(cGMP)-dependent manner [23]. DPP-4 inhibitors increase the levels of GLP-1, possibly leading to vasodilatation and blood pressure reduction. In addition, Gutzwiller et al. [24] showed that a pharmacological dose of GLP-1 increases sodium excretion in the proximal renal tubule in obese and insulin-resistant men. Therefore, GLP-1-induced increases in urinary sodium excretion might also contribute to blood pressure reduction after sitagliptin treatment.

In our study, serum levels of TC and TG also decreased after 3 months of treatment with sitagliptin. Qin et al. [25] showed that GLP-1 decreases the intestinal lymph flow and reduces triglyceride absorption and apo B and apo A-IV production in rats. Vildagliptin, another DPP-4 inhibitor, has been shown to reduce the hepatic expression of genes important for cholesterol synthesis, including phosphomevalonate kinase and mevalonate decarboxylase in wild-type mice [26]. Prolonged DPP-4 inhibition modulates the expression of genes important for fatty acid oxidation, including acyl-coenzyme dehydrogenase medium chain and Acyl-CoA synthetase. In addition, DPP-4 inhibitors reduce the levels of hepatic mRNA transcripts for acetyl coenzyme A acyltransferase 1 and carnitine palmitoyltransferase 1, independent of incretin receptor actions [26]. Because these modulations depend on and/or are independent of incretin receptor actions, sitagliptin may have the ability to decrease the levels of TC and TG.

QOL and diabetes

QOL, whose evaluation is the major goal of our study, is improved after sitagliptin treatment. The sleep quality and PSQI scores decreased after 12 months of treatment with sitagliptin. Particularly, in the subgroup of poor sleepers with PSQI scores above 5.5 points, the scores were significantly reduced not only after 12 months of treatment, but also after 3 months of treatment. Sleep disorders are common in patients with diabetes. Sleep debts decrease carbohydrate tolerance and insulin resistance and increase sympathetic tone, cortisol levels, and nocturnal catecholamine levels [27,28]. Improving sleep disorders with sitagliptin therapy might improve these states, possibly preventing cardiovascular disease in patients with T2DM.

Our own QOL assessment scores for diabetes, the Diabetes Symptomatic Scores, also decreased after sitagliptin treatment. Particularly, the scores regarding urinary frequency and paresthesia of the extremities significantly decreased 12 months after sitagliptin treatment. Urinary frequency, which often appears in T2DM patients, is caused by hyperglycemia-induced polyposia and/or neurogenic bladder. We suppose that polypepsia and polyposia are improved by reductions in FPG after sitagliptin treatment, thereby decreasing the urinary frequency. Paresthesia of the extremities is characterized by striking atrophy and/or loss of myelinated and unmyelinated fibers [29]. Hyperglycemia leads to the development of macrovascular and endoneural microvascular disease in diabetic nerve tissue via several mechanisms, including the polyol pathway. We suppose that both reductions of FPG and vasodilatation, a direct action of DPP-4 inhibitors, leads to improved nerve blood flow and nerve fiber damage in patients with diabetic neuropathy.

The EQ-5D score represents an independent predictor of mortality and future cardiovascular events in patients with T2DM [30]. In our study, however, the EQ-5D scores did not change after treatment with sitagliptin. Because the EQ scores before sitagliptin treatment were as high as 0.84 points, which is close to the cut-off point for a healthy state, they might not change significantly after sitagliptin treatment.

Limitations/clinical implications

This was a preliminary, single-arm study of a small number of subjects. A large-scale, randomized study conducted over a longer period is needed in the future. However, we found that sitagliptin exerts significant effects, not only on glycemic control, but also on improving QOL, blood pressure, and lipid profiles in subjects with T2DM. Although our results showed efficacy of the drug, we could not precisely evaluate subjects' adherence to their dosing regimens. As far as we know, there is no reported data on patient adherence to DPP-4 inhibitor treatment regimes. However, adherence to a drug taken once a day is supposed to be higher than conventional drugs taken two or three times a day, which may affect efficacy. In this study, the subjects whose rates of adherence were less than 75% were to be reported as "poor adherence"; all evaluated patients had good adherence to the dosing regimen.

In this study, treatment with sitagliptin achieved adequate reductions in the levels of HbA1c and significant increases in the rate of accomplishment of glycemic control. The use of sitagliptin was shown to be safe and improved the PSQI and Diabetes Symptomatic scores.

Conclusions

The clinical use of the DPP-4 inhibitor sitagliptin has beneficial effects not only for glucose control, but also for improving blood pressure, lipid profiles, and QOL regarding sleep quality and diabetes symptoms in addition to being safe with a high rate of adherence to treatment.

Abbreviations

1.5-AG, 1.5-anhydro-D-glucitol; α-GI, α-glucosidase inhibitors; BMI, Body mass index; BW, Body weight; CGM, Continuous glucose monitoring; DPP-4, Dipeptidyl peptidase-4; EQ-5D, Euro QOL-5 dimensions; EQ-VAS, EQ-visual analogue scale; FPG, Fasting plasma glucose; GI, Gastrointestinal; GLP-1, Glucagon-like peptide-1; GIP, Glucose-dependent insulinotropic polypeptide; HDL-C, High density lipoprotein cholesterol; LDL-C, Low density lipoprotein cholesterol; NGSP, National Glycohemoglobin Standardization Program; PSQI, Pittsburgh Sleep Quality Index; QOL, Quality of life; TC, Total cholesterol; TG, Triglycerides; T2DM, Type 2 diabetes mellitus; TZD, Thiazolidinediones; SUs, Sulfonylureas

Competing interest

The authors declare that they have no conflicts of interest.

Authors' contributions

YS, JO, MS, TI, HI, KK, AH, and KN were deeply involved in the conception and design of the study. JO was responsible for the analyses of the data. YS drafted the manuscript. All authors read and approved the final manuscript.

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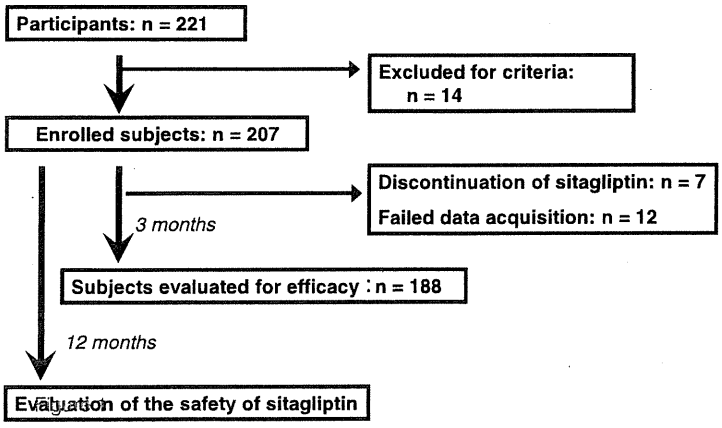
Participants: n = 221
Excluded for criteria:
n = 14
Enrolled subjects: n = 207
Discontinuation of sitagliptin: n = 7
Failed data acquisition: n = 12
3 months
Subjects evaluated for efficacy : n = 188
12 months
Evaluation of the safety of sitagliptin

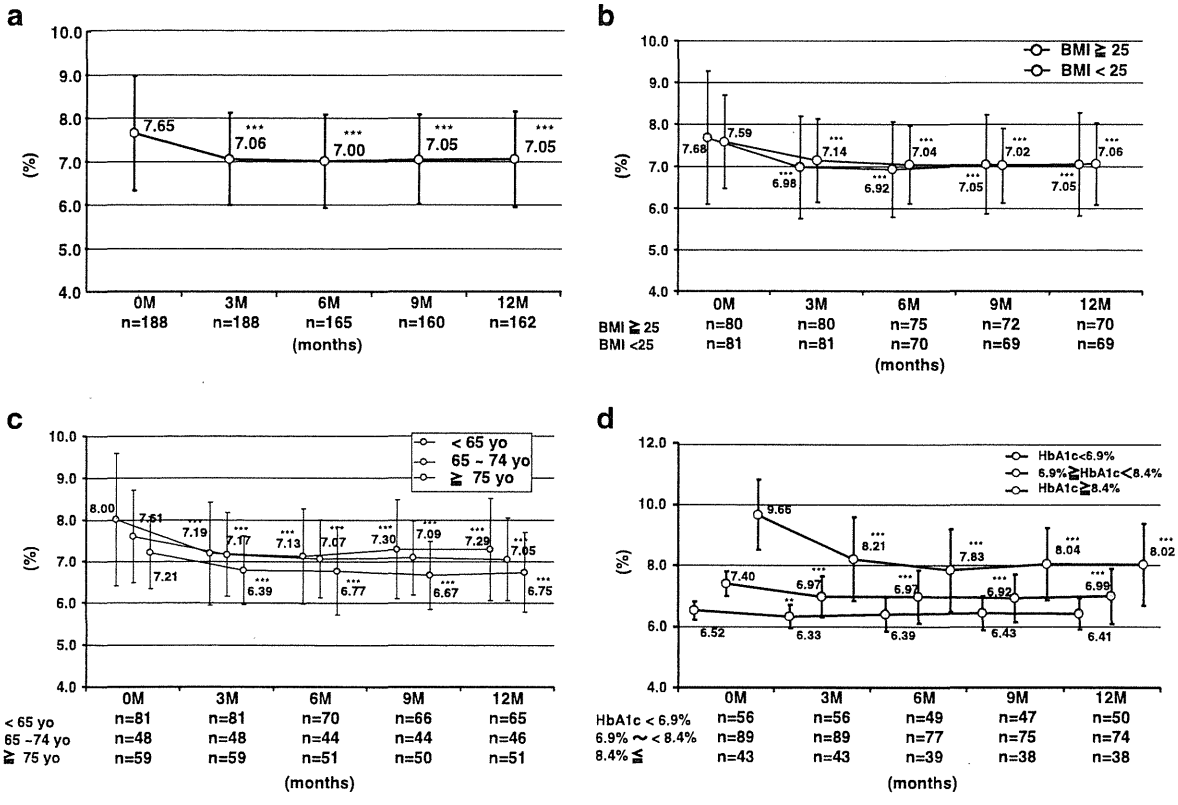
a
(%)
7.65
7.06
7.00
7.05
7.05
0M n=188
3M n=188
6M n=165
9M n=160
12M n=162
(months)
b
BMI ≧ 25
BMI < 25
7.68
7.59
6.98
7.14
6.92
7.04
7.05
7.02
7.05
7.06
BMI ≧ 25 n=80 n=80 n=75 n=72 n=70
BMI <25 n=81 n=81 n=70 n=69 n=69
(months)
c
< 65 yo
65 ~ 74 yo
≧ 75 yo
8.00
7.61
7.21
7.19
7.17
6.39
7.13
7.07
6.77
7.30
7.09
6.67
7.29
7.05
6.75
< 65 yo n=81 n=81 n=70 n=66 n=65
65 -74 yo n=48 n=48 n=44 n=44 n=46
≧ 75 yo n=59 n=59 n=51 n=50 n=51
(months)
d
HbA1c<6.9%
6.9%≦HbA1c<8.4%
HbA1c≧8.4%
9.66
8.21
7.40
6.97
6.52
6.33
5.97
6.39
7.83
6.92
6.43
8.04
6.99
6.41
8.02
HbA1c < 6.9% n=56 n=56 n=49 n=47 n=50
6.9% ~ < 8.4% n=89 n=89 n=77 n=75 n=74
8.4% ≦ n=43 n=43 n=39 n=38 n=38
(months)
e
(mg/dL)
145
129
125
132
129
0M n=84
3M n=84
6M n=62
9M n=64
12M n=65
(months)

Figure 2

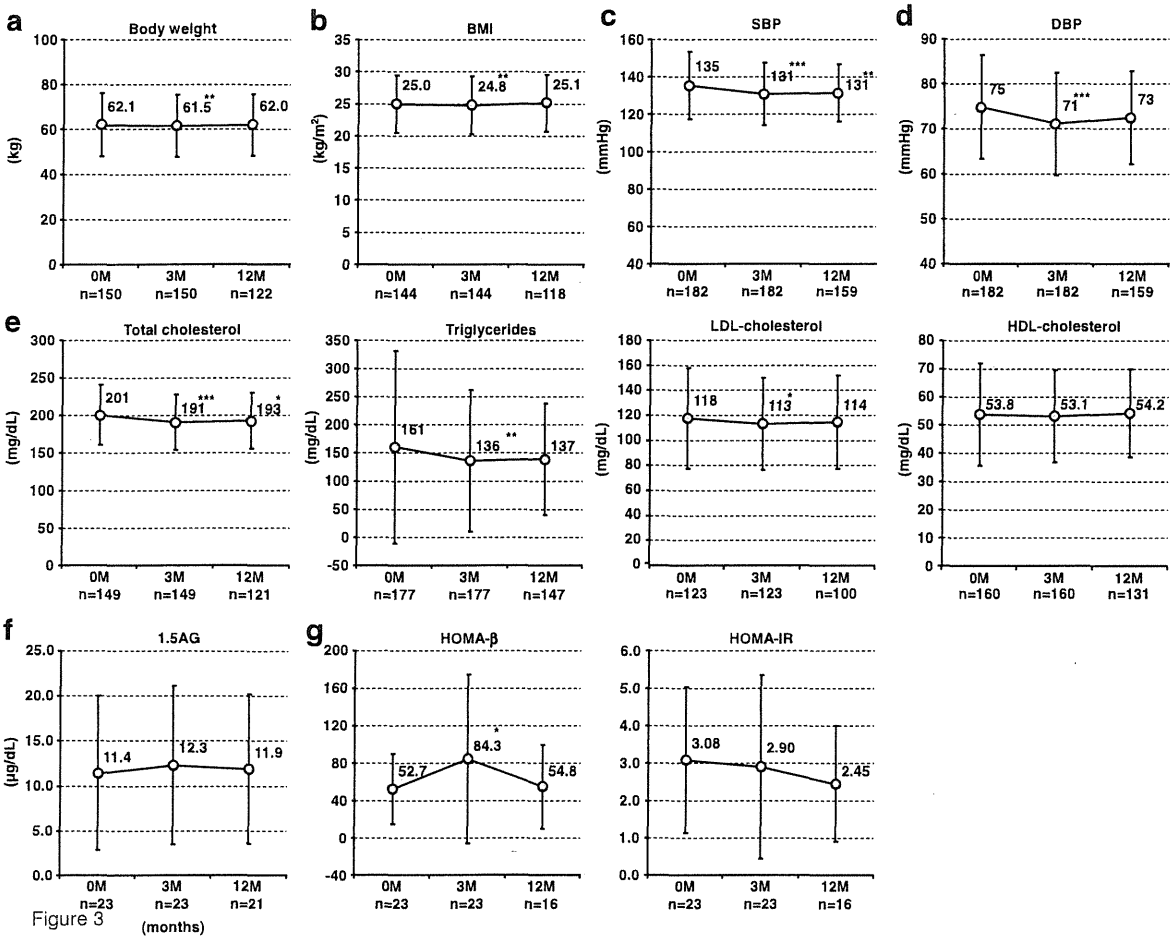
a
Body weight
(kg)
62.1
61.5
62.0
0M n=150
3M n=150
12M n=122
b
BMI
(kg/m²)
25.0
24.8
25.1
0M n=144
3M n=144
12M n=118
c
SBP
(mmHg)
135
131
131
0M n=182
3M n=182
12M n=159
d
DBP
(mmHg)
75
71
73
0M n=182
3M n=182
12M n=159
e
Total cholesterol
(mg/dL)
201
191
193
0M n=149
3M n=149
12M n=121
Triglycerides
(mg/dL)
151
136
137
0M n=177
3M n=177
12M n=147
LDL-cholesterol
(mg/dL)
118
113
114
0M n=123
3M n=123
12M n=100
HDL-cholesterol
(mg/dL)
53.8
53.1
54.2
0M n=160
3M n=160
12M n=131
f
1.5AG
(μg/dL)
11.4
12.3
11.9
0M n=23
3M n=23
12M n=21
(months)
g
HOMA-β
52.7
84.3
54.8
0M n=23
3M n=23
12M n=16
HOMA-IR
3.08
2.90
2.45
0M n=23
3M n=23
12M n=16

Figure 3

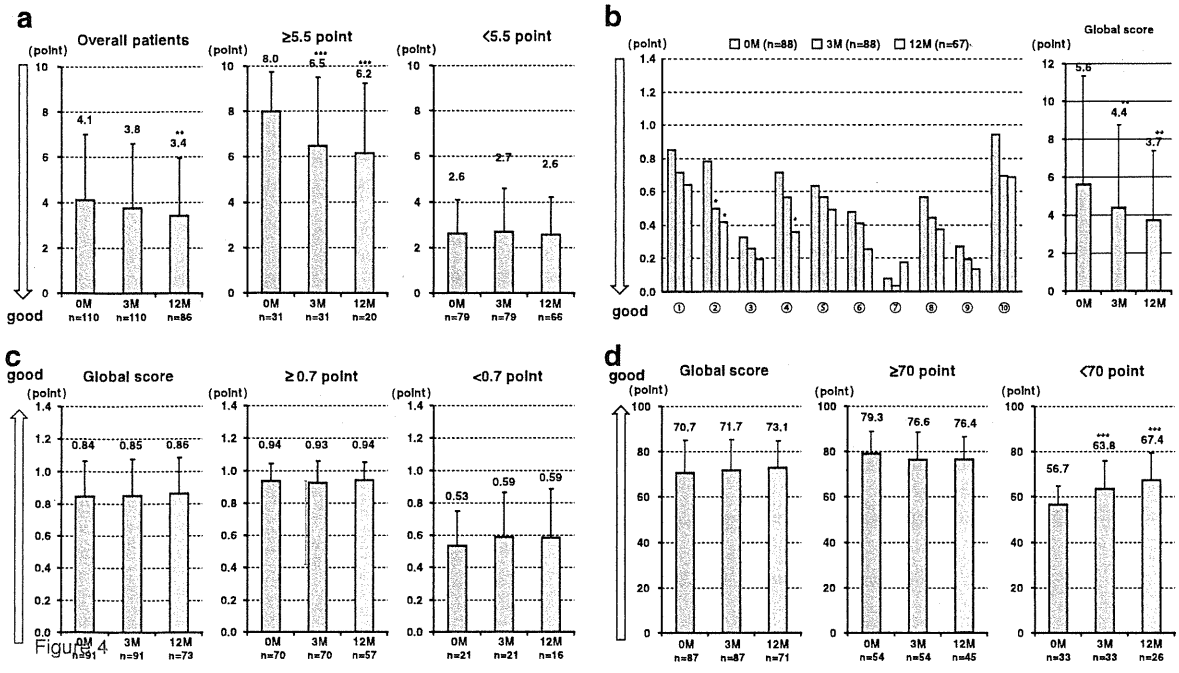
a
Overall patients
≥5.5 point
<5.5 point
(point)
good
4.1
3.8
3.4
8.0
6.5
6.2
2.6
2.7
2.6
0M n=110
3M n=110
12M n=86
0M n=31
3M n=31
12M n=20
0M n=79
3M n=79
12M n=66
b
0M (n=88)
3M (n=88)
12M (n=67)
Global score
5.6
4.4
3.7
c
Global score
≥0.7 point
<0.7 point
0.84
0.85
0.86
0.94
0.93
0.94
0.53
0.59
0.59
0M n=91
3M n=91
12M n=73
0M n=70
3M n=70
12M n=57
0M n=21
3M n=21
12M n=16
d
Global score
≥70 point
<70 point
70.7
71.7
73.1
79.3
76.6
76.4
56.7
63.8
67.4
0M n=87
3M n=87
12M n=71
0M n=54
3M n=54
12M n=45
0M n=33
3M n=33
12M n=26

Figure 4

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LATE BREAKING CLINICAL TRIAL (JCS 2013)

Effects of Pitavastatin in Japanese Patients With Chronic Heart Failure

– The Pitavastatin Heart Failure Study (PEARL Study) –

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on behalf of the PEARL Study Investigators

Background: Recent clinical trials using rosuvastatin, a hydrophilic statin, did not show beneficial effects on cardiovascular events in patients with heart failure. We examined the cardioprotective effects of pitavastatin, a lipophilic statin, on Japanese patients with chronic heart failure (CHF).

Methods and Results: A total of 574 Japanese patients with CHF were randomly assigned to the pitavastatin group (n=288) or the control group (n=286). There was no significant difference between the 2 groups for the primary outcome, which was a composite of cardiac death and hospitalization for worsening HF (adjusted hazard ratio (aHR): 0.922, 95% confidence interval (CI): 0.632–1.345, P=0.672). A strongly significant statistical interaction between the effect of pitavastatin and left ventricular ejection fraction (LVEF) was found (P=0.004). In patients with LVEF ≥30%, a significant reduction in the primary outcome (aHR: 0.525, 95% CI: 0.308–0.896, P=0.018) was observed in the pitavastatin group. Pitavastatin did not show any effects on the primary outcome (aHR: 1.582, 95% CI: 0.890–2.813, P=0.118) in the subgroup of patients with LVEF <30%.

Conclusions: Pitavastatin did not reduce cardiac death or hospitalization for worsening HF in Japanese patients with CHF. (UMIN-ID: UMINC000000428). (*Circ J* 2013; **77:** 917–925)

Key Words: Heart failure; Hypercholesterolemia; Pitavastatin; Randomized controlled trial

The number of patients with heart failure (HF) has been increasing and it is becoming a major public health problem. Although there has been considerable progress in the treatment of chronic HF (CHF) with the advent of angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, β-blockers, and aldosterone antagonists, the number of deaths from HF has been increasing steadily and further strategies are needed.

Editorial p 895

The 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (ie, statins) are the most widely used agents for the treatment of hypercholesterolemia. Clinical trials have shown that treatment with statins significantly reduces the incidence of cardiovascular events in patients with coronary artery disease (CAD).[1–3] In addition to their lipid-lowering action, statins have also been reported to have various pleiotropic effects, such as antiinflammatory effects, antioxidant effects, angiogenic effects, protective effects on endothelial cells, and inhibitory effects on neurohormonal activation.[4] It has been demonstrated that statins inhibit the progression of HF in animal models of nonischemic HF.[5,6] These effects of statins suggest a potential to ameliorate components of the

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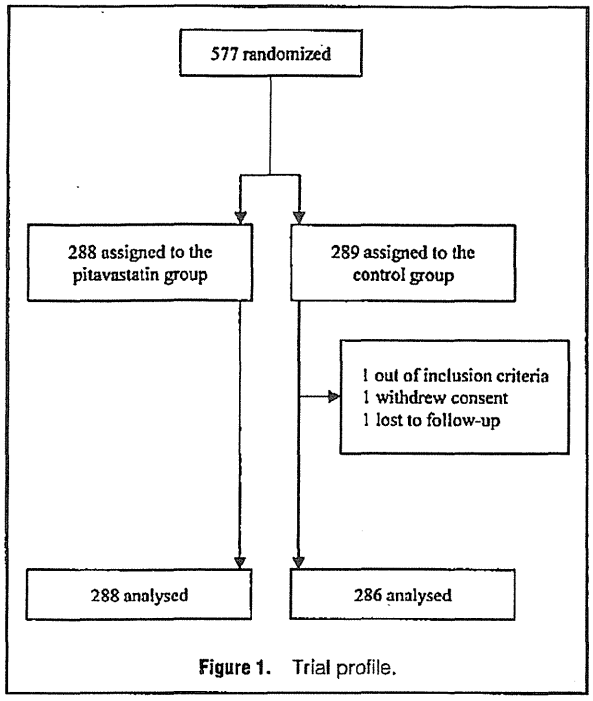

Figure 1. Trial profile.

complex pathophysiology of HF and a promising treatment for CHF in the future.

Many observational studies and retrospective analyses have suggested that treatment with statins decreases the incidence of HF in patients with CAD and reduces the mortality of patients with CHF.[7–9] Prospective trials have also confirmed the beneficial effects of statins on HF.[10–12] On the other hand, 2 recent well-controlled randomized clinical trials have shown that statin treatment has no effect on the clinical outcomes of patients with CHF.[13,14] So, it remains unclear whether treatment of patients with CHF with statins will show the same results in different studies in relation to the type of statin used, characteristics of the patients, severity of HF, and the endpoints examined.

Pitavastatin is a lipophilic statin and has longer-acting effects on decreasing low-density lipoprotein (LDL) cholesterol and increasing high-density lipoprotein (HDL) cholesterol. Pitavastatin also has high bioavailability and is minimally metabolized by the cytochrome P450 system.[15,16] The Pitavastatin Heart Failure (PEARL) study was designed to evaluate the beneficial effects of pitavastatin on the incidence of cardiac death and hospitalization for worsening HF in Japanese patients with CHF.[17]

Methods

Study Design and Patients

The rationale and design of the PEARL study (UMIN-ID: UMINC000000428) have been previously described in detail.[17] It was a multicenter, prospective, randomized, open-label, blinded-endpoint (PROBE) trial carried out in 116 Japanese institutes. The trial was approved by each center's ethics committee and all patients provided written informed consent. Eligibility criteria for enrollment were: age 20–79 years; New York Heart Association (NYHA) functional class II or III; left ventricular ejection fraction (LVEF) as measured by echocardiography ≤45%; stable NYHA class for 2 or more weeks prior to study randomization; mild hypercholesterolemia (serum total cholesterol level ≤250 mg/dl and/or serum LDL-cholesterol level ≤170 mg/dl); written informed consent of the patient. The exclusion criteria included: receiving treatment with a statin prior to randomization; history of acute myocardial infarction within 3 months prior to the randomization; percutaneous coronary intervention (PCI), coronary artery bypass grafting, or cardiac resynchronization therapy-pacemaker or -defibrillator implantation performed within 3 months prior to the randomization; malignancy; serious renal or hepatic dysfunction; collagen disease; pregnancy or possible pregnancy; and lack of informed consent.

The eligible patients were randomly assigned to either the pitavastatin group (2 mg daily) or the control group (no statin) at the PEARL data center using a minimization method[18] with biased-coin assignment balancing on age (<50 years or ≥50 years), sex, serum total cholesterol level (<230 mg/dl or ≥230 mg/dl), LVEF (<30% or ≥30%), history of ischemic heart disease, and history of hospitalization for HF. If any patients in the control group needed further reduction of the serum total cholesterol level, lipid-lowering agents other than statins could be administered.

Study Outcomes

The primary outcome was a composite of cardiac death and hospitalization for worsening HF (hospitalization and clinical symptoms including dyspnea, shortness of breath, and peripheral edema, together with LV dysfunction by echocardiography according to AHA/ACC guidelines). For all patients, the first of these events was noted as the primary outcome. The secondary outcomes were all-cause death, cardiac death, hospitalization for worsening HF, myocardial infarction (hospitalization, chest pain, ECG-changes, and biomarkers of myocardial infarction), unstable angina (hospitalization and diagnosed by both ECG-changes corresponding with chest symptoms and coronary angiography showing >75% stenosis according to AHA/ACC guidelines), stroke (hospitalization and diagnosed by CT and/or MRI), PCI, and surgical therapy for worsening HF. Death was classified as cardiac unless a definite non-cardiovascular reason was identified. All outcomes recorded in this study were adjudicated blindly by an independent endpoint committee (**Appendix S1**) on the basis of prespecified definitions and procedures.

Statistical Analysis

The sample size calculation has been previously described in detail.[17] Our trial required 470 patients with a primary outcome occurring within 48 months to achieve 80% power to detect 43% relative reduction in the risk of the primary outcome in the pitavastatin group as compared with the control group (with a 2-sided α of 0.05) on the condition of an expected mortality rate at 24 months of 20% in the control group. Efficacy was evaluated in 2 interim analyses performed by an independent data and safety monitoring committee at the last patient registration and 1 year after the completion of enrollment. Significance was evaluated using the method of Lan and DeMets and the O'Brien-Fleming boundary (the stopping boundary, $P \leq 0.000011$ at the first interim analysis, $P \leq 0.0089$ at the second interim analysis, and $P \leq 0.041$ at the final analysis).

Comparability of baseline characteristics between the 2 groups was assessed by 2-sample t-test with equal variance or the Mann-Whitney U test for continuous variables, and Fisher's exact test for categorical variables. The analyses of the adju-

Table 1. Baseline Characteristics of the Patients

	Control (n=286)	Pitavastatin (n=288)	P-value
Age			
Age (years)	62.2±12.0	62.9±11.7	0.47
Age ≥50 years, n (%)	246 (86.0)	249 (86.5)	0.87
Female, n (%)	51 (17.8)	55 (19.1)	0.69
NYHA functional class, n (%)			0.50
II	259 (90.6)	256 (88.9)	
III	27 (9.4)	32 (11.1)	
LVEF (%)	34.0±7.7	33.9±8.9	0.88
LVEF ≥30%, no. (%)	206 (72.0)	207 (71.9)	0.96
Blood pressure (mmHg)			
Systolic	118.4±17.7	120.3±18.0	0.20
Diastolic	71.3±11.2	72.4±11.0	0.23
Heart rate (beats/min)	72.6±11.4	73.2±13.0	0.64
HF cause, n (%)			0.80
IHD	80 (28.0)	77 (26.7)	
DCM	149 (52.1)	161 (55.9)	
Hypertensive heart disease	11 (3.8)	10 (3.5)	
Valvular disease	12 (4.2)	15 (5.2)	
Others	34 (11.9)	25 (8.7)	
Medical treatment, n (%)			
Digitalis	72 (25.2)	71 (24.7)	0.86
β-blockers	204 (71.3)	212 (73.6)	0.58
Diuretic drugs	218 (76.2)	211 (73.3)	0.37
ACE inhibitors or ARBs	235 (82.2)	247 (85.8)	0.21
Calcium channel blockers	49 (17.1)	42 (14.6)	0.39
Anticoagulants	132 (46.2)	117 (40.6)	0.18
Antiplatelet agent	128 (44.8)	121 (42.0)	0.43
Medical history, n (%)			
Hospitalization for HF			0.90
At least 2 months before	131 (45.8)	127 (44.1)	
Within 2 months	47 (16.4)	50 (17.4)	
MI	73 (25.5)	71 (24.7)	0.80
CABG or PCI	56 (19.6)	60 (20.8)	0.70
Hypertension	129 (45.1)	131 (45.5)	0.92
Diabetes mellitus	79 (27.6)	78 (27.1)	0.88
Stroke	24 (8.4)	15 (5.2)	0.12
Laboratory measurements			
Total cholesterol (mg/dl)	201.2±32.6	203.2±32.2	0.45
LDL-cholesterol (mg/dl)	125.5±32.7	125.2±28.1	0.93
HDL-cholesterol (mg/dl)	50.8±15.1	50.7±14.5	0.92
hsCRP (ng/ml)			
Median	839.0	834.0	0.85
Interquartile range	394.0–2,300.0	391.0–2,535.0	

These data are the number of patients (%) or mean (SD).
NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; HF, heart failure; IHD, ischemic heart disease; DCM, dilated cardiomyopathy; ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; MI, myocardial infarction; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; LDL, low-density lipoprotein; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein.

dicated primary and secondary outcomes were conducted on data from all patients who had undergone randomization, according to the intention-to-treat principle, with the use of Kaplan-Meier estimates and Cox proportional-hazards models. Hazard ratio, 95% confidence interval (CI), and P value were calculated with the use of models adjusted for the following prespecified baseline prognostic factors: age, sex, serum total cholesterol level, LVEF, history of ischemic heart disease, and history of hospitalization for HF. Sensitivity analyses were also performed by means of unadjusted Cox models.

The consistency of the treatment effect was assessed among 19 prespecified subgroups. The effect in each subgroup was analyzed with a Cox proportional-hazards model without adjustment for covariates. The interaction between treatment and subgroup was evaluated by Cox proportional-hazards model with terms for treatment, subgroup, and their interaction.

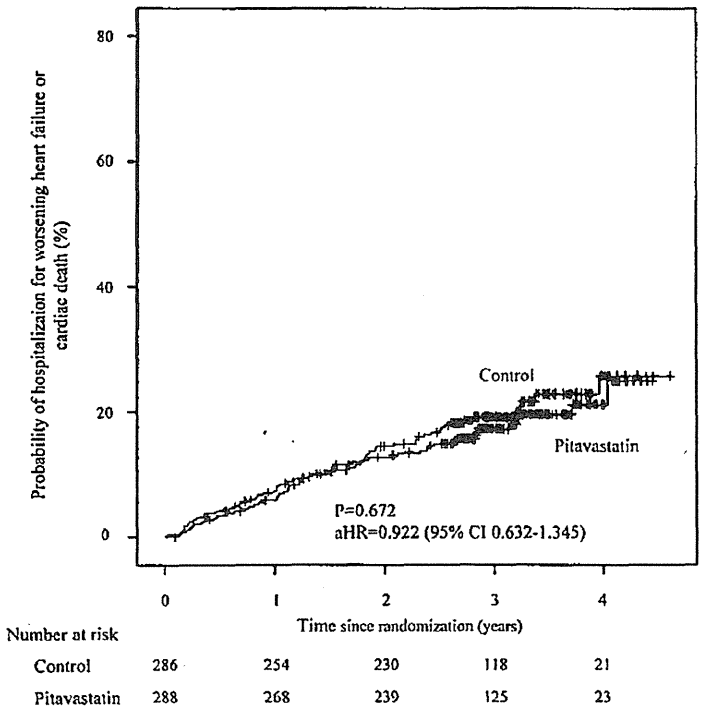

Figure 2. Kaplan-Meier curve for the primary outcome. The P-value was calculated by log-rank test. aHR, adjusted hazard ratio.

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

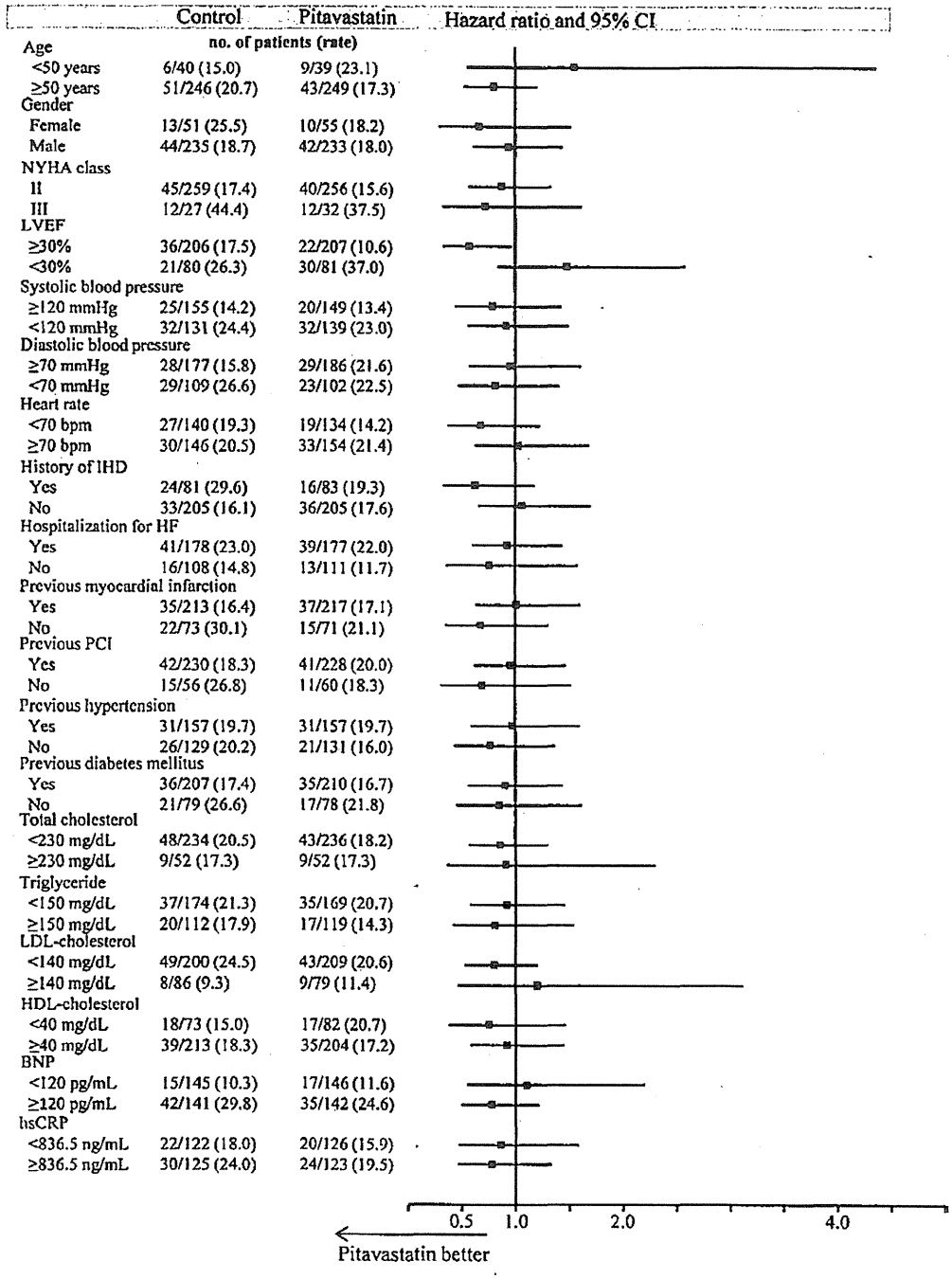

Figure 3. Predefined subgroup analysis for the primary outcome. bpm, beats/min; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; IHD, ischemic heart disease; HF, heart failure; PCI, percutaneous coronary intervention; LDL, low-density lipoprotein; HDL, high-density lipoprotein; 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

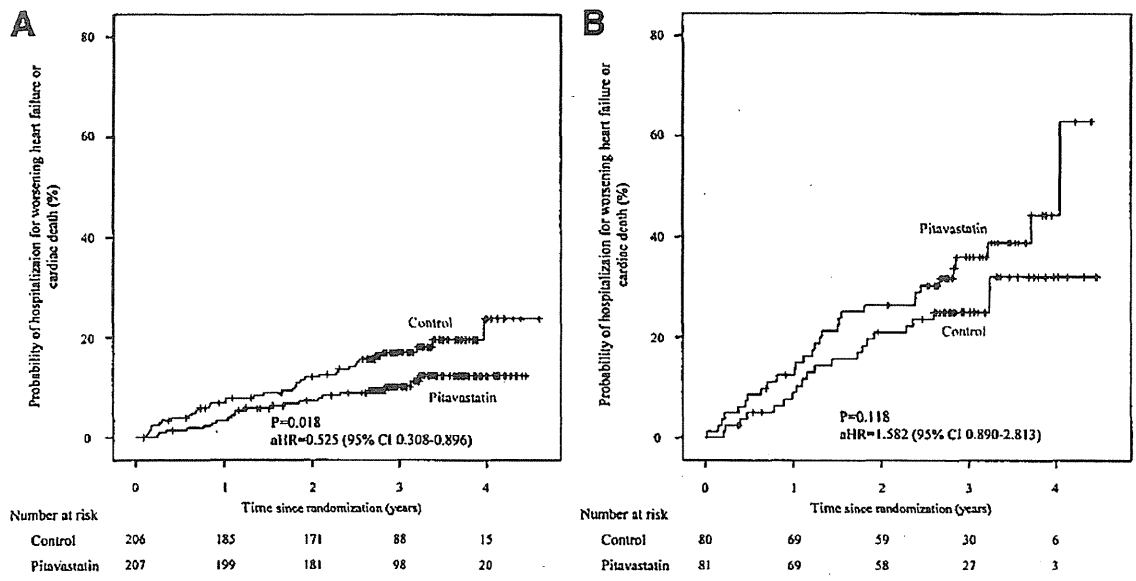

Figure 4. Kaplan-Meier curves for the primary outcome in the subgroup of patients with LVEF ≥30% (**A**) and in the subgroup of patients with LVEF <30% (**B**). The P-values were calculated by log-rank test. aHR, adjusted hazard ratio; LVEF, left ventricular ejection fraction.

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.

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

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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.