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Home Screening for Detecting Subclinical Atrial Fibrillation

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Abstract

The advent of cardiac implanted electronic devices with accurate atrial arrhythmia diagnostic capabilities has revealed a large burden of "silent " atrial fibrillation that is present in the cardiac population. Many studies have been completed, and many more are ongoing, to determine the correct treatment course when these atrial arrhythmias are detected. Alongside the development of accurate atrial diagnostics within the devices, has been the growth an entire network of wireless home monitoring capability. It is now possible to see, over the internet, individual patients' atrial arrhythmia burden on every day. This capability has tremendous promise for patient care, with the possibility of reducing strokes, decreasing heart failure, preventing cardiomyopathies, and likely substantially reducing health care costs. As this innovative diagnostic capability is generating large amounts of data, protocols for what should be done with the plethora of new information are being developed. In the pages that follow, we will present what is known about home monitoring for silent atrial fibrillation, and present the results of recent studies published in this arena.

Prevalence of Atrial Fibrillation (AF) in the Cardiac Implantable Electronic Devices (CIED) Population

Patients with CIEDs have a unique advantage over cardiac patients who do not have a continuous arrhythmia monitor in place because clinically silent arrhythmias can be detected. The incidence of previously unrecognized AF has been reported to range from 30-60%. Older studies, performed before device diagnostics were sophisticated and before home monitoring was available, reported an incidence of device detected AF in about half of the population. Gillis et al. reported atrial arrhythmias in 68% of 231 patients with pacemakers implanted for sinus node disease.[1] More recently, the ASSERT trial and the MOST study also found that AF was present in about 50% of unselected populations of patients with implanted pacemakers.[2,3]

Studies specifically designed to exclude subgroups of patients who may have had AF in the past (history of AF, history of oral anticoagulation use, history of anti-arrhythmic drug use), have found an incidence of newly detected AF (NDAF) or "silent AF" in about 30% of device patients. For example, patients from the TRENDS trial (1,368) who had no prior history of AF, no previous stroke/TIA, and no warfarin or antiarrhythmic drug use were analyzed to look for NDAF.[4] NDAF was defined as device-detected atrial arrhythmias lasting at least 5 minutes on any day of the study. Thirty percent of patients (416) experienced NDAF. The incidence of NDAF was consistent across patients with intermediate (virtual CHADS2 score of 1) (30%), high (virtual CHADS2 score of 2) (31%), and very high (virtual CHADS2 score of ≥3) (31%) stroke risk factors ($p = 0.92$). (A virtual CHADS score is calculated in a patient who has never previously had AF.) However, a significant increase was seen in the proportion of patients having days with >6 hours of AT/AF as the virtual CHADS2 score increased; 12%, 15%, and 18% for intermediate, high, and very high risk, respectively; $p = 0.04$.

In another analysis from the TRENDS trial, NDAF was analyzed in patients (319) who had a prior history of stroke or TIA.[5] Patients (156) with a documented history of AF, warfarin use, or antiarrhythmic drug use were excluded from analysis. NDAF was again defined as device-detected atrial arrhythmias lasting at least 5 minutes on any day of the study. NDAF was identified by the implantable device in 45 of 163 patients (28%) over a mean follow-up of 1.1 years.

In the ASSERT trial, a study of 2,580 patients with a history of hypertension and no prior history of AF, NDAF (defined as lasting at least 6 minutes in duration) was detected at least once in 34.7% of the patients over a mean follow-up of 2.5 years.[6] Only 10% of

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Table 1: Summary of Studies Regarding AF Detected by Dual-Chamber CIEDs and Thromboembolic Risk

Year	Trial	Number of patients	Duration of Follow-up	Atrial Rate Cutoff	AF Burden Threshold	Hazard Ratio for TE Event	TE Event Rate (below vs. above AF burden threshold)
2003	Ancillary MOST[47]	312	27 months (median)	>220 bpm	5 minutes	6.7 (p=0.020)	3.2% overall (1.3% vs. 5%)
2005	Italian AT500 Registry[49]	725	22 months (median)	>174 bpm	24 hours	3.1 (p=0.044)	1.2% annual rate
2009	Botto et al.[50]	568	1 year (mean)	>174 bpm	CHADS2+AF burden	n/a	2.5% overall (0.8% vs. 5%)
2009	TRENDS[51]	2486	1.4 years (mean)	>175 bpm	5.5 hours	2.2 (p=0.060)	1.2% overall (1.1% vs. 2.4%)
2012	Home Monitor CRT[52]	560	370 days (median)	>180 bpm	3.8 hours	9.4 (p=0.006)	2.0% overall
2012	ASSERT[31]	2580	2.5 years (mean)	>190 bpm	6 minutes	2.5 (p=0.007)	(0.69% vs. 1.69%)

the patients (1/3 of those who ultimately developed NDAF) had the NDAF detected in the first 3 months of the study.

Prevalence of AF in Cryptogenic Stroke Patients with Insertable Cardiac Monitors (ICMs)

When it was discovered that implanted pacemakers and implantable cardioverter defibrillators (ICDs) were identifying atrial arrhythmias in patients who had no prior AF history and were entirely asymptomatic, it became clear that there may be a need for an insertable monitor whose sole purpose would be to detect previously undiagnosed arrhythmias such as AF. The most recent version of these monitors are ideally suited to look for AF in the cryptogenic stroke population. Several studies have used ICMs to look for AF in the cryptogenic stroke population.[7-12] According to the results, the rate of detection of AF by ICMs in cryptogenic stroke patients ranges from 15-30% and is a function of: length of monitoring, the definition of what duration of AF constitutes an episode, the interval from the index stroke to the start of monitoring, and patient selection.[13] These numbers are remarkably similar to the incidence of AF found in the CIED population in general. Data from ICMs can also be monitored remotely allowing clinicians to act as soon as AF is discovered.

Stroke Risk Associated with Device Detected AF

Several studies that have evaluated the thromboembolic (TE) risk of device detected AF episodes have demonstrated an increased stroke rate associated with the AF episodes. A minimum of five minutes of AF was found to have clinical relevance first in 2003 in the ancillary MOST trial.[14] 312 patients were enrolled and followed for 27 months. When AF (lasting at least 5 mins in duration) was detected, the hazard ratio for TE event was 6.8 (p=0.020) (Table 1). Alternative burden cut-points have been explored over the last 10 years ranging from 5 minutes to 24 hours. In the AT500 Italian Registry[15] (725 patients, 22-month follow-up), AF episodes longer than 1 day were associated with a 3.1 fold increased risk of embolism (95% CI 1.1 - 10.5, p = 0.044) after adjustment for known embolism predictors (Table 1). In the TRENDS trial[16] (2486 patients, 14-month follow-up), 30 day windows with AF burden > 5.5 hours on any day conferred an increased risk of stroke that was more than double that of 30 day windows with no AF detected. (HR 2.2 (95% CI 0.96 – 5.05, p=0.06) . Thirty day windows with low AF burden (< 5.5 hours/day) had an hazard ratio of 0.98 (95% CI 0.34-2.82, p=0.97) compared to zero burden (Table 1).

Pooled data analysis from two prospective, multi-center, international, observational studies in patients with ICDs with Cardiac Resynchronization Therapy (CRT-Ds) everesT and HomeCARE[17] (570 patients, 1-year follow-up) demonstrated that patients with NDAF or a prior history of AF were more likely to develop TE events than patients without NDAF or prior AF history. Patients with AF lasting > 3.8 hours per day were nine times more likely to develop TE complications (p = 0.006) than patients without AF(Table 1).

The ASSERT Trial6 (2580 pts, 2.5-year follow-up) showed that 6-minutes of AF detected in a 3 month period was associated with a doubling of TE risk (HR 2.49 95% CI 1.28 to 4.85, p = 0.007). When patients were stratified according to the longest duration of AF episodes by quartiles,(≤0.86 hours, 0.87 to 3.63 hours, 3.64 to 17.72 hours, and >17.72 hours), the annual rates of stroke or systemic embolism were 1.23 (95% CI, 0.15 to 4.46), 0 (95% CI, 0 to 2.08), 1.18 (95% CI, 0.14 to 4.28), and 4.89 (95% CI, 1.96 to 10.07), respectively. Accordingly, patients with AF episodes longer than 18 hours seemed to carry the greatest risk in that study. In a pooled analysis of 10,016 patients from 3 large clinical trial data bases, 1 hour of AF doubled the risk of stroke after adjustment for stroke risk factors and anticoagulation use[18] (Table 1).

A combination of AF burden and clinical risk scores has also been tested to identify patients at lower/higher risk. Botto et al[19] studied 568 patients with implanted pacemakers and a history of AF followed for 1 year. Three AF groups were considered: patients with <5-minutes AF (AF-free); patients with >5-minutes AF but <24 hours (AF-5 minutes); and patients with AF episodes >24 hours (AF-24 hours). By combining AF presence/duration with CHADS2 score, two subpopulations with markedly different risks of TE events (0.8% vs 5%, p = 0.035) were identified. The low risk group included patients who were AF-free with CHADS2 ≤2, AF-5 minutes with CHADS2 ≤1, and AF-24 hours with CHADS2 = 0. The high risk group included patients who were AF-free with CHADS2 >3, AF-5 minutes with CHADS2 ≥ 2, and AF-24 hrs with CHADS2 ≥ 1 (Table 1). In all of these studies the AF threshold cutpoints were arbitrarily chosen, or were the results of the data itself (i.e., median values). There is still uncertainty regarding the minimum duration of device detected AF that increases TE risk. Risk seems to be increased by relatively brief AF episodes. What does seem to be consistent is the finding that the appearance of NDAF increases TE event rates and that TE risk is increased by a mere 5 minute episode.

Temporal Proximity of Silent AF Episodes to Thromboembolic Event

There does not seem to be a proximate temporal relationship of device detected AF to the occurrence of stroke, despite the fact that patients who have AF are at increased risk of stroke. Several

Table 2: Temporal Proximity of Silent AF Episodes to TE

Year	Trial	Definition of AF	Any AF prior TE	AF only after TE	No AF in 30 days prior TE	AF at the time of TE
2011	TRENDS	5 minutes	50%	15%	73%	n.a
2012	Home CARE + EveresT	14 minutes per day>180 ppm	64%	n.a.	n.a.	27%
2014	ASSERT	6 minutes	35%	16%	84%	n.a
2015	IMPACT	36/48 atrial beats>200 ppm	29%	13%	94%	n.a

studies have highlighted this point and are outlined in Table 2.[17, 20-22] As seen, in the majority of patients (73-94%) there was no AF on the device recordings in the 30 days prior to the TE events. These data imply that, in the majority of device patients with AF and TE , the mechanism of stroke may not be solely related to the AF episodes. Other vascular disease risk factors may play a role in thromboembolism.

Early Detection of AF by Remote Monitoring

Despite a very high sensitivity of CIEDs for AF detection, detection in asymptomatic patients may be difficult because of infrequent office visits. Remote monitoring of CIEDs, with automatic alerts for AF, provides an opportunity for early identification of AF, potentially reducing stroke risk, heart failure, and mortality. This is critical, because lack of symptoms from AF does not translate to freedom from risk of thromboembolic, heart failure, or mortality sequelae. Furthermore, continuous monitoring may allow monitoring of the efficacy of individual patient treatment regimens, and the opportunity to modify therapy early in the course of disease.

The ability of RM to early detect AF has been consistently demonstrated by several observational and randomized trials. Initially, 276 consecutive patients[23] implanted with pacemakers that had automatic daily remote monitoring capability were studied in 2005. AF was documented within 1 year of follow-up in 10.5% of patients, with details of AF arrhythmia episode number and duration. Most patients were asymptomatic and unaware of their arrhythmias. In another single-center study[24] of 166 patients (73% pacemakers; 27% ICD) followed for 16 months, 20% had alerts triggered by AF, of which 88% needed clinical interventions, such as drug therapy modification, device reprogramming, or electrical cardioversion. The median reaction time to AF was advanced 148 days compared to standard scheduled follow-up.

In the worldwide Home Monitoring database analysis[25],3,004,763 transmissions were sent by 11,624 patients with pacemakers, ICDs and CRT-Ds. AF was responsible for more than 60% of alerts in pacemakers and CRT-D devices, and for nearly 10% of alerts in dual chamber ICDs. RM has been demonstrated to have a sensitivity of nearly 95% for true AF detection,[26] with 90% of AF episodes triggering alerts being asymptomatic.[24] Even when using an inductive RM system (without automatic alerts) RM performed better than standard follow-up in pacemaker patients for detection of AF in the randomized PREFER trial (980 patients).[27] The number of events reported per patient after 1-year follow-up was significantly higher in the remote monitoring arm (0.061 vs 0.037 for new onset AF and 0.198 vs 0.105 for AF lasting more than 48 hours) than in the standard scheduled follow-up arm.

1,339 ICD patients were followed for 15 months in the randomized TRUST trial.[28] AF detection occurred at 5.5 days in the remote monitoring arm versus at 40 days in the standard follow-up arm (34.5 days earlier). In the randomized CONNECT trial[29] (1,997 ICD patients followed for 15 months) the interval between detection of an AF episode longer than 12 hours and the clinical reaction was 8 times shorter with remote monitoring when compared with standard follow-up (3 versus 24 days). In that same study, high ventricular rates during AF (>120 beats per minute for at least six hours) were detected within 4 days with remote monitoring versus 23 days with standard follow-up.

Due to this strong evidence from published trials, remote monitoring use for the early detection and quantification of AF has a Class of Recommendation I, Level of Evidence A, in the recent HRS Remote Monitoring Consensus Statement Recommendations.[30]

AF Alert setting and Clinical Reaction Planning

Comprehensive diagnostic data regarding AF that can be obtained from RM include AF Burden Trends, AF Episode Histogram and Log, Ventricular Rate during AF, Stored Electrogram (EGM) records with EGM details (event markers, refractory markers and event intervals), and with some devices, a chronologic plot of all AF events and their individual durations that have occurred in the last year.

AF alert setting may be challenging for individual patients. First, there are major differences in proprietary systems, either in the alert setting itself (web based or directly in the implanted device) or in the available options for programming alert triggers for burden level, arrhythmia duration, internal EGM strips, and ventricular rate in AF. Some systems will transmit only during scheduled transmissions, or during manual transmission at the time of symptoms. Others will automatically transmit when an arrhythmia is detected based on previously programmed parameters. The availability of daily alerts for single short episodes may increase clinic work burden, and make it more difficult to identify clinically meaningful events. Alert settings should be modified during follow-up for individual patients according to the individual clinical profile of each patient.

An additional void that RM can fill is the assessment of success rates of AF therapies, in particular of catheter ablation. AF recurrences are often asymptomatic even in patients who were previously severely symptomatic. It has been suggested that RM could help determine whether anticoagulation therapy could be discontinued during follow-up.[31]

AF Impact on Heart Failure and Mortality and Role of RM

Several epidemiologic studies have shown strong associations between AF and risk of developing heart failure, and AF and increased mortality.[32-38] In addition, studies have demonstrated a relationship of AF to heart failure specifically in patients with implanted CRT devices.[39] Potential deleterious effects of unrecognized AF in CRT patients include inappropriate ICD shocks, thromboembolism, and loss of CRT therapy leading to increased sympathetic tone, hemodynamic compromise, heart failure exacerbations, and increased frequency of hospitalizations. In one large multicenter study (1,193 CRT-D patients), AT/AF >10 min occurred in 361 (30%) patients during a median follow-up period of 13 months. Freedom from the composite endpoint of death, heart transplantation, or heart failure hospitalization was significantly higher for patients without vs. those with AF during follow-up (hazard ratio: 2.16, p = 0.032).[40] In the pooled data analysis from EveresT and HomeCARE, patients with a prior history of AF and NDAF were at higher risk for heart failure

hospitalization than those without prior AF history and no NDAF (16.5% vs 5.1%, p = 0.001).[17]

Prevention Of AF Related Stroke, Heart Failure, and Mortality With RM

At present, there is no definitive evidence for stroke risk reduction, or decreased hospitalizations for AF related heart failure or mortality due to remote monitoring despite promising results of initial studies. Data generated by running repeated Monte Carlo simulations based on a real population of 166 patients suggested that daily monitoring could reduce the 2-year stroke risk from 18% to 9% for an absolute reduction from 0.6% to 0.2% per every 2 years, compared to conventional follow-up at intervals of 6 to 12 months.[41] In the COMPAS trial the incidence of hospitalizations for atrial arrhythmias and related stroke was 7.3% in the control group and 2.4% in the RM group (p=0.02), with stroke rates of 3.3% and 0.8% respectively.[42] In the HomeGuide Registry[26] patients (1650) were followed remotely for 20±13 months; stroke incidence was extremely low (0.4% at 4 years), lower than that expected for the estimated TE risk profile of the enrolled population.

In the prospective randomized study (IMPACT) of oral anticoagulation therapy for AF guided by RM,[22] there was no improvement in the outcomes of stroke or all cause mortality for the intervention group (RM) compared with controls. The study protocol called for discontinuation of oral anticoagulation if there was no AF detected for 30 days in patients with 1 or 2 CHADS2 scores, and no AF detected for 90 days in patients with 3 and 4 CHADS2 scores. The primary outcome of TE or bleeding event was similar in the two arms at 5 years of follow-up (2.4% patient-years vs. 2.3%; p = 0.78). Mortality rates were also similar (5.4% patient-years vs. 5.1%; p = 0.66). Poor compliance to anticoagulation plan and per protocol discontinuation of oral anticoagulation in case of no AF recurrences may be responsible for this finding. Considering the temporal dissociation of atrial fibrillation events and stroke events previously discussed, it may be that oral anticoagulation should not be stopped in any subgroups at any time once there is an indication.

The Future

Many studies are currently ongoing in this field of silent AF. Some are looking merely to determine the incidence and prevalence of silent AF. Some are looking to see if the pattern and progression of AF can be elucidated. Some are investigating starting and stopping oral anticoagulation based on information from the device diagnostics, and treating patients ONLY when they are actually in AF and sparing them the risks of bleeding when the rhythm is normal. In addition, studies are ongoing randomizing patients who have silent AF detected to: oral anticoagulation vs. ASA alone. All of these studies take into account CHADSVASC risk factors when prescribing treatment regimens.

Conclusions

The absense of symptoms due to AF does not translate into freedom from risk of thromboembolic events, heart failure hospitalizations , or mortality. We have shown that the prevalence of silent AF in patients with CIEDs, including patients with implanted cardiac monitors is as high as 30%. As is written in the recent Heart Rhtyhm Society guidelines, remote monitoring should be offered to all patients for the early detection and quantification of AF (Class I, Level A). We have also shown that there is an increased risk of TE events in patients who have AF detected by their implanted devices. Remote home monitoring is an accurate way to monitor every atrial arrhythmia episode in every patient every day, thereby being highly effective for early detection AF. Studies are ongoing to demonstrate potential benefit of RM for hard endpoints such as stroke prevention, heart failure hospitalizations, and mortality.

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