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ORIGINAL ARTICLE

# Comprehensive Cardiac Rehabilitation Following Acute Myocardial Infarction Improves Clinical Outcomes Regardless of Exercise Capacity

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***Background:*** Reduced exercise capacity is a prognostic indicator of adverse outcomes in patients with acute myocardial infarction (AMI). However, few studies have evaluated the effectiveness of comprehensive cardiac rehabilitation (CR) in this population. This study aimed to clarify the efficacy of comprehensive CR in patients with AMI and reduced exercise capacity.

***Methods and Results:*** This cohort study included 610 patients with AMI who underwent percutaneous coronary intervention. Major adverse cardiovascular events (MACE) were compared between patients who participated in comprehensive outpatient CR for 150 days (CR group; n=430) and those who did not (non-CR group; n=180). During the mean (±SD) follow-up period of 6.1±4.0 years, the CR group exhibited a lower incidence of MACE (log-rank P=0.002). Multivariable analysis revealed that Killip classification, diuretics at discharge, and participation in comprehensive CR were independently associated with MACE. The CR group was further divided into 2 groups, namely reduced exercise capacity (% predicted peak $\dot{V}O_2$ <80%; n=241) and preserved exercise capacity (≥80%; n=147), based on the initial cardiopulmonary exercise test. Despite distinct exercise capacities, the incidence of MACE was comparable and physical parameters improved similarly after comprehensive CR in both groups.

***Conclusions:*** Comprehensive CR in patients with AMI effectively reduced the incidence of MACE regardless of initial exercise capacity. Cardiologists should actively encourage patients with low exercise capacity to participate in comprehensive CR.

**Key Words:** Acute myocardial infarction; Cardiopulmonary exercise test; Comprehensive cardiac rehabilitation; Exercise capacity

Acute myocardial infarction (AMI) is a life-threatening cardiovascular disease requiring prompt diagnosis, timely coronary revascularization, and optimal medical therapy. Over the past 2 decades, evidence-based treatments have been established, resulting in improved survival and reduced risk of recurrent ischemic events in patients with AMI.[1] Comprehensive cardiac rehabilitation (CR), including exercise training, lifestyle modifications, and education, has been shown to significantly reduce the risk of recurrent cardiovascular events and mortality in patients with AMI.[2,3] However, patients with reduced exercise capacity have worse clinical outcomes than those with preserved exercise capacity.[4] Nevertheless, few studies have investigated the efficacy and safety of comprehensive CR in patients with AMI and reduced exercise capacity. Therefore, the aim of this study was to evaluate the efficacy of comprehensive CR in reducing the incidence of cardiac events in patients with AMI, regardless of exercise capacity.

## Methods

### Study Population

This study included 685 patients with AMI who underwent percutaneous coronary intervention (PCI) at Sakakibara Heart Institute (Tokyo, Japan) between 2008 and 2015. AMI was defined as the presence of pathological and/or new Q waves on an electrocardiogram (ECG) along with elevated troponin T and/or creatine kinase myocardial band levels exceeding the upper limit of normal.[5] Patients with valvular disease Grade ≥2+, respiratory disorders, or those lost to follow-up were excluded. After applying these exclusions, patients who received supervised CR were divided into 2 groups based on its duration: a non-CR group, in which CR was performed during the acute and

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in-hospital phases until discharge; and a continued comprehensive CR group, which continued CR during the outpatient phase. Patient characteristics and clinical outcomes were compared between these 2 groups.

Within the comprehensive CR group, patients who did not undergo a cardiopulmonary exercise test (CPET) at the beginning of the program were excluded, and the remaining patients were further categorized into a reduced exercise capacity group (% predicted peak oxygen consumption [$\dot{V}O_2$] <80%) and a preserved exercise capacity group (% predicted peak $\dot{V}O_2$ ≥80%) based on the results of the initial CPET in order to investigate associations between exercise capacity and clinical outcomes.

All medical treatment decisions, including participation in the comprehensive CR program, were made by the attending physicians, without any intervention from the researchers. All information was obtained retrospectively from medical records or via telephone interviews, which were performed once a year. AMI patients with and without comprehensive CR were investigated through regular visits to the Sakakibara Heart Institute every 3 months during the first year following AMI. Subsequently, after the initial year, patients underwent annual checkups, which included physical examinations, blood laboratory tests, 12-lead ECG, chest X-rays, and transthoracic echocardiograms, all conducted at the Sakakibara Heart Institute and coordinated with their visits to primary care physicians. Additional assessments, including coronary artery computed tomography, myocardial scintigraphy, and coronary angiography, were not part of the routine protocol, but were performed when deemed necessary.

This study was approved by the Research Ethics Board of Sakakibara Heart Institute (Approval no. 16-005) and was conducted in compliance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients involved in the study.

### Exercise Program

At the Sakakibara Heart Institute, we adhere to the Japanese Circulation Society's 2012 guidelines for rehabilitation in patients with cardiovascular disease[6] and routinely implement a CR program as part of our cardiovascular treatment protocols. Patients who participated in acute-phase CR at the bedside a few days after revascularization then underwent in-hospital recovery-phase CR in a rehabilitation room for 1–2 weeks. Following this, patients were shifted to outpatient recovery-phase CR, which was conducted between 1 and 3 times per week up to 150 days and consisted of supervised exercise program at a workload corresponding to 1 min before the anaerobic threshold (AT), with or without resistance training. According to a patient's load (W) at AT-1 min, the load was then adjusted by their heart rate at the AT level and 11–13 on the Borg scale. A 10-min stretching routine was performed as a gradual warm-up before exercises were initiated. Medical staff monitored patients' vital signs every 10 min throughout the exercise session, and the duration of each exercise session was limited to 30 min of continuous activity without rest intervals.

Treadmill walking and the use of a bicycle ergometer were the main exercises performed. The exercise intensity for both treadmill walking and the bicycle ergometer was determined on the basis of the AT level. Following the exercise session, there was a gradual cooling-down period of up to 10 min.

In cases of atrial fibrillation, in which the heart rate is considered difficult to use for exercise prescription, the CR program was organized according to the AT level as for cases of sinus rhythm. However, when the heart rate response was too intense, the intensity of the exercise was adjusted to Borg 13 to ensure that the heart rate did not exceed 120 beats/min. We allowed a target heart rate of 120 beats/min in all patients provided Borg 13 was not exceeded.

Handgrip strength and lower limb muscle strength were routinely assessed before and after the CR program. In addition to the hospital-based exercise program, patients were advised to engage in home exercises, which included 30 min of anaerobic exercises at least 3 times per week.

### Comprehensive CR Supervised by a Multidisciplinary Rehabilitation Team

A multidisciplinary rehabilitation team comprising cardiologists, cardiac care nurses, expert physical therapists, certified public psychologists, registered dietitians, and social workers supervised patients throughout the exercise program. Cardiologists played a crucial role in assessing patients, prescribing medications, and providing medical guidance during rehabilitation. Cardiac care nurses monitored patients' vital signs during exercise, administered medications, and provided education on lifestyle modifications, including diet, exercise habits, stress management, and medication adherence on at least 3 occasions: initially (before the CR program), mid-term (1 month after starting the CR program), and at the conclusion of the 3-month CR program. Physical therapists designed and implemented exercise programs tailored to individual patients, monitored their progress, and provided education on safe and effective physical activity. Certified public psychologists played a critical role in addressing the psychological and emotional aspects of CR. Psychologists implemented a patient dementia and anxiety questionnaire twice throughout the CR program: at the beginning and end of the CR program. Psychologists provided counseling and support to help patients manage stress, anxiety, depression, and lifestyle adjustments. Dietitians provided nutritional counseling twice during the CR program, helping patients make appropriate dietary choices to promote heart health and manage conditions such as hypertension, hypercholesterolemia, and diabetes. Social workers in CR provided essential psychosocial support and advocacy to patients and their families. Multidisciplinary conferences were held each morning as huddle meetings, and all members met once a week.

### Echocardiography

Transthoracic echocardiography was routinely performed before comprehensive CR. All echocardiographic assessments were performed by experienced echocardiographers according to the guidelines of the American Society of Echocardiography.[7] Measurements were taken for left atrial diameter, interventricular septal wall thickness, left ventricular (LV) posterior wall thickness, LV end-diastolic and end-systolic diameters, LV ejection fraction (LVEF; modified Simpson's method), and right ventricular systolic pressure.

### CPETs

CPET was generally conducted twice, at the beginning and end of comprehensive CR, to assess exercise capacity. CPET was performed using a bicycle ergometer (Strength

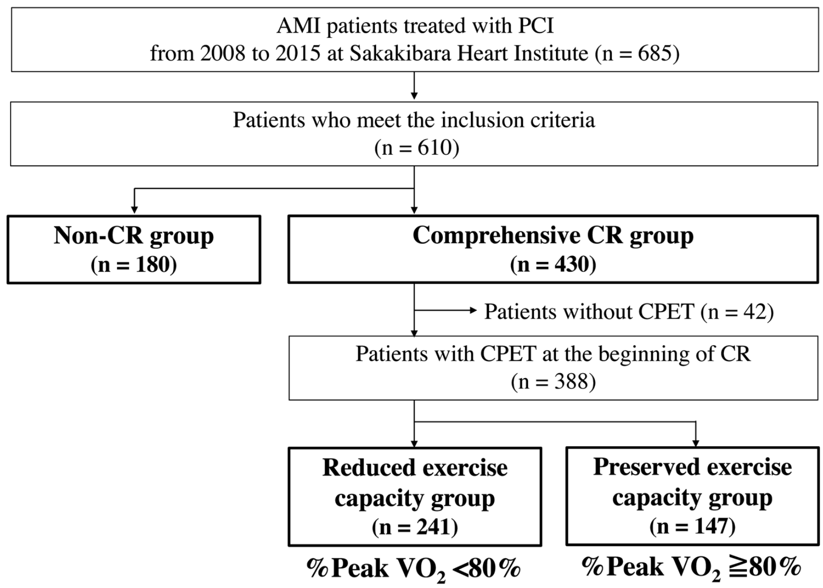


**Figure 1.** Flowchart showing patient disposition in this study. AMI, acute myocardial infarction; CPET, cardiopulmonary exercise test; CR, cardiac rehabilitation; PCI, percutaneous coronary intervention; $\dot{V}O_2$, oxygen consumption.

Ergo 8; Mitsubishi Electric Engineering Co., Ltd., Tokyo, Japan). After a 4-min rest on the bicycle ergometer, exercise began with a 4-min warm-up at 0 or 20 W. After the warm-up, the workload was increased by 10 or 20 W/min until the patients reached their symptomatic limit or met the termination criteria, which included exhaustion, angina, drop or elevation in blood pressure, ST segment changes, and arrhythmias. For elderly patients or those without exercise habits prior to AMI, CPET was adjusted to a low-intensity protocol: a 4-min warm-up at 0 W and a workload increase with 10 W/min to prevent reaching the AT level during warm-up.

Peak $\dot{V}O_2$, carbon dioxide ($CO_2$) production, and minute ventilation were continuously recorded using an ML-9000 system (Fukuda Denshi Co., Ltd., Tokyo, Japan). AT, peak $\dot{V}O_2$, ventilatory equivalent for carbon dioxide ($\dot{V}E/\dot{V}CO_2$), end-tidal oxygen tension ($PetO_2$), end-tidal carbon dioxide tension ($PetCO_2$), and the respiratory exchange ratio (RER) were determined. AT was determined using a combination of V-slope, ventilatory equivalent, and the end-tidal methods.[8,9] In the V-slope method, AT was identified as the point at which the V-slope started to exceed 45°. In the ventilatory equivalent method, AT corresponds to the $\dot{V}O_2$ at which $\dot{V}E/\dot{V}O_2$, after reaching the lowest point, starts to increase consistently, while $\dot{V}E/\dot{V}CO_2$ remains unchanged. In the end-tidal method, AT was identified when $PetO_2$ started to increase while $PetCO_2$ remained stable. AT and peak $\dot{V}O_2$ values were adjusted for age and sex (% predicted AT and % predicted peak $\dot{V}O_2$, respectively) using the predictive equations of Itoh et al.[10]

### Outcomes

The primary endpoint was major adverse cardiovascular events (MACE) occurring after discharge. MACE was defined as cardiovascular death, stroke (including brain hemorrhage or infarction), either ST-elevation myocardial infarction (STEMI) or non-STEMI, unstable angina, and hospitalization for heart failure.[11]

### Statistical Analysis

Continuous variables are presented as the mean±SD, whereas categorical variables are reported as numbers and percentages. The normality of distribution of continuous variables was assessed using the Shapiro-Wilk test. Continuous variables were compared using Mann-Whitney U test or McNemar test, as appropriate. Categorical variables were compared using the Fisher's exact test or Chi-squared test, as appropriate. For survival analysis, Kaplan-Meier curves were plotted to demonstrate the cumulative incidence of MACE. The log-rank test was used for comparisons between groups. To identify the predictors of MACE, candidate variables were analyzed using a Cox proportional hazard model. For the multivariable analysis, variables were selected in the model based on univariate analyses and clinical consideration. Predictors for MACE were expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). Statistical significance was set at 2-sided $P<0.05$. All statistical analyses were performed using JMP software version 17.0.0 (SAS institute Inc., Cary, NC, USA) and R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

## Results

### Impact of Comprehensive CR on Clinical Outcomes Following AMI

Of 685 consecutive patients with AMI who underwent PCI, 610 met the inclusion criteria (**Figure 1**). Among these patients, 180 (defined as the non-CR group) participated in acute and in-hospital recovery-phase CR, whereas 430 patients (defined as the CR group) participated in outpatient recovery-phase CR. Baseline characteristics of the non-CR and CR groups are presented in **Table 1**. There was a higher proportion of women in the CR group. In addition, patients in the non-CR group had a longer distance from home to hospital, a higher prescription rate of diuretics at discharge, and a higher right ventricular systolic pressure than the CR group. The prevalence of

**Table 1. Patient Characteristics at Baseline**

| | Non-CR group (n=180) | CR group (n=430) | P value |
|---|---|---|---|
| Age (years) | 68.0±13.3 | 66.0±11.7 | 0.07 |
| Female sex | 60 (33.3) | 187 (43.5) | 0.02 |
| BMI (kg/m²) | 24.1±3.4 | 24.5±3.9 | 0.32 |
| Hypertension | 103 (57.2) | 272 (63.3) | 0.17 |
| Diabetes | 67 (37.2) | 145 (33.7) | 0.46 |
| Dyslipidemia | 165 (91.7) | 386 (89.8) | 0.46 |
| CKD (eGFR <60 mL/min/1.73 m²) | 53 (29.4) | 121 (28.1) | 0.77 |
| Current and past smoker | 120 (66.7) | 279 (64.9) | 0.67 |
| Family history of CAD | 36 (20.0) | 102 (23.7) | 0.34 |
| Atrial fibrillation | 16 (8.9) | 23 (5.3) | 0.11 |
| Road distance from home to hospital ≥30 km | 13 (7.2) | 12 (2.8) | 0.01 |
| STEMI | 158 (87.8) | 380 (88.4) | 0.84 |
| Killip class I | 163 (90.6) | 375 (87.2) | 0.24 |
| Peak creatine kinase (U/L) | 2,650±2,580 | 2,840±2,774 | 0.45 |
| **Culprit coronary artery** | | | 0.75 |
| Left main trunk | 2 (1.1) | 5 (1.2) | |
| Left anterior descending artery | 93 (51.7) | 237 (55.1) | |
| Left circumflex artery | 19 (10.6) | 50 (11.6) | |
| Right coronary artery | 65 (36.1) | 138 (32.1) | |
| Bypass graft | 1 (0.6) | 0 (0.0) | |
| **Laboratory data at discharge** | | | |
| Hemoglobin (g/dL) | 13.8±1.75 | 14.0±1.73 | 0.17 |
| Serum albumin (mg/dL) | 4.01±0.45 | 4.09±0.44 | 0.07 |
| eGFR (mL/min/1.73 m²) | 70.5±22.1 | 73.1±19.4 | 0.20 |
| Triglyceride (mg/dL) | 160±116 | 160±122 | 0.99 |
| HDL-C (mg/dL) | 47.7±13.3 | 49.1±12.5 | 0.27 |
| LDL-C (mg/dL) | 125±38.0 | 132±40.5 | 0.09 |
| NT-proBNP (pg/mL) | 1,316±2,140 | 917±1,634 | 0.06 |
| CRP (mg/dL) | 1.33±3.15 | 1.06±2.74 | 0.36 |
| **Medication at discharge** | | | |
| Statin | 158 (87.8) | 362 (84.2) | 0.25 |
| β-blocker | 169 (93.9) | 389 (90.5) | 0.17 |
| ACEi/ARB | 149 (82.8) | 337 (78.4) | 0.23 |
| Diuretics | 41 (22.8) | 57 (13.3) | 0.004 |
| **Echocardiographic parameters before CR** | | | |
| LA diameter (mm) | 36.4±5.9 | 35.8±5.0 | 0.23 |
| LV end-diastolic diameter (mm) | 46.2±5.7 | 45.8±5.2 | 0.39 |
| LV end-systolic diameter (mm) | 32.2±5.6 | 31.9±5.5 | 0.55 |
| LVEF (%) | 53.5±10.8 | 53.0±10.6 | 0.57 |
| RV systolic pressure (mmHg) | 22.2±8.0 | 20.4±8.4 | 0.02 |

Unless indicated otherwise, data are given as the mean ± SD or n (%). ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; CR, cardiac rehabilitation; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LA, left atrium; LDL-C, low-density lipoprotein cholesterol; LV, left ventricle; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro B-type natriuretic peptide; RV, right ventricle; STEMI, ST-elevation myocardial infarction.

STEMI, peak creatine kinase concentrations, and the culprit coronary artery were similar between the 2 groups.

During the mean follow-up period of 6.1±4.0 years, all-cause death and cardiovascular death occurred in 67 (11.0%) and 31 (5.1%) patients, respectively. The causes of cardiovascular deaths were sudden cardiac death (n=19), heart failure (n=4), cerebral hemorrhage (n=3), AMI (n=2), aortic dissection (n=1), rupture of an abdominal aortic aneurysm (n=1), and subarachnoid hemorrhage (n=1). The cumulative incidence of all-cause death and cardiovascular death was 1.5% and 1.1%, respectively, at 1 year and 6.2% and 2.3%, respectively, at 5 years.

At the final evaluation, MACE was observed in 98 (16.1%) patients. **Figure 2** shows Kaplan-Meier curves of the cumulative incidence of MACE, which was lower in the CR than non-CR group (log-rank P=0.002). Kaplan-Meier curves of cardiovascular death, stroke, acute coronary syndrome (including AMI and unstable angina), and

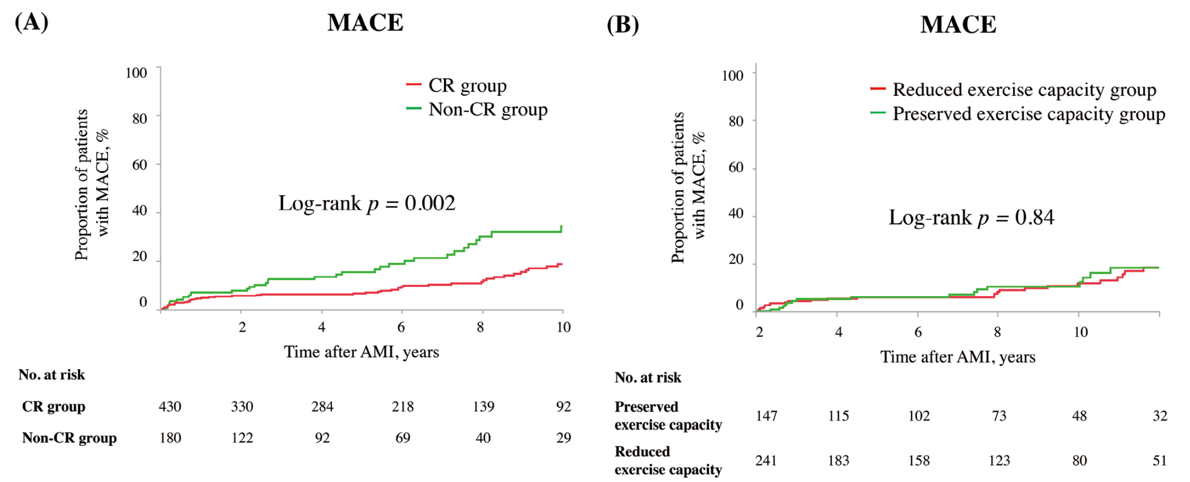


**Figure 2.** Kaplan-Meier curves showing the cumulative incidence of major adverse cardiovascular events (MACE) from the time of acute myocardial infarction (AMI) onset according to (**A**) participation in comprehensive cardiac rehabilitation (CR) and (**B**) exercise capacity among those participating in comprehensive CR. (**A**) During the follow-up period, the incidence of MACE was lower in the CR than non-CR group. (**B**) In the CR group, there was no significant difference in the incidence of MACE between those with reduced and preserved exercise capacity.

**Table 2. Factors Predictive of Major Adverse Cardiovascular Events**

| | Univariate | | | Multivariable | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | P value | aHR | 95% CI | P value |
| Age, per 10-year increase | 1.37 | 1.14–1.67 | 0.001 | 1.18 | 0.96–1.48 | 0.13 |
| Female sex | 0.78 | 0.52–1.18 | 0.25 | | | |
| BMI, per 1-kg/m² increase | 0.99 | 0.93–1.04 | 0.65 | | | |
| Hypertension | 0.94 | 0.59–1.38 | 0.64 | | | |
| Diabetes | 1.50 | 1.00–2.23 | 0.049 | 1.10 | 0.68–1.79 | 0.70 |
| Dyslipidemia | 0.91 | 0.42–1.98 | 0.82 | | | |
| CKD (eGFR <60 mL/min/1.73 m²) | 1.96 | 1.29–2.98 | 0.002 | 1.23 | 0.75–2.03 | 0.42 |
| Current and past smoker | 1.14 | 0.74–1.75 | 0.55 | | | |
| Family history of CAD | 0.81 | 0.51–1.30 | 0.39 | | | |
| Atrial fibrillation | 2.18 | 1.13–4.20 | 0.020 | 1.27 | 0.60–2.72 | 0.53 |
| Road distance from home to hospital ≥30 km | 1.42 | 0.57–3.49 | 0.45 | | | |
| STEMI | 1.06 | 0.53–2.10 | 0.86 | | | |
| Killip Class I | 0.42 | 0.26–0.69 | <0.001 | 0.51 | 0.25–0.88 | 0.02 |
| Peak creatine kinase, per 100-U/L increase | 1.01 | 1.00–1.01 | 0.053 | | | |
| Hemoglobin, per 1-g/dL increase | 0.93 | 0.82–1.05 | 0.22 | | | |
| Serum albumin, per 1-g/dL increase | 0.64 | 0.39–1.05 | 0.075 | | | |
| HDL-C, per 10-mg/dL increase | 0.81 | 0.67–0.95 | 0.030 | 0.84 | 0.68–1.19 | 0.98 |
| LDL-C, per 10 mg/dL increase | 0.96 | 0.91–1.01 | 0.21 | | | |
| NT-proBNP, per 100-pg/mL increase | 1.01 | 1.00–1.01 | 0.22 | | | |
| CRP, per 1-mg/dL increase | 0.97 | 0.86–1.05 | 0.50 | | | |
| Statin | 1.35 | 0.68–2.69 | 0.39 | | | |
| $\beta$-blocker | 3.79 | 0.93–15.4 | 0.062 | | | |
| ACEi/ARB | 0.80 | 0.48–1.33 | 0.39 | | | |
| Diuretics | 3.51 | 2.33–5.29 | <0.001 | 2.67 | 1.61–4.43 | <0.01 |
| LA diameter, per 1-mm increase | 1.49 | 1.00–2.17 | 0.044 | | | |
| LV end-diastolic diameter, per 1-mm increase | 1.32 | 0.90–1.93 | 0.15 | | | |
| LV end-systolic diameter, per 1-mm increase | 1.81 | 1.31–2.44 | <0.001 | | | |
| LVEF, per 5% increase | 0.87 | 0.81–0.95 | <0.001 | 0.94 | 0.86–1.04 | 0.24 |
| RV systolic pressure, per 10-mmHg increase | 1.33 | 1.02–1.72 | 0.032 | | | |
| Comprehensive CR participation | 0.53 | 0.35–0.80 | 0.002 | 0.61 | 0.38–0.98 | 0.04 |

aHR, adjusted hazard ratio; CI, confidence interval; HR, hazard ratio. Other abbreviations as in Table 1.

**Table 3. Baseline Characteristics of Patients Participating in Comprehensive CR According to Exercise Capacity**

| | Reduced exercise capacity (n=241) | Preserved exercise capacity (n=147) | P value |
|---|---|---|---|
| Age (years) | 63.9±13.3 | 68.1±11.2 | <0.01 |
| Female sex | 133 (55.2) | 36 (24.5) | <0.01 |
| BMI (kg/m²) | 25.1±4.2 | 23.6±2.8 | <0.01 |
| Hypertension | 141 (58.5) | 101 (68.7) | 0.04 |
| Diabetes | 89 (36.9) | 41 (27.9) | 0.07 |
| Dyslipidemia | 218 (90.5) | 133 (90.5) | 0.99 |
| CKD (eGFR <60 mL/min/1.73 m²) | 68 (28.2) | 38 (25.9) | 0.64 |
| Current and past smoker | 154 (63.9) | 97 (66.0) | 0.68 |
| Family history of CAD | 71 (29.5) | 31 (21.1) | 0.08 |
| Atrial fibrillation | 13 (5.4) | 6 (4.1) | 0.64 |
| Road distance from home to hospital ≥30 km | 12 (5.0) | 0 (0.0) | <0.01 |
| STEMI | 215 (89.2) | 130 (88.4) | 0.87 |
| Killip Class I | 204 (84.6) | 138 (93.9) | <0.01 |
| Peak creatine kinase (U/L) | 2,998±2,920 | 2,670±2,508 | 0.27 |
| **Culprit coronary artery** | | | 0.78 |
| Left main trunk | 2 (0.8) | 0 (0.0) | |
| Left anterior descending artery | 137 (56.9) | 77 (52.4) | |
| Left circumflex artery | 29 (12.0) | 17 (11.6) | |
| Right coronary artery | 73 (30.3) | 52 (35.4) | |
| Bypass graft | 0 (0.0) | 1 (0.7) | |
| **Laboratory data at discharge** | | | |
| Hemoglobin (g/dL) | 14.1±1.74 | 14.1±1.56 | 0.88 |
| Serum albumin (mg/dL) | 4.08±0.44 | 4.11±0.46 | 0.55 |
| eGFR (mL/min/1.73 m²) | 73.4±19.9 | 74.9±16.3 | 0.50 |
| Triglyceride (mg/dL) | 163±124 | 156±125 | 0.63 |
| HDL-C (mg/dL) | 47.5±12.0 | 51.9±12.4 | <0.01 |
| LDL-C (mg/dL) | 136±44.2 | 124±32.5 | 0.02 |
| NT-proBNP (pg/mL) | 911±1,511 | 893±1,890 | 0.94 |
| CRP (mg/dL) | 1.12±2.97 | 0.85±2.24 | 0.44 |
| **Medication at discharge** | | | |
| Statin | 204 (84.6) | 127 (86.4) | 0.66 |
| β-blocker | 217 (90.0) | 134 (91.2) | 0.72 |
| ACEi/ARB | 184 (76.3) | 119 (81.0) | 0.31 |
| Diuretics | 50 (20.7) | 22 (15.0) | 0.18 |
| **Echocardiographic parameters before CR** | | | |
| LA diameter (mm) | 36.1±5.0 | 35.1±4.7 | 0.07 |
| LV end-diastolic diameter (mm) | 45.9±5.4 | 45.9±4.7 | 0.98 |
| LV end-systolic diameter (mm) | 32.2±5.7 | 31.3±4.8 | 0.18 |
| LVEF (%) | 52.1±11.5 | 54.6±8.3 | 0.04 |
| RV systolic pressure (mmHg) | 20.1±8.6 | 20.4±8.3 | 0.80 |

Unless indicated otherwise, data are given as the mean ± SD or n (%). Abbreviations as in Table 1.

hospitalization for heart failure (**Supplementary Figure**) did not differ significantly between the CR and non-CR groups. After performing univariate analyses, several baseline variables, including age, diabetes, chronic kidney disease, atrial fibrillation, Killip class I, high-density lipoprotein cholesterol (HDL-C), diuretics at discharge, LVEF, and participation in comprehensive CR were included in the multivariable Cox regression analysis to identify predictors of MACE (**Table 2**). The results showed that Killip Class I (adjusted [a] HR 0.51; 95% CI 0.25–0.88; P=0.02), diuretics at discharge (aHR 2.67; 95% CI 1.61–4.43; P<0.001), and participation in comprehensive CR (aHR 0.61; 95% CI 0.38–0.98; P=0.04), were independently associated with MACE.

## Association Between Exercise Capacity and Clinical Outcomes

Next, we investigated the association between exercise capacity and patient characteristics, clinical outcomes, and physical parameters. Of the 430 patients in CR group, the 388 who underwent CPET at the beginning of the comprehensive CR were further divided into 2 groups based on the results of the initial CPET (**Figure 1**): those with reduced exercise capacity (mean peak $\dot{V}O_2$ 17.2±3.9 mL/min/kg, % predicted peak $\dot{V}O_2$ 63.7±1.1%; n=241) and those with preserved exercise capacity (mean peak $\dot{V}O_2$ 23.1±4.6 mL/min/kg,

**Table 4. Cardiopulmonary Exercising Test and Physical Assessment Test Parameters of Patients Participating in Comprehensive CR According to Exercise Capacity**

| | Reduced exercise capacity (n=241) | Preserved exercise capacity (n=147) | P value |
|---|---|---|---|
| **Cardiopulmonary exercising test parameters** | | | |
| Peak $\dot{V}O_2$ (mL/kg/min) | 17.2±3.9 | 23.1±4.6 | <0.01 |
| % Predicted peak $\dot{V}O_2$ | 63.7±1.1 | 93.5±1.1 | <0.01 |
| AT (mL/kg/min) | 11.5±1.9 | 13.9±2.4 | <0.01 |
| % Predicted | 75.5±1.7 | 95.5±1.4 | <0.01 |
| $\dot{V}E/\dot{V}CO_2$ slope | 32.2±6.1 | 30.5±4.9 | <0.01 |
| Resting heart rate (beats/min) | 69.2±9.49 | 67.0±10.4 | 0.03 |
| Resting SBP (mmHg) | 114±20.0 | 118±21.8 | 0.05 |
| Resting DBP (mmHg) | 69.3±12.2 | 69.8±11.4 | 0.69 |
| Peak RER | 1.13±0.11 | 1.16±0.09 | <0.01 |
| Borg scale | 17.7±1.4 | 17.5±1.8 | 0.21 |
| **Physical assessment test parameters** | | | |
| Hand grip strength (kg) | 29.1±10.6 | 32.2±8.6 | 0.02 |
| Lower-limb muscle strength (kg) | 31.8±12.4 | 35.5±11.5 | 0.01 |
| Lower-limb muscle strength per body weight (%) | 48.3±1.0 | 56.5±1.3 | <0.01 |
| No. CR sessions | 13.6±0.7 | 15.9±0.9 | 0.04 |

Unless indicated otherwise, data are given as the mean±SD. AT, anaerobic threshold; CR, cardiac rehabilitation; DBP, diastolic blood pressure; RER, respiratory exchange ratio; SBP, systolic blood pressure; $\dot{V}E/\dot{V}CO_2$, ventilator equivalent for carbon dioxide; $\dot{V}O_2$, oxygen consumption.

% predicted peak $\dot{V}O_2$ 93.5±1.1%; n=147). The baseline characteristics of each group are presented in **Table 3**.

The reduced exercise capacity group was younger, had a higher prevalence of women, a higher body mass index, a lower prevalence of hypertension, a longer distance from home to hospital, a lower prevalence of Killip Class I, lower HDL-C concentrations, higher low-density lipoprotein cholesterol (LDL-C) concentrations, and a lower LVEF than the group with preserved exercise capacity. Medications at discharge were similar between the 2 groups. CPET results revealed similar peak exercise intensity in both groups according to Borg scale; however, the reduced exercise capacity group had a lower AT level, a higher $\dot{V}E/\dot{V}O_2$ slope, higher resting heart rate, and lower resting systolic blood pressure than the group with preserved exercise capacity (**Table 4**). In addition, physical parameters were worse (lower hand grip strength and lower-limb muscle strength) in the reduced exercise capacity group. Kaplan-Meier curves showed that there were no significant differences in the cumulative incidence of MACE between the reduced and preserved exercise capacity groups (**Figure 2**; log-rank P=0.84).

### Association Between Exercise Capacity and Physical Parameters

Of the 388 participants in the CR group, 300 (77.3%) underwent CPET at both the beginning and end of the CR program (184 patients in the reduced exercise capacity group and 116 patients in the preserved exercise capacity group). Both groups showed significant improvements in AT, peak $\dot{V}O_2$ levels, and the lower-limb muscle strength index after CR (**Figure 3**). The $\dot{V}E/\dot{V}CO_2$ slope improved significantly after CR in the group with reduced exercise capacity, but not in the group with preserved exercise capacity. After the CR program, 135 (73.4%) of 184 patients in the reduced exercise capacity group and 72 (62.1%) of 116 patients in the preserved exercise capacity group demonstrated an improvement in peak $\dot{V}O_2$. There were no significant differences in the incidence of MACE after the CR program between patients who did and did not achieve an improvement in peak $\dot{V}O_2$ (**Figure 4**).

## Discussion

The main findings of this study are as follows: (1) approximately 60% of patients with AMI who participated in comprehensive CR after PCI had reduced exercise capacity based on baseline CPET results; (2) comprehensive CR significantly reduced MACE in patients with AMI, regardless of exercise capacity; (3) Killip classification, diuretics at discharge, and participation in a comprehensive CR program were identified as independent predictors of MACE following AMI; (4) improvements in exercise capacity parameters after the CR program were similar between AMI patients with reduced and preserved exercise capacity; and (5) improvements in peak $\dot{V}O_2$ after the CR program were not associated with MACE.

At the beginning of the CR program, approximately 60% of patients with AMI had reduced exercise capacity based on initial CPET results. Given that % predicted peak $\dot{V}O_2$ is defined in reference to data from healthy volunteers, it is assumed that patients with AMI will initially have low exercise capacity due to a lack of exercise habits.[10] In addition, because the acute CR program was started during hospitalization, the period of bed rest during hospitalization may have contributed to decreased activity among patients with AMI. The multidisciplinary team strongly encouraged patients with AMI, especially those with low exercise tolerance, to participate in comprehensive CR. These factors may have contributed to the increase in the proportion of patients with reduced exercise capacity in the present study.

Previous studies have reported that reduced exercise capacity, as assessed by CPET, is associated with poor

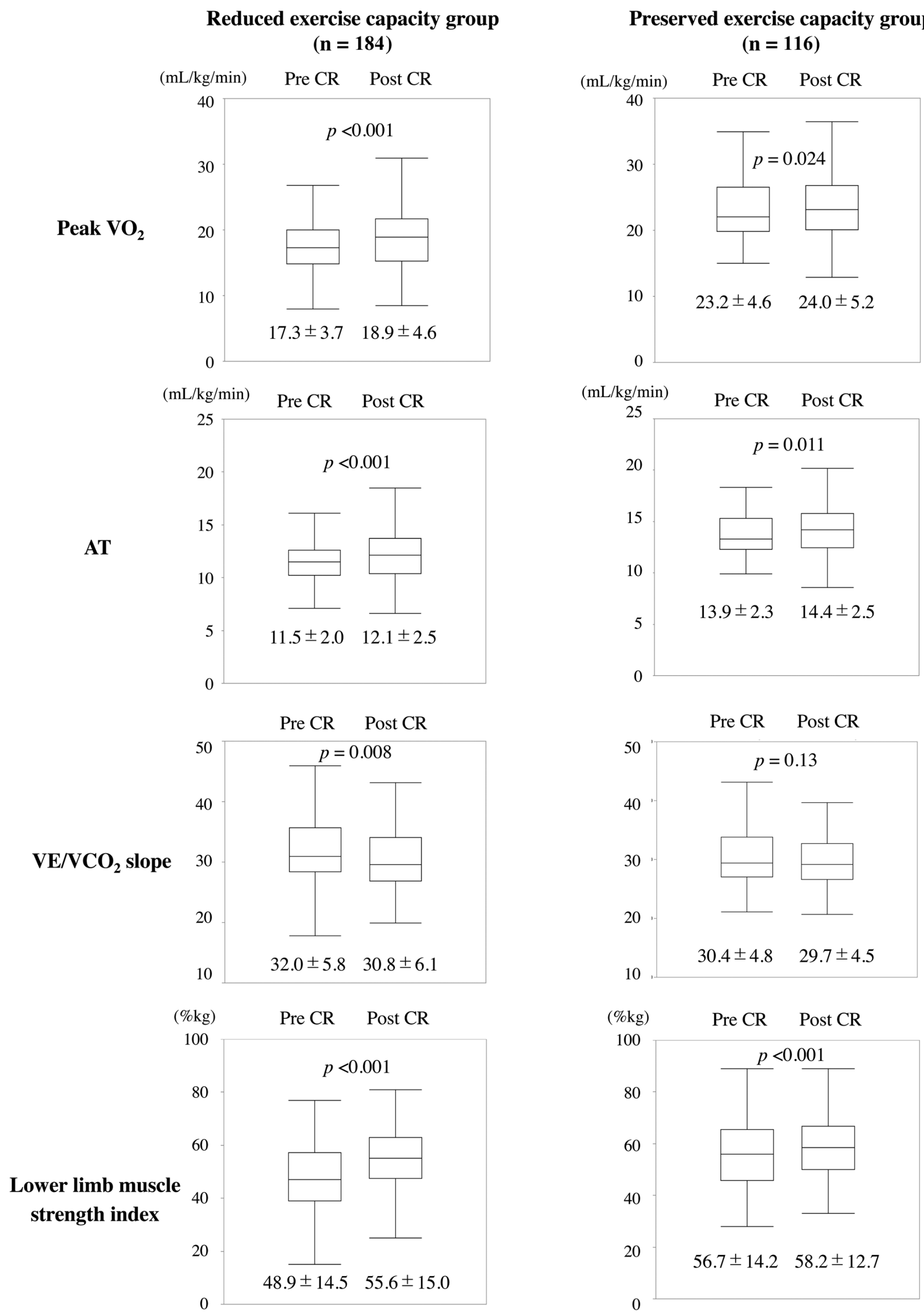


**Figure 3.** Association between exercise capacity in patients participating in comprehensive cardiac rehabilitation (CR) and physical parameters measured before (pre) and after (post) the CR program. The boxes show the interquartile range, with the median value indicated by the horizontal line; whiskers show the range. Values below each box plot are the mean±SD. AT, anaerobic threshold; $\dot{V}E/\dot{V}CO_2$, ventilatory equivalent of carbon dioxide; $\dot{V}O_2$, oxygen consumption.

prognosis in patients with heart failure, regardless of preserved or reduced LVEF.[12,13] In contrast, there are limited studies on the association between exercise capacity and clinical outcomes in patients with AMI. A previous study reported that AMI patients with reduced exercise capacity had significantly higher rates of mortality and hospitalization for heart failure within 1 year after AMI.[4] However, the effect of comprehensive CR on this patient population remains unclear. To the best of our knowledge, the present study is the first to evaluate the effects of comprehensive

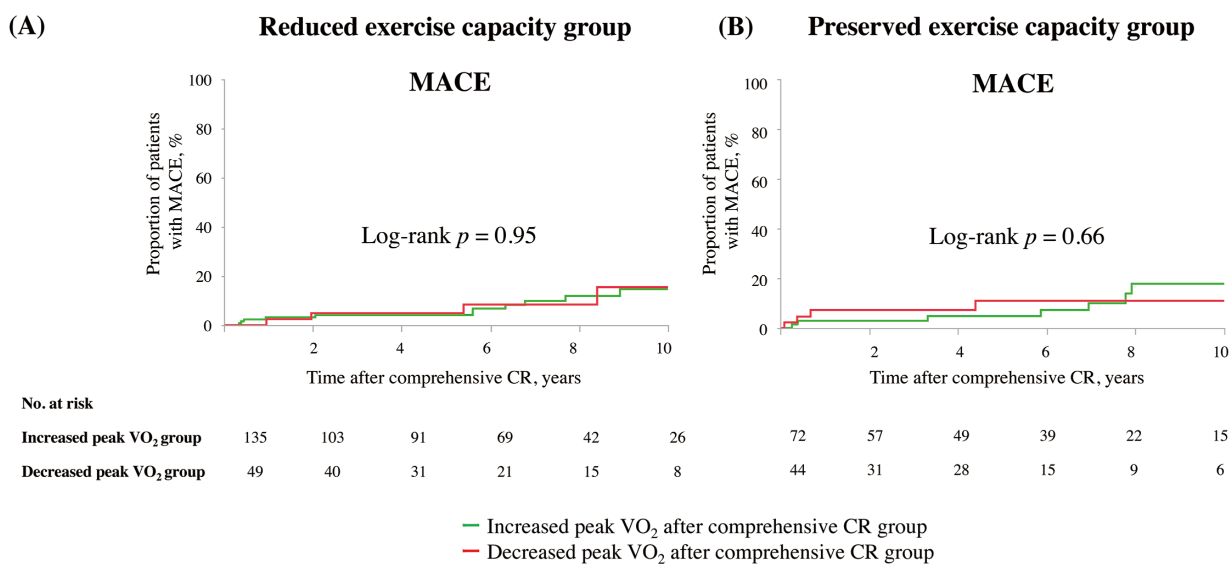


**Figure 4.** Kaplan-Meier curves showing the cumulative incidence of major adverse cardiovascular events (MACE) from the end of the comprehensive cardiac rehabilitation (CR) program in patients with (**A**) reduced and (**B**) preserved exercise capacity. The incidence of MACE was comparable between patients with and without improvements in peak oxygen consumption ($\dot{V}O_2$) after the CR program in both the reduced (**A**) and preserved (**B**) exercise capacity groups.

CR in patients with AMI with reduced exercise capacity. We found that comprehensive CR was independently associated with a reduction in the incidence of MACE following AMI. However, there are several discrepancies between the present and previous studies. For example, a CR program after AMI has been reported to decrease mortality and the recurrence of AMI;[14] however, in the present study, we did not find any significant differences in the incidence of these endpoints. One possible explanation for this apparent discrepancy is the low rate of recurrent AMI in our cohort: during the follow-up period, only 22 (3.6%) of 610 patients experienced recurrent AMI. The rate of cardiovascular death in our study was also low (5.1%), as noted above. The relatively low rate of these endpoints may have made it difficult for us to detect a statistically significant difference between the CR and non-CR groups in this study.

In the present study, a significant proportion of participants in the comprehensive CR group underwent exercise capacity assessment using CPET and received personalized exercise prescriptions based on their AT levels.[6] CPET serves as a valuable tool in helping patients understand the appropriate exercise intensity that is suitable for them, thereby facilitating effective and safe progression of their exercise regimen. Indeed, in addition to patients in the preserved exercise capacity group, those in the reduced exercise capacity group exhibited significant improvement after the CPET-based CR program. As shown in **Figure 3**, $\dot{V}E/\dot{V}O_2$ slope and the lower-limb muscle strength index improved after the CR program in the reduced exercise capacity group. Improvements in these respiratory and skeletal muscle parameters should have contributed to the enhanced oxygen uptake at AT and peak $\dot{V}O_2$ levels. Notably, in approximately one-third of patients who participated in the comprehensive CR, peak $\dot{V}O_2$ measured at the end of the program decreased compared with the initial CPET results. Importantly, the lack of short-term improvements in exercise capacity did not significantly impact long-term outcomes. These findings suggest that the benefits of participating in comprehensive CR extend beyond improvements in exercise capacity alone, emphasizing the importance of patient education, including medication adherence, nutritional guidance, lifestyle modifications, maintaining motivation, and regular medical checkups. Nevertheless, clinicians should investigate factors contributing to the decrease in exercise capacity after comprehensive CR, such as low attendance rates for the program, inadequate evaluation of initial CPET, and inappropriate exercise intensity (either too low or too high) during comprehensive CR programs.

The low participation rate in comprehensive CR following coronary revascularization requires urgent attention. Furthermore, despite the well-known health benefits of CR, the participation rate in comprehensive CR remains relatively stable, with only one-third of AMI patients taking part in CR.[15] The CR participation rate is lower among patients who undergo PCI than among those who undergo coronary artery bypass grafting (CABG) in Japan.[16] Only 6.9% of AMI patients treated with PCI participate in comprehensive CR, and participation rates vary significantly across PCI facilities (ranging from 0% to 36%).[17] This problem is particularly serious in Japan, where the participation rate in comprehensive CR after AMI was reported to be only 1.8%, compared with an in-hospital participation rate of 73.3% between 2014 and 2015.[18] At the Sakakibara Heart Institute, all patients with AMI participate in acute-phase in-hospital CR; however, approximately 30% do not transition to outpatient CR programs, although this rate is lower than that in previous studies.[17,18] Transitioning to outpatient CR programs is influenced by various patient-related factors, such as age, comorbidities, occupation, motivation, family support, and access to hospitals. Patients who work during the day find it difficult to manage their time to allow regular participation in a CR program. A long distance between the hospital and a patient's place of residence was also associated with a lower participation rate in outpatient CR.[19] Furthermore, the outbreak of the SARS-CoV-2 infection in 2019 made it difficult to gather in one place for exercise while maintaining social distancing. In recent years, studies have reported the effectiveness and safety of home-based CR programs, under remote supervision, for patients with heart failure.[20,21] These programs are expected to improve the CR participation rate among patients with heart disease who face difficulties related to geographic or social accessibility, even during the COVID-19 era.

Nevertheless, the low participation rate in comprehensive CR is not solely a patient-related issue, and is affected by insufficient recognition by healthcare professionals of the importance of comprehensive CR, as well as the lack of infrastructure and medical staff to implement CR programs.

In contrast with the widespread adoption of acute-phase invasive treatment for AMI, the implementation of comprehensive CR is notably poor in Japan.[22] The key to improving the participation rate is to address the significant decline in participation from acute-phase in-hospital CR to recovery-phase outpatient CR. Cardiologists should not underestimate the significance of comprehensive CR, because it can reduce cardiovascular events in patients. Multidisciplinary rehabilitation teams should actively encourage patients to participate in comprehensive CR.

### Study Limitations

This study has several limitations. First, this was a retrospective observational study conducted at a single institution. Second, the baseline exercise capacity of the patients in the non-CR group was not available. Third, the study predominantly included patients with Killip Class I, which limited our ability to assess the effectiveness of comprehensive CR in severe cases of AMI, and the rate of MACE was lower than studies that included severe cases of AMI. Fourth, patients who underwent CABG were not included in this study to eliminate concerns about potential differences in post-procedural outcomes between PCI and CABG. Fifth, patients who did not undergo CPET, including those who underwent an exercise capacity evaluation using a treadmill test, were excluded from the comprehensive CR group. Sixth, referral bias could have affected our study, given that the Sakakibara Heart Institute is a specialized heart disease center, leading to an underestimation of the incidence of cerebrovascular events. Seventh, we lack data confirming whether patient education was sufficient to ensure patients' appropriate medication adherence, nutritional guidance, and home exercises. The impact of these social factors should not be underestimated when assessing mortality in AMI patients. Mortality can be improved not only by exercise, but also by social interventions, such as dietary advice,[23] smoking cessation,[24] disease education,[25] and stress management,[26] from multidisciplinary CR staff. The important issue is that it was difficult to evaluate each intervention's contribution to patient mortality during the CR program, as noted in a previous meta-analysis.[27] This may be a potential limitation of all CR trials worldwide. Although it remains debatable whether difference of baseline RER affect the peak $\dot{V}O_2$ or not, previous studies reported that differences in baseline RER did not affect peak $\dot{V}O_2$,[28] and we believe that the result of the peak Borg scale was sufficient to signal the end of the CPET.

## Conclusions

Comprehensive CR after PCI in patients with AMI effectively reduces the incidence of MACE, regardless of the patients' baseline exercise capacity. Cardiologists should actively encourage patients with low exercise capacity to participate in comprehensive CR.

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### Disclosures

There are no conflicts of interest to declare.

### Author Contributions

Conceptualization: T. Hiruma and A.N.; Data curation: T. Hiruma, A.N., and J.S.; Formal analysis: T. Hiruma; Investigation: T. Hiruma and A.N.; Methodology: T. Hiruma and A.N.; Project administration: A.N.; Writing original draft: T. Hiruma; Writing review and editing: T. Hiruma, A.N., J.S., and K.H.; Supervision: M.N, T. Hosoda, and M.I.

### Data Availability

The datasets generated and analyzed during the present study are available from the corresponding author upon reasonable request.

### References

1. Szummer K, Wallentin L, Lindhagen L, Alfredsson J, Erlinge D, Held C, et al. Improved outcomes in patients with ST-elevation myocardial infarction during the last 20 years are related to implementation of evidence-based treatments: Experiences from the SWEDEHEART registry 1995–2014. *Eur Heart J* 2017; **38:** 3056–3065, doi:10.1093/eurheartj/ehx515.
2. Anderson L, Oldridge N, Thompson DR, Zwisler AD, Rees K, Martin N, et al. Exercise-based cardiac rehabilitation for coronary heart disease: Cochrane systematic review and meta-analysis. *J Am Coll Cardiol* 2016; **67:** 1–12, doi:10.1016/j.jacc.2015.10.044.
3. Makita S, Yasu T, Akashi YJ, Adachi H, Izawa H, Ishihara S, et al. JCS/JACR 2021 guideline on rehabilitation in patients with cardiovascular disease. *Circ J* 2022; **87:** 155–235, doi:10.1253/circj.CJ-22-0234.
4. Tashiro H, Tanaka A, Ishii H, Motomura N, Arai K, Adachi T, et al. Reduced exercise capacity and clinical outcomes following acute myocardial infarction. *Heart Vessels* 2020; **35:** 1044–1050, doi:10.1007/s00380-020-01576-1572.
5. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth universal definition of myocardial infarction (2018). *J Am Coll Cardiol* 2018; **72:** 2231–2264, doi:10.1016/j.jacc.2018.08.1038.
6. JCS Joint Working Group. Guidelines for rehabilitation in patients with cardiovascular disease (JCS 2012). *Circ J* 2014; **78:** 2022–2093, doi:10.1253/circj.CJ-66-0094.
7. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP 3rd, Gentile F, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: Executive summary: A report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *Circulation* 2021; **143:** e35–e71, doi:10.1161/CIR.0000000000000932.
8. Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. *J Appl Physiol* 1986; **60:** 2020–2027, doi:10.1152/jappl.1986.60.6.2020.
9. Sietsema KE, Stringer WW, Sue DY, Ward S, editors. Wasserman

& Whipp's principles of exercise testing and interpretation, 6th edn. Philadelphia: Wolters-Kluwer, 2020.
10. Itoh H, Ajisaka R, Koike A, Makita S, Omiya K, Kato Y, et al. Heart rate and blood pressure response to ramp exercise and exercise capacity in relation to age, gender, and mode of exercise in a healthy population. *J Cardiol* 2013; **61:** 71–78, doi:10.1016/j.jjcc.2012.09.010.
11. Hicks KA, Tcheng JE, Bozkurt B, Chaitman BR, Cutlip DE, Farb A, et al. 2014 ACC/AHA key data elements and definitions for cardiovascular endpoint events in clinical trials: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (Writing Committee to Develop Cardiovascular Endpoints Data Standards). *J Am Coll Cardiol* 2015; **66:** 403–469, doi:10.1016/j.jacc.2014.12.018.
12. Shafiq A, Brawner CA, Aldred HA, Lewis B, Williams CT, Tita C, et al. Prognostic value of cardiopulmonary exercise testing in heart failure with preserved ejection fraction: The Henry Ford HospITal CardioPulmonary EXercise Testing (FIT-CPX) project. *Am Heart J* 2016; **174:** 167–172, doi:10.1016/j.ahj.2015.12.020.
13. Keteyian SJ, Patel M, Kraus WE, Brawner CA, McConnell TR, Piña IL, et al. Variables measured during cardiopulmonary exercise testing as predictors of mortality in chronic systolic heart failure. *J Am Coll Cardiol* 2016; **67:** 780–789, doi:10.1016/j.jacc.2015.11.050.
14. Hammill BG, Curtis LH, Schulman KA, Whellan DJ. Relationship between cardiac rehabilitation and long-term risks of death and myocardial infarction among elderly Medicare beneficiaries. *Circulation* 2010; **121:** 63–70, doi:10.1161/CIRCULATIONAHA.109.876383.
15. Peters AE, Keeley EC. Trends and predictors of participation in cardiac rehabilitation following acute myocardial infarction: Data from the behavioral risk factor surveillance system. *J Am Heart Assoc* 2017; **7:** e007664, doi:10.1161/JAHA.117.007664.
16. Ohtera S, Kato G, Ueshima H, Mori Y, Nakatani Y, Ozasa N, et al. A nationwide survey on participation in cardiac rehabilitation among patients with coronary heart disease using health claims data in Japan. *Sci Rep* 2021; **11:** 20096.
17. Beatty AL, Doll JA, Schopfer DW, Maynard C, Plomondon ME, Shen H, et al. Cardiac rehabilitation participation and mortality after percutaneous coronary intervention: Insights from the Veterans Affairs clinical assessment, reporting, and tracking program. *Am Heart Assoc* 2018; **7:** e010010, doi:10.1161/JAHA.118.010010.
18. Komiyama J, Sugiyama T, Iwagami M, Ishimaru M, Sun Y, Matsui H, et al. Hospital-level variation in cardiac rehabilitation after myocardial infarction in Japan during fiscal years 2014–2015 using the national database. *Circ Rep* 2023; **5:** 177–186, doi:10.1253/circrep.CR-22-0113.
19. Nakayama A, Nagayama M, Morita H, Kawahara T, Komuro I, Isobe M. The use of geographical analysis in assessing the impact of patients' home addresses on their participation in outpatient cardiac rehabilitation: A prospective cohort study. *Environ Health Prev Med* 2020; **25:** 76, doi:10.1186/s12199-020-00917-x.
20. Kikuchi A, Taniguchi T, Nakamoto K, Sera F, Ohtani T, Yamada T, et al. Feasibility of home-based cardiac rehabilitation using an integrated telerehabilitation platform in elderly patients with heart failure: A pilot study. *J Cardiol* 2021; **78:** 66–71, doi:10.1016/j.jjcc.2021.01.010.
21. Nakayama A, Takayama N, Kobayashi M, Hyodo K, Maeshima N, Takayuki F, et al. Remote cardiac rehabilitation is a good alternative of outpatient cardiac rehabilitation in the COVID-19 era. *Environ Health Prev Med* 2020; **25:** 48, doi:10.1186/s12199-020-00885-882.
22. Goto Y, Saito M, Iwasaka T, Daida H, Kohzuki M, Ueshima K, et al. Poor implementation of cardiac rehabilitation despite broad dissemination of coronary interventions for acute myocardial infarction in Japan: A nationwide survey. *Circ J* 2007; **71:** 173–179, doi:10.1253/circj.71.173.
23. Li S, Chiuve SE, Flint A, Pai JK, Forman JP, Hu FB, et al. Better diet quality and decreased mortality among myocardial infarction survivors. *JAMA Intern Med* 2013; **173:** 1808–1818, doi:10.1001/jamainternmed.2013.9768.
24. Gerber Y, Rosen LJ, Goldbourt U, Benyamini Y, Drory Y; Israel Study Group on First Acute Myocardial Infarction. Smoking status and long-term survival after first acute myocardial infarction a population-based cohort study. *J Am Coll Cardiol* 2009; **54:** 2382–2387, doi:10.1016/j.jacc.2009.09.020.
25. Garvey N, Noonan B. Providing individualized education to patients post-myocardial infarction: A literature review. *Br J Cardiac Nurs* 2011; **6:** 73–79, doi:10.12968/bjca.2011.6.2.73.
26. Blumenthal JA, Jiang W, Babyak MA, Krantz DS, Frid DJ, Coleman RE, et al. Stress management and exercise training in cardiac patients with myocardial ischemia. Effects on prognosis and evaluation of mechanisms. *Arch Intern Med* 1997; **157:** 2213–2223, doi:10.1001/archinte.1997.00440400063008.
27. O'Connor GT, Buring JE, Yusuf S, Goldhaber SZ, Olmstead EM, Paffenbarger RS Jr, et al. An overview of randomized trials of rehabilitation with exercise after myocardial infarction. *Circulation* 1989; **80:** 234–244, doi:10.1161/01.cir.80.2.234.
28. Goedecke JH, St Clair Gibson A, Grobler L, Collins M, Noakes TD, Lambert EV. Determinants of the variability in respiratory exchange ratio at rest and during exercise in trained athletes. *Am J Physiol Endocrinol Metab* 2000; **279:** E1325–E1334.

## Supplementary Files

Please find supplementary file(s);
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