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STUDY DESIGN

Kyoto Congestive Heart Failure (KCHF) study: rationale and design

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Abstract

Aims Over the last decade, major developments in medicine have led to significant changes in the clinical management of heart failure patients. This study was designed to evaluate the recent trends in clinical characteristics, management, and short-term and long-term prognosis of patients with acute decompensated heart failure (ADHF) in Japan.

Methods and results The Kyoto Congestive Heart Failure study is a prospective, observational, multicentre cohort study, enrolling consecutive ADHF patients from 19 participating hospitals in Japan from November 2014 to March 2016. A total of 4000 patients will be enrolled into the study and patients' anthropometric, socio-economic, and clinical data from hospital admission to discharge will be collected. In addition, in a pre-determined subgroup of patients (n=1500), a longitudinal follow-up for 2 years is scheduled.

Conclusions The Kyoto Congestive Heart Failure study will provide valuable information regarding patients with ADHF in the real-world clinical practice of Japan and will be indispensable for future clinical and policy decision-making with respect to heart failure.

Keywords Heart failure; Decompensation; Prognosis; Cohort study

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Introduction

Heart failure constitutes a major public health burden worldwide.[1] The number of annual hospitalizations for acute decompensated heart failure (ADHF) continues to rise, and the quality of life for these patients declines along with repeat hospitalizations. In addition, mortality rates among patients hospitalized with ADHF remain high.[1] In Japan, the proportion of people over 65 years reached 25% of the population in 2013 and will increase steadily until 2035, at which point the Japanese population will start to decline. The number of Japanese patients with heart failure was 979 000 in 2005 and is predicted to increase gradually as the population ages, reaching 1.3 million by 2030. [2] Moreover, the westernization of lifestyle and nutrition transition has facilitated the development of coronary artery disease and a higher proportion of ischaemic heart disease among heart failure patients.[3,4] Consequently, Japanese patients with heart failure have several unique clinical characteristics that might affect their prognosis including a high prevalence of preserved ejection

fraction (HFpEF), multiple comorbidities, and lack of established treatment in elderly patients,[5–7] and a longer length of hospital stay.[4] Furthermore, there is a higher prevalence of angiotensin II receptor blockers use compared with angiotensin-converting enzyme inhibitors use,[4] and common use of tolvaptan, a vasopressin V2 receptor antagonist, which is newly approved for heart failure only in Japan.[4,8,9]

Although several observational studies of Japanese patients with heart failure have been conducted during the last two decades, these studies excluded patients who could not agree in writing to the study consent form, which resulted in non-consecutive patient enrolment and a sample that is not truly representative of the current real-world clinical practice of Japan.[4,10,11] In addition, information regarding physical findings and the socio-economic background of patients with ADHF were limited in these previous studies. Therefore, the Kyoto Congestive Heart Failure (KCHF) study was designed to capture recent trends in clinical characteristics, socio-economic factors, management, and prognosis of patients with ADHF in the real-world clinical practice of Japan using a prospective, observational, multicentre cohort design.

Study design

The participating study centres include 19 tertiary hospitals in Tokai, Kinki, Chugoku, and Kyushu districts in Japan (*Figure 1*). The KCHF study is a prospective observational registry of patients hospitalized with ADHF. The KCHF study employs consecutive enrolment and captures comprehensive data on clinical and socio-economic characteristics, management and outcomes, including in-hospital data assessment. In addition, a longitudinal follow-up of 2 years is scheduled for a pre-determined subgroup of patients.

Registry for consecutive patients with ADHF

All patients admitted to the participating centres with ADHF as defined by the modified Framingham criteria who undergo heart failure-specific treatment involving intravenous drugs within 24 h after hospital admittance are eligible for the registry (*Figure 2*). Heart failure treatment will be at the discretion of the treating physician, according to the local practice. Patient enrolment started on October 2014 and finished on March 2016 at each participating hospital. The estimated number of patients that will be enrolled in the KCHF study is 4000.

Longitudinal cohort study in a pre-determined subgroup of patients

The KCHF longitudinal prospective cohort study involves a follow-up period for 2 years from admission. Not all subjects eligible for the KCHF registry will participate in the longitudinal study (*Figure 2*). Exclusion criteria included: no consent given for the longitudinal study, age <20 years, fever

Figure 1 Participating study centres include 19 hospitals in Tokai, Kinki, Chugoku, and Kyushu districts in Japan.

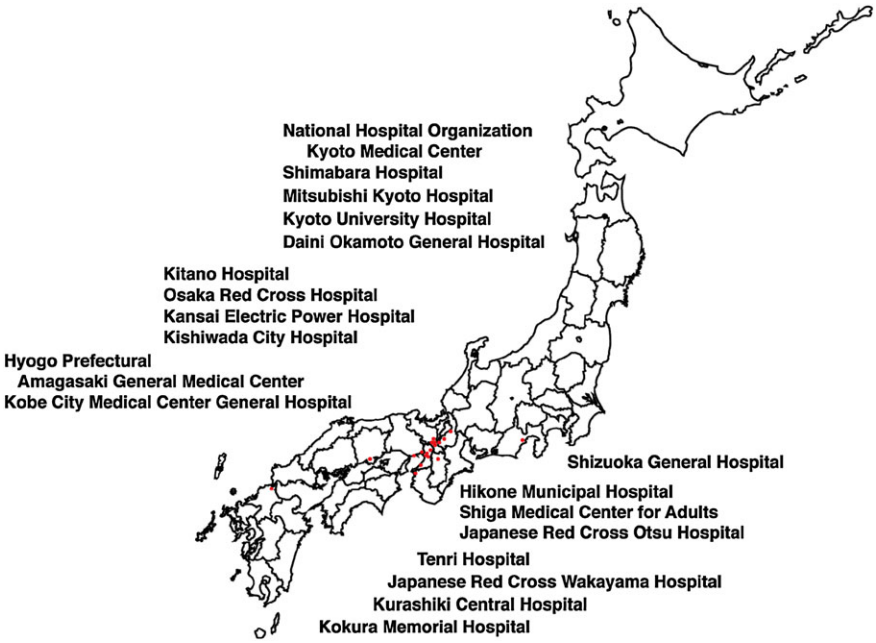

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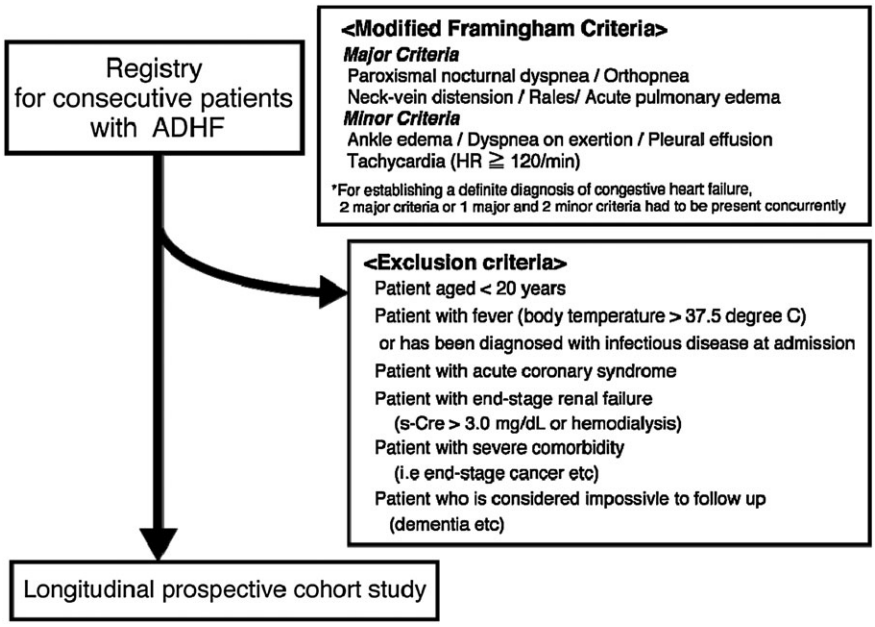
Figure 2 Study design.



(temperature >37.5°C) or diagnosed with infectious diseases at admission, acute coronary syndrome, end-stage renal failure (serum creatinine, s-Cr >3.0 mg/dL or on haemodialysis), severe comorbidity (i.e. end-stage cancer, end-stage liver cirrhosis, or severe respiratory disease), or considered impossible to follow-up (i.e. patients with dementia or cognitive impairment, and patients living abroad). The estimated number of the subgroup of patients that will be enrolled in the longitudinal prospective cohort study is 1500.

Ethical issues and patient registration

The KCHF study was approved by the ethical committee at Kyoto University Hospital (local identifier: E2311) and at all of the participating study hospitals. All studies will be conducted in concordance with the principles outlined in the *Declaration of Helsinki.* Written informed consent was obtained from patients enrolled in the longitudinal prospective cohort study. This study was registered with Clinicaltrials.gov (Clinicaltrials.gov identifier: NCT02334891).

Data collection in the registry for consecutive patients with ADHF

Data collection will be conducted by the attending physicians or the research assistants under the supervision of the clinicians responsible for this study at each participating hospital. Data will be recorded with original recording paper or digital files using Filemaker Pro 12 or 13 (Filemaker, Inc., Santa Clara, CA, USA) at each participating hospital and then sent to the data centre.

The proposed time frame for data collection during hospitalization and post-discharge is shown in *Table 1*. Physician-investigators will enrol patients during the index admission and collect data on patient demographics, past medical history, socio-economic status (i.e. working status, long-term care insurance status, place of residence and distance from the hospitals, and the person(s) who live with the patient). These factors are considered to affect the disease course of heart failure. Laboratory, echocardiography, and electrocardiogram data, which were limited in previous studies, will also be collected. Data regarding drugs used for the acute management of heart failure as well as the medications taken at admission and discharge will be collected. The signs and symptoms of congestive heart failure have been reported to be associated with the risk of exacerbation of heart failure. Therefore, symptoms and physical findings will be evaluated including: paroxysmal nocturnal dyspnoea, orthopnoea, dyspnoea on exertion, rales, ankle oedema, neck-vein distention, pleural effusion, pulmonary oedema, appetite loss, lack of sleep, general malaise, and thirst. Physical findings will be assessed by attending physicians using a four-level symptomatic grading (0, None; 1, Seldom/Mild; 2, Frequent/Moderate; 3, Continuous/Severe) at four time points: at hospital arrival, on admission, 24 h after hospital arrival, and at discharge. In addition, ambulatory status (categorized as ambulatory, wheelchair [outdoor only], wheelchair [outdoor and indoor], or bedridden) will be evaluated at admission and at discharge. The type of clinical scenario (CS; 1,2,3,4,5)[12] on admission, Nohria classification (warm & dry, warm & wet,

Table 1 Data collection schedule for the Kyoto Congestive Heart Failure study

	Registry		Longitudinal follow-up study (month)		
	Hospitalization	Hospital discharge	6	12	24
Patient background	○				
Physical findings	○	○	○		
Electrocardiogram	○		○		
Echocardiography	○		○		
Laboratory data/ Biomarker	○	○	○		
Medication	○	○	○		
Treatment	○	○	○		
Event	→	→	→	→	→

KCHF, Kyoto Congestive Heart Failure

cold & dry, or cold & wet)[13], New York Heart Association functional classification (NYHA; I, II, III, VI)[14] on admission and at discharge will be evaluated. The rate of dyspnoea relief at discharge will be evaluated by both patients and the attending physician using a seven-level Likert-scale. Details are shown in *Table S2*.

Clinical events such as in-hospital death (all-cause death, cardiac death, heart failure death, sudden death, and non-cardiac death), arrhythmic events (malignant ventricular tachyarrhythmia, supraventricular tachyarrhythmia, appropriate or inappropriate implantable cardioverter defibrillator shock, and symptomatic bradyarrhythmia), stroke (cerebral infarction and haemorrhage), moderate to severe bleeding events (global use of strategies to open occluded coronary arteries bleeding definition; moderate to severe),[15] adverse drug events (ADEs), acute coronary events, and infectious diseases during hospitalization will be evaluated. Cardiovascular interventions (surgical and catheter procedures) and device implantation during the index hospitalization will be regarded as clinical events. In addition, worsening heart failure (WHF) during hospitalization (defined as additional intravenous drug administration for heart failure treatment, haemodialysis, or mechanical circulatory or respiratory support) and worsening renal function (WRF; defined as a rise in Cr $\geq$0.3 mg/dl compared with the Cr level at admission), will be regarded as clinical events.

Data collection in the longitudinal cohort study

In the pre-specified subgroup of patients enrolled in the longitudinal cohort study, clinical data at 6, 12, and 24 months after enrolment will be collected (*Table 1*). Data on clinical events will be collected including all-cause death and a composite endpoint of all-cause death and hospitalization for heart failure exacerbation. Secondary endpoints include cardiac death, non-cardiac death, sudden death, heart failure death, hospitalization for heart failure exacerbation, hospitalization for any reason, arrhythmia, stroke, cardiac operation, moderate to severe bleeding events, ADEs, symptoms of heart failure, changes in biomarkers, WRF, and changes in echocardiographic parameters. Follow-up data collection will be conducted through a review of medical records, or by contacting the referring physicians or patients.

Quality assurance

To ensure the quality of the data, a study management committee will meet every 2 months. For each meeting, three or four participating hospitals will be randomly chosen to be evaluated regarding the progress of data collection and quality of the data by the chief of the study management committee. The status of data collection and quality will be assessed at the study management committee meeting.

Statistical analysis plan

(1) Registry for consecutive patients with ADHF

The primary analyses of the registry for consecutive patients with ADHF aim to evaluate the quality of care in the real-world clinical practice according to the current clinical guidelines for heart failure. The proportion of patients receiving optimal therapy at hospital discharge will be analysed as one of the quality indicators for evidence-based medicine. Variations in practice patterns and clinical outcomes among the patients, participating hospitals, and regions will be analysed. The outcomes included in the primary analyses are the clinical characteristics, proportion of elderly patients, comorbidities, medications taken pre-admission, aetiology of heart failure, direct causes of ADHF, pre-hospital activities, socio-economic factors, acute management, clinical course during index hospitalization, and differences in treatment decisions among the hospitals. Short-term mortality and the prevalence of WHF during the index hospitalization will also be analysed.

The secondary analyses include the examination of relationships between clinical characteristics and in-hospital mortality and pre-specified in-hospital adverse events. Patient age and various causes of ADHF such as pneumonia and poor

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adherence are expected to influence the prognosis and length of hospital stay. Blood pressure, heart rate, body temperatures, and physical findings at hospital arrival and on admission are expected to impact improvement in clinical status; therefore, we will also analyse the relationship between these factors and improvement in physical signs and symptoms. Analysis of laboratory data at hospital arrival or on admission and at discharge (including the status of congestion, myocardial damage, WRF, inflammatory responses, and nutritional status), is expected to elucidate the clinical characteristics of patients with ADHF that link closely to the prognosis and clinical events. The analysis of the data regarding the medication administered intravenously or orally and the timing of newly administered drugs is expected to elucidate the response to therapy and the prevalence of WHF. The impact of the intervention on the short-term prognosis and underlying ischaemic heart disease during the hospitalization and invasive monitoring will also be analysed.

Changes during hospitalization (including WRF, changes in biomarkers, changes in symptoms and signs of heart failure, and the changes in the patient's activity) will be included in focused analyses. Cross-sectional analyses of electrocardiographic parameters, laboratory findings, and the findings of echocardiography will also be performed. The mode of discharge (discharge to the patient's home, discharge to another hospital for rehabilitation, or discharge to somewhere other than the patient's home such as a care home) will be analysed along with socio-economic and geographic factors. The association between the prevalence of atrial fibrillation and cerebral infarction will be analysed along with the data regarding administered novel anticoagulants and haemodynamic changes. For the short-term outcomes presented as binominal variables (i.e. in-hospital death), univariate and multivariate logistic regression will be applied to determine the factors that affect the outcome.

(2) Longitudinal prospective cohort study in a pre-determined subgroup of patients

The primary analyses of the longitudinal cohort will include the analysis of factors related to all-cause death, as well as a composite endpoint of all-cause death and hospitalization for the exacerbation of heart failure after hospital discharge. The pre-designed secondary endpoints will also be included in the analyses. The in-hospital factors linking to the remote clinical events are the points in which many clinicians are interested. Thus, the associations between follow-up endpoints and the status at presentation, WRF, exacerbation of heart failure, poly-pharmacy, the status at discharge, non-pharmacological treatments, invasive monitoring, and the use of inotropic agents and remote events will be examined. A multivariate Cox proportional hazard model will be applied to evaluate the factors associated with long-term outcomes.

In addition, data regarding echocardiogram findings, symptoms and signs, and laboratory findings of patients with ADHF in the chronic phase (6 months after hospital discharge) will be analysed. Specifically, factors associated with changes in the left ventricular dimension and ejection fraction in the echocardiography, changes in brain natriuretic peptides and troponins, changes in the sinus rhythm and atrial arrhythmias or other arrhythmias, clinical characteristics, and medications at hospital discharge will be analysed. When the data is continuous, a linear regression model will be applied to determine the association between the changes of these two variables. In addition, multivariate logistic regression analysis will be applied to evaluate the factors that affect the binominal variables.

Furthermore, the titration and withdrawal of medications at discharge and the continuation of drugs and add-on treatments will be evaluated during the follow-up period. The echocardiography data are expected to clarify the remodelling and reverse remodelling of the left ventricle and will help elucidate the overall clinical course of ADHF with various aetiology and multiple comorbidities. In addition, the use of anti-diabetic drugs will be evaluated, and the association between the clinical course and the laboratory data will be analysed. The impact of infectious diseases, thirst provoked by decongestion, and appetite or malnutrition status on clinical events will be assessed.

Missing data

When analysing data, we will report losses to observation and to follow-up. If participants are excluded from analyses because of missing or incomplete data, we will provide a supplementary table that compares the observed characteristics between participants with complete and incomplete data, and we will include an assessment of data, whether missing at random or not at random. Multiple imputation methods will be used to impute missing data, if appropriate.

Discussion

The KCHF study is a prospective, observational, multicentre cohort study designed to capture the recent trends in clinical characteristics, socio-economic factors, management, and prognosis of patients with ADHF in the real-world clinical practice of Japan. The KCHF registry includes all patients admitted to the participating centres with ADHF, avoiding selection bias to elucidate a more complete picture of the clinical characteristics, medications, and outcomes of patients with ADHF.

The post-discharge readmission rate among heart failure patients has been reported to be approximately 30% within 60 to 90 days, readmission ensures a significant financial

burden to the healthcare system.[16,17] Despite these high rates, very few previous studies on ADHF have collected detailed data regarding post-discharge follow-up.[18] The KCHF study will collect post-discharge clinical data for 2 years in a subgroup of patients. Detailed data regarding the management of heart failure, signs and symptoms, electrocardiographic findings, and laboratory findings will be collected at 6-months follow-up. Punnoose and colleagues[19] have reported that a significant proportion of patients with HFpEF have a history of reduced ejection fraction, and these patients appeared to be clinically distinct from the residual HF population.[19] However, the details of serial changes in ejection fraction of these patients have not been clearly demonstrated.[20] The KCHF study is designed to monitor changes in ejection fraction and will provide further information regarding this heart failure paradigm.

The longitudinal prospective cohort study does consist of a non-consecutive group of patients from the KCHF registry. We exclude patients with acute coronary syndrome, infectious diseases, end-stage renal failure, and severe comorbidity from the longitudinal cohort study, because the clinical course of these patients depends largely on revascularization therapy or other specific treatments unrelated to heart failure. Thus, including such patients would make the interpretation of the data complicated.

Over the last decade, all clinical trials involving new drugs, apart from a few exceptions,[21–24] have failed to demonstrate improvement in the mortality of patients with ADHF and chronic heart failure. Possible reasons may include heterogeneity in the aetiology of heart failure and failure to match the study therapy to the appropriate patient subset. It is noteworthy that up to half of the patients with heart failure have a normal or near-normal ejection fraction,[4] and that the mortality rate for HFpEF may be as high as that for heart failure with reduced ejection fraction, yet there is no effective treatment to improve clinical outcomes in these patients.[5–7]

In addition, major developments in medicine have led to significant changes in the clinical management of heart failure patients. Several new drugs have been approved by the Japanese government: eplerenone was approved on November 2007, and tolvaptan was approved for the first time in the world as a drug for heart failure treatment on December 2010.[9] Although a large-scale randomized controlled trial failed to demonstrate the efficacy of tolvaptan on survival in patients with heart failure[25] and it is not yet recommended as a first line therapy for ADHF in clinical guidelines,[26,27] it has grown in popularity as an effective drug treatment for dyspnoea and oedema caused by heart failure in Japan.[8] Indeed, some of these pharmacological treatments are unique to Japan. Other than tolvaptan, carperitide is also available only in Japan, and the use of nicorandil and landiolol for ADHF management is at present limited in Japan.[28] In addition, the estimated prevalence of HF in Japan is less than 1% at present, which is relatively low compared with Western countries, and the ischaemic aetiology of ADHF is less common in Japan than in Western countries.[29] Although there are several differences between Japan and other countries in both characteristics and management of ADHF, a comprehensive strategy for ADHF management ultimately should not differ significantly between Japan and other countries. Moreover, compared with other countries, Japan has experienced a marked increase in the ageing population, [30] and the incidence of new onset heart failure has also rapidly increased in recent years.[2,29] As the result of the increase in the ageing population, we are currently facing a worldwide heart failure pandemic, and the risk is particularly great in developed countries. The data that we plan to obtain in this study from Japanese patients can provide valuable information that can help to direct future clinical and policy decision-making not only in Japan but also in other countries.

Moreover, ADEs related to polypharmacy, including the new drugs described earlier as well as conventional medication for heart failure, will be prospectively evaluated in the KCHF study. It has been reported that the epidemiology and nature of ADEs and medication errors in Japan are similar to other countries, although more frequent per admission.[31] Evaluating the prevalence and severity of ADEs in heart failure is highly important in order to provide optimal medication, especially for elderly ADHF patients who were excluded from previous studies.

In conclusion, the KCHF study promises to provide the most comprehensive dataset regarding heart failure in Japan to date. The analyses from this study will potentially influence future clinical and policy decision-making, as well as improve our understanding of the factors affecting the disease course.

Acknowledgement

Everyone who contributed significantly to this work has been listed in *Table S1*.

Conflict of interest

None declared.

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Supporting information

Supporting information may be found in the online version of this article.

Table S1. The KCHF steering committee members. 2. The KCHF chairs

Table S2. Data collected during hospitalization. 2. Data collected at hospital discharge

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