FOLLOWPACE study

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FOLLOWPACE study: a prospective study on the cost-effectiveness of routine follow-up visits in patients with a pacemaker

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Aims This communication describes the design of the FOLLOWPACE study. The overall aim of FOLLOWPACE is to quantify the cost-effectiveness of routine follow-up visits in patients with a pacemaker (PM). Specific aims are (i) to quantify the incidence of complications and the quality of life 1 year after PM implantation; (ii) to quantify which baseline characteristics measured during implantation are predictors of the occurrence of complications and quality of life after 1 year; (iii) to determine the added predictive value of follow-up measurements to improve the efficiency of follow-up and to demonstrate which follow-up measurements are redundant.

Methods and results FOLLOWPACE is a prospective, observational, prognostic cohort study. About 40 PM centres in the Netherlands will participate to include about 2500 patients. Each patient aged ≥18 receiving a PM for the first time is eligible. At baseline, i.e. time of implantation, all potential predictors of complications and quality of life after 1 year are documented. After implantation, follow-up visits will be carried out conforming with routine care, usually three in the first year. At these visits, other potential prognostic predictors will be documented. Primary outcome is the incidence of PM- or cardiac complications at 1 year. Secondary outcome parameters are quality of life and costs after 1 year.

Conclusion This study will lead to definition of a more efficient routine follow-up schedule for patients with a PM, aiming to reduce time and energy while preserving the safety of pacing therapy and the prognosis of the patient. The study will ultimately provide evidence-based guidelines for PM follow-up including knowledge of the responsibilities of cardiologists, technicians, and representatives of PM manufacturers.

Introduction

In the Netherlands, approximately 5200 patients yearly undergo a first pacemaker (PM) implantation for AV block, sinus node dysfunction, or other reasons.[1,2] At present, it is estimated that in the Netherlands, 70 000 patients have a PM. In >70% of the first implants, an atrioventricular pacing system is implanted, and in the remainder, a right ventricular system (25%) or pure atrial system (5%) is used.[1,2]

After PM implantation, two to three outpatient follow-up visits are commonly carried out in the first year and about twice a year in subsequent years. For example, in the Netherlands, about 150 000 PM follow-up visits are performed yearly, yielding a total of 50 000 working hours. During these visits, the physical condition of the patient is checked as well as the technical function of the pacing system, including battery status, pacing and sensing parameters, and lead condition. Follow-up visits are commonly executed by a PM technician in co-operation with a cardiologist, sometimes in combination with PM industry personnel. The aim of the follow-up visits is to detect the occurrence of potential complications at an appropriate time, to optimize the condition of the patient and the PM, and to prevent future complications and/or technical failures of the pacing system.[3–5]

Complications may occur during or shortly (within days) after the PM implantation as well as weeks to even years after the implantation.[6–8] The incidence of early complications (mostly defined as within 6 weeks) varies from 0.5–11%.[3,4,6–15] Implantation-related complications include perforation of the vessels and cardiac chambers, infection of the implanted system, lead displacement, and pocket problems. The early complication rate after single-chamber PM implantation appears to be <2% and rates consistently above these levels have been reported as a cause of concern.[6,8,9,12,13] Although one study did not find differences in the incidence of early complications after the

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implantation of dual-chamber PMs compared with single-chamber systems,[9] most others showed and discussed that the incidence of early complications was higher after dual-chamber system implantation.[4,8,10–12,14,15] This was said to be due to complications associated with the atrial leads with active fixation properties and implantation of two leads. In addition, the overall implantation time is significantly longer, which may predispose to wound infection. Various studies have reported on the incidence of late(r) complications after PM implantation.[4,7,8,10,11,15–17] Recently, a large study among 1000 PM patients in the United States showed that, in a period of 7 years after implantation, the frequency of complications (including inadequate capture or sensing, PM pocket infection, and erosion) varied between 4.5 and 15.9%.[17]

At present, data on the quality of life of PM patients and the impact of follow-up measurements and visits on this quality of life are lacking. Similarly, there is hardly any quantitative evidence on which, patient and PM, characteristics measured during implantation may predict the occurrence of short and long(er)-term complications and which measurements at the routine follow-up visits indeed have added predictive value. It is unknown whether all routine PM follow-up visits are truly needed. It might be well that some follow-up visits may not provide any additional prognostic information and may, therefore, not be necessary in terms of patient outcome. If so, reducing the routine follow-up strategy by one or perhaps two visits would reduce patient burden and costs without compromising patient outcome.

Given the increase in number of PM implantations,[1] the limited figures on (longer term) complications and quality of life after implantation and the absence of knowledge on prognostic factors for these complications, we designed the FOLLOWPACE study. In this article, we describe the rationale, design, and implications of the results of this large prospective prognostic study.

Design and analysis of the FOLLOWPACE study

Objectives

The FOLLOWPACE study is a prospective cohort study, performed in 40 PM centres in the Netherlands. The overall objective of the study is to quantify the cost-effectiveness of routine follow-up visits in patients who receive a PM for the first time. This study will help to improve the quality and efficiency of the initial PM implantation and follow-up and to develop more evidence-based guidelines on the responsibilities of different parties involved in the PM follow-up.

Specific objectives are (i) to determine the incidence of complications occurring in the first year after implantation of a PM; (ii) to determine the quality of life at 1 year after PM implantation in comparison with the quality of life before implantation; (iii) to determine which baseline (patient and PM related) characteristics measured during implantation are prognostic predictors for the occurrence of complications and quality of life after 1 year; (iv) to determine which characteristics measured during follow-up visits have truly added predictive value and to what extent; (v) to determine to what extent responsibilities for

PM check-up can safely be delegated to non-cardiologists (e.g. PM technicians or manufacturers' representatives).

Patients

Each patient aged ≥ 18 receiving a PM for the first time in one of the participating centres is a potential candidate for the study. Patients are not eligible if they refuse to sign informed consent. Patients who are taking any investigational (new) drug or have a non-approved or investigational PM system, which requires unusual follow-up, are also excluded. In addition, patients having diseases that are likely to cause death or significant morbidity during the study period, such as neoplasia and immune, infectious, or degenerative diseases will be excluded.

Measurements

The moment of implantation is considered the baseline visit of the present study. Before PM implantation, the patients are asked to sign an informed consent and to fill out a systematic questionnaire on the quality of life, using the standardized EuroQol and Aquarel questionnaires. Next, information on patient characteristics is systematically documented. The PM implantation takes place following normal centre-specific routine. Information on the implantation procedure and types of PM and leads are also systematically registered. All possible complications during the implantation are documented.

Following implantation, the patient enters the regular post-implantation follow-up. All visits after discharge are considered as follow-up visits. These follow-up visits will be performed according to the standard practice in each participating centre. During follow-up visits, the health status of the patient and the technical function of the pacing system will be checked to investigate possible complications in the patient and failures of the PM system. At 1 year, the last follow-up visit in this study is performed. At this visit, the baseline questionnaires regarding quality of life will be repeated.

Cardiologists and PM technicians of the participating centres will perform the registration of the necessary data at baseline and during follow-up, using an electronic case record form (internet WebPages; www.followpace.nl).

At the implantation visit, each patient receives a diary in which they can document all events, including medical or paramedical consultations, treatments, and potential cardiovascular related complications, occurring during the study period.

Prognostic predictors under study

The potential prognostic predictors of the various outcomes (discussed subsequently) that are considered in this study are placed in two categories: (i) predictors documented at baseline (i.e. measured just before and during the PM implantation) and (ii) predictors documented at the follow-up visits.

Predictors recorded at baseline

The potential prognostic predictors recorded just before and during the implantation are, in turn, categorized into three groups as follows.

(i) Patient characteristics such as age, sex, body mass index, cardiovascular risk factors, medical history, and prescribed medication.

(ii) Implantation-related characteristics such as indication for pacing, duration of the implantation procedure, site and type of vascular entrance, experience of the implanting team, and contribution of persons supporting the implantation procedure (e.g. PM technicians and PM manufacturers' representatives).

(iii) PM- and lead-related characteristics such as type of *PM* and leads, default values, pacing and sensing parameters, pulse duration, output, sensitivity, measured lead resistance, PM programming, and changes in default values. The reason(s) why and by whom these changes are performed and ordered are also recorded.

Predictors recorded at the follow-up visits

Following implantation, each patient will attend follow-up visits in agreement with local routine practice. All data collected at routine PM follow-up visits will be documented. Potential predictors measured at each follow-up visit include symptoms and signs of the patient, changes in medication use, and results of diagnostic tests such as Holter-monitoring, echocardiography, laboratory tests, and X-rays. Furthermore, all changes made in PM programming or default values, reasons for change as well as the persons who ordered and carried out these changes are also recorded.

Outcomes

Primary outcome

The primary outcome is the incidence of complications within 1 year after implantation. During implantation as well as at every follow-up visit, the presence of complications will be determined. These complications include cardiac complications, traumatic complications (cardiac perforation related), wound complications (such as haematomas or infections), lead-related complications (pacing/sensing problems), arrhythmias (newly developed during or after implantation), non-cardiac muscle stimulation (diaphragmatic or pocket), non-PM-related complications, and death (cardiac and non-cardiac).

Time of occurrence of the complication and duration of the complication (if applicable), person responsible for detecting the complication, and action undertaken as a result of it will also be documented at each follow-up visit. We will also study the diaries of the patients for relevant data on complications, medical interventions, visits to medical or paramedical services, medication changes, and other factors potentially related to the occurrence of complications.

Secondary outcome

Secondary outcomes include the quality of life after 1 year and costs (to enable comparison of the cost-effectiveness of the current follow-up process with the expected cost-effectiveness of alternative follow-up strategies as indicated by the results of the present study).

Quality of life will be measured using the standardized EuroQol and Aquarel. These questionnaires contain general and more disease-specific questions on physical and mental health perception.[18–21] Both questionnaires are measured at baseline (before implantation) and at 1 year after implantation. Changes in health perception can thus be measured.

Costs are estimated in terms of actual cost prices (society perspective). Medical consumption or volume of resource use will be recorded. Actual costs per item, including the follow-up visits with all necessary measurements, general practice visits, medical specialist visits, cardiac (re)interventions, and hospitalization will be determined. Multiplying average resource use with the pertaining prices will yield an estimate of costs per individual PM patient. Where unavailable or insignificant in terms of volume or costs, tariffs may be used as a proxy of the actual costs. To compare the cost-effectiveness of the current follow-up strategy with that of alternative follow-up strategies, see Data analysis.

Data analysis

First, the incidence of complications within 1 year with 95% confidence interval (Objective 1) and the difference in mean quality of life at 1 year and at baseline (Objective 2) will be estimated.

To quantify which baseline characteristics are predictors of the occurrence of complications within 1 year (Objective 3) and which follow-up measurements have truly added predictive value (Objective 4), stepwise multivariable logistic regression analysis will be used. This stepwise analysis will follow the chronological order in which measurements are performed in daily practice. Hence, we first estimate which baseline predictors have independent prognostic value and we quantify the predictive accuracy (using receiver operating characteristic curves as well as calibration curves[22,23]) of these predictors. Subsequently, we quantify which predictors measured at the first follow-up visit have prognostic value additional to the baseline predictors, using the same analytical approaches. Then, the incremental predictive value of the predictors measured at the second and third follow-up visit will be estimated.

All these analyses will yield which baseline measurements and which follow-up measurements are truly predictive and thus necessary in terms of patient outcome. This, in turn, provides an indication of who should perform and, thus, who is responsible for these (follow-up) measurements (Objective 5). This will lead to the definition of a more efficient strategy for follow-up of patients receiving a PM. We also aim to define simple prognostic scores that can be used by care providers to estimate a patient's risk of developing a complication. These prognostic scores will be validated and adjusted for overoptimism using bootstrapping techniques.[23]

Similarly, using stepwise multivariable linear (not logistic as quality of life is a continuous outcome variable) regression analysis, we will also quantify which, combination of, baseline characteristics are predictors for the patient's quality of life after 1 year and which follow-up measurements have truly added predictive value.

To quantify the cost-effectiveness, the balance of estimated costs and effects of various follow-up strategies, including the current routine strategy and alternative strategies with less measurements or visits as indicated by the earlier described analysis, will be estimated and compared. Overall costs will be directly compared, as well as overall effects (expressed in terms of expected number of

complications and QALYs). The ratio of these two parameters between two different follow-up strategies, i.e. the incremental costs per additional complication, will be reported using the following formula.

$$\frac{\text{Costs}_{\text{alternative strategy}} - \text{Costs}_{\text{current strategy}}}{\text{Effects}_{\text{alternative strategy}} - \text{Effects}_{\text{current strategy}}}$$

The follow-up strategy yielding the highest health effect per unit of (monetary) input can thus be identified. Cost-effectiveness will eventually be reported in terms of costs per complication averted and costs per QALY gained. Univariate and multivariate probabilistic sensitivity analysis will be performed to assess uncertainty around the incremental cost-effectiveness ratios. For long-term cost-effectiveness analysis, and extrapolation, time preference will be accounted for by a 4% discount rate.

Number of patients required

In clinical practice, estimating a patient's prognosis is a multivariable concern *per se*. No prognosis is set by one single predictor. Physicians commonly consider various prognostic factors together to estimate a patient's probability of developing a complication. To serve practice, scientific prognostic studies must follow this multivariable process in design and analysis. This, however, raises problems for the estimation of the required number of patients for prognostic studies. When the prognostic value of several predictors together needs to be quantified, no straightforward methods to estimate the required patient number, as exist for therapeutic research, are yet available. A frequently used 'rule of thumb' recommends that for each predictor included in the analysis, at least 10 patients with an event (i.e. with a complication) are necessary.[23-25] This rule of thumb is increasingly applied in prognostic studies. It is expected that after pre-selection of predictors based on clinical reasoning, about 20–30 predictors will be selected for the analysis. Therefore, 200–300 patients with a complication are needed.

Prior research showed that ~10–15% PM-related or cardiac complications occur within 1 year. This means that for the primary analysis, about 2500 patients with new implanted PMs need to be included allowing for a sufficient number of events (about 250–375). Because the mean number of PMs implanted in the Netherlands is about 70 PMs per centre per year, about 40 centres need to participate in this study to include a sufficient number of patients.[1,26]

Implications of study results

Follow-up visits aim to determine the stability of the patients health, to customize the PM programme to the patient, and to further prevent the occurrence of cardiac or PM-related complications. During these visits, numerous data from the patient, the PM and the leads, are measured and documented. Until now, no studies are available on how important these measurements really are with respect to patient outcomes. It may be well that some of these measurements or even complete follow-up visits are redundant and can thus be omitted from routine follow-up. Hence, it is relevant to know which pacing and patient-related characteristics are prognostically important, i.e.

have true predictive value for the occurrence of future complications and quality of life. In previous studies using quality of life as outcome in PM patients, quality of life was measured with a generic instrument (SF 36), on the basis of patient cohorts of a particular age (mainly elderly), receiving a specific pace mode and with a limited sample size.[27-31] In the FOLLOWPACE study, quality of life is not measured using the SF-36 but with the Aquarel questionnaire.[20,21] Besides generic questions, this questionnaire also contains questions on quality of life specifically designed for patients with a PM. Previous (validation) studies have proven that Aquarel is both a feasible and a useful tool in evaluating health perception of PM patients.[20,21] Furthermore, the FOLLOWPACE study is a prospective study across all ages, including all types of pacing modes, and with a large sample size, guaranteeing sufficient representativeness and generalizability of the study results.

Finally, the FOLLOWPACE study will also provide knowledge on who should be involved in the PM follow-up visits (e.g. cardiologist, PM technician, and industry personnel) and to what extent. Eventually, this study will help to improve quality and efficiency of implantation and follow-up of patients with a PM.

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