

Rationale and design of the NEO-NORMAL-AF study examination of the usefulness of implantable loop recorder for arrhythmia detection including atrial fibrillation in heart failure with non-reduced ejection fraction cases: a pilot study

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ABSTRACT

Introduction The incidence of arrhythmia in heart failure with non-reduced ejection fraction (HFnon-rEF) in patients who have a history of hospitalisation is unclear. The aim of this study is to investigate the usefulness of an implantable loop recorder (ILR) for arrhythmia detection including atrial fibrillation (AF) in HFnon-rEF patients after discharge.

Methods and analysis This is a multicentre single arm study to evaluate the usefulness of ILR for detecting arrhythmia. The eligible patients are HFnon-rEF patients (left ventricular ejection fraction $\geq 40\%$) aged ≥ 20 years with a history of hospitalisation. The ILR will be implanted for qualified patients, and ECGs will be monitored and recorded for 1 year to check for arrhythmias. The primary endpoint is new-onset 6 min or more persistent AF detected by ILR. Secondary endpoints are 30 s or more persistent supraventricular tachycardia and ventricular tachycardia, 3 s or more persistent pause, bradycardia with 40 beats per minutes or lower heart rate, AF burden, all-cause death, cardiovascular death, hospital readmission due to exacerbation of HF, acute coronary syndrome, ischaemic or haemorrhagic stroke, non-pharmacological therapy such as pacemaker implantation and ablation.

Conclusions This study is expected to provide valuable findings regarding arrhythmia in HFnon-rEF patients, and elucidate a potential new therapeutic approach for HFnon-rEF.

Trial registration number This trial has been registered in the Japan Registry of Clinical Trials (JRCT) (Trial Registration: jRCTs052210060).

INTRODUCTION

In Japan, the number of heart failure (HF) patients has been increasing due to the effect of Japan's ageing society and is expected to reach about 1.3 million by 2030.¹ Over

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Although the incidence of arrhythmia in HFrEF patients was reported before, the incidence of arrhythmia in heart failure with non-reduced ejection fraction (HFnon-rEF)-rEF patients who had prior hospitalisation is unknown.

WHAT THIS STUDY ADDS

⇒ This trial investigates arrhythmia in HFnon-rEF patients by implantable loop recorder implantation.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The result of this trial may have effects on the clinical practice for HFnon-rEF patients after discharge, such as aggressive examination to detect arrhythmia.

the past 30 years, the prognosis of patients suffering HF has remarkably improved due to comprehensive treatment options, including optimal medical therapy, cardiac implantable electronic devices and cardiac rehabilitation. However, the prognosis for HF remains poor, with various risks including rehospitalisation for HF exacerbations, death from HF and sudden cardiac death.²⁻³ According to the results of JROAD-HF study, the 4-year survival rate in patients with a history of hospitalisation for acute decompensated heart failure (ADHF) was 55.8%.⁴ Their prognosis was worse than that of all cancers in Japan.⁵

Atrial fibrillation (AF) is most commonly observed arrhythmia in clinical practice. Similar to HF, the incidence of AF increases with age, and the number of patients with AF has been predicted to reach about 1 million

by 2050 in Japan, which is equal to approximately 1.1% of the total population.⁶ AF generally increases the risk of sudden death and cardiovascular death due to HF or stroke, especially due to cardiogenic embolism, and leads to a decrease of quality of life.⁷ Therefore, the frequency of both HF and AF is expected to increase in Japan and is related to poor prognosis. In addition, AF often occurs in HF patients. The frequency of AF has been reported to be 30%–50%.⁸ Comorbidity of HF and AF has been reported to be associated with a poorer prognosis for the patient than HF alone. It is associated with increased risk of rehospitalisation for HF, cardiovascular death and all-cause death.^{8,9}

Sudden death accounts for the cause of death in approximately 20% of reported ADHF patient deaths.¹⁰ Although it is speculated that the cause for sudden death is fatal arrhythmia, it is difficult to confirm this speculation and it remains conjectural. AF itself is suspected not to be the cause of sudden death in ADHF patients. However, the acute exacerbation of HF due to AF may be associated with sudden death, and not all patients with AF have symptoms such as palpitations. Previous studies have shown that approximately 40%–50% of AF patients are asymptomatic, and that in symptomatic patients the initial symptoms are often associated with HF and cardiogenic embolism.^{11,12} The earlier AF is detected, the earlier anticoagulation therapy can be initiated to prevent cardiogenic embolism. Cardiogenic embolism has been known to worsen the prognosis of patients with HF because it causes a decrease in activities associated with daily living and frailty.¹³ Therefore, an early detection and anticoagulation therapy for AF in HF patients could be expected to improve their long-term prognosis. In addition, from the EAST-AFNET4 trial,¹⁴ early rhythm control therapy with antiarrhythmic drugs and detection within 1 year of onset and catheter ablation was shown to significantly improve outcomes, including all-cause mortality in approximately 30% of patients included HF patients.¹⁴ Thus showing that early detection and diagnosis for AF can lead to early rhythm control therapy, and improved prognosis.

On the other hand, although there is various evidence based on established therapies for heart failure patients with reduced ejection fraction (HFrEF), there is little evidence regarding heart failure with non-reduced ejection fraction (HFnon-rEF). However, early comprehensive therapy such as detection of AF, subsequent rhythm control, and prevention of cardiogenic embolism for AF in HFnon-rEF patients may improve prognosis. Therefore, it is important for HF patients to be properly diagnosed and for AF to be detected at an early stage. In general, the 12-lead ECG or Holter ECG is recorded in clinical practice only if HF outpatients have an irregular pulse, or symptoms due to arrhythmia or HF exacerbation. Accordingly, it is difficult to adequately detect AF in HF patients with these modalities. Moreover, it is more difficult to detect asymptomatic AF or low frequency paroxysmal AF (PAF) using conventional 12-lead ECG or Holter ECG.

Implantable loop recorder (ILR) may overcome these challenges, because the ILR implanted in the subcutaneous precordium can record a long-term ECG to explore arrhythmia including AF as a cause for syncope, and embolic stroke of undetermined source (ESUS). In Japan, ILR is covered by insurance only for the diagnosis of syncope and ESUS. A previous study has shown that ILR detects AF more adequately than conventional modalities such as Holter ECG in patients with one or more risk factors for stroke including hypertension and diabetes mellitus.¹⁵ Moreover, Kort *et al* reported the incidence of arrhythmia using ILR in HF patients including HFrEF and HFnon-rEF.¹⁶ However, there are no reports investigating the incidence of arrhythmias, or comparing the ability of arrhythmia detection between ILR and conventional modality in HFnon-rEF patients, to our knowledge. Therefore, early AF detection using implanting ILR for HFnon-rEF patients without established treatment improving prognosis, compared with conventional modalities such as 12-lead ECG or Holter ECG, will lead to early and appropriate treatment for AF, and may improve the prognosis for HFnon-rEF patients.

Our study aims to demonstrate the usefulness of ILR for arrhythmia detection including AF in HFnon-rEF, and compare this novel procedure to conventional modalities such as 12-lead ECG or Holter ECG. In addition, the result of this study will provide basic data for therapeutic strategy after ADHF hospitalisation in HFnon-rEF patients, and randomised control trial demonstrating the effectiveness of cardiac implanted electrical devices and catheter ablation for arrhythmia.

METHODS

Design

This is a prospective, multicentre (Nara Medical University, Kashihara, Japan; Nara Prefecture General Medical Center, Nara, Japan; Nara City Hospital, Nara, Japan; Nara Prefecture Seiwa Medical Center, Ikoma, Japan; Yamato Kashihara Hospital, Kashihara, Japan), single arm, intervention study to demonstrate the usefulness of ILR (Reveal LINQ, Medtronic) for arrhythmia detection including AF in HFnon-rEF in comparison with conventional modalities such as 12-lead ECG or Holter ECG (figure 1). Only one model of ILR is used in this study, Medtronic's Reveal LINQ. Eligible participants are ADHF inpatients aged ≥ 20 years with EF $\geq 40\%$ within 2 weeks from obtaining informed consent. Diagnosis of ADHF is based on the Framingham criteria.¹⁷ The doctors in charge of this study in each participating centre, select eligible patients, describe this study protocol and obtain written informed consent. The inclusion and exclusion criteria are listed in table 1.

To obtain baseline patient data, laboratory test, transthoracic echocardiography and 12-lead ECG will be performed. The ILR will be implanted for patients who meet the eligible participants and will be used to monitor and record ECG, and check arrhythmia for 1 year. All

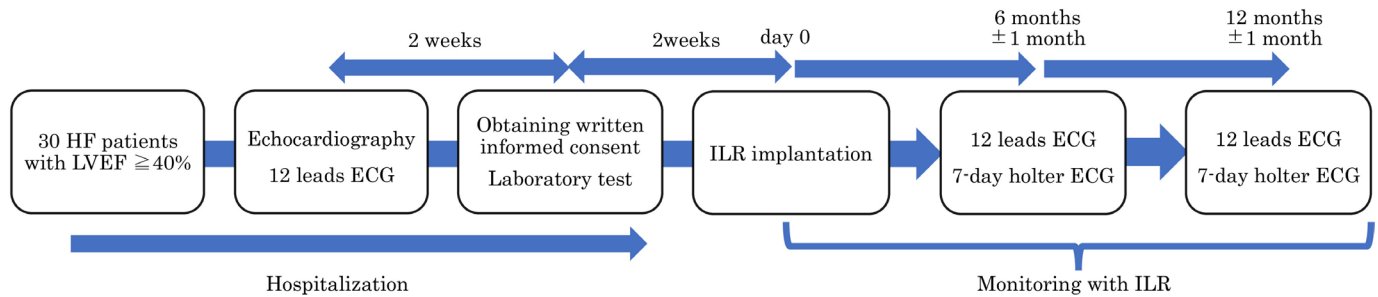


Figure 1 Study flow chart. HF, heart failure; ILR, implantable loop recorder; LVEF, left ventricular ejection fraction.

participants will be examined with 12-lead ECG, 7-day Holter ECG 6 months and 12 months after ILR implantation. The overview of all visits and tests schedule is shown in [table 2](#).

Intervention

Implantation of ILR will be performed on all participants. All ILR will be removed at the end of the study. The specific implantation and removal methods are described in online supplemental methods.

Endpoints

The primary endpoint is new-onset 6 minutes or more persistent AF detected by ILR after implantation. Secondary endpoints are followings: (1) 30 s or more persistent supraventricular tachycardia that heart rate is more than $(220 - \text{age})$ beats per minutes, (2) 30 s or more ventricular tachycardia that heart rate is more than $(220 - \text{age})$ beats per minutes, (3) 3 s or more persistent pause, (4) bradycardia with 40 beats per minutes or less heart rate, (5) AF burden (AF duration/total ILR record duration) and number of AF occurrence detected by ILR, (6) all-cause death, cardiovascular death (composite outcomes of sudden cardiac death, death due to myocardial infarction, HF, arrhythmia, ischaemic and haemorrhagic stroke), hospital readmission due to exacerbation of HF, acute coronary syndrome, ischaemic and

haemorrhagic stroke, (7) class IIa or more strong indication for non-pharmacological therapy, including cardiac implantable electrical device, catheter ablation, defined by JCS/JHRS 2020 Guideline on Pharmacotherapy of Cardiac Arrhythmias,¹⁸ (8) AF occurrence detected by 12-lead ECG, 3 min ECG and 7-day Holter ECG, (9) occurrence of arrhythmias defined as (1)–(4), including supraventricular tachycardia, ventricular tachycardia, pause and bradycardia detected by 12-lead ECG, 3 min ECG and 7-day Holter ECG.

An arrhythmia specialist will categorise arrhythmia as supraventricular tachycardia or ventricular tachycardia by checking the ECG wave detected by the ILR, and measure the presence, number and total detection duration of arrhythmias defined as (1)–(4), (8) and (9). For the safety analysis, adverse events (AEs) will be collected. An AE is defined as any unfavourable or unintended sign, symptom or disease.

Sample size

The sample size was set at 30 for feasibility, since our trial was a pilot study. The primary endpoint is considered whether the binary outcome of AF occurred, or was not detected by ILR. Estimating the AF incidence proportion and its 95% CI, the width of 95% CI is widest when the incidence proportion is 0.5, with a 95% CI width of about 0.38. The actual width of 95% CI is expected to be narrower than 0.38; when the incidence proportion is 20% (or 80%), the width of 95% CI would be about 0.3.

Statistical analysis

For our primary endpoint, we will use the Kaplan-Meier method to estimate the incidence proportion of new-onset AF (or recurrent in the case of PAF) and 95% CI at 1 year after ILR implantation.

For our secondary endpoint, we will perform our analysis as follows:

For (1)–(4) and (6), the same analysis as for the primary endpoint will be performed for each endpoint.

For (5), the observation time of burden, the percentage of AF time in the total observation time should be determined and summarised by histogram and summary statistics.

For (7), we will make a list of the types of arrhythmias, the treatment applied and the treatment implemented, and summarise the results.

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Hospitalisation for ADHF or exacerbation of chronic heart failure
	Left ventricular ejection fraction $\geq 40\%$ measured by echocardiography performed within 2 weeks before obtaining written informed consent
Exclusion criteria	Age ≥ 20 years
Exclusion criteria	Persistent AF or bradycardia indicated for permanent pacemaker implantation detected by ECG during hospitalisation
	Tachyarrhythmia indicated for catheter ablation or CIED implantation detected by ECG during hospitalisation
	Scheduled CIED implantation
	Estimated prognosis < 1 year
	Inappropriate case judged by doctor in charge
ADHF, acute decompensated heart failure; AF, atrial fibrillation; CIED, cardiac implantable electronic device.	

Table 2 The overview of all visits and tests schedule

Time	Screening	Informed consent	ILR implantation	7-day holter ECG (1)	Visit (1)	7-day holter ECG (2)	Visit (2)
	14 days before informed consent	screening by discharge	14 days within informed consent (0 day)	7 days before visit (1)	6 months±1 months	7 days before visit (2)	12 months±1 months
Visit			⊙	⊙	⊙		⊙
Informed consent		⊙					
Patient characteristics		⊙					
ILR Implantation			⊙				
Medical examination		⊙			⊙		⊙
Trans thoracic echocardiography	⊙						
Laboratory test		⊙*					
12-lead ECG (including 3 min ECG)	⊙†				⊙		⊙
7-day Holter ECG				⊙	⊙	⊙	⊙
ILR monitoring‡			⊙				⊙
ILR removal							⊙
Check of clinical symptom and outcome			⊙				⊙
Change or addition of treatment			⊙				⊙
Check of adverse event			⊙				⊙

*Each examination 2 weeks within gaining informed consent is available.

†3 minutes ECG is not essential.

‡Including data sending with remote monitoring system.

ILR, implantable loop recorder.

For (8) and (9), we will estimate the incidence proportion and 95% CI for each endpoint among those who underwent ECG measurement at 6 months and 1 year after ILR implantation. We will also estimate the proportion and 95% CI of those who are able to detect each endpoint at either 6 months or 1 year.

Patient and public involvement

Patients and public were not involved in designing this study. Our ethics committee includes public representatives. Results will be presented to patients as part of regular information events.

Limitations

Reveal LINQ is only used in this study. The AF detection capabilities in Reveal LINQ are the biggest limitations. Various studies reported the excellent abilities to detect AF with Reveal LINQ; accuracy for AF burden were more than 97%.^{19–21} However, in fact, use a validate device against gold standard Holter measurement; as this type of device was still prone to false positives a p-wave logic detection has been added to address the concern of R-wave dependent detection.¹⁹ Moreover, further optimisation has been introduced creating an adaptative sensitivity level.²⁰ Therefore, AF detection capability of Reveal LINQ will have little impact on the result of this study.

DISCUSSION/CONCLUSION

The incidence of arrhythmia in HFnon-rEF patients with a history of hospitalisation is unclear. Our pilot study will give an answer for this clinical question and demonstrate the effectiveness of ILR for detecting arrhythmia. In addition, the result of this study, if found to be effective, will be to the establishment of a new therapy improving the prognosis for HFnon-rEF.

This study has the following limitations: a short observation period and small number of patients, because of it is a pilot study.

Ethics and dissemination

This study will be carried out in compliance with the articles of the Declaration of Helsinki (revised in October 2013) and according to the Ethical Guidelines for Medical and Health Research Involving Human Subjects established by the Ministry of Health, Labour and Welfare in Japan. The investigator will give a sufficient explanation of the study to each patient and will obtain written informed consent. The independent ethics committees at each institute approved the study protocol. This study protocol was approved by the Nara Medical University Certified Review Board (CRB5200002).

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Competing interests None declared.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval This study involves human participants and this study protocol was approved by the Nara Medical University Certified Review Board (CRB5200002). Participants gave informed consent to participate in the study before taking part.

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-Examination of the usefulness of Implantable Loop Recorder for arrhythmia detection including atrial fibrillation in Heart Failure with non-reduced Ejection Fraction cases-, a pilot study

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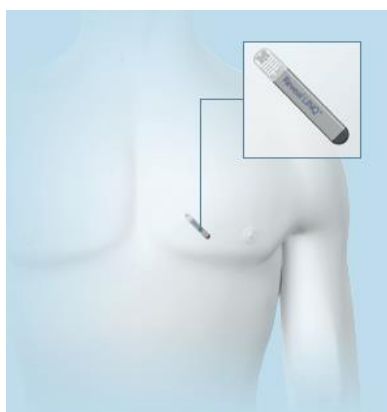
Supplementary method

The specific way of ILR (implantable loop recorder) implantation and removal is described below.

- ILR implantation

The operation of ILR implantation is performed with local anesthesia and takes about 30 minutes. The specific way is following.

- ① After local anesthesia for incision site shown in **Figure** below, approximately 1 cm incision is made for anterior chest.
- ② ILR (Reveal LINQ[®]) is inserted to subcutaneous tissue.
- ③ After checking hemostasis, surgical incision is closed by suture etc.



Figure

• ILR removal

ILR removal is performed in the same way as ILR implantation with local anesthesia.