International Journal of Cardiology 292 (2019) 13–18

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Differential prognostic impact between completion and non-completion of a 5-month cardiac rehabilitation program in outpatients with cardiovascular diseases

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ARTICLE INFO

Article history:
Received 5 November 2018
Received in revised form 11 May 2019
Accepted 10 June 2019
Available online 12 June 2019

Keywords:
Successful group
Long-term
Clinical outcomes
Death
Hospital admission

ABSTRACT

Background: Cardiac rehabilitation (CR) is an essential component of care for patients with cardiovascular diseases (CVD). We aimed to evaluate clinical outcomes in outpatients with CVD who did and did not complete a 5-month CR program.

Methods: Three hundred thirty-two outpatients with CVD who participated in a 5-month CR program and were followed-up for maximum 5 years were registered. We divided the patients into two groups: those who completed the CR program (success group, $n = 175$) and those who could not (non-success group, $n = 157$). Both long-term (5 years) and short-term (5 months) clinical outcomes were compared between the two groups.

Results: There were no significant differences in patient characteristics at baseline between the success and non-success groups. With regard to both long-term and short-term clinical outcomes, the rates of all-cause death and hospital admission in the success group were significantly lower than those in the non-success group by a Kaplan-Meier analysis. There was a significant difference in short-term CVD death and hospital admission between the groups, but not for long-term CVD death and hospital. In long-term period, all-cause death and hospital admission was independently associated with completion of the CR program in addition to the presence of peripheral artery disease and VE vs. VCO_2 slope after adjusting for age, gender, body mass index, types of CVD and medications.

Conclusions: Completion of a 5-month CR program was associated with the prevention of all-cause death and hospital admission, but not CVD death and hospital admission in the long-term, which suggests that we need to reconsider this issue.

1. Introduction

Comprehensive cardiac rehabilitation (CR) is a program that was designed to optimize the outcomes in patients with cardiovascular disease (CVD). CR has evolved from simple physical exercise into a comprehensive program that also addresses other CVD risk factors and provides education and social support [1]. CR has been shown to improve cardiac function and prognosis in patients with CVD [2–5]. Patients who underwent percutaneous coronary intervention for acute coronary syndrome and completed a CR program had lower mortality than their non-CR counterparts [6]. Recently, we reported that a CR program significantly decreased blood pressure (BP) [7] and improved atherosclerosis and sympathetic nerve activity [8,9]. Nonetheless, CR still plays just a small part in the overall treatment of CVD. Two important observational studies using large, administrative databases demonstrated a significant association between the cumulative number of CR sessions attended and this reduction in the risk of mortality [10,11]. Unfortunately, <25% of outpatients with CVD, and <10% of elderly patients, enroll in CR. Furthermore, within this small number of patients participating in CR, 30% to 40% of patients discontinue CR after 6 months, and up to 50% drop out after 1 year [12].

CR classically consists of three phases. Phase I refers to inpatient CR during the index hospitalization. Phase II refers to physician-

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https://doi.org/10.1016/j.ijcard.2019.06.017
0167-5273/© 2019 Published by Elsevier B.V.

supervised, outpatient generally-monitored CR within 5 months after discharge in Japan. Thereafter, patients may continue to phase III, which is an enduring unmonitored CR program. Little is known about the long-term clinical outcomes in patients who have completed a 5-month CR program in Phase II. Therefore, the aim of this study was to explore the effects of a 5-month CR program on clinical outcomes in outpatients with CVD.

2. Methods

2.1. Subjects

We registered 332 consecutive outpatients (111 females and 221 males, age 67 ± 12 years) with CVD who participated in a 5-month CR program and were followed up for maximum 5 years. We divided the patients into those who completed the CR program (success group, $n = 175$) and those who did not (non-success group, $n = 157$). Average follow-up period in the success and non-success groups were 2.7 ± 1.5 and 2.4 ± 1.7 years, respectively. The success group included 6 patients who achieved the 5-month program, although they had the events (all-cause hospital admission) during the program. This study was approved by the Independent Review Board of Fukuoka University Hospital (#16-5-12). We retrospectively collected and analyzed all data at the just before starting CR program and at the end of follow-up using the database of Fukuoka University Hospital.

2.2. Exercise protocol

CR consisted of a supervised exercise training program at the hospital's gym for 5 months. Exercise intensity was chosen at anaerobic threshold (AT) according to a cardio pulmonary exercise test (CPX) or Borg's scale 11–13 during exercise. Each session lasted about 1 h and consisted of a warm-up exercise (10 min) followed by 30 min of cycling or walking at the indicated exercise intensity and 20 min of cooling down and stretching. BP and heart rate (HR) were measured at rest and at the end of exercise, and an electrocardiogram [Central Monitor (DS-5700) Fukuda Denshi Co. Ltd., Tokyo, Japan] and Borg's scale were recorded during exercise. CR generally performed 1–3 times/week.

2.3. Data collection

Patient characteristics including age, gender, body mass index (BMI), prevalence of hypertension (HTN), dyslipidemia (DL) and diabetes mellitus (DM), and medications were assessed at baseline. Patients who had a current systolic BP (SBP)/diastolic BP (DBP) ≥140/90 mmHg or who were receiving antihypertensive therapy were considered to have HTN. DM was defined using the Japan Diabetes Society Criteria or if the patient was being treated with an oral hypoglycemic agent or insulin. Patients with low-density lipoprotein cholesterol ≥140 mg/dl, triglyceride ≥150 mg/dl, and/or high-density lipoprotein cholesterol <40 mg/dl, or who were receiving lipid-lowering therapy, were considered to have DL. Ischemic heart disease (IHD) was defined as lumen diameter stenosis >50% in at least 1 major coronary artery as determined by coronary angiography and as diagnosed by old myocardial infarction. Heart failure (HF) was assumed based on the medical history, including medications and cardiac function. Medications included angiotensin II receptor blocker (ARB)/angiotensin converting enzyme inhibitor (ACE—I), diuretic, β-blocker, calcium channel blocker (CCB) and statin.

Data regarding both long-term (up to 5 years) and short-term (5 months) clinical outcomes were collected from April 2011 to March 2016 and compared between the success and non-success groups. Primary endpoint was defined as a combined of all-cause death and all-cause hospital admission at 5 years. Secondary endpoints were defined as all-cause death at 5 months and 5 years, CVD-induced death at 5 months and 5 years, all-cause hospital admission at 5 months and 5 years, CVD-induced hospital admission at 5 months and 5 years, a combined of all-cause death and all-cause hospital admission at 5 months, a combined of CVD-induced death and CVD-induced hospital admission at 5 months and 5 years, and a combined of non-CVD-induced death and hospital admission.

2.4. CPX

Patients underwent symptom-limited CPX using a cycle ergometer with respiratory gas exchange analysis at baseline. The testing consisted of an initial 2 min of rest, 1 min of warm-up at 0 W, and full exercise under a ramp protocol with increments of 10 W/min. Expired gas analysis was performed throughout testing on a breath-by-breath basis, and work rate at AT, volume of oxygen uptake (VO_2) at, O_2 pulse at, peak VO_2, minimum ventilation (VE)/volume of exhaled carbon dioxide (VCO_2), ventilatory equivalent versus carbon dioxide output slope (VE vs. VCO_2 slope), and peak gas exchange data were collected.

2.5. Statistics

Statistical analysis was performed using BellCurve for Excel ver 2.0 (Social Survey Research Information Co., Ltd., Japan). Data are expressed as the mean ± standard deviation or number (%). Categorical and continuous variables were compared between the groups by a chi-square analysis and t-test, respectively. Kaplan-Meier analysis (log-rank test) was applied to verify the time-dependent occurrence of clinical outcomes in groups stratified according to whether they did or did not complete a 5-month CR program. To identify the factors associated with all-cause death and hospital admission, we performed a cox regression analysis and obtained hazard ratios. Variables with p-values <0.05 in the univariate regression analysis were subjected to a multivariate analysis to identify independent factors related to all-cause death and hospital admission. A value of $p < 0.05$ was considered significant.

3. Results

3.1. Patient characteristics at baseline in all patients, and in the success and non-success groups

Table 1 shows the patient characteristics at baseline in the success and non-success groups. In the success group, the percentages (%) of male, HTN, DM, DL, IHD and HF were 65%, 66%, 27%, 57%, 53% and 31%, respectively. There were no significant differences in patient characteristics between the success and non-success groups. Average times of CR in the success and non-success groups were 36 ± 15 and 10 ± 9 times/5 months, respectively.

3.2. Clinical outcomes (all-cause death and hospital admission or CVD death and hospital admission) in all patients, and in the success and non-success groups

Clinical outcomes in the success and non-success groups are shown in Supplementary Table 1. As for primary endpoint, the rates of all-cause death and hospital admission in the success group were significantly lower than those in the non-success group for both the short-term ($p < 0.001$) and long-term ($p = 0.04$) periods. There was a significant difference in the rates of CVD death and hospital admission between the groups in the short-term (p = 0.04), but not in the long-term ($p = 0.48$). In addition, there were significant differences in the rates of non-CVD death and hospital admission in the short-term ($p = 0.001$) and long-term periods ($p = 0.03$), all-cause death in the short-term period ($p = 0.02$), all-cause hospital admission in the short-term ($p = 0.003$) and long-term periods (p = 0.03) and CVD hospital admission in the short-term period ($p = 0.009$) between the groups.

Duration of CR in the success and non-success groups were 19.2 ± 14.8 and 1.5 ± 1.4 months, respectively. In the success group, the duration of CR in patients without all-cause death and hospital admission (22.0 ± 16.0 months) was significantly longer than that in patients

Table 1
Patient characteristics at baseline in all patients, the success and non-success groups.

	All	Success group	Non-success group	*p* value Success group vs. Non-success group
Age, y	67 ± 12	67 ± 12	65 ± 12	0.09
Gender (male), n (%)	221 (67)	113 (65)	108 (69)	0.16
BMI, kg/m^2	24 ± 4.5	24 ± 4.3	24 ± 4.7	0.23
HTN, n (%)	207 (65)	110 (66)	97 (64)	0.80
DM, n (%)	105 (33)	45 (27)	60 (39)	0.05
DL, n (%)	179 (56)	96 (57)	83 (55)	0.70
CVD				
IHD, n (%)	183 (55)	93 (53)	90 (58)	0.51
HF, n (%)	107 (32)	54 (31)	53 (34)	0.64
Valve disease, n (%)	45 (14)	24 (14)	21 (13)	0.96
PAD, n (%)	30 (9)	16 (10)	14 (9)	0.97
Others, n (%)	42 (13)	23 (13)	19 (12)	0.86
LVEF, %	55 ± 16	56 ± 16	55 ± 15	0.78
Medications				
ARB/ACE-I, n (%)	207 (67)	107 (66)	100 (68)	0.76
Diuretics, n (%)	135 (44)	71 (44)	64 (44)	0.97
β-Blocker, n (%)	177 (58)	91 (57)	86 (59)	0.72
CCB, n (%)	129 (42)	60 (37)	69 (47)	0.13
Statin, n (%)	166 (54)	89 (55)	77 (53)	0.70
CPX				
AT	13 ± 8	12 ± 3	14 ± 15	0.24
Peak VO_2	15 ± 4	15 ± 4	15 ± 5	0.70
VE vs. VCO_2 slope	30 ± 7	29 ± 7	31 ± 9	0.21

BMI, body mass index; HTN, hypertension; DM, diabetes mellitus; DL dyslipidemia; CVD, cardiovascular disease; IHD, ischemic heart disease; HF, heart failure; PAD, peripheral artery disease; LVEF, left ventricular ejection fraction; ARB/ACE-I, angiotensin II receptor blocker/angiotensin converting enzyme inhibitor; CCB, calcium channel blocker; CPX, cardiopulmonary exercise test; AT, anaerobic threshold; Peak VO_2, peak oxygen uptake; VE vs. VCO_2 slope, ventilatory equivalent versus carbon dioxide output slope.

with them (13.9 ± 10.6 months) ($p = 0.0006$). Moreover, in the success group, the times of CR in patients without all-cause death and hospital admission (117 ± 89 times) was significantly higher than that in patients with them (89 ± 69 times) ($p = 0.046$).

A Kaplan-Meier analysis regarding the long-term clinical outcomes also indicated that the frequencies of all-cause death and hospital admission in the success group were significantly lower than those in the non-success group ($p < 0.01$) (Fig. 1A). There was no difference in CVD death and hospital admission in the long term between the groups ($p = 0.48$) (Fig. 1B), whereas there was a significant differences in non-CVD death and hospital admission ($p < 0.0001$) (Fig. 1C).

3.3. Relationships between various parameters and all-cause death and hospital admission in the long-term period examined by a univariate logistic regression analysis

Regarding the relationships between various parameters and all-cause death and hospital admission in the long-term period (Table 2),

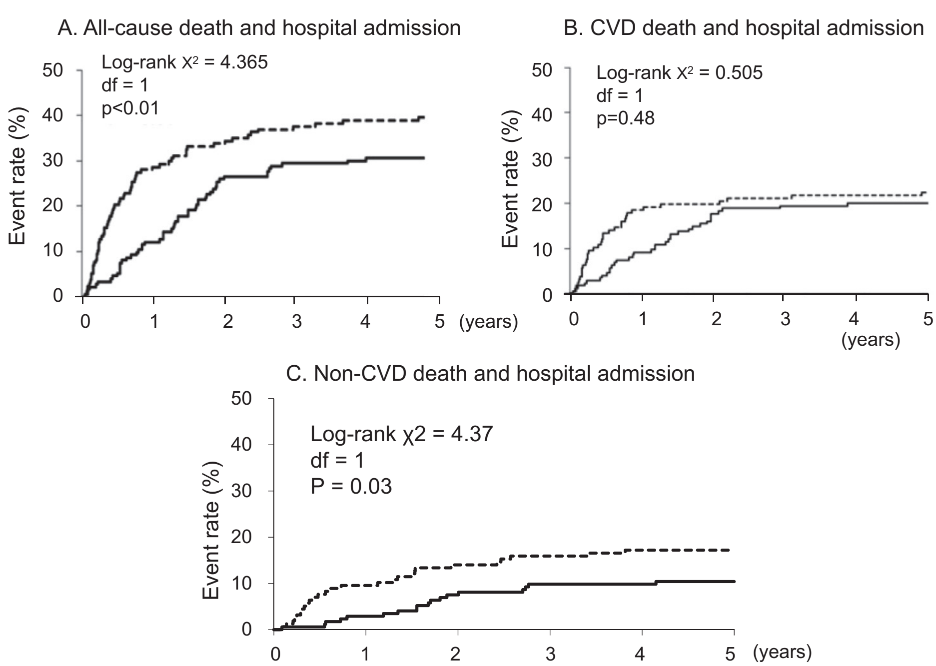

Fig. 1. Kaplan-Meier analysis of all-cause death and hospital admission (A), CVD death and hospital admission (B) and non-CVD death and hospital admission (C) in the long-term period in the success (solid lines) and non-success (dotted lines) groups.

Table 2
The relationship between various parameters and all-cause death and hospital admission in long-term 5 years period analyzed by a univariate logistic regression analysis.

Factors	HR (95% CI)	*p* values
Age	1.01 (0.99–1.03)	0.28
Gender (male)	1.06 (0.72–1.56)	0.77
BMI	0.97 (0.93–1.01)	0.10
HTN	1.11 (0.76–1.64)	0.58
DM	1.31 (0.90–1.92)	0.16
DL	1.03 (0.71–1.48)	0.89
CVD		
IHD	0.87 (0.61–1.26)	0.47
HF	1.40 (0.95–2.04)	0.09
Valve disease	0.92 (0.53–1.58)	0.75
PAD	2.39 (1.46–3.92)	<0.001
Others	0.62 (0.32–1.18)	0.15
LVEF	0.99 (0.98–1.00)	0.24
Medications		
ARB/ACE-I	0.91 (0.62–1.34)	0.64
Diuretics	1.36 (0.94–1.97)	0.11
β-Blocker	0.78 (0.54–1.14)	0.20
CCB	1.02 (0.70–1.48)	0.93
Statin	0.80 (0.55–1.16)	0.24
CPX		
AT	0.97 (0.89–1.06)	0.52
Peak VO_2	0.95 (0.88–1.03)	0.25
VE vs. VCO_2 slope	1.05 (1.01–1.08)	<0.001
Completion of the 5-month CR program	0.68 (0.47–0.98)	0.04

HR, hazard ratio; CI, confidence interval; BMI, body mass index; HTN, hypertension; DM, diabetes mellitus; DL dyslipidemia; CVD, cardiovascular disease; IHD, ischemic heart disease; HF, heart failure; PAD, peripheral artery disease; LVEF, left ventricular ejection fraction; ARB/ACE-I, angiotensin II receptor blocker/angiotensin converting enzyme inhibitor; CCB, calcium channel blocker; CPX, cardiopulmonary exercise test; AT, anaerobic threshold; Peak VO_2, peak oxygen uptake; VE vs. VCO_2 slope, ventilatory equivalent versus carbon dioxide output slope; CR, cardiac rehabilitation.

significant relationships were observed for completion of the 5-month CR program ($p = 0.04$), the presence of peripheral artery disease (PAD) ($p < 0.001$) and VE vs. VCO_2 slope ($p < 0.001$).

3.4. Relationships between completion of the 5-month CR program or the presence of PAD and all-cause death and hospital admission in the long-term period examined by a multivariate logistic regression analysis

In Table 3, Model 1 shows unadjusted data, and Models 2 and 3 were adjusted for age, and adjusted for age, gender and BMI, respectively. In addition, Models 4 and 5 were adjusted for age, gender, BMI and types of CVD, and adjusted for age, gender, BMI, types of CVD and medications, respectively. As a result, all-cause death and hospital admission in the long-term period were independently associated with completion of the CR program ($p = 0.04$), presence of PAD ($p < 0.01$) and VE vs. VCO_2 slope ($p < 0.006$) after adjusting for age, gender, BMI, types of CVD and medications (Model 5).

4. Discussion

We assessed the effectiveness of a 5-month CR program with regard to clinical outcomes at both 5 years (long term) and 5 months (short term). For the long term, the frequencies of all-cause death and hospital admission in the success group were significantly lower than those in the non-success group by a Kaplan-Meier analysis. The clinical outcome was independently associated with completion of the 5-month CR program in addition to the presence of PAD and VE vs. VCO_2 slope by a multivariate logistic regression analysis. In addition, there was a difference in CVD death and hospital admission between the groups in the short-term period, but not the long-term period.

Completion of a 5-month CR program was associated with the prevention of all-cause death and hospital admission and CVD death and hospital admission during the initial 5 months and reduced all-cause death and hospital admission up to 5 years. All-cause death and hospital admission were significantly associated with the presence of PAD. This significant association is reasonable because patients with PAD have about a three-fold higher risk of CVD and all-cause mortality compared to those without PAD [13]. Even when patients receive percutaneous transluminal angioplasty, restenosis is a major limitation for favorable outcomes [14]. In addition, Faglia et al. noted an amputation rate of 15% in a diabetic cohort of critical limb ischemia during 3.4 years of follow up [15]. The patients with PAD are limited to perform long distance walking and the ability to perform physical activity as part of their CR program is limited. Thus, there is no doubt that all-cause death and hospital admission was significantly associated with the presence of PAD. In addition, all-cause death and hospital admission were also significantly associated with higher VE vs. VCO_2 slope. VE vs. VCO_2 slope is widely used as an index of exercise capacity. Our data was reasonable because the high value of VE vs. VCO_2 means that a large amount of ventilation is required to emit a certain amount of CO_2. In fact, La Rovere et al. reported that VE vs. VCO_2 slope (>34) was associated with the prognosis after myocardial infarction [16].

Interestingly, although completion of 5-month CR program was significantly associated with all-cause death and hospital admission in long term, the benefits of CR program against CVD death and hospital admission did not last for 5 years. Thus, completion of a 5-month CR program helps to protect against non-CVD death and hospital admission for up to 5 years. There may be two main reasons. First, this may be due to the legacy effect of high exercise capacity for reducing non-CVD death and hospital admission. In this study, the causes of non-CVD death and hospital admission were mainly due to cancer (29%) and digestive diseases (13%). Low cardiorespiratory fitness is associated with future cancer mortality in Japanese men [17]. Structured exercise training is a safe

Table 3
The relationship between completion of the 5-month CR program, the presence of PAD or VE vs. VCO2 slope and all-cause death and hospital admission in long-term 5 years period analyzed by a multivariate logistic regression analysis.

Factors	Model 1		Model 2		Model 3		Model 4		Model 5	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Completion of the 5-month CR program	0.68 (0.47–0.98)	0.04	0.67 (0.46–0.96)	0.03	0.63 (0.44–0.91)	0.01	0.63 (0.43–0.91)	0.02	0.67 (0.45–0.98)	0.04
The presence of PAD	2.39 (1.46–3.91)	<0.001	2.29 (1.38–3.80)	0.001	2.20 (1.29–3.76)	0.004	2.33 (1.27–4.30)	0.007	2.28 (1.22–4.26)	0.01
VE vs. VCO_2 slope	1.05 (1.01–1.08)	0.009	1.05 (1.01–1.08)	0.01	1.05 (1.01–1.08)	0.01	1.05 (1.01–1.09)	0.006	1.06 (1.02–1.10)	0.006

Model 1. Unadjusted.
Model 2. Adjusted for age.
Model 3. Adjusted for age, gender and BMI.
Model 4. Adjusted for age, gender, BMI and types of CVD.
Model 5. Adjusted for age, gender, BMI, types of CVD and medications.
CR, cardiac rehabilitation; PAD, peripheral artery disease; VE vs. VCO2 slope, ventilatory equivalent versus carbon dioxide output slope; HR, hazard ratio; CI, confidence interval.

and well-tolerated therapeutic strategy associated with significant improvements in a broad range of cancer-related toxicities including fatigue, exercise capacity, and physical quality of life [18–20]. Exercise capacity is a valuable initial prognostic screening tool in patients with systolic left ventricular dysfunction [21]. The patients who had higher exercise capacity showed a good prognosis in a 5-year follow-up study. In addition, CR induced a significant improvement in the parasympathetic tone and may improve digestive diseases [22]. Although there were no significant differences in the event rates of non-CVD death and hospital admission due to cancer and digestive diseases between the success and non-success groups in this study, the reason may be due to very low event rates (4% and 2% in all patients were due to cancer and digestive diseases, respectively). Second, completion of 5-month CR program did not show a significant beneficial effect on CVD death and hospital admission in long term probably because the event rates in both success and non-success groups did not increase after 2 years (Fig. 1B), although there was a tremendously difference in the event rates between the groups before 2 years. At all events, the patients should continue to participate in CR to improve clinical outcomes regarding CV death and hospital admission.

This study included various kinds of CVD such as IHD, HF, valve disease and others. Most cases of CVD were IHD and HF, which showed a reduction in mortality by CR. Anderson et al. reported that exercise-based CR reduces cardiovascular mortality and provided important data showing reductions in hospital admissions and improvements in quality of life in patients with IHD [23]. For HF, CR was effective for combined endpoints (all-cause mortality or all-cause hospital stay) in the HF-ACTION trial [24]. Thus, the various kinds of CVD may not have affected the benefits of a 5-month CR program.

Comprehensive CR consists of exercise training and various factors including education and psychological input focusing on health, lifestyle changes, risk-factor modification, and psychosocial well-being [23–27]. The differences in clinical outcomes between the success and non-success groups in this study may have been due to not only exercise training, but also to various other factors.

Next, 47% of patients dropped out of a 5-month CR program. Although this percentage was relatively high, there were no significant differences in patient characteristics such as age, gender, BMI and kinds of CVD between the success and non-success groups. The characteristics of the patients who dropped out are not clear. Ruano-Ravina reported that older participants, females, patients with comorbidities, unemployed and unpartnered persons, less-educated people and those with lower incomes had to be monitored for CR adherence [28]. To improve the continuation rate of exercise, countermeasures are needed.

Finally, DM in the non-success group tended to be higher than that in the success group in Table 1. The prevalence of PAD in patients with DM was between 10% and 42% [29,30], and it was higher than the prevalence in non-DM. PAD with DM affects the continuation of CR. DM was not proven to be related to all-cause death and hospital admission in Table 2. It may be due to the lower % of patients with PAD in this study.

The present study has several limitations. First, this was a retrospective, single-center study with a relatively small sample size for analyzing the prognosis. Second, the patients received different duration, doses and kinds of medications and had different disease duration of CVD. Although it is difficult to evaluate the data after adjusting all major potential confounders, the data was shown after adjusting for age, gender, BMI, types of CVD and medications in Model 5. In addition, we did not take into account for a patient with completion of a 5-month CR program who interrupted CR after 5 months. The duration of CR in patients without all-cause death and hospital admission was significantly longer than that in patients with them. It was indicated that the elevated dropout rate of CR program after 5 months in the success group is also a problem. Therefore, a large-scale long-term study should be performed to confirm these results.

In conclusion, completion of a 5-month CR program helped to protect against all-cause death and hospital admission, but not CVD death and hospital admission, for a long-term period, which indicates that we need to reconsider the issue.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.06.017.

Declaration of Competing Interest

None.

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