Changes in Management Following Detection of Previously Unknown Atrial Fibrillation by an Insertable Cardiac Monitor (from the REVEAL AF Study)

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The REVEAL AF study demonstrated a high incidence of previously undetected atrial fibrillation (AF) using insertable cardiac monitors (ICMs) in patients with risk factors for AF and stroke. This analysis evaluated whether ICM monitoring led to changes in clinical management after AF detection. Patients with $CHADS_2$ scores ≥3 (or =2 with ≥1 additional AF risk factor) but no history of AF received an ICM and were followed 18 to 30 months. Physicians recorded changes in clinical management in response to AF detection at scheduled (every 6 months) and unscheduled follow-up visits. Changes in clinical management included oral anticoagulation, rhythm or rate control pharmacotherapy, cardioversion, ablation, and cardiac subspecialist referral. In 387 patients who met inclusion criteria and received an ICM, AF was found in 115. A change in clinical management was taken in 87 patients with AF (76%). In 80 of these 87, a change was taken at the first visit after AF detection. In total, 31 patients (27%) with AF had ≥2 visits at which changes in clinical management were taken. The most common change was initiation of oral anticoagulation (n = 73, 63% of patients with AF). Patients with a change in clinical management at the first visit after AF detection tended to have longer AF episodes and a higher maximal daily AF burden compared with AF patients for whom no change was taken (longest episode: 52 vs 28 minutes; maximal daily AF burden:112 vs 23 minutes). Changes in management more frequently occurred at visits where patients reported AF-compatible symptoms (65% vs 46% of visits, p = 0.01). In conclusion, ICM monitoring to identify AF guides both immediate and long-term patient management in a population at high risk for stroke. **(Am J Cardiol 2019;124:864−870)**

Atrial fibrillation (AF) is the most frequent clinically significant cardiac arrhythmia[1] and a major cause of stroke, heart failure, cardiovascular morbidity, and mortality.[2] It is also a major contributor to the costs of health care.[3,4] The prevalence of AF is predicted to rise significantly in the coming years due to the aging of the population and growing frequency of other risk factors.[5,6] Considering the rising burden and clinical sequelae of AF, strategies that enable early detection and treatment are needed.

The advent of insertable cardiac monitors (ICMs) capable of AF detection has enabled continuous long-term monitoring for up to 3 years.[7] Several studies have evaluated AF incidence using ICMs in patients at risk of AF and stroke and observed a high incidence of AF not identified in routine clinical care (21% to 40% over a follow-up of 12 to 30 months).[8−11] These findings suggest that ICMs are an effective tool for identifying subclinical AF in patients at risk. Although ICMs may facilitate early identification of AF, it is unknown whether this leads to meaningful changes in therapy. To gain insight, we assessed changes in clinical management taken in response to AF detection with ICMs in patients at risk for AF and stroke in the REVEAL AF study. Here we report the nature and timing of changes in patient management for AF, and assess possible factors influencing treatment decisions.

Methods

REVEAL AF (www.clinicaltrials.govNCT01727297) was a prospective, single-arm, open-label, multicenter, clinical study. Detailed study methods have been previously

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published.[12] Briefly, high-risk patients were identified using the $CHADS_2$ score (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, previous stroke or transient ischemic attack (TIA) or thromboembolism [doubled]). Specifically, patients without a history of AF, but who had either a $CHADS_2$ score ≥3 or a $CHADS_2$ score = 2 plus ≥1 additional AF risk factor (coronary artery disease, renal impairment, sleep apnea, and/or long-term obstructive pulmonary disease) were enrolled at 57 centers in Europe and the United States. Patients were excluded if they had an ischemic stroke or a TIA in the previous 12 months, a history of hemorrhagic stroke, were taking long-term oral anticoagulation (OAC), or had a contraindication for long-term OAC. All patients had negative (no AF detected) external monitoring ≥24 hours within 90 days previous to enrollment or before ICM insertion. A mix of electrophysiologists (41%), interventional cardiologists (32%), and general cardiologists (27%) served as principal investigators.

The primary objective was to determine incidence of adjudicated AF ≥6 minutes in duration at 18 months (results previously published).[11] A secondary end point was to characterize the types and timing of changes in clinical management after AF detection.

This study was conducted in accordance with the Declaration of Helsinki. The protocol was approved by each site's institutional Review Board or Ethics Committee, and all patients provided written informed consent before participating in the study. A steering committee was responsible for the study design, conduct, and reporting. Data monitoring, collection, and analysis were performed by the sponsor and Steering Committee in partnership.

Patients who received an ICM (Reveal XT or Reveal LINQ; Medtronic, Minneapolis, Minnesota) were followed for 18 to 30 months. Remote device transmissions were completed each month, in-person visits took place every 6 months, and unscheduled visits were performed as needed. At each follow-up visit, physicians recorded whether AF was detected, and whether any changes in clinical management were taken in response to AF detection. All changes were at the discretion of the treating physician and not prescribed by the protocol. For this analysis, AF detection was based on local investigator classification of device data. Notably, this differs from the primary objective analysis where AF detection was based on the final classification of device data provided by the study's Endpoint Adjudication Committee.

To gain insight into possible factors influencing OAC treatment decisions, we evaluated the relation between OAC initiation at the first visit after AF and: CHA_2DS_2-VASc score (congestive heart failure, hypertension, age ≥ 75 [doubled], diabetes mellitus, previous stroke or TIA [doubled], vascular disease, and age 65 to 74, female), age, renal impairment, previous stroke or TIA and longest AF episode. The CHA_2DS_2-VASc score was assessed since current guidelines recommend its use to evaluate stroke risk in patients with AF, and to inform OAC treatment decisions.[2,13] Age was evaluated as OAC prescription has been reported to be lower in elderly patients with AF,[14,15] which may be due to perceived fall and/or bleed risk.[16] Renal impairment was evaluated as chronic kidney disease increases the risk of bleeding events with OAC therapy.[17] Previous stroke/TIA was also included as physicians may be more likely to initiate OAC for secondary stroke prevention; this is supported by higher rates of OAC initiation after AF detection with ICM monitoring in patients with versus without a recent ischemic stroke.[8,9,11,18,19] Lastly, the longest duration of an AF episode was evaluated due to previous publications demonstrating that device-detected AF exceeding various duration thresholds is more strongly associated with an increased risk of thromboembolic events.[20–22]

Descriptive statistics were used to summarize changes in clinical management when AF was identified, and to summarize factors that may have influenced clinical decisions. A Kaplan-Meier curve was generated with time 0 at the first in-person visit post-AF detection, and the event time as the time until the first action taken for AF. Fisher's exact tests were used to assess the effect of clinical characteristics on the likelihood of OAC initiation, and the effect of specific symptoms on any changes in clinical management taken. A GEE logistic regression model was fit to assess the effect of AF symptoms on changes in clinical management across visits at which new episodes of AF were detected.

Results

A total of 446 patients were enrolled in the study. Of these, 387 underwent device insertion and met inclusion criteria (Figure 1). Baseline characteristics of this cohort are presented in Table 1.

Patients were followed for a mean of 22.8 ± 7.6 months. During this period, physicians documented new AF episodes in 115 patients at 239 visits. A total of 57 of the 239 visits were unscheduled, including 35 of the 115 first visits where AF was diagnosed.

Of the 115 patients with AF, a change in clinical management was taken in 87 (76%). A change in clinical management occurred at the first in-person visit after AF was

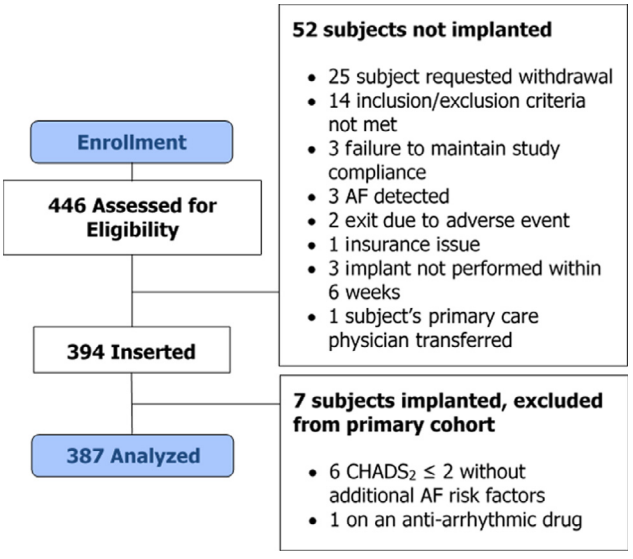

Figure 1. Patient flow diagram.

Table 1
Baseline demographics and clinical characteristics

Variable	Analysis cohort (n = 387)
Age (years)	71.5 ± 9.9
Men	202 (52%)
Body mass index (kg/m^2)	31.2 ± 6.5
$CHADS_2$ score	3.0 ± 1.0
Renal dysfunction	165 (43%)
Congestive heart failure	81 (21%)
Coronary artery disease	232 (60%)
Hypertension	362 (94%)
Chronic obstructive pulmonary disease	76 (20%)
Sleep apnea	103 (27%)
Diabetes mellitus	246 (64%)
Cerebrovascular accident (stroke)	80 (21%)
Transient ischemic attack	76 (20%)
Symptoms within 3 months of consent	
None	38 (10%)
Palpitations	198 (51%)
Dizziness/lightheadedness/presyncope	140 (36%)
Dyspnea	140 (36%)
Fatigue/weakness	117 (30%)
Rapid heart beat	80 (21%)
Chest pain	78 (20%)
Syncope	74 (19%)
Edema	51 (13%)
Other	19 (5%)

Data are mean ± standard deviation or n (%). $CHADS_2$, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, previous stroke or transient ischemic attack or thromboembolism (doubled). Renal dysfunction was defined as having a medical history of renal impairment or a glomerular filtration rate of 30-60 ml/min.

identified in 80 of these 87 patients. For the remaining 7, a first change in clinical management was taken at the second (n = 6) or third (n = 1) visits. Importantly, 31 patients with AF (27%) had ≥2 visits with changes in clinical management, and 12 (10%) had ≥3. The incidence rate of a second and third change in management for AF at 18 months after diagnosis was 39.2% and 10.8%, respectively (Figure 2).

The frequency of changes in clinical management is displayed in Table 2. The most common change was prescription of OAC. Overall, 80% of OACs prescribed during study follow-up were direct OACs. AF was diagnosed at follow-up at 44 sites; the percentage of AF patients at a site prescribed OAC ranged from 0% (10 sites) to 100% (15 sites), with 34 sites prescribing OAC in at least 50% of their AF patients. The timing of changes in clinical management in relation to visits with AF detection is shown in Figure 3. Generally, only 1 clinical action was taken at a visit; however, rhythm control medication was initiated in 5 of the 38 first visits after AF detection in which OAC was also prescribed.

Patients who had a change in clinical management at the first visit after AF detection tended to experience longer AF episodes and a higher maximal daily AF burden than patients in whom no change was taken. The same trend was observed when assessing only the longest AF episode and maximal daily AF burden during the 30 days before the first visit after AF detection (Table 3).

During follow-up, patients reported no symptoms at 87 (36%) of 239 visits where new episodes of AF were detected. At the 152 visits (64%) when AF-compatible symptoms were reported, dizziness and shortness of breath were the most common. Dizziness was reported by 37 patients at 61 visits, and 38 patients reported shortness of breath at 60 visits. Changes in clinical management were taken more frequently when patients reported AF-associated symptoms (99 of 152 visits, 65%) compared with visits at which patients did not report symptoms (40 out of 87 visits, 46%, p = 0.01). At the first visit after AF diagnosis, a change in clinical management was taken in 54 of 71 patients (76%) who reported symptoms, compared with 26 of 44 patients (59%) who did not (p = 0.06). The only specific symptom associated with increased incidence of a change in clinical management at the first visit after AF detection was fatigue/weakness (p = 0.02); at 94% of visits in which fatigue was reported, a change in management occurred (10 of which involved OAC), whereas a change in management only occurred at 65% of visits in which fatigue was not reported. Patients reported AF-compatible symptoms at 682 of 1313 visits (52%) when AF was not detected by ICM monitoring.

In evaluating the impact of changes to rhythm or rate control medications on symptoms, we compared the symptoms each patient experienced at the visit in which a rhythm or rate control change for AF was made with the symptoms reported at the next visit. There was not a significant reduction in the incidence of any specific symptom after a rhythm control change (p >0.05 for each symptom). In the case of rate control, there was only 1 symptom (palpitations) for which the incidence significantly changed. Palpitations were reported in 35% of the 17 visits in which AF was reported and a rate control medication was prescribed, whereas palpitations were reported in 100% of the 10 subsequent visits that occurred in this cohort. Thus, there was no evidence of a reduction of specific symptoms due to rhythm or rate control medication actions.

The CHA_2DS_2-VASc score, age, renal impairment, history of stroke/TIA, and duration of the longest AF episode were evaluated for their relation to OAC prescription at the first visit after AF detection. None of these factors were significant univariate predictors (all p >0.05; Table 4). Notably, the trial was not prospectively powered to assess predictors of OAC.

Discussion

REVEAL AF and other studies have demonstrated that ICM monitoring detects a high rate of AF typically missed during routine clinical care in patients at risk of AF and stroke.[8–11] Here we report that most physicians in the REVEAL AF study found ICM-detected AF actionable, with 76% of patients diagnosed with AF prompting ≥1 change in clinical management. Overall, there was significant practice variation among physicians in the changes in clinical management undertaken for device-detected AF. The most common change was initiation of OAC, followed by rhythm and then rate control medications. Most physicians acted promptly, with 70% of patients diagnosed with AF who underwent a change in clinical management at the

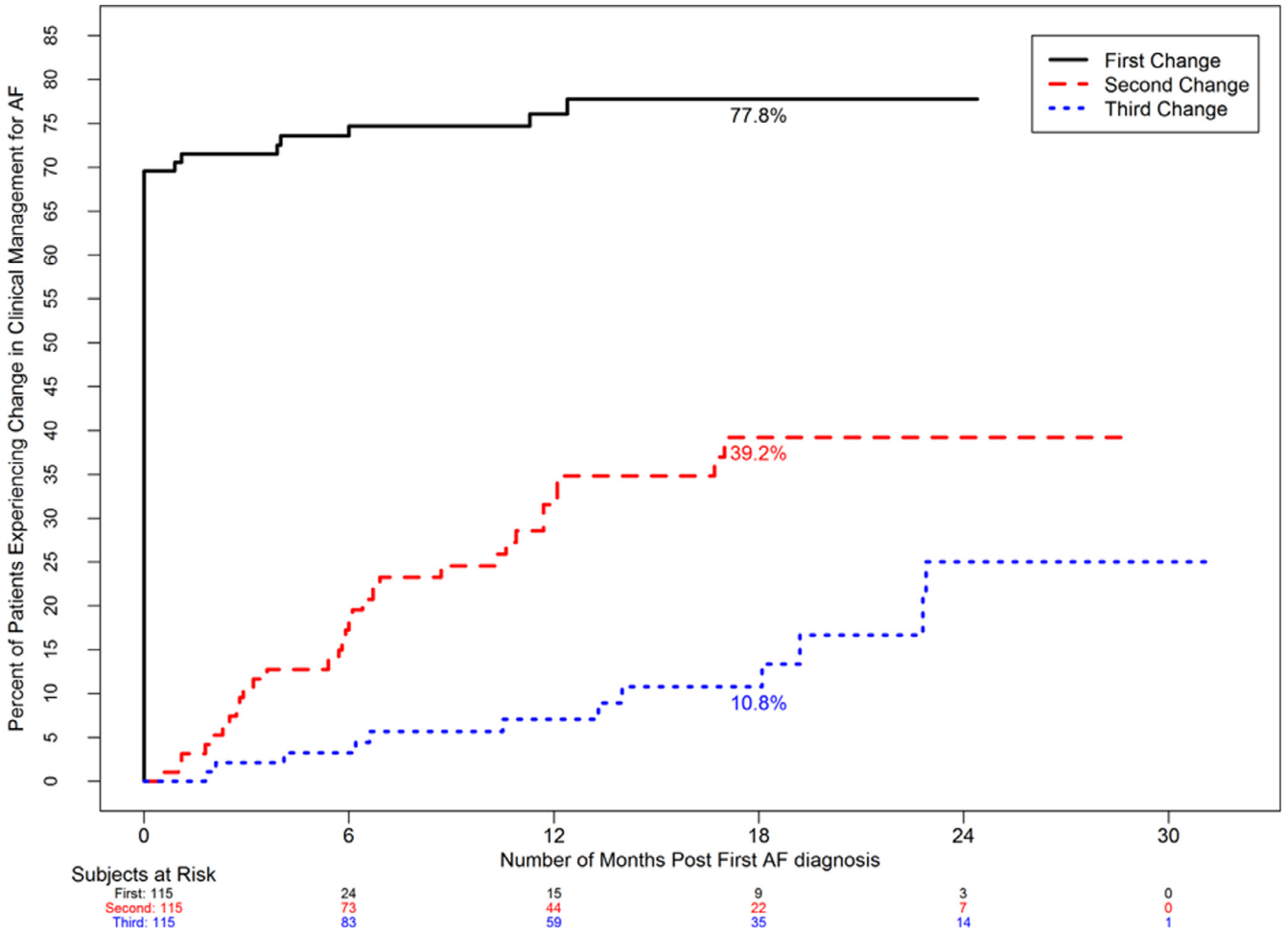

Figure 2. Time to first, second, and third change in clinical management for atrial fibrillation.

Table 2
Changes in clinical management

Change in clinical management	Frequency n (% of patients with atrial fibrillation)
Oral anticoagulation	73 (63%)
Rhythm control medication	15 (13%)
Rate control medication	11 (10%)
Cardioversion	4 (3%)
Ablation	5 (4%)
Cardiac subspecialist referral	5 (4%)

Actions taken are not mutually exclusive.

first visit after AF detection. Importantly, 39% of patients had multiple changes in clinical management within 18 months of the initial diagnosis of AF. Together, these findings demonstrate that ICM monitoring can successfully identify AF and guide both immediate and long-term patient management in a population at high risk for stroke.

In REVEAL AF, changes in clinical management primarily focused on reducing stroke risk through initiation of OAC, with 63% of patients diagnosed with AF prescribed OAC. This rate was lower than expected, as all enrolled patients met current guidelines for OAC therapy in the presence of AF.[2,13] There was significant variation in practice between centers, with 15 starting OAC in all patients with AF, and 10 not starting OAC in any of their patients diagnosed with AF. Overall, the rate of OAC prescription in the REVEAL AF study is in line with rates previously reported in smaller studies with similar populations when treatment decisions were based on physician discretion (50% to 76%).[8,9]

The practice variation in OAC prescription observed in REVEAL AF is not surprising considering current knowledge gaps around the benefit of OAC for device-detected AF. Although AF detected via cardiac implantable electronic devices is associated with an increased risk of both clinical AF and stroke, the increase in stroke risk is lower than observed in patients with clinical AF.[23,24] Nevertheless, a recent retrospective analysis of 10,212 Veteran's Health Administration patients demonstrated a reduction in stroke events with OAC in patients with device-detected AF burden as low as 6 minutes.[25] Several studies are currently underway to prospectively evaluate the clinical benefit of OAC for device-detected AF (Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical AF [ARTESiA NCT01938248]; Nonvitamin K Antagonist Oral Anticoagulants in Patients

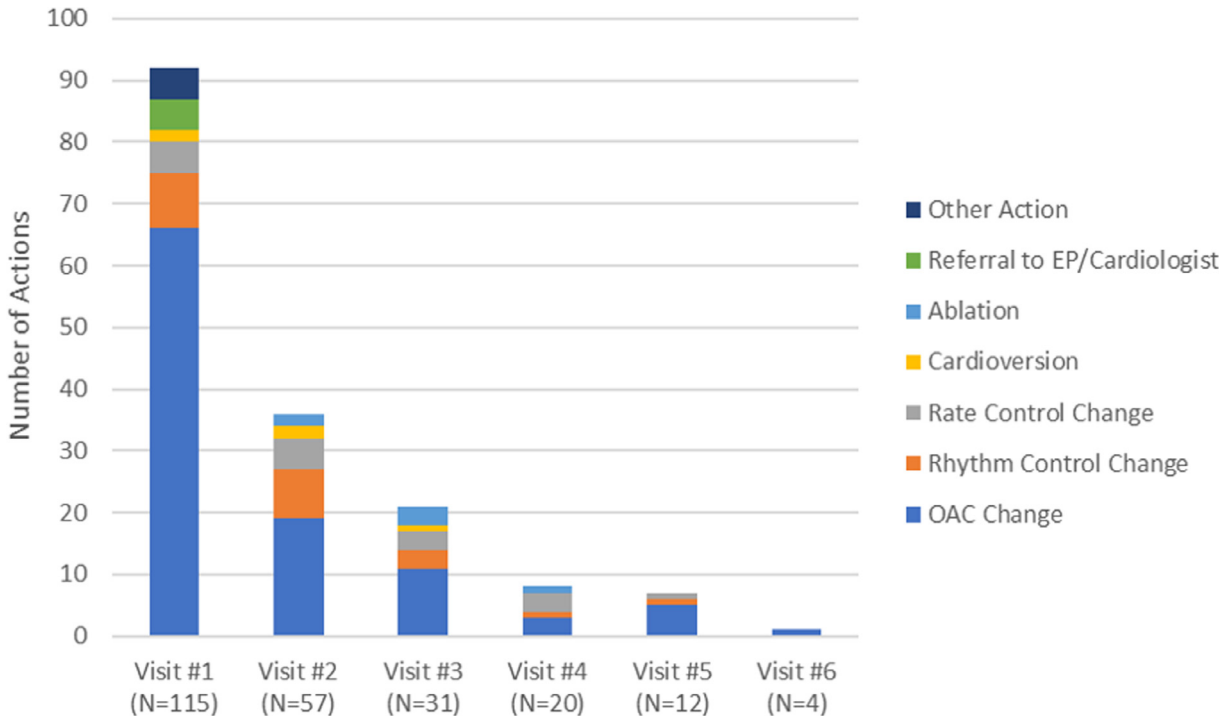

Figure 3. Changes in clinical management taken at visits with atrial fibrillation detected.

With Atrial High Rate Episodes [NOAH NCT02618577]; and AF Detected by Continuous ECG Monitoring [LOOP NCT02036450]).

To investigate possible factors influencing physician decisions around OAC use in REVEAL AF, we assessed whether clinical characteristics were independently predictive of OAC initiation at the first in-person visit after AF detection. This analysis focused on the CHA_2DS_2-VASc score, age, renal impairment, history of stroke/TIA, and the longest AF episode. None of the factors assessed were predictive, although patients were excluded from the REVEAL AF study if they had a stroke/TIA in the year before enrollment. Although this analysis was not prospectively powered, our findings suggest that physicians likely consider a multitude of clinical factors when making treatment decisions.

In the present analysis, patients for whom physicians took action at the first visit after AF detection tended to have higher maximal daily AF burden and longer AF episode(s) (although group differences were not statistically significant). This observation is in line with evidence that greater device-detected AF burden is associated with higher thromboembolic risk.[24] The relation between AF burden and thromboembolic risk is not linear,[24] however, and the threshold of AF that merits treatment for any given level of AF burden may differ in patients with varying underlying pathophysiology and intrinsic risk of stroke.[26,27] Accordingly, a fairly large range of maximal daily AF burden was observed in patients in whom a change in clinical management was not taken at the time of first AF detection.

Patients frequently reported AF-compatible symptoms throughout follow-up, both at visits with and without AF detection. As such, symptoms were a poor indication of AF occurrence. This corroborates previous studies demonstrating poor symptom-arrhythmia correlation in patients with cardiac implantable electronic devices and ICMs.[28,29] Physicians initiated changes in clinical management more frequently at visits when AF was detected in patients who were symptomatic versus asymptomatic. This was unexpected, as OAC initiation was the most common change in management, and stroke risk is similar in patients with and without AF-related symptoms.[30] However, it is less surprising for the initiation of treatment for rate and/or rhythm control, where the benefits are largely symptom driven. In the present analysis we did not observe a reduction in specific symptoms after rhythm or rate control medication changes.

This analysis has multiple limitations. As REVEAL AF was a single-arm trial and thromboembolic events were uncommon, we are unable to assess whether changes in clinical management had an impact on clinical outcomes. Yet, this study provides insight into how physicians handle treatment decisions in the face of knowledge gaps and in the absence of clear guideline recommendations.

In addition, all device-detected AF episodes in REVEAL AF underwent adjudication by multiple reviewers for the primary analysis. However, investigators were not informed of final episode classification during the study. As such, this analysis evaluated whether physicians acted based on their own interpretation of device data. Importantly, this reflects real world practice. Moreover, there was strong agreement between physician classification and final adjudication of episodes; overall 92% of episodes classified by physicians to be AF were adjudicated as AF, and 96% of episodes adjudicated to be AF were also classified by clinicians as AF.

Table 3
Longest atrial fibrillation episode and maximal daily atrial fibrillation burden by change in clinical management initiated at the first visit after atrial fibrillation detection

		Median (interquartile range)			
	Subjects (n)	Longest atrial fibrillation episode (minutes) in last 30 days	Longest atrial fibrillation episode (minutes) since last visit	Most atrial fibrillation burden (minutes) in a day in last 30 days	Most atrial fibrillation burden (minutes) in a day since last visit
No change in clinical management	35	8 (8-44)	28 (14-72)	1 (0-8)	23 (4-100)
Change in clinical management	80	67 (19-194)	52 (18-217)	42 (0-226)	112 (17-390)
Change in clinical management					
Oral anticoagulation	66	60 (19-194)	46 (17-168)	56 (2-188)	112 (18-396)
Rhythm Control Medication	9	73 (43-193)	316 (46-638)	66 (4-96)	370 (18-926)
Rate control medication	5	27 (26-28)	26 (24-100)	4 (0-68)	70 (4-118)
Cardioversion	2	10 (10-10)	83 (10-156)	719 (0-1438)	821 (204-1438)
Ablation	0	N/A	N/A	N/A	N/A
Cardiac subspecialist referral	5	24 (6-330)	130 (15-283)	8 (0-60)	60 (8-236)

Actions taken are not mutually exclusive.

In conclusion, physicians found ICM data actionable in patients at high risk for stroke, with 76% of patients having ≥1 change in clinical management for AF. For most of these patients, physicians acted at the first visit after AF detection. Additionally, ICM data guided multiple clinical actions over time in approximately 27% of patients with AF detected. Significant practice variation was observed with regard to specific changes in clinical management. This analysis demonstrates that ICM monitoring can identify AF and guide ongoing patient management in patients at high risk for AF and stroke. Further studies are needed to evaluate the clinical impact of treating device-detected AF in larger populations.

Disclosures

Atul Verma has research grants from Medtronic, Bayer, Bristol-Myers Squibb, and is a consultant for Medtronic, Biosense Webster, and Servier. Rolf Wachter is on the Speakers Bureau and is a consultant for Medtronic. Peter R. Kowey has ownership interest in Biotelemetry and is a consultant for Medtronic. Jonathan L. Halperin is a consultant for Bayer, Janssen, Medtronic, Pfizer, and Boehringer Ingelheim. Bernard J. Gersh is a consultant for Medtronic and receives minor honoraria from: St. Lukes, Mount Sinai, Boston Scientific, Teva Pharmaceutical Industries, Janssen Scientific Affairs, St. Jude Medical, Cipla Limited, Thrombosis Research Institute, Duke Clinical Research Institute, Kowa Research Institute, Cardiovascular Research Foundation and Janssen Research & Development. Mitchell S.V. Elkind receives research support from BMS-Pfizer Alliance and Roche; is an Expert Witness for Hi-Tech Pharmaceuticals, Merck/Organon, Auxilium, and LivaNova; is a consultant for Abbott; and receives minor honoraria from Up-To-Date. Dr. Elkind's institution receives monies from Medtronic for his effort as a consultant. Rachelle Kaplon, Paul

Table 4
CHA_2DS_2-VASc score, age, renal impairment, previous stroke/transient ischemic attack, and longest atrial fibrillation episode duration in patients who did and did not initiate oral anticoagulation at the first visit after atrial fibrillation detection

Characteristic	Oral anticoagulation initiation at the time of first atrial fibrillation detection (n = 66)	No oral anticoagulation initiation at the time of first atrial fibrillation detection (n = 49)	p Value
CHA_2DS_2-VASc score	4 (4 − 5)	4 (4 − 5)	0.91
Age (years)			0.72
<65 (n = 16)	9 (56%)	7 (44%)	
65 − 74 (n = 33)	21 (64%)	12 (36%)	
≥75 (n = 66)	36 (55%)	30 (46%)	
Renal impairment			0.35
Yes (n = 59)	31 (53%)	28 (48%)	
No (n = 56)	35 (63%)	21 (38%)	
Prior stroke/transient ischemic attack			0.84
Yes (n = 34)	19 (56%)	15 (44%)	
No (n = 81)	47 (58%)	34 (42%)	
Longest atrial fibrillation episode (min)	40 (12 − 146)	18 (4 − 76)	0.78

Data are median (interquartile range) or n (%). CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75 (doubled), diabetes mellitus, previous stroke or transient ischemic attack (doubled), vascular disease, and age 65 to 74, female. Renal impairment was defined as having a medical history of renal impairment or a glomerular filtration rate of 30 to 60 ml/min. Previous Stroke/transient ischemic attack was defined as a history of stroke or transient ischemic attack at the time of enrollment, though stroke/transient ischemic attack within 12 months before enrollment was an exclusion criterion for the study.

Ziegler, and Lou Sherfesee are employed by, and stock owners of, Medtronic. James A. Reiffel is a consultant for Medtronic, Janssen, Portola, Acesion, In Cardia Therapeutics, Roivant, Sanofi; is an investigator for Medtronic; and is on the Speakers Bureau for Janssen.

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