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ORIGINAL ARTICLE

Association of adherence to a 3 month cardiac rehabilitation with long-term clinical outcomes in heart failure patients

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Abstract

Aims Although comprehensive cardiac rehabilitation (CCR) is recommended for patients with heart failure (HF), participants often show low adherence. The aim of this study was to evaluate the association of CCR completion and response with long-term clinical outcomes.

Methods and results We screened 824 HF patients who participated in a 3 month CCR programme and underwent baseline assessment, including cardiopulmonary exercise testing (CPX). After excluding 52 participants who experienced all-cause death or HF hospitalization within 180 days, long-term outcomes were compared between those who attended 3 month follow-up assessment including CPX (completers) and those who did not (non-completers). We also compared the prognostic value of the changes in peak oxygen uptake (VO_2) vs. quadriceps muscle strength (QMS) during the 3 month CCR programme. Among the 772 study patients, there were no significant differences in baseline characteristics, including left ventricular ejection fraction, B-type natriuretic peptide levels, and peak VO_2, between the completers (n = 561) and non-completers (n = 211), except for a higher age (63.2 ± 14.2 vs. 59.4 ± 16.2 years; P = 0.0015) and proportion of females (27% vs. 17%; P = 0.0030) among the completers. During a median follow-up of 55.4 months, the completers had lower rates of the composite of all-cause death or HF hospitalization (34.4% vs. 44.6%; P = 0.0015) and all-cause death (16.9% vs. 24.6%; P = 0.0037) than the non-completers. After adjustment for prognostic baseline characteristics, including age and sex, CCR completion was associated with 34% and 44% reductions in the composite outcome and all-cause death, respectively. Among the completers, peak VO_2 and QMS increased significantly (8.9 ± 15.8% and 10.5 ± 17.9%, respectively) over 3 months. Patients who had an increase in peak $VO_2 \geq 6.3\%$ (median value) during the CCR programme had significantly lower rates of the composite outcome (27.0% vs. 33.8%; P = 0.048) and all-cause mortality (10.0% vs. 17.4%; P = 0.0069) than those who did not. No statistically significant difference was observed in the composite outcome (30.5% vs. 30.4%; P = 0.76) or all-cause mortality (13.0% vs. 14.4%; P = 0.39) between those with and without an increase in QMS $\geq$8.3% (median value).

Conclusions In HF patients who participated in a 3 month CCR programme, its completion was associated with lower risks of subsequent HF hospitalization and death. Within the group of patients who completed the programme, the improvement in exercise capacity, but not in skeletal muscle strength, over the 3-month period was associated with better outcomes. These findings highlight the importance of the post-CCR follow-up assessment, including CPX, to identify a patient's adherence and response to the CCR programme.

Keywords Heart failure; Cardiac rehabilitation; Adherence; Outcome; Exercise capacity; Muscle strength

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Introduction

The prevalence of heart failure (HF) is increasing due to an ageing population, with a concurrent increase in the prevalence of obesity, hypertension, and diabetes, as well as an improved survival after initial cardiac events such as acute coronary syndrome. Despite recent advances in pharmacological and non-pharmacological treatments, the prognosis of HF patients remains poor.[1,2]

Comprehensive cardiac rehabilitation (CCR) is a multidisciplinary intervention involving supervised exercise training, education, lifestyle modification, and psychological counselling. Based on accumulated evidence for its long-term benefits,[3] the current practice guidelines highly recommend HF patients to participate in a CCR programme to improve exercise capacity and quality of life and to reduce HF hospitalization risk.[4–6] However, the CCR programme is still severely underutilized with poor referral and participation,[7,8] and even those who participate often drop out of the programme early.[9] Although HF patients who participated in CCR (defined as those who participated in at least one CCR session) were reported to have lower rates of HF hospitalization and death than non-participants,[10] it remains unclear whether CCR completion is associated with subsequent long-term outcomes among HF patients who participate in CCR.

Both exercise capacity, as determined by peak oxygen uptake (VO_2), and skeletal muscle strength have been shown to be independent predictors of clinical outcomes in HF patients[11–14] and to be improved by aerobic and resistance exercise training in the course of the CCR programme for HF patients.[15–17] However, it remains unclear which of their improvements during the CCR programme is associated with subsequent clinical outcomes; the result would suggest a suitable target parameter of exercise training to improve clinical outcomes.

The primary aim of this study is to evaluate the association of CCR completion, defined as attendance at a 3 month post-CCR assessment, including cardiopulmonary exercise testing (CPX), with subsequent long-term outcomes among HF patients who participated in a CCR programme. The secondary aim is to compare the prognostic value of the changes in peak VO_2 vs. quadriceps muscle strength (QMS) during the 3 month CCR programme.

Methods

Study population

Of consecutive HF patients who participated in a CCR programme at our institution between January 2002 and March 2020, those who underwent baseline assessment, including CPX (CPX-1), were screened retrospectively. Patients were eligible for CCR participation if they had a prior HF hospitalization, regardless of their left ventricular ejection fraction (LVEF), or if they had a reduced LVEF (≤40%) or an elevated B-type natriuretic peptide (BNP) level (≥80 pg/mL). Patients with a serum creatinine level of >2.5 mg/dL, a history of myocardial infarction within the previous 3 months, severe valvular heart disease, or significant pulmonary or neuromuscular diseases affecting the possibility of performing CPX were excluded from the study. Patients lost to follow-up within a year of CCR participation were also excluded. The presence of ischaemic heart disease was shown by coronary angiography or documentation of a myocardial infarction. The treatment for HF was tailored for all patients according to contemporary guidelines. The study complied with the Declaration of Helsinki and was approved by the Institutional Ethics Committee (M26-015). Written informed consent was obtained from all patients.

Comprehensive cardiac rehabilitation programme

A 3 month CCR programme was initiated with supervised in-hospital exercise sessions consisting of combined aerobic exercise training and low-intensity resistance training for 10–20 min per session, with a gradual increase of 20–40 min per session, 3–5 times per week. If clinically stable, patients were encouraged to begin home-based, non-supervised exercises combined with supervised outpatient exercise sessions once or twice per week. All participants also received HF education for self-care and behavioural strategies. The assessment visits were scheduled at baseline and the 3 month follow-up where laboratory data were collected and CPX was carried out. The duration of the exercise was finally increased to 30–60 min, and the intensity of the aerobic exercise was individually tailored to a heart rate corresponding to 30–50% of a heart rate reserve or anaerobic threshold level based on the result of CPX-1, or to Levels 12–13 of the original Borg's scale. After completing the 3 month CCR programme, all patients were encouraged to continue their individually prescribed home exercises based on the 3 month CPX (CPX-2) result.

Clinical outcomes by comprehensive cardiac rehabilitation status

Follow-up data were collected from outpatient medical records. The endpoints of this study were the composite outcome (defined as all-cause death or HF hospitalization) and all-cause death, analysed as the time from the date of CCR participation to that of the first event. HF hospitalization was valid only when a patient had the typical symptoms and signs, was treated with diuretics, and had at least an overnight hospital stay. We defined CCR completion as

attendance at a 3 month post-CCR assessment, including CPX-2, regardless of the number of in-hospital or outpatient CCR sessions attended, and the clinical outcomes were compared between the completers and the non-completers. To prevent a deterioration of the patient's HF status from affecting the attendance at the 3 month assessment, only participants who did not experience all-cause death or HF hospitalization within 180 days from the date of CCR participation were analysed. We also assessed the consistency of the effect of CCR completion on the incidence of the composite of all-cause death or HF hospitalization across subgroups.

Cardiopulmonary exercise testing parameters

Symptom-limited CPX was performed using a cycle ergometer with an individualized ramp protocol. Expired gas analysis was performed throughout testing on a breath-by-breath basis, and minute ventilation (VE), VO_2, and carbon dioxide production (VCO_2) data were obtained at 6 s intervals throughout the testing duration (AE-300 S, Minato Medical Science, Osaka, Japan). All subjects undergoing CPX were strongly encouraged to exercise towards exhaustion with a target peak respiratory exchange ratio, an objective index of effort adequacy, of >1.20.[18]

Peak VO_2 was identified as either the greatest VO_2 during exercise or the average VO_2 of the last three data points (18 s) before termination of exercise, whichever was higher, and was expressed as a value (mL/kg/min) adjusted to body weight (BW) and a value (%) calculated as actual peak VO_2/predicted peak VO_2.[19] The slope of the linear relationship between VE and VCO_2 (VE/VCO_2 slope), an index of ventilatory efficiency, was determined by excluding the part after the respiratory compensation point. The change during CCR was determined as the relative change (%) in peak workload (Watt) or peak VO_2 (mL/min) from baseline to 3 months.

Quadriceps muscle strength

Quadriceps muscle strength (QMS) was determined as a measure of isometric knee extensor muscle strength obtained using a handheld dynamometer (μ-tas F1; ANIMA, Tokyo, Japan).[20] The measurements were performed twice on both the left and right sides. The maximum for each knee was averaged (kilogram-force [kgf]) and expressed as a value adjusted to BW (%). The change during CCR was determined as the relative change (%) in QMS (kgf) from baseline to 3 months.

Other parameters

Baseline echocardiography was performed in all patients (iE 33; Philips Healthcare, Best, the Netherlands), and left atrial diameter and left ventricular end-diastolic and end-systolic diameter were determined as linear anteroposterior dimensions. LVEF was measured by echocardiography, radionuclide ventriculography, cardiac magnetic resonance, or left ventricular angiography. Laboratory data were collected to analyse serum creatinine, haemoglobin, and BNP levels at baseline and 3 months.

Statistical analysis

Continuous variables (presented as means ± standard deviation) and categorical variables were compared using the unpaired Student's *t* test and χ^2 test, respectively. Cox proportional hazard analysis was used to assess the unadjusted and adjusted associations of specific variables with time to outcomes, which were expressed as hazard ratios (HRs) and 95% confidence intervals (CIs). Cumulative events were assessed using the Kaplan–Meier method, and the differences in events were compared using a log-rank test. Pearson's correlation coefficients were used to assess the linear association between the change in peak VO_2 or QMS and the respective parameters. A value of $P < 0.05$ was considered to be statistically significant. All statistical analyses were conducted using SAS 9.2 (SAS Institute Inc., Cary, NC).

Results

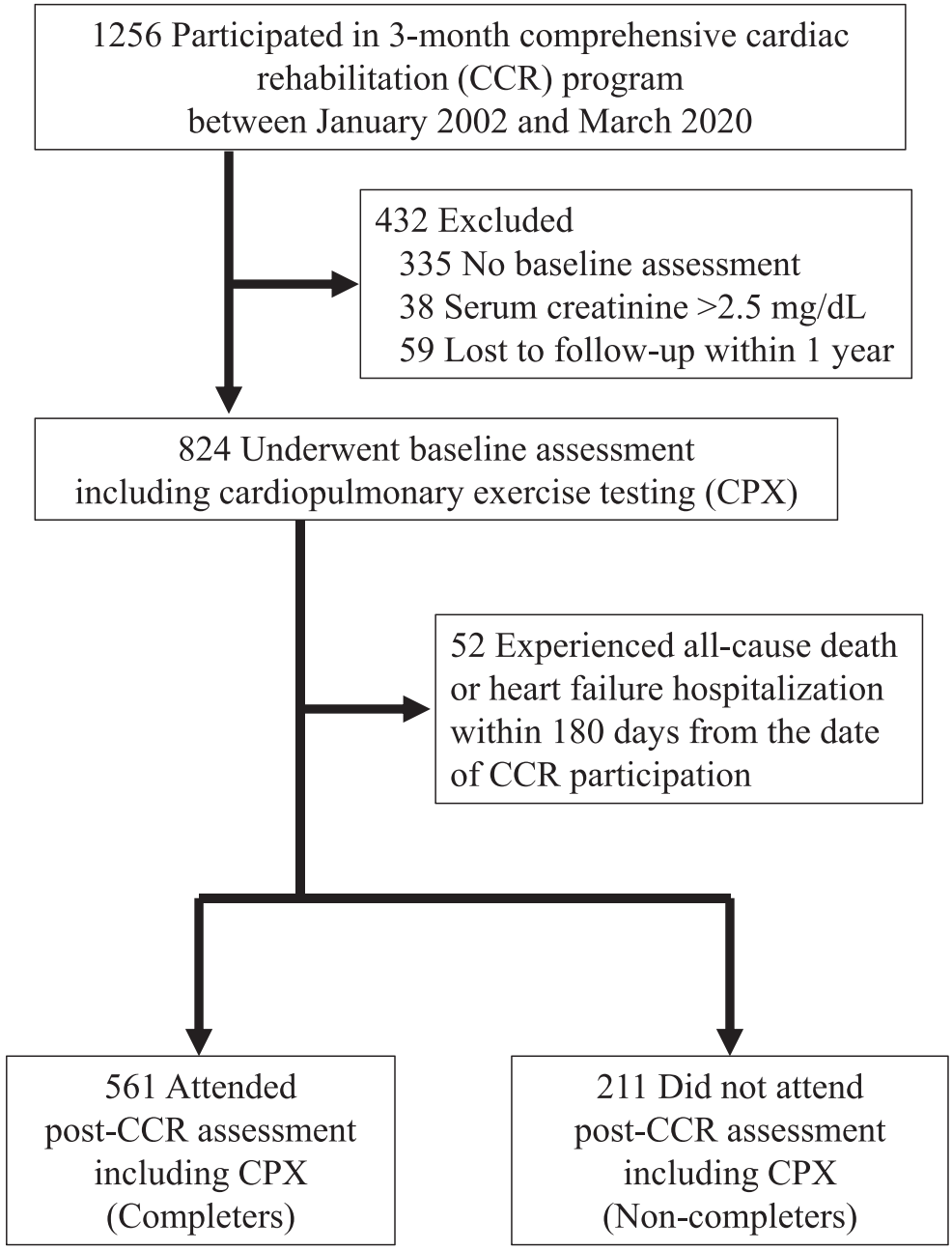
Baseline characteristics

A flowchart depicting the study design is shown in *Figure 1*. Of the consecutive 1256 HF patients who participated in the CCR programme, 824 met the inclusion criteria. Fifty-two patients who experienced all-cause death or HF hospitalization within 180 days from the date of CCR participation were excluded, to prevent a deterioration of the patient's HF status from affecting the attendance at the 3 month assessment.

Among the remaining 772 study patients, the mean age was 62.2 ± 14.9 years, 584 (76%) were male, the mean LVEF was 30.8 ± 13.1%, 118 (15%) had a preserved LVEF (≥45%), and 541 (70%) had a history of hospitalization for worsening HF. The CCR programme was initiated during or soon after hospitalization for worsening HF or evaluation in 742 patients (96%) and as ambulatory care in 30 patients (4%).

A total of 561 patients (73%) attended the 3 month post-CCR assessment including CPX (completers), while the remaining 211 patients (27%) did not (non-completers). There were no statistically significant differences in baseline characteristics, including BNP levels and guideline-directed medical and device therapy, between the two groups, except for a higher age (63.2 ± 14.2 vs. 59.4 ± 16.2 years; $P = 0.0015$)

Figure 1 Flowchart depicting the study design.



and proportion of female patients (27% vs. 17%; $P = 0.0030$) among the completers (*Table 1*).

The attained peak respiratory exchange ratio was similarly high between the completers and non-completers (1.25 ± 0.12 vs. 1.24 ± 0.12, respectively). No significant between-group differences were observed regarding CPX-1 parameters, including peak workload (96.9 ± 33.7 W vs. 101.0 ± 38.9 W) and peak VO_2 (17.3 ± 4.6 vs. 17.6 ± 5.1 mL/kg/min) (*Table 2*). Among the 551 patients with available QMS data (completers, $n = 401$; non-completers, $n = 150$), QMS/BW was similar in both groups (51.0 ± 14.2% vs. 52.0 ± 14.3%, respectively).

Adherence and response to comprehensive cardiac rehabilitation programme

The completers attended more outpatient sessions than the non-completers (10.6 ± 9.7 vs. 3.4 ± 5.7, $P < 0.0001$). There were no occurrences of serious adverse events related to ex-

Table 1 Baseline characteristics stratified by CCR status among 772 study patients

	All patients (n = 772)	Non completers (n = 211)	Completers (n = 561)	P value[a]
Age (years)	62.2 ± 14.9	59.4 ± 16.2	63.2 ± 14.2	0.0015
Male sex	584 (75.6)	175 (82.9)	409 (72.9)	0.0030
Hypertension	432 (56.0)	115 (54.5)	317 (56.5)	0.62
Diabetes	286 (37.0)	83 (39.3)	203 (36.2)	0.42
BMI (kg/m^2)	22.5 ± 3.8	22.6 ± 4.1	22.4 ± 3.6	0.43
Ischaemic	272 (35.2)	69 (32.7)	203 (36.2)	0.36
AF rhythm	152 (19.7)	40 (19.0)	112 (20.0)	0.75
Prior HF hospitalization	541 (70.1)	153 (72.5)	388 (69.2)	0.36
Creatinine (mg/dL)	1.05 ± 0.36	1.06 ± 0.34	1.05 ± 0.36	0.77
Haemoglobin (g/dL)	13.4 ± 1.8	13.4 ± 1.8	13.4 ± 1.8	0.92
Plasma BNP (pg/mL)	254.7 ± 248.8	254.0 ± 264.1	254.9 ± 243.1	0.97
LVDd (mm)	60.8 ± 10.7	61.8 ± 11.5	60.4 ± 10.3	0.12
LVDs (mm)	50.8 ± 12.8	51.6 ± 13.6	50.5 ± 12.4	0.28
LVEF (%)	30.8 ± 13.1	30.3 ± 13.2	31.0 ± 13.0	0.51
LVEF ≥45%	118 (15.3)	33 (15.6)	85 (15.2)	0.87
LAD (mm)	44.4 ± 8.8	44.6 ± 8.6	44.3 ± 8.9	0.71
β-blocker	719 (93.1)	201 (95.3)	518 (92.3)	0.14
ACEI or ARB	643 (83.3)	182 (86.3)	461 (82.2)	0.17
Diuretic	547 (70.9)	155 (73.5)	392 (69.9)	0.33
ICD/CRT	157 (20.3)	41 (19.4)	116 (20.7)	0.70

ACEI, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation or flutter; ARB, angiotensin-receptor blocker; BMI, body mass index; BNP, B-type natriuretic peptide; CCR, comprehensive cardiac rehabilitation; CRT, cardiac resynchronization therapy; HF, heart failure; ICD, implantable cardioverter-defibrillator; LAD, left atrial diameter; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction. BMI is the weight in kilograms divided by the square of the height in meters. Variables are expressed as means ± SD or n (%).
[a]P value for comparison of non-completers vs. completers.

Table 2 Changes in laboratory and CPX parameters from baseline to 3 months

	Non-completers (n = 211)			Completers (n = 561)			P value	P value
	Baseline	3 months[d]	P value[e]	Baseline	3 months	P value[e]	(baseline)[f]	(3 months)[g]
Creatinine (mg/dL)[a]	1.07 ± 0.34	1.11 ± 0.39	0.29	1.05 ± 0.36	1.09 ± 0.38	0.061	0.65	0.70
Plasma BNP (pg/mL)[b]	260.9 ± 267.6	226.0 ± 256.8	0.21	256.4 ± 243.6	216.8 ± 223.0	0.0048	0.83	0.63
Body weight (kg)	62.3 ± 14.3			60.1 ± 12.7	60.8 ± 12.5	0.38	0.043	
Peak RER	1.24 ± 0.12			1.25 ± 0.12	1.25 ± 0.11	0.81	0.18	
Peak workload (Watt)	101.0 ± 38.9			96.9 ± 33.7	105.9 ± 39.5	<0.0001	0.15	
Peak VO_2 (mL/kg/min)	17.6 ± 5.1			17.3 ± 4.6	18.6 ± 5.4	<0.0001	0.45	
% Predicted peak VO_2 (%)	68.6 ± 16.1			70.9 ± 16.4	75.7 ± 18.2	<0.0001	0.082	
VE/VCO_2 slope	33.9 ± 7.2			33.5 ± 6.7	32.4 ± 6.6	0.012	0.46	
Resting heart rate (bpm)	73.8 ± 13.1			73.6 ± 14.0	72.1 ± 12.7	0.060	0.86	
Peak heart rate (bpm)	124.1 ± 30.7			125.8 ± 29.3	126.7 ± 28.4	0.62	0.46	
Resting SBP (mmHg)	111.4 ± 20.8			110.7 ± 19.2	113.0 ± 20.3	0.049	0.64	
Peak SBP (mmHg)	145.1 ± 29.4			144.9 ± 29.2	148.4 ± 30.4	0.052	0.93	
QMS/body weight (%)[c]	52.0 ± 14.3			51.0 ± 14.2	54.9 ± 14.4	0.0001	0.49	

Variables are expressed as the mean ± SD. BNP, B-type natriuretic peptide; bpm, beats per minute; CPX, cardiopulmonary exercise testing; QMS, quadriceps muscle strength; RER, respiratory exchange ratio; SBP, systolic blood pressure; VCO_2, carbon dioxide production; VE, minute ventilation; VO_2, oxygen uptake.
[a]Creatinine: data available both at baseline and 3 months for 203 non-completers and 560 completers.
[b]Plasma BNP: data available both at baseline and 3 months for 199 non-completers and 556 completers.
[c]QMS/body weight: data available for 150 non-completers and 401 completers.
[d]3 month: data around 90 days after baseline CPX.
[e]P value for comparison of baseline vs. 3 months for each group.
[f]P value for comparison of non-completers vs. completers at baseline.
[g]P value for comparison of non-completers vs. completers at 3 months.

ercise training in either group. Among the completers, both peak workload and peak VO_2 increased significantly by 9.7 ± 15.2% (median, 7.9%) and 8.9 ± 15.8% (median, 6.5%), respectively, with a duration of 96.5 ± 16.8 days between CPX-1 and CPX-2. BNP levels significantly decreased over the 3 months only among the completers, but there was no significant between-group difference in BNP levels at 3 months. QMS was significantly augmented by 10.5 ± 17.9% (median, 8.3%) among the 401 completers with available QMS data (*Table 2*).

Clinical events according to comprehensive cardiac rehabilitation status or the number of outpatient sessions

Over a median follow-up of 55.4 months, the composite of all-cause death or HF hospitalization occurred in 287 (37.2%) patients and all-cause death occurred in 147 (19.0%) patients. The completers had lower rates of the composite outcome (HR: 0.67 [95% CI: 0.52–0.85], *P* = 0.0015) and all-cause death (HR: 0.60 [95% CI: 0.43–0.84], *P* = 0.0037) than the non-completers (*Figure 2*). After adjustment for prognostic baseline characteristics, the completers had a 34% lower risk of the composite outcome (HR: 0.66 [95% CI: 0.52–0.86], *P* = 0.0017) and 44% lower risk of all-cause death (HR: 0.56 [95% CI: 0.39–0.81], *P* = 0.0020) than the non-completers (*Tables 3* and *S1*). The effect of CCR completion on the incidence of the composite outcome was generally consistent across subgroups, including patients with reduced or preserved LVEF (*Table S2*).

In the entire cohort, patients with the number of outpatient CCR sessions attended ≥7 (median value) had a trend towards lower rates of the composite outcome (*P* = 0.069) and all-cause death (*P* = 0.11) than those with the number ≤6 (*Figure S1A,B*), but as a continuous variable, there was no statistically significant association between the number of outpatient CCR sessions attended and the composite outcome (HR: 0.99 [95% CI: 0.98–1.004], *P* = 0.19) or all-cause death (HR: 0.99 [95% CI: 0.97–1.01], *P* = 0.23). Among the completers, no difference was observed in either endpoint between patients with and without the number of outpatient CCR sessions attended ≥10 (median value) (*Figure S1C,D*). Similarly, there was no difference in either endpoint between patients with and without the number ≥1 (median value) among the non-completers (*Figure S1E,F*).

Clinical events according to response to the comprehensive cardiac rehabilitation programme

Figure 3 shows the Kaplan–Meier cumulative curves for clinical outcomes according to each median value of the changes in peak VO_2 (6.3%) and QMS (8.3%) during the CCR programme among the 401 completers with available data for both changes; the median change in peak VO_2 was nearly equal to the clinically meaningful value of 6%.[21,22]

Patients who had a change in peak $VO_2 \geq 6.3\%$ had significantly lower rates of the composite of all-cause death or HF hospitalization (*P* = 0.048) and all-cause mortality (*P* = 0.0069) than those who did not (*Figure 3A,B*). In contrast, no difference was observed in either endpoint between those with and without a change in QMS ≥ 8.3% (*Figure 3C,D*).

As a continuous variable, the percentage change in peak VO_2 over the 3 months was significantly associated with the composite outcome and all-cause death, whereas the change in QMS was not. After adjustment for prognostic baseline characteristics and the number of outpatient CCR sessions, the change in peak VO_2 remained an independent predictor of the composite outcome and all-cause mortality (*Table 4*).

Figure 2 Kaplan–Meier cumulative curves for clinical outcomes by CCR status among 772 study patients. The completers (*n* = 561) have lower rates of the composite of all-cause death or heart failure hospitalization (A) and all-cause death (B) than the non-completers (*n* = 211). CCR, comprehensive cardiac rehabilitation.

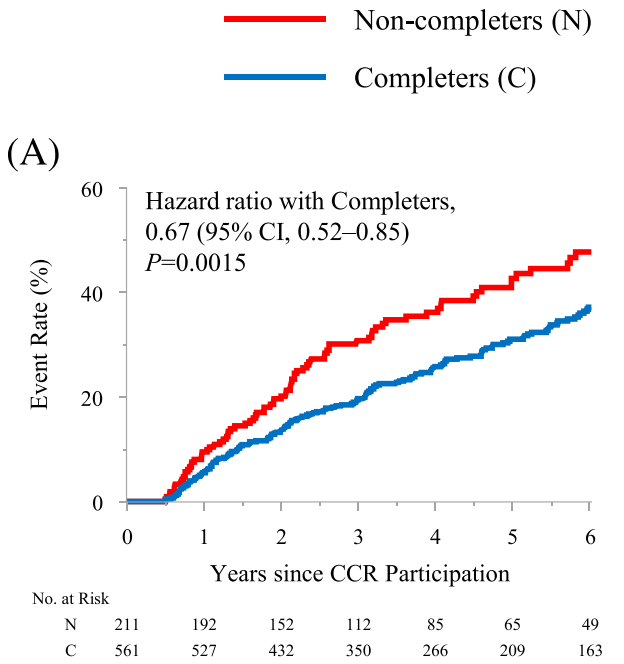


Table 3 Univariate and multivariate associations of variables with the composite of all-cause death or HF hospitalization among 772 participants

	Univariate			Multivariate	
	χ^2	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Age (years)	11.0	1.015 (1.006–1.024)	0.0009	0.998 (0.987–1.009)	0.71
Male sex	6.4	1.44 (1.08–1.96)	0.011	0.998 (0.72–1.41)	0.99
Diabetes	8.7	1.42 (1.13–1.79)	0.0031	1.09 (0.85–1.40)	0.48
AF rhythm	2.9	1.28 (0.96–1.68)	0.090	0.96 (0.70–1.32)	0.82
ICD/CRT	20.7	1.86 (1.44–2.40)	<0.0001	1.54 (1.15–2.05)	0.0039
Prior HF hospitalization	35.3	2.35 (1.74–3.22)	<0.0001	1.63 (1.19–2.28)	0.0022
Creatinine (mg/dL)	59.8	3.13 (2.38–4.06)	<0.0001	1.53 (1.11–2.10)	0.011
Haemoglobin (g/dL)	35.9	0.81 (0.76–0.87)	<0.0001	0.96 (0.89–1.03)	0.26
BNP (per 10-pg/mL)	39.2	1.011 (1.008–1.014)	<0.0001	1.003 (0.999–1.007)	0.099
LAD (mm)	63.9	1.05 (1.04–1.07)	<0.0001	1.04 (1.02–1.06)	<0.0001
LVDd (mm)	16.3	1.02 (1.01–1.04)	<0.0001	1.014 (0.998–1.031)	0.096
LVEF (%)	3.5	0.991 (0.981–1.0004)	0.060	1.003 (0.990–1.017)	0.63
Peak VO_2 (mL/kg/min)	100.7	0.87 (0.84–0.89)	<0.0001	0.93 (0.90–0.97)	0.0005
VE/VCO_2 slope	61.4	1.06 (1.05–1.08)	<0.0001	1.022 (1.003–1.040)	0.021
CCR completion	10.1	0.67 (0.52–0.85)	0.0015	0.66 (0.52–0.86)	0.0017

CCR completion is defined as attendance at the 3 month post-CCR assessment including CPX.
AF, atrial fibrillation or flutter; BNP, B-type natriuretic peptide; CCR, comprehensive cardiac rehabilitation; CI, confidence interval; CPX, cardiopulmonary exercise testing; CRT, cardiac resynchronization therapy; HF, heart failure; ICD, implantable cardioverter-defibrillator; LAD, left atrial diameter; LVDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; VCO_2, carbon dioxide production; VE, minute ventilation; VO_2, oxygen uptake.

Association between variables and response to the comprehensive cardiac rehabilitation programme

There was no significant association between the number of outpatient CCR sessions attended and the change in peak VO_2 or QMS (*Table 5*). Whereas the change in QMS was significantly higher in male than in female patients (11.9 ± 18.1% vs. 7.0 ± 16.8%, respectively, $P = 0.014$), no statistically significant difference was observed in the change in peak VO_2 between the sexes (9.5 ± 16.3% vs. 7.3 ± 14.2%, $P = 0.13$). The change in peak VO_2 had the greatest correlation with age ($R = -0.23$, $P < 0.0001$), followed by LVEF ($R = -0.11$, $P = 0.011$), and a multiple regression model for the best correlates of the change in peak VO_2 included age and baseline peak VO_2 (adjusted $R^2 = 0.10$). The change in QMS had the greatest correlation with baseline QMS ($R = -0.29$, $P < 0.0001$), followed by age ($R = -0.27$, $P < 0.0001$), and a multiple regression model for the best correlates of the change in QMS included age, sex, and baseline QMS (adjusted $R^2 = 0.26$).

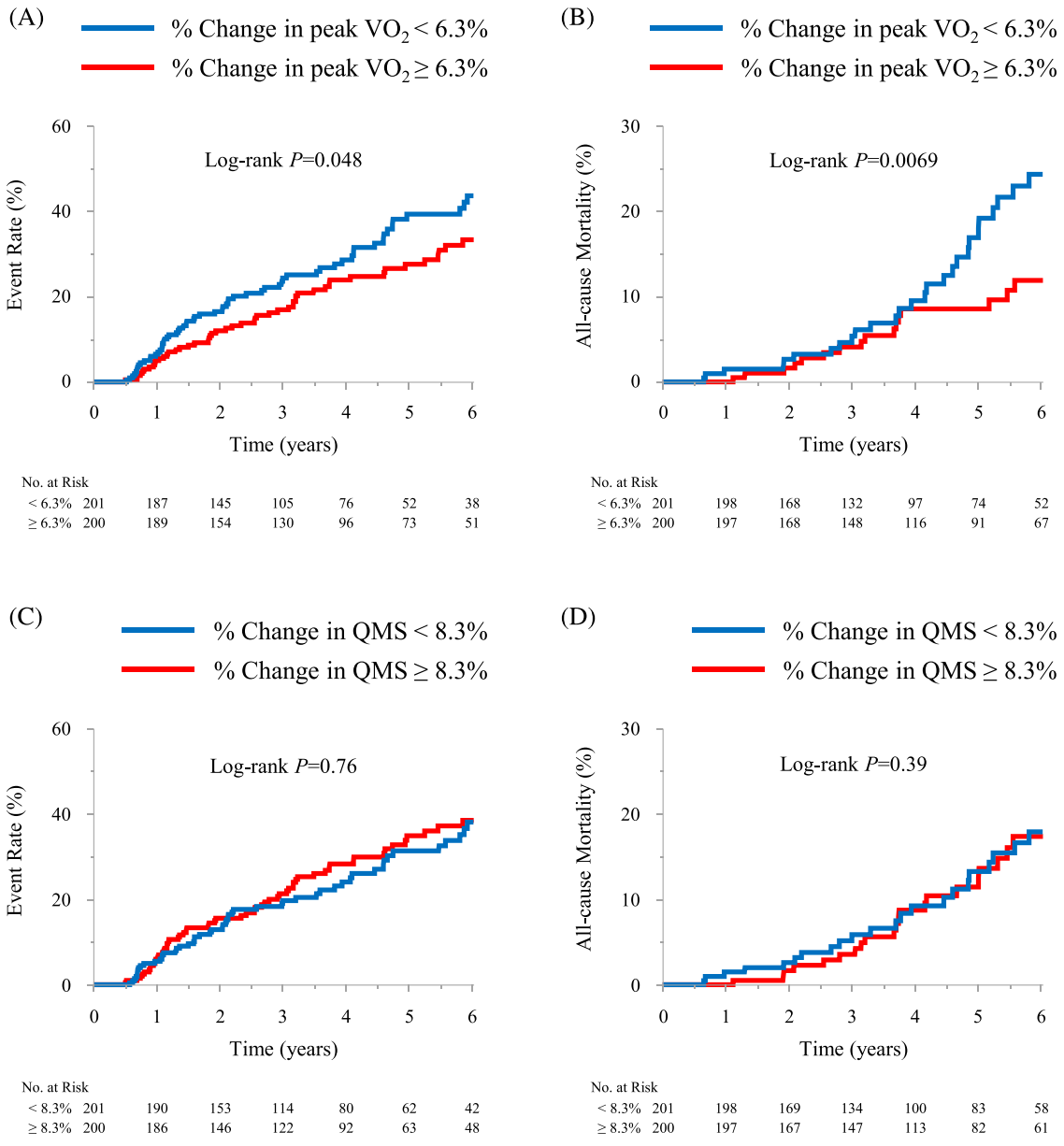
Discussion

The present study demonstrated that among the HF patients who participated in the 3 month CCR programme, those who attended the post-CCR follow-up assessment (completers) had a lower risk of subsequent HF hospitalization and death than those who did not (non-completers) over a median follow-up period of 4.6 years. Furthermore, the improvement in exercise capacity, but not in skeletal muscle strength, over the 3-month period was associated with better long-term outcomes among the completers. These findings highlighted the importance of the post-CCR follow-up assessment, including CPX, to identify the adherence and response to the CCR programme, both of which were associated with subsequent long-term prognosis.

Adherence among comprehensive cardiac rehabilitation participants

Despite its multiple benefits and strong guideline recommendations,[3–6] only a small proportion of eligible HF patients are referred to and participate in a CCR programme,[7,8] and low adherence is often noted even among those who participate.[9] While the importance of baseline assessment, including a symptom-limited exercise test, is widely recognized for developing an individualized CCR programme, the clinical significance of post-CCR follow-up assessment is not fully elucidated. In the present study, CCR completion was defined as attendance at the 3 month post-CCR assessment, including CPX. A substantial proportion (27%) of the CCR participants did not complete the programme, and the non-completers were younger and had a higher proportion of male patients than the completers. This finding was contrary to that reported among CCR participants with coronary artery disease (CAD), where female patients and elderly patients were less likely to complete the programme.[23] Although the reason for this difference is unclear, possible explanations include differences in patient populations (HF vs. CAD) and healthcare systems between countries.

Figure 3 Kaplan–Meier cumulative curves for clinical outcomes according to median value of the changes in peak VO_2 and QMS during the CCR programme among the 401 completers with available data for both changes. Patients who had a change in peak $VO_2 \geq 6.3\%$ have significantly lower rates of the composite of all-cause death or heart failure hospitalization (A) and all-cause mortality (B) than those who did not. No difference is observed in the composite outcome (C) or all-cause mortality (D) between patients with and without a change in QMS ≥8.3%. CCR, comprehensive cardiac rehabilitation; QMS, quadriceps muscle strength; VO_2, oxygen uptake.



Association of comprehensive cardiac rehabilitation completion and response with clinical outcomes

After adjustment for prognostic baseline characteristics, including age and sex, CCR completion remained associated with substantially lower risks of HF hospitalization and death. Martin *et al*. had previously shown that among CCR participants with CAD, those who attended a 12 week post-CCR assessment had a better outcome than those who did not.[23] Thus, the present study extended the association between CCR completion and subsequent favourable outcomes to the HF patient cohort. Furthermore, among the completers, the increase in peak VO_2 over the 3 months was associated with better long-term outcomes, a finding which is consistent with that from the HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) study.[24] Although a causal relationship between CCR completion or

Table 4 Association of changes in peak VO_2 and QMS with the composite of all-cause death or HF hospitalization and all-cause death among the 401 completers with available data for both changes

			Unadjusted		Adjusted[a]	
	Event	χ^2	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
% Change in peak VO_2	All-cause death or HF hospitalization	7.7	0.982 (0.969–0.995)	0.0054	0.980 (0.966–0.993)	0.0030
	All-cause death	14.6	0.959 (0.937–0.981)	0.0001	0.970 (0.945–0.994)	0.014
% Change in QMS	All-cause death or HF hospitalization	0.8	1.005 (0.994–1.014)	0.38	0.997 (0.985–1.009)	0.62
	All-cause death	0.8	0.992 (0.975–1.009)	0.38	0.994 (0.972–1.015)	0.57

AF, atrial fibrillation or flutter; BNP, B-type natriuretic peptide; CCR, comprehensive cardiac rehabilitation; CI, confidence interval; CRT, cardiac resynchronization therapy; HF, heart failure; ICD, implantable cardioverter-defibrillator; LAD, left atrial diameter; LVDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; QMS, quadriceps muscle strength; VCO_2, carbon dioxide production; VE, minute ventilation; VO_2, oxygen uptake.
[a]Adjusted for number of outpatient CCR sessions and baseline values including age, sex, diabetes, AF, ICD/CRT, prior HF hospitalization, creatinine, haemoglobin, BNP, LAD, LVDd, LVEF, VE/VCO_2 slope, and peak VO_2 (for QMS) or QMS (for peak VO_2).

Table 5 Relationships between variables and change in peak VO_2 or QMS

	% Change in peak VO_2 (n = 561)		% Change in QMS (n = 401)	
	R	*P* value	*R*	*P* value
No. of outpatient sessions attended	−0.002	0.97	−0.01	0.77
Age (years)	−0.23	<0.0001	−0.27	<0.0001
LAD (mm)	−0.04	0.37	0.01	0.77
LVDd (mm)	0.10	0.031	0.12	0.017
LVEF (%)	−0.12	0.011	−0.17	0.0008
Creatinine (mg/dL)	−0.04	0.39	0.01	0.77
Haemoglobin (g/dL)	0.05	0.33	−0.02	0.71
BNP (pg/mL)	−0.005	0.92	0.06	0.21
Baseline peak VO_2 (mL/kg/min)	−0.05	0.29	−0.03	0.55
Baseline VE/VCO_2 slope	−0.02	0.62	0.01	0.90
Baseline QMS (%)	0.03	0.59	−0.29	<0.0001

BNP, B-type natriuretic peptide; LAD, left atrial diameter; LVDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; QMS, quadriceps muscle strength; VCO_2, carbon dioxide production; VE, minute ventilation; VO_2, oxygen uptake.

response and clinical outcomes cannot be proven by its retrospective analysis, this study shows that the setting of a 3 month follow-up assessment, including CPX, could provide an appropriate opportunity for identifying its attendance as well as the change in exercise capacity, both of which were associated with subsequent long-term prognosis.[25]

There may be several potential mechanisms by which CCR completion was associated with favourable long-term outcomes. First, a multidisciplinary disease management programme improves HF-related outcomes.[4–6] Contrary to CCR completion (*Figure 2*), the number of outpatient CCR sessions attended was not significantly associated with clinical outcomes (*Figure S1*), suggesting that the post-CCR assessment visits are more important than exercise training alone for improving clinical outcomes. Given that the visits involve comprehensive multidisciplinary management that provides education, individualized lifestyle intervention, and exercise prescription, it could allow patients and clinicians to review and discuss the 3 month clinical course of HF, based on the follow-up CPX and laboratory data, and help optimize HF therapies, modify lifestyle behaviours including daily physical activity, and develop self-monitoring and management skills to prevent HF hospitalizations. Second, the completers attended significantly more outpatient sessions during the CCR programme than the non-completers. This shows that the completers were more motivated and adherent to the programme. In the HF-ACTION study, poor exercise adherence was associated with a higher risk of cardiovascular death or HF hospitalization.[26] Moreover, adherence, even to placebo, was related to clinical outcomes in a randomized trial for HF patients, probably because high adherence is a surrogate marker for healthy lifestyle behaviours.[27] Therefore, it is likely that the completers maintain lifelong adherence to regular exercise, beneficial medications, and a salutary lifestyle beyond the formal CCR programme,[28] possibly leading to improved subsequent outcomes.

There was no significant relationship between the number of outpatient CCR sessions attended and the change in peak VO_2. This is likely because the effect of the CCR programme is proportional to the total volume of exercise,[29] including home exercise, which was not assessed in this study. The mean extent of the increase in peak VO_2 during the CCR programme (8.9%) in our patients was less than that previously reported (13–17%).[15,16] Given that older age was identified as an independent determinant of an impaired response to exercise training (*Table 5*), and the number of outpatient sessions was small even in the completers (median, 10 sessions for 3 months), the relatively high age (median, 65 years) as well as the modest intensity (30–50% of heart rate reserve) and the possibly small total volume of exercise training may

have contributed to the lower response to CCR. Further studies are needed to establish an individually tailored programme incorporating centre-based and home-based exercises aimed at improving the response to CCR.[30]

To the best of our knowledge, this is the first study that compared the prognostic value of the changes in exercise capacity and skeletal muscle strength simultaneously, and showed that the improvement in exercise capacity, but not in skeletal muscle strength, was associated with better long-term outcomes. Since the changes in exercise capacity and skeletal muscle strength are considered to reflect global (including cardiac) and peripheral reserve, respectively, this finding supports the assumption that HF-related outcome is more determined by the global than peripheral reserve.[25] Thus, HF patients should perform exercise training, targeting the improvement in exercise capacity for improving subsequent clinical outcomes, although further studies are needed to assess whether the improvement in skeletal muscle strength could be more beneficial for selected patients, such as those with frailty or sarcopenia.

Limitations

This study had some limitations. First, this was a retrospective observational study; a prospective randomized study would be essential to determine whether the attendance at the 3 month follow-up assessment, including CPX, would directly improve subsequent long-term outcomes among HF patients who participate in a CCR programme. Second, although baseline HF-related characteristics were well balanced between the completers and non-completers, the possibility that unmeasured residual confounders may have affected our findings could not be excluded. Third, only CCR participants who were able to perform CPX and did not experience the composite outcome within 180 days from the date of CCR participation were included; this might have introduced a selection bias towards a better outcome. Fourth, among the non-completers, data on exercise capacity after 3 months were not available owing to their defined characters, making it unclear whether CCR completion was associated with the improvement in exercise capacity. Finally, only patients at a single medical centre were included, and subgroup analysis was not adequately powered due to a limited number of patients, especially for female patients and patients with preserved LVEF. Therefore, our findings should be validated externally in a more general and larger HF patient cohort.

Conclusions

The present study demonstrated that among the HF patients who participated in the 3 month CCR programme, CCR completion (defined as attendance at post-CCR follow-up assessment including CPX) was associated with a lower risk of subsequent HF hospitalization and death. Additionally, within the group of patients who completed the programme, the greater improvement in exercise capacity, but not in skeletal muscle strength, over the 3-month period was associated with better long-term outcomes. These findings highlight the importance of the post-CCR follow-up assessment, including CPX, to identify a patient's adherence and response to the CCR programme, both of which were associated with subsequent long-term clinical outcomes.

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Conflict of interest

None declared.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Univariate and multivariate associations of variables with all-cause death among 772 participants.
Table S2. The effect of CCR completion on the incidence of the composite of all-cause death or HF hospitalization according to subgroups based on baseline characteristics.
Figure S1. Kaplan–Meier cumulative curves for clinical outcomes according to median value of the number of outpatient CCR sessions attended during the CCR program among the 762 patients for whom data were available.
In the entire cohort, patients with the number (N) of outpatient sessions attended $\geq$7 shows a trend towards lower rates of the composite of all-cause death or heart failure hospitalization (S1A) and all-cause death (S1B) than those with the number $\leq$6. No difference is observed in either endpoint between patients with and without the number $\geq$10 among the completers (S1C, S1D). There is no difference in either endpoint between patients with and without the number $\geq$1 among the non-completers (S1E, S1F). CCR, comprehensive cardiac rehabilitation.

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