Characteristics and Outcomes of Patients With Heart Failure in General Practices and Hospitals — Japanese Cardiac Registry of Heart Failure in General Practice (JCARE-GENERAL) —

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Background  The characteristics and outcomes of patients discharged from hospitals with a diagnosis of heart failure (HF) have been described by a number of previous epidemiological studies. However, very little information is available on this issue in general practice in Japan.

Methods and Results  The Japanese Cardiac Registry of Heart Failure in General Practice (JCARE-GENERAL) is designed to study the characteristics, treatment and outcomes prospectively in a broad sample of outpatients with HF who were managed by cardiologists in hospital (Hospital-HF) and primary care physicians in general practice (GP-HF). Out of 2,685 patients with HF, 1,280 patients were Hospital-HF and 1,405 GP-HF. Compared to the Hospital-HF patients, GP-HF patients were more likely to be elderly and female, and they had a higher prevalence of hypertensive heart disease as a cause of HF. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and ß-blockers were more prescribed to Hospital-HF than GP-HF patients. At the follow-up of 1.2 year, after adjustment, the mortality was comparable between the Hospital-HF and GP-HF groups, whereas HF-related admission was higher in the Hospital-HF group than in the GP-HF group.

Conclusions  Based on the JCARE-GENERAL, the characteristics, treatment and outcomes of GP-HF patients differed from those of Hospital-HF patients in Japan. (Circ J 2007; 71: 449–454)

Key Words: General practice; Heart failure; Hospital; Outcome; Registry

Heart failure (HF) is 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 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. HF is a leading cause of morbidity and mortality in industrialized countries. It is also a growing public health problem, mainly because of aging populations and the increase in the prevalence of HF in the elderly. The clinical characteristics, treatment and outcomes of these patients have been well described by a number of hospital-based registries performed in the United States of America, Europe and Japan. However, most patients with HF are managed not only by hospital cardiologists but also by primary healthcare physicians in the community (general practitioners). Accordingly, primary care physicians must play a key role in the identification and management for these patients. Nevertheless, much less is known of HF in general practice. There have been no studies reported that provide information on the characteristics, treatment and outcomes in this setting in Japan.

The Japanese Cardiac Registry of Heart Failure in General Practice (JCARE-GENERAL) was developed to provide a large, national prospective registry database describing the clinical characteristics, treatment and outcomes of outpatients with HF. The main aim of the present study was to compare the characteristics and outcomes between patients managed by hospital cardiologists with those managed by primary care physicians in general practice.

Methods  The JCARE-GENERAL is a prospective multicenter registry designed to compile a large clinical database on the characteristics, treatment and outcomes of the outpatients with HF in Japan. Baseline data were collected during November 2004. Follow-up data were collected 1 year after the enrollment.

Study Patients  Eleven participating areas, Hakodate, Shiogama, Mishima, Kahoku in Ishikawa, Motosu in Gifu, Ibaraki, Kasai, Hata in Kochi, Ube, Higashi in Fukuoka, and Kurume, have been selected throughout Japan (Fig 1).
each participating area, hospital cardiologists and primary healthcare physicians enrolled HF outpatients into the present study. HF patients managed by the hospital cardiologists were categorized as “Hospital-HF” and those managed by primary care physicians in general practice as “GP-HF”. HF was 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. For this registry, patients with current HF symptoms as well prior HF were enrolled. The presence of HF was confirmed by the simultaneous presence of at least 2 major criteria or 1 major criterion in conjunction with 2 minor criteria according to the Framingham criteria (Table 1).\(^{12}\) Patients must have been at least 15 years old at the time of enrollment. Eligibility is not contingent on the use of any particular therapeutic agent or regimen.

Data Collection and Processing

The study protocol, study procedures and data-collection forms were reviewed by the co-investigators at each study area during the central meetings and also presented to all participating physicians during training sessions before commencing the present study. The participating physicians were encouraged to register all patients meeting the entry criteria as consecutively as possible. Duplicated registry of the same patient at different institutions was avoided by ensuring 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 at Kyushu University. Informed consent was attained for each patient.

Patient Confidentiality

The JCARE-GENERAL 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 at Kyushu University. Informed consent was attained for each patient. The present study did not include any protocol-specified alterations of treatment or any other aspects of hospital care. Patient confidentiality was preserved because direct patient identifiers, such as name, address and identification number, were not collected.

Statistical Analysis

Data are expressed as means±SD. Differences in clinical characteristics, treatment and outcomes were evaluated using the chi-square test or Student's t-test. Survival was estimated with the Kaplan and Meier methods. Differences in survival between the groups were evaluated using the log rank test. After the adjustment for age, sex, etiology of HF, atrial fibrillation and prior history of HF, the relative risk for outcomes including all-cause death, cardiac death and HF-related admission was estimated for the Hospital-HF and GP-HF groups. They were adjusted as categorical

<table>
<thead>
<tr>
<th>Table 1 Framingham Criteria for HF</th>
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<tr>
<td><strong>Major criteria</strong></td>
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<tr>
<td>Paroxysmal nocturnal dyspnea</td>
</tr>
<tr>
<td>Neck vein distension</td>
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<tr>
<td>Tachycardia (rate ≥ 120 /min)</td>
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<tr>
<td>Decrease in vital capacity by one-third from maximum value recorded</td>
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<tr>
<td><strong>Minor criteria</strong></td>
</tr>
<tr>
<td>Weight loss ≥ 4.5 kg in 5 days in response to treatment</td>
</tr>
</tbody>
</table>

The diagnosis of HF was established by the simultaneous presence of at least 2 major criteria or 1 major criterion in conjunction with 2 minor criteria. HF: heart failure.
variables, except for age, which was a numerical variable. Two-tailed tests of significance are reported. \( p<0.05 \) was considered to be statistically significant.

**Results**

**Patient Characteristics**

The present study included 2,685 outpatients with HF from 11 areas in Japan; 1,280 patients from 55 hospitals as Hospital-HF and 1,405 patients from 180 general practitioners as GP-HF. The mean number of patients at each hospital and GP was 23±27 and 8±9, respectively. The mean age was 74±12 years (range 15 to 101), and 56% of patients were >75 years of age (Table 2). The mean age and the proportion of aged patients were greater in GP-HF patients compared to Hospital-HF patients (Table 2). Overall, 46% were men and 54% women. The GP-HF patients were more often women (45% vs 62%, \( p<0.01 \)).

Ischemic heart disease was the predominant cause of HF in both groups, but this was more prevalent in the Hospital-HF group. Hypertensive heart disease was more common in the GP-HF group than in the Hospital-HF group and it was the leading cause of HF in this group of patients. In contrast, cardiomyopathy was less common in GP-HF patients.

The prevalence of atrial fibrillation was greater and the prior history of HF was more frequent in Hospital-HF patients than in the GP-HF group (Table 2).

**Medication Use**

Angiotensin-converting enzyme (ACE) inhibitors were administered to 32% of the patients, angiotensin receptor blockers (ARBs) to 31%, \( \beta \)-blockers to 27%, diuretics to 62% and digitalis to 43% (Table 3). ACE inhibitors and ARBs were more prescribed to Hospital-HF than GP-HF patients (Table 3). Beta-blockers were prescribed to approximately 38% of Hospital-HF patients whereas they were prescribed to only 18% of GP-HF patients. Prescription rates of diuretics and digitalis were also higher in Hospital-HF patients. In contrast, calcium antagonists were prescribed more often to GP-HF patients.

**Mortality and HF-Related Admission**

Among 2,685 patients, 57 patients were lost during the follow up (2.1%). The mean follow-up periods for patients with HP-HF and GP-HF were 431±93 days and 424±91 days, respectively, which were not significantly different.

During the follow-up, 165 patients (6.3%) died; 59 (36%) from cardiac causes, 53 (32%) from non-cardiac causes and 53 (32%) from unknown causes. The rates of all-cause death as well as cardiac death tended to be greater in Hospital-HF patients than in the GP-HF group (Table 2).
patients than GP-HF (Table 4, Fig 2). For the age and sex categories studied, these rates were higher in Hospital-HF patients than in GP-HF, except for all-cause death in female patients (Table 4). However, after adjusting for age or variables including age, sex, causes of HF, atrial fibrillation and prior history of HF, the rates of all-cause death and cardiac death did not differ between Hospital-HF and GP-HF patients (Tables 4, 5).

During the same study period, 235 patients (9%) had a hospital admission due to an exacerbation of HF. The HF-related hospital admission rate was significantly higher in Hospital-HF than in GP-HF patients ($p<0.01$; Table 4), which did not alter even after adjustment (Table 5).

### Table 5 Adjusted Relative Risk for Outcomes by Hospital-HF and GP-HF

<table>
<thead>
<tr>
<th></th>
<th>Relative risk (95%CI)</th>
<th>p value</th>
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<tbody>
<tr>
<td>All cause death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital-HF</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>GP-HF</td>
<td>0.83 (0.59–1.18)</td>
<td>0.30</td>
</tr>
<tr>
<td>Cardiac death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital-HF</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>GP-HF</td>
<td>0.69 (0.39–1.22)</td>
<td>0.20</td>
</tr>
<tr>
<td>HF-related admission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital-HF</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>GP-HF</td>
<td>0.62 (0.47–0.82)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Adjusted for age, sex, etiology of HF, atrial fibrillation, and prior history of HF. Abbreviations see in Tables 1, 2, 4.

The characteristics and outcomes of outpatients with HF in general practice have been poorly described, despite the importance of this disease to public health. The JCARE-GENERAL is the first diverse, large-scale, prospective multicenter database of this population in Japan. An important finding is that HF outpatients in the general practice were more likely to be elderly and women with hypertension as a predominant cause of HF. Evidence-based medications for HF, including ACE inhibitors, ARBs and β-blockers, were less prescribed to GP-HF patients compared to Hospital-HF patients. In contrast, calcium antagonists were prescribed more often to GP-HF patients. At the follow-up of 1.2 years after adjustment, the mortality was comparable between Hospital-HF and GP-HF patients, whereas HF-related admission was higher in Hospital-HF than in GP-HF patients, which might be caused by them having more definite and severe HF.

We have previously reported the characteristics and outcomes of patients hospitalized to the cardiology departments in Fukuoka, Japan. These studies highlighted several important features of “real world” patients with HF, which were not found in large-scale clinical trials. One key feature was the old age of HF patients. The mean age of the patients was 69 years; 70% were ≥65 years of age. Women especially were mostly over 70 years of age. This is consistent with previous community-based studies. Another important feature was a relatively good survival prognosis; the 1-year mortality rate being 8.3%. A prognosis of patients with decreased ejection fraction (<40%) was still good; the 1-year mortality rate being 9.1%. At the first glance, this finding appears to be contradicted by the generally held notion that advanced age and more comorbidity may be related to poor survival. In contrast to the relatively low mortality, rates of readmission due to worsening HF were as high as 40% within 1 year after discharge. This value was comparable to those in prior studies (a 3- to 6-month readmission rate 30 to 50%). The most commonly identified precipitating cause for hospital readmission was lack of compliance with medical and dietary treatment (48%).

Even though our previous studies have provided a valuable insight into the clinical characteristics, outcomes and the potential effective treatment strategies for HF patients, the generality of these results is questioned because our previous studies were conducted in hospitalized patients with HF. Outpatients with HF are managed mostly in the community by primary care physicians. Nevertheless, few studies provide objective information about these patients. Therefore, it is of critical importance to analyze the realistic data for HF outpatients in general practice, and to form a database on a national basis for future investigations. For this purpose, JCARE-GENERAL was designed to focus on the demographic and clinical characteristics, treatment strategies and outcomes in “real-world” outpatients managed by primary care physicians in general practice.

The present study demonstrated that, compared to Hospital-HF patients, GP-HF patients were more often elderly and female, and had a higher prevalence of hypertensive heart disease as a cause of HF. In concordance with the
present study, previous studies have shown that the majority of HF patients are elderly and women in the community.\textsuperscript{17–20} In contrast, more severe cases of HF are referred to hospital cardiologists, and these patients are most comparable to the HF patients included in the randomized clinical trials with respect to a high proportion of younger and male patients. This might explain, at least in part, our findings that Hospital-HF patients had higher rates of mortality and HF-related hospital admission than GP-HF patients.

Another important feature of the present study is the description of the contemporary pharmacological management of HF in general practice in Japan. Even though previous randomized controlled trials have shown that drugs such as ACE inhibitors can improve the survival of HF patients, GP-HF patients were significantly less likely to be prescribed the evidenced-based medications.\textsuperscript{11,22} However, these medications are indicated when LV systolic function is reduced and not when it is preserved. GP-HF patients are elderly and more likely to be female and hypertensive, which is more often associated with preserved LV systolic function and may explain, at least in part, the difference in the medication use between Hospital-HF and GP-HF patients.\textsuperscript{11}

**Limitations**

Several crucial limitations inherent in the present study should be considered when these data are interpreted. First, although the present study intended to determine the differences between HF patients in general practice and those treated by the hospital cardiologists, the selection or referral bias might be a potential limitation of the present study. This form of bias occurs when younger patients, particularly those at lower risk, are treated by the hospital cardiologists. Elderly patients are then disproportionately represented in general practice. Therefore, the present study compared the outcomes after adjustment for the differences between patients in hospital and general practice. However, more importantly, it is not known whether HF patients treated by general practices have a different outcome from those managed in hospitals. Second, the JCARE-GENERAL data are based on the decisions made by the participating primary care physicians and hospital cardiologists according to the Framingham diagnostic criteria, which may be incomplete or imprecise. 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. Moreover, the information regarding the study protocol was regularly provided at national as well as local meetings in each area. Third, even though data validation included manual verification and correction of all numeric fields in the present study, the validation of the registered data regarding the diagnosis by comparison with the source data were not performed. Further, even though the participating physicians were encouraged to register all patients meeting entry criteria as consecutively as possible, it was not verified whether all patients were indeed registered. Fourth, the present study did not determine the prevalence of patients who met 2 major Framingham criteria for HF or 1 major and at least 2 minor criteria. Fifth, the information on cardiac structure and function especially by using echocardiography were not available in the present study, which might make it difficult to diagnose structural heart disease as a cause of HF and its disease severity, and further differentiate between patients with reduced and preserved systolic function. Nevertheless, the main focus of the present study as well as most other epidemiological studies is to obtain information on the realistic picture of HF based on the symptoms, rather than LV systolic dysfunction. Sixth, the majority of HF patients in the present study had prior history of HF although it was more prevalent in Hospital-HF than in GP-HF patients (Table 2). The data regarding the length between the initial diagnosis of HF and the enrollment to this registry were not available in the study patients and might differ between Hospital-HF and GP-HF patients, which could be a potential variable affecting their outcomes. Seventh, the present study defined cardiac death as death due to cardiac events including sudden cardiac death, fatal myocardial infarction and HF death. The cause of death was diagnosed in each patient by the participating physician based on the clinical information and not verified by the death certificate.

**Conclusions**

The JCARE-GENERAL has provided the first, valuable information on the characteristics, management and outcomes in a broad sample of “real world” outpatients with HF in general practice in Japan. They were different from those managed by cardiologists in hospital. The mortality was comparable between Hospital-HF and GP-HF patients, whereas HF-related admission was higher in Hospital-HF patients. By helping to characterize this disease state better, it will ultimately have a significant impact on public health at the national level in Japan.

**Acknowledgments**

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**References**


Appendix 1

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