Relation of Antecedent Symptoms to the Likelihood of Detecting Subclinical Atrial Fibrillation With Inserted Cardiac Monitors

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Atrial fibrillation (AF) comes to attention clinically during an evaluation of symptoms, an evaluation of its adverse outcomes, or because of incidental detection during a routine examination or electrocardiogram. However, a notable number of additional individuals have AF that has not yet been clinically apparent or suspect—subclinical AF (SCAF). SCAF has been recognized during interrogation of pacemakers and defibrillators. More recently, SCAF has been demonstrated in prospective studies with long-term monitors—both external and implanted. The REVEAL AF trial enrolled a demographically "enriched" population that underwent monitoring for up to 3 years with an insertable cardiac monitor. SCAF was noted in 40% by 30 months. None of these patients had AF known before the study; however, some had nonspecific symptoms common to patients with known AF. The current study assessed whether patients with versus without such symptoms were more likely to have SCAF detected. We found that only palpitations had an association with AF detection when controlling for other baseline symptoms (hazard ratio 1.61 (95% confidence interval 1.12 to 2.32; p = 0.011). No other prescreening symptoms evaluated were associated with an increased likelihood of SCAF detection although patients without detected SCAF had an even higher frequency of symptoms than those with detected SCAF. Thus, REVEAL AF demonstrated that the presence of palpitations is associated with an increased likelihood of SCAF whereas other common symptoms are not; and, symptoms, per se, may more likely be consequent to associated disorders than they are a direct consequence of SCAF. **(Am J Cardiol 2021;145:64–68)**

Atrial fibrillation (AF), our most common sustained tachyarrhythmia, may become clinically apparent through evaluation of arrhythmia-associated symptoms and/or arrhythmia-associated adverse outcomes.[1–10] AF may also be clinically recognized although asymptomatic (so-called "silent" AF), via incidental detection during a routine electrocardiographic recording or assessment of an asymptomatic pulse irregularity. In yet additional patients, AF may be subclinical (SCAF), ie, not yet clinically apparent or suspect. SCAF has been documented and characterized with the use of repetitive or prolonged electrocardiographic monitoring.[3,4,11–18] SCAF rates have been highest—up to 40% by 30 months—using continuously recording insertable cardiac monitors (ICM) in "enriched populations" selected utilizing a combination of demographic, laboratory, and/or imaging characteristics commonly present in populations of patient with AF.[11–15] In such trials comparison of the patients in whom SCAF was detected versus those in which SCAF was not detected suggests that certain characteristics may be predictive for SCAF, including older age, male gender, higher body mass index (BMI), higher Troponin-T and NT-proBNP levels, and some specific genetic markers.[11–19] Yet, these alone did not fully separate SCAF positive versus negative patients, thereby suggesting that additional predictive markers might be sought. We hypothesized that patients who reported symptoms would be more likely to have SCAF detected. Thus, in our trial, REVEAL AF,[13] an evaluation of symptoms noted by patients, if any were, was also assessed re: predictive value, and our observations form the basis of this manuscript.

Methods

The REVEAL AF study (ClinicalTrials.gov NCT01727297) was a prospective, single-arm, open-label, multicenter trial performed in 57 centers in the United

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See page 67 for disclosure information.

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States and Europe. The study protocol was approved by all relevant institutional review boards or ethics committees. All patients provided written informed consent before randomization. Since the study design and primary results have already been reported,[13,20] they will be only briefly reviewed here. The REVEAL AF study assessed the presence of SCAF in a demographically defined high-risk population as frequently encountered clinically using an ICM that provided continuous recording for up to 36 months. The AF detection algorithm and performance of the 2 devices used in this study have been described in detail. Briefly, compared to Holter monitoring, the ICM correctly identified AF in 97.4% (Reveal LINQ) and 96.1% (Reveal XT) of patients (diagnostic sensitivity) and correctly excluded AF in 97.0% (Reveal LINQ) and 85.4% (Reveal XT) of patients (diagnostic specificity). The reported overall accuracy to detect durations of AF was 99.4% and 98.5% for Reveal LINQ and Reveal XT, respectively.[19]

Participants were *≥18 years old with no AF history but deemed at risk for AF* based on demographic characteristics, with or without symptoms. Importantly, all patients were recruited based on risk factors, independent of symptoms. All patients had either a $CHADS_2$ score ≥3 or a score of 2 with ≥1 of the following risk factors: coronary artery disease, renal impairment, sleep apnea, and/or chronic obstructive pulmonary disease. Patients were excluded if they had any history of AF, an ischemic stroke or TIA in the previous 12 months, a history of hemorrhagic stroke, were taking oral anticoagulation, had contraindications to oral anticoagulation, or had another implanted cardiac device. All patients underwent ≥24 hours of external monitoring within 90 days before enrollment or before ICM insertion; detection of any AF also led to exclusion. The follow-up period was 18 to 30 months of ICM monitoring with monthly remote transmissions and in-person visits every 6 months plus additional visits if needed for any reason. The primary endpoint was the incidence of adjudicated AF ≥6 minutes in duration at 18 months detected by the ICM (Reveal XT or Reveal LINQ). Other exploratory endpoints included AF incidence at 6, 12, 24, and 30 months and assessment of predictors of AF detection. In the primary results manuscript, we reported that SCAF was encountered more often in older subjects and in those with elevated BMIs. In a separate manuscript, prediction by genetic profiling will be reported. For this present study, we examined the role of specific symptoms (Table 1) encountered during the 3 months before enrollment with respect to prediction of SCAF detection. More specifically, our purpose was to characterize AF detection rates in patients with versus without AF-compatible symptoms at baseline, and, to assess the predictive value of specific symptoms for AF detection in the REVEAL AF study.

Kaplan-Meier estimates were used to compare AF detection rates between patients with versus without compatible symptoms at baseline. Cox proportional hazards modeling was used to assess if individual baseline symptoms predicted the detection of SCAF, after adjusting for other baseline symptoms. Pearson's chi-square test was used to compare qualitative baseline demographics and co-morbidities between patients with and without baseline symptoms. Mann-Whitney was used to do the same for quantitative measures.

Table 1
Baseline demographics, medical history, and specific symptoms in patients with and without symptoms at baseline

	Baseline symptoms	
Demographics, mean +/- SD	Yes (n = 346)	No (n = 39)
Age	71.2 +/- 10.0	74.1 +/- 8.2
Body mass index (kg/m^2)	31.5 +/- 6.6	29.0 +/- 5.0
$CHADS_2$ score	3.0 +/- 1.0	3.0 +/- 0.9
CHA_2DS_2-VASc score	4.4 +/- 1.3	4.3 +/- 1.2
Men	172 (49.7%)	29 (74.4%)
Renal dysfunction	150 (43.4%)	15 (38.5%)
Heart failure	74 (21.4%)	7 (18.0%)
Coronary artery disease	205 (59.3%)	26 (66.7%)
Chronic obstructive pulmonary disease	69 (19.9%)	7 (18.0%)
Hypertension	322 (93.1%)	38 (97.4%)
Sleep apnea	96 (27.8%)	7 (18.0%)
Diabetes mellitus	221 (63.9%)	25 (64.1%)
Remote stroke	69 (19.9%)	10 (25.6%)
Transient ischemic attack	71 (20.5%)	4 (10.3%)
Symptoms		
Palpitations	198 (57.2%)	0
Fatigue	117 (33.8%)	0
Chest pain	78 (22.5%)	0
Rapid heartbeat	80 (23.1%)	0
Syncope	72 (20.8%)	0
Dizziness/lightheadedness	140 (40.5%)	0
Dyspnea	140 (40.5%)	0
Other	19 (5.5%)	0

Results

A total of 346 patients (age 71.2 ± 10.0 years, 50% male) with and 39 patients (age 74.1 ± 8.2 years, 74% male) without arrhythmia-compatible symptoms (Table 1) at baseline received an ICM and were followed for 22.4 ± 8.0 months. Baseline demographics and medical histories are also shown in Table 1.

Baseline $CHADS_2$ scores of 2, 3, and 4 or more were numerically but not statistically different between symptomatic (40.2%, 33.0%, 26.9%) and asymptomatic (33.3%, 38.5%, 28.2%) patients (p = 0.69). AF was detected in 6.5% of the entire cohort at 30 days whereas by 12 months, >20% of both cohorts experienced AF. At 18 months, the AF detection rates for symptomatic versus asymptomatic patients were 30.6% versus 23.6% (p = 0.44; Figure 1). In both groups, the majority of AF detection occurred beyond the recording time frame of traditional external monitors. With respect to the symptoms we examined in our multivariate analysis, only palpitations had an association with AF detection when controlling for other baseline symptoms (Table 2). The hazard ratio was 1.61 (95% confidence interval 1.12 to 2.32; p=0.011) for palpitations but did not reach statistical significance for fatigue, chest pain, rapid heartbeat, syncope, dizziness/lightheadedness, presyncope, dyspnea, or any other baseline complaint. Interestingly, while the sense of palpitations was the most frequently reported symptom in patients with SCAF detected and the least frequently reported symptom in patients without SCAF detected (Table 3), palpitations were reported more often by patients without SCAF (60.6%) than by patients with detected SCAF (39.4%). Moreover, all symptoms were

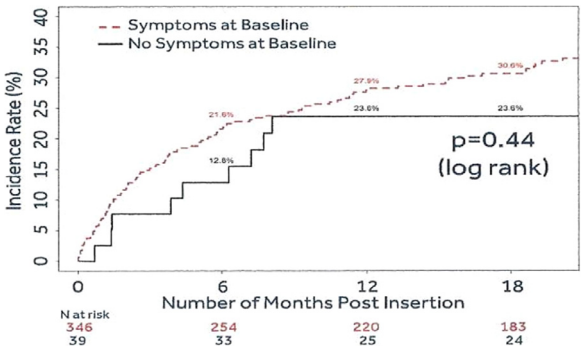

Figure 1.

reported more frequently by patients without detection of any AF compared with those with SCAF detected (Table 3).

Discussion

The majority of AF patients are symptomatic. When symptomatic, most complain of palpitations, chest discomfort, dyspnea, fatigue, exercise limitations, and/or lightheadedness.[1–10] Yet, none of these symptoms are specific for AF and only palpitations have been reliably reported in "lone AF."

Importantly, several sources suggest that symptoms are commonly temporally discordant with respect to AF episodes indicating that a direct symptom-AF relationship may not be present.[21,22] Mehall et al, for example,[21] reported that in 50 AF patients who underwent continuous monitoring while simultaneously recording any symptoms in an electronic diary, only 52% of the symptomatic events were concordant with AF. Certainly, the common underlying co-morbidities rather than AF per se could be the proximate cause of some symptoms such as dyspnea, chest discomfort, fatigue, lightheadedness, and more. This concept is likely the explanation for our observations (Table 3) that (1) only the minority of patients with SCAF detected in our study had symptoms; (2) only palpitations but no other symptom had a statistically significant relationship with SCAF detection (Table 2); (3) the majority of patients with symptoms did not have SCAF (Table 3) although most had one or more underlying co-morbidity that could serve as a cause of the symptoms reported; and (4) as many or more patients without SCAF than patients with SCAF were symptomatic and had the same symptom list. Finally, one might surmise that as co-morbidities become more numerous and/or severe, AF events will become longer and more clinically apparent, and that in these circumstances, AF may more likely become more directly and synergistically contributory to symptom presentation.

Table 2
Only palpitations had an association with subclinical atrial fibrillation (SCAF) detection when controlling for other baseline symptoms

Symptoms	Hazard ratio (95% CI)	p value
Palpitations	1.61 (1.12-2.32)	0.011
Fatigue	0.65 (0.42-1.01)	0.056
Chest pain	0.66 (0.39-1.09)	0.104
Rapid heartbeat	0.70 (0.43-1.13)	0.141
Syncope	0.74 (0.44-1.23)	0.247
Dizziness/lightheadedness	1.20 (0.81-1.78)	0.369
Dyspnea	1.02 (0.67-1.55)	0.917
Other	1.10 (0.51-2.41)	0.805

Table 3
Percent of patients by baseline symptom that had atrial fibrillation (AF) detected

Symptoms (n = 346)	AF detected
Palpitations	39.4%
Other	36.8%
Dizziness/lightheadedness	32.9%
Dyspnea	30.7%
Chest pain	26.9%
Fatigue	26.5%
Syncope	26.4%
Rapid heartbeat	26.3%

Relatedly, not all forms of AF tend to have the same symptoms. One large registry reported that symptoms were noted more often in paroxysmal AF (77%) than persistent AF patients (71%) and that the reported symptoms differed.[8] Paroxysmal AF patients were more likely to complain of palpitations (70% vs 50%) and/or chest discomfort (23% vs 16%) while persistent AF patients were more likely to complain of dyspnea (55% vs 43%), fatigue (51% vs 41%), and exercise intolerance (29% vs 19%).[8] Permanent AF patients were even less likely to note palpitations,[1,9,23] an observation that has been repeatedly confirmed.[1,5] Thus, patients can lose awareness of the sense of an altered heart rhythm in their chest over time when AF lasts longer. Our results additionally suggest that short paroxysmal AF episodes are not associated with palpitations in most patients. Interestingly, patients with asymptomatic AF have been reported to have more adverse outcomes than those with symptomatic AF,[24] likely because of the absence of prophylactic therapies such as chronic anticoagulation or rate control agents.

As suggested above, some symptoms, other than palpitations, may relate to the associated underlying cardiovascular co-morbidities and their pathophysiology[1–4,25,26] and/or side effects of medications, such as beta blockers.[1–4] Notably, palpitations are not dependent upon the underlying state of the atria or the ventricles for their sensation. Thus, palpitations might be the most likely symptom to be noted by patients with SCAF, if any are, and accordingly to be the most likely symptom to suggest the presence of SCAF on monitoring—as was the case in REVEAL AF and one other recent non-ICM trial.[13,27] Clinically, this suggests that when monitoring for SCAF, even when choosing a population "enriched" by demographic, echocardiographic, other laboratory, and/or genetic characteristics, there might be an even higher yield in patients who also note palpitations.

Like all studies, ours has some limitations. First, the study is limited by all the issues known to affect investigations that are retrospective rather than prospective, and post hoc subanalyses rather than planned primary or secondary analyses. Second, monitoring was not in place during the pre-enrollment period from which the history of symptoms was elicited. Thus, we cannot be certain that the symptoms, even palpitations, were necessarily produced in

association with a period of SCAF. That the symptoms and periods of AF may not be temporally concordant, however, may not matter with respect to our observations as discordance between symptoms and AF arrhythmic periods has been repeatedly reported.[21,22] One may have asymptomatic AF and symptoms from another mechanism. Nonetheless, that does not negate the significant predictive observation that we made regarding palpitations. Third, we did not collect a symptom diary during the time the patient underwent ICM monitoring. Thus, we cannot use the detected SCAF episodes to further assess any relationship with symptoms. Fourth, although the symptoms listed in Tables 1 and 2 are listed individually, some patients had more than one. However, since we were examining each type of symptom as a predictor, we assessed them separately. We recognize that we might have tried to analyze the predictive capability of combinations of symptoms or some categorical number of symptoms, or the like. However, the various possibilities would have been quite large and the numbers in some likely too small to be meaningful. Moreover, our analysis was done so as to possibly help clinicians; and, busy clinicians are unlikely to take the time to calculate outcomes based upon multiple combined factors. Fifth, our study was not designed to assess the degree to which the history of palpitations added to the predictive accuracy of the combination of other known predictors, including age and BMI which were predictors of SCAF in REVEAL AF. Lastly, since our trial only dealt with device-detected SCAF, we cannot know whether or not these same relationships hold with longer episodes of clinically apparent AF.

In conclusion, given the costs involved in screening and the desire to avoid its inconvenience in a low yield population, especially a population in whom the finding of AF would not likely result in high prognostic value or clinical intervention, maximizing the monitoring's value by choosing the highest risk population would seem worthwhile.[26,28] Based on our observations, in defining such populations, complaints of palpitations would appear to be helpful to ascertain. If one is not certain as to whether or not an "enriched" population is at high enough risk to make screening useful, our findings suggest that the addition of palpitations to the patient's history should push one toward screening. Finally, in a patient with symptoms that are commonly reported by patients with AF, our data confirm that the astute clinician should not assume AF is the cause even if AF is detected. Although AF may be present in such patients, and should be considered, especially if the symptom is palpitations, adequate attention needs to be paid to the potential contribution from any underlying co-morbidities.

Author Contribution

Each of the authors listed contributed to the conception of the manuscript, writing and review of the manuscript, and consented to its submission.

Disclosures

During the past year:

James Reiffel: Investigator for Medtronic, Janssen, and Sanofi. Consultancy for Medtronic, Sanofi, Acension, Correvio, and Amarin.

Atul Verma: Consultancy for Bayer, Biosense Webster, Medtronic, Thermedical, Ablacon, Volta Medical. Grants from Bayer, Biosense Webster, Biotronic, Medtronic. Speaker fees from Servier.

Peter Kowey: Consultancy for Medtronic, equity interest in Biotelemetry, Steering Committee for the Apple Heart Watch Study

Jonathan Halperin: Consultancy for Bayer AG Healthcare, Boehringer Ingelheim, Johnson & Johnson, Ortho-McNeil-Janssen Pharmaceuticals, Abbott

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Erika Pouliot and Paul D. Ziegler are employed by, and stock owners of, Medtronic.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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