POP-ECG-HF-AF

A Prospective Observational Study of Prolonged Electrocardiographic Monitoring in Patients with Heart Failure in Sinus Rhythm or Atrial Fibrillation

<Version 1 23.09.2015>

MAIN SPONSOR: Imperial College London

Protocol authorised by:

Name & Role	**Date**	**Signature**

Study Management Group

Chief Investigator: John Cleland

Co-investigators: Alex Lyon, Nick Peters

Statistician: Jufen Zhang

Study Management: Professor Cleland and Peters and Dr Lyon and Mareev supported by Jufen Zhang (Statistician – University of Hull) will constitute the Trial Management Group (TMG). No Independent Data Monitoring Committee (IDMC) or Trial Steering Committee (TSC) is envisaged.

Study Coordination Centre *not applicable*

Clinical Queries

Clinical queries should be directed to Yura Mareev who will direct the query to the appropriate person

Sponsor

Imperial College London/Imperial College Healthcare NHS Trust is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

Joint Research Compliance Office
Imperial College London
5th Floor, Lab Block
Charing Cross Hospital
Fulham Palace Road
London
W6 8RF
Tel: 0203 311 0212
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Funder

Dr Mareev is supported by a fellowship from the European Society of Cardiology. Funding for monitoring patches will be provided from funds held by Professor Cleland.

This protocol describes the POP-ECG-HF-AF study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the NHS Research Governance Framework for Health and Social Care (2nd edition). It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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GLOSSARY OF ABBREVIATIONS

AE	ADVERSE EVENT
AF	ATRIAL FIBRILLATION
AR	ADVERSE REACTION
ASR	ANNUAL SAFETY REPORT
CI	CHIEF INVESTIGATOR
CRF	CASE REPORT FORM
DMC	DATA MONITORING COMMITTEE
ECG	ELECTROCARDIOGRAM
GAFREC	GOVERNANCE ARRANGEMENTS FOR NHS RESEARCH ETHICS
GCP	GOOD CLINICAL PRACTICE
GMP	GOOD MANUFACTURING PRACTICE
ICF	INFORMED CONSENT FORM
ISF	INVESTIGATOR SITE FILE
	MUST MALNUTRITION UNIVERSAL SCREENING TOOL
NHS R&D	NATIONAL HEALTH SERVICE RESEARCH & DEVELOPMENT
PI	PRINCIPAL INVESTIGATOR
PIS	PARTICIPANT INFORMATION SHEET
QA	QUALITY ASSURANCE
QC	QUALITY CONTROL
	RCT RANDOMISED CONTROL TRIAL
REC	RESEARCH ETHICS COMMITTEE
SAR	SERIOUS ADVERSE REACTION
SAE	SERIOUS ADVERSE EVENT
SDV	SOURCE DOCUMENT VERIFICATION
SSA	SPECIFIC ASSESSMENT SITE
TMG	TRIAL MANAGEMENT GROUP
TSC	TRIAL STEERING COMMITTEE

KEYWORDS
Observational study, Heart falure, Atrial fibrillation, heart rate, ambulance ECG monitor,

STUDY SUMMARY

TITLE A Prospective Observational Study of Prolonged Electrocardiographic Monitoring in Patients with Heart Failure in Sinus Rhythm or Atrial Fibrillation

DESIGN prospective observational study

AIMS Primary Objective: To quantify, in patients with heart failure who are either in sinus rhythm or in atrial fibrillation, the burden of brady- and tachy-arrhythmias and provide insights into the relationship between resting daytime heart rate and nocturnal heart rhythms

Secondary Objective: Identify the relationship between the burden of brady- and tachy-arrhythmias and clinical events

OUTCOME MEASURES Primary:

Co-primary endpoints

1. Identification of an arrhythmia for which there is a Class I or IIa recommendation for treatment with medication or devices

2. Either the above or one or more of the following (expanded endpoint) even if it does not otherwise meet guideline-indication for treatment:-

• Sinus bradycardia ≤30bpm for ≥one minute

• High-degree atrioventricular (AV) block (3rd degree or Mobitz Type I or II)

• Pauses lasting ≥3 seconds (either sinus or AV block)

• Frequent ventricular ectopy defined as >1,000 ectopic beats per day.

• Ventricular tachycardia with rate ≥100 bpm for ≥5 beats.

Secondary: Relationship of the above to all-cause mortality, cardiovascular mortality, hospitalization for heart failure or arrhythmia, implantation of a device with a capacity to pace the heart.

POPULATION Patients with Heart failure (HF)

ELIGIBILITY

1. Diagnosis of heart failure
2. Treated with loop diuretics for at least six weeks
3. Willing and legally able to sign informed consent
4. At least 18 years of age
5. New York Heart Association (NYHA) class II – IV

DURATION 5 years (clinical phase 18 months)

1. INTRODUCTION

1.1 BACKGROUND

Patients with heart failure may experience a variety of irregular heart rhythms (arrhythmia) that may or may not be symptomatic. Remarkably little-detailed information on arrhythmias in patients with heart failure has been published in the last decade, whilst methods of monitoring and the management of some types of heart failure has improved dramatically making older studies on this topic out-of-date. The emphasis in the 'old' literature was on fast heart rhythms, but there is growing awareness that slow heart rhythms might be even more important. Older technologies only assessed heart rhythm over 24-48 hours, but new, wearable, patient-friendly devices can monitor for much longer, creating a much richer patient arrhythmia profile.
We intend to conduct an observational study in patients with heart failure, investigating the incidence of arrhythmias using a wearable device that can monitor heart rhythm for up to 14 days. In addition to gathering routine clinical information, research assessments include a symptoms questionnaire and a corridor walk test. Patients will be followed for clinical events (interventions for arrhythmias, hospitalisation, death) for up to 5 years.

1.2 RATIONALE FOR CURRENT STUDY

The purpose of this study is to quantify the total arrhythmia burden (both slow and fast rhythms) in patients with heart failure using a wearable patch that can monitor the heart for up to 14 days. We then intend to follow the patients' progress over the next 5 years. We may find serious rhythm problems, in which case we will recommend treatment according to expert international guidelines (Guidelines on pacing 2013 and on sudden death 2015).
This information will provide information on the incidence of severe arrhythmias that guidelines indicate should be treated and of the association of less severe arrhythmias (or their absence) with prognosis. This should improve patient care and inform the design of further research.

2.STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

To quantify, in patients with heart failure who are either in sinus rhythm or in atrial fibrillation, the burden of brady- and tachy-arrhythmias and provide insights into the relationship between resting daytime heart rate and nocturnal heart rhythms

2.2 SECONDARY OBJECTIVES

Identify the relationship between the burden of brady- and tachy-arrhythmias and clinical events.

3. STUDY DESIGN

Observational study; non-commercial.
Duration 5 years (clinical phase 18 months).
400 patients with heart failure

We will include patients with heart failure. We are investigating the prevalence of subclinical arrhythmias in this population and their association with clinical outcomes The patient will have a 7-14 days ambulatory ECG after which we will follow them up every 6 months for up to 5 years. At each time point, we will contact patients by phone or post and ask them if they have any hospital admissions. Every effort will be made to ensure that we know the patients

mortality status, before each planned follow up. We will call the patient's GP prior to making any direct contact with the patients.

3.1 STUDY OUTCOME MEASURES

Primary:

Co-primary endpoints

1. Identification of an arrhythmia for which there is a Class I or IIa recommendation for treatment with medication or devices

2. Either the above or one or more of the following (expanded endpoint) even if it does not otherwise meet guideline-indication for treatment:-

• Sinus bradycardia ≤30bpm for ≥one minute

• High-degree atrioventricular (AV) block (3rd degree or Mobitz Type I or II)

• Pauses lasting ≥3 seconds (either sinus or AV block)

• Frequent ventricular ectopy defined as >1,000 ectopic beats per day.

• Ventricular tachycardia with rate ≥100 bpm for ≥5 beats.

Secondary:
Relationship of the above to all-cause mortality, cardiovascular mortality, hospitalization for heart failure or arrhythmia, implantation of a device with a capacity to pace the heart.

4. PARTICIPANT ENTRY

4.1 PRE-REGISTRATION EVALUATIONS

Review of the patients medical record for inclusion/exclusion criteria

4.2 INCLUSION CRITERIA

1. Heart Failure
2. Treated with Loop Diuretics for at least six weeks
3. Willing and legally able to sign informed consent
4. At least 18 years of age
5. New York Heart Association (NYHA) class II - IV

4.3 EXCLUSION CRITERIA

1. Myocardial infarction in the previous six weeks,
2. Implanted pacemaker, including cardiac resynchronisation device, or defibrillator
3. Already participating in an interventional randomized controlled trial assessing effects on morbidity and mortality (this study does not preclude participation in future clinical trials).

4.4 WITHDRAWAL CRITERIA

No withdrawal criteria. Patients may decide to remove the monitoring patch, may request that their data are not analysed or that they are not followed up for clinical events. They may also decline any intervention advised based on the findings of the monitoring test. Patients with incomplete data for any reason will be replaced. All patients will be followed up unless they refuse. There are no stopping rules.

5. ADVERSE EVENTS

5.1 DEFINITIONS

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.

Serious Adverse Event (SAE): any untoward and unexpected medical occurrence or effect that:

- **Results in death**
- **Is life-threatening** – *refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*

- **Requires hospitalisation, or prolongation of existing inpatients' hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

5.3 REPORTING PROCEDURES

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

5.3.1 Non serious AEs

All such events, whether expected or not, should be recorded.

5.3.2 Serious AEs

An SAE form should be completed and faxed to the Chief Investigator within 24 hours. However, relapse and death due to heart failure, and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs should be reported to the London - Brent Research Ethics Committee where in the opinion of the Chief Investigator, the event was:

- 'related', ie resulted from the administration of any of the research procedures; and
- 'unexpected', ie an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all SAEs.

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Contact details for reporting SAEs
email: j.cleland@imperial.ac.uk and Y.Mareev@rbht.nhs.uk
Please send SAE forms to: John Cleland
Tel: 01895-823737 Bleep - 6085 **(Mon to Fri 09.00 – 17.00)**

6. ASSESSMENT AND FOLLOW-UP

SCREENING ASSESSMENTS
None other than entry criteria.

BASELINE ASSESSMENTS
1) Prolonged ECG (up to 7 days) monitoring using a patch-electrode
2) Symptom Questionnaire
3) Evaluation of NYHA functional class.
4) Physical examination including blood pressure
4) 6-min corridor walk distance for patients who are willing and able.
5) Most recent, clinically indicated, haematology, biochemistry, ECG and Echo results (these will not be repeated for research purposes).

TREATMENT PROCEDURE
Not applicable. No protocol driven treatment. Patients will be treated according to guidelines if electrocardiographic abnormalities are identified.

10.4 SUBSEQUENT ASSESSMENTS
We will contact patients every 6 months by telephone or post (according to their preference) or opportunistically at NHS clinics to identify hospitalizations. We will ensure that the patient is still alive just before making remote contact by checking the hospital electronic record and with the GP reception staff. Hospitalizations and deaths will also be identified through electronic patient records.

Definition of end of study
The end of the study will occur when the last patient enrolled has been followed for 5 years. A long-term extension is considered. Dr Mareev's fellowship is only for 2 years and other personnel are required for longer follow-up.

7. STATISTICS AND DATA ANALYSIS

The design is a prospective, observational trial with two cohorts of 200 patients; one in sinus rhythm and the other in atrial fibrillation.

This should generate in excess of 50 deaths in the year following observation assuming a substantial proportion of patients are enrolled soon after an episode of worsening heart failure. We will investigate which measured variables predict overall mortality, sudden death and out-of-hospital sudden death with a particular focus on electrocardiographic findings. We will investigate mode of death, if necessary, by contacting medical and nursing staff (including the patients GP) who attended the patient around the time of death.

SAMPLE SIZE AND RECRUITMENT
The sample size is based on the precision of the estimated prevalence of serious arrhythmia. As this is, surprisingly, virtually unknown for similar contemporary populations we intend to study with the proposed technology, this should be considered a pilot. Assuming the incidence of events is low, medium or high (eg:- 5%, 25% or 50%), 200 patients provides a precision around these estimates of approximately ±5%, ±10% and ±12% with 90% power.

We aim to recruit this population over 12 months – this will entail enrolling about two patients every working day. Due to the small imposition on the patient, the lack of many exclusion criteria and the potential for referrals from across North-West London we believe this is feasible.

ENDPOINTS
Primary endpoint
1. Identification of an arrhythmia for which there is a Class I or IIa recommendation for treatment with medication or devices
2. Either the above or one or more of the following (expanded endpoint) even if it does not otherwise meet guideline-indication for treatment:-
• Sinus bradycardia ≤30bpm for ≥one minute
• High-degree atrioventricular (AV) block (3rd degree or Mobitz Type I or II)
• Pauses lasting ≥3 seconds (either sinus or AV block)
• Frequent ventricular ectopy defined as >1,000 ectopic beats per day.
• Ventricular tachycardia with rate ≥100 bpm for ≥5 beats.

Secondary endpoints
Relationship of the above to all-cause mortality, cardiovascular mortality, hospitalization for heart failure or arrhythmia, implantation of a device with a capacity to pace the heart.

STATISTICAL ANALYSIS PLAN
The design is a prospective, observational trial with two cohorts of 200 patients; one in sinus rhythm and the other in atrial fibrillation.
Data will be expressed as proportions for categorical data and median with quartile range for continuously distributed data.
Loss to follow-up for the primary or secondary endpoints is not anticipated. It is anticipated that monitoring data may not be acquired in some patients. This will be recorded. Missing data will not be imputed. Monitored events will be expressed as a rate per day of monitoring data and per patient regardless of the duration of monitoring.

Primary endpoint analysis
The primary analysis is the incidence rate of the primary composite endpoint.

We will investigate factors associated with the primary point. Pre-specified variables include: age, sex, NYHA class, body mass index, heart rate measured at examination, left ventricular ejection fraction, presence of calcific aortic or mitral valve disease, left atrial volume, conduction abnormalities on the 12-lead ECG, serum potassium and serum creatinine.

Secondary endpoint analysis
Secondary analyses include the incidence rate of each component of the primary composite endpoint and their association with the above variables.

Multi-variable models will be developed to investigate associations between the above variables, the components of the primary endpoint and all-cause mortality, cardiovascular mortality and the composite outcome measure.
Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study, including the follow-up period.

8. REGULATORY ISSUES

8.1 ETHICS APPROVAL

The Chief Investigator has obtained approval from the London - Brent Research Ethics Committee. The study must be submitted for Site Specific Assessment (SSA) at each participating NHS Trust. The Chief Investigator will require a copy of the Trust R&D approval letter before accepting participants into the study. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

8.2 CONSENT

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

8.3 CONFIDENTIALITY

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

8.4 INDEMNITY

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study

8.5 SPONSOR

Imperial College London will act as the main sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

8.6 FUNDING

Dr Mareev is supported by an ESC fellowship. Prof Cleland has the resources to cover costs of patch-monitors and statistical analysis.

8.7 AUDITS

The study may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).

9. STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated through Dr Mareev

10. PUBLICATION POLICY

Data ownership rights will lie with the institution. The results will be presented at local, national and international meetings and published in a peer-reviewed journal.

Appendix 1. Summary of investigations, treatment and assessments

	Baseline
Informed consent	X
Demographic Data	X
Symptom Questionnaire	X
NYHA Class	X
Physical Examination	X
6 min corridor walk test (if willing & able)	X
Prolonged ECG (up to 14 days) monitoring	X
Haematology	X (nearest in time clinical result)
Biochemistry	X (nearest in time clinical result)
ECG	X (nearest in time clinical result)
Echo	X (nearest in time clinical result)

Patient Study Number:

INFORMED CONSENT FORM

Full Title of Project: A Prospective Observational Study of Prolonged Electrocardiographic Monitoring in Patients with Heart Failure in Sinus Rhythm or Atrial Fibrillation

Name of Principal Investigator: Dr Alex Lyon and Dr Rebecca Lane

Please initial the boxes

1. I confirm that I have read and understand the information sheet (Version 3, 14-12-2015) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, although data collected until that point may be used for research purposes with my agreement, without my medical care or legal rights being affected. ☐
3. I understand that sections of my medical notes relating to the study, may be looked at by regulatory bodies conducting inspections which may include members of staff within the NHS Trust who are outside of the immediate clinical and research teams. I give permission for these individuals to have access to my records. ☐
4. I agree to my GP being informed of my participation in the study. ☐
5. I agree to take part in the above study. ☐
6. I wish to receive feedback on the study results when available. ☐

Name of Patient	Date	Signature
Name of Person taking consent (if different from researcher)	Date	Signature
Researcher	Date	Signature