Study protocol, version 1.7

Arrhythmias and sudden cardiac death in patients with chronic kidney disease

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Abstract

Patients with severe chronic kidney disease have very high mortality due to predominantly cardiovascular causes. Sudden cardiac death (SCD) is the single most common form of death in dialysis patients, accounting for 20% to 30% of all deaths in this cohort. Surprisingly little is known about actual mechanism – bradycardia or tachycardia – of SCD in these patients. Other arrhythmias such as nonsustained ventricular tachycardia and atrial fibrillation are also prevalent in this population, but the characteristics and significance of them is poorly known. Current state of knowledge also precludes giving appropriate treatment, as different arrhythmias would benefit from different medical or device therapy. One reason for clearly insufficient knowledge of arrhythmias has been the lack of adequate means of detecting brady- or tachyarrhythmia over extended periods of months or years. This protocol describes the first study in patients with chronic kidney disease to use a subcutaneously implanted loop recorder (ILR), which is clearly the most advanced method of gathering long-term arrhythmic data. The longevity of ILR is three years, and the data is collected with remote monitoring. We aim to recruit 100 patients with stage 4 or 5 chronic kidney disease within a period of three years. Additional tests such as Holter recording with sophisticated signal processing analytics and thorough ultrasound examination of the heart are also performed. The project may open a plethora of new information on arrhythmias and their temporal association to electrolyte disturbances and dialysis schedule, which will guide needs for rate-control medication and anticoaculation. The study will give fundamentally new data regarding the actual mode of SCD, which may be useful in advising implantation of cardioverter defibrillation particularly in patients waiting for a kidney transplant. From a broader view, the project will significantly complement our knowledge and understanding of arrhythmias and related risk factors in patients with severe chronic kidney disease.

Introduction

The worldwide prevalence of chronic kidney disease is strongly increasing with the rise in hypertension and diabetes.[1] Patients with severe chronic kidney disease have very high mortality

due to predominantly cardiovascular causes. Sudden cardiac death (SCD) is the single most common form of death in dialysis patients, accounting for 20% to 30% of all deaths in this cohort.[2] This patient group has a particularly high burden of coronary artery disease (CAD), and a proportion of SCD events could be due to obstructive CAD. However, epidemiological and observational studies have demonstrated that the overall incidence of SCD in this population is much greater than the incidence of coronary events,[3] and the risk of SCD persists even after coronary revascularization.[4] This is reflected in the Study of Heart and Renal Protection (SHARP),[5] which recently demonstrated that statins do not improve overall survival in patients with chronic kidney disease despite a decrease in cardiovascular events.

These findings suggest a possibility of a primary increase in the risk of fatal ventricular arrhythmias, which is the most common cause of SCD.[6] Surprisingly little is known about actual mechanism of sudden death in patients with severe chronic kidney disease. Specifically, it is not known which portion of deaths are due to bradycardia or direct asystole and which portion is caused by tachyarrhythmia; previous studies have inferred the mode of SCD from clinical clues, since the technology has been inherently lacking to reveal the actual disturbances of heart rhythm. Moreover, it is not known which characteristics are harbingers of either pathway or pathophysiology of SCD, rendering prevention of sudden death particularly challenging for these people.

High-grade ventricular ectopic activity and nonsustained ventricular tachycardia are commonly seen in dialysis patients, particularly around a dialysis session.[7] Silent myocardial ischemia and sudden changes in electrolytes have been reported to be associated with higher risk of such arrhythmias.[8,9] The cause and significance of these arrhythmias are still not clear.[6] Interestingly, the predictive value of such nonsustained arrhythmia recorded during routine hemodialysis sessions in the risk assessment of SCD has not been explored adequately.[6,10] It is known that frequent hemodialysis of five times a week is beneficial in terms of prognosis as compared with conventional hemodialysis;[11] it is unknown which proportion of the change is attributable to fewer arrhythmias.

Little attention has been paid to atrial fibrillation in kidney patients,[1,12] although this arrhythmia is very frequent with a prevalence of 13 to 27% in patients on long-term hemodialysis; 10-20-fold

higher than in the general population.[1] Respective numbers for other levels of chronic kidney disease are not available. Atrial fibrillation in patients with end-stage renal disease has a strong relationship to structural heart disease, therefore, the direct impact of atrial fibrillation on morbidity and mortality is problematic to assess.[1,13] One confounding factor is the fact that burden, rate and other characteristics of atrial fibrillation has been assessed with intermittent ECG monitoring,[12] which is not an adequate means to evaluate arrhythmic status over months or years. A more detailed knowledge of burden of atrial fibrillation would be helpful in commencing and terminating anticoagulation, as risk of both stroke and bleeding are greatly elevated in this patient group.[14] It deserves to be mentioned that some of the novel oral anticoagulants (NOAC) may be safer in this patient group than warfarin, making anticoagulation the patients with atrial fibrillation and chronic kidney disease a more viable strategy than previously.

One reason for clearly insufficient knowledge of arrhythmias in this high-risk population has been the lack of appropriate tools of detecting brady- or tachyarrhythmia over extended periods of months or years. Current state of knowledge also precludes giving appropriate treatment, as different arrhythmias would benefit from different medical or device therapy. Implantable loop recorders (ILR) are the most advanced method of gathering long-term arrhythmic data. ILR has been validated to be clearly superior of recognizing atrial fibrillation than any non-implantable devices.[15] In addition, ILR has been successfully been used in elucidating mechanism of death.[16] However, no previous study has used ILR in patients with chronic kidney disease, which is a remarkable lack in our knowledge regarding cardiovascular morbidity of this high-risk patient group.

Aims

The project has several major aims:

- Using the data from ILR, presence and burden of atrial fibrillation, atrial flutter, bradycardia, sustained and non-sustained ventricular tachycardia, ventricular premature contractions, asystole and ventricular fibrillation are quantified.

- Clinical-decision making and therapy pathways based on the findings from the ILR will be closely documented.
- Temporal association between dialysis and the above-mentioned arrhythmias is assessed.
- Prevalence of arrhythmias is compared between groups receiving different dialysis treatment modes.
- Presence and burden of the above-mentioned arrhythmias are linked to survival.
- Mode of sudden death in patients with severe chronic kidney disease will be defined based on the actual heart rhythm disturbance recorded in ILR.
- The concordance of data from ILR and Holter devices is assessed.
- Extensive Holter and ILR data are thoroughly analyzed for the development of hazard profiles with elevated arrhythmic risk.
- Hemodynamic state as assessed with two bioimpedance method is correlated with arrhythmias.

Study sites and personnel

Päijät-Häme Central Hospital

- Dr. Tuomas Kerola, MD, Consultant in internal medicine and cardiology
- Dr. Atte Aitkoski, MD, PhD student
- Dr. Olli Anttonen, MD, PhD, Chief physician of cardiology
- Dr. Seppo Ojanen, MD, PhD, Docent, Consultant in internal medicine and nephrology, Chief physician of internal medicine
- Dr. Mari Vilpakka, MD, Consultant in internal medicine and nephrology
- Dr. Jani Ahvonen, MD, Consultant in internal medicine and nephrology

Satakunta Central Hospital

- Dr. Antti Ylitalo, MD, PhD, Docent, Chief physician of cardiology
- Dr. Kaisa Laine, MD, Chief physician of nephrology

Keski-Suomi Central Hospital

- Dr. Kai Nyman, MD, PhD, Chief physician of internal medicine
- Dr. Marja Miettinen, MD, Chief physician of nephrology
- Dr. Kati Vääräniemi, MD, Consultant in internal medicine and nephrology

Vaasa Central Hospital

- Prof. Juhani Koistinen, MD, PhD, Consultant in internal medicine and cardiology, Professor of Cardiology (University of Turku)

South Karelia Central Hospital

- Dr. Jari Hartman, MD, Departmental chief physician of nephrology, Consultant in internal medicine and nephrology
- Prof. Tuomo Nieminen (principal investigator), MD, PhD, M.Sc. (Tech.), Consultant in internal medicine and cardiology, Chief physician of internal medicine, Professor of Internal Medicine (University of Helsinki), Certified Clinical Investigator (Qualisan Oy)

Helsinki University Central Hospital / Meilahti Triangle Hospital

- Dr. Kati Kaartinen, MD, PhD, Consultant in internal medicine and nephrology
- Prof. Tuomo Nieminen (principal investigator)

Methods

Patient population

Patients with planned active treatment to be recruited have chronic kidney disease as follows:

- stage 4 (pre-dialysis, glomerular filtration rate 15-29 mL/min/1.73m^2) or
- stage 5 (end-stage renal disease, <15 mL/min/1.73m^2 or dialysis).[17]

Planned active treatment is either hemodialysis or peritoneal dialysis, or kidney transplantation. The hemodialysis also includes short daily home hemodialysis.

Exclusion criterias

- Age >75 years
- Age <18 years
- Presence of a non-cardiovascular and non-renal disease which limits the expected life-span to less than 1 year.
- Probable noncompliance

The study aims to recruit 100 patients (at least 70) within a period of four years. The three first sites participating in the project have a pool of approximately 200 patients in the dialysis treatment. About 75 patients/year enter the dialysis phase. Thus, reaching the target within the expected time frame is a reasonable objective.

Mortality of chronic patients undergoing dialysis is 20-25%/year. Hence, we expect that 49 to 59 patients will die within the follow-up of three years. Nonfatal ventricular arrhythmias are clearly

more prevalent than death, rendering this as another important endpoint. A hundred patients is a fairly typical number of participants in a study recruiting dialysis patients. Also, few studies employing ILR encompass more than a hundred patients.

The study will have >80% power with an α-level of p=0.05 to detect a difference in equally sized groups A and B with 40% and 70% prevalence in an endpoint, respectively, with a total number of patients of 100. The groups A and B would be, as an example, patients divided according to an ECG marker or laboratory value.

Recruitment modalities

The patients to be recruited pay frequent visits to the nephrology clinic, where they will be asked about willingness to enter the study. Declining participation does not affect standard treatment and follow-up.

Withdrawal criteria

The participants are allowed to withdraw at any point of the study without giving any reason for withdrawal.

Study flow

The flow chart (Fig. 1) depicts measurements performed for all the patients. Clinically indicated tests are not shown, as they may or may not be needed for a patient. Venous blood sampling taken in the beginning of the study is shown, while repetitive routine laboratory tests are not; they will be taken at clinically indicated intervals. All the patients are followed up until death, withdrawal, removal of ILR, or until the battery of ILR wears out (3 years).

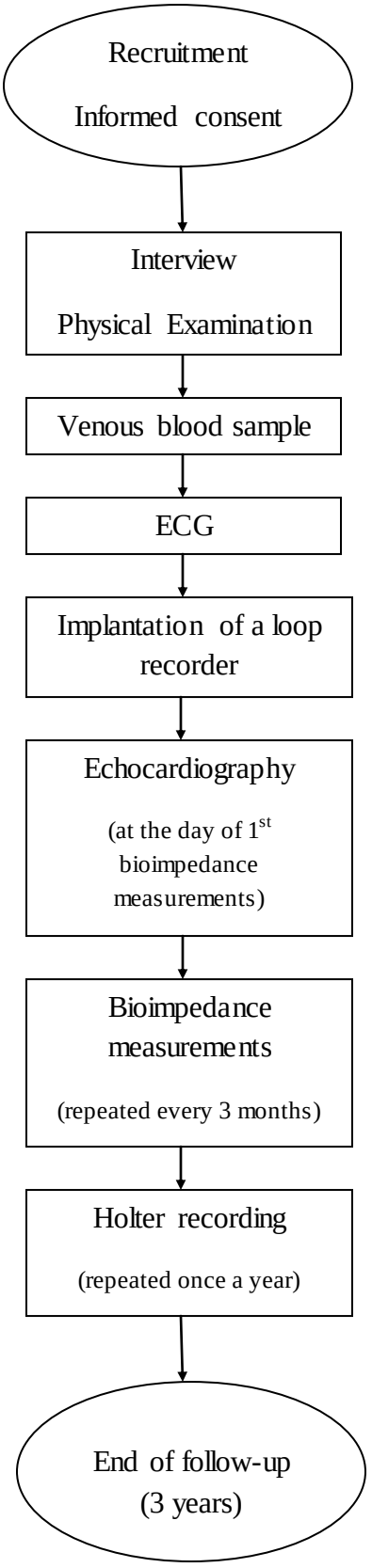

Figure 1. Study flow for each patient.

Implantable loop recorder

Implantable ECG loop recorders or implantable cardiac monitors have a retrospective (loop) memory which continuously records and deletes the patient's ECG. The device includes a patient-activation function that allows the patient to activate ECG storage as a result of symptoms and an auto-activation feature that allows the capture of arrhythmic events without relying on patient compliance or perception of symptoms.[16] The device stores at least 6 min of ECG preceding an event, which enables using signal processing techniques to detect changes and trends in parameters reflecting activity of autonomic nervous system (e.g., heart rate variability) or electrical instability (e.g., T-wave alternans).

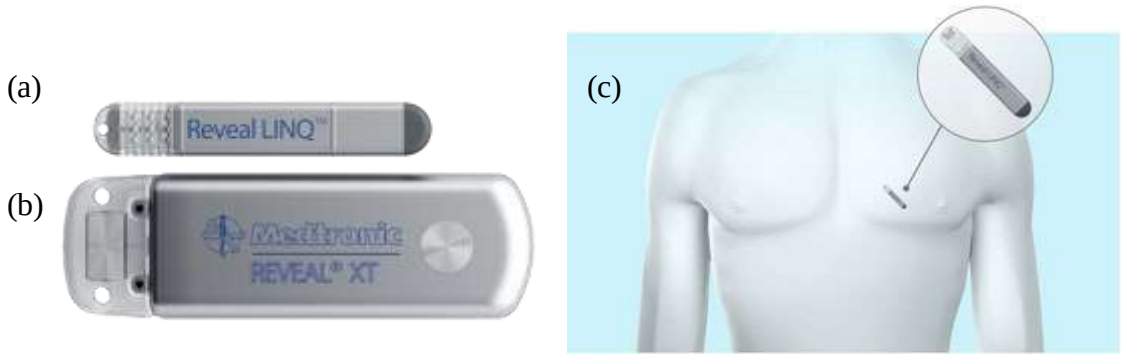

Figure 2. The implantable loop recorders used in the study at the same scale: (a) Reveal LINQ and (b) Reveal XT. (c) Reveal LINQ inserted subcutaneously to the left side of the chest.

The devices used in the study are Reveal XT or Reveal LINQ (Medtronic Inc, Minneapolis, Minn). These are leadless device implanted subcutaneously on the left side of the chest using local anesthesia. The battery longevity of both ILR is up to 3 years. Weight of Reveal XT is 15 g, and the dimensions are 62 x 19 x 8 mm (Figure 2). Data retrieval from the Reveal XT via induction link is performed noninvasively when the patient visits the hospital for dialysis or routine nephrologic check-up. The newer version of the device, Reveal LINQ, is approximately one-third the size of a AAA battery (~1 cm^3). Data retrieval from the Reveal LINQ is totally automatic via a radiofrequency (RF) link; each patient is given an RF receiver.

The device is compatible with magnetic resonance imaging. Having a cardiac pacemaker is not a contraindication for an ILR. If the patient has a pacemaker applicable for a widespread data capture, no additional ILR is needed.

Rationale for using implantable loop recorder

Recently, extended ECG monitoring methods have been introduced, including transtelephonic ECG transmissions, 7-day Holter recording, and 30-day event recording. There is a clear relationship between the duration of monitoring and the diagnostic yield. Depending on the specific external monitoring method in the diagnosis of atrial fibrillation, the sensitivity lies between 31.3% and 71.0%, whereas the negative predictive value ranges between 21.5% and 64.6%.[18-20] Thus, the diagnostic capacity of these devices is limited.

Patients with symptoms have an increased likelihood that atrial fibrillation is diagnosed. However, there is a well-known poor correlation between symptoms and episodes of atrial fibrillation: episodes may be asymptomatic, and symptoms may not relate to atrial fibrillation.[15] Recent studies showed that only 13% to 21% of episodes with symptoms suggestive of atrial fibrillation reported by patients with implanted pacemakers were episodes of atrial fibrillation according to the pacemaker log.[21,22]

Continuous rhythm monitoring over long periods of time is superior to intermittent recording using external monitors. Such a monitoring is only possible by using an implantable device. One of these devices is Reveal XT. Recently, the Reveal XT Performance Trial (XPECT) evaluated the performance of the device in the detection of atrial fibrillation. The sensitivity, specificity, positive predictive value, and negative predictive value for identifying patients with any type of atrial fibrillation were 96.1%, 85.4%, 79.3%, and 97.4%, respectively.[15] The burden of atrial fibrillation measured with the implantable cardiac monitor was very well correlated with the reference value derived from the Holter recorder (Pearson coefficient 0.97). The overall accuracy of the implantable cardiac monitor for detecting atrial fibrillation was 98.5%.[15]

Cardiac Arrhythmias and Risk Stratification after Acute Myocardial Infarction (CARISMA) study was designed to document the incidence and prognostic significance of cardiac arrhythmias after acute myocardial infarction in patients with left ventricular ejection fraction ≤40%.[23] Significant brady- and/or tachyarrhythmias were recorded in 137 patients (46%) during a 2 year follow-up, as large a proportion as 86% of these being asymptomatic. ILR documented a 27% incidence of new onset atrial fibrillation (≥125 bpm), 13% non-sustained ventricular tachycardia (≥16 bpm), 10% high-degree atrioventricular block (≤30 bpm, duration ≥8 s), 7% sinus bradycardia (≤30 bpm, ≥8 s), 5% sinus arrest (≥4.5 s), 3% had sustained ventricular tachycardia, and 3% experienced ventricular fibrillation.[24]

The experience of CARISMA study showed that ILR is well suited for clinical research of cardiac arrhythmias in various clinical settings, as stated in a recent expert consensus statement and a position paper by the European Heart Rhythm Association.[16] This panel also recommends using implantable cardiac monitors for detecting atrial fibrillation in studies estimating the burden of this arrhythmia.[16] Furthermore, efficacy of ILR in disclosing the etiology of unexplained syncope has been demonstrated.[25]

Holter recording

All patients will undergo a 48 h ambulatory two or three-channel ECG recording within the first weeks after enrollment and once a year thereafter. The following variables are among those to be analysed: average heart rate, total number and frequency of premature ventricular beats, number of foci eliciting extrasystoles, episodes of nonsustained ventricular tachycardia (≥3 consecutive beats), heart rate variability in time and frequency domains, short-term fractal exponent of heart rate variability, the onset and slope of heart rate turbulence, and T-wave alternans. In the beginning of the Holter recording, a standard 6 minute walking test is performed if reasonable based on the condition of the patient.

For patients under hemodialysis, Holter recording is commenced and terminated at the regular visits to the dialysis department. If the patient is not receiving hemodialysis treatment, the recording is started while visiting the nephrologic clinic; for these patients, removal of the device would typically require an additional visit to the hospital.

Laboratory analysis

The following laboratory parameters are routinely assessed in patients with severe chronic kidney disease: complete blood count, CRP, Na, K, Mg, Ca, Pi, Krea, Uraat, fP-Gluc, ALAT, AFOS, Kol, HDL, Trigly, LDL, proBNP and Alb. Blood and plasma samples are stored for additional determinations, potentially including inflammatory markers, metabolomic parameters and genetic testing relevant to renal diseases and cardiac arrhythmia.

Bioimpedance measurements

Volume status of the participants is measured after recruitment and every three months with Body Composition Monitor (Fresenius Medical Care Deutschland GmbH, Bad Homburg, Germany).[26,27] An additional set of hemodynamic parameters (stroke volume, cardiac output, systemic vascular resistance, pulse wave velocity, etc.) is noninvasively assessed with CircMon Model B202 (JR Medical, Tallinn, Estonia), another application of whole-body impedance cardiography.[28,29] Bioimpedance measurements will be performed prior to dialysis of the day.

Echocardiography

Experienced echocardiographers will perform a thorough ultrasound examination of the heart. The examination is performed in the morning of whole-boby impedance cardiography measurements.

Electrocardiography

A 12-lead ECG is taken and it will be analyzed for several parameters, including QT interval and other QT indices, QRS-T angle, and the width of the QRS complex.

Electrophysiology study

Coronary angiographies will not be performed solely for the study purposes. For the patients with a clinically indicated coronary angiography, experienced cardiologist may perform a programmed ventricular stimulation. The procedure provides valuable additional information on vulnerability to ventricular tachyarrhythmia.[30] Programmed ventricular stimulation contains minimal risks. The procedure has not caused a single death in the unpublished Finnish experience on more than 10,000 patients during the past 20 years. Ventricular arrhythmias induced during the test are an essential part of the procedure, not a complication, and they are treated immediately. Pericardial effusion is very infrequent; not a single case has occurred in the experience with approximately 1,000 patients with an electrophysiology study from Päijät-Häme Central hospital over 11 years. Local puncture complications with venous access are scarce, exact number are not available, and clearly less frequent than that for arterial puncture complications related to coronary angiography.

Clinically indicated tests

Particularly, patients applicable to kidney transplantation undergo a battery of tests, including coronary angiography. This data would be used in this project without costs.

Deaths

SCD is defined as an unexpected death due to cardiac causes occurring within 1 h of symptom onset.[31]. Autopsies will be performed based on clinical decision-making; the eventual data will be available for the project. Death certificates listing causes of death using the tenth revision of the International Classification of Diseases (ICD-10) will be received from the Causes of Death Register, maintained by Statistics Finland.

Administrative procedures

Insurance

The study patients are covered by the insurance of each hospital, insurance against treatment injury (potilasvakuutus) and physician's professional liability insurance (lääkärin vastuuvakuutus).

Compensation

The study subjects will not be given any financial remuneration, as they will not have to make extra visits to the hospital because of the study. The participants will receive thorough information about their arrhythmias in the course of the study. The investigators taking absence of leave for full-time research period in the study will be given financial compensation for conducting the study. However, this arrangement is exceptional, as patient recruitment and routine follow-ups will only cause a very limited monthly work load.

Ethical considerations

The subcutaneous implantation of ILR with local anesthesia is a minor procedure with a minimal risk of complications. Programmed ventricular stimulation includes a venous catheterization; the procedure is only performed if the patient in undergoing coronary angiography using arterial catheterization. Other tests performed in the study are noninvasive. The study group has extensive experience with all the tests and devices used in the study, including ILR. The study will be conducted according to the Declaration of Helsinki. The study protocol and informed consent have been approved by the Ethics Committee of the Pirkanmaa Hospital District. Written informed consent will be necessitated prior to including a volunteer into the study. Data will be treated confidentially and handled only by the investigators named in this protocol and study nurses.

Publication plans

The project will open a plethora of new information on arrhythmias and their temporal association to electrolyte disturbances and dialysis schedule. Specifically, the project will give fundamentally new data regarding the actual mode of SCD in patients with chronic kidney disease.

The results will be published in international publication series. Parts of the results will also be presented in international cardiologic and nephrologic conferences. The first publications will form the basis for the doctoral thesis of Atte Aitkoski, MD. In all likehood, the data will support preparation of at least one more doctoral thesis.

Clinical implications

The project is a major platform of cooperation between two specialties, cardiology and nephrology, which ensures that considerations from both specialties are carefully embedded into the protocol. The project will provide clearly more accurate data on burden of atrial fibrillation in this patient group, which will guide needs for anticoaculation and rate-control medication. Assessing the risk factors for tachyarrhythmic sudden death will be essential in advising antiarrhythmic medication and implantation of cardioverter defibrillation, particularly in patients waiting for a kidney transplant. From a broader view, the project will significantly complement our knowledge and understanding of arrhythmias and related risk factors in patients with severe chronic kidney disease.

Cost estimation

Working months	**Months**	**a**	**Total**	**Note**
Physician researchers	2	7 000	14 000	Incl. overhead
Doctoral student	12	4 200	50 400	Incl. overhead
Research nurse	8	3 000	24 000	Incl. overhead
Total			**88 400**	eur

Devices	**Pcs.**	**a**	**Total**	**Note**

Holter devices	3	3 200	9 600	
Reveal XT	100	1 600	160 000	
Total			**169 600**	eur

Others	**Pcs.**	**a**	**Total**	**Note**
Logistics for project coordination			6 000	
Storage of blood samples			3 000	
Laboratory analyses			10 000	
Total			**19 000**	eur

Grand Total	**277 000**	eur

Current status

We started the study in December 2011. During the first year, we organized the local permission for each of the three hospitals, educated the study personnel in each center and started the recruitment process. At the moment, we have recruited 32 patients, 23 of whom from the Päijät-Häme Central Hospital, five from the Satakunta Central Hospital, and four from the Keski-Suomi Central Hospital. The fluent flow of the remote monitoring of the ILR data has been arranged to the central database. Two more central hospitals will join the project within months. Additional efforts to facilitate and speed up the recruitment have been started.

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