Home Monitoring in Patients with Implantable Cardiac Devices: Is There a Potential Reduction of Stroke Risk? Results from a Computer Model Tested Through Monte Carlo Simulations

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Potential Stroke Prevention by Home Monitoring. ***Introduction:*** **Patients with pacemakers and implantable defibrillators (ICD) may experience asymptomatic atrial fibrillation (AF), detected with a delay depending on the in-person follow-up schedule. Home monitoring (HM) remote control with automatic alerts for AF may drive early anticoagulation, potentially reducing stroke risk.**

Methods and Results: **A sample of 136 pacemaker (103) and ICD (33) patients with or without cardiac resynchronization therapy not taking anticoagulation at implant were monitored remotely with HM. Upon HM alerts for AF, patients were recalled to update therapy. Two-year data were entered in a computer Monte Carlo model, simulating 4,000 virtual subjects with the same AF and $CHADS_2$ stroke risk distribution of our real population. Simulations reproduced a 2-year follow-up. Two thousand subjects were supposed to be followed with HM (HM group) and 2,000 with standard in-person follow-up (SF group) at 3, 6, 9, or 12 months.**

Two-year Kaplan-Meier cumulative probability of ≥24-hour AF was 15.6% (95%CI 8.5–23.3%); the AF-related symptom rate was 27% and the median $CHADS_2$ score was 2. As a result of simulations, stroke incidence in case of AF was 2.3 ± 1.1% in the HM group and 2.4 ± 1.1%, 2.5 ± 1.2%, 2.7 ± 1.2%, and 2.9 ± 1.3% in the SF group with 3-, 6-, 9-, and 12-month follow-up programs, with odds ratios of 0.97 (95%CI 0.93–1.01), 0.91 (0.88–0.95), 0.87 (0.84–0.90), and 0.82 (0.79–0.85) (HM better if odds ratios <1), respectively.

Conclusions: **Daily HM potentially reduces the stroke risk by 9% to 18% with respect to SF with intervisit intervals of 6 to 12 months.** *(J Cardiovasc Electrophysiol, Vol. 20, pp. 1244-1251, November 2009)*

remote monitoring, pacemakers, implantable defibrillators, atrial fibrillation, stroke, anticoagulation, Monte Carlo simulation

Introduction

Daily remote monitoring of patients with pacemakers and implantable cardioverter-defibrillators (ICD) equipped with the wireless Biotronik Home Monitoring® (HM) function (Biotronik GmbH, Berlin, Germany) has been demonstrated to be feasible, safe, and reliable.[1-3] Expected benefits of remote monitoring include continuous technical surveillance of the device, health care resource optimization, early detection of tachyarrhythmias, and heart failure progression, permitting a prompt clinical reaction.[4-6] Introduction of HM in clinical practice has shown a deep impact on patient management, mainly consisting of early drug therapy modification or device reprogramming.[7] This may hold clinical relevance particularly with regard to atrial fibrillation (AF) that is responsible for more than 50% of HM alerts.[2,7] It is well known that AF is very common in patients with implanted devices, as well as in those without a history of AF before implant, and that a majority of episodes are asymptomatic.[8,9] In a significant percentage of patients presenting with stroke, this is due to previously unrecognized AF. This provides an important impetus to early detection. It has been documented that arrhythmia episodes lasting more than 24 hours are independent predictors for stroke and mortality, regardless of symptoms.[10-12] Observational clinical studies have demonstrated[13,14] that HM allows early introduction of anticoagulation therapy in patients with asymptomatic AF, significantly in advance if compared with standard in-person follow-up. Early anticoagulation in these patients may potentially prevent stroke occurrence. Clinical evidence that early anticoagulation driven by HM actually reduces stroke incidence is still needed. We evaluated a computer model tested by running repeated Monte Carlo simulations based on a real population of 163 patients prospectively followed by HM, in order to investigate the potential benefit of HM on 2-year incidence of stroke as compared with different standard follow-up scheduling.

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Methods

Patient Population and Follow-Up Protocol

This analysis included consecutive patients implanted with dual-chamber pacemakers or ICD—with or without cardiac resynchronization therapy (CRT) functions—implementing HM technology for remote control. This population has been already studied in a former investigation on AF detection and clinical management optimization by HM.[13] All the implantable devices were provided with the same basic detection and remote diagnostics for atrial arrhythmias. Each patient was followed for up to 2 years, both remotely with the HM service and with in-person visits scheduled with prolonged intervals. All the patients gave their written informed consent to be remotely controlled by the HM service.

HM Service

HM system has been described in detail elsewhere.[1,2,7] Briefly, each patient implanted with a pacemaker or ICD device capable of ultra-low power 403 MHz band radio transmissions (MICS) is provided with a specific mobile unit, CardioMessenger, consisting of an MICS receiver and a quad band GSM (global system for mobile communication) cellular phone. Transmissions from the implanted device occur every day at a specific programmable time (generally during nighttime) or immediately upon detection of preselected critical events of which the physician is directly alerted. Transmissions are automatically triggered: patients play no role in initiating a transmission and can be even unaware of it. The CardioMessenger forwards the received transmissions to a unique service center located in Berlin, Germany. Here, messages are decrypted and uploaded in a secure (https) Internet website through a fully automatic procedure. The responsible physician or the ambulatory personnel can retrieve HM data by accessing with a password to their own web area. The amount of transmitted data have grown rapidly in the past few years and now they include almost the same basic information concerning diagnostics, device status, and test measurements that one can normally get with a full device interrogation during an in-person follow-up.

Ambulatory Procedures for HM Data Management

In our center, HM data management complied with a specific protocol.[7] In brief, an expert nurse regularly accessed the HM website for report reviewing at least every 15 days or as soon as possible whenever receiving an e-mail/ SMS message of critical events at a dedicated e-mail box/ commercial mobile phone. After data screening, the nurse submitted the critical events to the responsible physician who took the appropriate clinical decision.

As regard to AF,[13] critical reports included new-onset AF, 5 or more consecutive days with AF burden $\geq$10%, or 1 or more days with AF burden $\geq$100%. Patients were contacted for an unscheduled follow-up to be performed either by phone or at hospital, unless they were judged already on optimal therapy. AF-related symptoms were then assessed and ranked as severe whenever symptoms interfered with patient's daily activities, required any medical intervention, or caused patient access to an emergency department. Symptoms were ranked as mild whenever the patient only felt something unusual but did not ask for any medical intervention, going on with his/her daily activities.

Atrial Arrhythmia Data Remote Collection

The number and the cumulative duration of atrial arrhythmias (burden as percentage of day) are available in the HM reports. The ICD models included in our analysis used an atrial sensing-dependent auto-adjusting sensitivity along with a specific criterion based on a 75% probabilistic counter (36 atrial beats out of the last 48 faster than a programmable rate limit) to detect atrial arrhythmia episodes, while pacemaker detection was based on a mode switch algorithm using a simple 5 on 8 counter. Appropriateness of episode detection has been assessed either by reviewing immediately the associated atrial and ventricular electrograms online (as in the most recent ICD models) or during the next in-person follow-up. As for the purpose of the present analysis, only AF episodes lasting 24 hours or more ($\geq$100% of HM reported AF burden during the last monitored 24 hours) were included in the analysis.

Stroke Incidence Estimation Through Monte Carlo Simulations

The potential effect of the HM remote control on 2-year incidence of stroke in case of AF lasting more than 24 hours was estimated as a function of the scheduled in-person visit intervals by studying a simple representative model through repeated Monte Carlo computer simulations.[15] The model was based on the following assumptions:

- Two "virtual" patient samples of 2,000 subjects each were considered. It was assumed that both samples had the same characteristics of our original population. In particular, the annual probability of experiencing an AF episode lasting more than 24 hours (hereafter indicated as $\geq$24-hour AF episode) was assumed to be equal to the Kaplan-Meier 2-year cumulative rate estimate of $\geq$24-hour AF obtained in our "real" population.
- One virtual group of patients was supposed to be followed up with a conventional schedule of in-person visits with varying intervisit intervals (standard follow-up [SF] group), while the other virtual group controlled only remotely with HM (HM group).
- Each simulated occurrence of a $\geq$24-hour AF episode was associated with mild or severe symptoms with a probability equal to the respective rate estimates of symptoms observed in our real population (18% of patients with mild symptoms and 9% with severe symptoms). In case of symptoms, it was assumed that a patient would have referred to the physician and started anticoagulation within 3 days. Otherwise, a virtual asymptomatic subject would have waited until the next scheduled follow-up for anticoagulation if belonging to the SF group, or only 3 days if belonging to the HM group.
- For each virtual subject experiencing $\geq$24-hour AF, an a priori risk of stroke was assigned basing on the corresponding $CHADS_2$ class.[16] $CHADS_2$ risk stratification is based on 7 classes indexed by adding 1 or 2 points for each risk factor (congestive heart failure, hypertension, age $\geq$75, diabetes mellitus, prior stroke, or transient ischemic attack). It was assumed that both virtual samples had the same

$CHADS_2$ risk class distribution of the original population. Whenever a virtual subject experienced a ≥24-hour AF episode during the simulated period, a daily probability of stroke was assigned to that subject corresponding to his/her own $CHADS_2$ class. The risk for stroke after anticoagulation initiation was not considered negligible but rather reduced by 62%, basing on meta-analysis of trials on anticoagulation therapy in AF.[17] Therefore, the simulation results also accounted for the anticipated adverse events possibly associated with anticoagulation (hemorrhagic strokes, for instance).

Follow-up simulations for both virtual groups were carried on simultaneously up to 2 years (710 days) and repeated 1,000 times. The entire procedure was replicated for different intervisit intervals in the SF group: 3, 6, 9, and 12 months, in accordance with the recommendations of the recent Expert Consensus document on monitoring of implantable cardiac devices.[18] Within the specified model, the main objective of the Monte Carlo simulations was to generate estimates of the 2-year frequency of strokes occurring in each group, the absolute and relative risk of stroke in case of ≥24-hour AF, and the delay of the anticoagulation initiation in the SF group with respect to the HM group.

In the original population, serving as a reference model for generating the Monte Carlo simulations, patients already on anticoagulation therapy at the time of implant were excluded. Therefore, the simulated stroke risk estimates should be regarded as essentially due to the delay of anticoagulation initiation caused by a periodic in-person follow-up strategy as compared to HM remote control in a standard cohort of pacemaker and ICD patients who are not on anticoagulation therapy at implant.

Statistical Analysis

Means and standard deviation were used for continuous variables if normally distributed, median and interquartile range for skew distributions. Categorical variables were expressed as percentages with standard deviation. The 95% confidence intervals (95% CI) were calculated and reported whenever appropriate. Two-year cumulative probabilities of ≥24-hour AF and their 95% CI were estimated by means of the product-limit method and the corresponding Kaplan-Meier plots were generated.

Monte Carlo simulations were performed on custom software edited in Visual Basic programming language. It was essentially based on repeated drawings, under binomial probabilities, of a computer-generated random variable uniformly distributed within the 0–1 range. Each simulation consisted of 1,000 iterations, including 4,000 virtual subjects divided into the SF and HM groups, and reproducing a follow-up period of 710 days. The results of the iterations were combined and treated with weighting methods,[19] reporting expected values and standard errors of the simulated variables. The between-group risk ratio estimates and their tolerance were obtained with the Yusuf's formula for odds ratio (OR) and 95% CI.

Statistical analysis was performed with Statistica 7.1 (StatSoft Inc., Tulsa, OK, USA) software package.

Results

Enrolled Population

One hundred sixty-three patients were implanted with dual-chamber pacemaker (Biotronik Cylos DR-T), dual-chamber ICD (Biotronik Lumos DR-T), and ICD-CRT (Biotronik Kronos LV-T or Lumax 300 HF-T), and routinely followed up both remotely by HM and with periodic in-person visits for up to 2 years. Population characteristics and pharmacological therapy are detailed in Table 1. This composite population was unselected for AF, as only 48 patients (29%) had documentation of prior paroxysmal AF. Twenty-seven patients (16%) were on anticoagulation therapy prior to implant, while 91 (56%) were assuming antiplatelet drugs.

Table 2 draws up the list of the $CHADS_2$ class distributions in case of AF along with the expected annual stroke rates (as reproduced from the National Registry of AF data), assuming that antiplatelet and anticoagulation were not taken.[16] The distributions listed refer to both the entire population and the subgroup of patients not assuming oral anticoagulation therapy at implant. No patient had absolute contraindication to anticoagulation. The median $CHADS_2$ score was 2 (interquartile range 1–2). Applying the expected risk for stroke to the actual $CHADS_2$ class distribution of our population, the mean stroke rate was 3.7% ± 1.6% (95%CI 0.6–6.9%) for the subgroup of patients with no oral anticoagulation therapy at implant. Of the 48 patients with documented AF episodes prior to implant, 15 (31% of this group) were taking oral anticoagulation therapy and 22 (46%) antiplatelets. For 11 (23%) patients, no antithrombotic therapy was being administered. In patients with prior AF and no oral anticoagulation therapy prescribed (including also patients taking antiplatelets), the median $CHADS_2$ class was 1 (interquartile range 1–2): 4 patients were in class 0, 14 in class 1, 7 in class 2, 6 in class 3, 2 in class 4, and none in classes 5 and 6. Decision of prescribing/not prescribing oral anticoagulation therapy at implant was left to the referring physician. Main reasons for not prescribing oral anticoagulation therapy in patients in $CHADS_2$ ≥2 were short duration of paroxysmal AF episodes, ongoing double antiplatelet therapy after coronary stenting, and physician preference.

Incidence of ≥24-Hour AF Episodes During Follow-Up

During a mean follow-up of 16 ± 7 months, HM alerts for AF episodes were notified in 42 patients (26%). In 4 of these patients, arrhythmia was not confirmed (false-positive episodes due to atrial far-field R-wave oversensing). AF with a 24-hour burden of 100% was reported in 18 patients (11%). True-positive arrhythmias were confirmed in all of them. Thirty-three patients were contacted for unscheduled phone interviews or in-person visits. Most of them were asymptomatic for AF (24/33, 73%), while 6 patients reported mild symptoms and 3 severe symptoms. The estimate of AF-related mild and severe symptom rate was 27.3% ± 7.8% (95%CI 13.3–45.5%) and 9.1% ± 5.0% (95% CI 1.9–24.3%) for severe symptoms only.

The product-limit estimates of 2-year cumulative probability of ≥24-hour AF were 15.9% ± 3.8% (95%CI 8.5–23.3%) for the entire population and 11.4% ± 3.8% (95%CI 4.0–18.8%) for the subgroup of patients with no anticoagulation therapy at implant. The Kaplan-Meier curves of time

TABLE 1
Patient Characteristics of the Original Population

	Pacemaker (N = 121)	Dual-Chamber ICD (N = 20)	ICD-CRT (N = 22)
Age (years)	75 ± 9	62 ± 14	71 ± 9
Male (%)	60 (50%)	18 (90%)	19 (86%)
Implant indication, n (%)	SSS: 67 (55%) AV block: 29 (24%) Neuromediated syncope: 25 (21%)	Primary prevention: 9 (45%) Secondary prevention: 11 (55%)	Primary prevention: 20 (91%) Secondary prevention: 2 (9%)
Ejection fraction (%)	53 ± 9	37 ± 13	30 ± 6
Structural heart disease, n (%)			
None	43 (36%)	3 (15%)	0 (0%)
Hypertension	48 (40%)	2 (10%)	4 (18%)
Ischemic	22 (18%)	10 (50%)	8 (36%)
Valvular	6 (5%)	0 (0%)	0 (0%)
Cardiomyopathy	2 (2%)	4 (20%)	10 (45%)
Prior MI, n (%)	10 (8%)	6 (30%)	4 (18%)
Prior revascularization, n (%)			
PCI	9 (7%)	1 (5%)	3 (14%)
CABG	3 (2%)	1 (5%)	2 (9%)
Prior stroke, n (%)	4 (3%)	0 (0%)	0 (0%)
Prior AF, n (%)	45 (37%)	1 (5%)	2 (9%)
Prior RF ablation, n (%)	3 (2%)	0 (0%)	0 (0%)
Drug therapy, n (%)			
Anticoagulation	18 (15%)	3 (15%)	6 (27%)
Antiplatelet	69 (57%)	10 (50%)	12 (54%)
Beta-blockers	26 (21%)	16 (80%)	18 (82%)
Calcium antagonists	7 (6%)	0 (0%)	0 (0%)
ACE inhibitors	54 (45%)	15 (75%)	20 (91%)
Sartans	31 (26%)	3 (15%)	2 (9%)
Diuretics:	44 (36%)	14 (70%)	21 (95%)
Furosemide	19 (16%)	12 (60%)	20 (91%)
Others	25 (21%)	2 (10%)	1 (5%)
Amiodarone	15 (12%)	3 (15%)	6 (27%)
Sotalol	2 (2%)	0 (0%)	0 (0%)
Class 1A AA	1 (1%)	0 (0%)	0 (0%)
Class 1C AA	16 (13%)	0 (0%)	0 (0%)

AA = antiarrhythmics; AF = atrial fibrillation; AV = atrioventricular; CABG = coronary artery bypass grafting; CRT = cardiac resynchronization therapy; ICD = implantable cardioverter-defibrillator; MI = myocardial infarction; PCI = percutaneous coronary intervention; RF = radiofrequency; SSS = sick sinus syndrome.

to first occurrence of ≥24-hour AF episodes are plotted in Figure 1. Times of occurrences are referred to the first HM notification of a ≥24-hour AF episode. No patient experienced stroke or transient ischemic attacks during the follow-up.

Monte Carlo Follow-Up Simulations: Stroke OR Estimates Between HM and SF Groups

Two series of 4 simulations each (a total of 8 simulations) were performed, varying several parameters as follows. It was assumed a 2-year cumulative probability of ≥24-hour AF of 11.4% ± 3.8%, while the probability of symptoms was set at 27.3% (as the total rate of symptomatic patients observed) and 9.1% (considering only severe symptoms). For each symptom rate, Monte Carlo simulations were repeated assuming a schedule of in-person visits with varying intervals of 3, 6, 9, and 12 months for the SF group.

The results of such simulations are displayed in Table 3. As compared with the immediate notification of the HM transmissions, the expected delay of ≥24-hour AF episode detections progressively increased in the SF groups as far as intervals between consecutive in-person visits increased. Focusing on the first set of simulations relative to the 2-year ≥24-hour AF rate of 11.4% and a symptom probability of 27.3%, the expected delay ranged from 33.6 ± 2.2 days with a 3-month intervisit schedule and 135.1 ± 9.0 days for an annual visit schedule. Such estimates were even higher with the 9.1% probability of severe symptoms: the delays increased from 41.4 ± 1.9 days with a 3-month follow-up program up to 168.7 ± 7.7 days with a 12-month follow-up program. As a result of the increasing delays of ≥24-hour AF detection, delayed anticoagulation initiation caused increasing rates of stroke occurrences: with a symptom probability of 27.3%, the estimated percentage of patients with strokes in case of ≥24-hour AF increased from 2.4% ± 1.1% for a 3-month follow-up program up to 2.9% ± 1.3% for an annual in-person visit schedule; stroke incidence estimates were very similar for a 9.1% probability of severe AF-related symptoms. The rate of stroke in the HM group was always estimated at 2.3% ± 1.1%. The percentage of strokes occurring during the delay before anticoagulation initiation progressively increased in the SF group with the increasing of the between-visit interval from a minimum of 12% (3-month intervisit interval, symptom probability 27.3%) to a maximum of 50% (annual visit schedule, symptom probability 9.1%).

The OR estimates (HM group better if OR<1) varied accordingly (Fig. 2) as a function of the follow-up program, with risk reductions in favor of the HM group of 3%, 9%, 13%, and 18%, assuming 27.3% of symptomatic patients, and 3%, 9%, 14%, and 21%, assuming 9.1% of symptomatic patients. Of note, the effect of AF-related symptoms on OR estimates was rather small within the considered range. With

TABLE 2
$CHADS_2$ Class Distribution of the Original Population

$CHADS_2$ Class	Patients (n, %) All	No OAT at Implant	Expected Stroke Rate per 100 Patient-Years*
0	20 (12%)	19 (13%)	1.9%
1	55 (34%)	48 (35%)	2.8%
2	65 (40%)	49 (36%)	4.0%
3	16 (10%)	14 (10%)	5.9%
4	6 (4%)	5 (4%)	8.5%
5	1 (1%)	1 (1%)	12.5%
6	0 (0%)	0 (0%)	18.2%
Total	163	136	
Median class (interquartile range)	2 (1–2)	2 (1–2)	
Expected mean annual stroke rate (mean ± SD)		3.7% ± 1.6%	

$CHADS_2$ class distribution in case of AF for the entire population and the subgroup of patients not taking OAT at implant.
*Expected annual rate of strokes in each class as reproduced from the US National Registry of Atrial Fibrillation results.[17]
AF = atrial fibrillation; OAT = oral anticoagulation therapy; SD = standard deviation.

our settings for Monte Carlo simulations, the only nonsignificant OR estimates were found for the 3-month follow-up program: in this case, the OR resulted 0.97 (95%CI 0.93–1.01) with 95% CI including the risk parity condition (OR = 1).

Discussion

Potential Benefits of HM in Case of AF Occurrence

Early detection of asymptomatic AF by HM allows prompt clinical reaction including antiarrhythmic therapy optimization, cardioversion, and timely introduction of anticoagulation therapy in patients with long-lasting episodes.[13] Early anticoagulation potentially reduces stroke risk. To demonstrate whether HM remote monitor actually reduces stroke risk when compared with in-person follow-up is an extremely challenging issue and requires large trials enrolling thousands of patients. The ongoing prospective IMPACT trial,[20] dealing with this issue, will enroll more than 2,700 patients and the results are expected by 2014.

Monte Carlo Simulations: Method and Assumptions

Monte Carlo methods are a special class of computer simulations often used in medical research,[21–23] when it is technically infeasible or ethically censurable to measure clinically relevant quantities by direct experiences on human beings. In the context of our work, computer simulations appeared naturally suited since our ultimate purpose was to assess whether arbitrarily increasing the interval between in-person visits may expose unselected patients with cardiac implantable devices to correspondingly higher risks for AF-related stroke when remote control with daily reporting is not active. Strokes are catastrophic events with absolutely unpredictable onset and relatively low probabilities to occur in a limited time frame. Computer simulations are particularly appealing for studying such intrinsically chaotic systems. Its fitness for easily treating rare and chaotic events can be regarded as the main strength of this approach and at the same time its weakness, since the results of simulations depend on the initial assumptions that represent an inevitably crude approximation of what would really happen in the "real world." In our model, the major assumptions could be briefly recalled as follows: 24-hour AF duration as the least limit to consider anticoagulation neglecting shorter episodes, 11.4% 2-year

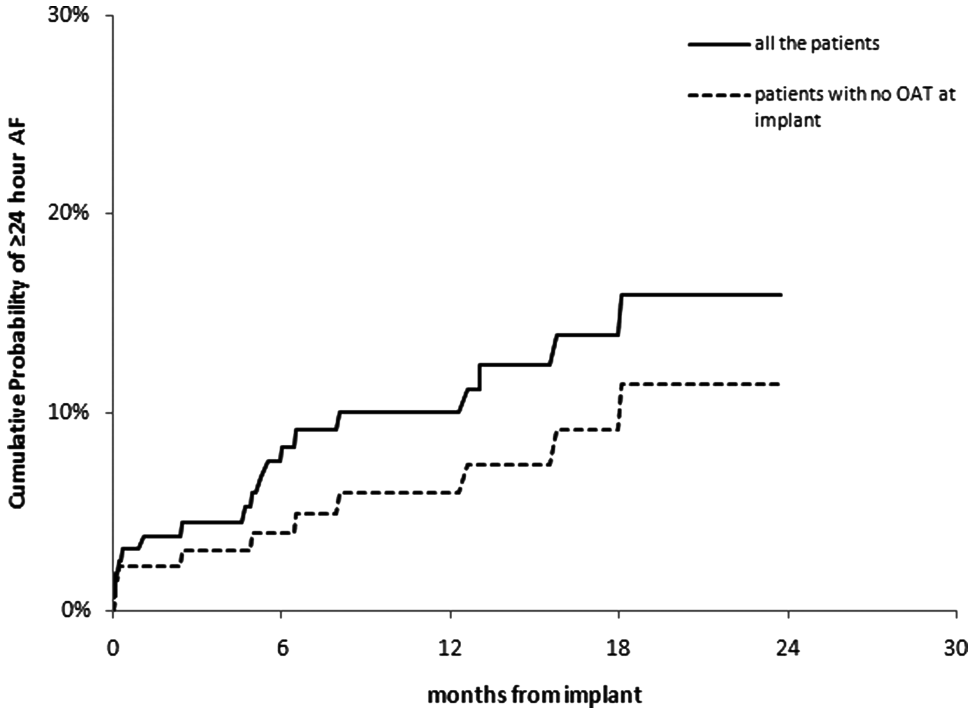

Figure 1. *Kaplan-Meier curves of the 2-year cumulative probabilities of atrial fibrillation episodes lasting 24 hours or more (≥24-hour atrial fibrillation) for all the patients of the original population and the subgroup of patients who were not taking OAT at implant. OAT = oral anticoagulation therapy.*

TABLE 3
Results of the Monte Carlo Simulations

Interval between scheduled in-person visits	Standard Follow-Up: Expected delay of significant AF detection (mean number of days ± SE)	Standard Follow-Up: Expected 2-year stroke rate in patients with significant AF (% ± SE)	Standard Follow-Up: Percentage of strokes occurring during the AF detection delay (% ± SE)	Home Monitoring: Expected 2-year stroke rate in patients with significant AF (% ± SE)	OR* (95% CI)
A. Probability of significant AF episode lasting more than 24 hours: 11.4% (as in patients not taking anticoagulation prior to implant)					
Probability of AF-related symptoms: 27.3%					
3 months	33.6 ± 2.2	2.4 ± 1.1	12.3 ± 16.5	2.3 ± 1.1	0.97 (0.93–1.01)
6 months	67.0 ± 4.4	2.5 ± 1.2	25.6 ± 21.7	2.3 ± 1.1	0.91 (0.88–0.95)
9 months	107.5 ± 6.7	2.7 ± 1.2	35.0 ± 24.8	2.3 ± 1.1	0.87 (0.84–0.90)
12 months	135.1 ± 9.0	2.9 ± 1.3	44.9 ± 23.8	2.3 ± 1.1	0.82 (0.79–0.85)
B. Probability of severe AF-related symptoms: 9.1%					
3 months	41.4 ± 1.9	2.4 ± 1.1	13.0 ± 16.4	2.3 ± 1.1	0.97 (0.93–1.01)
6 months	83.4 ± 3.8	2.6 ± 1.2	27.7 ± 21.9	2.3 ± 1.1	0.90 (0.87–0.94)
9 months	134.2 ± 5.4	2.7 ± 1.3	38.1 ± 24.4	2.3 ± 1.1	0.86 (0.82–0.89)
12 months	168.7 ± 7.7	2.9 ± 1.3	50.3 ± 22.7	2.3 ± 1.1	0.79 (0.76–0.82)

Monte Carlo simulations were performed assuming 2,000 patients in each group (standard follow-up group and home monitoring group) and followed for 2 years. It was also assumed an annual rate of AF episodes of more than 24 hours equal to that observed in the patient subgroup of the original population not taking anticoagulation at implant. Patients in the standard follow-up group would have referred to the attending physician and initiated anticoagulation within 3 days in case of AF-related symptoms or at the next scheduled in-person visit in case of no symptoms. Home monitoring patients would have started anticoagulation 3 days after ≥24-hour AF onset, regardless of symptoms. Simulations were repeated 1,000 times.
*Home Monitoring better if OR <1.
AF = atrial fibrillation; CI = confidence interval; OR = odds ratio; SE = standard error.

probability of experiencing ≥24-hour AF episodes, 27.3% or 9.1% rate of symptoms, stroke risk stratification based on the $CHADS_2$ index, and 62% risk reduction after oral anticoagulation therapy initiation. Also, it was tacitly assumed that HM remote control would have been perfectly managed without any misreporting, misinterpretation, or delay of event detection, so that any ≥24-hour AF episode would have always initiated oral anticoagulation therapy within 3 days. However, although included in a simulated model, these assumptions reflected our clinical experience and were essentially based both on our 163 patient population data and on widely accepted published results; therefore, they should be robust enough to give significant hint for future applications or design of "real" trials. Our results might somewhat represent anticipated estimates of the outcome of the ongoing IMPACT study[20] and a reliable reference for its power calculation: the

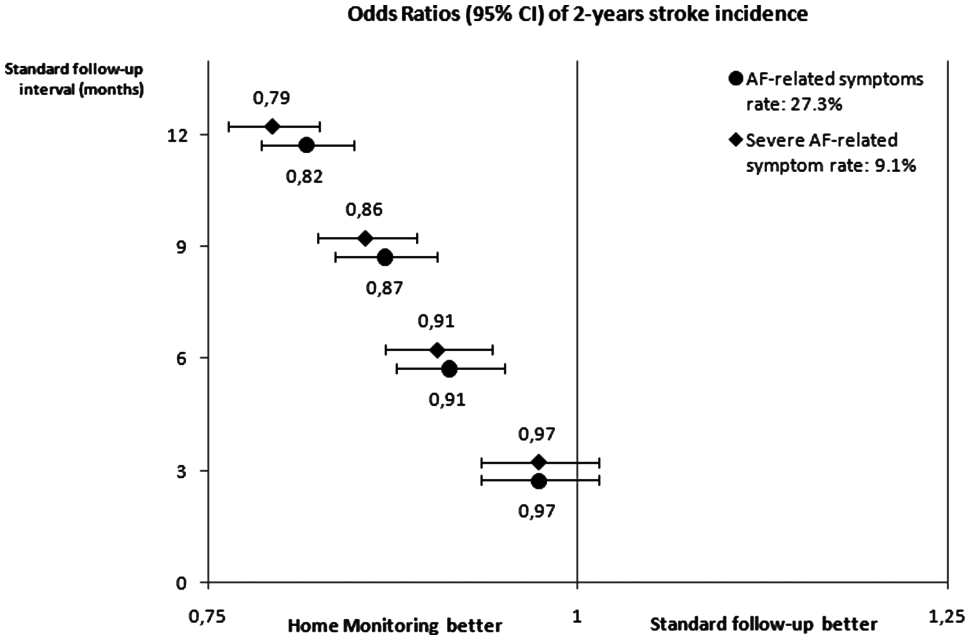

Figure 2. *Estimated odds ratios (ORs) of 2-year stroke occurrence in case of significant atrial fibrillation as generated by Monte Carlo simulations. ORs and their 95% CI are plotted as a function of the interval between two consecutive scheduled in-person visits. Circles refer to ORs resulting by assuming 27.3% atrial fibrillation-related symptoms, squares to ORs obtained by considering only 9.1% rate of severe atrial fibrillation-related symptoms. CI = confidence interval.*

study has similar purpose and design of the model simulated here, except for the inclusion criteria recruiting ICD patients only.

Main Finding of Our Analysis

The main result of our simulation is that HM may reduce stroke risk by 9% to 18% if compared with standard in-person visits scheduled every 6 to 12 months, with an absolute reduction of 0.2% to 0.6%. Although this result was derived from a clinical experience performed using a particular paradigm for remote control, it may apply to any remote monitoring system, provided that this is based on wireless automatic daily transmissions with immediate (within 24 hours) notification of AF episodes. Despite that the estimated risk reduction may appear rather small, it comes with all the already mentioned benefits associated with HM (device failure surveillance, early detection of and prompt reaction to atrial and ventricular arrhythmias, heart failure progression, therapy and device programming optimization). That is particularly meaningful if we take into account that HM requires only organizational changes with negligible costs and is associated with a reduction of health care resource consumption, as confirmed by the recently presented data of the TRUST study, in which remote monitoring of ICD patients reduced clinic visits by $>40\%$ over 12 months, with no difference in mortality and adverse events between the 2 groups.[14] In-person visits for cardiac device control are generally scheduled every 3 to 6 months, therefore, our computer simulations for 9- and 12-month intervals may overstate the case. However, due to the increasing follow-up burden, more and more centers are compelled to extend the between-visit intervals up to 12 months, as it was also acknowledged in the recent Expert Consensus on management of cardiac devices.[18] This makes even more appealing the benefits of remote monitoring. Safety of extending between-visit intervals by simultaneously applying remote monitoring had been previously documented.[4]

Guideline Implementation

European surveys demonstrated that 33% to 50% of patients with indication for anticoagulation because of AF are not actually treated.[24,25] Similarly, in our series 31% of patients with prior AF and $CHADS_2$ score ≥ 2 were not actually anticoagulated. Main reasons for that were short duration of paroxysmal AF episodes, ongoing double antiplatelet therapy after coronary stenting, and physician preference. From this point of view, remote monitoring may represent a useful tool to implement guideline application in standard clinical practice. Daily monitoring of arrhythmia recurrences may lead to further tailored risk stratification by combining $CHADS_2$ score with the actual arrhythmia burden. It has been reported that patients with $CHADS_2$ 2 score but without arrhythmia recurrences may be considered at low risk and may need only antiplatelet therapy. On the contrary, patients with $CHADS_2$ 1 score but with AF episodes lasting more than 24 hours are at high risk and need anticoagulation therapy.[26]

Study Limitations

Limitations of this study are ultimately related to the assumptions defining the simulated computer model. Most of them were already discussed, but 2 further points should be outlined. First, in our model it was assumed that without remote monitoring an AF episode (asymptomatic or mildly symptomatic) would have been undetected until the next follow-up. Actually, there might be several circumstances (general practitioner visits, electrocardiogram exams due for any reason, etc.) in which asymptomatic AF may be detected or suspected. The chance of such an occurrence is difficult to estimate and any attempt to introduce it in our model appeared speculative. Admittedly, neglecting such occurrences might have biased the simulation outcomes in favor of HM.

As a second limitation of this analysis, we assumed that paroxysmal AF episodes shorter than 24 hours would have been associated with a negligible risk for stroke. Actually, it has been reported that even occasional occurrences of AF may give rise to thromboembolic events.[11,26,27] However, an unambiguous and widely accepted AF burden limit to introduce antithrombotic therapy is less established.[11,12,28] As for the purpose of our analysis, our choice was therefore prudently based on a documented though conservative correlation between stroke occurrences and sustained $\geq$24-hour AF episodes.[10] This may have introduced a distortion in our results, potentially underestimating the actual proportion of patients at risk of stroke and in turn the estimated benefit of HM.

Conclusion

In conclusion, daily remote monitoring of patients with implanted devices potentially reduces the stroke risk by 9% to 18% with respect to standard follow-up with intervisit intervals of 6 to 12 months.

References

1. Wallbrück K, Stellbrink C, Santini M, Gill J, Hartmann A, Wunderlich E: The value of permanent follow-up of implantable pacemakers–first results of an European trial. Biomed Tech (Berl) 2002;47(Suppl 1 Pt 2):950-953.
2. Lazarus A: Remote, wireless, ambulatory monitoring of implantable pacemakers, cardioverter defibrillators, and cardiac resynchronization therapy systems: Analysis of a worldwide database. Pacing Clin Electrophysiol 2007;30:S2-12.
3. Calcagnini G, Censi F, Floris M, Pignalberi C, Ricci R, Biancalana G, Bartolini P, Santini M: Evaluation of electromagnetic interference of GSM mobile phones with pacemakers featuring remote monitoring functions. Pacing Clin Electrophysiol 2006;29:380-385.
4. Brugada P: What evidence do we have to replace in-hospital implantable cardioverter defibrillator follow-up? Clin Res Cardiol 2006;95(Suppl 3):iii3-iii9.
5. Fauchier L, Sadoul N, Kouram C, Briand F, Chauvin M, Babuty D, Clementy J: Potential cost savings by telemedicine-assisted long-term care of implantable cardioverter defibrillator recipients. Pacing Clin Electrophysiol 2005;28(Suppl 1):S255-259.
6. Siaplaouras S, Buob A, Neuberger HR, Mewis C: Remote detection of incessant slow VT with an ICD capable of home monitoring. Europace 2007;8:512-514.
7. Ricci RP, Morichelli L, Santini M: Home monitoring remote control of pacemaker and implantable cardioverter defibrillator patients in clinical practice: Impact on medical management and health-care resource utilization. Europace 2008;10:164-170.
8. Defaye P, Dournaux F, Mouton E: Prevalence of supraventricular arrhythmias from the automated analysis of data stored in the DDD pacemakers of 617 patients: The AIDA multicenter study group. Automatic interpretation for diagnosis assistance. Pacing Clin Electrophysiol 1998;21:250-255.
9. Orlov MV, Ghali JK, Araghi-Niknam M, Sherfesee L, Sahr D, Hettrick DA, for the Atrial High Rate Trial Investigators: Asymptomatic atrial fibrillation in pacemaker recipients: Incidence, progression, and determinants based on the atrial high rate trial. Pacing Clin Electrophysiol 2007;30:404-411.

10. Capucci A, Santini M, Padeletti L, Gulizia M, Botto G, Boriani G, Ricci R, Favale S, Zolezzi F, Di Belardino N, Molon G, Drago F, Villani GQ, Mazzini E, Vimercati M, Grammatico A, Italian AT500 Registry Investigators: Monitored atrial fibrillation duration predicts arterial embolic events in patients suffering from bradycardia and atrial fibrillation implanted with antitachycardia pacemakers. J Am Coll Cardiol 2005;46:1913-1920.
11. Glotzer TV, Hellkamp AS, Zimmerman J, Swenney MO, Yee R, Marinchak R, Cook J, Paraschos A, Love J, Radoslovich G, Lee KL, Lamas GA: Atrial high rate episodes detected by pacemaker diagnostics predict death and strokes. Report of the atrial diagnostics ancillary study of the mode selection trial (MOST). Circulation 2003;107:1614-1619.
12. Israel CW, Gronefeld G, Ehrlich JR, Li YG, Hohnloser SH: Long-term risk of recurrent atrial fibrillation as documented by an implantable monitoring device. Implication for optimal patient care. J Am Coll Cardiol 2004;43:47-52.
13. Ricci RP, Morichelli L, Santini M: Remote control of implanted device through home monitoring technology improves detection and clinical management of atrial fibrillation. Europace 2009;11:54-61.
14. Varma N: Evaluation of efficacy and safety of remote monitoring for ICD follow-up: The TRUST trial. Paper presented at American Heart Association 2008 Scientific Session, November 11, 2008, New Orleans, LA. New Trials in Electrophysiology and Pacing.
15. Fishman GS: *Monte Carlo: Concepts, Algorithms, and Applications*. New York: Springer-Verlag, 1996.
16. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ: Validation of clinical classification schemes for predicting stroke. Results from the National Registry of Atrial Fibrillation. JAMA 2001;285:2864-2870.
17. Lip GYH, Hart RG, Conway DSG: Antithrombotic therapy for atrial fibrillation. BMJ 2002;325:1022-1025.
18. Wilkoff BL, Auricchio A, Brugada J, Cowie M, Ellenbogen KA, Gillis AM, Hayes DL, Howlett JG, Kautzner J, Love CJ, Morgan JM, Priori SG, Reynolds DW, Schoenfeld MH, Vardas PE: HRS/EHRA Expert Consensus on the monitoring of cardiovascular implantable electronic devices [CIEDs]: Description of techniques, indications, personnel, frequency and ethical considerations. Europace 2008;10:707-725.
19. Armitage P, Berry G, Matthews JNS: *Statistical Methods in Medical Research*, 4th ed. Malden: Blackwell Science, 2002, p. 127.
20. http://clinicaltrials.gov/ct2/show/NCT00559988. Accessed January 14, 2009.
21. Saito I, Kobayashi M, Matsushita Y, Mori A, Kawasugi K, Saruta T: Cost-utility analysis of antihypertensive combination therapy in Japan by a Monte Carlo simulation model. Hypertens Res 2008;31:1373-1383.
22. Smolen HJ, Cohen DJ, Samsa GP, Toole JF, Klein RW, Furiak NM, Lorell BH: Development, validation and application of a microsimulation model to predict stroke and mortality in medically managed asymptomatic patients with significant carotid artery stenosis. Value Health 2007;10:489-497.
23. Sullivan PW, Arant TW, Ellis SL, Ulrich H: The cost effectiveness of anticoagulation management services for patient with atrial fibrillation and at high risk of stroke in the US. Pharmacoeconomics 2006;24:1035-1038.
24. Nieuwlaat R, Capucci A, Camm AJ, Olsson SB, Andresen D, Davies DW, Cobbe S, Breithardt G, Le Heuzey JY, Prins MH, Lévy S, Crijns HJ, European Heart Survey Investigators: Atrial fibrillation management: A prospective survey in ESC member countries: The Euro heart survey on atrial fibrillation. Eur Heart J 2005;26:2422-2434.
25. Friberg L, Hammar N, Ringh M, Pettersson H, Rosenqvist M: Stroke prophylaxis in atrial fibrillation: Who gets it and who does not? Report from the Stockholm cohort-study on atrial fibrillation (SCAF-study). Eur Heart J 2006;27:1954-1964.
26. Botto GL, Padeletti L, Santini M, Capucci A, Gulizia M, Zolezzi F, Favale S, Molon G, Ricci R, Biffi M, Russo G, Vimercati M, Corbucci G, Boriani G: Presence and duration of atrial fibrillation detected by continuous monitoring: Crucial implications for the risk of thromboembolic events. J Cardiovasc Electrophysiol 2009;20:241-248.
27. Barthélémy JC, Féasson-Gérard S, Garnier P, Gaspoz JM, Da Costa A, Michel D, Roche F: Automatic cardiac event recorders reveal paroxysmal atrial fibrillation after unexplained strokes or transient ischemic attacks. Ann Noninvasive Electrocardiol 2003;8:194-199.
28. Liao J, Khalid Z, Scallan C, Morillo C, O'Donnell M: Noninvasive cardiac monitoring for detecting paroxysmal atrial fibrillation or flutter after acute ischemic stroke. A systematic review. Stroke 2007;38:2935-2940.