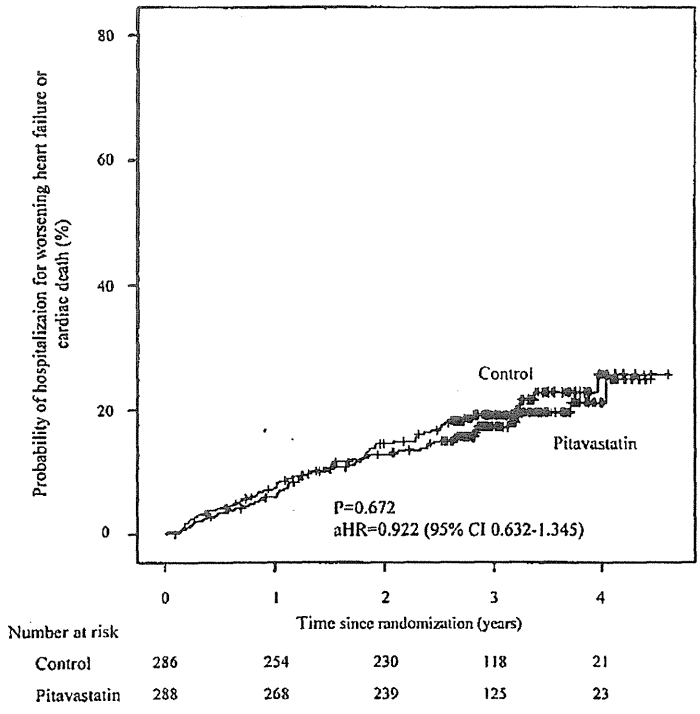


**Figure 2.** Kaplan-Meier curve for the primary outcome. The P-value was calculated by log-rank test. aHR, adjusted hazard ratio.

All comparisons were planned and the tests were 2-sided. P<0.05 was considered to indicate a statistically significant difference. All statistical analyses were conducted using SAS software program, version 9.2 (SAS Institute Inc, Cary, NC, USA).

### Study Management

Data on the primary and secondary outcomes and adverse events were collected at various time points and interim analyses were performed every year after the initiation of the study to evaluate both the events and treatment safety. An independent endpoint committee (**Appendix S1**) consisting of 3 members, who were blinded to any information relating to the group allocations, evaluated each event and classified the results. An independent data and safety monitoring board (**Appendix S2**) comprised 3 members who reviewed all reports from the endpoint committee to advise early termination of the study for safety, scientific or ethical reasons. A steering committee (**Appendix S3**) was responsible for the study design and scientific execution of the study.

The independent data and safety monitoring board's charter specified interim analyses of the primary outcome at the last patient registration and 1 year after the last registration, with a statistical stopping guideline for an overwhelming benefit.

## Results

We enrolled 577 symptomatic CHF patients with mild hypercholesterolemia from June 2006 to June 2008. All the patients were followed up until April 2011 for primary and secondary outcomes. Finally, 577 patients were randomly assigned to the 2 groups (**Figure 1**). Of them, 288 were assigned to the pitavastatin group and 289 to the control group. As shown in **Figure 1**, 1 patient was excluded, 1 patient withdrew consent after random allocation, and 1 patient was lost to follow-up. We obtained complete endpoint information at the end of the study for 574 patients. The median duration of follow-up was 35.5 months. **Table 1** shows the baseline characteristics of the patients enrolled; there were no significant differences between the 2 groups. The patients had a mean age of 62.6 years and 86.2% of them were older than 50 years. The mean LVEF was 34.0% and 89.7% of the patients were classified as NYHA class II. The cause of HF was ischemic heart disease in 157 (27.4%) patients and dilated cardiomyopathy in 310 (54.0%) patients.

The primary outcome occurred in 52 (18.0%) patients in the pitavastatin group and 57 (19.9%) patients in the control group. There was no significant difference in the primary outcome between the 2 groups (adjusted hazard ratio (aHR): 0.922, 95% CI: 0.632–1.345, P=0.672) (**Figure 2**). In the secondary outcomes, there were no significant differences between the 2 groups (**Table 2**). The number of non-cardiac death was smaller in the pitavastatin group (n=3) than in the control group (n=15). In the predefined subgroup analysis (**Figure 3**), we found a strongly significant statistical interaction between the effect of pitavastatin and LVEF (P=0.004). In the subgroup of patients with LVEF ≥30% (n=413), pitavastatin was associated significantly fewer occurrences of the primary outcome (aHR: 0.525, 95% CI: 0.308–0.896, P=0.018) (**Figure 4A**). On the other hand, pitavastatin did not show any effects for the primary outcome in the subgroup of patients with LVEF <30% (aHR: 1.582, 95% CI: 0.890–2.813, P=0.118) (**Figure 4B**). As for the secondary outcomes, pitavastatin significantly reduced all-cause death and hospitalization due to worsening HF in the subgroup of patients with LVEF ≥30% (**Table 3**).

In the pitavastatin group, serum level of LDL-cholesterol

Table 2. Outcomes

| | Control (n=286) | Pitavastatin (n=288) | *aHR (95% CI) | P value |
|---|---|---|---|---|
| Primary | | | | |
| Composite of cardiac death and hospitalization due to worsening HF | 57 (19.9%) | 52 (18.0%) | 0.922 (0.632–1.345) | 0.672 |
| Secondary | | | | |
| All-cause death | 37 (12.9%) | 27 (9.37%) | 0.727 (0.441–1.198) | 0.211 |
| Cardiac death | 22 (7.7%) | 24 (8.3%) | 1.097 (0.611–1.969) | 0.756 |
| Hospitalization due to worsening HF | 47 (16.4%) | 39 (13.5%) | 0.836 (0.547–1.282) | 0.411 |
| MI or unstable angina | 8 (2.8%) | 3 (1.0%) | 0.396 (0.103–1.519) | 0.177 |
| Stroke | 9 (3.2%) | 8 (2.8%) | 0.886 (0.340–2.306) | 0.804 |
| PCI | 6 (2.1%) | 3 (1.0%) | 0.374 (0.083–1.687) | 0.200 |
| Surgical therapy for HF | 11 (3.8%) | 12 (4.2%) | 1.043 (0.458–2.374) | 0.920 |

*Adjusted for the primary outcome in age, sex, total cholesterol, LVEF, IHD, and history of hospitalization for HF.
Data are the numbers of patients (%).
aHR, adjusted hazard ratio; CI, confidence interval. Other abbreviations as in Table 1.

significantly decreased from 125.3 mg/dl at baseline to 83.6 mg/dl after 2 years (–32.5% [–29.4 to –35.6]), P<0.0001, paired t-test). The serum level of LDL-cholesterol also significantly decreased from 125.5 mg/dl at baseline to 115.4 mg/dl after 2 years in the control group (–7.2% [–10.7 to –3.7], P<0001, paired t-test). The percent change in LDL-cholesterol in the pitavastatin group was significantly high compared with the control group after 2 years (P<0.001, Mann-Whitney U test). In the pitavastatin group, the serum level of HDL-cholesterol significantly increased from 50.7 mg/dl at baseline to 52.1 mg/dl after 2 years (5.1% [2.1 to 8.1], P=0.0009, paired t-test). In the control group, the serum level of HDL-cholesterol did not significantly change (50.8 mg/dl at baseline to 50.2 mg/dl after 2 years (0.5% [–2.5 to 3.6], P=0.73, paired t-test)). The percent change in HDL-cholesterol in the pitavastatin group was significantly high compared with the control group after 2 years (P=0.023, Mann-Whitney U test). Although there was a trend for higher rates of muscle-related symptoms and elevation in level of creatine phosphokinase, we did not note any significant differences in the adverse events between the 2 groups (Table 4).

## Discussion

The PEARL study aimed to investigate the effects of pitavastatin on the incidence of cardiac death and hospitalization for worsening HF in Japanese patients with CHF. Our findings confirm that pitavastatin does not reduce cardiac death and hospitalization for worsening HF entirely, but significantly reduces those events in the subgroup of patients with LVEF ≥30%.

It is well known that treatment with statins significantly reduces the incidence of cardiovascular events in patients at high risk, especially those with CAD, irrespective of the baseline cholesterol levels.[19] Several retrospective analyses and large observational studies have suggested that treatment with statins decreases the incidence of HF and reduces mortality in patients with CHF.[7–9] Furthermore, prospective trials assessing the effects of statins on surrogate endpoints such as biomarkers and echocardiographic parameters demonstrated the beneficial effects of statins on patients with CHF.[10–12] Meta-analyses of statin treatment in randomized clinical trials also confirmed a reduction of cardiovascular mortality in patients with CHF of both ischemic and nonischemic etiologies.[4] These results support the pleiotropic effects of statins demonstrated by basic research and the beneficial effects of statins on patients with CHF.

Recently, the results of 2 well-controlled randomized trials have been published.[13,14] The CORONA (Controlled rosuvastatin multinational study in heart failure) study randomized 5,011 patients with symptomatic CHF of ischemic etiology to 10 mg rosuvastatin or placebo.[13] The GISSI (Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza cardiaca)-HF (Heart failure) trial randomized 4,631 patients with symptomatic CHF of both ischemic and nonischemic etiologies to 10 mg rosuvastatin or placebo.[14] The treatment with rosuvastatin did not affect the primary endpoints in the 2 studies.[13,14] It remains unknown at present whether the results of the CORONA study and the GISSI-HF trial can be applied in the different patient selection or in the different kind of statin. Interestingly, meta-analysis has reported that the effects of statins on HF are not a class effect and a significant benefit was noted using lipophilic atorvastatin but not hydrophilic rosuvastatin.[20] Several studies have also reported that atorvastatin has beneficial effects on the patients with HF, but rosuvastatin does not show the beneficial effects.[21–24] Therefore, there is a possibility that lipophilic statins are more useful than hydrophilic statins for the treatment of CHF.

In the PEARL study, we used pitavastatin to evaluate the beneficial effects of statin therapy on Japanese patients with CHF. Pitavastatin is a lipophilic agent, whereas rosuvastatin is a hydrophilic agent. Statins potently reduce the serum LDL-cholesterol level by inhibiting the synthesis of mevalonate and inducing the expression of LDL receptors, mainly in the hepatocytes. Among statins, pitavastatin has been reported to most strongly increase LDL receptor mRNA expression.[25] These data indicate that there is minimal likelihood of deleterious effects resulting from inhibition of the mevalonate pathway in the case of pitavastatin. As pitavastatin is hardly metabolized through the cytochrome P450-mediated pathway, pitavastatin is expected to have little interaction with other agents metabolized through the P450 pathway.[26] This property may be potentially beneficial for patients with CHF who take several kinds of medicines for the treatment of HF.

There are some differences in the characteristics of patients and protocol among the PEARL study, the CORONA study, and the GISSI-HF trial. The ratio of patients with ischemic HF was 40% in the GISSI-HF trial and 100% in the CORONA study, while only 27.4% of patients had ischemic HF in the

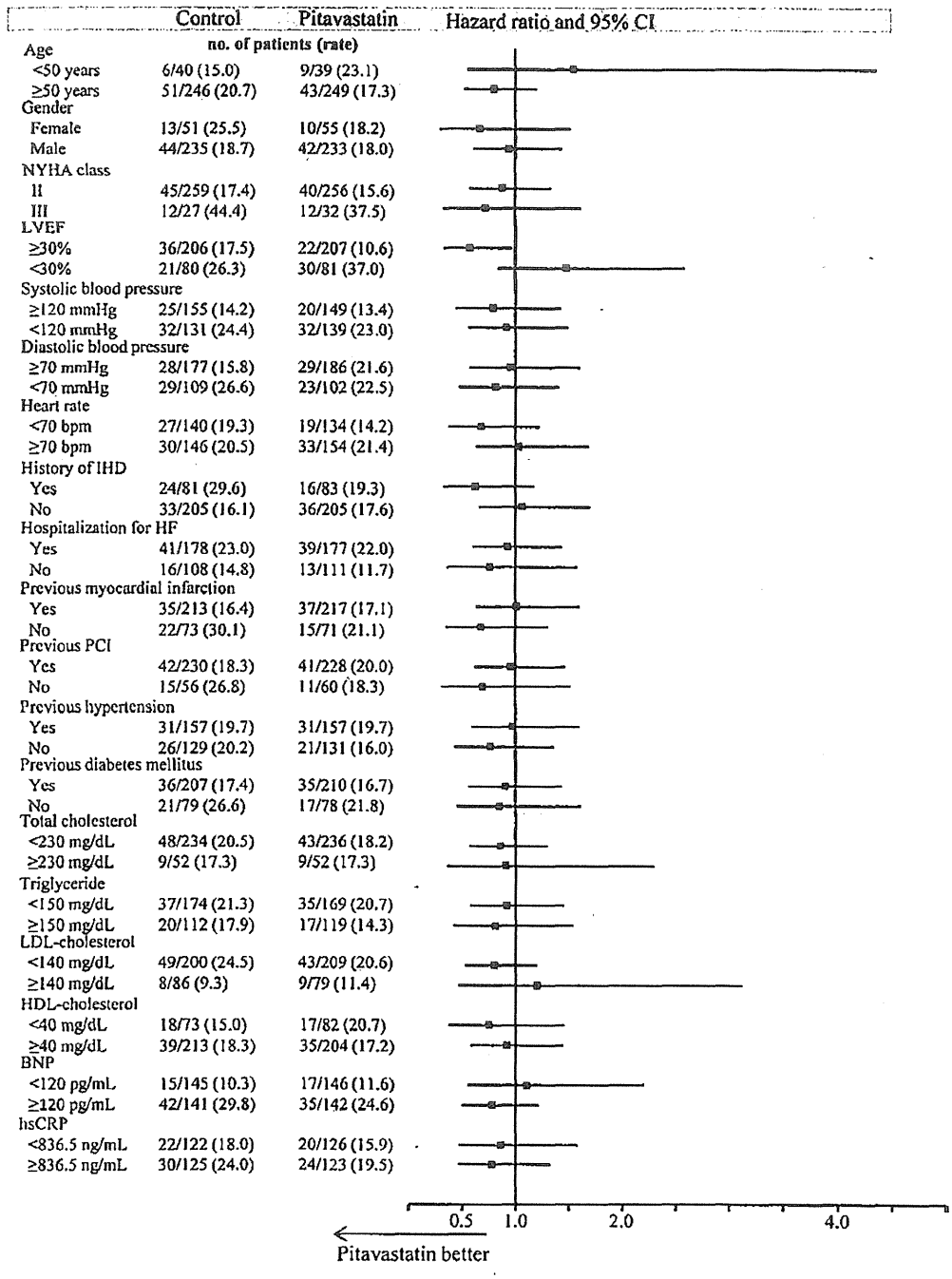


**Figure 3.** Predefined subgroup analysis for the primary outcome. bpm, beats/min; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; IHD, ischemic heart disease; HF, heart failure; PCI, percutaneous coronary intervention; LDL, low-density lipoprotein; HDL, high-density lipoprotein; BNP, B-type natriuretic peptide; hsCRP, high-sensitivity C-reactive protein.

PEARL study. The mean age of the patients was 73, 68, and 63 years in the CORONA, the GISSI-HF, and the PEARL, respectively. The enrolled patients appear to be less symptomatic in the PEARL study (NYHA II 89.7%, III 10.3%, IV 0%) than in the CORONA study (NYHA II 37.0%, III 61.5%, IV 1.5%) and the GISSI-HF trial (NYHA II 62.5%, III 35.0%, IV 2.5%). Furthermore, all the patients enrolled in the PEARL study were Japanese. There are differences in the responses to therapeutic drugs between Asian and Western populations.[27] Pharmacokinetic studies have demonstrated higher plasma

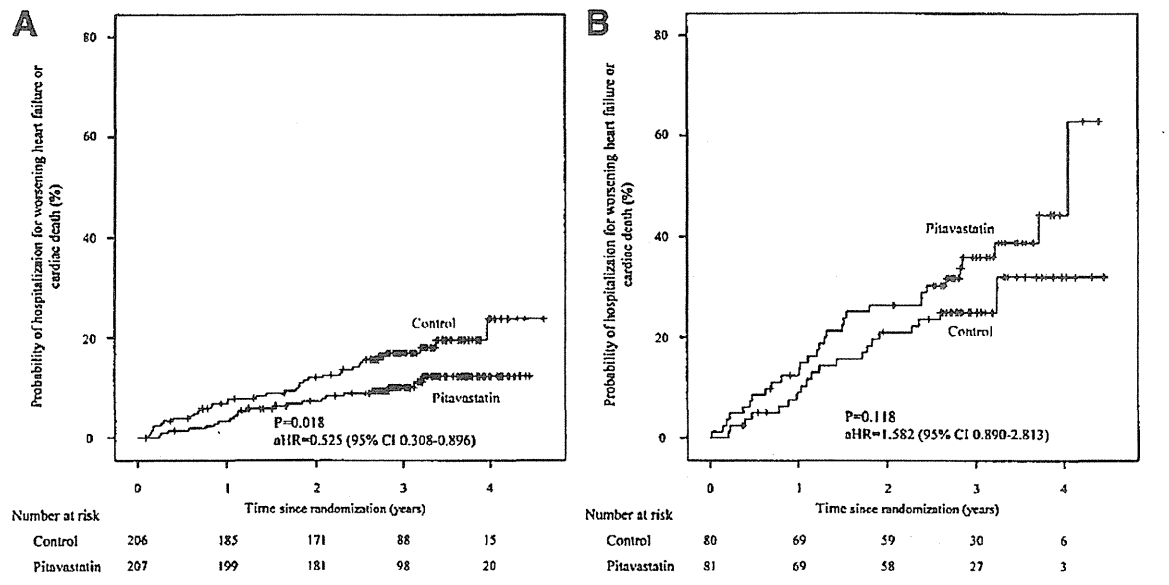


**Figure 4.** Kaplan-Meier curves for the primary outcome in the subgroup of patients with LVEF ≥30% (**A**) and in the subgroup of patients with LVEF <30% (**B**). The P-values were calculated by log-rank test. aHR, adjusted hazard ratio; LVEF, left ventricular ejection fraction.

**Table 3. Outcomes of Subgroup of Patients With LVEF ≥30% or <30%**

| | Control (n=206) | Pitavastatin (n=207) | *aHR (95% CI) | P value |
|---|---|---|---|---|
| **LVEF ≥30%** | | | | |
| **Primary** | | | | |
| Composite of cardiac death and hospitalization due to worsening HF | 36 (17.5%) | 22 (10.7%) | 0.525 (0.308–0.896) | 0.018 |
| **Secondary** | | | | |
| All-cause death | 22 (10.7%) | 12 (5.8%) | 0.485 (0.238–0.989) | 0.046 |
| Cardiac death | 12 (5.9%) | 9 (4.3%) | 0.695 (0.290–1.666) | 0.415 |
| Hospitalization due to worsening HF | 30 (14.6%) | 18 (8.7%) | 0.508 (0.282–0.915) | 0.024 |
| MI or unstable angina | 7 (3.4%) | 3 (1.4%) | 0.432 (0.110–1.701) | 0.229 |
| Stroke | 5 (2.5%) | 8 (3.9%) | 1.484 (0.481–4.578) | 0.492 |
| PCI | 4 (2.0%) | 3 (1.4%) | 0.406 (0.074–2.223) | 0.299 |
| Surgical therapy for HF | 6 (3.0%) | 6 (2.9%) | 0.994 (0.317–3.116) | 0.992 |
| **LVEF<30%** | **Control (n=80)** | **Pitavastatin (n=81)** | ***aHR (95% CI)** | **P value** |
| **Primary** | | | | |
| Composite of cardiac death and hospitalization due to worsening HF | 21 (26.3%) | 30 (37.0%) | 1.582 (0.890–2.813) | 0.118 |
| **Secondary** | | | | |
| All-cause death | 15 (18.7%) | 15 (18.5%) | 0.931 (0.440–1.972) | 0.85 |
| Cardiac death | 10 (12.5%) | 15 (18.5%) | 1.363 (0.587–3.162) | 0.471 |
| Hospitalization due to worsening HF | 17 (21.2%) | 21 (25.9%) | 1.417 (0.735–2.729) | 0.298 |
| MI or unstable angina | 1 (1.2%) | 0 (0.0%) | NA | 0.999 |
| Stroke | 4 (5.0%) | 0 (0.0%) | NA | 0.997 |
| PCI | 2 (2.5%) | 0 (0.0%) | NA | 0.999 |
| Surgical therapy for HF | 5 (6.3%) | 6 (7.4%) | 1.019 (0.293–3.544) | 0.976 |

*Adjusted for the primary outcome in age, sex, total cholesterol, IHD, and history of hospitalization for HF.
Data are the numbers of patients (%).
NA, not available. Other abbreviations as in Tables 1,2.

| Table 4. Adverse Events | | |
|---|---|---|
| | Control (n=286) | Pitavastatin (n=288) |
| Myalgia or arthralgia | 1 (0.35) | 4 (1.39) |
| CK increase | 0 (0.00) | 3 (1.04) |
| Gastrointestinal disorders | 3 (1.04) | 2 (0.69) |
| Giddiness | 0 (0.00) | 4 (1.39) |
| Liver disorder | 2 (0.70) | 2 (0.69) |
| Renal disorder | 0 (0.00) | 3 (1.04) |
| Rashes | 2 (0.70) | 1 (0.35) |
| Anemia | 1 (0.35) | 1 (0.35) |

Data are the numbers of patients (%).
CK, creatine kinase.

levels of statins in Asians as compared with Caucasians.[28] The high responses of Asians to statins are thought to be related to genetic differences in the metabolism of statins.[28] The kind of statins used in the PEARL study, the CORONA study, and the GISSI-HF trial was also different.

Concerns have been raised about the possible deleterious effects of statins. Circulating lipoproteins have the ability to bind and detoxify bacterial lipopolysaccharide. Because lipopolysaccharide stimulates the release of inflammatory cytokines, statins may increase inflammation in patients with HF.[29] Moreover, statins decrease the synthesis of not only cholesterol but also other downstream products in the mevalonate pathway. Coenzyme Q10 (ubiquinone), which is an essential cofactor in the mitochondrial electron transport chain, plays an important role in the mitochondrial respiratory chain and has an antioxidant function.[30,31] However, a substudy of the CORONA demonstrated that plasma coenzyme Q10 concentration was not an independent predictor of clinical outcomes in the patents with HF.[32] Indeed, the serious adverse effects were not recognized in the CONONA, the GISSI-HF, and the PEARL.

### Study Limitations

First, as the number of the enrolled patients was small, it is possible that the follow-up period was too short to demonstrate statistical significance. We assumed that the hazard ratio of cardiac events (cardiac death and hospitalization for worsening HF) of the pitavastatin group to the control group was 0.57 as previously reported.[17] However, the hazard ratio of cardiac events recognized between the 2 groups was more than 0.57 in the present study because the number of cardiac events was small. In the subgroup of patients with LVEF ≥30%, pitavastatin showed significantly fewer cardiac events of the primary outcome because the hazard ratio was close to 0.57. Therefore, sufficient statistical power was achieved to address the objective in the subgroup analysis. Second, we used a PROBE design but not a double-blind design in the present study. However, the PROBE design is a cost-effective alternative to the double-blind trial, and has advantages of being more similar to clinical practice and improved patient compliance without affecting the valuable blinded endpoint information. Third, the inclusion criteria of the study were NYHA class II or III, and LVEF ≤45%, but the majority of the enrolled patients had mild HF symptoms. Therefore, the number of the primary outcome was relatively low compared with other studies (the rate of cardiac death: 8% in the PEARL, 19% in the CORONA, and 21% in the GISSI-HF; the rate of hospitalization due to worsening HF: 15% in the PEARL, 26% in the CORONA, and 28% in the GISSI-HF).[13,14] Fourth, pitavastatin showed the significant reduction in cardiac death and hospitalization for worsening HF in the subgroup of patients with LVEF ≥30%, but our study was not designed to investigate the effects of pitavastatin on HF patients with LVEF ≥30%. And the pathophysiological mechanisms underlying the effects of pitavastatin on the HF patients with LVEF ≥30% in the present study remain largely unexplained. These findings require confirmation in a larger randomized clinical trial.

The PEARL study is the first to evaluate the effects and safety of pitavastatin in Japanese patients with CHF. Pitavastatin showed significant reduction of cardiac death and hospitalization for worsening HF in the group of patients with LVEF ≥30%, although not in the entire population. These results suggest that pitavastatin has protective effects on Japanese patients with mild HF.

### Acknowledgments

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### Disclosures

None.

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## Supplementary Files

Supplementary File 1

Appendix S1. Independent Endpoint Committee

Appendix S2. Independent Data and Safety Monitoring Board

Appendix S3. Steering Committee

Appendix S4. Investigators

Please find supplementary file(s);
http://dx.doi.org/10.1253/circj.CJ-12-1062

BMJ open accessible medical research

# Home telemonitoring study for Japanese patients with heart failure (HOMES-HF): protocol for a multicentre randomised controlled trial

Norihiko Kotooka,[1] Machiko Asaka,[1] Yasunori Sato,[2] Yoshiharu Kinugasa,[3] Kotaro Nochioka,[4] Atsushi Mizuno,[5] Daisuke Nagatomo,[1] Daigo Mine,[6] Yoko Yamada,[7] Kazuo Eguchi,[8] Hideki Hanaoka,[2] Takayuki Inomata,[9] Yoshihiro Fukumoto,[4] Kazuhiro Yamamoto,[3] Hiroyuki Tsutsui,[10] Tohru Masuyama,[11] Masafumi Kitakaze,[12] Teruo Inoue,[13] Hiroaki Shimokawa,[4] Shin-ichi Momomura,[7] Yoshihiko Seino,[14] Koichi Node,[1] on behalf of the HOMES-HF study investigators

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For numbered affiliations see end of article.

**Correspondence to**
Dr Norihiko Kotooka;
kotooka@cc.saga-u.ac.jp

## ABSTRACT

**Introduction:** Despite the encouraging results from several randomised controlled trials (RCTs) and meta-analyses, the ability of home telemonitoring for heart failure (HF) to improve patient outcomes remains controversial as a consequence of the two recent large-scale RCTs. However, it has been suggested that there is a subgroup of patients with HF who may benefit from telemonitoring. The aim of the present study was to investigate whether an HF management programme using telemonitoring could improve outcomes in patients with HF under the Japanese healthcare system.

**Methods and analysis:** The Home Telemonitoring Study for Japanese Patients with Heart Failure (HOMES-HF) study is a prospective, multicentre RCT to investigate the effectiveness of home telemonitoring on the primary composite endpoint of all-cause death and rehospitalisation due to worsening HF in recently admitted HF patients (aged 20 and older, New York Heart Association classes II–III). The telemonitoring system is an automated physiological monitoring system including body weight, blood pressure and pulse rate by full-time nurses 7 days a week. Additionally, the system was designed to make it a high priority to support patient's self-care instead of an early detection of HF decompensation. A total sample size of 420 patients is planned according to the Schoenfeld and Richter method. Eligible patients are randomly assigned via a website to either the telemonitoring group or the usual care group by using a minimisation method with biased-coin assignment balancing on age, left ventricular ejection fraction and a history of ischaemic heart disease. Participants will be enrolled until August 2013 and followed until August 2014. Time to events will be estimated using the Kaplan-Meier method, and HRs and 95% CIs will be calculated using the Cox proportional hazards models with stratification factors.

**Trial Registration:** The study is registered at UMIN Clinical Trials Registry (UMIN000006839).

## ARTICLE SUMMARY

### Article focus

- This study focuses on a role of the home telemonitoring system for patients with chronic heart failure (HF) to reduce hospital readmission under the Japanese healthcare system.

### Key messages

- The ability of home telemonitoring for HF care to improve patient outcomes remains controversial. However, recent studies have suggested the existence of a subgroup of patients who might be able to benefit from the telemonitoring.
- The Home Telemonitoring Study for Japanese Patients with Heart Failure (HOMES-HF) study was specially designed for the participants and health-care professionals to maintain adherence to daily measurement of body weight and blood pressure, to enhance clinician–patient communication and to empower their self-management by introducing a concept based on the idea of patient-centered care into the telemonitoring system.

### Strengths and limitations of this study

- The HOMES-HF study will be the first trial of home telemonitoring for Japanese patients with HF.
- Multidisciplinary HF management systems have been underdeveloped and there are still no practicable telemonitoring systems for HF management operated by either the public or private sector in Japan. Therefore, devices using the HOMES-HF study are not designed exclusively for HF management; rather, they are based on a commercial-based health-maintenance product and customised for the study.
- The responsibility for acting on the information from the telemonitoring centre rests with each patient's physician; therefore, treatment will vary with each physician and institute.

## INTRODUCTION

Heart failure (HF) is one of the most common causes of hospital admission in developed countries. Hospital discharges of HF increased from 399 000 in 1979 to 1 099 000 in 2004 in the USA. Moreover, of the $33.2 billion in overall costs for HF care in 2007, $17.8 billion was spent on in-hospital care.[1] Available data for Japanese patients with HF indicate that approximately 70% of HF patients are older than 65 years of age and that about 35% of patients are readmitted for acute HF decompensation within 1 year of hospital discharge.[2–5] Owing to the rapid ageing of the population, there are growing concerns about the increased incidence and prevalence of HF, and the high readmission rates and medical costs of hospitalisation have become a growing burden on the healthcare system.

Multidisciplinary HF management programmes and home-based care might be able to reduce hospital readmissions due to worsening HF.[6–9] Telemonitoring has grown to have a place in the HF disease management programmes. Chaudhry *et al*[10] have expounded on the details of telemonitoring, categorising it into three groups with regard to the types of intervention, including telephone-based symptom monitoring, automated monitoring of signs and symptoms and automated physiological monitoring.

Recent meta-analyses and comprehensive reviews of several randomised controlled trials (RCTs) and cohort studies have shown that home telemonitoring as an adjunct to usual care reduces HF-related hospitalisations. In some trials, home telemonitoring has been found to reduce all-cause mortality and improve health-related quality of life.[10–14] In contrast, recently published, well-designed, large, prospective, multicentre RCTs have ended with disappointing results. In the Telemonitoring to Improve Heart Failure Outcomes (Tele-HF) trial, there were no significant differences between the automated monitoring of the signs and symptoms group and the usual care group with regard to the primary composite endpoint of all-cause readmission and death or the secondary endpoints including HF readmission.[15] Although there has been criticism concerning patient adherence in the Tele-HF study, the incidences of the primary endpoint of all-cause mortality and the secondary endpoints of the composite of cardiovascular death and HF hospitalisation did not differ between the automated physiological monitoring group and the usual care group in the Telemedical Interventional Monitoring in Heart Failure (TIM-HF) study; nevertheless, the patient adherence to the telemonitoring intervention was acceptable.[16] Therefore, the ability of home telemonitoring for HF care to improve patient outcomes remains controversial.[17 18] The prospectively defined subgroup analysis of the TIM-HF study, which attempted to identify patients who may potentially benefit from telemonitoring, showed that treatment was significantly effective in the subgroup of patients with a prior history of HF decompensation, implantable cardiac defibrillator/cardioverter (ICD) implants or Patient Health Questionnaire (PHQ-9) scores of <10 for outcome days lost due to HF hospitalisation or death.[19]

## AIMS AND OBJECTIVES

In Japan, multidisciplinary HF management remains underdeveloped and there are few data regarding telemonitoring for HF management. Although Japan has a unique universal health insurance system, home telemonitoring for HF management has not been covered by the system except telemonitoring using implantable devices. Therefore, we aimed to investigate whether an HF management programme using a telemonitoring system consisting of automated physiological monitoring devices could reduce mortality and hospital readmission for acute decompensated HF among patients recently hospitalised for HF under the Japanese healthcare system.

Swedberg *et al*, in their correspondence to the authors of the Tele-HF study, suggested that patient-centred care (PCC) would increase the effectiveness of telemonitoring. They emphasised that telemonitoring needs to focus on patients' self-care instead of reporting data.[20 21] Therefore, we introduced the concept of PCC into the telemonitoring system used in the present study in order to motivate the patients assigned to the telemonitoring group to maintain adherence to daily measurement of body weight and blood pressure, to enhance clinician–patient communication and to empower patients in their self-management.

## METHODS AND ANALYSIS

### Study patients

Patients aged 20 or older with New York Heart Association functional classes II–III who are discharged or scheduled to be discharged following admission for acute HF or acute decompensated chronic HF within 30 days of enrolment into the study are eligible for this study (box 1). The exclusion criteria are as follows: patients with an implantable device (ie, pacemaker, ICD), because an alternating-current signal travels through the body when the patients measure their body weight and body fat using an electronic scale; patients undergoing dialysis or those with a serum creatine level ≥3.0 mg/dl; patients with severe liver dysfunction; patients with planned percutaneous coronary intervention or coronary artery bypass grafting; patients unable to stand on a scale safely; patients with a limited life

**Box 1 Inclusion criteria**

- Scheduled to discharge or discharged from an admission for acute heart failure (HF) or acute decompensated chronic HF within 30 days.
- Age ≥20 years.
- New York Heart Association functional classes II–III.

**Box 2** Exclusion criteria

- Patients with an implantable device (ie, pacemaker, implantable cardioverter defibrillator), because an alternating-current signal travels through the body when the patients measure their body weight and body fat using an electronic scale.
- Undergoing dialysis or serum creatine level ≥3.0 mg/dl.
- Severe liver dysfunction.
- Planned percutaneous coronary intervention or coronary artery bypass grafting.
- Unable to stand on a scale safely.
- Limited life expectancy (malignancy or other cause).
- Severe depression (eg, Patient Health Questionnaire score ≥20).
- Severe dementia.
- Pregnancy.
- Without access to a telephone line.

expectancy due to malignancy or other cause; patients in whom severe depression is highly suspected (eg, PHQ-9≥20); patients with severe dementia; in pregnancy; and patients without access to a telephone line (box 2). Patients suspected of having mild-to-moderate depression (eg, PHQ score: 5–19) are recommended to receive adequate intervention from a psychiatrist or clinical psychologist.

## Study design

The Home Telemonitoring Study for Japanese Patients with Heart Failure (HOMES-HF) is a multicentre, prospective RCT, funded by the Japanese Ministry of Health, Labor and Welfare (Clinical Trials registration number UMIN000006839; http://www.umin.ac.jp/ctr/index.htm) and conducted to compare automated physiological data monitoring with usual care. Written informed consent will be obtained by the patient's physician prior to discharge or within 30 days of hospital discharge after admission for acute HF or acute exacerbation of HF. Eligible patients are randomly assigned via a website to either the telemonitoring group or the usual care group by using a minimisation method with biased-coin assignment balancing on age (≥65 vs <65 years), left-ventricular ejection fraction (LVEF) (≥30% vs <30%), and having a history of ischaemic heart disease (IHD; IHD vs non-IHD). The patients and treating physicians are not masked to the treatments, while assessment of the outcome is masked. According to the study protocol, participants will be enrolled until August 2013 and followed until August 2014.

## Endpoints

The primary endpoint is a composite of all-cause death and rehospitalisation due to worsening HF. The secondary endpoints are: all-cause death; cardiac death; all-cause rehospitalisation; rehospitalisation due to a cardiovascular cause; rehospitalisation due to worsening HF; worsening of symptoms; cost of medical care; worsening of LVEF or the levels of N-terminal pro B-type natriuretic peptide, high-sensitivity C reactive protein, pentraxin-3 (PTX3), high-sensitivity cardiac troponin T or high-molecular weight adiponectin; changes in the Mini Mental State Examination (MMSE) score, the General Self Efficacy Scale (GSES), the Minnesota Living With Heart Failure (MLWHF) score or the PHQ-9 score and adherence to medication.

## Telemonitoring system

The telemonitoring system of the HOMES-HF study consists of an electronic scale, a sphygmomanometer and a device that receives acquired physiological data (blood pressure, pulse rate and body weight) wirelessly and transmits the data to the central web server via the internet. It is commercially available as a health-maintenance product (Karada Karte Tanita health-link Co. Ltd, Tokyo, Japan). These devices are distributed to the participants assigned to the telemonitoring group when they are discharged from the hospital. Patients' physicians encourage the participants assigned to the telemonitoring group, when they demonstrate how to use the monitoring devices after obtaining the informed consent, to measure their body weight and blood pressure by themselves at least once a day at approximately the same time in order to minimise daily variance caused by meals, micturition and bowel movement. The acquired physiological data are automatically transmitted to a central web server immediately after measurement. The telemonitoring centre was newly established at Saga University for the present study, and full-time nurses monitor the acquired data on the secure website 7 days a week (see online supplementary appendix 1). At first contact with the participant by telephone, the monitoring nurses establish communication connection between the monitoring devices and the central web server and arrange a time zone convenient to the participant for regular measuring. Before telemonitoring is started, the patient's physician determines an acceptable range of body weight, blood pressure and pulse rate for each patient and makes a declaration of these ranges to the telemonitoring centre. If the body weight, blood pressure or heart rate would exceed the acceptable range, the monitoring nurses serve a notice to the patient's physician. There are no restrictions on the ability of the patient's physician to perform any interventions in response to the notice, such as providing telephone guidance, changing or adding medications and ordering hospital readmission, with the exception that the physician must provide feedback regarding their interventions to the telemonitoing centre. The patient's physician assumes responsibility for acting on the information.

## Introducing the concept of PCC into the telemonitoring system to encourage adherence in participants

After hospital discharge, the patients and their family, especially among elderly persons, have a tendency to be

socially isolated, and that makes it difficult to practice self-management. In order to motivate the patients assigned to the telemonitoring group to maintain adherence to daily measurement of their body weight and blood pressure, the concept of PCC was proactively introduced into the telemonitoring system for the HOMES-HF study. Enhanced clinician–patient communication, patient empowerment and self-management are the elements of PCC.[22 23] To this end, professionals (typically nurses, although sometimes the patients' physicians) provide advice and education to the patients assigned to the telemonitoring group and create a care plan until the next visit referring to the patients' electronic health records acquired by daily monitoring on the website using a tablet computer in collaboration with the patients at every visit of theirs to the outpatient clinic. According to the protocol, the patients' physicians or nurses have to report to the monitoring centre what they performed for the patient according to the notice from the monitoring nurses. Moreover, we designed the monitoring system to be accessible to the patients' family in order for them to watch over their parents, spouse, siblings or relatives. In this way, we intend to enable the patients to recognise that all healthcare professionals around them and their family are not only monitoring on the website, but also communicating with each other. We believe that these efforts may help reassure patients and their family, as well as encourage them to participate in decision-making on their own treatment by collaborating with healthcare professionals and improve adherence to medical treatment.

### Usual care

Patients assigned to the usual care group are treated by their physician in accordance with the Japanese Circulation Society Guidelines for treatment of chronic HF 2010. Clinicians provide discharge education and encourage the patients to measure their body weight by themselves every day.

### Sample size calculation

We assumed that the HR of the primary endpoint (all-cause death and hospitalisation for worsening HF) of the telemonitoring group to the control group would be 0.60 and that the cumulative annual event rate in the usual care group would be 0.30, based on the result of previous studies.[10 13] This trial is designed to have 80% power to detect a 40% relative reduction in the risk of the primary outcome in the telemonitoring group within 12 months, as compared with the control group, based on an expected death rate at 12 months of 30% in the control group using a log-rank test with a two-sided $\alpha$ of 0·05. A total sample size of 420 patients is planned according to the Schoenfeld and Richter method,[24] with a 2-year period for patient enrolment and a follow-up period of 1 year.

### Statistical analysis

All statistical analyses will be independently performed at the Chiba University Hospital Clinical Research Center (see online supplementary appendix 2). The analyses of the adjudicated primary and secondary outcomes will be conducted using data for all patients who had undergone randomisation, according to the intention-to-treat principle. For the baseline variables, summary statistics will be constructed employing frequencies and proportions for categorical data and means and SD for continuous variables. The patient characteristics will be compared using Fisher's exact test for categorical outcomes and t tests for continuous variables, as appropriate. The primary endpoint of a composite of all-cause death and rehospitalisation for worsening HF will be analysed using the stratified log-rank test for eligible patients with age (≥65 vs <65 years), LVEF (≥30% vs <30%) and history of ischaemic heart disease (IHD vs non-IHD) as stratification factors. Time to events will be estimated using the Kaplan-Meier method, and HRs and 95% CIs will be calculated using the Cox proportional hazards models with stratification factors. Sensitivity analyses will also be performed by means of the unadjusted Cox models.

All comparisons are planned, and all p values will be two-sided. A p value of less than 0.05 will be considered to be statistically significant. All statistical analyses will be performed using SAS software V.9.3 (SAS Institute, Cary, North Carolina, USA).

### Data collection schedule

At the time each patient is enrolled into the study, investigators at each local site (see online supplementary appendix 6) perform a baseline history and physical examination and conduct a survey of the baseline scores of three types of questionnaires (PHQ-9, MMSE and GSES). The outcomes are assessed at 6 and 12 months after enrolment into the study. Clinicians at each local site submit a report to the data centre at these time points to assess psychosocial status, self-care skills, quality of life and rehospitalisations. We will evaluate the cost-effectiveness of the telemonitoring interventions, incorporating the costs associated with hospitalisations, outpatient visits, emergency department visits and home care services.

### Study management

Data on the primary and secondary endpoints and adverse events are collected when the events occur. All data are collected by the independent data management centre established for the present study at the Chiba University Hospital Clinical Research Center (see online supplementary appendix 2). There will be no direct communication between HOMES-HF investigators and the Coordinating Data Center. The clinical data entry (double data entry), cording, data management and reporting will be performed by a data management system, HITCANDIS/DM (HITachi Computer Assisted

New Drug Information System/Data Management for clinical trial, Hitachi, Ltd Tokyo, Japan). Trained coding specialists will code the clinical data using standard coding dictionaries including MedDRA for adverse events and medical history and considering WHO-DD for concomitant medications. All the data management processes are tracked electronically, allowing regular updates on patient status, data receipt including missing segments or pages, data entry and verification, data query status and protocol deviations. In order to ensure consistency, integrity and accuracy for this study, these processes are based on the standard operating procedures.

An independent endpoint committee (see online supplementary appendix 3) consisting of three members, who are blinded to any information relating to the group allocations, evaluates each event and classifies the results. An independent data and safety monitoring board (see online supplementary appendix 4) composed of three members reviews all reports from the endpoint committee to advise early termination of the study for safety, scientific or ethical reasons. A steering committee (see online supplementary appendix 5) is responsible for the study design and scientific execution of the study.

## Laboratory measurements

The plasma PTX3 levels are measured with a sandwich ELISA kit (Perseus Proteomics Inc, Tokyo, Japan) based on a previously described method.[25] The plasma HMW-adiponectin levels are measured using a sandwich ELISA kit (Fujirebio, Tokyo, Japan) based on a monoclonal antibody to human HMW-adiponectin, IH7.[26]

**Author affiliations**
[1]Department of Cardiovascular Medicine, Saga University, Saga, Japan
[2]Chiba University Hospital Clinical Research Center, Chiba University, Chiba, Japan
[3]Division of Cardiolovascular Medicine, Department of Molecular Medicine and Therapeutics, Tottori University, Yonago, Japan
[4]Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan
[5]Department of Cardiology, St. Luke's International Hospital, Tokyo, Japan
[6]Department of Cardiology, Saga Prefectural Hospital Koseikan, Saga, Japan
[7]Division of Cardiovascular Medicine, Saitama Medical Center, Jichi Medical University, Omiya, Japan
[8]Department of Medicine, Division of Cardiovascular Medicine, Jichi Medical University, Shimotsuke, Japan
[9]Department of Cardio-Angiology, Kitasato University School of Medicine, Sagamihara, Japan
[10]Department of Cardiovascular Medicine, Hokkaido University Graduate School of Medicine, Sapporo, Japan
[11]Cardiovascular Division, Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya, Japan
[12]Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, Suita, Japan
[13]Department of Cardiovascular Medicine, Dokkyo Medical University, Mibu, Japan
[14]Department of Cardiology, Nippon Medical School Chiba-Hokusoh Hospital, Inzai, Japan

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**Competing interests** All authors have completed the ICMJE form for disclosure of potential conflicts of interest at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that NK is currently an endowed chair from Fukuda Denshi Co., Ltd, which is a medical equipment manufacturer. The company has no relation to the monitoring equipment used in this study. All authors have no other relationships or activities that could appear to have influenced the submitted work.

**Ethics approval** All participants will provide their written informed consent, and the study protocol has been approved by the institutional review board of Saga University and each participating site.

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ORIGINAL ARTICLE

# Interrelation between myocardial oxidative metabolism and diastolic function in patients undergoing surgical ventricular reconstruction

**Satoru Chiba · Masanao Naya · Hiroyuki Iwano · Keiichiro Yoshinaga · Chietsugu Katoh · Osamu Manabe · Satoshi Yamada · Satoru Wakasa · Suguru Kubota · Yoshiro Matsui · Nagara Tamaki · Hiroyuki Tsutsui**

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**Abstract**
*Purpose* Diastolic function is impaired in patients with end-stage heart failure. Favorable structural changes by surgical ventricular reconstruction (SVR) are thought to improve diastolic function, however, previous studies reported the contradictory results. We hypothesized that cardiac oxidative metabolism and diastolic dysfunction might improve in parallel to the reduction of left ventricular chamber size after SVR.
*Methods* We studied 11 patients underwent SVR associated with mitral valve repair for end-stage heart failure due to dilated cardiomyopathy. Diastolic function was assessed by echocardiography and myocardial oxidative metabolism was measured by the monoexponential clearance (k-mono) of $^{11}$C-acetate positron emission tomography at baseline and 1 month after SVR.
*Results* All patients had preoperative severe diastolic dysfunction [E/A 4.11±1.18, deceleration time (DT) 134± 26 ms]. The study patients were divided into 2 groups according to the changes in diastolic function after SVR; unchanged or worsened diastolic function in 6 patients (55 %, Non-responder) and improved diastolic function in 5 (45 %, Responder). K-mono and wall stress decreased only in responder. The changes in k-mono before and after SVR correlated with those in deceleration time ($r$= –0.63; $p$< 0.05) and wall stress ($r$=0.75; $p$<0.01).
*Conclusions* Improvement of diastolic dysfunction in patients with end-stage heart failure by SVR was in parallel to that in oxidative metabolism. It suggests that SVR reduced excessive metabolism during the diastolic phase, in part, via the improvement in diastolic function and the reduction in LV wall stress.

**Keywords** Diastolic function · Heart failure · Oxidative metabolism · Wall stress · Surgical ventricular reconstruction

## Introduction

Not only systolic function but also diastolic function is severely impaired in patients with end-stage heart failure. The observational cohorts in heart failure patients with and without diastolic dysfunction show that the effects of diastolic dysfunction on cardiac death are as high as those of systolic dysfunction [1]. Surgical ventricular reconstruction (SVR) modifies spherical left ventricle (LV) shape into elliptical one and reduces chamber size and wall stress in left ventricle [2]. Although the appropriate morphological changes in LV by SVR are thought to improve LV diastolic function, previous clinical studies show the controversy about the effect of SVR [3]. The heterogeneous results are due to the complexity of etiologies of restrictive LV (LV wall stiffness and stress). For example, LV wall stiffness in patients with severely dilated LV is associated with massive scar burden and loss of viable myocardium. Elevated LV

S. Chiba · M. Naya (✉) · H. Iwano · S. Yamada · H. Tsutsui
Department of Cardiovascular Medicine, Hokkaido University Graduate School of Medicine, Kita-15, Nishi-7, Kita-ku, Sapporo 060-8638, Japan
e-mail: naya@med.hokudai.ac.jp

K. Yoshinaga · C. Katoh · O. Manabe · N. Tamaki
Department of Nuclear Medicine, Hokkaido University Graduate School of Medicine, Sapporo, Japan

S. Wakasa · S. Kubota · Y. Matsui
Department of Cardiovascular Surgery, Hokkaido University Graduate School of Medicine, Sapporo, Japan

wall stress is associated with large LV dimension, spherical shape, and volume overload with mitral regurgitation. Thus, SVR could improve the latter, but not the former. Another reason for the controversy may be the lack of information about the effects of SVR on myocardial metabolism in patients with restrictive LV. Beta-blocker therapy and cardiac resynchronized therapy can improve cardiac metabolism [4, 5]. If the reduction of LV chamber size is also effective on myocardial metabolism as well as LV diastolic function, these variables would change in parallel after SVR. We, thus, test the hypothesis that cardiac oxidative metabolism will decrease in patients whose diastolic dysfunction improve after SVR and that its potential mechanism may be the reduction of excessive energy loss during LV relaxation due to the improvement in diastolic dysfunction.

## Material and methods

### Study patients

Forty-one patients with end-stage HF undergoing overlapping left ventriculoplasty (OLVP) in our institution between June 2006 and January 2012 were prospectively enrolled in the study (Fig. 1). Nineteen had incomplete data acquisition (6 mechanical support before and/or after OLVP, 4 death, 1 incomplete echocardiography data, and 8 not consent to have a test). Eleven patients without severe diastolic dysfunction were excluded. Thus, the study population consisted of 11 patients with severe diastolic dysfunction. The

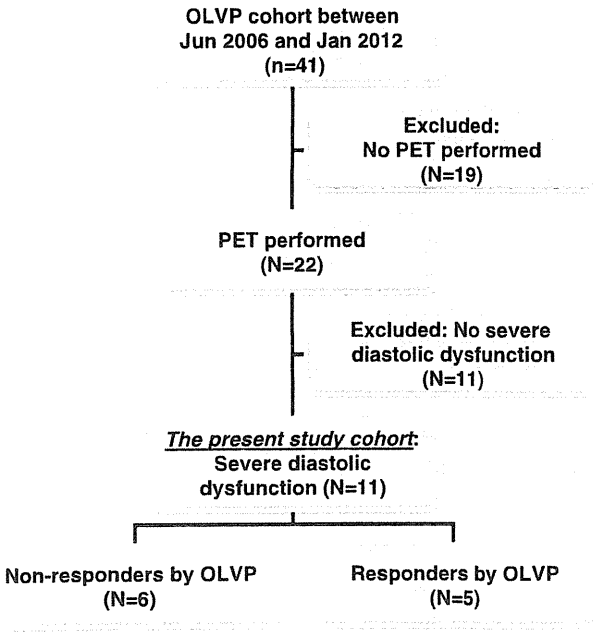


**Fig. 1** Flow chart of the SVR study cohort

study was approved by the institutional ethical committee and the procedures were in accordance with institutional guidelines. Informed consent was obtained from each study patient.

### Surgical techniques

We performed OLVP and its technique has been described previously in detail [6, 7]. It was combined with mitral complex reconstruction (MCR) [7], which included MV repair, such as papillary muscle approximation (PMA), papillary muscle suspension (PMS), and mitral annuloplasty (MAP) in the presence of mitral regurgitation (MR).

### Study protocol

Echocardiographic assessment and $^{11}$C-acetate PET were performed before and after the surgical procedures. Echocardiography and $^{11}$C-acetate PET was repeated in all patients (33± 10 days) after OLVP. All patients had MV repair (MAP in 11, PMA in 10, and PMS in 10) with OLVP. Six out of 11 patients had concomitant coronary artery bypass grafting.

### Echocardiography

Echocardiographic examination (Artida ultrasound system, Toshiba Medical Systems) was performed by experienced sonographers and experienced cardiologists. Left ventricular end-diastolic dimension (LVDd), Left ventricular end-systolic dimension (LVDs), end-diastolic posterior wall thickness (LVPWD), end-systolic posterior wall thickness (LVPWS) were measured. Left ventricular mean wall stress (WS) was calculated according to following formula: [8]

$$\mathrm{WS} = \text{systolic blood pressure} \times [(\mathrm{LVDd} + \mathrm{LVDs})/2 \times (\mathrm{LVPWD} + \mathrm{LVPWS})]$$

LV end-diastolic volume (EDV), end-systolic volume (ESV), and EF were measured from apical 2-chamber and 4-chamber views using the biplane method of disks. The LV shape was characterized by means of the sphericity index (SI), which is the ratio of the short axis to the long axis, and was calculated in systole and diastole [9].

Mitral regurgitation (MR) was classified as none (grade 0), mild (grade 1), moderate (grade 2), moderately severe (grade 3), and severe (grade 4) according to the AHA guideline [10]. The Doppler sample volume was placed at the tip of mitral valve leaflets, and a pulsed-wave Doppler recording was obtained. Early (E) and late (A) transmitral velocity as well as the deceleration time (DT) were measured and the early/late transmitral diastolic peak flow velocity (E/A) ratio was also calculated [11]. An echocardiographic assessment of LV diastolic function was classified into 4 categories: normal,

impaired relaxation, pseudo-normal, and restrictive filling pattern (RFP: severe diastolic dysfunction) [12–14].

After surgery, diastolic function was defined as improved (at least one class less), unchanged (no difference in diastolic pattern), or worsened (E/A ratio increase of at least 20 %) [15]. Patients with preoperative RFP were divided into two groups: patients with unchanged or worsened diastolic function (Non-responder) and patients with improved diastolic function (Responder) after OLVP. Definition of responder was based on the improvement of echocardiographic restrictive filling pattern after OLVP. Accordingly, E/A<2 and DT>140 ms were considered as responder. Definition of non-responder was based on the persistence of restrictive filling pattern defined as E/A>=2 or 0.75<E/A<2 plus DT<=140 ms after OLVP. This cut-off value was chosen from the previous studies by Bursi et al [14]. and Pozzoli et al [16].

Forward stroke volume (FSV) was derived from the velocity-time integral of the pulsed Doppler LV outflow tract velocity signal and the LV outflow tract diameter [7]. Forward stroke volume index (FSVI) was derived by dividing FSV by the body surface area (BSA). Cardiac output was calculated according to following formula: echocardiographic cardiac output = FSV × heart rate.

### $^{11}$C-acetate PET

PET was performed using a whole-body scanner (ECAT/EXACT HR+; Siemens/CTI, Knoxville, TN, USA). 740 MBq of $^{11}$C-acetate was administered intravenously for 60 s under resting conditions. Dynamic PET acquisition was performed (10×10 s, 1×60 s, 5×100 s, 3×180 s, 2×300 s) [17]. PET data analysis was performed using the dedicated software [17]. The images were iteratively reconstructed and were resliced along the short axis. Blood pressure and heart rate were monitored during PET scan to calculate a rate-pressure product. A mono-exponential function was fit to the myocardial time activity data, and the clearance rate constant (k-mono) was determined as described previously [7, 17]. Myocardial blood flow (MBF) was also calculated from $^{11}$C-acetate PET data [18].

### Myocardial efficiency

Myocardial efficiency (Work Metabolic Index) was assessed by effective (forward) work divided by myocardial oxygen consumption as follows; [4]

$$[\text{Systolic blood pressure} \times \text{heart rate} \times \text{FSV}] \div \text{BSA} \div \text{k-mono}.$$

We also computed another Work Metabolic Index to count for LV mass; [19]

$$\text{WMI}_{\text{LVM}} = (\text{Mean blood pressure} \times \text{heart rate} \times \text{FSV})/(\text{k-mono} \times \text{LV mass}).$$

### Statistical analysis

Data are expressed as mean ± standard deviation or percentages of patients. Differences were compared by Wilcoxon non-parametric test for Gaussian variable. The ratio between baseline and after OLVP was compared by $\chi^2$ test. $P<0.05$ was considered significant for all tests.

## Results

### Patient characteristics

Clinical characteristics, hemodynamics, and echocardiographic data are summarized in Tables 1 and 2. Mean age was 59 years and all were male. Mean NYHA functional class was 3.1 (91 % was class III or IV) and mean ejection fraction was 26 %. Etiologies of heart failure were ischemic in 6 patients and

**Table 1** Patient characteristics

| Variables | $n$=11 |
|---|---|
| Age (years) | 59±8 |
| Male, n (%) | 11 (100) |
| BSA ($m^2$) | 1.7±0.1 |
| BMI ($kg/m^2$) | 23±3 |
| Etiologies of heart failure | |
| Ischemic, n (%) | 6 (55) |
| Non-ischemic, n (%) | 5 (45) |
| Hypertension, n (%) | 2 (18) |
| Diabetes mellitus, n (%) | 5 (45) |
| Dyslipidemia, n (%) | 6 (55) |
| Smoking, n (%) | 10 (91) |
| Medications | |
| ACEI/ARB, n (%) | 8 (73) |
| Beta blocker, n (%) | 9 (82) |
| Diuretics, n (%) | 11 (100) |
| Spironolactone, n (%) | 7 (64) |
| Digitalis, n (%) | 2 (18) |
| Nitrate, n (%) | 4 (36) |
| Amiodarone, n (%) | 2 (18) |
| Dobutamine, n (%) | 1 (9) |
| Carperitide, n (%) | 1 (9) |
| Device implantation | |
| CRT-D, n (%) | 1 (9) |

*BSA* body surface area, *BMI* body mass index, *ACEI* ACE inhibitor, *ARB* angiotensin-receptor blocker, *CRT-D* cardiac resynchronization therapy with defibrillator

**Table 2** Effects of OLVP on NYHA functional class, hemodynamic parameters, echocardiographic parameters, and oxidative metabolism

| | Baseline | After OLVP | P |
|---|---|---|---|
| NYHA | 3.1±0.5 | 1.5±0.5 | <0.001 |
| NYHA 3 or 4, n (%) | 10 (91) | 0 (0) | <0.001 |
| Hemodynamic parameters | | | |
| HR (/min) | 70±12 | 84±14 | <0.01 |
| SBP (mmHg) | 99±20 | 101±15 | 0.71 |
| Echocardiographic parameters | | | |
| EDV (mL) | 324±93 | 201±70 | <0.01 |
| ESV (mL) | 241±71 | 160±72 | <0.01 |
| EF (%) | 26.0±6.6 | 30.3±5.7 | 0.14 |
| FSVI (ml/m$^2$) | 26.9±9.7 | 31.8±10.6 | 0.08 |
| MR grade | 3.3±0.9 | 0.3±0.5 | <0.001 |
| PASP (mmHg) | 55.2±8.4 | 45.9±12.7 | 0.06 |
| IVC (mm) | 18.6±3.4 | 17.3±3.9 | 0.31 |
| E/A | 4.11±1.18 | 2.87±1.16 | 0.09 |
| DT (ms) | 134±26 | 179±35 | <0.05 |
| WS (g/cm$^2$) | 316±91 | 277±66 | <0.05 |
| LAD (mm) | 59.2±7.6 | 56.4±6.8 | <0.01 |
| SI systole | 0.61±0.13 | 0.62±0.13 | 0.63 |
| PET measures | | | |
| k-mono (/min) | 0.049±0.006 | 0.048±0.006 | 0.97 |
| MBF (mL/g/min) | 0.57±0.76 | 0.60±0.22 | 1.00 |
| WMI×10$^6$ (mmHg· mL/m$^2$) | 3.90±1.47 | 5.58±1.88 | <0.01 |
| $WMI_{LVM}$×10$^3$ (mmHg· mL· g$^{-1}$) | 12.2±4.6 | 19.5±7.3 | <0.01 |

*NYHA* New York heart association functional class, *SBP* systemic blood pressure, *HR* heart rate, *EDV* end-diastolic volume, *ESV* end-systolic volume, *EF* ejection fraction, *FSVI* forward stroke volume index, *MR* mitral regurgitation, *PASP* pulmonary artery systolic pressure, *IVC* inferior vena cava diameter, *LAD* left atrial diameter, *SI* sphericity index, *WS* LV mean wall stress, *E/A* early/late transmitral diastolic peak flow velocity ratio, *DT* deceleration time of E wave, k-mono: myocardial clearance rate constant, *MBF* myocardial blood flow, *WMI* work metabolic index

non-ischemic in 5 patients. All patients received the standard pharmacological treatment including ACE inhibitors, angiotensin receptor blockers, and diuretics.

## Effects of OLVP

The effects of OLVP on clinical variables are shown in Table 2. The improvement in NYHA functional class was observed in all patients ($p<0.001$). The prevalence of patients in NYHA functional class III–IV decreased from 91 % to 0 %.

OLVP significantly decreased ESV ($p<0.01$) and LV wall stress ($p<0.05$). ESV did not dilate from 1 month to chronic phase between 6 months and 12 months after OLVP [ESV 175± 89 mL to 119±26 mL; $p=0.25$, $n=5$]. Cardiac output significantly increased from 3.1±0.9 to 4.2±1.5 L/min·m$^2$ after OLVP ($p<0.01$). LV ejection function slightly increased, which, however, did not reach statistical significance. Severe mitral regurgitation disappeared. The change in E/A was only modest. DT significantly prolonged by 34 % ($p<0.05$). FSV index tended to increase while k-mono did not change ($p=0.97$), which was associated with increase in work metabolic index ($p<0.01$). MBF did not change after operation ($p=1.00$).

When we compared the changes in clinical variables between patients with ($n=11$) and without ($n=11$) severe diastolic dysfunction, there were no significant variables between groups. We further determined the effects of OLVP on echocardiographic diastolic parameters. The study was divided into two groups according to the diastolic function at 1 month after SVR: 6 patients (55 %) with unchanged (36 %) or worsened (18 %) diastolic function (Non-responder) and 5 (45 %) with improved diastolic function (Responder) after OLVP. Etiologies of heart failure was ischemic ($n=4$) and non-ischemic ($n=2$) for non-responder, and ischemic ($n=2$) and non-ischemic ($n=3$) for responder.

Only MBF was significantly higher in responder than in non-responder (1.23±0.98 mL/g/min vs 0.42±0.11 mL/g/min, $p<0.05$) among baseline parameters. There were no differences in preoperative k-mono, EDV, ESV, MR grade, FSVI, LVEF, WMI, NYHA, E/A, DT, LV wall stress, and sphericity index between the two groups. After OLVP, ESV was significantly decreased ($p<0.01$) and the degree of changes (delta ESV: −80 mL) was similar between 2 groups (Fig. 2a). As expected, the increase in DT was significantly greater in responders than non-responders (74.2±23.5 versus 19.7±44.4; $p<0.05$)(Fig. 2c). The changes in LV wall stress (ΔWS) in responders was greater than non-responders (Fig. 2d) as did that in k-mono (Δk-mono) (Fig. 2e). Work metabolic index increased in both groups (Fig. 2f). The changes in WMI and $WMI_{LVM}$ were not significantly different between responder and non-responder.

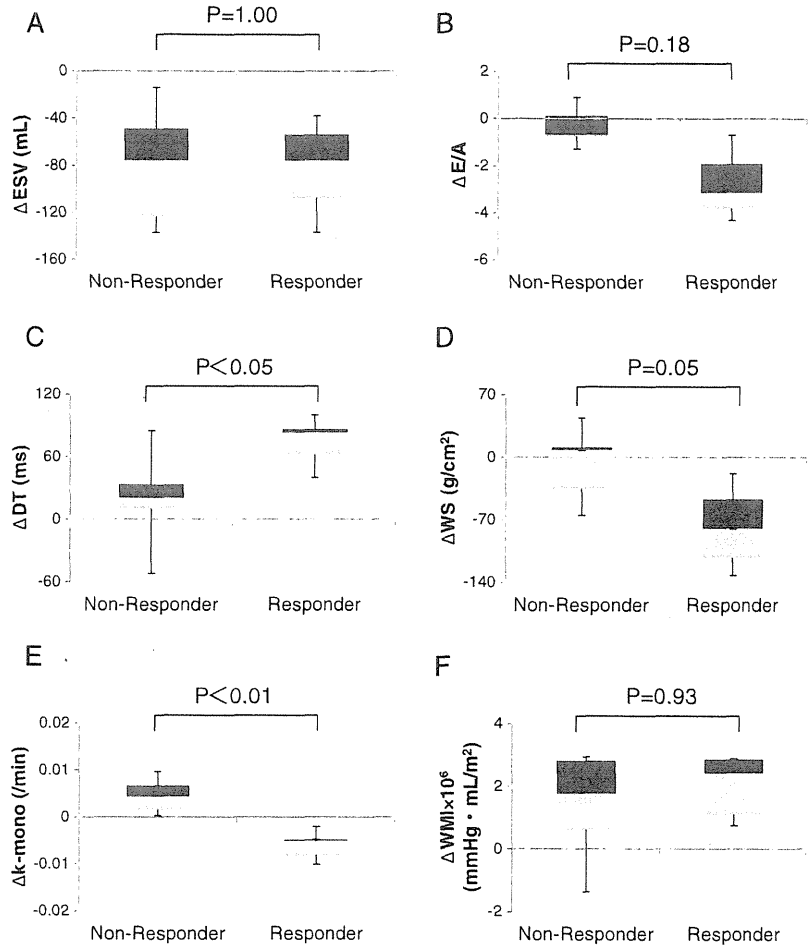


**Fig. 2** Comparison of non-responders ($n$=6) versus responders ($n$=5) in the changes from baseline to postoperative data. **a** End-systolic volume (ESV), **b** E/A, **c** Deceleration time (DT), **d** LV wall stress (WS), **e** k-mono, **f** Work metabolic index (WMI)

Regarding outcome, four patients of 11 (36 %) died in all patients with severe diastolic dysfunction. One of 5 (20 %) died in responder, and 3 of 6 (50 %) died in non-responder, during the follow up (1,391±1,180 days).

Univariate regression analysis confirmed the changes in LV wall stress (ΔWS) after OLVP negatively correlated with those in DT (ΔDT) ($r$=–0.65, $P$<0.05). Likewise, the significant relationship was observed between Δk-mono and ΔDT (Fig. 3a) or ΔWS (Fig. 3b). ΔDT positively correlated with ΔFSVI ($r$=0.71, $p$< 0.05). ΔCardiac output by OLVP did not correlate with Δk-mono ($r$=0.085, $p$=NS). Likewise, ΔLVEF and ΔFSVI did not correlate with Δk-mono ($r$=0.033, $p$=NS and $r$=–0.37, $p$=NS, respectively). ΔMBF did not correlate with delta in any parameters.

## Discussion

The present study demonstrated that a half of patients with severe dilated cardiomyopathy were responders for OLVP in terms of diastolic function. In these responders, oxidative metabolism significantly decreased, suggesting the interrelation between cardiac metabolism and diastolic function in heart failure.

### Effects of SVR on diastolic function

In patients with severe dilated cardiomyopathy, decreased LV compliance is common and has been shown to be associated with symptoms and outcomes [12]. E/A and DT, reflecting diastolic function, are more sensitive to evaluate these abnormalities than systolic function in this population [20]. Our data demonstrated that a half of patients had improvement in DT and E/A after OLVP, suggesting that these patients were thought to be responders of intensive surgical treatment. The proportion of responders by SVR in diastolic dysfunction is consistent with the prior studies [15]. However, there are some advantages in our OLVP in combination with MCR. Unlike Dor and SAVE procedures, no use of patches in our OLVP procedure may have an advantage for improvement in diastolic function. LV diastolic function is impaired after tetralogy of Fallot repair probably due to the use of ventricular septal defect patch [21] and that surgical anterior ventricular restoration with stiff patch increased the LV stiffness compared to no use of patch in the dilated LV [22]. These studies support the superiority of our procedural concept. In addition, MCR could

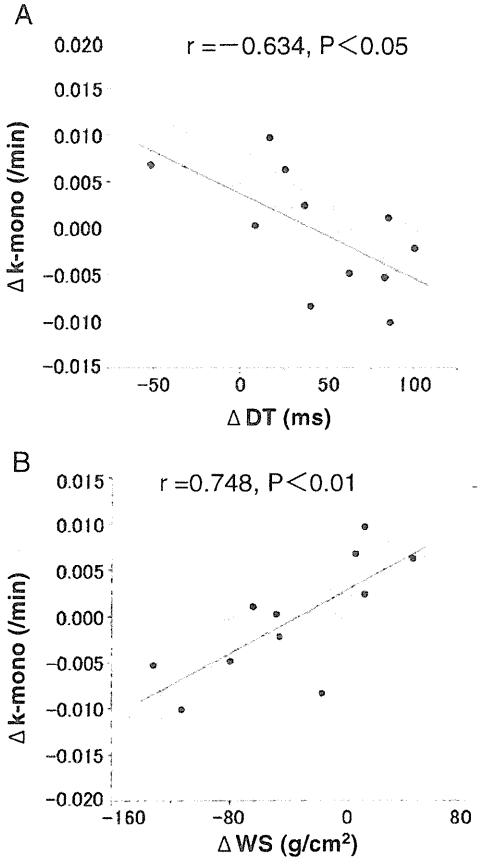


**Fig. 3** Correlation between Δk-mono and ΔDT (**a**) or ΔWS (**b**)

prevent LV from remodeling because this procedure theoretically shortens circumferential LV dilation and reduces volume overload by correction of mitral regurgitation [23, 24]. In fact, the previous study and ours demonstrated that adequate reduction of LV volume is associated the improvement in heart failure symptom and outcome [25].

## Interaction between diastolic function and myocardial oxygen metabolism

There is little information about the interrelation between diastolic function and cardiac metabolism except the study by Meyer et.al showing that elevated LV stiffness is correlated with peak oxygen consumption [26]. Although LV oxidative metabolism is reduced in advanced heart failure with extensive scar myocardium [27], the present study further demonstrated that the oxidative metabolism could be influenced by OLVP in patients with severe diastolic dysfunction and that the metabolic changes was observed in parallel with the changes in wall stress and diastolic function. The studies by Meyer et al and ours suggest that diastolic dysfunction may be the potential determinant of oxidative metabolism in addition to heart rate, wall stress, and contractility [28]. However, the changes in systolic function by OLVP did not correlate with those in LV oxidative metabolism, rather wall stress had a greater effect on LV oxidative metabolism only in responder. 91 % of patients, which had moderate to severe MR had been treated with MV surgery in this study. Chow et.al reported MV surgery did not change k-mono [29], because MR loaded a volume, but not a pressure. Some explanation that diastolic dysfunction is associated with increasing cardiac metabolism might be provided. In histopathologic studies, sarcomere loss and myocardial fibrosis were observed in the segments with dysfunctional but viable myocardium. The presence of sarcomere loss and fibrosis prevent functional recovery after revascularization [30]. In fact, non-responders in terms of diastolic function had no changes in oxidative metabolism. Other factor which influences metabolism is LV wall stress. This is also demonstrated in the present study that wall stress tended to decrease and k-mono significantly decreased in responders, but not in non-responders. Although we did not examine the variables to help select responders by OLVP in terms of diastolic function, this information and the relation between responders and outcome should be further examined.

## Study limitations

First, The number of patients is too small to draw the definite conclusions. Further studies are clearly needed. Second, there was no control group for patients without use of patches, who were treated with SVR, therefore, it is difficult to directly compare the LV diastolic dysfunction in patients treated with and without use of patches. Third, the population was mixed including ischemic and non-ischemic heart failure because patients with non-ischemic heart failure are prevalent in Japan. Forth, we recognize that early changes in diastolic function and oxidative metabolism may not direct lead to an improved clinical outcome.

## Conclusion

The present study demonstrated that a half of patients with severe dilated cardiomyopathy were responders for OLVP in terms of diastolic function. In these responders, oxidative metabolism significantly decreased, suggesting that OLVP reduced excessive metabolism during the diastolic phase, in part, via the improvement in diastolic function as well as the reduction in LV wall stress.

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**Conflicts of interest** None.

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LATE BREAKING CLINICAL TRIAL (JCS 2013)

# Urgent Management of Rapid Heart Rate in Patients With Atrial Fibrillation/Flutter and Left Ventricular Dysfunction

## – Comparison of the Ultra-Short-Acting β1-Selective Blocker Landiolol With Digoxin (J-Land Study) –

Ryozo Nagai, MD, PhD; Koichiro Kinugawa, MD, PhD; Hiroshi Inoue, MD, PhD; Hirotsugu Atarashi, MD, PhD; Yoshihiko Seino, MD, PhD; Takeshi Yamashita, MD, PhD; Wataru Shimizu, MD, PhD; Takeshi Aiba, MD, PhD; Masafumi Kitakaze, MD, PhD; Atsuhiro Sakamoto, MD, PhD; Takanori Ikeda, MD, PhD; Yasushi Imai, MD, PhD; Takashi Daimon, PhD; Katsuhiro Fujino, MSc; Tetsuji Nagano, MSc; Tatsuaki Okamura, MSc; Masatsugu Hori, MD, PhD; the J-Land Investigators

***Background:*** A rapid heart rate (HR) during atrial fibrillation (AF) and atrial flutter (AFL) in left ventricular (LV) dysfunction often impairs cardiac performance. The J-Land study was conducted to compare the efficacy and safety of landiolol, an ultra-short-acting β-blocker, with those of digoxin for swift control of tachycardia in AF/AFL in patients with LV dysfunction.

***Methods and Results:*** The 200 patients with AF/AFL, HR ≥120 beats/min, and LV ejection fraction 25–50% were randomized to receive either landiolol (n=93) or digoxin (n=107). Successful HR control was defined as ≥20% reduction in HR together with HR <110 beats/min at 2 h after starting intravenous administration of landiolol or digoxin. The dose of landiolol was adjusted in the range of 1–10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ according to the patient's condition. The mean HR at baseline was 138.2±15.7 and 138.0±15.0 beats/min in the landiolol and digoxin groups, respectively. Successful HR control was achieved in 48.0% of patients treated with landiolol and in 13.9% of patients treated with digoxin (P<0.0001). Serious adverse events were reported in 2 and 3 patients in each group, respectively.

***Conclusions:*** Landiolol was more effective for controlling rapid HR than digoxin in AF/AFL patients with LV dysfunction, and could be considered as a therapeutic option in this clinical setting. (*Circ J* 2013; **77:** 908–916)

**Key Words:** Atrial fibrillation; Atrial flutter; β-blocker; Landiolol; Left ventricular dysfunction

Atrial fibrillation (AF) and atrial flutter (AFL) are common arrhythmias in patients with left ventricular (LV) dysfunction. Over 20% of patients with heart failure exhibit AF.[1,2] In these patients, AF/AFL are often associated with a rapid ventricular response during the worsening of heart failure.[3,4] However, a sustained rapid ventricular response may

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Jichi Medical University, Shimotsuke (R.N.); Department of Cardiovascular Medicine, University of Tokyo Graduate School of Medicine, Tokyo (K.K., Y.I.); The Second Department of Internal Medicine, University of Toyama, Graduate School of Medicine, Toyama (H.I.); Department of Internal Medicine, Nippon Medical School Tama-Nagayama Hospital, Tokyo (H.A.); Department of Cardiology, Nippon Medical School Chiba-Hokusoh Hospital, Chiba (Y.S.); The Cardiovascular Institute, Tokyo (T.Y.); Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, Suita (W.S., T.A., M.K.); Department of Anesthesiology, Nippon Medical School, Tokyo (A.S.); Department of Cardiovascular Medicine, Toho University Faculty of Medicine, Tokyo (T.I.); Department of Biostatistics, Hyogo College of Medicine, Nishinomiya (T.D.); Ono Pharmaceutical Co Ltd, Osaka (K.F., T.N., T.O.); and Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka (M.H.), Japan

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The first seven authors contributed equally to this clinical trial (R.N., K.K., H.I., H.A., Y.S., T.Y., W.S.).

The members of the J-Land study group are listed in the Appendix.

Clinical Trial Registration: JapicCTI-111448 (http://www.clinicaltrials.jp/user/ctiMenu.jsp).

Mailing address: Masatsugu Hori, MD, PhD, Osaka Medical Center for Cancer and Cardiovascular Diseases, 1-3-3 Nakamichi, Higashinari-ku, Osaka 357-8511, Japan. E-mail: hori-ma@mc.pref.osaka.jp

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