

Feasibility of Extended Ambulatory Electrocardiogram Monitoring to Identify Silent Atrial Fibrillation in High-risk Patients: The Screening Study for Undiagnosed Atrial Fibrillation (STUDY-AF)

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ABSTRACT

Background: Identification of silent atrial fibrillation (AF) could prevent stroke and other sequelae.

Hypothesis: Screening for AF using continuous ambulatory electrocardiographic (ECG) monitoring can detect silent AF in asymptomatic in patients with known risk factors.

Methods: We performed a single-center prospective screening study using a wearable patch-based device that provides up to 2 weeks of continuous ambulatory ECG monitoring (iRhythm Technologies, Inc.). Inclusion criteria were age ≥ 55 years and ≥ 2 of the following risk factors: coronary disease, heart failure, hypertension, diabetes, sleep apnea. We excluded patients with prior AF, stroke, transient ischemic attack, implantable pacemaker or defibrillator, or with palpitations or syncope in the prior year.

Results: Out of 75 subjects (all male, age 69 ± 8.0 years; ejection fraction $57\% \pm 8.7\%$), AF was detected in 4 subjects (5.3%; AF burden $28\% \pm 48\%$). Atrial tachycardia (AT) was present in 67% (≥ 4 beats), 44% (≥ 8 beats), and 6.7% (≥ 60 seconds) of subjects. The combined diagnostic yield of sustained AT/AF was 11%. In subjects without sustained AT/AF, 11 (16%) had ≥ 30 supraventricular ectopic complexes per hour.

Conclusions: Outpatient extended ECG screening for asymptomatic AF is feasible, with AF identified in 1 in 20 subjects and sustained AT/AF identified in 1 in 9 subjects, respectively. We also found a high prevalence of asymptomatic AT and frequent supraventricular ectopic complexes, which may be relevant to development of AF or stroke. If confirmed in a larger study, primary screening for AF could have a significant impact on public health.

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and accounts for 15% of strokes.¹ However, 18% of AF-related strokes present with asymptomatic AF that is newly detected at the time of stroke.² Subclinical AF has been associated with similar morbidity and

mortality rates as symptomatic AF³ and with similar rates of silent embolic events.⁴ More recently, AF has been associated with silent cerebral infarcts and stroke among patients with type 2 diabetes mellitus (DM), even among patients age < 60 years with no history of cerebrovascular disease.⁵

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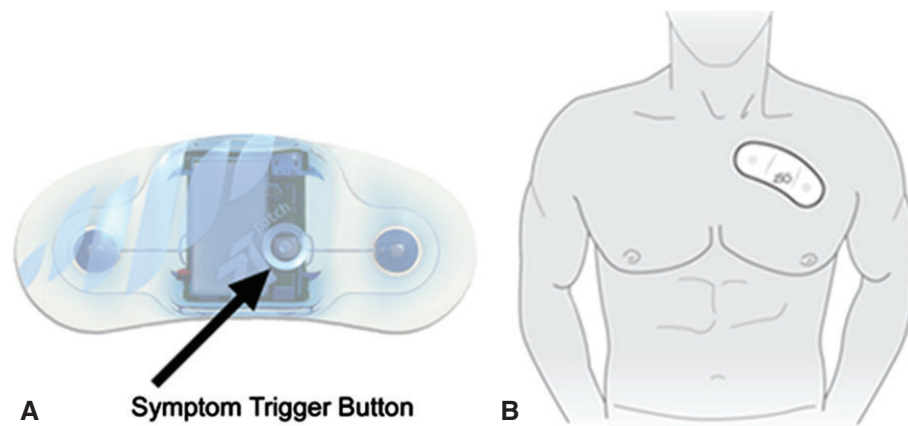


Figure 1. Zio patch symptom trigger button and device placement. Subjects were instructed to press the symptomatic event trigger (A) if symptoms such as dizziness, chest pain, shortness of breath, or heart palpitations developed during monitoring. Device placement (B) for the wearable adhesive patch-based device is over the patient's left pectoral region. (Images courtesy of iRhythm Technologies Inc., San Francisco, CA.)

International guidelines on primary prevention of AF-related stroke recommend opportunistic pulse detection in patients age ≥ 65 years.^{6,7} However, this diagnostic approach can be unreliable due to infrequent and inconsistent sampling, particularly among asymptomatic patients, who are less likely to seek medical care. Earlier detection of AF and anticoagulation could reduce the total public-health burden of treating stroke, particularly with the use of low-cost, noninvasive methods of screening.

We performed a prospective screening study to evaluate the feasibility of outpatient screening for AF using a small, wearable patch-based ambulatory electrocardiographic (ECG) monitoring device in patients with risk factors but no prior AF and no prior embolic history.

Methods

Study Design

The Screening Study for Undiagnosed Atrial Fibrillation (STUDY-AF) is a single-center, single-arm AF pilot screening study conducted at the Veterans Affairs (VA) Palo Alto Health Care System. Participants were enrolled between May 2012 and August 2013 from outpatient cardiology, echocardiography, and stress-testing clinics to participate in 2 weeks of continuous outpatient ambulatory monitoring. We chose inclusion and exclusion criteria for the study based on prior risk models^{8,9} to identify patients with risk factors but with no symptoms or medical history indicative of AF. All participants included in the study were ≥ 55 years old and had ≥ 2 of the following AF risk factors: coronary disease, heart failure, hypertension, DM, and sleep apnea (central, obstructive, or other). We excluded patients with previously documented AF, supraventricular tachycardia (SVT), stroke, transient ischemic attack, systemic embolism, palpitations or syncope in the 12 months prior to screening, or with presence of an implantable pacemaker or defibrillator. Candidates for enrollment were prescreened by a trained investigator (A.J.U.) using patient medical records to identify all prior medical history. Eligibility criteria were then confirmed by

direct subject interview. The study was approved by the local institutional review board and was conducted in accordance with the Declaration of Helsinki.

Monitoring was conducted using the Zio wearable patch-based device (iRhythm Technologies, Inc., San Francisco, CA; Figure 1), which records up to 14 days of uninterrupted monitoring on a single vector. Study subjects were instructed to press a symptomatic event trigger on the device if symptoms developed. Subjects were asked to wear the adhesive device for up to 14 days and then return the monitor by mail along with a patient diary detailing any symptoms.

Baseline characteristics including demographics, medical history, echocardiographic parameters, and health behaviors were abstracted from the patient medical record by 2 trained investigators (Table 1).

Outcomes

The primary outcome was the presence of AF identified with Zio patch monitoring. Each AF episode was defined as the presence of ≥ 30 seconds of continuous AF during monitoring. Arrhythmias were identified by the device using a 2-step process; these methods have been previously described.¹⁰ First, a digital signal processing algorithm is applied to the ECG data from continuous recording to identify candidate arrhythmia episodes. Potential arrhythmias are located using heart rate, irregularity, and morphology. The algorithm also includes heart rate increase from the preceding heart rate regularity (sinus rhythm) to confirm candidate episodes. Candidate AF episodes are therefore identified by the algorithm based on R-R irregularity. Onset of candidate AF episodes is identified by deviation of regularity from the preceding rhythm. Next, trained and certified cardiovascular technicians who are employed by the servicer confirm arrhythmia diagnoses and classify the arrhythmias as appropriate. Arrhythmia adjudication was performed for clinical findings by technicians with no knowledge of the present study. A board-certified cardiac electrophysiologist (M.P.T.) further adjudicated all arrhythmias. A prior study of simultaneous

Table 1. Baseline Characteristics (N = 75)

Characteristic	Value ^a
Age, y	69 ± 8.0
Male sex	75 (100)
BMI, kg/m ²	32 ± 4.9
Race	
White	67 (89)
Nonwhite	8 (11)
CHADS ₂ score	
0	2 (2.7)
1	22 (29)
2	37 (49)
3	11 (15)
4	3 (4.0)
5	0 (0.0)
6	0 (0.0)
CHA ₂ DS ₂ -VASc score	
0	0 (0.0)
1	2 (2.7)
2	14 (19)
3	29 (39)
4	19 (25)
5	9 (12)
6	2 (2.7)
7	0 (0.0)
8	0 (0.0)
9	0 (0.0)
CHF	13 (17)
Ischemic cardiomyopathy	5 (6.7)
Nonischemic cardiomyopathy	8 (11)
NYHA functional class	
I	10 (13)
II	3 (4.0)
III	0 (0.0)
IV	0 (0.0)
Hypertension	71 (95)
Age ≥75 years	15 (20)
DM	42 (56)
Coronary disease	58 (77)
Prior MI	26 (35)

Table 1. continued

Characteristic	Value ^a
Sleep apnea	25 (33)
COPD	12 (16)
Hyperlipidemia	71 (95)
LVEF, % (n = 60) ^b	57 ± 8.7
Moderate to severe LVH	10 (13)
History of significant valvular disease	24 (32)
Prior valve replacement	7 (9.3)
Family history of AF	3 (4.0)
Smoking history	
Current regular smoker	11 (15)
Past regular smoker	56 (75)
Alcohol use	42 (56)
Alcohol use, U/week	4.9 ± 12
Currently receiving AAD therapy	0 (0.0)
Received CABG	30 (40)
Received PCI	32 (43)

Abbreviations: AAD, antiarrhythmic drug; AF, atrial fibrillation or atrial flutter; BMI, body mass index; CABG, coronary artery bypass graft; CHADS₂, CHF, hypertension, age ≥75 years, DM, prior stroke/TIA or thromboembolism; CHA₂DS₂-VASc, CHF, hypertension, age >75 years, DM, prior stroke/TIA or systemic embolism, vascular disease, age 65–75 years, female sex; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SD, standard deviation; TIA, transient ischemic attack.

Data are presented as mean ± SD or n (%).

^aAll numbers and percentages calculated using all 75 subjects who completed monitoring unless otherwise specified (N = 75). ^bCalculated only for study subjects with echocardiographic data closest to device monitoring, within a window of 2 years before or 1 month after monitoring (n = 60).

Zio Patch and 3-channel Holter recordings has shown 100% sensitivity of AF detection by the Zio patch compared with Holter and high correlation in quantification of AF burden between both modalities ($r = 0.96$).¹¹

Secondary outcomes included SVTs, ventricular tachycardias (VTs), and supraventricular ectopy (SVE) during monitoring. For SVE, we used a binary threshold of ≥30 beats/hour, which has been shown to predict the development of AF.^{12,13} All episodes of SVT were further adjudicated by the same cardiac electrophysiologist into atrial tachycardia (AT) or other SVTs.

Statistical Analysis

Proportions and means were compared using the χ^2 test and t test with unequal variance, respectively. P values <0.05 were considered significant. All analyses were performed

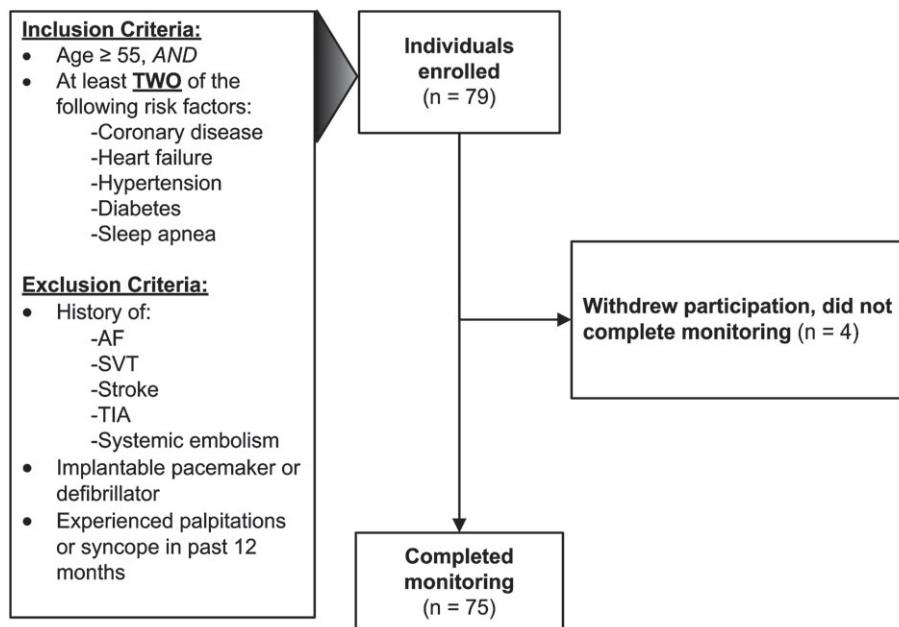


Figure 2. The study flow chart shows detailed inclusion and exclusion criteria for study participation and completion. Abbreviations: AF, atrial fibrillation; SVT, supraventricular tachycardia; TIA, transient ischemic attack.

using STATA software version 11.0 (StataCorp, College Station, TX).

Results

We enrolled 79 subjects, and a total of 75 subjects (mean age, 69 ± 8 years; 100% male) completed monitoring (Figure 2). Of subjects that did not complete monitoring, 1 subject lost the device during use, 2 subjects lost devices by mail, and 1 subject returned the device without any recorded data. All 4 subjects were given an option to wear a replacement Zio patch but declined. Baseline characteristics for the 75 subjects who completed monitoring are shown in Table 1. The majority of subjects were at moderate to high risk of stroke and met indications for anticoagulation based on current guidelines ($\text{CHADS}_2 \geq 1$ in 97% of subjects; $\text{CHA}_2\text{DS}_2\text{-VASc} \geq 2$ in 97% of subjects).^{14,15}

The median and mean device wear time was 13 days (interquartile range, 7.8–14 days) and 10.4 ± 4.5 days, respectively. The median percent analyzable time was 98% (interquartile range, 93%–99%). Nine subjects (12%) experienced skin irritation at the site of the adhesive-based device. Of these, 2 discontinued device monitoring early, and the remaining 7 subjects continued monitoring until the end of the 2 weeks or until the device lost its adhesion to the skin. In all cases, skin irritation resolved without need for medical intervention. No other adverse events were reported.

Detected arrhythmia events during monitoring are shown in Table 2. Overall, any arrhythmia of ≥ 8 consecutive beats was detected in 36 subjects (48%); 18 subjects (24%) had no arrhythmias. Atrial fibrillation was detected in 4 subjects (5.3%; all with $\text{CHADS}_2 \geq 1$ and $\text{CHA}_2\text{DS}_2\text{-VASc}$ score ≥ 2), with mean AF burden of $28\% \pm 48\%$ and mean heart rates of 70 ± 7.2 bpm (152 ± 31 bpm maximum; 44 ± 10 bpm

minimum). All 4 patients who were detected with AF had ≥ 1 episode in the first 48 hours, and 3 of 4 experienced the longest episode after the first 48 hours of monitoring. An additional 26 participants (35%) experienced an initial arrhythmia other than AF after the first 48 hours. No subjects reported symptoms during AF episodes.

All episodes of SVT were AT; no other forms of SVT were identified. Atrial tachycardia ≥ 4 and ≥ 8 beats was observed in 50 (67%) and 33 (44%) subjects, respectively. Sustained AT (≥ 60 seconds) was observed in 5 (6.7%) subjects, with 1 subject experiencing AT ≥ 6 minutes. Combining sustained AF and AT ≥ 60 seconds, the total diagnostic yield was 11% (8 of 75). All 8 of these subjects had a $\text{CHA}_2\text{DS}_2\text{-VASc}$ score ≥ 2 and CHADS_2 score ≥ 1 .

Supraventricular ectopy was detected in 74 of 75 subjects (99%) overall and in 67 of 67 subjects without sustained AT/AF. There was considerable variation in number of SVE complexes per hour (mean, 36 ± 129 ; range, 0.0–1023). Supraventricular ectopy of ≥ 30 beats/hour was present in 15 of 75 study participants (20%), 14 of 71 (20%) without AF, and 11 of 67 (16%) without sustained AT or AF.

Nonsustained ventricular tachycardia (NSVT) of ≥ 4 beats was detected in a total of 17 subjects (23%), and NSVT ≥ 8 beats was found in 6 (8.0%) subjects. No sustained VT was detected. Three sample ECG strips are shown, exhibiting episodes of AF (Figure 3A), sustained SVT that was determined to be AT (Figure 3B), and NSVT (Figure 3C) detected in separate study participants.

Discussion

We found that among study participants, all with age ≥ 55 years and ≥ 2 AF risk factors, 5.3% had AF and 11% had sustained AT or AF after screening with up to 14 days of continuous ECG monitoring. We found a high prevalence of

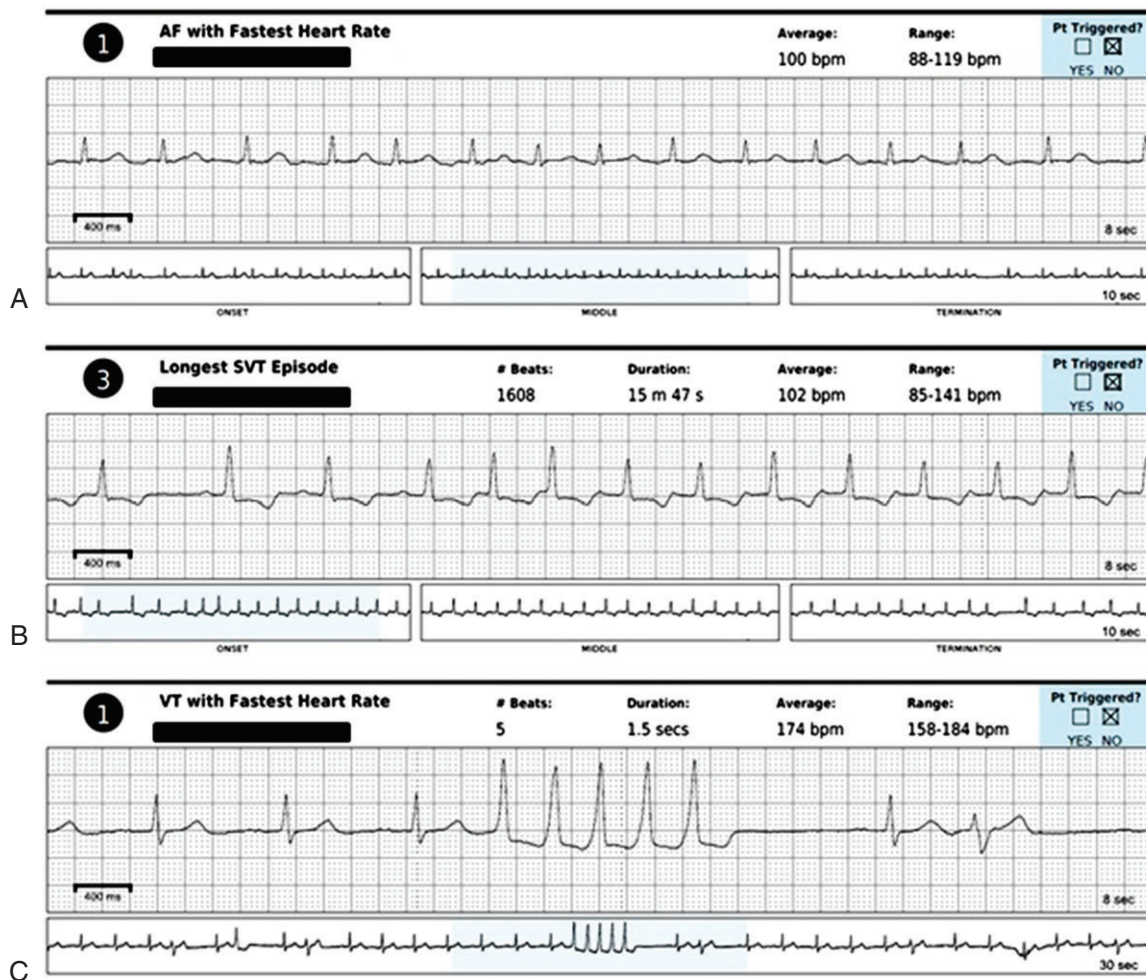


Figure 3. Sample rhythm strips exhibiting episodes of (A) AF, (B) sustained SVT that was determined to be AT, and (C) NSVT detected in separate study participants. Abbreviations: AF, atrial fibrillation; AT, atrial tachycardia; NSVT, nonsustained ventricular tachycardia; SVT, supraventricular tachycardia.

nonsustained AT in our cohort, with 2 in 3 subjects having ≥ 1 episode ≥ 4 beats during monitoring. These findings confirm that targeted extended ambulatory ECG screening in patients at risk of AF is feasible and can generate a clinically meaningful diagnostic yield.

Previous comparable studies of outpatient AF screening have used thumb-based ECG devices that provide intermittent ECG readings. In one study, AF was found in 12 of 606 (2.0%) patients, although a younger and healthier study population and shorter monitoring duration (2 days) may explain the low diagnostic yield.¹⁶ A subsequent study using the same ECG device in a select Swedish cohort with no known history of AF reported new AF in 30 patients (7.4%) over a monitoring period of 14 days.¹⁷ Although AF was more frequently detected in the study, the cohort was restricted to patients age ≥ 75 years and CHADS₂ score ≥ 2 . Stroke was also not an exclusion criterion. Other smaller AF screening studies have focused on select populations with prior stroke or transient ischemic attack, rather than general populations.^{18–22} Among these studies, prevalence of new paroxysmal AF has ranged from 5% to 20%, with detection rates typically increasing with greater follow-up

time.²³ However, the higher yield is expected given the greater likelihood of subclinical AF that may be causally linked to the embolic event.

More traditional AF screening studies have relied on standard ECGs or Holter monitor devices for screening. The largest systematic review to combine data from 30 cross-sectional studies ($n = 122\,571$) found an overall incidence of undiagnosed AF at 1.0% in the general population, increasing to 1.4% in patients age ≥ 65 years with 2-lead, 7-lead, or 12-lead ECG screening.²⁴ As with most ECG-based studies that assess presence of AF at a single time point, the key limitation is the difficulty in detecting arrhythmias that are paroxysmal.^{3,4} For example, 3 of 4 participants with AF in our study experienced the longest AF episode outside of the first 48 hours of monitoring, and 35% experienced an initial arrhythmia other than AF after the first 48 hours.

In context, our data suggest that targeted and extended screening based on risk factors for AF and stroke can increase yield compared with screening a general adult population, though larger confirmatory studies are necessary. Targeted screening can be particularly cost-effective, as anti-coagulation has been repeatedly shown to reduce stroke,

Table 2. Primary and Secondary Outcomes (N = 75)

Outcome	Value ^a
Atrial arrhythmias	
Sustained AF or AT, ≥ 60 seconds	8 (11)
AF	4 (5.3)
AF burden, (n = 4) ^b	28% \pm 48%
AF burden, (n = 4) ^b	6.0% (1.5%–54.5%)
HR, mean \pm SD, (n = 4) ^b	70 \pm 7.2
Maximum HR, mean \pm SD, (n = 4) ^b	152 \pm 31
Minimum HR, mean \pm SD, (n = 4) ^b	44 \pm 10
Sustained AT, ≥ 60 seconds	5 (6.7)
AT ≥ 30 seconds	6 (8.0)
AT ≥ 8 beats	33 (44)
AT ≥ 4 beats	50 (67)
SVE beats	
SVE, any	74 (99)
Hourly SVE count ≥ 30 beats/hour	15 (20)
Hourly SVE count ≥ 30 beats/hour in subjects without AF (n = 71) ^c	14 (20)
Hourly SVE count ≥ 30 beats/hour in subjects without sustained AF or AT ≥ 60 seconds (n = 67) ^d	11 (16)
Hourly SVE count	36 \pm 129
Total SVE burden	0.8% \pm 2.8%
Ventricular arrhythmias	
VT ≥ 60 seconds	0 (0.0)
VT ≥ 30 seconds	0 (0.0)
NSVT ≥ 8 beats	6 (8.0)
NSVT ≥ 4 beats	17 (23)
PVCs	
Hourly PVC count	72 \pm 204
Total PVC burden	1.7% \pm 4.5%
Any arrhythmia ≥ 8 beats	36 (48)
First arrhythmia after 48 hours of monitoring	26 (35)
3-second pauses	2 (2.7)
No arrhythmias	18 (24)

Abbreviations: AF, atrial fibrillation or atrial flutter; AT, atrial tachycardia; HR, heart rate; IQR, interquartile range; NSVT, nonsustained ventricular tachycardia; PVC, premature ventricular contraction; SD, standard deviation; SVE, supraventricular ectopy; VT, ventricular tachycardia.

Data are presented as mean \pm SD, n (%), or median (IQR).

^aAll numbers and percentages calculated using all 75 subjects unless otherwise specified (N = 75). ^bCalculated only for study subjects with AF (n = 4). ^cCalculated based on 71 study subjects who did not have AF detected during monitoring (n = 71). ^dCalculated based on 67 study subjects who did not have sustained AF or AT (≥ 60 seconds) detected during monitoring (n = 67).

mortality, and costs of care,^{25–27} whereas new oral anti-coagulants such as dabigatran, rivaroxaban, and apixaban help address the typical practical considerations that make anticoagulation unsuitable in some low-risk patients.²⁸

Multiple studies currently in progress may help to establish more effective target groups for AF screening and stroke prevention. First, the Population Screening of 75- and 76-Year-Old Men and Women for Silent Atrial Fibrillation (STROKE-STOP) study in Sweden will evaluate whether intermittent ambulatory ECG screening for AF in men and women age 75 to 76 years can reduce stroke incidence.²⁹ Other studies, such as Incidence of AF in High-Risk Patients (REVEAL-AF), will conduct targeted screening using implantable technology and will screen patients based on preexisting symptoms and demographic risk factors rather than a narrow target age.³⁰ Data from these and other screening studies will clarify the overall cost-benefit of preventive AF-detection strategies and will help identify specific patient profiles that are likely to develop future AF.

Atrial Tachyarrhythmias and Stroke Risk

We found a high prevalence of asymptomatic AT in our cohort. The Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT) previously linked subclinical atrial tachyarrhythmias with increased risk of clinical AF or stroke.³¹ Only 1 subject in our study experienced an episode of AT meeting ASSERT detection criteria (≥ 6 minutes), but 5 experienced sustained episodes of >60 seconds. The significance of shorter episodes of AT remains unclear but could represent a precursor for the development of sustained AT or AF, thereby indicating a patient population that may benefit from ongoing AF surveillance.

In addition to asymptomatic AT, we found that 8 subjects (11%) were detected with asymptomatic, sustained AT/AF during monitoring. In The Relationship Between Daily Atrial Tachyarrhythmia Burden From Implantable Device Diagnostics and Stroke (TRENDS) study, an AT/AF burden of 5.5 hours over a 30-day period was associated with twice the annualized risk of thromboembolic events (TE) compared with no AT/AF (2.4% vs 1.1%; $P < 0.001$).³² A separate subgroup analysis of TRENDS reported that 28% of patients with prior TE in the cohort were newly detected with AT/AF during the study.³³ These findings suggest a link between sustained AT/AF and stroke in a clinical setting; however, the difference in time to TE was not statistically significant between patients with high AT/AF burden vs no AT/AF burden in the TRENDS study (adjusted hazard ratio: 2.20, 95% confidence interval: 0.96–5.05, $P = 0.06$).

Additional studies are needed to clarify the mechanism of increased thromboembolic risk with AT/AF. For example, the Multicenter, Randomized Study of Anticoagulation Guided By Remote Rhythm Monitoring in Patients With Implantable Cardioverter-Defibrillator and Resynchronization Devices (IMPACT) will use remote telemonitoring to detect atrial high-rate episodes and assess the impact of early anticoagulation in the intervention group.³⁴ This study may also clarify whether higher stroke risk in patients with

AF is related to factors other than atrial arrhythmia burden alone.

Supraventricular Ectopy

A secondary finding of our study was that 16% of patients without sustained AT/AF had an SVE count ≥ 30 /hour. An atrial premature complexes (APC) count ≥ 30 /hour predicts 15-year risk of AF with 90% specificity,¹³ and most SVE beats are usually APCs.¹² Recently, APCs have been found to significantly improve AF risk discrimination when added to the Framingham AF risk score. Therefore, high SVE count, along with AT detection, may identify patients at high risk for future AF.

Nonsustained Ventricular Tachycardia

Nonsustained ventricular tachycardia of ≥ 4 beats and ≥ 8 beats were detected in 23% and 8% of participants, respectively. These NSVT episodes are of uncertain clinical significance in this population and merit longitudinal investigation.

Study Limitations

In this study of Veteran Affairs Health Care System patients, all participants were male, which may limit the generalizability to women. The sample size of this study was underpowered to evaluate individual risk factors or create risk models for detection of AF. Finally, although events were carefully adjudicated by a board-certified cardiac electrophysiologist, classification of SVT or SVE using a single-vector ambulatory monitor can be difficult, because P waves are not as easily discernible as with a standard 12-lead ECG.

Conclusion

Extended outpatient ECG screening for asymptomatic AF in targeted moderate-risk to high-risk patients is feasible, with AF detected in 1 in 20 subjects with up to 2 weeks of monitoring. We also detected sustained AT/AF in 1 in 9 study subjects. If confirmed in a larger study, then primary screening for AF could have a significant impact on public health.

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