minutes and 24 hours.^{6,12,13} A similar discrepancy is observed when the analyses are repeated by taking into consideration the daily burden of arrhythmia, where stroke risk escalates as the cumulative burden exceeds a threshold changing between 3.8 and 5.5 hours.^{14,15} Comparable information from patients without prior diagnosis of any arrhythmia or pacemaker/implantable cardioverter-defibrillator implantation is unknown and difficult to acquire. Our study, with its cross-sectional case-control design, does not provide a straightforward answer to this conundrum, but offers a certain insight via highlighting the higher prevalence of <30-s-long AF episodes in ischemic stroke patients in comparison to stroke- and arrhythmia-free controls.

The presence of an association between 2 entities does not automatically imply the presence of causality, which was also the case in our study. Even former studies, which focused on longer duration of atrial tachyarrhythmias or atrial high-rate episodes, have highlighted the lack of a temporal

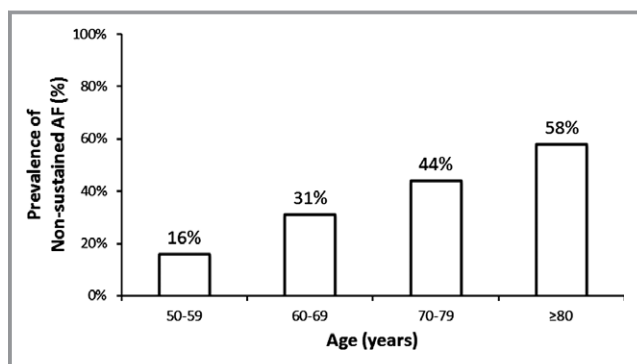


Figure 2. Relationship between age and prevalence of nonsustained atrial fibrillation. AF indicates atrial fibrillation.

Table 3. Predictors of Nonsustained AF in the Multivariable Model

	OR (95% CI)	P Value
Age	1.07 (1.05–1.09)	<0.001
Female sex	1.39 (1.01–1.92)	0.045
Diabetes mellitus	0.69 (0.49–0.98)	0.039
Ischemic stroke	1.43 (1.01–2.02)	0.041

AF indicates atrial fibrillation; OR, odds ratio.

relationship between ischemic stroke and the arrhythmia episode in many cases.^{16,17} Considering that the etiologic classification of our ischemic stroke patients was performed irrespective of the nonsustained AF status, theoretically one would expect to find a higher prevalence of these episodes in cryptogenic patients if there is indeed a causal relationship. The contribution of certain pathologies to stroke etiology, such as patent foramen ovale or hemorrhagic carotid plaques without significant stenosis, has been uncovered by such analyses.^{18,19} Contrary to those observations, the proportion of patients with and without <30-s-long AF did not differ significantly between cryptogenic and noncryptogenic stroke patients. Moreover, the positive association observed in the overall stroke population was not strengthened, and even decreased, when the analyses were restricted to the cryptogenic population. Another finding that hampered the causality hypothesis was the absence of a higher burden of silent cortical infarcts in nonsustained AF cases, which is quite opposite to observations in persistent AF populations where the pathophysiological link to ischemic stroke is well established.^{20,21}

Certain limitations of our study merit consideration. We did not have 24-hour Holter monitoring data for all of our ischemic stroke patients admitted during the study period. In our center, according to our stroke unit policy, all patients without apparent AF are planned to undergo Holter monitoring regardless of their age, risk factors, and stroke etiology, yet this goal cannot be achieved in some of them due to various reasons such as early mortality, transfer to another hospital or

Table 4. Prevalence of Nonsustained AF Among Stroke Subtypes

Large artery atherosclerosis (n=169)	33%
Cardioaortic embolism (n=32)	34%
Small artery occlusion (n=47)	38%
Other causes (n=42)	41%
Cryptogenic causes (n=155)	40%
Unclassified causes (n=35)	43%

AF indicates atrial fibrillation.

rehabilitation facility, and loss to follow-up, leading to an unintentional selection bias. Nonetheless, baseline clinical characteristics were not significantly different between patients with and without Holter data, except for higher admission National Institutes of Health Stroke Scale scores among patients lacking Holter monitoring. Additionally, our controls and ischemic stroke patients were not matched with respect to baseline variables; although we tried to adjust for these disparities by multivariable analyses, there might still be residual confounding arising from the differences in study populations and missing Holter data in the ischemic stroke group. In both study groups, we monitored cardiac rhythm for a period of only 24 hours, and therefore our results are not applicable to invasive or noninvasive monitoring strategies involving more extended durations. Still, considering that this approach is the most commonly used tool for long-term rhythm monitoring, we believe that the implications are closely related to routine clinical practice. The borderline significance between ischemic stroke and control groups regarding a new diagnosis of ≥ 30 -s-long AF episodes on Holter monitoring is probably a reflection of the fact that various tools such as ECG or inpatient rhythm monitoring capture new AF episodes in many stroke patients and thereby lead to an inevitable drop in the yield of Holter monitoring among ischemic stroke patients in this regard. Finally, MRI data were available in most, but not all of our controls. However, there were no differences in the demographic and clinical characteristics of those cases with and without MRI.

In conclusion, despite highlighting the presence of an association, our observations do not support the presence of a direct causality between nonsustained AF and ischemic stroke. These findings, together with the recent observations of a lower stroke risk in the setting of paroxysmal AF,^{2–4} suggest that the pathophysiological link between AF and embolic complications weakens as the duration of AF episodes shortens. However, the questions of why < 30 -s-long AF episodes are more commonly encountered in ischemic stroke patients, and more importantly, how these patients should be managed are still unanswered. The higher prevalence of nonsustained AF cannot be only considered as a reflection of high-risk vascular status, as the association remains significant regardless of the vascular risk factor burden, as highlighted by our observations. One explanation could be that this aberration in cardiac rhythm might be a substrate of an underlying left atrial cardiomyopathy, which is emerging as a stroke-prone setting.²² However, as this setting has a questionable and complex cause–effect relationship, the role of anticoagulation for secondary prophylaxis remains debatable and subject to further investigation in ischemic stroke patients with nonsustained AF. The high frequency of this arrhythmia even in controls in the current study, though being unexpected, might be reasonable considering that the prevalence of related arrhythmias, such as ≥ 3

runs of supraventricular tachycardia and ectopic supraventricular complexes, is in the range of $\approx 50\%$ and 66% on long-term cardiac rhythm monitoring, respectively, in population-based studies.^{23,24} The lack of a standard terminology for short duration atrial tachyarrhythmias unfortunately contributes further to the complexity in this field.²⁵ Aberrations detected in atrial rhythm with surface recordings (such as nonsustained AF, and ectopic supraventricular complexes) or pacemakers/defibrillators (such as atrial high-rate episodes)—although being related—might signify different phenomena, and their contribution to cardiovascular pathologies would be clarified once unanimity is reached regarding their definition, which would include but would not be limited to features such as duration and recording methodology.

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Disclosures

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