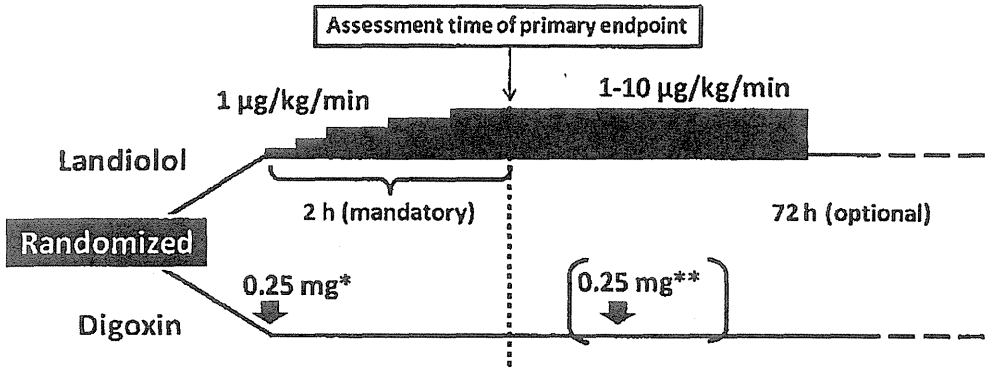


**Figure 1.** Study protocol. *Dose could reduce to 0.125 mg in patients being treated with oral digitalis preparations. **Additional doses of digoxin administered as deemed necessary.

further deteriorate cardiac function,[5] accelerating the symptoms of heart failure.[6–8]

**Editorial p 893**

Intravenous administration of digoxin is considered the standard therapy for controlling the rapid ventricular response in AF/AFL patients with cardiac dysfunction or heart failure.[4,9] Although digoxin has some beneficial effects for treating heart failure, because of its positive inotropic effects, digoxin may also have a negative chronotropic effect as a result of vagal stimulation that develops much more slowly, often taking several hours to reach the maximal effect.[9,10] Short-acting parenteral $\beta$-blockers can act more rapidly than digoxin, and may provide swift control of the heart rate (HR) in these clinical settings. However, there is concern that $\beta$-blockers may depress cardiac function and further deteriorate ventricular dysfunction, accelerating heart failure.

Landiolol, an ultra-short-acting $\beta$-blocker, is rapidly metabolized to inactive forms in the blood and liver, resulting in a short half-life of approximately 4 min in human blood. In addition, it selectively binds to $\beta$1 receptors, with a $\beta$1 receptor selectivity ($\beta$1/$\beta$2) as high as 251.[11] Based on these properties, landiolol has been reported to be useful for treating several acute disorders, including arrhythmias during heart surgery,[12] acute myocardial infarction,[13] acute decompensated heart failure,[14] and refractory electrical storm.[15]

Ultra-short-acting $\beta$-blockers may be useful to control the HR with minimal effects on cardiac function because the negative inotropic effect is not sustained after decreasing the dose or stopping administration of these drugs. Therefore, the present study was designed to evaluate the efficacy and safety of intravenous landiolol for achieving rapid control of tachycardia in patients with AF/AFL and LV dysfunction.

## Methods

### Study Design and Patients

This study was designed as a central registration, prospective, multicenter, single-blind, randomized, parallel-group study for examining tachycardia in patients with AF/AFL and LV dysfunction. It was conducted in 95 hospitals in Japan between March 2011 and August 2012. The main inclusion criteria were: male or female inpatients aged ≥20 years; New York Heart Association (NYHA) class III or IV; and AF/AFL with an LV ejection fraction (EF) of 25–50% and a HR ≥120 beats/min. The main exclusion criteria were: necessity for electrical cardioversion; serious valve stenosis; confirmed or suspected hyperthyroidism; implantable cardiac pacemaker and/or implantable defibrillator; necessity for mechanical ventilation; and cardiogenic shock (systolic blood pressure (BP) <90 mmHg). The use of antiarrhythmic drugs, sympathomimetic drugs, sympatholytic drugs, defibrillator use, catheter ablation, and pacemaker therapy were prohibited from administration until completing all observations at 2 h after starting treatment. However, patients being treated with oral $\beta$-blockers (carvedilol or bisoprolol) or oral digitalis preparations for chronic heart failure, chronic AF, and/or chronic AFL could participate in the study under continued treatment without changes in their doses.

The enrolled patients gave informed consent before randomization to either treatment. The study protocol was approved by the institutional review boards at all of the participating institutions, and the study was conducted in accordance with the Declaration of Helsinki.

### Study Protocol

The study protocol is shown in **Figure 1**. After enrolment, each patient was randomized to receive landiolol or digoxin using the permuted block method. In the landiolol group, continuous intravenous administration of landiolol was started at a dose of 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and titrated to a maximum dose of 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ according to the patient's condition. Landiolol was administered for ≥2 h and up to 72 h. In the digoxin group, digoxin was intravenously administered at an initial dose of 0.25 mg and could be uptitrated within 72 h according to the patient's condition. For patients treated with oral digitalis, the parenteral digoxin dose could be reduced to 0.125 mg according to the patient's condition to prevent digitalis intoxication.

The primary efficacy endpoint was the percentage of patients with both a HR <110 beats/min and ≥20% decrease from baseline at 2 h after administration. The secondary endpoints were HR at 0.5, 1, and 2 h, conversion to normal sinus rhythm, and subjective symptoms and objective findings (palpitations,

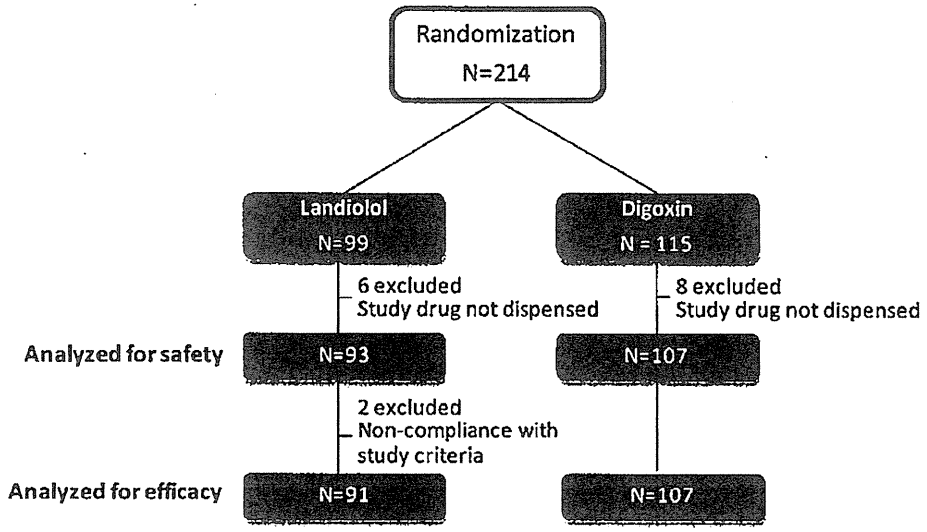


**Figure 2.** Patient disposition.

chest pain, dizziness, dyspnea, and edema) at these times.

The safety endpoint was the incidence of adverse events related or unrelated to the study drugs. Adverse events that resulted in death, were life-threatening, required hospitalization or prolonged hospitalization, resulted in persistent or significant disability/incapacity, and crucial medical events were classified as serious adverse events.

After completing the observations at 2 h after starting the administration of landiolol, it was replaced with an oral β-blocker, as deemed necessary, at the investigator's discretion.

### Statistical Analysis

Data are expressed as the mean±standard deviation or percentages of patients. Student's t-test and $\chi^2$ test were used to compare the means and percentages, respectively, between the 2 groups. The primary endpoint was compared between the 2 groups using a linear probability model with HR and LVEF measured immediately before starting the study drug as covariates. The changes in HR and BP after starting the study drugs were compared between the 2 groups using a linear mixed-effects model with adjustment for HR/BP and LVEF before starting the study drug. The following covariance structures were considered: unstructured, compound symmetrical, first-order autoregressive, and Toeplitz. The covariance structure that provided the best fit according to the Akaike information criterion was used in the analysis. Assessment times were treated as categorical factors. Student's t-test was used to compare outcomes between the 2 groups at each time, while the paired t-test was used to compare values between baseline and each time within each group. Bonferroni correction was used for multiple comparisons, except for the change in BP, which was assessed as a safety parameter. Subjective symptoms and objective findings (palpitations, chest pain, dizziness, dyspnea, and edema) were analyzed using the Wilcoxon rank sum test for comparisons between the 2 groups and the Wilcoxon signed rank sum test for comparisons within each group. Values of $P<0.05$ were considered statistically significant (2-sided). All analyses were performed using SAS version 9.2 for Windows (SAS Institute, Cary, NC, USA).

## Results

### Patient Disposition and Baseline Characteristics

The disposition of patients in this study is shown in **Figure 2**. A total of 214 patients were randomized to either landiolol (n=99) or digoxin (n=115). Of these, 14 patients were not treated (landiolol group, n=6; digoxin group, n=8) and 2 patients in the landiolol group did not comply with the protocol. Therefore, 200 patients (landiolol, n=93; digoxin, n=107) were included in the safety analysis set and 198 patients were included in the efficacy analysis set (landiolol group, n=91; digoxin group, n=107).

The demographics of the study patients are shown in **Table 1**. There were no differences in the general characteristics of the 2 groups. The mean age was 71.6±11.5 years, and 106 patients (53.0%) were male. The type of atrial tachyarrhythmia at entry was AF in 174 patients (87.0%), AFL in 21 patients (10.5%), and a mixture of AF/AFL in 4 patients (2.0%). The cardiovascular disease was hypertension in 133 patients (66.5%), ischemic heart disease in 30 patients (15.0%), and cardiomyopathy in 13 patients (6.5%). The mean HR was 138.1±15.3 beats/min and the mean LVEF was 36.6±7.6%. The NYHA class was III in 163 patients (81.9%) and IV in 36 patients (18.1%). Before starting study treatment, diuretics were used in 100 patients (50.0%), oral β-blockers were used in 41 patients (20.5%), and nitrate was used in 29 patients (14.5%).

### Effects of Landiolol on AF and AFL

The changes in HR and BP for 2 h after starting the administration of landiolol and digoxin are shown in **Figure 3**. Landiolol and digoxin significantly decreased the HR from baseline for over 30 min after administration. However, the

**Table 1. Baseline Characteristics of Patients With Atrial Fibrillation or Flutter and Left Ventricular Dysfunction**

| | Total (n=200) | Landiolol (n=93) | Digoxin (n=107) | P value |
|---|---|---|---|---|
| **Demographic characteristics** | | | | |
| Age (years) | 71.6±11.5 | 70.5±12.0 | 72.5±11.0 | 0.221 |
| Male, n (%) | 106 (53.0) | 50 (53.8) | 56 (52.3) | 0.840 |
| Weight (kg) | 60.5±13.2 | 60.8±13.4 | 60.2±13.1 | 0.732 |
| **Baseline arrhythmia, n (%)** | | | | |
| Atrial fibrillation | 174 (87.0) | 80 (86.0) | 94 (87.9) | 0.095 |
| Atrial flutter | 21 (10.5) | 8 (8.6) | 13 (12.1) | |
| Atrial fibrillation or flutter | 4 (2.0) | 4 (4.3) | 0 (0) | |
| Other | 1 (0.5) | 1 (1.1) | 0 (0) | |
| **History of heart failure, n (%)** | 120 (60.0) | 57 (61.3) | 63 (58.9) | 0.728 |
| **Baseline CV disease, n (%)** | | | | |
| Hypertension | 133 (66.5) | 63 (67.7) | 70 (65.4) | 0.729 |
| Ischemic heart disease | 30 (15.0) | 12 (12.9) | 18 (16.8) | 0.439 |
| DCM | 11 (5.5) | 6 (6.5) | 5 (4.7) | 0.582 |
| HCM | 2 (1.0) | 2 (2.2) | 0 (0) | 0.127 |
| **Hemodynamic parameters** | | | | |
| HR (beats/min) | 138.1±15.3 | 138.2±15.7 | 138.0±15.0 | 0.934 |
| SBP (mmHg) | 125.7±21.8 | 124.6±19.8 | 126.6±23.5 | 0.523 |
| DBP (mmHg) | 84.2±19.2 | 81.5±16.5 | 86.5±21.1 | 0.068 |
| LVEF (%) | 36.6±7.6 | 36.4±7.9 | 36.7±7.3 | 0.753 |
| Creatinine (mg/dl) | 0.98±0.32 | 0.98±0.33 | 0.97±0.32 | 0.883 |
| BNP (pg/ml) | 661.7±561.0 | 688.0±663.8 | 639.0±456.6 | 0.540 |
| **NYHA class, n (%)** | | | | |
| III | 163 (81.9) | 71 (77.2) | 92 (86.0) | 0.108 |
| IV | 36 (18.1) | 21 (22.8) | 15 (14.0) | |
| **Treatment before administration, n (%)** | | | | |
| Diuretic | 100 (50.0) | 48 (51.6) | 52 (48.6) | 0.671 |
| hANP | 67 (33.5) | 28 (30.1) | 39 (36.4) | 0.343 |
| β-blocker (oral) | 41 (20.5) | 18 (19.4) | 23 (21.5) | 0.708 |
| ARB | 31 (15.5) | 13 (14.0) | 18 (16.8) | 0.579 |
| Nitrate | 29 (14.5) | 11 (11.8) | 18 (16.8) | 0.317 |
| Aldosterone antagonist | 25 (12.5) | 11 (11.8) | 14 (13.1) | 0.789 |
| ACE inhibitor | 17 (8.5) | 7 (7.5) | 10 (9.3) | 0.645 |
| Digitalis (oral) | 8 (4.0) | 6 (6.5) | 2 (1.9) | 0.099 |

Data are mean±standard deviation, or n (%).
One patient with PSVT who violated the study protocol was enrolled, but the NYHA class was missing.
ACE, angiotensin-converting enzyme; ARB, angiotensin type 1 receptor blocker; BNP, B-type natriuretic peptide; CV, cardiovascular; DBP, diastolic blood pressure; DCM, dilated cardiomyopathy; hANP, human atrial natriuretic peptide; HCM, hypertrophic cardiomyopathy; HR, heart rate; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PSVT, paroxysmal supraventricular tachycardia; SBP, systolic blood pressure.

HR was significantly lower in the landiolol group than in the digoxin group at 1 h (117.3 vs. 125.4 beats/min) and 2 h (110.2 vs. 122.3 beats/min) after starting administration. The magnitude of the reduction in HR was significantly greater in the landiolol group than in the digoxin group (mixed-effects model: group, P=0.0001; time, P<0.0001; interaction [group×time], P<0.0001). The change in HR from baseline to 2 h was −27.0±13.3 beats/min in the landiolol group and −16.0±13.0 beats/min in the digoxin group. By contrast, the changes in systolic and diastolic BPs over time were not significantly different between the 2 groups (mixed-effects model: group, P<0.0001 and P=0.06; time, P=0.001 and P=0.03; interaction [group×time], P=0.14 and P=0.14, respectively). However, systolic BP was significantly different between the 2 groups at 30 min onward (30 min: 118.1 vs. 129.5 mmHg; 1 h: 112.9 vs. 127.9 mmHg; 2 h: 114.1 vs. 127.7 mmHg). Diastolic BP was also significantly different between the landiolol and digoxin groups at 30 min (79.7 vs. 85.3 mmHg) and 1 h (76.4 vs. 84.5 mmHg).

The results for the primary endpoint are shown in **Figure 4**. The percentage of patients with both a HR <110 beats/min and ≥20% decrease from baseline to 2 h after administration was determined to examine the influence of HR and LVEF at baseline. Overall, 48.0% (n=40/82) of patients in the landiolol group and 13.9% (n=13/98) of patients in the digoxin group achieved the primary endpoint, with a between-group difference of 34.1% (95% confidence interval, 22.1–46.2; P<0.0001). AF/AFL was converted to sinus rhythm within 2 h in 2 patients (2.2%) in the landiolol group and in 2 patients (1.9%) in the digoxin group. The mean dose of landiolol at 2 h was 6.7±3.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The percentage of patients who achieved the primary endpoint

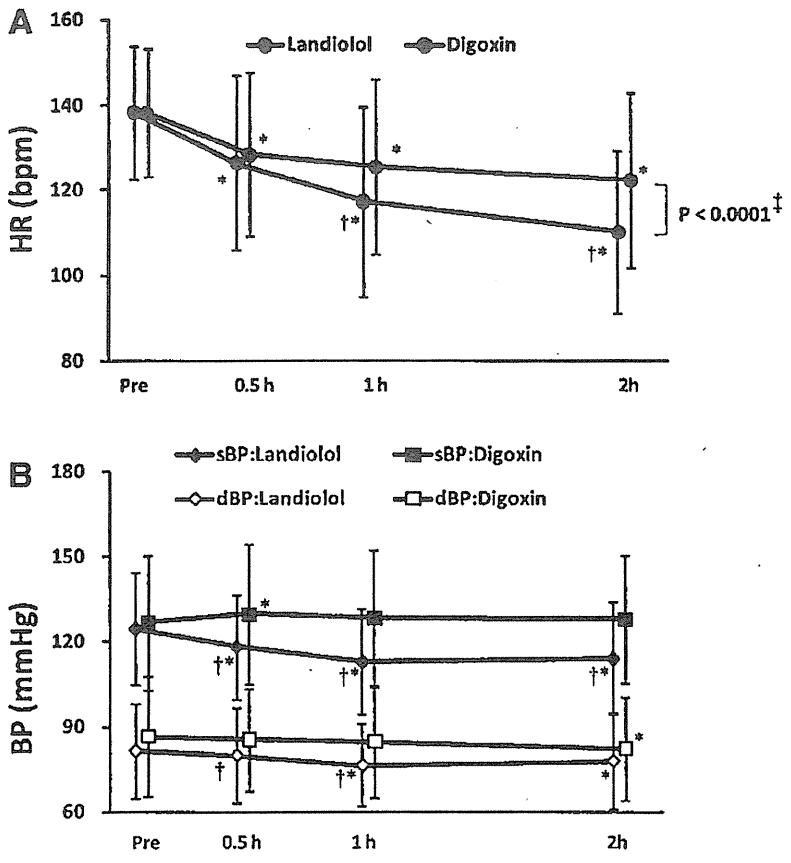


**Figure 3.** Time course of hemodynamic parameters of patients with atrial fibrillation/atrial flutter and left ventricular dysfunction treated with landiolol or digoxin. (**A**) Changes in mean heart rate (HR) during the study in the efficacy population (landiolol, n=87; digoxin, n=102). (**B**) Changes in blood pressure (BP) in the safety population (landiolol, n=93; digoxin, n=107). Data are mean±standard deviation. ‡Mixed-effects model used to compare data between the landiolol and digoxin groups (interaction: group×time). †P<0.05 vs. digoxin, *P<0.05 vs. baseline.

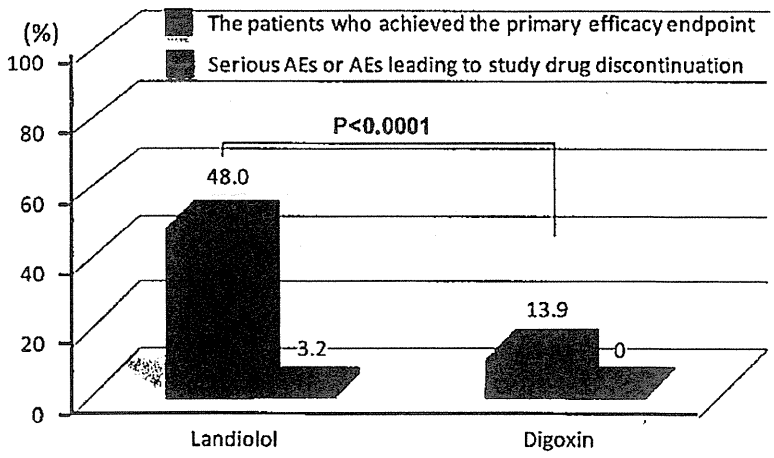


**Figure 4.** Comparison of the primary endpoint with the incidence of serious adverse events (AEs) or AEs resulting in study drug discontinuation. The percentages of patients with the primary endpoint (based on both heart rate <110 beats/min and ≥20% decrease in heart rate from baseline at 2 h after administration) were compared using a linear probability model with heart rate and left ventricular ejection fraction at baseline as covariates (landiolol, n=82; digoxin, n=98). Safety data are expressed as the incidence of serious AEs or AEs leading to study drug discontinuation within 2 h after administration (landiolol, n=93; digoxin, n=107).

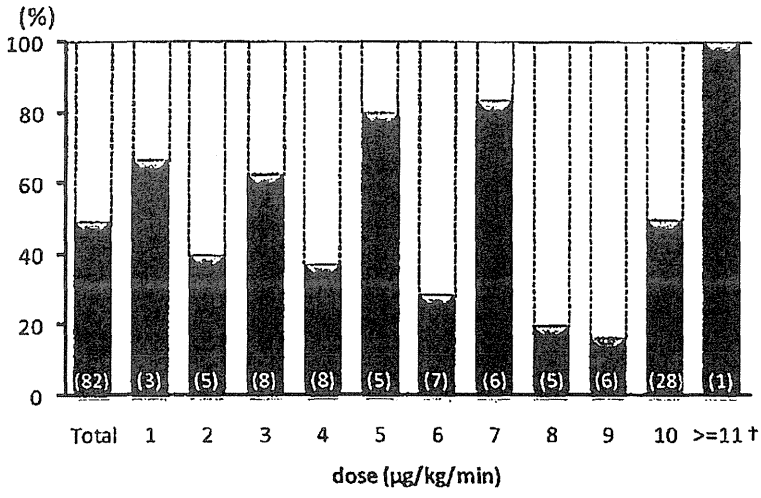


**Figure 5.** Percentages of patients who achieved the primary endpoint (based on both heart rate <110 beats/min and ≥20% decrease in heart rate from baseline at 2 h after administration) according to the dose of landiolol (total n=82). †One patient treated at a dose of 15 $\mu g \cdot kg^{-1} \cdot min^{-1}$ violated the protocol. Data are shown as the percentage of patients in each dose. Values in parentheses are the numbers of patients given each dose.

**Table 2. Incidence of AEs in Patients With Atrial Fibrillation or Flutter and Left Ventricular Dysfunction Treated With Landiolol or Digoxin**

| | Landiolol (n=93) | | Digoxin (n=107) | |
|---|---|---|---|---|
| | 0–2 h | Total | 0–2 h | Total |
| All, n (%) | 8 (8.6) | 30 (32.2) | 2 (1.9) | 35 (32.7) |
| Any serious AE, n (%) | 1 (1.1) | 2 (2.2) | 0 (0) | 3 (2.8) |
| Any AE leading to study drug discontinuation, n (%) | 3 (3.2) | 3 (3.2) | 0 (0) | 0 (0) |
| AEs occurring in >3%, n (%) | | | | |
| Hypotension | 3 (3.2) | 7 (7.5) | 0 (0) | 4 (3.7) |
| Vomiting | 0 (0) | 4 (4.3) | 0 (0) | 1 (0.9) |
| Nausea | 0 (0) | 3 (3.2) | 0 (0) | 0 (0) |
| Increased creatinine* | 0 (0) | 3 (3.2) | 0 (0) | 3 (2.8) |
| Increased urea* | 0 (0) | 3 (3.2) | 0 (0) | 1 (0.9) |
| Constipation | 0 (0) | 0 (0) | 0 (0) | 4 (3.7) |

Data are n (%). "0–2 h" included the number of patients with events occurring within 2 h after starting treatment. "Total" included the number of patients with events occurring between the start of treatment and the final observation. Only AEs occurring at a frequency of ≥3% are shown.
*Defined as an increase in values from normal to abnormal or worsening of the parameter from baseline; these events were judged by the investigators as an AE based on the clinical significance of the change. AEs, adverse events.

**Table 3. Changes in Parameters at the Final Observation in Patients With Atrial Fibrillation or Flutter and Left Ventricular Dysfunction Treated With Landiolol or Digoxin**

| | Landiolol (n=93) | | Digoxin (n=107) | |
|---|---|---|---|---|
| | Pre | Final | Pre | Final |
| HR (beats/min) | 138.2±15.7 | 98.3±17.6 | 138.0±15.0 | 102.3±19.8 |
| SBP (mmHg) | 124.6±19.8 | 113.3±18.4 | 126.6±23.5 | 115.5±18.0 |
| DBP (mmHg) | 81.5±16.5 | 72.8±14.3 | 86.5±21.1 | 72.1±15.1 |
| LVEF (%) | 36.4±7.9 | 43.1±13.1 | 36.7±7.3 | 44.2±11.0 |
| Creatinine (mg/dl) | 0.98±0.33 | 0.99±0.35 | 0.97±0.32 | 0.94±0.31 |
| NYHA class, n (%) | | | | |
| None | | 0 (0) | | 1 (0.9) |
| I | | 12 (13.6) | | 12 (11.3) |
| II | | 50 (56.8) | | 51 (48.1) |
| III | 71 (77.2) | 24 (27.3) | 92 (86.0) | 40 (37.7) |
| IV | 21 (22.8) | 2 (2.3) | 15 (14.0) | 2 (1.9) |

The final observation was performed at 48 h after the end of administration of landiolol or at 48 h after the final dose in the digoxin group. Abbreviations as in Table 1.

in the landiolol group at each dose is shown in Figure 5. The effective dose of landiolol ranged from 1 to 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ without dose-dependency.

The changes in subjective symptoms and objective findings (palpitations, chest pain, dizziness, dyspnea, and edema) during the study treatment are shown in Table S1. Palpitations, dyspnea, and edema improved significantly from baseline to 2 h in both groups. However, there were no clinically relevant differences in subjective symptoms or objective findings between the 2 groups. The mean duration of treatment with landiolol was 20.4±20.8 h (range, 0.8–72 h), and the mean dose of landiolol throughout the treatment was 6.3±3.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$. After the study treatment period, landiolol was replaced bisoprolol in 47 patients (50.5%) and by carvedilol in 27 patients (29.0%), at maintenance doses of 1.8±1.3 mg and 3.2±2.7 mg, respectively.

### Safety

The incidence of adverse events is shown in Table 2. Adverse events occurred in 30 patients (32.3%) in the landiolol group and in 35 patients (32.7%) in the digoxin group, which was not statistically significant (P=0.95). During the 2-h treatment period, adverse events occurred in 8 patients (8.6%) in the landiolol group and in 2 patients (1.9%) in the digoxin group, which was statistically significant (P=0.029). Hypotension was reported as an adverse event in 7 patients (7.5%) in the landiolol group and in 4 patients (3.7%) in the digoxin group, showing no significant difference between the 2 groups (P=0.24). Vomiting and nausea were reported in 4 patients (4.3%) and 3 patients (3.2%), respectively, in the landiolol group. Vomiting was reported in 1 patient (0.9%) in the digoxin group, but nausea was not reported in this group.

Serious adverse events were reported in 2 patients in the landiolol group (congestive heart failure and embolic stroke in 1 patient each) and in 3 patients in the digoxin group (sinus arrest, diabetes insipidus, and pneumonia in 1 patient each). One patient in the landiolol group developed acute exacerbation of congestive heart failure at 12 h after the end of administration of landiolol. Despite the intensive treatments, the patient died at 31 h after the end of administration of landiolol. The administration of landiolol was stopped in 3 patients because of an adverse event (embolic stroke, hypotension, and asthma in 1 patient each).

The changes in the hemodynamic parameters, renal function, and symptoms at the final observation are shown in Table 3. The period to the final observation was 66.6±22.5 h in the landiolol group and 49.9±11.9 h in the digoxin group. None of the laboratory parameters worsened from baseline to the end of the study in either group. The brain natriuretic peptide levels did not increase from baseline in either group (Figure S1).

## Discussion

The results of this study show that continuous intravenous administration of landiolol in a dose-escalating manner effectively controlled rapid HR in patients with AF/AFL and LV dysfunction. Landiolol and digoxin were effective in 48.0% and 13.9% of patients, respectively, at 2 h after starting treatment, indicating that the ultra-short-acting landiolol is more useful than the slow-acting digoxin. Regarding the safety of these drugs for rapid control of HR, the incidence of hypotension was similar in both groups. During treatment with landiolol, which rapidly reaches steady state and has a half-life of 4 min, the risk of hypotension may be low because its dose can be carefully adjusted according to the patient's condition. Other adverse effects associated with a reduction in HR include gastrointestinal symptoms such as nausea/vomiting caused by blood flow stasis. However, there were no abnormal changes in laboratory data, including serum bilirubin levels.

It has been reported that the control of HR in patients with tachycardic AF/AFL helps to prevent worsening of heart failure and ventricular dysfunction, because it contributes to improvements in circulatory dynamics and subjective symptoms.[16–18] However, the optimal target HR in the treatment of AF/AFL in patients with LV dysfunction has not been clearly established. In patients with LV dysfunction, a rapid and vigorous decrease in HR might be detrimental if accompanied by a decrease in cardiac output. However, in the RACE II study, which was conducted in patients with persistent AF and normal to moderate LV dysfunction, there were no differences in prognosis, including mortality, incidence of heart failure, and improvements in subjective symptoms, between the lenient control (resting HR <110 beats/min) and strict control (resting HR <80 beats/min and HR during moderate exercise <110 beats/min) groups.[19] In the present study conducted in patients with LV dysfunction and NYHA class III or IV symptoms, the target HR of <110 beats/min, corresponding to the lenient criterion in the RACE II study, may be reasonable based on the results of earlier studies. In addition, a 20% decrease in HR from baseline has been conventionally used to verify the drug-induced HR reduction in AF.[20,21] Accordingly, the primary endpoint in this study combined both criteria.

In general, the optimal dose of β-blockers in patients with LV dysfunction should be determined according to the patient's cardiac function and general condition. It should also be noted that the response to β-blockers in patients with AF varies depending on polymorphisms (eg, G389R and S49G) in the β1 receptor gene.[22] In fact, the present study showed that the optimal dose varied among the patients with variable response to landiolol. Therefore, the optimal dose of β-blocker for HR control cannot be determined before treatment. The dosage of rate-controlling drugs for treating AF/AFL in patients with LV dysfunction should be highly adjustable, according to the patient's hemodynamic response. The efficacy and safety results of this study provide support for the ultra-fast-acting and easily adjustable landiolol for swift control of rapid HR in patients with AF/AFL and LV dysfunction. However, in the present study, there were no significant differences between the 2 groups in the subjective symptoms reported within 2 h after starting administration. The rapid decrease in HR elicited by landiolol may not necessarily be associated with symptomatic relief in these patients. These findings suggest that it is difficult to evaluate how rapid HR contributes to the hemodynamic status and symptoms of heart failure in patients with AF/AFL.

The guidelines of the American Heart Association and the European Society of Cardiology recommend digitalis and amiodarone for acute rate-control therapy in patients with AF and LV dysfunction.[9,23,24] Although amiodarone is classified as a rhythm-control drug, it can also decrease the HR because it blocks $K^+$ channels, $Ca^{2+}$ channels, and β receptors. However, because amiodarone has a long half-life, it is difficult to adjust its dose according to the patient's condition.

In the present study, we observed better control of HR with landiolol than with digoxin. As landiolol was the only intravenous β-blocker used in this study, the efficacy of esmolol, propranolol, and amiodarone in this setting remains unknown. Thus, we cannot confirm whether landiolol is more effective than these drugs. Nevertheless, landiolol may be easier to use

than other drugs for acute rate-control therapy in patients with AF/AFL and LV dysfunction because it is faster-acting and shows greater selectivity for $\beta$1 receptors than esmolol, propranolol or amiodarone. In addition, this study was intended to test the usefulness of landiolol in acute rate-control therapy with up to 5 days of follow-up. Therefore, the medium- and long-term prognosis of these patients after treatment with landiolol should be studied in future.

## Conclusions

In the treatment of AF/AFL in patients with LV dysfunction, landiolol rapidly decreased the HR in approximately 50% of the patients, and was more effective for urgent HR control than digoxin, without an increase in the incidence of adverse events. Landiolol is an ultra-short-acting, highly cardioselective intravenous $\beta$-blocker that could be a promising drug for controlling rapid HR in patients with AF/AFL and LV dysfunction.

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### Disclosures

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## Supplementary Files

**Supplementary File 1**

**Table S1.** Subjective Symptoms and Objective Findings in Patients With Atrial Fibrillation or Flutter and Left Ventricular Dysfunction Treated With Landiolol or Digoxin

**Figure S1.** Distribution of levels of B-type natriuretic peptide (BNP).

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# Direct comparison of the diagnostic capability of cardiac magnetic resonance and endomyocardial biopsy in patients with heart failure

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**Aims** The diagnostic performance of cardiac magnetic resonance (CMR) has not been compared with that of other imaging modalities. Therefore, this study investigated the diagnostic capabilities of CMR and endomyocardial biopsy (EMB) in patients with heart failure (HF).

**Methods and results** We studied 136 patients with cardiomyopathy who underwent both CMR and EMB. Independent diagnoses were made according to the results of (i) CMR alone; (ii) EMB alone; (iii) clinical data plus echocardiogram; (iv) clinical data, echocardiogram, plus CMR; and (v) clinical data, echocardiogram, plus EMB. These diagnoses were then compared with the final diagnosis (gold standard) that was made using the complete clinical data, including EMB and CMR. The sensitivities of the diagnosis strategies of (i–v) relative to the final diagnosis were 67, 79, 86, 97, and 100%, respectively. CMR alone demonstrated better sensitivity for cardiac sarcoidosis and greater specificity for dilated cardiomyopathy than EMB alone. CMR also tended to show better sensitivity for hypertensive heart disease. There was no difference between the diagnostic capability of CMR and EMB for hypertrophic cardiomyopathy (HCM). However, CMR showed excellent sensitivity (100%) for apical and obstructive HCM, whereas EMB displayed better sensitivity for dilated HCM. Moreover, combined diagnosis with clinical data, echocardiogram, plus CMR achieved superior agreement with the final diagnosis in comparison with EMB alone.

**Conclusion** Non-invasive CMR demonstrated excellent diagnostic capability for patients with HF and was as effective as or superior to EMB. In particular, the use of CMR in combination with clinical data unrelated to EMB may provide excellent diagnostic accuracy for HF.

**Keywords** Heart failure • CMR • Endomyocardial biopsy • Diagnosis • Aetiology • Cardiomyopathy

## Introduction

Heart failure (HF) is a common clinical syndrome caused by various cardiovascular diseases.[1] Despite the discovery, development, and adoption of novel therapies for HF, the mortality and morbidity resulting from this condition have remained high and are currently increasing. Accordingly, accurate diagnosis of the underlying aetiology of HF is important for appropriate management and treatment. In addition to conventional clinical methods, gadolinium-enhanced cardiac magnetic resonance (CMR) and endomyocardial biopsy (EMB) are useful diagnostic modalities for identifying the aetiology of HF. EMB is considered

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to be the gold standard for diagnosing myocarditis as well as certain infiltrative cardiac diseases, such as amyloidosis, sarcoidosis, and haemochromatosis. In contrast, CMR is also required to identify patients with cardiomyopathy accurately, according to the Consensus Panel Report.[2] CMR is a non-invasive, accurate, and reproducible imaging technique that can be used to evaluate cardiac morphology and function, and provide valuable information for tissue characterization. In addition, several studies have suggested that CMR techniques using late-gadolinium enhancement (LGE) are useful for diagnosing various types of cardiomyopathies. Indeed, both CMR and EMB have demonstrated good performance in patients with troponin-positive acute chest pain but without coronary artery disease.[3] However, there have been no reports directly comparing the diagnostic utility of CMR and EMB in patients with HF.

Therefore, we compared the diagnostic capability of CMR and EMB in HF patients and also assessed the diagnostic performance of the combined use of CMR and all clinical data in comparison with EMB alone.

# Methods

## Selection of patients

A total of 1034 consecutive patients with HF of unknown aetiology were evaluated between January 2007 and July 2009. Patients who were admitted to our institution for the management of HF, who had LV hypertrophy and/or LV dysfunction, and who had received EMB and LGE CMR were included in this study. Patients were excluded if they had one or more of the following conditions: substantial valvular or ischaemic heart disease; congenital heart disease; constrictive pericarditis; idiopathic restrictive cardiomyopathy; an ambiguous final diagnosis; dilated cardiomyopathy (DCM) with an LVEF > 55%; poor-quality CMR; or an inadequate myocardial biopsy. Of the patients examined, 25 were given an ambiguous final diagnosis for the following reasons: 17 patients did not receive sufficient detailed investigations to reach the final diagnosis; 3 patients were suspected as having arrhythmogenic right ventricular cardiomyopathy (ARVC) but they did not fulfil the Task Force Criteria;[4] 3 patients were suspected as having dilated hypertrophic cardiomyopathy (HCM) but hypertrophic stage was not detected; and 2 patients were diagnosed as LV non-compaction and we excluded these patients because EMB cannot diagnose this condition. As a result, we enrolled 136 patients in this study (*Figure 1*).

For all patients, a careful medical history was collected and physical examinations, laboratory tests, echocardiography, coronary angiography, and right heart catheterization were performed. EMB and CMR were also performed in all patients to evaluate evidence of HF. We identified the aetiology of HF using all possible diagnostic approaches in addition to EMB and CMR.

This study was approved by our Institutional Research Ethics Committee. The Committee decided that informed consent from the 136 subjects was not required according to the Japanese Clinical Research Guidelines because this was a retrospective, observational study. Instead, we made a public announcement as per the request of the Ethics Committee.

## Aetiology of cardiomyopathy

According to the clinical data, echocardiogram, CMR, and EMB, six diagnoses were made for each patient, including (i) CMR diagnosis; (ii) EMB diagnosis; (iii) the combined diagnosis with clinical data

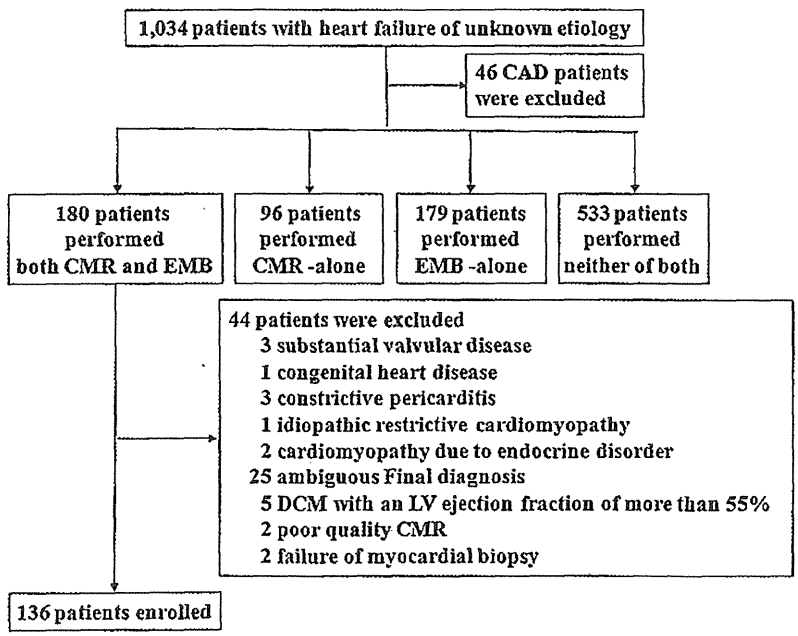


**Figure 1** Study profile. Flow chart of the 1034 consecutive patients with heart failure of unknown aetiology admitted to our institution. The chart shows the immediate exclusion of cardiomyopathy due to significant coronary artery disease (CAD) and the further management of these patients. CMR, cardiac magnetic resonance; DCM, dilated cardiomyopathy; EMB, endomyocardial biopsy.

plus echocardiogram; (iv) the combined diagnosis with clinical data, echocardiogram, plus CMR; (v) the combined diagnosis with clinical data, echocardiogram, plus EMB; and (vi) the final diagnosis. The CMR and EMB diagnoses (i and ii) were established according to the results of CMR or EMB alone, and the investigators were blinded to all of the other data. Clinical data were defined as any method that could be used to diagnose HF other than echocardiography, CMR, or EMB, such as the collection of a patient's medical history, laboratory tests, scintigraphy, and coronary angiography. The final diagnosis (vi) was made prior to patient discharge by an expert team of cardiologists using all of the available data, including the results of EMB, CMR, and other diagnostic modalities. In addition, an expert team of cardiologists, who were not specialists in either CMR or EMB but could interpret these studies, was recruited. The final diagnoses were based on the recommendations of the 2008 European Society of Cardiology (ESC) report for the classification of cardiomyopathies.[5] In patients with several causes of HF, the most significant cause was associated with the diagnosis.

Each diagnosis was assigned according to one of the following categories: DCM, HCM, hypertensive heart disease (HHD), ARVC, muscular dystrophy, infiltrative myocardial disease (i.e. amyloidosis and sarcoidosis), myocarditis, or other causes.

## Cardiac magnetic resonance images and analysis

Images were acquired using a 1.5 T scanner (Sonata, Siemens Medical Solutions, Erlangen, Germany). The CMR protocol consisted of a cardiac functional study, spin-echo imaging, and LGE imaging, as previously described.[6] For the cardiac functional study, three standard long-axis slices and a stack of contiguous short-axis slices (slice thickness, 6 mm; slice gap, 4 mm) were acquired as ECG-gated steady-state free-precession cine images with radial scans and breath-holding. T2-weighted spin-echo images were acquired using half-Fourier acquisition single shot turbo spin-echo (HASTE) before contrast injection with an echo time of 82 ms and fat saturation in the same position as the cine images. LGE images were acquired in the same positions as the cine images at 2, 5, 10, and 20 min after i.v. injection of 0.15 mmol/kg of gadolinium-diethyltriaminepentaacetic acid. The inversion delay time was 300 ms.

The cine and LGE images were evaluated by several observers who were blinded to the clinical data. The EF and volumes were measured quantitatively for the left and right ventricles according to the end-diastolic and end-systolic endocardial contours from a stack of short-axis cine images using ARGUS software. The LV mass (LVM) was calculated as the total myocardial volume multiplied by the specific gravity of the myocardium (1.05 g/mL). The ventricular end-diastolic and end-systolic volumes (EDV and ESV, respectively) and the LVM were standardized according to the body surface area ($m^2$). The presence, location, and extent of LGE were determined using a standard 17 segment LV model.[7] We classified the pattern of enhancement as subendocardial, midwall (longitudinal stripes), subepicardial, or transmural, as well as patchy (focal enhancement not following the coronary vascular territories) or diffuse.

## Endomyocardial biopsy and analysis

Biopsy specimens were taken from the endocardium at the right interventricular septum using Technowood disposable biopsy forceps (TONOKURA IKA KOGYO CO., LTD, Tokyo, Japan) via the right internal jugular vein or right femoral vein, as described elsewhere.[8] Three to five specimens were obtained from each patient. No complications related to EMB were observed. Biopsy specimens were immediately fixed in 15% formalin for 24 h, embedded in paraffin, and cut into 4 μm thick sections. The sections were stained with haematoxylin and eosin and Masson's trichrome. Some of the EMB specimens were frozen for polymerase chain reaction (PCR) analysis for the detection of enterovirus when myocarditis was suspected. Congo red staining was added when amyloidosis was suspected. Immunohistochemistry was performed in ARVC, myocarditis, amyloidosis, dystrophic cardiomyopathy, and some cases of HCM, as appropriate.

While EMB analysis at final diagnosis was made as above using all of the other data, EMB diagnosis was evaluated using only haematoxylin and eosin and Masson's trichrome stains by several cardiac pathologists who were not aware of the clinical features of the patients in this study.

## Diagnosis of cardiomyopathy by cardiac magnetic resonance or endomyocardial biopsy

The diagnosis of cardiomyopathy by CMR and EMB was based on well-established and widely accepted definitions.[9,10] A CMR diagnosis was made according to the dimensions, regional and global wall motion, wall thickness, and the presence and pattern of LGE,[11–14] whereas an EMB diagnosis was made according to the report for classification of cardiomyopathies.[4,5,15,16]

A histological diagnosis of DCM was performed by examining the following criteria: interstitial fibrosis, replacement fibrosis, inflammatory cell infiltrates, cellular hypertrophy, and myocardial cell degeneration.[17] Histopathological criteria for HCM included severe myocyte hypertrophy, myocyte disarray > 10%, plexiform fibrosis, and nuclear hypertrophy. The diagnosis of HHD was made according to the presence of moderate myocyte hypertrophy,[18] interstitial fibrosis, and the lack of myocyte disarray. The presence of non-caseating epithelioid granulomas with giant cells was considered indicative of cardiac sarcoidosis (CS).[16] The diagnosis of myocarditis was based on the Dallas criteria modified by the Japanese Circulation Society Guidelines.[19] Based on this modified version of the Dallas criteria, the immunohistochemistry was used to characterize the inflammatory infiltrates. The cut-off for mononuclear cell infiltrates was an inflammatory infiltrate count of at least 5/high power field. We confirmed the diagnoses of cardiac amyloidosis by electron microscopy and performed immunohistochemistry for amyloid typing. The histology diagnosis for ARVC was made according to the Task Force Criteria.[4]

The characteristics of DCM for CMR included dilation and impaired contraction of one or both ventricles and an LVEF <55%.[20] Moreover, the wall thickness is normal or decreased. HCM is characterized by hypertrophy of the left ventricle and occasionally the right ventricle, normal or reduced LV volume, and normal LV contraction or hypercontraction. Apical HCM was regarded as hypertrophy of the apex, and hypertrophic obstructive cardiomyopathy (HOCM) was regarded as an obstruction to the LV outflow tract. We defined dilated HCM as an LVEF ≤ 50%[21,22] and evidence of wall thickening prior to the study. Generally, dilated HCM is characterized by a relative wall thickness with a dilated LV cavity. LV hypertrophy is common in HHD, and additional common findings include a relative wall thickness with or without a dilated LV cavity. The use of CMR for CS can demonstrate certain characteristic features, such as septal thinning, ventricular dilatation, segmental systolic dysfunction, global systolic dysfunction, or ventricular aneurysm. We referred to the typical LGE pattern for diagnosis of DCM, HCM, HHD, and CS. The typical LGE pattern regarded a DCM LGE pattern as patchy or longitudinal midwall enhancement, a HCM LGE pattern as patchy and located at the LV–RV junction, a CS LGE pattern as a non-ischaemic pattern with enhancement of the midwall or epicardium at various sites, especially the anteroseptal

and inferolateral walls, and a HHD LGE pattern as similar to the DCM LGE pattern based upon a previous report.[10] Myocarditis was diagnosed when subepicardial and midwall areas demonstrated an increased signal in the T2-weighted image or when the lateral and inferolateral walls demonstrated an LGE distribution in the epicardium toward the mid myocardial wall. ARVC is characterized by regional or global dysfunction, dilatation, and focal aneurysm of the right ventricle noted in the 2010 guideline,[4] whereas amyloidosis is characterized by concentric hypertrophy with normal or reduced contractility, a thickened interatrial septum, bi-atrial dilation, and a circumferential pattern of LGE, preferentially involving the subendocardium but occasionally demonstrating a patchy transmural pattern. Dystrophic cardiomyopathy in LGE preserves the subendocardium and is more frequently located in the LV lateral wall.

### Statistical analysis

Continuous variables were expressed as the mean ± standard deviation (SD), whereas categorical variables were expressed as numbers and percentages. Comparisons between groups were performed using a two-sample *t*-test for normally distributed continuous variables and the Wilcoxon test for variables that did not demonstrate a normal distribution. For categorical variables, we used the $\chi^2$ test and Fisher's exact test, as appropriate. For each type of cardiomyopathy, the sensitivity, specificity, diagnostic accuracy, positive predictive value (PPV), negative predictive value (NPV), and 95% confidence interval (CI) for the CMR diagnosis, EMB diagnosis, and combined diagnosis with clinical data, echocardiogram, plus CMR were calculated in comparison with the final diagnosis, which served as the gold standard. The PPV and NPV were computed using the following formulae: PPV = true positive/(true positive + false positive); and NPV = true negative/(true negative + false negative). Diagnostic accuracy was calculated using the following formulae: diagnostic accuracy = (true positive + true negative)/total. A comparison of the diagnostic methods was performed using McNemar's test. The analyses were performed using JMP version 7 statistical software. All of the presented 95% CI are two.

## Results

### Study population and patient characteristics

A total of 136 patients were studied (Supplementary material, *Table S1*). The mean age of these patients was 52 ± 17 years (range 16–81 years): 83 of the patients were male, and 18 patients suffered from AF. EMB and CMR with LGE were performed in all patients, and none of the 136 patients was diagnosed with significant coronary artery disease. The most common diagnosis was DCM (54 patients, 40%), which was followed by HCM (36 patients, 26%). The remaining 46 patients were diagnosed with a secondary cardiomyopathy or HHD. The HCM patients included 4 cases of apical hypertrophy, 11 cases of HOCM, and 15 cases of HCM in the dilated phase.

The CMR results revealed asymmetric septal hypertrophy (septal/free wall thickness ratio ≥ 1.3) in 25 patients (18%), most of whom had either HCM (84%) or HHD (12%) detailed in the Supplementary material, *Table S1*.

The median patient follow-up period was 655 days (range 243–1143 days), and no diagnoses were changed during this time.

### Comparison between cardiac magnetic resonance, endomyocardial biopsy, and the combined diagnosis

The sensitivity of EMB, CMR, and the combined diagnosis with clinical data plus echocardiogram, with clinical data, echocardiogram, plus CMR, and with clinical data, echocardiogram, plus EMB was 67, 79, 86, 97, and 100% relative to the final diagnosis, respectively. *Table 1* shows the diagnostic performance of CMR, EMB, and the combined diagnosis with clinical data, echocardiogram, plus CMR. The use of CMR demonstrated a diagnostic capability comparable with EMB for all causes of HF. The highest level of sensitivity of EMB was for DCM (89%) followed by HCM (75%) and HHD (36%) (*Table 2*), whereas the greatest sensitivity of CMR was observed for DCM (83%) followed by HCM (81%) and CS (76%). Furthermore, to explore the relative merits of CMR vs. EMB, we investigated indications of EMB noted in the 2007 guidelines.[23] EMB demonstrated a better diagnostic yield for DCM and dilated HCM, whereas CMR demonstrated better diagnostic performance for cases of CS and HHD even when the indication for EMB was a class I. The diagnostic analysis is listed in *Table 3*. We gave six patients with dilated HCM an incorrect diagnosis of CS and also gave five patients with HHD an incorrect diagnosis of DCM using CMR. In contrast, we tended to misdiagnose CS and HHD as DCM and HCM as HHD when using EMB. Specifically, the six patients with HCM who were misdiagnosed for HHD by EMB included three patients with HOCM diagnoses, two with apical HCM diagnoses, and one with a diagnosis of dilated HCM. *Table 2* shows the sensitivity and specificity for the use of EMB, CMR, and the combined diagnosis with clinical data, echocardiogram, plus CMR. Overall, CMR demonstrated increased specificity for DCM compared with EMB, and CMR also tended to be more sensitive for the diagnosis of CS and HHD. In contrast, EMB demonstrated lower sensitivity than CMR for most diagnoses, with the exception of DCM.

We also examined the diagnostic accuracy of CMR, EMB, and the combined diagnosis with clinical data, echocardiogram, plus CMR (*Table 2*). The sensitivity of the combined diagnosis with clinical data, echocardiogram, plus CMR was greater than that of EMB for the detection of HCM, CS, and HHD. The agreement of both CMR and EMB with a final diagnosis of DCM, HCM, CS, and HHD was noted to be 72, 58, 23, and 21%, respectively (*Figure 2*). Conversely, both CMR and EMB misdiagnosed 6, 3, 12, and 21% of patients with DCM, HCM, CS, and HHD, respectively. Importantly, all of the patients who received accurate diagnoses with EMB alone were also correctly diagnosed using the combined diagnosis with clinical data, echocardiogram, plus CMR.

### Characteristics and details of cardiac magnetic resonance

We analysed the frequency of the use of the typical LGE pattern only in cases in which we diagnosed DCM, HCM, CS, and HHD. The CMR results revealed a DCM LGE pattern, HCM LGE pattern, CS LGE pattern, or HHD LGE pattern in 78, 53, 82, and 79% of the patients with DCM, HCM, CS, and HHD, respectively (*Figure 3*). In addition, the patients with typical LGE patterns were more likely to receive an accurate diagnosis. LGE in the papillary

**Table 1 Agreement of endomyocardial biopsy, cardiac magnetic resonance, or combined diagnosis with clinical data, echocardiogram, plus cardiac magnetic resonance with final diagnosis in 136 patients based on endomyocardial biopsy indication**

| Final diagnoses, *n* | Number | | EMB diagnosis, *n* (%) | | CMR diagnosis, *n* (%) | | Combined diagnosis, *n* (%) |
|---|---|---|---|---|---|---|---|
| EMB indication (class) | I | IIa/IIb | I | IIa/IIb | I | IIa/IIb | |
| DCM, 54 | 30 | 24 | 26 (87) | 22 (92) | 24 (80) | 21 (88) | 51 (94) |
| HCM, 36 | 11 | 25 | 7 (64) | 20 (80) | 6 (55) | 23 (92) | 35 (97) |
| Dilated HCM, 15 | 9 | 6 | 7 (78) | 5 (83) | 4 (44) | 5 (83) | 15 (100) |
| Obstructive HCM, 11 | 0 | 11 | 0 (0) | 9 (82) | 0 (0) | 11 (100) | 11 (100) |
| Apical HCM, 4 | 0 | 4 | 0 (0) | 2 (50) | 0 (0) | 4 (100) | 4 (100) |
| Sarcoidosis, 17 | 8 | 9 | 2 (25) | 4 (44) | 6 (75) | 7 (78) | 17 (100) |
| HHD, 14 | 5 | 9 | 2 (40) | 3 (33) | 5 (100) | 4 (44) | 14 (100) |
| Others | | | | | | | |
| ARVC, 5 | 1 | 4 | 0 (0) | 0 (0) | 1 (100) | 4 (100) | 5 (100) |
| Myocarditis, 4 | 4 | 0 | 3 (75) | 0 (0) | 1 (25) | 0 (0) | 4 (100) |
| Amyloidosis, 3 | 0 | 3 | 0 (0) | 2 (67) | 0 (0) | 3 (100) | 3 (100) |
| Dystrophic cardiomyopathy, 3 | 1 | 2 | 0 (0) | 0 (0) | 1 (100) | 2 (100) | 3 (100) |
| Total | 60 | 76 | 40 (67) | 51 (67) | 44 (73) | 64 (84) | 132 (97) |

ARVC, arrhythmogenic right ventricular cardiomyopathy; CMR, cardiac magnetic resonance; DCM, dilated cardiomyopathy; EMB; endomyocardial biopsy HCM, hypertrophic cardiomyopathy; HHD, hypertensive heart disease.

muscle was frequently found in patients with HCM or sarcoidosis, while it was rarely or never seen in patients with DCM or HHD.

## Discussion

This was the first study to compare the diagnostic performance of EMB and CMR in patients with HF. Non-invasive CMR, especially when combined with clinical data and echocardiogram, may provide an excellent diagnostic capacity for identifying the underlying aetiology in patients with HF, equal to or better than invasive EMB. Moreover, CMR is a powerful modality which in combination with clinical data including echocardiogram is sufficient for defining the pathophysiology of HF.

Although it is important to compare the diagnostic potential of EMB and CMR across a large number of patients with HF, comparisons using a large population have not been possible because it is extremely difficult to perform both EMB and CMR with LGE in sufficient patients. Our findings revealed that both the invasive EMB technique and the non-invasive CMR technique demonstrated good diagnostic performance (67% vs. 79%), whereas the use of CMR in combination with clinical data including echocardiogram unrelated to the EMB findings demonstrated excellent diagnostic performance (97%). Importantly, CMR alone could not surpass the diagnostic accuracy of EMB, which underscores the importance of EMB. However, the combined diagnosis was more accurate, which suggests that the use of CMR in combination with clinical data plus echocardiogram is the most reliable, non-invasive method for the diagnosis of HF in a routine clinical setting. Thus, we concluded that CMR is equal to or possibly superior to the use of EMB for the diagnosis of the underlying aetiology of HF, especially in patients with sarcoidosis, HHD, others, and those with a class II indication for EMB.

These results suggest that CMR should be used more often than EMB for the initial diagnosis of HF. In addition, the cost of EMB is approximately three times greater than that of delayed enhancement CMR, and most patients can receive CMR at a clinic but would require a hospital stay to undergo EMB and perform EMB with right heart catheterization (which also contributes to the high cost of EMB). Indeed, the 2009 American College of Cardiology (ACC)/American Heart Association (AHA) chronic HF guidelines proposed that EMB should not be performed for the routine evaluation of patients with HF,[24] as EMB is often associated with sampling errors and complications. Therefore, although we do not deny the usefulness of EMB for the diagnosis of the underlying aetiology of HF, we suggest that CMR should be used more frequently for this type of diagnosis.

### Diagnostic performance of cardiac magnetic resonance and endomyocardial biopsy

Although EMB provides suggestive findings in patients with DCM, HHD, and dystrophic cardiomyopathy, these findings are non-specific, and a definitive diagnosis cannot be made by EMB *per se*. In contrast, cardiac amyloidosis, CS, HCM, and myocarditis have specific histological characteristics and can be conclusively diagnosed using EMB alone if myocardial biopsy specimens contain these lesions (*Figure 4*). In our study, an accurate and conclusive diagnosis of such conditions could be reached using EMB alone in 38 out of 60 patients (*Table 1*), and we tended to misdiagnose CS and HHD as DCM, and HCM as HHD by EMB (*Table 3*).

**Table 2 Sensitivity, specificity, positive predictive value, negative predictive value, accuracy of cardiac magnetic resonance diagnosis, and combined diagnoses with clinical data, echocardiogram, plus cardiac magnetic resonance vs. endomyocardial biopsy diagnosis**

A. Cardiac magnetic resonance vs. endomyocardial biopsy

| | n | Sensitivity | | rTPF | 95% CI | n | Specificity | | rFPF | 95% CI |
|---|---|---|---|---|---|---|---|---|---|---|
| | | CMR | EMB | | | | CMR | EMB | | |
| DCM | 54 | 83% | **89%** | 1.07 | 0.89–1.28 | 82 | **93%** | 69% | **4.3** | **1.72–10.7** |
| HCM | 36 | **81%** | 75% | 0.93 | 0.69–1.26 | 100 | **98%** | 94% | 3 | 0.48–18.64 |
| CS | 17 | **76%** | 35% | 0.46 | 0.20–1.07 | 119 | 92% | **100%** | **0** | – |
| HHD | 14 | **64%** | 36% | 0.56 | 0.22–1.43 | 122 | **96%** | 92% | 2 | 0.59–6.81 |

B. Cardiac magnetic resonance vs. endomyocardial biopsy

| | n | PPV | | rPPV | 95% CI | n | NPV | | rNPV | 95% CI | Accuracy | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | CMR | EMB | | | | CMR | EMB | | | CMR | EMB |
| DCM | 54 | **88%** | 66% | **0.75** | **0.60–0.93** | 82 | 89% | **90%** | 1.01 | 0.89–1.15 | **89%** | 75% |
| HCM | 36 | **94%** | 82% | 0.87 | 0.71–1.08 | 100 | **93%** | 91% | 0.98 | 0.89–1.07 | **93%** | 89% |
| CS | 17 | 57% | **100%** | **1.77** | **1.18–2.66** | 119 | **96%** | 92% | 0.95 | 0.88–1.02 | 90% | **92%** |
| HHD | 14 | **64%** | 33% | 0.52 | 0.20–1.31 | 122 | **96%** | 93% | 0.97 | 0.90–1.04 | **93%** | 86% |

C. Combined procedure using clinical data with echocardiogram plus cardiac magnetic resonance vs. endomyocardial biopsy

| | n | Sensitivity | | rTPF | 95% CI | n | Specificity | | rFPF | 95% CI |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Combined | EMB | | | | Combined | EMB | | |
| DCM | 54 | **94%** | 89% | 0.94 | 0.82–1.08 | 82 | **100%** | 69% | – | – |
| HCM | 36 | **97%** | 75% | **0.77** | **0.61–0.97** | 100 | **99%** | 94% | 6 | 0.54–67.19 |
| CS | 17 | **100%** | 35% | **0.35** | **0.17–0.74** | 119 | 99% | **100%** | 0 | – |
| HHD | 14 | **100%** | 36% | **0.36** | **0.16–0.80** | 122 | **98%** | 92% | 5 | 0.88–28.27 |

D. Combined procedure using clinical data with echocardiogram plus cardiac magnetic resonance vs. endomyocardial biopsy

| | n | PPV | | rPPV | 95% CI | n | NPV | | rNPV | 95% CI | Accuracy | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Combined | EMB | | | | Combined | EMB | | | Combined | EMB |
| DCM | 54 | 100% | 66% | **0.65** | **0.52–0.81** | 82 | **96%** | 90% | 0.94 | 0.85–1.03 | **98%** | 75% |
| HCM | 36 | **97%** | 82% | 0.84 | 0.69–1.02 | 100 | **99%** | 91% | **0.92** | **0.86–0.99** | **99%** | 89% |
| CS | 17 | **94%** | 100% | 1.06 | 0.93–1.20 | 119 | **100%** | 92% | **0.92** | **0.86–0.97** | **99%** | 92% |
| HHD | 14 | **88%** | 33% | **0.38** | **0.16–0.89** | 122 | **100%** | 93% | **0.93** | **0.87–0.98** | **99%** | 86% |

CI, confidence interval; CMR, cardiac magnetic resonance; CS, cardiac sarcoidosis; DCM, idiopathic dilated cardiomyopathy; EMB, endomyocardial biopsy; FPF, false positive fraction; HCM, hypertrophic cardiomyopathy; HHD, hypertensive heart disease; NPV, negative predictive value; PPV, positive predictive value; TPF, true positive fraction. 95% CIs were calculated according to the ratio of CMR diagnosis and combined diagnosis to EMB diagnosis. The bold values indicate a significant difference.

These misdiagnoses were attributed to non-specific changes in the biopsy specimens or the inappropriate sampling of sites separate from the lesions due to the patchy distribution of the lesions.[17,25–27] However, there are merits in the classification of infiltrating inflammatory cells by either immunohistochemistry or a PCR method to guide treatment. The ESC 2012 guidelines also stated that the use of EMB may be needed to confirm the diagnosis in patients with suspected myocarditis, sarcoidosis, and amyloidosis.[1]

Cardiac magnetic resonance is a safe procedure, and images of diagnostic quality can be obtained in ≥ 98% of patients.[28] The use of CMR also allowed us to obtain detailed images of not only functional and morphological abnormalities but also tissue pathology. In this study, EMB was superior to CMR for diagnoses of DCM and dilated HCM, whereas CMR demonstrated an improved diagnostic yield over EMB in cases of non-dilated HCM, CS, HHD, and other rare diseases (with the exception of myocarditis). Moreover, this tendency was the same independent of the EMB indication. In contrast to previous studies demonstrating a high level of sensitivity and specificity within only a limited study population, our study observed lower diagnostic agreement between methods. Because CMR was used to differentiate between a broad spectrum of diagnostic characteristics in HF patients, which resembles the clinical setting, CMR alone could

**Table 3 Comparison of cardiac magnetic resonance diagnosis or endomyocardial biopsy diagnosis with final diagnosis**

| Final diagnosis CMR diagnosis | DCM ($n$ = 54) | HCM ($n$ = 36) | CS ($n$ = 17) | HHD ($n$ = 14) | Others ($n$ = 15) |
|---|---|---|---|---|---|
| DCM, $n$ (%) | **45 (83)** | 0 | 1 | 5 (36) | 0 |
| HCM, $n$ (%) | 1 | **29 (81)** | 1 | 0 | 0 |
| CS, $n$ (%) | 2 (4) | 6 (17) | **13 (76)** | 0 | 2 (13) |
| HHD, $n$ (%) | 3 (5) | 1 | 0 | **9 (64)** | 0 |
| Others, $n$ (%) | 3 (5) | 0 | 2 (12) | 0 | **12 (80)** |
| **Final diagnosis EMB diagnosis** | **DCM ($n$ = 54)** | **HCM ($n$ = 36)** | **CS ($n$ = 17)** | **HHD ($n$ = 14)** | **Others ($n$ = 15)** |
| DCM, $n$ (%) | **48 (89)** | 3 (8) | 10 (59) | 7 (50) | 6 (40) |
| HCM, $n$ (%) | 3 (6) | **27 (75)** | 0 | 2 (14) | 1 (7) |
| CS, $n$ (%) | 0 | 0 | **6 (35)** | 0 | 0 |
| HHD, $n$ (%) | 2 (4) | 6 (17) | 0 | **5 (36)** | 2 (13) |
| Others, $n$ (%) | 1 | 0 | 1 | 0 | **5 (33)** |

The bold values indicate diagnostic concordance between cardiac magnetic resonance diagnosis or endomyocardial biopsy diagnosis and final diagnosis.

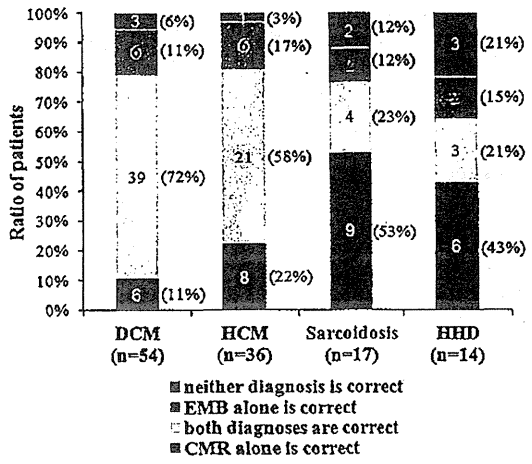


**Figure 2** Diagnostic capabilities of endomyocardial biopsy (EMB), cardiac magnetic resonance (CMR), and the combined diagnosis with CMR and EMB. DCM, idiopathic dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; CS, cardiac sarcoidosis; HHD, hypertensive heart disease. The ratio between EMB and CMR for the diagnosis of DCM, HCM, CS, and HHD.

not assign a correct diagnosis for 28 patients (21%) (*Table 1*). The use of CMR tended to misdiagnose HCM as CS, and HHD as DCM. Additionally, six HCM patients who were misdiagnosed with CS all had dilated HCM. A study by Hansen *et al.* suggested that the use of CMR in CS patients demonstrates similar results to those obtained in patients with HCM or idiopathic cardiomyopathy,[29] which is consistent with the present data (*Table 3*). In the five cases where HHD was misdiagnosed, they were consistently misdiagnosed as DCM due to the similarity of the images.[10] However, in HCM patients, CMR demonstrated excellent diagnostic performance (100%) for apical HCM and HOCM, which suggests that CMR has the ability to evaluate the heterogeneous appearance of HCM better than any other imaging modality,[30,31] and this represents the main difference between CMR and EMB. We could not refer to the diagnostic accuracy of CMR in patients with myocarditis in our study because the number with myocarditis was too small. On the other hand, Marvorogeni *et al.* importantly concluded that both CMR and PCR prove useful for the detection of myocarditis, while CMR is important to detect the development of HF.[32] Our data are consistent with the previous study[32] showing that CMR and EMB have equivalent ability to reach the diagnosis and judge the pathophysiology.

Although the merits and demerits of CMR differ from those of EMB, its diagnostic capability was shown to be equivalent or even superior to that of EMB.

## Superiority of the combined diagnosis

The combined diagnosis with non-invasive clinical data provides a sharp impact on an accurate diagnosis of HF.[33] Likewise, the combined diagnosis with clinical data, echocardiogram, plus CMR was shown to be very effective in the current study. Out of 54 DCM patients, 9 were misdiagnosed by CMR, but 6 of these 9 patients were correctly diagnosed using the combined diagnostic technique. Of 36 HCM patients, 7 were misdiagnosed by CMR, although 6 of these 7 patients were correctly assessed using the combined diagnosis (*Tables 2* and *3*). Moreover, the other misdiagnosed patients were also correctly assessed using the combined diagnosis.

Regarding the combined diagnosis with echocardiogram, the present study suggests that even the use of only clinical characteristics including echocardiogram can provide relatively high diagnostic performance compared with that in a previous report,[33] since our Department is specialized in diagnosing patients with non-ischaemic HF. However, the addition of CMR and EMB on top of the clinical information with echocardiogram increases the accuracy to 97% and 100%, respectively. Our original conclusion

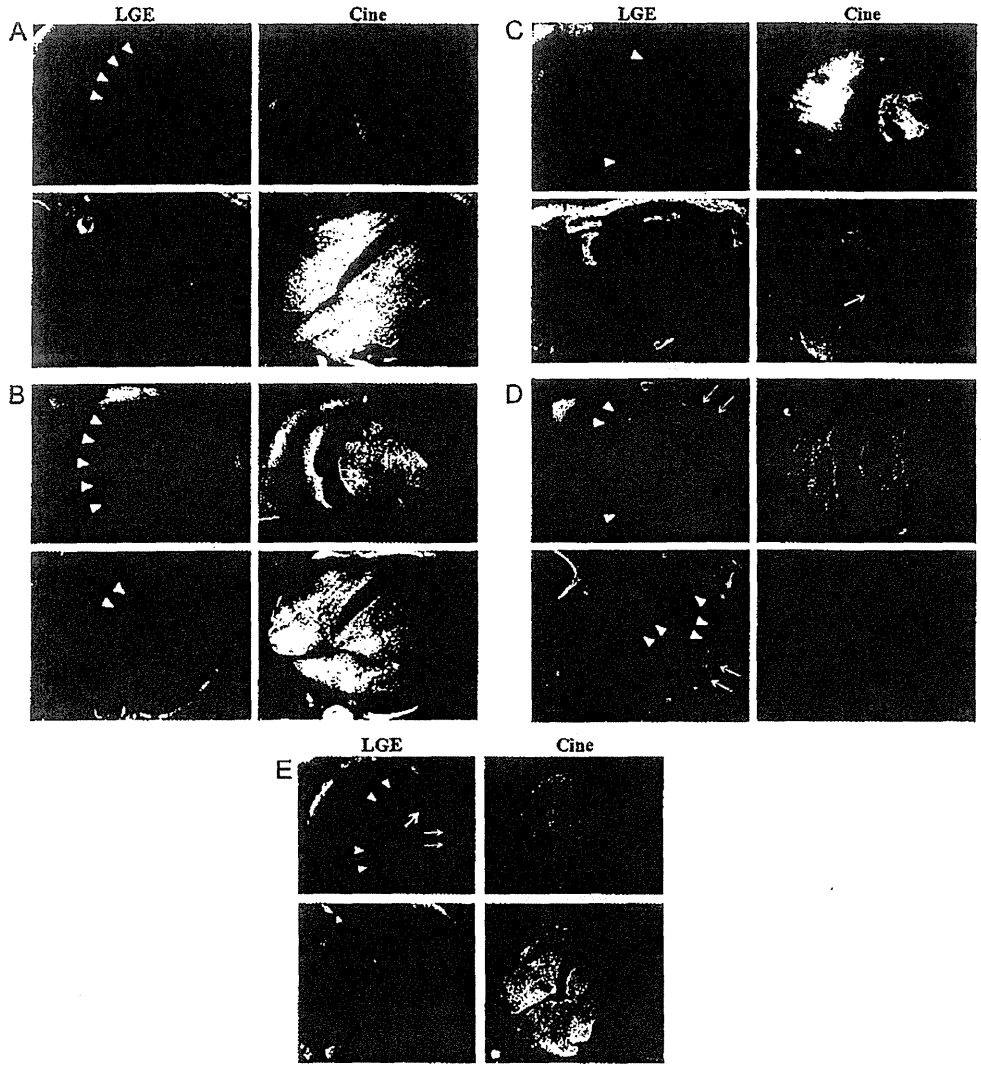


**Figure 3** Representative cardiac magnetic resonance (CMR) findings. (*A*) Dilated cardiomyopathy (DCM): midwall longitudinal thin late-gadolinium enhancement (LGE) in the anteroseptum wall without wall thickening (arrowheads). (*B*) Hypertensive heart disease (HHD): broad, ill-defined, and mild LGE in the midwall of the septum (arrowheads) with LV concentric hypertrophy. (*C*) Hypertrophic obstructive cardiomyopathy (HOCM): LGE in the LV–RV junctions of the anteroseptum and inferoseptum (arrowheads). Note: left atrial dilatation, LV asymmetric hypertrophy, papillary muscle hypertrophy, and LV outflow tract obstruction (arrow). (*D*) Dilated phase HCM: midwall patchy LGE in the anteroseptum and inferoseptum (arrowheads) and epicardial LGE in the anterior and posterior regions (arrow). (*E*) Cardiac sarcoidosis: subepicardial LGE of the anteroseptum with wall thinning and inferoseptum (arrowheads), subendocardial LGE of the lateral region (thin arrow), and LGE in the papillary muscle (thick arrow).

that CMR provides a diagnostic capability comparable with EMB seems to be true even with the clinical information including echocardiogram. Furthermore, all of the patients who were correctly diagnosed by EMB were correctly diagnosed using the combined technique, which indicates that the combined method was superior to the use of EMB in this study. Previous studies performed in populations with only one clinically suspected disease reported high diagnostic accuracy,[11,12,34] and our results indicate that CMR would probably be available for a broad spectrum of HF patients, particularly those with a class II indication for EMB, for differentiation between unknown aetiologies. Furthermore, the knowledge of diseases that are prone to misdiagnosis would increase the diagnostic performance for determining the aetiology of HF in a routine clinical setting. Although CMR is a non-invasive method, as is an echocardiogram, it is equal or superior to an echocardiogram because it can provide specific tissue characterization in addition to cardiac morphology and function. Accordingly, we suggest that it would be better initially to perform CMR in all patients, especially those with a class II indication for EMB, and diagnose the underlying aetiology of HF through the use of

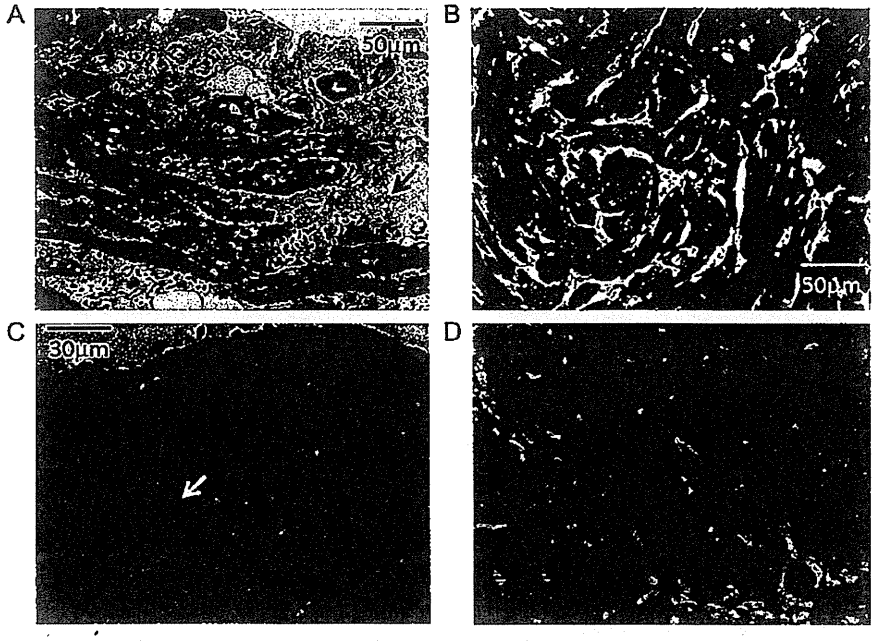


**Figure 4** Representative examples of histological findings from endomyocardial biopsies. (*A*) Dilated cardiomyopathy (DCM): the photomicrograph demonstrates replacement fibrosis (blue areas, black arrow) and moderate myocyte hypertrophy (Masson trichrome stain, bar = 50 μm). (*B*) Hypertrophic cardiomyopathy (HCM): severe hypertrophy of myocytes, myocyte disarray, and bizarre nuclei are shown (Masson trichrome stain, bar = 50 μm). (*C*) Cardiac sarcoidosis: non-caseating epithelioid granulomas with giant cells (white arrow) are shown (haematoxylin and eosin stain, bar = 30 μm). (*D*) Cardiac amyloidosis: amorphous amyloid deposits (blue-grey) in the perimyocytes were consistent with amyloidosis in the interstitium of the myocardium (Masson's trichrome, bar = 50 μm).

CMR and other non-invasive modalities. Then, if the combined diagnosis fails, EMB can be used as a second diagnostic modality.

## Study limitations

This study had several limitations. First, all of the patients with HF of unknown aetiology were not assigned to receive both EMB and CMR; EMB was performed to reveal the underlying aetiology of HF, according to the Scientific Statement,[23] whereas CMR was performed in all patients without contraindications for CMR. Secondly, we included patients admitted to the Department with HF, and there were remarkably few patients in our Department who had coronary artery disease. However, even if such patients had been included, CMR would have probably been more useful to diagnose prior myocardial infarction due to spontaneous recanalization or coronary vasospasm than EMB. Thirdly, in the clinical setting, there are always cases with an ambiguous diagnosis despite a detailed investigation. We excluded these cases primarily on the premise that we would achieve a more precise diagnostic yield by avoiding these cases. Regarding EMB procedures, we took 3–5 biopsy specimens for each patient in our study, in accordance with the appropriate guidelines.[23] Additionally, all samples were taken from the right ventricle according to the protocol of our facility. In most patients, we took five samples to decrease sampling error, although the sampling number was decreased to three specimens in patients with both a pre-existing LBBB with a high risk for developing complete atrioventricular block[8] and obvious idiopathic DCM. The collection of samples from both ventricles may have increased the significance of the findings, but we collected the minimum requirement to decrease the procedural risk of EMB. Finally, this was also a retrospective study from a single centre. Our findings must be carefully interpreted and should be replicated in a prospective, large, multicentre investigation. Despite these limitations, our study has important strengths, such as the inclusion of a sufficient number of patients administered both EMB and CMR, a more precise final diagnosis using all available data, and broad clinical applications.

## Supplementary material

Supplementary material is available at *European Journal of Heart Failure* online.

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ORIGINAL ARTICLE

# Derivation of a mathematical expression for predicting the time to cardiac events in patients with heart failure: a retrospective clinical study

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**The prognoses for patients with certain diseases are estimated by averaging the results of clinical trials. To investigate the possibility of deriving a mathematical formula for the estimation of prognosis, we formulated the equation $\tau = f(x_1, \ldots, x_p)$, where $x_1, \ldots, x_p$ are clinical features and $\tau$ represents the clinical outcome for heart failure (HF). We attempted to determine the function to mathematically formulate the relationship between clinical features and outcomes for these patients. We followed 151 patients (mean age: 68.6 ± 14.6 years; men: 61.6%) who were consecutively hospitalized and discharged as a result of acute decompensated HF (ADHF) between May 2006 and December 2009. The mathematical analysis was performed through a probabilistic modeling of the relational data by assuming a Poisson process for rehospitalization owing to HF and by linearly approximating the relationship between the clinical factors and the mean elapsed time to rehospitalization. The former assumption was validated by a statistical test of the data, and the contribution of each parameter was assessed based on the coefficients of the linear relation. Using a regularization method to analyze 402 clinical parameters, we identified 252 factors that substantially influenced the elapsed time until rehospitalization. With the probability model based on the Poisson process, the actual ($X$; 388 ± 377 days) and estimated ($Y$; 398 ± 381 days) elapsed times to rehospitalization were tightly correlated ($Y = 1.0076X + 6.5531$, $R^2 = 0.9879$, $P < 0.0001$). We established a mathematical formula that closely predicts the clinical outcomes of patients who are hospitalized with ADHF and discharged after appropriate treatment.**
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**Keywords:** heart failure; mathematical model; prognosis; rehospitalization

## INTRODUCTION

Studies show that numerous factors, including disease severity, treatment protocols and the environment, independently determine patients' prognoses. For example, in patients with chronic heart failure (CHF), many studies have shown that various independent indices of the severity of CHF, such as plasma B-type natriuretic peptide (BNP) level, left ventricular function, exercise tolerance or New York Heart Association (NYHA) functional class affect the time to hospitalization or cardiac death.[1–5] However, because we could not identify the elapsed time until hospitalization in certain patients with CHF, we estimated this time using knowledge of the pathophysiology of CHF, our experience with previous comparable patients and Kaplan–Meier plots of their hospitalization in the clinical studies; we then explained our estimation to each patient. This procedure led us to conclude that estimating the elapsed time to rehospitalization is a type of problem that is specific to clinical medical science because the results and outcomes of biology or basic medical sciences can be derived from mathematically formulated equations. Furthermore, other fields of basic science, such as physics and mathematics or applied sciences, such as mechanics, thermodynamics and fluid dynamics, are mathematically formulated; the observational phenomena in applied sciences other than medical science can be predicted by mathematical equations, for example, the law of universal gravitation.[6] The most important issue in deriving a mathematical expression for relationships among two or more factors is the prediction of the future value of one variable based on the other factor(s). All phenomena, such as the severity of CHF and the patients' characteristics before the occurrence of clinical events, may therefore provide a mathematical equation for the clinical outcome if we can relate factors in the patient's clinical status to clinical outcomes such as rehospitalization.

To investigate this possibility, we sought to solve the equation $\tau = f(x_1, \ldots, x_p)$, where $x_1, \ldots, x_p$ represent clinical features affecting the clinical outcome for CHF. We attempted to determine the

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