BMJ Open

Registry for Evaluating Healthy Life Expectancy and Long-Term Outcomes after Catheter Ablation of Atrial Fibrillation in the Very Elderly (REHEALTH AF) study: rationale and design of a prospective, multicentre, observational, comparative study

Yasuo Okumura [1] , Koichi Nagashima,[1] Ryuta Watanabe,[1] Katsuaki Yokoyama,[2] Takeshi Kato,[3] Hidehira Fukaya,[4] Hidemori Hayashi,[5] Shiro Nakahara,[6] Wataru Shimizu,[7] Yu-ki Iwasaki,[7] Yuhi Fujimoto,[7] Yasushi Mukai,[8] Koichiro Ejima,[9] Takayuki Otsuka,[10] Shinya Suzuki,[10] Masato Murakami,[11] Masaomi Kimura,[12] Masahide Harada,[13] Junjiroh Koyama,[14] Hideharu Okamatsu,[14] Teiichi Yamane,[15] Seigo Yamashita,[15] Michifumi Tokuda [16] , Ryohsuke Narui,[17] Mitsuru Takami,[18] Morio Shoda,[19] Tomoo Harada,[20] Ikutaro Nakajima,[20] Katsuhito Fujiu,[21] Kenichi Hiroshima,[22] Kojiro Tanimoto,[23] Tadashi Fujino,[24] Keijiro Nakamura,[25] Koji Kumagai,[26] Ayako Okada,[27] Hideki Kobayashi,[27] Tatsuya Hayashi,[28] Yuji Watari,[29] Mina Hatsuno,[29] Eizo Tachibana,[30] Kazuki Iso,[30] Kazumasa Sonoda,[31] Yoshiyasu Aizawa,[32] Akio Chikata,[33] Satoru Sakagami,[34] Masaru Inoue,[34] Hitoshi Minamiguchi,[35] Nobuhiko Makino,[35] Kazuhiro Satomi,[36] Yoshinao Yazaki,[36] Hideshi Aoyagi,[37] Makoto Ichikawa,[38] Hironori Haruta,[39] Takafumi Hiro,[40] Kimie Okubo,[41] Ken Arima,[42] Taiki Tojo,[43] Hajime Kihara,[44] Satoru Miyanaga,[45] Yoshiaki Fukuda,[46] Koji Oiwa,[47] Tamami Fujiishi,[48] Masashi Akabane,[49] Norikazu Ishikawa,[50] Kengo Kusano,[51] Koji Miyamoto,[51] Haruna Tabuchi,[52] Tomoyuki Shiozawa,[53] Kenjiro Miyamoto,[54] Hiroshi Mase,[55] Kenta Murotani [56] , For the REHEALTH AF study

ABSTRACT

Introduction Data are lacking on the extent to which patients with non-valvular atrial fibrillation (AF) who are aged ≥80 years benefit from ablation treatment. The question pertains especially to patients' postablation quality of life (QoL) and long-term clinical outcomes.

Methods and analysis We are initiating a prospective, registry-based, multicentre observational study that will include patients aged ≥80 years with non-valvular AF who choose to undergo treatment by catheter ablation and, for comparison, such patients who do not choose to undergo ablation (either according to their physician's advice or their own preference). Study subjects are to be enrolled from 52 participant hospitals and three clinics located throughout Japan from 1 June 2022 to 31 December 2023, and each will be followed up for 1 year. The planned sample size is 660, comprising 220 ablation group patients and 440 non-ablation group patients. The primary endpoint will be the composite incidence of stroke/transient ischaemic attack (TIA) or systemic embolism (SE), another cardiovascular event, major bleeding and/or death from any cause. Other clinical events such as postablation AF recurrence, a fall or bone fracture will be recorded. We will collect standard clinical background information plus each patient's Clinical Frailty Scale score, AF-related symptoms, QoL (Five-Level Version of EQ-5D) scores, Mini-Mental State Examination (optional) score and laboratory test results, including measures of nutritional status, on entry into the study and 1 year later, and serial changes in symptoms and QoL will also be secondary endpoints. Propensity score matching will be performed to account for covariates that could affect study results.

Ethics and dissemination The study conforms to the Declaration of Helsinki and the Ethical Guidelines for Clinical Studies issued by the Ministry of Health, Labour and Welfare, Japan. Results of the study will be published in one or more peer-reviewed journals.

Trial registration number UMIN000047023.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This registry-based study is a multicentre observational study designed to compare the quality of life, physical status and long-term clinical outcomes between patients aged 80 years or more who elect to undergo ablation for atrial fibrillation (AF) (ablation group) and those who do not (non-ablation group).

⇒ Propensity score matching will substantially alleviate any selection bias within the two groups of patients whose characteristics will be similar because the investigators will include only relatively healthy patients in the non-ablation group.

⇒ Selection bias and potential confounding factors cannot be completely eliminated.

⇒ Because patients' AF-related symptoms and quality of life will be assessed by means of simple self-report questionnaires, and physical status will be judged simply according to the Clinical Frailty Scale, patients' status may not be fully reflected.

⇒ Patients to be included in the study are of a single race/ethnicity.

INTRODUCTION

Atrial fibrillation (AF) increases the risk of stroke, heart failure and mortality.[1 2] Early intervention such as catheter ablation for maintenance of sinus rhythm has been reported to yield favourable clinical outcomes.[3–5] With new developments in ablation technology over the past two decades, indications for AF ablation have gradually been expanded to include not only young patients but also middle-aged and elderly patients. Because of Japan's now 'super-aged' society, AF ablation is being applied increasingly in patients aged 80 years or more. In 2009, researchers estimated the overall prevalence of AF among persons in Japan aged 40 years or more to be approximately 0.56% (716 000 persons) and projected that the overall prevalence will increase by decade, starting at 0.65% in 2010 and reaching 1.09% by 2050.[6] Among persons aged 80 years or more (ie, very elderly persons), in particular, they documented a prevalence of 4.4% for men but 2.2% for women. In light of these trends, electrophysiologists ask a simple question: what can be improved by catheter ablation in very elderly patients with AF? Numerous studies related to catheter ablation in elderly patients have defined this patient population as being of age ≥75 years, and, although each was carried out as a retrospective single-centre or multicentre observational study, all have focused on recurrence of AF and ablation-related complications.[7–9] These studies showed a similar AF recurrence rate between elderly patients and those who are younger but a modestly increased risk of complications in the elderly.[7–9] The database analysis[7] included over 100 000 patients, but there were several critical limitations; for example, heart failure was not clearly defined, details regarding patients' status such as symptoms, quality of life (QoL), frailty or falls, and type of AF were unavailable, and serial changes in biomarkers and physical or mental functioning were not assessed. Only a few studies have investigated both the effects of catheter ablation on QoL and long-term clinical outcomes in patients aged ≥65 or ≥75 years.[10–14] Thus far, no study has focused on patients aged ≥80 years because adequate data collection is challenging, with only a small number of such patients undergoing AF ablation worldwide. Because Japan has become a 'super-aged society', we consider it urgent to determine the clinical significance of catheter ablation for AF in patients aged ≥80 years. To resolve clinical questions that cannot be addressed by database and retrospective studies, we aim to explore the multiple effects of catheter ablation on clinical outcomes, focusing especially on long-term AF-related events and healthy life expectancy, by collecting real-world data regarding patients aged ≥80 years with AF who undergo catheter ablation and those who do not.
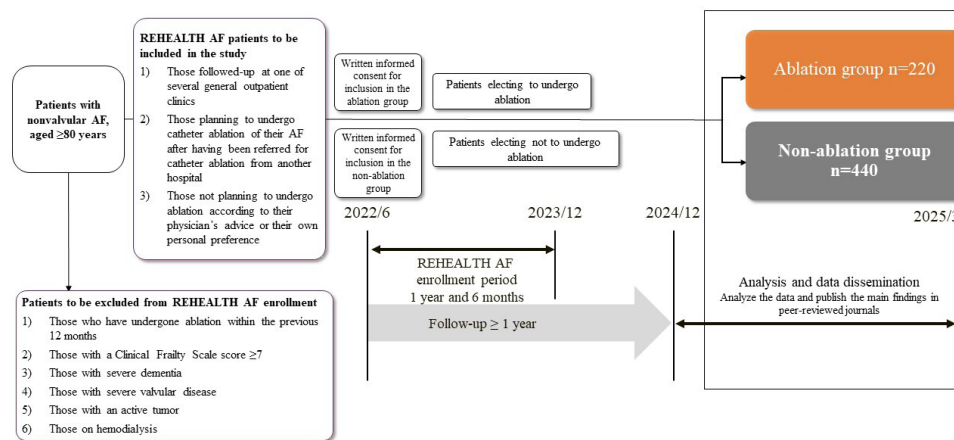
METHODS

Study design and setting

The study will be based on Registry for Evaluating Healthy life Expectancy And Long-Term outcomes after CatHeter ablation of Atrial Fibrillation in the very elderly (REHEALTH AF), a large-scale, multicentre prospective registry of patients with AF in Japan. Enrolment began on 1 June 2022; the inclusion is scheduled to end on 31 December 2023, and all patients enrolled will be followed up for at least 1 year (with final follow-up occurring on or before 31 December 2024). Fifty-five institutions in Japan are registry participants (as shown in online supplemental figure 1), and these include 42 hospitals where ablation is performed and 10 hospitals and three private clinics where ablation is not performed. A flow diagram of the REHEALTH AF study, showing the overall patient pool, criteria for inclusion in and exclusion from the study, follow-up time and data analysis is shown in figure 1.

Eligibility and non-eligibility

All patients included the study will be aged ≥80 years and diagnosed with non-valvular AF. All will have been visiting an outpatient clinic and have elected either to undergo or not undergo ablation for treatment of the AF. A patient's decision to undergo ablation will have been based on their physician's recommendation, whereas a patient's decision to not undergo ablation will have been based on their physician's recommendation or on their own personal preference. Therefore, the patients who have decided not to undergo ablation will be of two types, that is, those advised by their physician not to undergo ablation and those who simply choose not to undergo ablation. The study will include patients with any type of AF, that is, paroxysmal AF (recovery of sinus rhythm within 7 days of onset), persistent AF (AF lasting more than 7 days after onset), long-lasting persistent AF (persistent AF lasting for more than 1 year after onset) or persistent AF of unknown duration. All those included in the study will provide written informed consent for their inclusion. None of the patients considered for inclusion in the study will have undergone ablation within the previous 12 months, will have a Clinical Frailty Scale score of ≥7,[15] will have severe dementia, will have severe valvular disease or

Figure 1 Flow diagram of the REHEALTH AF study. AF, atrial fibrillation; REHEALTH AF, Registry for Evaluating Healthy life Expectancy And Long-Term outcomes after catHeter ablation of Atrial Fibrillation in the very elderly.

an active tumour, will be on haemodialysis, or will have been judged by the research director or research coordinator not to be suitable for the study.

Study schedule

A website was created for the REHEALTH AF study and will be used to store all pseudonymised patient data, collected through a web-based registration system. Each patient's name and hospital ID number will be replaced with a code but linked to the original record through the use of a key code. The coded data and key code will be stored separately. All participating investigators and/or research coordinators have been trained in how to use the study website, and for security purposes, each received his or her own ID for access to it. The study schedule is summarised in table 1.

In brief, after being screened for eligibility and providing written informed consent, study patients will undergo assessment of their physical status according to the Clinical Frailty Scale,[15] of their QoL by means of the Five-Level Version of EQ-5D (EQ-5D-5L) questionnaire[16] a two-part generic measure of health status, and of their AF-related symptoms by means of a patient-reported outcome measure (PROM). AF-related symptoms assessed by means of the PROM include palpitations, dizziness/ lightheadedness, rapid heartbeat, dyspnoea/shortness of breath, general fatigue and/or fainting/syncope.[17 18] The PROM, including the response alternatives, is shown in online supplemental figure 2. The first part of the EQ-5D-5L questionnaire is designed to assess health in five dimensions (mobility, self-care, usual activities, pain/ discomfort and anxiety/depression), each of which has five response levels. A summary index score based on the five dimensions ranges from 0 (meaning worst health) to 1 (meaning full health). The second part of the EQ-5D-5L questionnaire consists of a Visual Analogue Scale by which the patient rates his or her perceived health from 0 ('worst health you can imagine') to 100 ('best health you can imagine').[16] If a patient desires assessment of dementia, that patient will be given the Mini-Mental State Examination (MMSE) at Nihon University Itabashi

Hospital, Nihon University Hospital, or another participating facility.[19] All patients' clinical characteristics, laboratory values (haemoglobin concentration, creatinine concentration, N-terminal probrain natriuretic peptide (NT-proBNP) or brain natriuretic peptide, and nutritional status (Controlling Nutritional Status score,[20] Glasgow Prognostic Score,[21] Prognostic Nutritional Index[22] and Geriatric Nutritional Risk Index[23]), electrocardiographic findings (sinus rhythm, AF/atrial tachycardia or other), transthoracic echocardiographic measures (left atrial diameter and left ventricular ejection fraction) and current medications will be determined at the time of registry enrolment but before ablation for patients who choose to undergo ablation (ablation group) or at the time of registry enrolment for patients who choose not to undergo ablation (non-ablation group). Because of the effect of changes in a patient's medical status, the time between registration and ablation will be no longer than 4 weeks. Ablation details will be obtained for patients in the ablation group. One year after entry into the study, each patient's symptoms, Clinical Frailty Scale score, QoL, MMSE score (if applicable), ECG, echocardiogram result and summary follow-up data will be obtained. If patients are followed up for more than 1.5 years, their symptoms, Clinical Frailty Scale score, QoL and ECG will be assessed and recorded 1.5 years after entry into the study if possible (table 1). Items obtained from each patient's record at the time of enrolment and those obtained at the 1-year follow-up are shown in online supplemental table 1). Each patient's pseudonymised baseline clinical information and follow-up data will be entered into an Excel spreadsheet at the participating hospital/clinic and saved to the website. For all study patients, the continuation, termination or initiation of oral anticoagulants, antiplatelet drugs and antiarrhythmic drugs will be investigated routinely and recorded. Onset and details of the occurrence of the primary and secondary study endpoints (see further) and invasive treatments (eg, catheter ablation and left atrial appendage closure) during the follow-up period will be also recorded. Any episode of AF occurring

Table 1 Study schedule (including items recorded) for ablation group and non-ablation group patients

Item(s) recorded		Registration*	Ablation	At 12 months after ablation† or registration†	Final follow-up‡
Patient information	Age, sex, height, weight, lifestyle habits, comorbidities, etc	●		● (Weight, blood pressure, pulse)	
	Symptoms (palpitations, dizziness/lightheadedness, rapid heartbeat, dyspnoea/shortness of breath, general fatigue and/or fainting/syncope)	●		●	●
	Laboratory test results	●		●	
ECG		●		●	●
Echocardiogram		●		●	
Clinical Frailty Scale score		●		●	●
MMSE score§		●		●	
EQ-5D-5L (summary index score and Visual Analogue Scale score)		●		●	●
Ablation procedure details			●		
Drug types	Antihypertensive drug(s), gastrointestinal drug(s), etc	●			
	Antiarrhythmic drug(s)	⟶			
	Oral anticoagulant(s)	⟶			
	Antiplatelet drug(s)	⟶			
Adverse clinical events		⟶			

*Within 3 months before ablation (ablation group) or within 3 months before or after registration (non-ablation group).
†Allowable range: within 3 months for both groups.
‡Allowable range: within 3 months from the final follow-up only for patients who are followed up for more than 1.5 years.
§If the patient desires to take the MMSE at Nihon University Itabashi Hospital, Nihon University Hospital or another participating facility.
¶
**
EQ-5D-5L, Five-Level Version of EQ-5D; MMSE, Mini-Mental State Examination.

after ablation, lasting >30 s and documented on a standard ECG, event recorder or 24-hour Holter monitor, will be considered recurrent AF. If a patient is transferred to another hospital and discontinues or remains on the prescribed medication(s) during the follow-up period, this information will be collected, if possible, at least until the end of the 1-year follow-up period. All patient data including follow-up data will generally be updated every 3–6 months from each patient's respective hospital/clinic. The general registry office will monitor and review the updated data in an independent manner every 6 months, and a patient's hospital/clinic will be queried if some information entered into the database is unclear. Clinical events/endpoints will be judged by a clinical event committee.

Primary and secondary endpoints
The primary study endpoint will be the composite incidence of stroke/TIA, SE, another cardiovascular event (other than stroke/TIA, SE or cardiovascular death), major bleeding[24] and/or all-cause death. Secondary endpoints are listed in box 1. In particular, we will focus on AF recurrence and changes in patients' symptoms, Clinical Frailty Scale score and QoL from the time of enrolment to 1 year after ablation.

Sample size and calculation data
A previous study (published in 2019), derived from a multicentre AF registry in Japan and covering mostly non-ablation patients, revealed a 17.8% incidence of the composite endpoint (stroke, all-cause mortality, major bleeding and cardiovascular events) among patients aged ≥75 years,[25] and the Edoxaban Low-Dose for Elder Care Atrial Fibrillation Patients (ELDERCARE-AF) trial (published in 2020) revealed a 22.4% incidence of cardiovascular hospitalisation of frail patients aged ≥80 years.[26] Accordingly, we set the 1-year incidence of the primary endpoint in non-ablation group at 20%. Furthermore, to estimate the therapeutic effect in the ablation group with respect to that in the non-ablation group, we set the HR as follows: in a multivariate analysis of Japan's ANAFIE registry consisting of 30 000 patients aged ≥75 years, most of whom have been treated by anticoagulants,[27] the HR when ablation was performed was 0.58 (95% CI 0.42 to

Box 1 Primary and secondary endpoints

⇒ Primary endpoint: composite incidence of stroke/TIA or SE, another cardiovascular event (a cardiovascular event other than stroke/TIA, SE or cardiovascular death), major bleeding and/or all-cause death.
⇒ Secondary endpoints.
  Occurrence of any of the following:
⇒ Stroke/TIA or SE.
⇒ Cardiovascular event (stroke/TIA or SE, myocardial infarction/unstable angina, cardiovascular death, sudden death or hospitalisation for heart failure).
⇒ Major bleeding (ISTH criteria*).
⇒ Death from any cause.
⇒ Clinically significant bleeding.
⇒ Myocardial infarction, unstable angina.
⇒ Heart failure requiring hospitalisation or other cardiovascular event requiring hospitalisation.
⇒ Cardiovascular death.
⇒ Recurrence of atrial fibrillation after ablation.
⇒ Pacemaker implantation.
⇒ Fall.
⇒ Bone fracture.
  Change in the following from the time of enrolment to 1 year:
⇒ Body weight.
⇒ Symptoms.
⇒ Blood pressure and pulse.
⇒ Clinical Frailty Scale score.
⇒ QoL (EQ-5D-5L: summary index score and visual analogue scale score).
⇒ MMSE score (optional item).
⇒ Electrocardiographic findings.
⇒ Echocardiographic measures.
⇒ Haemoglobin and creatinine.
⇒ NT-proBNP or BNP.
⇒ Nutritional status markers.
⇒ Use of antiarrhythmic drugs, anticoagulants or antiplatelet drugs.

*The ISTH defines major bleeding as follows: fatal bleeding, bleeding into a major organ or critical area (eg, intracranial, retroperitoneal, pericardial, intraspinal, intra-articular and intraocular bleeding), a decrease in the haemoglobin concentration of 20 g/L or more, or transfusion of at least 2 units of blood.[24]
BNP, brain natriuretic peptide; EQ-5D-5L, Five-Level Version of EQ-5D; ISTH, International Society for Thrombosis and Haemostasis; MMSE, Mini-Mental State Examination; NT-proBNP, N-terminal probrain natriuretic peptide; SE, systemic embolism; TIA, transient ischaemic attack.

0.79) for stroke, 0.66 (95% CI 0.47 to 0.94) for major bleeding and 0.55 (95% CI 0.44 to 0.69) for death from any cause. On the basis of these data, we set an HR of 0.6 as the expected therapeutic effect of ablation. Thus, the 1-year primary event rate in our non-ablation group will be 20%; the therapeutic effect of ablation will be an HR of 0.6, as necessary to detect a difference at α=0.05 (two-sided) and 1−β of ≥0.8. In calculating the number of patients needed by means of the Lakatos method, we found a need for 183 per group. We used PROC POWER (SAS V.9.4) to calculate the required number of cases and set the required number at 200 for each group. We realise that clinical characteristics of the non-ablation group patients are likely to differ from those of the ablation group patients. However, when 1:1 nearest neighbour matching was performed at a calliper width of 0.5 for the 2930 patients from SAKURA AF who did not undergo ablation and the 3451 AF Frontier Ablation Registry patients who underwent ablation, 48% (n=1414) of patients who did not undergo ablation were matched to patients in the ablation group.[11] Thus, it appears that about twice as many patients who do not undergo ablation are needed for analysis, so we set that number to 400. The target numbers are 220 and 440, respectively, totalling 660, under the expectation that about 10% of patients will drop out or be censored.

Statistical analysis
Continuous variables will be presented as mean±SD or median (25th, 75th percentile) values and categorical variables as the number (%) of patients. Between-group differences in continuous variables will be analysed by t-test or Mann-Whitney U test; and between-group differences in categorical variables will be analysed by χ^2 or Fisher's exact test. Groups will be balanced by means of 1:1 nearest neighbour propensity score matching at a calliper width of 0.5 or by the inverse probability of treatment weighting method. Variables in the propensity score model will be selected in a data-driven manner, with the number of events taken into account. Variables that are unrelated to the exposure but related to the outcome will be preferentially included in the model.[28] If overlap in the propensity scores is small, weighting estimation will be performed. Results obtained for all cohorts (including patients who were excluded by propensity score matching) will be shown as supplemental material. Cumulative event rates will be calculated by the Kaplan-Meier method and compared between the two main study groups and between the propensity score-matched groups by log-rank test. Event rates will be calculated as the total number (%) of events and the number per 100 person-years. The same method will be used for occurrence of each secondary endpoint. For serial changes in haemoglobin, creatinine, NT-proBNP, EQ-5D-5L and all other clinical variables from the time of enrolment to 1 year thereafter, difference in the change (%) between the ablation group and non-ablation group will be analysed. Factors related to occurrence of the primary endpoint will be subjected to multivariate Cox proportional hazards analysis, and HRs (with 95% CIs) for the ablation group in relation to the non-ablation group will be calculated, allowing for identification of any risk-lowering effect of ablation. The Cox proportional hazards model will also be adjusted for factors such as age, sex, weight and comorbidities to test for any interactions.

Ethics and dissemination
The study is registered with the UMIN Clinical Trials Registry. It conforms to the Declaration of Helsinki[29] and the Ethical Guidelines for Clinical Studies issued by the Ministry of Health, Labour and Welfare, Japan. All study participants will provide written informed consent

and may withdraw their consent at any time. This study protocol has been approved by the institutional review board (IRB) of Nihon University Itabashi Hospital, Clinical Research Judging Committee, and the participating hospitals' IRBs. Results of the study will be published in one or more peer-reviewed journals.

Patient and public involvement statement
Neither patients nor members of the public have been or will be involved in the design of the study, its planning or the data collection or data analysis.

DISCUSSION
This registry-based study is a prospective multicentre cohort study designed to examine the differences in symptoms, QoL, physical status and long-term clinical outcomes in patients aged 80 years or older who choose to undergo ablation therapy (ablation group) and those who do not (non-ablation group). The benefits of ablation may not be fully realised among elderly patients. A subanalysis of our previously reported registry data showed no beneficial effect on the composite mid-term clinical outcome—stroke, death, cardiovascular events and major bleeding—among patients aged ≥75 years,[11] in keeping with results reported for patients aged ≥65 years from a subanalysis of the Catheter Ablation vs Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA)[12] and Catheter Ablation for Atrial Fibrillation with Heart Failure (CHASTLE-AF) trials.[13] However, subanalysis of the CABANA data revealed QoL in the ablation group to be significantly improved even in patients aged ≥75 years,[14] as reported out of a prospective multicentre Japanese registry of patients aged ≥70 years.[30] In particular, whether the benefit of AF ablation, with respect to symptoms, QoL and clinical outcomes, holds true for patients aged ≥80 years has not been determined.

The REHEALTH AF study has several strengths in terms of its design. Being conducted as a multicentre observational study, it overcomes the obstacles that would be posed by a randomised controlled trial. Such a trial aimed at comparing outcomes among patients who do and do not undergo AF ablation can be ethically challenging in Japan. In addition, there are few patients aged ≥80 years who undergo ablation at any one hospital, so the study was designed in such a way that enrolling the necessary number of patients would be clinically feasible. Second, we chose a simple symptom questionnaire, a general QoL questionnaire (EQ-5D-5L) and the Clinical Frailty Scale (for assessment of patients' physical status) because these instruments are not complex and thus are easy to administer in the context of the large number of busy hospitals/clinics that treat outpatients in Japan. Although the Atrial Fibrillation Effect on Quality-of-Life is a well-established instrument,[14 30] it may be challenging for patients aged ≥80 years to complete; it has been used in only a few Japan-based registry-enrolled patients aged ≥80 years so far.[30] Third, patients who undergo ablation

are generally healthier than those who do not, so we plan to use propensity score matching to balance our two study groups. Propensity score matching is generally performed in retrospective studies, but unmeasured variables and potential selection bias remain problematic. To avoid these problems as much as possible, we plan to document important variables specific to elderly patients (body weight, frailty, history of falls, nutrition status, etc), and we asked the participating investigators to enrol healthy (Clinical Frailty Scale score of 1–4 and absence of dementia) patients who choose not to undergo AF ablation according either to their physician's advice or their own preference. Prospectively collecting data on well-matched patients who do and do not undergo AF ablation will allow comparison of the multiple effects of ablation on symptoms, QoL and clinical outcomes between the two patient groups.

Regardless of its strengths, the study has its limitations. First, although it is an observational study that incorporates patient matching, selection bias and confounding factors cannot be completely controlled for. Second, because of the use of a simple PROM for AF-related symptoms, the EQ-5D-5L and the Clinical Frailty Scale, patient status specific to AF may not be fully captured. In particular, the PROM we are using for AF-related symptoms has not been methodically validated. However, two published registry-based studies addressing outcomes ablation for AF, one of the Japanese patients with AF[18] and the other of patients with AF from 26 countries[17] assessed, at 1 year after ablation, change in the same AF-related symptoms covered by our PROM, and significant improvement in these AF-related symptoms was documented in both studies. Third, the study's patient population is of a single racial/ethnic background.

The REHEALTH AF study will stand as a prospective multicentre registry-based study designed specifically to investigate the effects of ablation as treatment for non-valvular AF in patients aged ≥80 years.

Author affiliations
[1]Department of Cardiology, Nihon University Itabashi Hospital, Itabashi-ku, Tokyo, Japan
[2]Department of Cardiology, Nihon University Hospital, Chiyoda-ku, Tokyo, Japan
[3]Department of Cardiovascular and Internal Medicine, Kanazawa University Hospital, Kanazawa, Ishikawa, Japan
[4]Department of Cardiovascular Medicine, Kitasato University School of Medicine, Sagamihara, Kanagawa, Japan
[5]Department of Cardiovascular Biology and Medicine, Juntendo University Graduate Schoool of Medicine, Bunkyo-ku, Tokyo, Japan
[6]Department of Cardiology, Dokkyo Medical University Saitama Medical Center, Koshigaya, Saitama, Japan
[7]Department of Cardiovascular Medicine, Nippon Medical School Hospital, Bunkyo-ku, Tokyo, Japan
[8]Department of Cardiovascular Medicine, Japanese Red Cross Fukuoka Hospital, Fukuoka City, Fukuoka, Japan
[9]Department of Cardiology, Minamino Cardiovascular Hospital, Hachioji, Tokyo, Japan
[10]Department of Cardiovascular Medicine, The Cardiovascular Institute, Minato-ku, Tokyo, Japan
[11]Division of Cardiology, Shonan Kamakura General Hospital, Kamakura, Kanagawa, Japan

Open access

[12]Divison of Cardiology, Pulmonary Medicine and Nephrology, Hirosaki University School of Medicine, Hirosaki, Aomori, Japan

[13]Department of Cardiology, Fujita Health University, Toyoake, Aichi, Japan

[14]Cardiovascular Center, Saiseikai Kumamoto Hospital, Kumamoto City, Kumamoto, Japan

[15]Division of Cardiology, Department of Internal Medicine, Jikei University School of Medicine, Minato-ku, Tokyo, Japan

[16]Division of Cardiology, Department of Internal Medicine, The Jikei University Katsushika Medical Center, Katsushika-ku, Tokyo, Japan

[17]Division of Cardiology, Department of Internal Medicine, The Jikei University Kashiwa Hospital, Kashiwa, Chiba, Japan

[18]Division of Cardiovascular Medicine, Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe, Hyogo, Japan

[19]Department of Cardiology, Tokyo Women's Medical University Hospital, Shinjuku-ku, Tokyo, Japan

[20]Department of Cardiology, St.Marianna University School of Medicine Hospital, Kawasaki, Kanagawa, Japan

[21]Department of Cardiovascular Medicine, The University of Tokyo Hospital, Bunkyo-ku, Tokyo, Japan

[22]Department of Cardiology, Kokura Memorial Hospital, Kitakyushu, Fukuoka, Japan

[23]Deparatment of Cardiology, National Hospital Organisation Tokyo Medical Center, Meguro-ku, Tokyo, Japan

[24]Department of Cardiovascular Medicine, Toho University Graduate School of Medicine, Ota-ku, Tokyo, Japan

[25]Division of Cardiovascular Medicine, Toho University Ohashi Medical Center, Meguro-ku, Tokyo, Japan

[26]Department of Cardiovascular Medicine, Tohoku Medical and Pharmaceutical University, Sendai, Miyagi, Japan

[27]Department of Cardiovascular Medicine, Shinshu University Hospital, Matsumoto, Nagano, Japan

[28]Division of Cardiovascular Medicine, Saitama Medical Center, Jichi Medical University, Omiya, Saitama, Japan

[29]Department of Cardiology, Teikyo University Hospital, Itabashi-ku, Tokyo, Japan

[30]Division of Cardiology, Kawaguchi Municipal Medical Center, Kawaguchi, Saitama, Japan

[31]Division of Cardiology, Department of Medicine, Tokyo Rinkai Hospital, Edogawa-ku, Tokyo, Japan

[32]Department of Cardiology, International University of Health and Welfare Narita Hospital, Narita, Chiba, Japan

[33]Department of Cardiology, Toyama Prefectural Central Hospital, Toyama City, Toyama, Japan

[34]Department of Cardiology, National Hospital Organization, Kanazawa Medical Center, Kanazawa, Ishikawa, Japan

[35]Department of Cardiology, Osaka Police Hospital, Osaka City, Osaka, Japan

[36]Department of Cardiology, Tokyo Medical University, Shinjuku-ku, Tokyo, Japan

[37]Department of Cardiovascular Medicine, St Luke's International University, Chuo-ku, Tokyo, Japan

[38]Department of Cardiology, Sekishin Clinic, Kawagoe, Saitama, Japan

[39]Department of Cardiology, TMG Asaka Medical Center, Asaka, Saitama, Japan

[40]Circulatory medicine, Akabane Central General Hospital, Kita-ku, Tokyo, Japan

[41]Department of Cardiology, Itabashi Medical Association Hospital, Itabashi-ku, Tokyo, Japan

[42]Department of Cardiology, Kasukabe Medical Center, Kasukabe, Saitama, Japan

[43]Department of Cardiovascular medicine, Kitasato University Kitasato Institute Hospital, Minato-ku, Tokyo, Japan

[44]Department of Internal Medicine, Kihara Cardiovascular Clinic, Asahikawa, Hokkaido, Japan

[45]Division of Cardiology, Department of Internal Medicine, The Jikei University Daisan Hospital, Komae, Tokyo, Japan

[46]Department of Cardiology, Higashi Saitama General Hospital, Satte, Saitama, Japan

[47]Cardiology, Japan Community Health are Organization, Yokohama Chuo Hospital, Yokohama, Kanagawa, Japan

[48]Department of Cardiology, JCHO Sagamino Hospital, Sagamihara, Kanagawa, Japan

[49]Department of Cardiology, Akabane Clinic, Outawara, Tochigi, Japan

[50]Department of Cardiology, Zengyodanchi Ishikawa Clinic, Fujisawa, Kanagawa, Japan

[51]Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, Suita, Osaka, Japan

[52]Department of Cardiology, Juntendo University Nerima Hospital, Nerima-ku, Tokyo, Japan

[53]Department of Cardiology, Juntendo University Shizuoka Hospital, Izunokuni, Shizuoka, Japan

[54]Department of Cardiology, Sapporo Shiroishi Memorial Hospital, Hokkaido, Sapporo, Japan

[55]Department of Cardiology, Showa University Fujigaoka Hospital, Yokohama, Kanagawa, Japan

[56]Biostatistics Center, Kurume University School of Medicine, Kurume, Fukuoka, Japan

ORCID iDs
Yasuo Okumura http://orcid.org/0000-0002-2960-4241
Michifumi Tokuda http://orcid.org/0000-0003-1960-5627
Kenta Murotani http://orcid.org/0000-0003-0623-9365

REFERENCES

1. Benjamin EJ, Levy D, Vaziri SM, *et al*. Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham heart study. *JAMA* 1994;271:840–4.
2. Stewart S, Hart CL, Hole DJ, *et al*. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the renfrew/paisley study. *Am J Med* 2002;113:359–64.
3. Kirchhof P, Camm AJ, Goette A, *et al*. Early rhythm-control therapy in patients with atrial fibrillation. *N Engl J Med* 2020;383:1305–16.
4. Rillig A, Magnussen C, Ozga A-K, *et al*. Early rhythm control therapy in patients with atrial fibrillation and heart failure. *Circulation* 2021;144:845–58.
5. Willems S, Borof K, Brandes A, *et al*. Systematic, early rhythm control strategy for atrial fibrillation in patients with or without symptoms: the EAST-AFNET 4 trial. *Eur Heart J* 2022;43:1219–30.
6. Inoue H, Fujiki A, Origasa H, *et al*. Prevalence of atrial fibrillation in the general population of Japan: an analysis based on periodic health examination. *Int J Cardiol* 2009;137:102–7.
7. Yokoyama Y, Miyamoto K, Nakai M, *et al*. Complications associated with catheter ablation in patients with atrial fibrillation: a report from the JROAD-DPC study. *J Am Heart Assoc* 2021;10:e019701.
8. Romero J, Ogunbayo G, Elayi SC, *et al*. Safety of catheter ablation for atrial fibrillation in the octogenarian population. *J Cardiovasc Electrophysiol* 2019;30:2686–93.
9. Lee W-C, Wu P-J, Chen H-C, *et al*. Efficacy and safety of ablation for symptomatic atrial fibrillation in elderly patients: a meta-analysis. *Front Cardiovasc Med* 2021;8:734204.
10. Su X, DU X, Lu S-X, *et al*. Catheter ablation for atrial fibrillation is associated with reduced risk of mortality in the elderly: a prospective cohort study and propensity score analysis. *J Geriatr Cardiol* 2020;17:740–9.
11. Iso K, Nagashima K, Arai M, *et al*. Clinical outcomes of ablation versus non-ablation therapy for atrial fibrillation in Japan: analysis of pooled data from the AF frontier ablation registry and SAKURA AF registry. *Heart Vessels* 2021;36:549–60.
12. Packer DL, Mark DB, Robb RA, *et al*. Effect of catheter ablation vs antiarrhythmic drug therapy on mortality, stroke, bleeding, and cardiac arrest among patients with atrial fibrillation: the CABANA randomized clinical trial. *JAMA* 2019;321:1261–74.
13. Marrouche NF, Brachmann J, Andresen D, *et al*. Catheter ablation for atrial fibrillation with heart failure. *N Engl J Med* 2018;378:417–27.
14. Mark DB, Anstrom KJ, Sheng S, *et al*. Effect of catheter ablation vs medical therapy on quality of life among patients with atrial fibrillation: the CABANA randomized clinical trial. *JAMA* 2019;321:1275–85.
15. Rockwood K, Song X, MacKnight C, *et al*. A global clinical measure of fitness and frailty in elderly people. *CMAJ* 2005;173:489–95.
16. Herdman M, Gudex C, Lloyd A, *et al*. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011;20:1727–36.
17. Rordorf R, Scazzuso F, Chun KRJ, *et al*. Cryoballoon ablation for the treatment of atrial fibrillation in patients with concomitant heart failure and either reduced or preserved left ventricular ejection fraction: results from the cryo AF global registry. *J Am Heart Assoc* 2021;10:e021323.
18. Kimura M, Kobori A, Nitta J, *et al*. Cryoballoon ablation for paroxysmal atrial fibrillation in Japan: 2-year safety and efficacy results from the cryo AF global registry. *J Interv Card Electrophysiol* 2022;64:695–703.
19. Folstein MF, Folstein SE, McHugh PR. " Mini-Mental state ". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189–98.
20. Ignacio de Ulíbarri J, González-Madroño A, de Villar NGP, *et al*. CONUT: a tool for controlling nutritional status. first validation in a hospital population. *Nutr Hosp* 2005;20:38–45.
21. Forrest LM, McMillan DC, McArdle CS, *et al*. Evaluation of cumulative prognostic scores based on the systemic inflammatory response in patients with inoperable non-small-cell lung cancer. *Br J Cancer* 2003;89:1028–30.
22. Onodera T, Goseki N, Kosaki G. Prognostic nutritional index in gastrointestinal surgery of malnourished cancer patients. *Nihon Geka Gakkai Zasshi* 1984;85:1001–5.
23. Bouillanne O, Morineau G, Dupont C, *et al*. Geriatric nutritional risk index: a new index for evaluating at-risk elderly medical patients. *Am J Clin Nutr* 2005;82:777–83.
24. Schulman S, Angerås U, Bergqvist D, *et al*. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients. *J Thromb Haemost* 2010;8:202–4.
25. Nishida T, Okumura Y, Yokoyama K, *et al*. Oral anticoagulant use and clinical outcomes in elderly Japanese patients: findings from the SAKURA AF registry. *Heart Vessels* 2019;34:2021–30.
26. Okumura K, Akao M, Yoshida T, *et al*. Low-Dose edoxaban in very elderly patients with atrial fibrillation. *N Engl J Med* 2020;383:1735–45.
27. Yamashita T, Suzuki S, Inoue H, *et al*. Two-Year outcomes of more than 30 000 elderly patients with atrial fibrillation: results from the all nippon AF in the elderly (ANAFIE) registry. *Eur Heart J Qual Care Clin Outcomes* 2022;8:202–13.
28. Brookhart MA, Schneeweiss S, Rothman KJ, *et al*. Variable selection for propensity score models. *Am J Epidemiol* 2006;163:1149–56.
29. World Medical A. World Medical association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2013;310:2191–4.
30. Miura K, Ikemura N, Kimura T, *et al*. Treatment strategies and subsequent changes in the patient-reported quality-of-life among elderly patients with atrial fibrillation. *Am Heart J* 2020;222:83–92.