SUPPLEMENTAL MATERIAL

Supplemental Methods

Translation of Guidelines for Rehabilitation in Patients with Cardiovascular Disease （JCS 2012）with some modification

Reference: https://www.jacr.jp/pdf/JCS2012_nohara_d_2015.01.14.pdf

Purpose of cardiac rehabilitation in patients with acute heart failure

1. Prevent further physical deconditioning
2. Make sure hospital discharge with stable condition
3. Improve QOL by improving exercise tolerance
4. Prevent heart failure exacerbation through patient education and disease control
5. Motivate patients to continue exercise

Ambulation program

Once hemodynamics is stabilized and there is no symptom at rest, even if during intravenous inotrope therapy, the ambulance program should proceed from the early stage of hospitalization. The ambulation program includes stretching, sitting upright, walk within room (10 m), walk to toilet (40 m), and walk within ward (80 m). These programs were conducted under monitoring of vital signs and symptoms. After completion of ambulation program, then

move on to the exercise program.

Exercise program

Cardiologists decide whether patients safely proceed to the exercise program, and the program is performed according to the exercise prescription, which are created based on clinical parameters or cardiopulmonary exercise testing. The program should be performed under supervision with electrocardiogram monitoring. The strength and type of program are listed below.

Type	Walking, ergometer, aerobic exercise, and low-level resistance training
Strength	[Initial phase] Walking 50-80 m/min or ergometer 10-20 W * 5-10 minutes Increment strength and time based on symptoms and vital signs
	[Stable phase] a. 40-60% of peak VO_2 or heart rate at aerobic threshold (AT) b. 30-50% of heart rate reserve or 50-70% of maximum heart rate c. Borg scale 11-13
Time	5-10 minutes * 2 times/day

	Increment to 30-60 minutes/day
Frequency	3-5/weeks

Sensitivity analyses

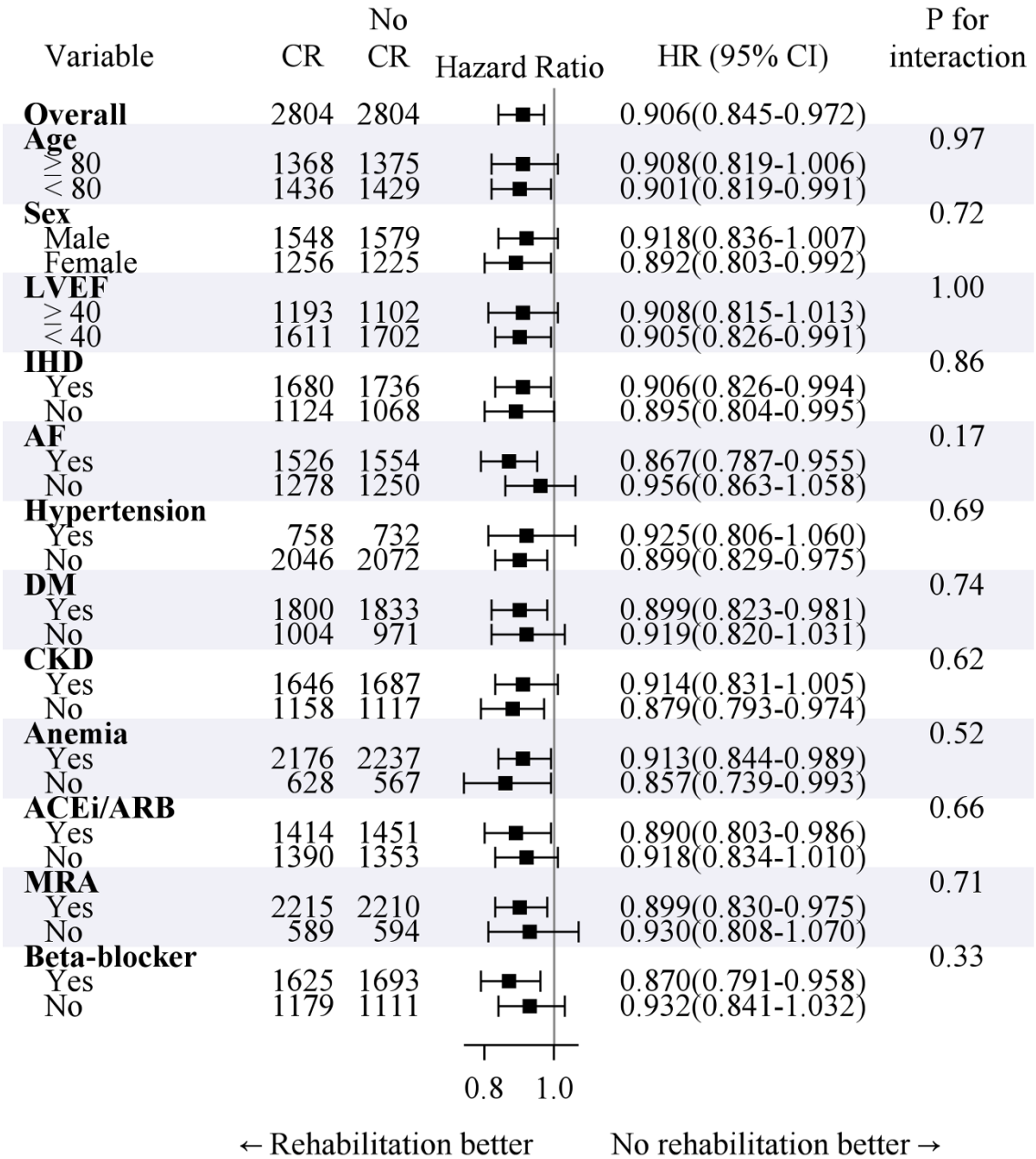
To avoid selection bias attributable to propensity score matching, we also used multivariable Cox regression analysis including variables used in the propensity score matching. In order to exclude potential bias caused by quality of treatment which differed between institution (e.g. institute which perform cardiac rehabilitation (CR) might provide better management than institutes which did not), we did the same multivariable analysis after excluding institution which did not provide CR. We also conducted multivariable analysis including outpatient CR as a covariate on top of the covariates used in the propensity score matching.

The analysis of outcomes by using combination of multiple imputation and inverse probability of treatment weighting was also conducted to assess the effects of missing data.[18] For the all baseline missing data, multiple imputation was performed (number of imputation = 10) by predictive mean matching for continuous variables and logistic regression model for binary variables. A propensity score was estimated by fitting a logistic-regression model which adjusted for all baseline covariates in each dataset. HR for outcomes was estimated by inverse

probability weighting in each imputed dataset. Estimates from 10 iterations were combined with the use of Rubin's rule. For comparison, we conducted univariate analysis in the dataset used in the multivariable analysis. Pearson correlation coefficient were calculated to test the correlation between CR and other baseline covariates. We also conducted a negative control analysis. In JROADHF, three types of non-cardiac death events were recorded, pneumonia, malignancy and other non-cardiac death. Given that pneumonia death is sometimes difficult to distinguish from HF death and rehabilitation might prevent pneumonia death, we chose malignancy and other non-cardiac death as negative controls. This outcome was analyzed with unadjusted analysis, propensity score matched analysis, multivariable analysis, and multiple imputation analysis as described above.

Supplemental Figures

Figure S1. Subgroup analysis



ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; AF, atrial fibrillation; CI, confidence interval; CKD, chronic kidney disease; CR, cardiac rehabilitation; DM, diabetes mellitus; HR, hazard ratio; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist.

Supplemental Tables

Table S1. Fine and Gray model in the propensity matched cohort

Outcomes	HR (95% CI)	P value
CV death or CV event admission	0.901 (0.840-0.966)	0.003
CV death	0.913 (0.814-1.025)	0.12
CV event admission	0.905 (0.841-0.974)	0.008

CI, confidence interval; CV, cardiovascular; HR, hazard ratio.

Table S2. Sensitivity analyses

Outcomes	HR (95% CI)	P value
Multivariable analysis		
CV death or CV event admission	0.935 (0.879-0.995)	0.035
CV death	0.950 (0.856-1.053)	0.33
CV event admission	0.935 (0.876-0.998)	0.042
Multiple imputation		
CV death or CV event admission	0.941 (0.907-0.977)	0.001
CV death	0.947 (0.891-1.008)	0.090
CV event admission	0.948 (0.911-0.986)	0.007

CI, confidence interval; CV, cardiovascular; HR, hazard ratio.

Table S3. Multivariable analysis limited to institutions which provide cardiac rehabilitation

Outcomes	HR (95% CI)	P value
CV death or CV event admission	0.930 (0.868-0.996)	0.038
CV death	0.984 (0.876-1.105)	0.78
CV event admission	0.940 (0.874-1.011)	0.094

CI, confidence interval; CV, cardiovascular; HR, hazard ratio.

Table S4. Multivariable analysis including outpatient cardiac rehabilitation as a covariate

Outcomes	HR (95% CI)	P value
CV death or CV event admission	0.924 (0.859-0.994)	0.035
CV death	0.981 (0.864-1.115)	0.77
CV event admission	0.921 (0.853-0.993)	0.033

CI, confidence interval; CV, cardiovascular; HR, hazard ratio.

Table S5. Correlation coefficient between cardiac rehabilitation and other baseline variables.

Variables	Correlation coefficient
Demographics	
Age, years	0.018
Male	-0.004
Prior HF admission	-0.006
NYHA III-IV	0.038
Smoking	0.000
Vital signs	
SBP, mmHg	-0.006
Heart rate, bpm	0.022
Etiology of heart failure	
Ischemic	0.044
Cardiomyopathy	0.023
Hypertensive	-0.016
Valvular	0.005
Adult congenital	-0.016
Arrhythmia	-0.023
Constrictive pericarditis	-0.002
Other	-0.028
Heart disease	
IHD	0.060
Atrial fibrillation	0.014
Prior procedures	
PCI/CABG	0.037
Pacemaker	0.009
ICD	0.018
CRT-D	0.021

Hemodialysis	-0.031
Comorbidities	
Hypertension	-0.004
Diabetes mellitus	0.007
Hyperurecemia	0.001
CKD	0.022
Stroke	0.008
PAD	0.002
Anemia	0.015
COPD	-0.014
Malignancy	0.020
Echocardiographic data	
LVEF, %	-0.085
LVDd, mm	0.014
LVDs, mm	0.051
LVMI, g/m^2	-0.023
LAD, mm	-0.013
MR III-IV	0.005
Laboratory data	
Hemoglobin, g/dl	0.021
Albumin, g/dl	-0.019
eGFR, $ml/min/1.73m^2$	-0.024
Uric acid, mg/dl	0.025
Sodium, mEq/l	-0.006
BNP, pg/ml	0.050
ln(BNP)	0.070
Medication	
Beta-blocker	0.042
ACEi/ARB	0.015
MRA	-0.010
Loop diuretics	-0.003
Thiazides	-0.006

Tolvaptan	0.016
Barthel index	
Independent	0.007
Moderately reduced	0.022
Low	-0.016
Very low	-0.009

ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker ; BMI, body mass index; BNP, brain-type natriuretic peptide; CABG, cardiac artery bypass grafting; CKD, chronic kidney disease; COPD chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy-defibrillator; eGFR, estimate glomerular filtration rate; HF; heart failure; ICD, implantable cardioverter defibrillator; IHD, ischemic heart disease; LAD, left atrial diameter; LVDd, left ventricular diastolic diameter; LVDs, left ventricular systolic diameter; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonist; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; SBP, systolic blood pressure.

Table S6. Effects of cardiac rehabilitation on malignancy or other non-cardiac death

Analysis	HR (95% CI)	P value
Univariate analysis	0.956(0.800-1.143)	0.62
Propensity-score matched analysis	1.039(0.843-1.280)	0.72
Multivariable analysis	0.971(0.811-1.163)	0.75
Multiple imputation analysis	0.929 (0.836-1.033)	0.17

CI, confidence interval; HR, hazard ratio.