Episodes of Atrial Fibrillation and Symptoms: A Temporal Analysis

Hamid Ghanbari, MD, MPH, FHRS,* Daniel Whibley, PhD,† H. Immo Lehmann, MD, PhD,* Zhi Li, PhD,* Anna Kratz, PhD,† Daniel J. Clauw, MD,‡ Brahmajee K. Nallamothu, MD, MPH*

*From the *Department of Internal Medicine, Division of Cardiovascular Medicine, University of Michigan Medical School, Ann Arbor, Michigan, †Department of Physical Medicine and Rehabilitation, University of Michigan Medical School, Ann Arbor, Michigan, and ‡Department of Internal Medicine, Division of Rheumatology, University of Michigan Medical School, Ann Arbor, Michigan.*

BACKGROUND Data on the relationship between symptoms and atrial fibrillation (AF) episodes are limited.

OBJECTIVE The objective of this study was to determine the strength of temporal association between AF episodes and symptoms.

METHODS This cross-sectional ambulatory assessment study was performed in a tertiary care center between June 2018 and December 2021. Patients with paroxysmal AF (1 episode of AF, burden not exceeding 95%) who used a mobile application and continuous wearable electrocardiogram monitor for 21 days were enrolled. The primary outcome was worse symptoms (symptoms above the mean score) over the study period. The association between worse symptoms and the presence of AF was evaluated for different time epochs. Multilevel mixed-effects models were used to quantify associations after accounting for confounders.

RESULTS Worse symptoms were more likely to be associated with the presence of AF episodes 15 minutes prior to the reporting of palpitations (OR, 2.8 [95% CI, 1.6–5.0]; $P < .001$), shortness of breath (OR, 2.2 [95% CI, 1.3–3.7]; $P = .003$), dizziness/lightheadedness (OR, 2.0 [95% CI, 1.0–3.7]; $P = .04$), and fatigue (OR, 1.7 [95% CI, 1.0–2.9]; $P = .03$). The correlation between the severity of symptoms and AF lessened as the time interval from AF events to symptoms increased.

CONCLUSION There is a significant relationship between onset of AF episodes and reporting of symptoms. This association diminishes over time and varies across different symptoms. If confirmed in larger studies, these findings may inform AF interventions that target symptoms just in time prior to a clinical visit.

KEYWORDS Atrial fibrillation; Heart rhythm monitoring; Onset of symptoms; Palpitations; Shortness of breath; Mobile health

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Introduction

Atrial fibrillation (AF) has been linked to symptoms such as shortness of breath, fatigue, palpitations, dizziness/lightheadedness, and chest pain that can result in decreased functional status and health-related quality of life.[1] However, not all patients with AF report symptoms, and many patients without AF report similar symptoms for reasons unrelated to their heart rhythm.[2] The current paradigm for symptom assessment in which patients are often asked to recall their symptoms during isolated clinic visits after a significant time has passed since the occurrence of AF makes it unclear if an episode was responsible for a specific symptom.[2] This approach also does not consider additional factors that may influence reporting of symptoms, such as the type of symptom being reported (eg, palpitations vs fatigue) or the underlying affect, the underlying experience of feeling, emotion or mood that could modify how an episode is experienced.[3,4] This makes treatments aimed at treating AF challenging. A better understanding of the temporal relationship between AF episodes and symptoms could help to understand what types of symptoms are most important in AF and what and when interventions for AF episodes may be most successful. Wearables combined with new and innovative digital health tools that simultaneously record physiological data, symptoms, and emotional states in the patient's natural setting are likely to generate insights to better understand the overall patient's experience of disease.

Methods

Participants who were ≥18 years old and had a prior diagnosis of AF were included. Patients who were functionally in persistent AF (defined as AF burden of ≥95%) were excluded, as they would not contribute to the variability

Address reprint requests and correspondence: Dr Hamid Ghanbari, Department of Internal Medicine, Division of Cardiovascular Medicine, Cardiac Electrophysiology Services, 1500 East Medical Center Dr, Ann Arbor, MI 48109-5853. E-mail address: ghhamid@med.umich.edu.

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observed in symptoms and heart rhythm. Participants used a mobile application (MiAfib) to record symptoms while wearing a continuous heart monitor (Preventice, Inc, Houston, TX) for 21 days. The details of the study protocol have been described previously.[5] MiAfib prompted participants at regular intervals (9 AM, 12 PM, 3 PM, and 6 PM) to record their symptoms. Items asked about symptoms (shortness of breath, fatigue, palpitations, dizziness/lightheadedness, and chest pain) and positive (happy, excited, content) and negative (worried, angry, sad) affect. Affect was included because it has been shown to modify how individuals perceive symptoms with AF episodes.[5] For response options, we used a Likert scale ranging from 0 (not at all) to 10 (extremely). We categorized symptoms as worse than usual if they were above the mean symptom score for the individual over the course of the study.

For identification of AF episodes, we used the electrocardiogram (ECG) labels generated by a proprietary deep neural network system. AF burden was calculated as the total duration of labeled AF events divided by the total duration of all labeled non-noise events.[6] AF burden was calculated as the total duration of labeled AF events divided by the total duration of all labeled non-noise events. We examined the temporal association and strength of the relationship between AF episode onset and symptoms in time epochs spanning 15 minutes, 15 minutes to 1 hour, 1–4 hours, and 4–24 hours.

Statistical Analysis

We analyzed these data using R 4.1.2 (R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org/). Multilevel models were created with the lme4 R package and used to quantify associations between heart rhythm and symptoms.[7] AF episodes that were present within 15 minutes of symptom occurrence were treated as a binary independent variable. Of note, AF episodes that transitioned from normal sinus rhythm within the 15-minute window or ongoing AF episodes were counted as positive for this variable. Individual participants and time-invariant variables were modeled at level 2 (age, sex, and body mass index [BMI]), while time-dependent variables (affect, symptoms, and AF episode time epoch) were modeled at level 1. Symptoms were generally categorized as worse than usual if they were above the mean symptom score for the individual over the course of the study. The "positive affect" variable was the sum of happy, content, and excited responses, while the "negative affect" variable was the sum of angry, sad, and worried responses. We used combinations for positive and negative affect to improve model interpretability. Empty models (only including the symptom of interest, with participant as a random effect) were used to calculate the intraclass correlation coefficient for each symptom. The full model included age, sex, BMI, AF episode time epoch, and positive and negative affect. Centering was applied to independent variables included in the model. Level 1 independent variables (AF episode time epoch, positive affect and negative affect) were centered about the mean for that individual (ie, each positive affect score minus the mean positive affect score for that participant). The group means of level 1 predictors by participants was also calculated and included as level 2 variables. Other level 2 demographic variables were centered using grand means. Confidence intervals (95% CI) were calculated using the Wald test. Continuously distributed variables are reported as mean ± standard deviation. Binary or discrete variables are presented using counts and percentages. We used multilevel logistic regression models to estimate the odds of having symptoms accounting for subject clusters. At level 1, the models were adjusted for AF episodes occurring at 4 different time epochs before the symptom and affect scores. The models were also adjusted for other demographic variables including age, sex, and BMI at level 2.

Table 1 Characteristics of patients in the study (N = 65)

Clinical values	Results
Age, mean (SD), years	65.2 (11.5)
Male, n (%)	38 (62.3)
BMI, mean (SD), kg/m^2	29.9 (6.3)
LVEF, mean (SD), %	59.7 (7.6)
Hypertension, n (%)	28 (45.9)
Coronary artery disease, n (%)	14 (23.0)
Stroke, n (%)	1 (1.6)
Diabetes, n (%)	8 (13.1)
Peripheral vascular disease, n (%)	3 (4.9)
History of prior AF ablations, n (%)	19 (32.8)
History of depression, n (%)	5 (8.6)
History of anxiety, n (%)	5 (8.6)

AF = atrial fibrillation; BMI = body mass index; LVEF = left ventricular ejection fraction; SD = standard deviation.

Results

We included 65 patients with paroxysmal AF in the study. Baseline characteristics of patients in the study are presented in Table 1. Participants had a median of 22 days of total ECG monitor wear time (range 10–35 days). At the participant level, the range of usable data from the ECG monitors was 21.5%–98.9%. Across all participants, the mean heart rate was 70.1 ± 10.1 beats per minute. The median overall AF burden was 6.1% (interquartile range [IQR], 0.06%–34.2%). A total number of 21,903 AF episodes were recorded. There were 1509 AF episodes present within the 4-to-24-hour time epoch prior to reporting of symptoms. Of those, 205 were continuously present prior and up to 24 hours prior to reporting of symptoms. We adjusted for AF episodes occurring at 4 different time epochs before the symptoms to account for continuous episodes of AF. AF episodes that occurred within 15 minutes of reporting of symptoms were associated with increased likelihood of worse symptoms after adjusting for AF episodes that occurred in other time frames (Supplemental Table 1). The median duration of AF episodes

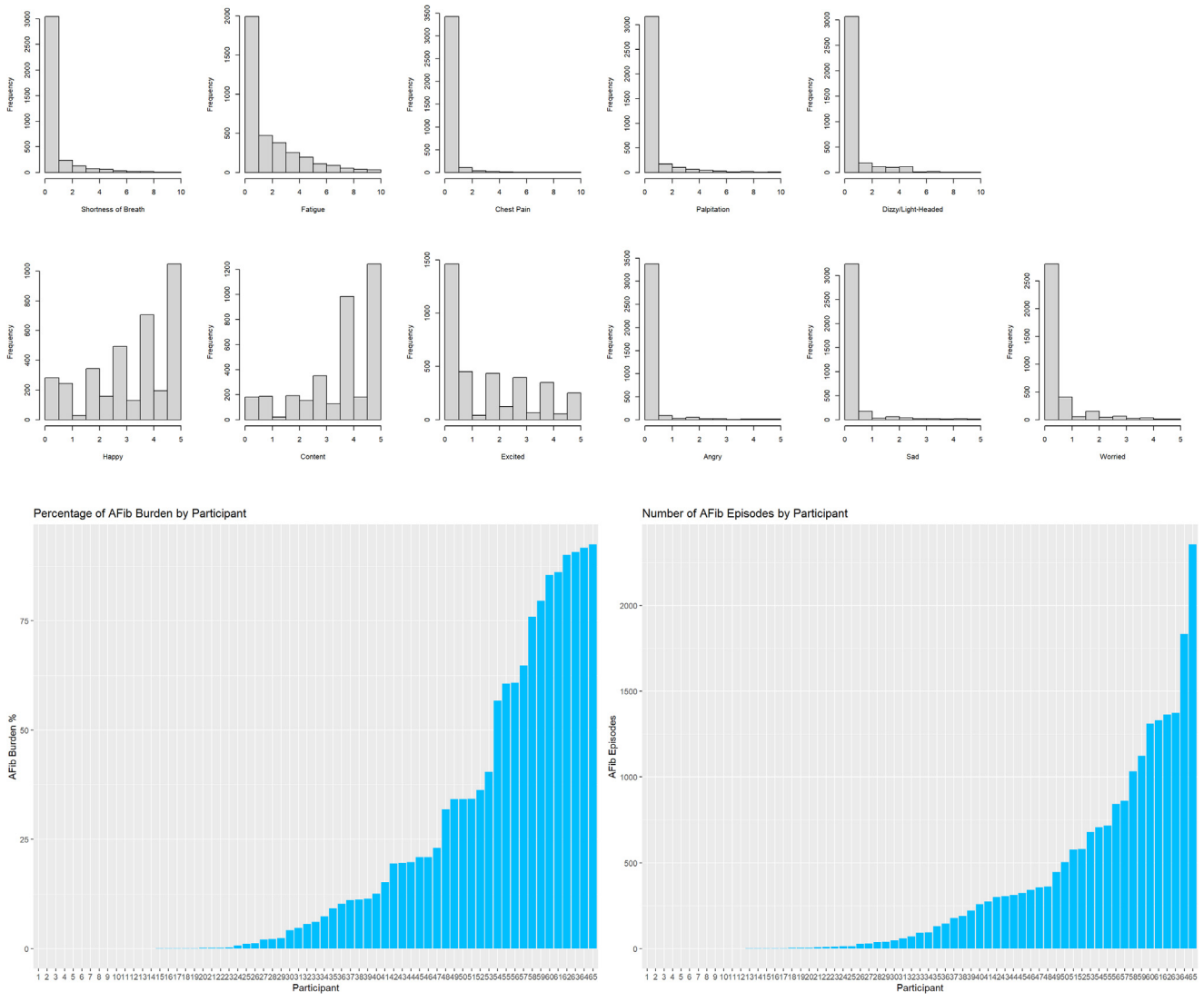

Figure 1 Upper row: Distribution of symptoms and affects in study participants. Lower row: Distributions of atrial fibrillation burden (left) and episodes (right) by study participant.

was 205.7 seconds (IQR, 73.1–720.0 seconds). The average number of AF episodes recorded per patient was 413.3 ± 529.3. Of the total AF episodes, 43.1% (9440/21,903) were greater than 5 minutes. The median heart rate during AF episodes was 82 beats per minute (IQR, 66.0–100.9 beats/min). Compliance with the assessment of symptoms was 74.8% (3622 completed random surveys collected from a total of 1210 days / 4840 total surveys [1210 × 4 prompts per day]). The average total number of responses was 55.7 ± 27.8 for an average of 18.6 ± 4.73 days. The median number of responses using the mobile application for each patient was 2.9 ± 1.2 per day. The distribution of symptoms, affect, overall AF burden, and episodes are represented in Figure 1.

AF episodes that occurred within 15 minutes before recording of symptoms were associated with worse palpitations (odds ratio [OR], 2.8 [95% CI, 1.6–5.0]; P = .0004), shortness of breath (OR, 2.2 [95% CI, 1.3–3.7]; P = .003), dizziness/lightheadedness (OR, 2.0 [95% CI, 1.0–3.7]; P = .04), and fatigue (OR, 1.7 [95% CI, 1.0–2.9]; P = .03, Figure 2). Of note, AF episodes that occurred in 15 minutes to 1 hour, 1–4 hours, and 4–24 hours time epochs were not associated with worse symptoms except for palpitations (Figure 2). The strength of the relationship between worse symptoms and AF decreased as the time from AF events to symptoms increased (Table 2 and Figure 2).

Negative affect was associated with worse symptoms when AF episodes were present within 15 minutes of reporting of shortness of breath (OR, 1.1 [95% CI, 1.0–1.2]; P = .01), fatigue (OR, 1.2 [95% CI, 1.1–1.2]; $P < .0001$), chest pain (OR, 1.2 [95% CI, 1.1–1.3]; $P < .001$), palpitations (OR, 1.2 [95% CI, 1.1–1.3; $P < .0001$), and dizziness/lightheadedness (OR, 1.2 [95% CI, 1.1–1.3]; $P < .0001$). Positive affect was associated with decreased shortness of breath (OR, 0.95 [95% CI, 0.90–0.99];

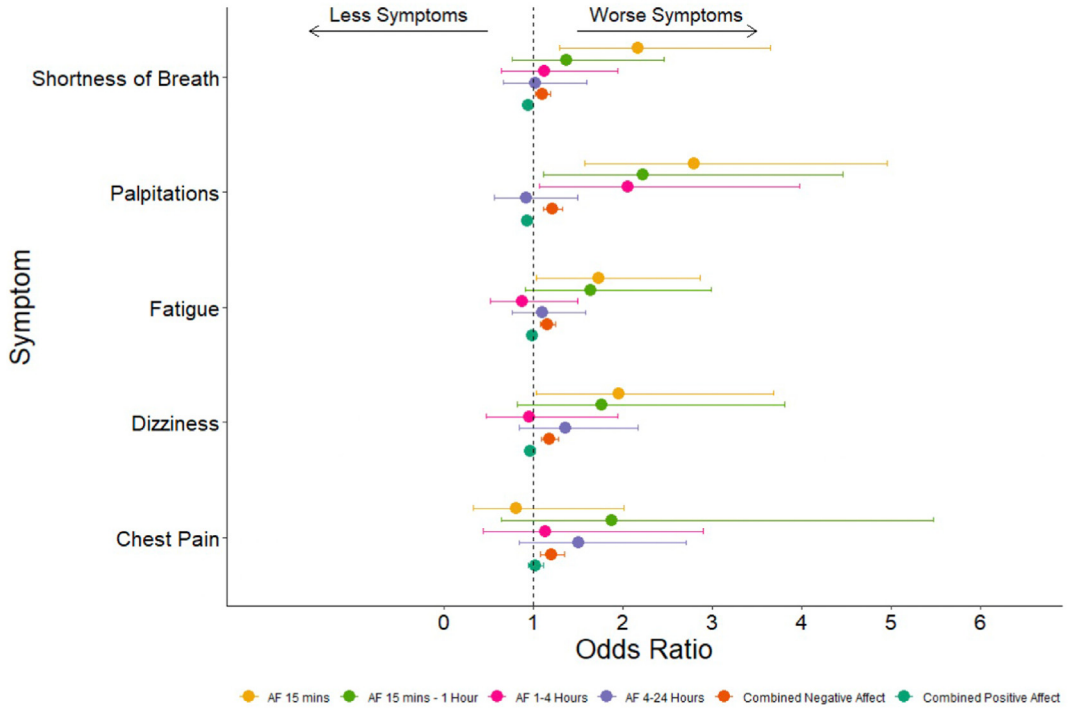

Figure 2 Multilevel model of symptoms as predicted by atrial fibrillation episode time epochs. Odds ratios with 95% confidence intervals obtained by the Wald test are shown (odds ratios given for age, sex, and body mass index are not shown).

$P = .046$) and palpitations (OR, 0.94 [95% CI, 0.89–0.99]; $P = .017$) when AF episodes were present within 15 minutes of reporting of symptoms (Supplemental Table 1).

Discussion

Data on temporal association of AF and symptoms are scarce. Here, we found the following: First, presence of AF within 15 minutes prior to reporting of symptoms was associated with worse symptoms, such as shortness of breath, palpitations, chest pain, dizziness/lightheadedness, and fatigue. Importantly, this relationship was very robust despite well-controlled median heart rates during AF. Secondly, the strength of the relationship between AF episodes and symptoms decreased as time from AF episodes to reporting of symptoms increased. Thirdly, negative affect was associated with worse symptoms, whereas positive affect was associated with less shortness of breath and palpitations within a timeframe of 15 minutes. Finally, we found that the association between palpitations and AF episodes remained significant up to 4 hours after AF episodes. Our study suggests that there is a significant association between timing of AF episodes and symptom in patients with AF; in this regard some symptoms are more temporally associated with AF than others.

The primary aim of most interventions for AF treatment is to improve symptoms and quality of life. However, these interventions are typically delivered with significant delay over the timeline of a particular AF episode. Our study highlights the importance of timing of AF episode occurrence as an important determinant of severity of symptoms in patients with AF. Therefore, effective therapeutic strategies require timely assessment and delivery close to the onset of a particular AF episode outside of the clinical setting. Current approaches for the assessment of symptoms during clinical visits require patients to summarize their experiences over a time period. The recall of an event can also be influenced by other events that are occurring after the recalled event, an individual's beliefs about the condition, and recency of events.[8] Our method of evaluation leveraging a digital tool to record symptoms at the time that the patient experiences them helps avoid recall bias and allows for evaluation of temporal relationship between heart rhythm and symptoms. Our observation is consistent with observations from other clinical conditions where patients report more severe symptoms closer to the onset of disease.[9]

We found that although all symptoms were associated with more severe symptoms within 15 minutes of AF episodes, palpitations remained strongly associated with AF up to 4 hours after. Palpitations may represent a more specific symptom for AF and result in worse symptoms attributed to AF episodes. Future interventions aimed at treating AF should consider the specific symptoms attributed to AF and its impact on the patient's overall quality of life.

We observed that positive and negative affect are temporally associated with worse symptoms. There is evidence that negative emotional states, specifically anxiety and depression, are linked to more severe symptoms in patients with AF.[10] We recently demonstrated that negative affect may be a stronger predictor of symptoms compared to arrhythmia burden in patients with AF.[5] Patient-reported symptoms are

Table 2 Odds ratio for the multilevel logistic model of symptoms as predicted by atrial fibrillation episode time epochs and affect

Predictors	Odds ratio (95% CI)	*P* value
Shortness of breath		
AF within 15 minutes	2.17 (1.29–3.65)	.003*
AF within 15 minutes – 1 hour	1.37 (0.76–2.46)	.290
AF within 1–4 hours	1.12 (0.64–1.94)	.688
AF within 4–24 hours	1.03 (0.66–1.59)	.900
Positive affect	0.95 (0.90–1.00)	.046*
Negative affect	1.10 (1.02–1.19)	.012*
Fatigue		
AF within 15 minutes	1.73 (1.04–2.87)	.034*
AF within 15 minutes – 1 hour	1.65 (0.91–2.99)	.101
AF within 1–4 hours	0.88 (0.52–1.49)	.629
AF within 4–24 hours	1.11 (0.77–1.59)	.584
Positive affect	0.98 (0.94–1.03)	.476
Negative affect	1.16 (1.08–1.25)	<.001*
Chest pain		
AF within 15 minutes	0.81 (0.32–2.02)	.645
AF within 15 minutes – 1 hour	1.88 (0.64–5.47)	.248
AF within 1–4 hours	1.13 (0.44–2.90)	.797
AF within 4–24 hours	1.51 (0.84–2.71)	.169
Positive affect	1.03 (0.95–1.12)	.516
Negative affect	1.21 (1.08–1.35)	.001*
Palpitations		
AF within 15 minutes	2.80 (1.58–4.96)	<.001*
AF within 15 minutes – 1 hour	2.23 (1.11–4.46)	.024*
AF within 1–4 hours	2.06 (1.07–3.98)	.032*
AF within 4–24 hours	0.92 (0.56–1.50)	.733
Positive affect	0.94 (0.89–0.99)	.017*
Negative affect	1.21 (1.12–1.32)	<.001*
Dizziness/lightheadedness		
AF within 15 minutes	1.96 (1.04–3.68)	.038*
AF within 15 minutes to 1 hour	1.77 (0.82–3.81)	.146
AF within 1–4 hours	0.96 (0.47–1.95)	.902
AF within 4–24 hours	1.36 (0.85–2.17)	.204
Positive affect	0.97 (0.91–1.02)	.230
Negative affect	1.19 (1.09–1.28)	<.001*

AF = atrial fibrillation.
*Indicates statistical significance.

complex processes that involve behavioral, physiological, emotional, and cognitive processes that evolve and change over time. Effective interventions aimed at treating AF symptoms should include timely interventions focused on treating emotions as well symptoms.

The primary aim of most interventions for AF is to improve symptoms and quality of life. However, these interventions are typically delivered with significant delays after onset of AF episodes. Our study highlights the importance of timing of AF episodes as an important determinant of severity of symptoms in patients with AF. Therefore, effective therapeutic strategies require timely assessment and may require delivery close to the onset of AF episodes outside of the clinical setting.

Our study should be interpreted in the context of the following limitations. First, we enrolled a relatively small number of patients; however, there were many total observations, given the follow-up period and frequent data collection (3622 completed random surveys collected from a total of 1210 days), leading to dense data that allowed for evaluation of temporal association of symptoms and AF episodes. Second, there is a need for larger study samples to evaluate the role of baseline physiologic and psychologic measures on patient-reported symptoms. Third, larger studies including patients with longer episodes of AF (less than 7 days and more than 24 hours) are needed to further elucidate the temporal relationship of symptoms and longer episodes of AF. Fourth, it is unclear whether these findings are stable over a longer period of observation. There is a need for long-term observational studies to assess the variability in symptoms, affect, and their relationship with heart rhythm over an extended period. Fifth, this is a single-center experience that also represents a patient population of a large academic practice in the United States.

Conclusion

There is a significant relationship between onset of AF episodes and reporting of symptoms. This association diminishes over time and varies across different symptoms. If confirmed in larger studies, these findings may inform AF interventions that target symptoms just in time prior to a clinical visit.

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Authorship

All authors attest they meet the current ICMJE criteria for authorship.

Patient Consent

All patients provided written informed consent.

Disclaimer

Given his role as Deputy Editor, Dr Hamid Ghanbari had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Dr David Duncker.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.cvdhj.2023.06.004.

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