Home Monitoring for the
Management of Patients with Atrial Tachyarrhythmia −
An International Multicenter Clinical Trial

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Summary

Using modern communication systems, Home Monitoring enables frequent transmissions of data from an electrotherapeutic implant to the attending physician. Hence, the physician receives diagnostic information without the patient having to make an office visit. Thus, new possibilities arise for detailed medical and event-correlated monitoring of the patient's therapy using electrically active implants. Adequacy and efficiency of both the implant therapy and the accompanying drug therapy could be optimized. In the following, we present the concept of the international multicenter clinical study "Home Monitoring for the Management of Patients with Atrial Tachyarrhythmia" (HomePAT). The objective of this study is to investigate the possible advantages of Home Monitoring for patients with sinus node disease with respect to recognition and treatment of atrial tachyarrhythmia (AT), especially paroxysmal atrial fibrillation (PAF). Patients with AT may benefit from daily documentation of their atrial rhythm for several reasons. First, the immediate information on the first onset of AT may indicate the necessity of antiarrhythmic measures. Second, the information on the onset of AT, especially PAF, within 24 hours of a recurrence enables an immediate therapeutic reaction, thus increasing the efficiency of orally administered antiarrhythmic agents, as well as avoiding or lowering the costs of cardioversion. Finally, the tailoring of antiarrhythmic therapy can be supported by direct feedback about the therapy's efficacy. The study shall include 490 patients with sinus node disease with or without previously documented AT. The patients will be monitored in the study for 6 months. The study will be conducted as a prospective, randomized, single-blinded investigation.

Key Words

Home Monitoring, telecardiology, clinical trial, atrial tachyarrhythmia

Introduction

In pacemaker therapy, appropriate treatment for the different kinds of supraventricular tachyarrhythmia in paced patients is still a challenging task. The appropriate type and implementation of treatment, including the use of antiarrhythmic medication or antitachycardia preventive pacing is an ongoing controversy. The current standard follow-up methods for pacemaker patients do not support optimal antitachycardia therapy. Presently, follow-ups are conducted at 3- to 6-month intervals, or even extending to as long as 12 months. Asymptomatic tachyarrhythmia is either hidden until the next routine follow-up, or detected by chance. Therefore, it is rarely possible to immediately respond to asymptomatic tachycardia episodes, both at first onset and after recurrences. It is also difficult to receive continuous feedback about the initiated antitachycardia therapy, consisting of both medication and therapeutic or preventive pacing.

Home Monitoring (HM) is an automatic, long-distance implantation telemetry system that has recently been developed to correct this situation. It provides frequent, regular transmissions of data from the pacemaker memory via a customized cellular phone to an HM Service Center that relays the data to the attending physician. Home Monitoring offers a high degree of automation and relies only to a small extent on the

Figure 1. Philos DR-T (Biotronik, Germany).

patient's cooperation. Hence, it is ideally suited for remote monitoring of pacemaker patients. The purpose of this paper is to present the concept of the "Home Monitoring for the Management of Patients with Atrial Tachyarrhythmia" (HomePAT) clinical study and the systems used in this investigation.

Materials and Methods

The Home Monitoring System

The HM system consists of four parts: the HM implant, the patient device, the HM Service Center, and the Cardio Report [1]. Preliminary results of the first clinical trial on feasibility and reliability of HM show that 90% of all HM messages can be successfully transmitted from the pacemaker to the HM Service Center [2]. In the HomePAT trial, the Philos DR-T (Biotronik, Germany) dual-chamber rate-adaptive pacemaker is used (Figure 1). Along with standard pacemaker capabilities, it offers three kinds of HM messages:

- Periodic message: Once every 24 hours at a time programmable by the physician, the pacemaker transmits an HM message, summarizing the preceding 24 hours.
- Patient-activated message: The patient can trigger the transmission of an HM message by applying a magnet over the pacemaker.
- Event-triggered message: If any of the event criteria are met, the pacemaker triggers the transmission of an HM message. The available trigger sources are:
  - atrial or ventricular lead check failed;
  - ventricular run, i.e., four to eight consecutive ventricular extrasystoles (VES) occurred;
  - ventricular episode, i.e., more than eight consecutive ventricular extrasystoles occurred;
  - mean P- or R-wave amplitude with less than a 50% safety margin, i.e., the amplitude is between 1 and 1.5 times the programmed sensitivity;
  - ERI (elective replacement indicator) condition occurred.

The contents of the three message types are identical and include the following diagnostic markers and information about the status of the system:

- mean ventricular heart rate;
- atrial and ventricular intrinsic events, as a percentage of all atrial or ventricular events (As/Ax, Vs/Vx);
- number of mode switches and duration of mode switches, as a percentage of the time since the last message;
- ventricular heart rate at mode switch;
- number of ventricular runs (i.e., 4...8 consecutive VES) and ventricular episodes (i.e., more than 8 consecutive VES);
- duration of the longest ventricular episode, classified into one of the following bins:
  $0 \le t_1 < 0.5 \text{min}$, $0.5 \text{min} \le t_2 < 1 \text{ min}$, $1 \text{min} \le t_3 < 2 \text{ min}$, $t_4 \ge 2 \text{ min}$ or longer;
- atrioventricular (AV) synchrony, as a percentage of AV-sequences with respect to all ventricular events (AxVx/Vx);
- AV conduction sequences, as a percentage of all AV-synchronous events (AsVs/AxVx, ApVs/AxVx, AsVp/AxVx, ApVp/AxVx);
- result of the atrial and ventricular lead check;
- mean P- and R-wave amplitude with respect to programmed atrial and ventricular sensitivity; i.e.; whether the mean signal amplitude is lower than 1.5 times the programmed sensitivity, between 1.5 and 2 times the sensitivity, or greater than 2 times the sensitivity;
- battery status.

Hence, the HM markers present data from the pacemaker memory that could facilitate remote supervision of the rhythmologic and device status of a patient.
All transmitted information is displayed in the so-called Cardio Report, which is sent to the physician at regular intervals (the physician may choose from "daily," "weekly," or "every two weeks"). In addition,
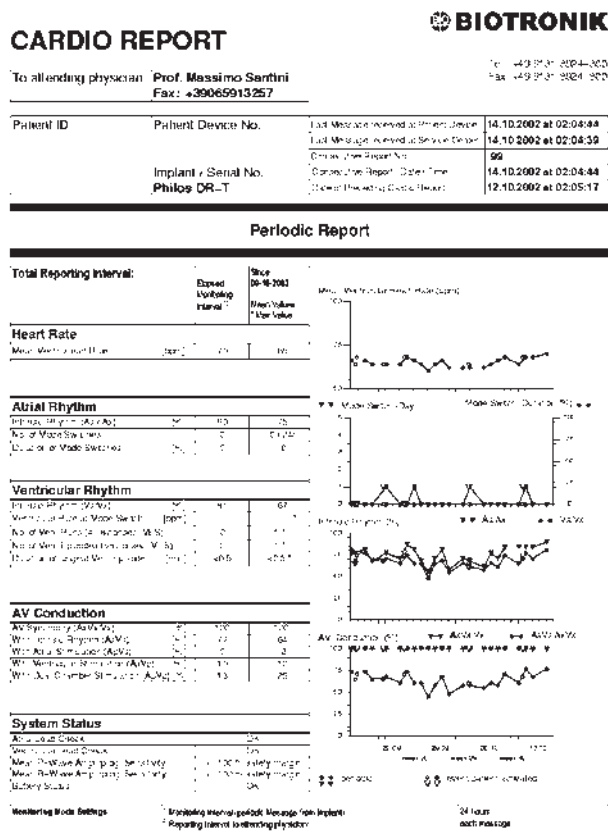
Figure 2. Periodic "Cardio Report" for the Philos DR-T pacemaker (Biotronik, Germany).

reports based on event-triggered or patient-activated messages can be faxed immediately to the physician. For every event-triggered source, the attending physician can choose whether or not the associated Cardio Reports should be forwarded immediately. The Cardio Report displays the markers of the most recent message and the average of the preceding 4 weeks in tabular format. The mean ventricular heart rate, number and duration of mode switches, atrial and ventricular intrinsic rhythm, and AV synchrony are displayed in graphs (Figure 2).

The HomePAT Trial

This study will focus on the diagnostic effectiveness of the telemetrically transmitted data with regard to the detection and treatment of atrial arrhythmia, especially paroxysmal atrial fibrillation (PAF). This will be done by comparing the incidence of atrial fibrillation (AF) for patients supervised by HM and for those who are

not. The comparison includes pacemaker memory data, symptom score data, and 24-hour ECG analyses. Additionally, the study will investigate the influence of HM on the patients' quality of life and gather data on the impact of HM on cost-effectiveness in combined pacemaker and antiarrhythmic therapy.

Primary Goal
As the primary goal, the trial investigates whether continuous diagnosis of PAF with the help of HM results in improved efficacy of antiarrhythmic therapy. The optimization of the antiarrhythmic therapy may involve atrial overdrive pacing by the pacemaker as well as antiarrhythmic medication. The investigation compares two groups:

- The "Cardio Report" group: HM is switched on and the Cardio Reports are forwarded to the physician based on pre-determined specifications.
- The "control" group: HM is also switched on for this group, but the Cardio Reports are not forwarded to the physician responsible for the patient. Only the event reports for atrial or ventricular lead check failure will be forwarded for this group, since this is not directly related to any of the endpoints, but may severely endanger the patient.

The efficacy of the antiarrhythmic therapy is believed to increase with HM if the incidence of significant AF in the Cardio Report group is less than it is in the control group. The occurrence of more than two episodes of AF lasting longer than 2 hours each will be classified as "incidence of significant AF." The incidence of AF and the total AF burden for each patient will be calculated from the mode switch counters interrogated at the follow-up visits. The HM transmissions will also be used to control the mode switch episode lists by comparing the summed duration of mode switch for all HM transmissions with the episode list interrogated at the follow-up visits.
The primary goal is investigated with the following null hypothesis (H_0), which maintains that the difference in the incidence of AF between the Cardio Report group and the control group is less than 35% of the incidence in the control group. The associated alternative hypothesis (H_1) is that the difference in the incidence of AF between the Cardio Report group and the control group is at least 35% of the incidence in the control group.

Secondary Goals

The secondary goals aim at an additional corroboration of the primary goal using an AT/AF symptom score, differences in quality-of-life for the Cardio Report group vs. the control group, and possible differences in the total costs of pacemaker and antiarrhythmic therapy due to the use of HM.

AT/AF symptom score: With the help of a patient questionnaire related to symptoms of atrial tachyarrhythmia, the effect of HM with respect to an increase in the efficacy of antiarrhythmic therapy shall be documented. The questionnaire asks about symptoms such as shortness of breath at rest and under physical stress, pain or pressure in the chest area, heart palpitations or skipping or racing, dizziness, etc. The patient questionnaire asks whether the patient has experienced these symptoms and to what extent they have limited the patient's daily life activities. The result is expressed as a symptom score. The associated alternative hypothesis is that the AF symptom score differs between the Cardio Report group and the control group.

Quality of life: In addition to the symptoms of atrial tachyarrhythmia, the general health perception of the patients is requested in the SF-36 health survey [3]. The SF-36 questionnaire is a widely used and accepted measure for quality of life in healthy individuals as well as in patients. Evaluation of SF-36 results will be performed by comparing baseline data with subsequent follow-up results. The associated secondary endpoint asks for differences between the Cardio Report group and the control group using the alternative hypo-thesis that the improvement in quality of life from pre-implantation to the 6-month follow-up shows a difference between the Cardio Report group and the control group. Furthermore, the analysis will comprise the evaluation of baseline and follow-up data among all patients according to age, gender, and pacemaker indication.

Costs of therapy: The economic aspects of HM for the management of patients with atrial tachyarrhythmia will be analyzed by estimating direct and indirect costs for scheduled and unscheduled (additional) follow-up examinations, costs of antiarrhythmic medication, and costs of arrhythmia-related adverse events, e.g., cardioversion, stroke, etc. Seven different cost categories are considered in detail:

- Cost D S: Costs d̲irectly associated with s̲tandard follow-up examinations, e.g., the examinations at discharge, 3 months, and 6 months after implantation.

- Cost D Ad: Costs d̲irectly associated with additi̲onal follow-up examinations, e.g., for cardioversion of AF; this category also comprises all follow-up examinations resulting from conclusions based on the Cardio Report.

- Cost ID S: Costs in̲directly associated with s̲tandard follow-up, e.g., traveling expenses and loss of productivity for patients and their travel companions, and the time spent on sick leave.

- Cost ID Ad: Costs in̲directly associated with addi̲tional follow-up.

- Cost M: Costs of acute and chronic m̲edication.

- Cost T: Costs associated with the treatment of adverse events by a t̲hird party, e.g., in an intensive care unit or rehabilitation clinic.

- Cost D HM: Cost d̲irectly associated with the use of HM̲, e.g., physician training, patient training, and Cardio Report analysis.

The total costs for the two groups are calculated by adding up all cost categories. The cost endpoint is investigated with the alternative hypothesis which contends that the costs in the control group Cost Control are not significantly different from the costs in the Cardio Report group CostCardio. The alternative hypothesis postulates no difference in costs between the control and Cardio Report groups because it is not expected that the impact of HM will be such that it will result in an overall cost reduction after only 6 months. It is expected that the additional costs of HM will be balanced by associated savings in therapy and reduced costs of arrhythmia-related events.

Study Design

The investigation is conducted as a

- prospective,
- randomized,
- single-blind,
- parallel group, and
- multicenter study.

It is single-blind, i.e., the participating patients are not aware that they are being monitored by HM. Randomization is done after hospital discharge. The physician does not know to which group a patient is randomized until the first HM message from the patient has reached the Service Center. Randomization is done by "blocks" of patients at each clinic, i.e., every clinic enrolls approximately the same number of patients into Cardio Report and control groups.

Population Sample Size

From a preliminary analysis of the recently terminated investigation on feasibility and reliability of HM, the following parameters for the determination of the sample size have been extracted: 35% of the patients with sick sinus syndrome as a pacemaker indication have asymptomatic atrial fibrillation, 5% of the sick sinus syndrome patients were started on or received revised antitachycardiac therapy during the follow-up period due to AT, either because the AT was symptomatic, or because an asymptomatic AT was detected by chance. For the primary goal of the investigation – estimating the reduction in the incidence of AF that can be achieved by HM – it is assumed that HM's close monitoring of antiarrhythmic therapy reduces the incidence of AF by 35%. A two-sided level of significance of $\alpha = 5\%$ and a power $1 - \beta = 80\%$ will be assumed. With the above-mentioned parameters, the estimation of the sample size yields 428 patients. As the total drop-out rate in the feasibility study was 14.7% (18 of 122 patients), 490 patients will be included into the investigation.

Indications and Contraindications

The indications for a Philos DR-T pacemaker are the standard indications for a DDDR pacemaker implantation according to the international guidelines for cardiac pacemakers [4]: Rate-adaptive, dual-chamber pacing (DDDR) is indicated for patients suffering from any kind of sinus node dysfunction, either in conjunction with impaired atrioventricular conduction, or if there are concerns about the future development of AV block. Dual-chamber pacing is contraindicated in patients with permanent atrial fibrillation or for patients with sinus node dysfunction with intact AV conduction.

Inclusion and Exclusion Criteria

As the main inclusion criteria, patients suffering from sinus node disease of any kind can be enrolled in the study. Furthermore, the patients' general medical condition must be stable enough to allow them to attend the follow-up examinations according to the protocol. Of course, patients must also be willing to give their informed consent. A patient who has a contraindication or who does not fulfill the inclusion criteria will not be included in the investigation. This includes patients with normal sinus .node function or patients who cannot attend regular follow-up examinations due to medical reasons. Furthermore, patients are excluded if they

live in an area with insufficient access to the Global System for Mobile Communication (GSM) network according to the GSM coverage data available on the Internet [5].

Follow-ups

All patients participating in the study are monitored with a standard follow-up scheme comprising 5 clinical examinations (Figure 3):

- pre-implantation;
- implantation;
- pre-hospital discharge;
- interim follow-up at 3 months (± 2 weeks) after implantation; and
- final follow-up at 6 months (± 3 weeks) after implantation.

At pre-hospital discharge and at the 3-month follow-up, 24-hour ECGs are performed. This enables a close comparison between the standard Holter ECG and the contents of the HM message. Therefore, the time covered by the Holter is matched as closely as possible with the 24 hours covered by the associated HM message.

The patient questionnaires on quality of life (SF-36) and on the symptoms of AT/AF are used before implantation, and at 3- and 6-month follow-up. The AT/AF symptom questionnaire is also used during every additional follow-up examination. Data covering medication, pacemaker programming, and direct and indirect costs of follow-up are collected for every follow-up examination.

Antiarrhythmic Therapy

The precise antiarrhythmic therapy that is selected is at the physician's own discretion. However, consideration of the ACC/AHA/ESC Guidelines for the Management of Patients with Atrial Fibrillation [6] is mandatory. Pacemaker programming is also at the physician's own discretion, except for the following parameters directly associated with HM and mode switch:

- mode switch: on;
- atrial lead polarity sense: bipolar;
- mode switch intervention rate: ≥ 170 bpm;
- mode switch onset criterion (X-out-of-8-criterion): X ≥ 6;
- mode switch offset criterion (Z-out-of-8-criterion): Z ≥ 6.

Pre-implantation data
Patient questionnaires: quality-of-life (SF-36),
AT symptoms

Implantation

Discharge
Start of Home Monitoring, 24-hour Holter ECG
Randomization

Cardio Reports available   Cardio Reports hidden
(Cardio Report group)   (Control group)

Periodic, event and patient-activated transmissions

**Follow-up visits due to
Cardio Report analysis**
Patient questionnaires: AT symptoms,
costs of follow-up

Interim follow-up (3 months)
Patient questionnaires: quality-of-life (SF-36),
AT symptoms,
costs of follow-up
24-hour Holter ECG

Periodic, event and patient-activated transmissions

**Follow-up visits due to
Cardio Report analysis**
Patient questionnaires: AT symptoms,
costs of follow-up

Final follow-up (6 months)
Patient questionnaires: quality-of-life (SF-36),
AT symptoms,
costs of follow-up

**End of Home Monitoring
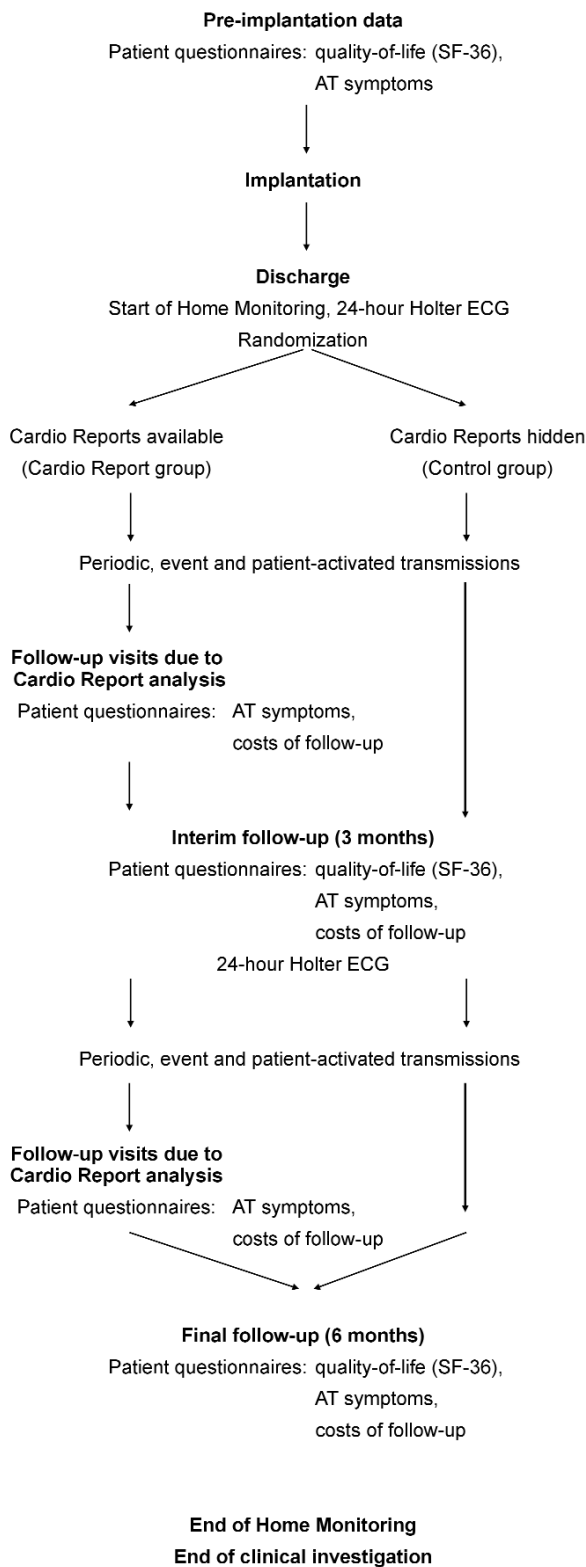End of clinical investigation**

*Figure 3. Flow chart of the HomePAT investigation. AT =
atrial tachycardia.*

Furthermore, the following programming for pacemaker AV delay and overdrive pacing parameters are recommended:

- AV delay: If the patient has intrinsic AV conduction with an AV delay of less than 200 ms, then the intrinsic AV conduction should be supported by programming the pacemaker AV delay to at least 200 ms.
- Overdrive pacing: After the first episodes of AF have been observed, overdrive pacing should be switched on, and the overdrive parameters (rate increase, rate decrease) should be programmed such that the incidence of atrial intrinsic events is as low as possible (≤ 3 %).

Discussion

After the clinical investigation on technical feasibility and reliability of HM in pacemaker therapy, our study of the concept presented above is the second investigation on pacemaker therapy using HM. It is targetted at patients who are either already suffering from paroxysmal atrial tachycardia at implantation or who are prone to or most likely will experience paroxysmal AT in the near future. This is an important subgroup in the population of patients with implantable pacemakers. In the AIDA study, 50.5% of all patients with sick sinus syndrome (SSS) experienced at least one supraventricular tachycardia (SVT) until the 28th day after implantation [7]. For the first 1000 patients in the MOST study, in which SSS was an inclusion criterion, the incidence of SVT, including AF prior to implantation, was 53% [8].

The necessity of concise information about the occurrence of AT is also substantiated by the observation that in the AIDA study 65% of all SVT episodes documented within the first 28 days were asymptomatic. In 21% of the patients, these asymptomatic episodes were documented as the patients' first tachycardia episode ever [7]. Furthermore, Mattioli et al. report that patients with SSS and atrial fibrillation seem to have a higher risk of cerebral ischemia (18%) than patients with AV block and AF (9%), despite insignificant differences in the incidence of AF [9]. The usefulness for permanent and seamless information about the atrial rhythm of patients with implantable pacemakers is further stressed by the observation that in permanently or predominantly paced patients, AF is

systematically under-recognized compared to unpaced patients. Anticoagulation therapy is less common in permanently paced patients compared to intermittently paced or unpaced patients [10].

Another aspect of the expected advantage of HM supervision for patients prone to atrial tachycardia, especially paroxysmal AF, is the importance of an immediate response to the onset of AF. For cases of AF that last for more than 48 hours before attempted cardioversion, anticoagulation with warfarin is recommended for 3 weeks before and 4 weeks after cardioversion [6]. Early cardioversion can be recommended only if intravenous heparinization followed by transoesophageal echocardiography for exclusion of a left atrial appendage thrombus is applied [6]. Hence, a fast reaction to the onset of AF could help minimize the costs of antiarrhythmic therapy.

The necessity of an immediate response to AF is also demonstrated by the observation that a longer duration of AF with loss of atrioventricular synchrony may result in electrical remodeling, thus promoting the arrhythmia. As a consequence, a decrease in atrial contractility by mechanical remodeling may result, which increases the chance of thromboembolic complications [11-13]. Thus, the chance to rapidly terminate AF may help reduce the incidence of persistent AF and thromboembolic events in patients with implantable pacemakers.

The investigation presented above is of course not designed to address all these points of interest. The follow-up period of 6 months will probably be too short to find differences in thromboembolic events or cardiac remodeling. However, the aspects related to the onset of asymptomatic atrial tachycardia, to a delayed vs. immediate reaction to the onset of AF, and to the influence on the use of the available spectrum of antiarrhythmic therapeutic options will clearly be met by the study. Therefore, we expect the HomePAT trial to be the first of a series of clinical trials showing the benefit of HM in pacemaker therapy.

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