Clinical Characteristics and Outcome of Hospitalized Patients with Heart Failure in Japan: Rationale and Design of Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD)

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Running title: Heart failure registry in Japan

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Abstract

Background Heart failure, defined as a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood, is a leading cause of mortality and hospitalization for adults older than 65 years in industrialized countries. The characteristics and outcome of patients with heart failure have been described by a number of previous epidemiological studies and large scale clinical trials, which have been performed mainly in the United States and Europe. Very little information is available on this issue in Japan.

Methods and Results The Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD) is designed to study prospectively the characteristics, treatment, and outcomes in a broad sample of patients hospitalized with heart failure at teaching hospitals throughout Japan between January 2004 to June 2005 and the outcomes including death and hospital readmission will be followed through 2006 (mean follow-up at least 1 year). Participating cardiologists identify patients admitted due to the worsening of heart failure symptoms. Demographics, medical history, severity of heart failure, treatment, and outcome data are collected and entered into a database via secure web browser technology. As of June 2005, baseline data on 2676 patients with HF have been registered from 164 participating hospitals.

Conclusions The JCARE-CARD will provide important insights into patients with heart failure in routine clinical practice in Japan. Moreover, it will provide the framework for improved management strategies for these patients.

Key Words: Heart failure; Registry; Management; Outcome

Introduction

Heart failure (HF) is defined as a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood according to the guidelines for the diagnosis and treatment of chronic heart failure of American College of Cardiology (ACC)/American Heart Association (AHA) and European Society of Cardiology (ESC).[1,2] The cardiac manifestations of HF are dyspnea and fatigue, which may limit exercise tolerance, and fluid retention, which may lead to pulmonary congestion and peripheral edema.[1,2] HF is a leading cause of morbidity and mortality in industrialized countries.[3] It is also a growing public health problem, mainly because of aging of the population and the increase in the prevalence of HF in the elderly.[4] The clinical characteristics, treatment, and outcome of these patients have been well described by a number of both community-based [5-7] and hospital-based studies,[8-11] as well as by clinical trials of HF treatment.[12-14] However, information derived from clinical trials that is not necessarily representative of "real world" patients with HF. Moreover, these studies have been performed mainly in the United States and Europe.

Very limited information is available on the characteristics and outcome of patients with HF in Japan.[15-17] Our previous studies were the first detailed analysis of clinical characteristics, management, and outcome including mortality and HF-related readmission in Japan.[18-20] They demonstrated that HF patients were elderly, contained a larger population of women especially at higher age, had a higher incidence of overt HF despite a relatively normal ejection fraction (EF). As many as 35 % of hospitalized patients with HF were readmitted within 1 year of hospital discharge. These characteristics are consistent with those of patient population encountered in community-based studies reported previously.[21,22]

The Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD) is developed to provide a national prospective registry database describing the clinical characteristics, treatment, and outcomes of patients hospitalized due to

the worsening of HF symptoms. It will also establish the framework for future initiatives to improve the outcomes of these patients. Specifically, this study is aimed to determine the influence of clinical characteristics on the patient outcomes and further identify the predictive risk of adverse outcomes. This report presents a detailed description of the rationale and design of JCARE-CARD.

Methods

Study Design

JCARE-CARD is a multicenter registry designed to compile a large clinical database on the characteristics, management, and outcomes of patients hospitalized for the worsening of HF in Japan. Baseline data are collected during the episode of index hospitalization from January 2004 to June 2005. Follow-up data will be collected at least 1 year after the index admission.

Study Objectives

The specific objectives of the JCARE-CARD include the following: (1) to describe the demographic and clinical characteristics of hospitalized patients with HF in Japan; (2) to describe the in hospital and long-term outcomes; and (3) to identify the factors including specific treatments associated with improved or worsened outcomes.

Study Hospitals

The study hospitals include the cardiology units serving as primary, secondary, and tertiary referral medical centers for cardiovascular patients across Japan. They are authorized as the teaching hospitals by the Japanese Circulation Society.

Study Patients

For this registry, HF is defined as a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood. The presence of HF was confirmed by using

the Framingham criteria (**Table 1**).[5] Patients readmitted to the hospital during the study period are included only by the first hospitalization (index admission). Patients must be at least 15 years old at the time of hospital admission. Eligibility is not contingent on the use of any particular therapeutic agent or regimen.

Data Collection and Processing

Data are entered using a web-based electronic data capture (EDC) system licensed by the JCARE-CARD (www.jcare-card.jp). The EDC system was chosen because of perceived advantages over the traditional, paper-based data entry process, including the ability to inform participating hospitals of missing or illogical data fields at the time of data submission. A study web site has been created with a public area providing general information regarding this study and a registry site-only area that provides information concerning data registry (**Figures 1 and 2**). The study hospitals are encouraged to register the patients as consecutively as possible. The diagnosis of HF was established by the simultaneous presence of at least two major criteria or one major criterion in conjunction with two minor criteria by use of the Framingham criteria (**Table 1**). Compliance with these methods of registry is not strictly monitored.

For each case, baseline data recorded on the form include (1) demography; (2) causes of HF; (3) precipitating causes; (4) comorbidities ; (5) complications; (6) clinical status; (7) electrocardiographic and echocardiographic findings; (8) treatment including discharge medications.

The status of all patients is surveyed at least 1 year after admission and the following information is obtained; (1) survival, (2) cause of death, and (3) the hospital readmission due to an exacerbation of HF that required more than continuation of their usual therapy on prior admission.

Patient Confidentiality

The JCARE-CARD protocol was organized to ensure compliance with the

Guidelines for the Epidemiological Research published by the Japanese Ministry of Health, Labour and Welfare. The original study protocol was approved by the Institutional review board (IRB) at Kyushu University. IRB approval at each participating hospital is also required for the participation in this registry. Informed consent is attained for each patient. The study does not include any protocol-specified alteration of treatment or any other aspect of hospital care. Patient confidentiality is preserved because direct patient identifiers, such as name, address, and identification number, are not collected. Access to the EDC system at each hospital is carefully controlled by the data management office.

Statistical Analysis

Descriptive statistics are used to summarize baseline characteristics, treatment, and outcomes for the patients and for specific subgroups of interest.

Results

The JCARE-CARD enrolled HF patients from January 2004 to June 2005. As of June 2005, baseline data on 2676 patients with HF have been registered from 164 participating hospitals (**Figure 3 and Table 2**）.

Discussion

The characteristics and outcomes of patients with HF are poorly defined despite the public health importance of this disease. The JCARE-CARD, aimed to better characterize this population, is the first diverse, large-scale, prospective multicenter database of patients hospitalized for HF in Japan.

We have previously reported the characteristics and outcomes of patients admitted to the urban cardiology departments in Fukuoka, Japan.[18-20] These studies highlighted several important features of Japanese patients with HF. One key feature was the old age of HF patients. The mean age of HF patients was 69 years; 70 % were ≥ 65 years of age. Especially, women were mostly found in over 70 years. This is consistent with the previous community-based studies.[21,22] Another important feature was the high proportion of patients with relatively preserved EF. The half of patients with definite HF who had echocardiography had normal EF (≥ 50 %), indicating the contribution of diastolic dysfunction in the pathogenesis of HF.[20] Most interesting and important finding was a relatively good survival prognosis in our study patients; the 1-year mortality rate being 8.3 %. A survival prognosis of patients with decreased EF (< 40 %) was still good; the 1-year mortality rate being 9.1 %. At the first glance, this finding appears to be contradicted the generally held notion that advanced age and more comorbidity may be related to the poor survival.[18] In contrast to the relatively low mortality, rates of readmission for HF were as high as 40 % within 1 year after discharge. This value is comparable to those in prior studies (a 3- to 6-month readmission rate 30 to 50 %).[23,24] The most commonly identified cause for hospital readmission was lack of compliance with medical and dietary treatment (48 %).[19]

Even though our previous studies have provided a valuable insight into the clinical characteristics, outcomes, and the potential effective treatment strategies for HF patients in Japan,[18-20] the generalization of these results is questioned because our investigation was conducted in a small number of patients (n=230). Therefore, it is of critical importance to analyze the data of HF patients in routine clinical practice on a national basis and to form a database for future investigations. For

this purpose, JCARE-CARD is designed to focus on the demographic and clinical characteristics, treatment strategies, and outcomes in patients admitted to the hospitals throughout Japan. It is important to consider the JCARE-CARD in the context of other large-scale databases such as ADHERE or EuroHeart that have been established to evaluate epidemiologic and clinical aspects of HF.[8,10,11] These administrative data sets have provided important insights concerning the prognostic and public health role of a number of classic epidemiologic factors as well as information on medication use. The JCARE-CARD is expected to provide us an important information regarding the characteristics, treatment, and outcomes of HF patients in Japan, which may be complementary to that gathered from the studies in Europe and USA. This information is often critical to our understanding of the clinical characteristics of HF, including independent prognostic predictors.

There have been 2 large-scale registries of HF reported; the EuroHeart Failure Survey from Europe and the Acute Decompensated Heart Failure National Registry (ADHERE) from the United States. The EuroHeart Failure Survey registererd 11304 HF patients in the departments of cardiology, cardiovascular surgery, general internal medicine and geriatrics at 115 hospitals including both general hospitals and university centers from 24 European Society of Cardiology (ESC) member countries over a 6-week period during March 2000 and May 2001.[9-11] Patients were enrolled as HF if they fulfilled at least one of the following criteria: 1) a clinical diagnosis of HF during the admission; 2) a diagnosis of HF recorded at any time in the last 3 years; 3) administration of a loop diuretic for any reason other than renal failure during 24 h of death or discharge; 4) pharmacological treatment for HF or ventricular dysfunction within 24 h of death or discharge. The Euro Heart Failure Survey described the quality of care, diagnostic and therapeutic for patients with HF in Europe. Outcome was further assessed by repeat interviews in 6-12 months.[25,26]

The ADHERE is a registry designed to study characteristics, management, and outcomes in a broad sample of patients hospitalized with acute decompensated HF throughout the United States.[8] Participating hospitals identify patients with a

primary or secondary discharge diagnosis of HF. Medical history, management, treatment, and outcome data are collected through review of medical records and entered into a database via secure web browser technology. Of available data (105388 patients from 274 hospitals), the mean age was 72.4 years old, and 52% were women. The most common comorbid conditions were hypertension (73%), coronary artery disease (57%), and diabetes (44%). Evidence of mild or no impairment of systolic function was found in 46% of patients. In hospital mortality was 4.0%. The ADHERE data provided important insights into the clinical characteristics and patterns of care of these patients. Similar to our previous studies,[20] the ADHERE demonstrated that many patients hospitalized with HF had mild or no impairment of systolic ventricular function.[27] These registry data demonstrates significant differences in the definition of HF between patients hospitalized due to HF and those enrolled in randomized clinical trials.[28]

Even though JCARE-CARD and ADHERE share many similarities in the study design and rationale, there are several important differences between these registries. Follow-up data are not obtained in the ADHERE; therefore, the subsequent clinical outcome including death and readmission of patients after the index hospitalization is unknown. Data are gathered retrospectively after hospital discharge in the ADHERE, which may preclude prospective analysis of particular treatments in these patients.

Limitations

Several crucial limitations inherent in the design of the JCARE-CARD should be considered. First, the JCARE-CARD data are based on the decisions made by the participating cardiologists. The lack of a precise, universal definition of HF makes this type of registry difficult and open to many criticisms. However, it is not the objective of this survey to restrict enrollment to the narrowly defined population of HF usually included in clinical trials but rather to include a broad range of patients reflecting the current reality of clinical practice rather than trials.

All participating hospitals are authorized as the teaching hospital by the Japanese Circulation Society. In addition, the information regarding the study protocol was regularly provided at the national as well as local meetings and also via monthly e-mail notice. Second, this survey relies on the hospitals to volunteer their support. This almost certainly biased the study towards larger centers, which could support research staff. In addition, we excluded other specialist wards than cardiology from this survey.

Conclusions

The JCARE-CARD will provide the first, valuable information on current patient characteristics, management, and outcomes in a broad sample of Japanese patients in routine clinical practice who are hospitalized with HF. These data may indicate that there are substantial opportunities to improve the efficiency of management for these patients. By helping to better characterize this disease state, it will ultimately have a significant impact on public health at the national level in Japan.

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Figure Legends

Figure 1 Screen-shot of a top page of JCARE-CARD web site (www.jcare-card.jp).

Figure 2 Sample screen-shot of a page of the electronic case report form with sample pull-down menus from the JCARE-CARD web site.

Figure 3 JCARE-CARD cumulative numbers of registered patients from January 2004 to June 2005.

Table 1. Framingham criteria for HF

Major Criteria
Paroxysmal nocturnal dyspnea
Neck vein distension
Rales
Radiographic cardiomegaly (increasing heart size on chest x-ray)
Acute pulmonary edema
S3 gallop
Increased central venous pressure (>16 cm water at right atrium)
Circulation time ≥ 25 seconds
Hepatojugular reflux
Pulmonary edema, visceral congestion, or cardiomegaly at autopsy
Minor Criteria
Bilateral ankle edema
Nocturnal cough
Dyspnea on ordinary exertion
Hepatomegaly
Pleural effusion
Decrease in vital capacity by one third from maximum value recorded
Tachycardia (rate ≥120/min)
Major or Minor Criteria
Weight loss ≥4.5 kg in 5 days in response to treatment

The diagnosis of HF was established by the simultaneous presence of at least two major criteria or one major criterion in conjunction with two minor criteria.

Table 2. Number of participating hospitals and registered patients among 8 regions in Japan

Region	Number of participating hospitals	Number of registered patients
Hokkaido	8	143
Tohoku	7	140
Kanto	44	728
Hokuriku	10	55
Tokai	20	499
Kinki	31	491
Chugoku	18	239
Shikoku		
Kyushu	26	381
Total	164	2676

Appendix 1

JCARE-CARD Investigators

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Appendix 3

Patient Data Form for JCARE-CARD

Step 1. Demographic data

1. Date of registry
2. Date of admission
3. Date of discharge
4. Date of birth
5. Age
6. Sex
10. Height
11. Weight
12. Body mass index

Step 2. Clinical data (Medical history)

1. Causes of heart failure
    1. Ischemic
    2. Hypertensive
    3. Cardiomyopathic, dilated
    4. Cardiomyopathic, hypertrophic
    5. Cardiomyopathic, dilated phase of hypertrophic cardiomyopathy
    6. Valvular heart disease
    7. Congenital heart disease
    8. Others
    9. Unknown
2. Precipitating causes of heart failure
    1. Lack of compliance with sodium and fluid restriction
    2. Lack of compliance with drugs
    3. Over activity
    4. Infection

5. Arrhythmias
6. Ischemia
7. Uncontrolled hypertension
8. Others
9. Unknown

3. Comorbidity

1. Hypertension (Blood pressure>140/90 mmHg)
2. Diabetes mellitus (Fasting blood sugar≧125mg/dL or 2-hours blood sugar ≧200 mg/dL)

   Insulin treatment
3. Hyperlipidemia (Total cholesterol≧220mg/dL or LDL≧140mg/dL)
4. Renal failure (Serum creatinine 2.5mg/dL or dialysis)

   Serum creatinine: [ ] mg/dL

   Hemodialysis
5. Hyperuricemia (Serum uric acid>7.0mg/dL)

   Serum uric acid: [ ] mg/dL
6. Cerebrovascular diseases

   (Brain infarction, Brain hemorrhage, Transient ischemic attack)
7. Anemia (Hemoglobin≦10g/dL)

   Hemoglobin: [ ] g/dL
8. COPD
9. Smoking

4. Complication

1. Prior myocardial infarction
2. Atrial fibrillation or flatter
3. Sustained ventricular tachycardia or ventricular fibrillation

5. Medical history

1. First-time diagnosis of HF
2. Interval after the initial diagnosis of HF

3. Prior hospitalization due to heart failure
4. Percutaneous coronary intervention
5. Coronary artery bypass surgery
6. Valve surgery

Step 3. Clinical data (Medical status)

1. New York Heart Association (NYHA) functional class on admission and at discharge
2. Heart rate
3. Blood pressure
4. Left bundle branch block

   QRS duration: [ ] msec
5. Left ventricular hypertrophy (SV_1+RV_5 or $V_6 \geqq 3.5$mV or RV_5 or V_6>2.6mV)
6. Echocardiographic data on admission and at discharge
   1. Left ventricular end-diastolic and end-systolic diameters
   2. Left ventricular ejection fraction
   3. Left ventricular wall thickness
   4. Mitral regurgitation
   5. Transmitral velocity (E/A ratio, Deceleration time of E wave)
7. Serum BNP levels at admission and discharge

Step 4. Discharge status and treatment

1. Discharge status
   1. In-hospital death

      Autopsy
   2. Discharge to home
   3. Transfer to other wards for heart failure treatment
   4. Transfer to other wards to treat other diseases
2. Discharge medications

1. Angiotensin converting enzyme inhibitors

[ ] Enalapril [ ] Lisinopril [ ] Perindopril

[ ] Imidapril [ ] Captopril [ ] Cilazapril

[ ] Temocapril [ ] Others [ ] No

2. Angiotensin II receptor blockers

[ ] Losartan [ ] Valsartan [ ] Candesartan

[ ] Telmisartan [ ] Others [ ] No

3. Beta-blockers

[ ] Carvedilol: daily dosage [ ] mg/dl

[ ] Bisoprolol: daily dosage [ ] mg/dl

[ ] Metoprolol: daily dosage [ ] mg/dl

[ ] Others: daily dosage [ ] mg/dl

[ ] No

4. Diuretics

[ ] Thiazide [ ] Furosemide [ ] Azosemide

[ ] Spironolactone [ ] Eplerenone [ ] Others

[ ] No

5. Digitalis

[ ] Yes [ ] No

6. Oral inotropic agents

[ ] Pimobendan [ ] Docarpamine [ ] Others

[ ] No

7. Calcium channel blockers

[ ] Amlodipine [ ] Nefedipine [ ] Diltiazem

[ ] Others [ ] No

8. Alpha-blockers

[ ] Doxazosin [ ] Others [ ] No

9. Nitrates

[ ] Yes [ ] No

10. Antiarrhythmic agents

[ ] Amiodarone [ ] Sotalol [ ] Bepridil

[ ] Disopyramide [ ] Aprindine [ ] Mexiletine

[ ] Flecainide [ ] Pilsicainide [ ] Cibenzoline

[ ] Others [ ] No

11. Aspirin

[ ] Yes [ ] No

12. Antiplatelet agents

[ ] Ticlopidine [ ] Cilostazol [ ] Others

[ ] No

13. Warfarin

[ ] Yes [ ] No

14. Statin

[ ] Pravastatin [ ] Fluvastatin [ ] Atorvastatin

[ ] Simvastatin [ ] Others [ ] No

15. Participation to clinical trials

[ ] J-CHF [ ] Bisoprolol

[ ] Others

[ ] No

3. Non-pharmacological therapy

1. Permanent pacemaker
2. Cardiac resynchronization therapy
3. Implantable cardioverter defibrillator
4. Left ventricular assist device
5. Cardiac transplantation

Step 5. Long term outcomes

1. Date of survey
2. Death
    1. Date of death
    2. All cause death

3. Cause of death

[ ] Cardiac death [ ] Non-cardiac death [ ] Unknown

4. Autopsy

3. Hospital readmission due to an exacerbation of heart failure

1. Date of readmission

2. Date of discharge

4. Sustained ventricular tachycardia or ventricular fibrillation

JCARE -CARD

Japanese CArdiac REgistry in CHF-CARDiology

慢性心不全の増悪のため
入院治療を要する患者を対象とした調査研究

D A T A B A S E

STEP 1 患者基礎データ

登録日	2005 年 3 月 11 日
入院日	年 月 日
退院日	年 月 日
施設名	
施設ID	
医師名	All Mighty
患者ID	先生が患者を特定できるもの。半角英数字の組み合せで最大12文字まで。"-" "/" は入力不可。ただし氏名は不可。
生年月日	年 月 日 年号の換算: 明治 年 換算 西暦 年
性別	
身長/体重	cm (□不明)/ kg (□不明)

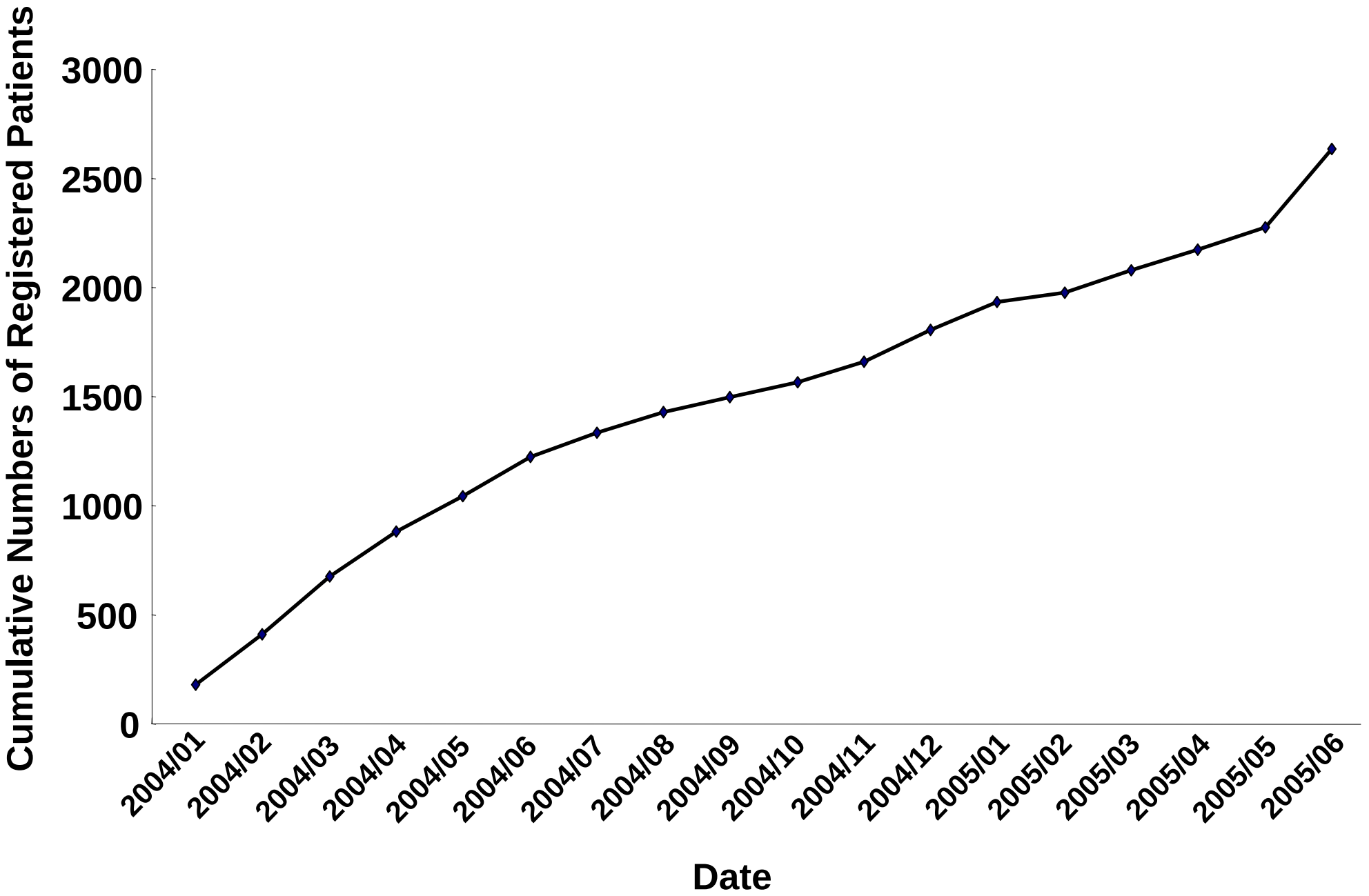
次のステップ 次のステップに進むには左のボタンを押してください。

各ステップに行きたい場合は、下のボタンで選択してください。
保存しないでこのままやめる場合はQUITを押してください。

STEP1 STEP2 STEP3 STEP4 QUIT

登録する場合は下の確認ボタンを押し、確認画面から登録してください。必須入力データの記入が完了しない場合登録できませんが、中断ボタンを押すと、終了し、続きのデータは、登録患者データ修正の画面から入力することが出来ます。

確認 中断して登録する


Cumulative Numbers of Registered Patients
3000
2500
2000
1500
1000
500
0
2004/01
2004/02
2004/03
2004/04
2004/05
2004/06
2004/07
2004/08
2004/09
2004/10
2004/11
2004/12
2005/01
2005/02
2005/03
2005/04
2005/05
2005/06
Date