Determinants of Left Ventricular Systolic Function Improvement Following Coronary Artery Revascularization in Heart Failure Patients With Reduced Ejection Fraction (HFrEF)

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SUMMARY

Revascularization therapy such as percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) should be considered for heart failure with reduced ejection fraction (HFrEF). However, revascularization therapy does not always improve left ventricular ejection fraction (LVEF). The purpose of this study was to investigate the determinants of LVEF improvement following revascularization in HFrEF patients. From 2,229 consecutive decompensated heart failure patients, a total of 47 HFrEF patients who underwent revascularization were included in the analysis. Improvement of LVEF was defined as $[(\text{LVEF during chronic phase}) - (\text{LVEF during acute phase})] \geq 10\%$. Univariate and multivariate logistic regression analyses were applied to investigate the determinants of LVEF improvement. The prevalence of revascularization by PCIs including chronic total occlusion (CTO) was significantly greater in the improved EF group (45.0%) as compared to the non-improved EF group (11.1%) ($P = 0.02$). Multivariate logistic regression analysis revealed that revascularization by PCIs including CTO was the significant determinant of the LVEF improvement after adjusting for confounding factors (OR 5.43, 95% CI 1.06-27.74, $P = 0.04$). Optimal medical therapy (angiotensin-converting enzyme (ACE) inhibitor and/or angiotensin II receptor blocker (ARB) and beta-blockers) was less frequently prescribed in patients with CABG (50.0% for ACE inhibitor and/or ARB and 41.7% for beta-blocker) than in patients without CABG (94.3% for both) ($P < 0.01$ and $P < 0.001$, respectively). In conclusion, revascularization by PCIs including CTO was the significant determinant of LVEF improvement in HFrEF patients. Our results underscore the importance of optimal medical therapy even if patients receive complete revascularization such as CABG. (Int Heart J 2016; 57: 565-572)

Key words: Percutaneous coronary intervention, Coronary artery bypass grafting, Chronic total occlusion

Heart failure is a common disease with a prevalence of 1-2% in the adult population,¹⁾ and still has high mortality in developed countries. One-year mortality rates in population-based studies have been reported to be 25% to 45%.²⁻⁵⁾ The mortality rate was higher in heart failure with reduced ejection fraction (HFrEF) than heart failure with preserved ejection fraction (HFpEF).⁶⁾ Mortality rates of HFrEF (ejection fraction $< 50\%$) patients were reported to be 32% at one year and 68% at 5 years.⁶⁾ The most common cause of HFrEF is coronary artery disease, which accounts for approximately two-thirds of HFrEF.⁷⁾

Revascularization therapy such as percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) should be considered in heart failure with coronary artery disease, and sometimes improves clinical outcomes including left ventricular function.⁸⁻¹²⁾ However, revascularization therapy is not always effective in heart failure with coronary artery disease.¹³⁾ It is unknown which types of patients receive the benefits such as improvement of left ventricular systolic function

from revascularization. The purpose of this study was to investigate the determinants of left ventricular ejection fraction (LVEF) improvement following revascularization in HFrEF patients with coronary artery disease.

METHODS

We identified 2,229 consecutive patients who were diagnosed as having decompensated heart failure including HFpEF and HFrEF regardless of etiology and were admitted to our department from 2006 to 2014. Patients who did not receive revascularization (PCI or CABG) during the hospitalization ($n = 2,098$) were excluded. Because our study purpose was to investigate the determinants of LVEF improvement, it was important to compare echocardiographic findings including LVEF in the acute phase with those in the chronic phase (approximately 6 months from revascularization). Echocardiography in the acute phase was defined as echocardiography per-

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formed in the echocardiographic laboratory most recently from the day of discharge from the hospital for heart failure with the patient in a compensated state. Patients who underwent revascularization during the first hospitalization and received additional revascularization within one month from the first revascularization were included in the analysis ($n = 2$). In these cases, echocardiography which were performed most recently from the discharge day of the first hospitalization was adopted as the initial echocardiography. Echocardiography in the chronic phase was defined as echocardiography which was performed most recently 6 months after the initial echocardiography in the echocardiographic laboratory. Therefore, patients who did not receive echocardiography in the acute phase ($n = 11$) and patients who did not receive follow-up echocardiography in the chronic phase ($n = 33$) were excluded. In addition, we excluded patients who were diagnosed as heart failure with acute myocardial infarction (AMI) ($n = 19$). AMI was defined as a rise in cardiac enzyme concentrations (troponin I and/or T, and/or creatine phosphokinase-MB) with at least one value above the 99th percentile upper reference limit in the first 24 hours and with at least one of the following: 1) symptoms of ischemia, 2) new or presumed new significant ST-segment-T wave (ST-T) changes or new left bundle branch block (LBBB), 3) development of pathological Q waves in the electrocardiogram, 4) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality, and 5) identification of an intracoronary thrombus by angiography or autopsy.^{14,15} Subacute myocardial infarction (≤ 1 week from onset) were also considered as AMI, whereas recent myocardial infarction (> 1 week from onset or unknown onset) were considered as old myocardial infarction, which were included in the present study. We excluded HFpEF patients (LVEF $\geq 50\%$ ^{6,16} at initial echocardiography) ($n = 17$). We also excluded patients who received cardiac resynchronization therapy (CRT) ($n = 1$) or surgical ventricular restoration ($n = 3$) during the hospitalization, which themselves may affect LVEF improvement.

Finally, a total of 47 HFrEF patients (LVEF $< 50\%$ at initial echocardiography) who underwent revascularization during the hospitalization and received initial and follow-up echocardiography were included in the present study (Figure).

All of the transthoracic echocardiography was performed by skilled sonographers in our echocardiographic laboratory at a compensated state. Only echocardiographic findings that were measured by the sonographers and cardiologists in the echocardiographic laboratory were used in the present study, while echocardiographic findings that were measured at bedside were excluded. Left ventricular volume was calculated by the single-plane area-length method on an apical 4-chamber view.¹⁷ Left ventricular ejection fraction (LVEF%) was calculated from end-diastolic and end-systolic left ventricular volumes (LVEDV and LVESV) as $(LVEDV - LVESV) \times 100 / LVEDV$.¹⁸ Left ventricle diastolic diameter (LVDd) and systolic diameter (LVDs) were measured by M-mode echocardiography, and left atrial diameter (LAD) was also measured by M-mode echocardiography. Improvement of LVEF was defined as $[(LVEF \text{ during chronic phase}) - (LVEF \text{ during acute phase})] \geq 10\%$.^{19,20}

At our institution, we usually follow the current guidelines when patients are referred for revascularization.^{21,22} Revascularization was considered for angiographically signifi-

Figure. Flow chart of study population. HFpEF indicates heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; LVEF, left ventricle ejection fraction; and CRT, cardiac resynchronization therapy.

cant stenosis ($\geq 75\%$ diameter reduction by visual assessment) and functionally significant stenosis (fractional flow reserve measurement < 0.80). Myocardial viability assessed by scintigraphy or echocardiography was considered for each PCI before revascularization. PCI was considered for patients with 1- or 2-vessel disease, whereas CABG was considered for patients with 3-vessel or left main disease, and occasionally for patients with 1- or 2-vessel disease, including the proximal left anterior descending artery. With respect to the stent type, drug-eluting stents were selected for small vessels (reference diameter < 2.5 mm) or diffuse lesions (> 30 mm), whereas bare metal stents were selected for large vessels (reference diameter > 4.0 mm) or short lesions (< 20 mm).

Clinical criteria were defined as follows. Hypertension was defined as systolic blood pressure > 140 mmHg, diastolic blood pressure > 90 mmHg, or medical treatment for hypertension on admission. Diabetes mellitus was defined as a hemoglobin A1c level in National Glycohemoglobin Standardization Program (NGSP) units $> 6.5\%$ or medical treatment for diabetes mellitus on admission. Dyslipidemia was defined as a low-density lipoprotein cholesterol level > 140 mg/dL or treat-

ment for dyslipidemia on admission. Chronic kidney disease was defined as serum creatinine > 2.0 mg/dL on admission or on hemodialysis. Hyperuricemia was defined as serum uric acid > 7.0 mg/dL or treatment for hyperuricemia on admission. Anemia was defined as hemoglobin < 13 g/dL (male) or < 12 g/dL (female) on admission. A chronic total occlusion (CTO) was defined as a complete coronary arterial obstruction with Thrombolysis In Myocardial Infarction (TIMI) flow grade of 0 for longer than (estimated) 3 months.²³⁾ This study was approved by the institutional review board and written informed consent was waived because of the retrospective design.

Statistical analysis: All analyses were performed using the statistical software SPSS version 18 (SPSS, Inc., Chicago, IL, USA). All study patients were divided into the improved EF group (delta LVEF $\geq 10\%$) or non-improved EF group (delta LVEF < 10%). We compared patient characteristics, echocardiographic findings, and types of revascularization between the groups. The categorical variables are presented as numbers (percentages) and were compared with Fisher's exact test. Continuous variables are presented as the mean $\pm$ standard deviation (SD). The Shapiro-Wilk test was performed to determine whether the continuous variables were normally distributed. Normally distributed continuous variables were compared using the Student *t* test. Otherwise, continuous variables were compared using the Mann-Whitney *U*-test. Univariate and multivariate logistic regression analyses were applied to investigate the determinants of the LVEF improvement. In the univariate logistic regression model, the dependent variable was LVEF improvement (delta LVEF $\geq 10\%$), and independent variables were age, sex, and potential confounding factors that showed a marginal difference ($P < 0.10$) between the improved EF and non-improved EF groups. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. In the multivariate logistic regression model, the dependent variable was LVEF improvement (delta LVEF $\geq 10\%$). Age, sex, and variables that showed a marginal association with LVEF improvement ($P < 0.10$) in the univariate logistic regression analyses were adopt-

ed as independent variables. OR and 95% CI were calculated. A value of $P < 0.05$ was considered statistically significant.

RESULTS

A total of 47 HFREF patients were divided into the improved EF group ($n = 20$) and the non-improved EF group ($n = 27$). The baseline characteristics of the study patients are shown in Table I. The mean age of the improved EF group (63.4 ± 11.6 years) was comparable to that of the non-improved EF group (65.4 ± 10.3 years) ($P = 0.53$). The prevalence of male sex in the improved EF group (75.0%) was also comparable to that in the non-improved EF group (74.1%) ($P = 1.00$).

The transthoracic echocardiography findings of the study patients are shown in Table II. In the initial echocardiography, all parameters were comparable in the improved EF group and non-improved EF group. On the other hand, in the follow-up echocardiography, LVEF was significantly greater in the improved EF group ($54.4 \pm 7.9\%$) than in the non-improved EF group ($36.8 \pm 10.1\%$) ($P < 0.01$), LVESV was significantly smaller in the improved EF group (60.1 ± 25.4 mL) than in the non-improved EF group (103.1 ± 55.9 mL) ($P < 0.01$), and LVDs was significantly smaller in the improved EF group (39.0 ± 8.3 mm) than in the non-improved EF group (47.0 ± 9.9 mm) ($P < 0.01$). The mean follow-up interval between initial and follow-up echocardiography was 8.0 ± 10.7 months. The mean echo follow-up interval was longer in the non-improved EF group (8.3 ± 14.0 months) than in the improved EF group (7.6 ± 2.9), although the difference was not statistically significant ($P = 0.07$). The mean interval from the last revascularization to follow-up echocardiography was 7.6 ± 10.7 months. The interval from the last revascularization to follow-up echocardiography in the improved EF group (7.1 ± 3.2 months) was comparable to that in the non-improved EF group (8.0 ± 14.0 months) ($P = 0.11$).

Table I. Patient Characteristics

	All (<i>n</i> = 47)	Improved EF group (<i>n</i> = 20)	Non-improved EF group (<i>n</i> = 27)	<i>P</i>
Age (years)	64.5 $\pm$ 10.8	63.4 $\pm$ 11.6	65.4 $\pm$ 10.3	0.53
Male sex, <i>n</i> (%)	35 (74.5)	15 (75.0)	20 (74.1)	1.00
BMI (kg/m ²)	24.5 $\pm$ 3.9	25.6 $\pm$ 4.6	23.7 $\pm$ 3.2	0.20
Hypertension, <i>n</i> (%)	37 (78.7)	18 (90.0)	19 (70.4)	0.15
Diabetes mellitus, <i>n</i> (%)	22 (46.8)	8 (40.0)	14 (51.9)	0.56
Dyslipidemia, <i>n</i> (%)	36 (76.6)	15 (75.0)	21 (77.8)	1.00
Chronic kidney disease, <i>n</i> (%)	7 (14.9)	2 (10.0)	5 (18.5)	0.68
Hemodialysis, <i>n</i> (%)	0 (0)	0 (0)	0 (0)	-
Hyperuricemia, <i>n</i> (%)	38 (80.9)	16 (80.0)	22 (81.5)	1.00
Stroke, <i>n</i> (%)	9 (19.1)	3 (15.0)	6 (22.2)	0.71
Anemia, <i>n</i> (%)	17 (36.2)	6 (30.0)	11 (40.7)	0.55
Chronic obstructive pulmonary disease, <i>n</i> (%)	1 (2.1)	1 (5.0)	0 (0)	0.43
Smoking, <i>n</i> (%)	35 (74.5)	15 (75.0)	20 (74.1)	1.00
Old myocardial infarction, <i>n</i> (%)	17 (36.2)	6 (30.0)	11 (40.7)	0.55
Atrial fibrillation, <i>n</i> (%)	12 (25.5)	4 (20.0)	8 (29.6)	0.52
Previous hospitalization for heart failure, <i>n</i> (%)	6 (12.8)	1 (5.0)	5 (18.5)	0.22
Post PPM, <i>n</i> (%)	0 (0)	0 (0)	0 (0)	-
Post ICD, <i>n</i> (%)	0 (0)	0 (0)	0 (0)	-
Post CRT, <i>n</i> (%)	0 (0)	0 (0)	0 (0)	-

Data are expressed as mean $\pm$ SD or numbers (%). BMI indicates body mass index; PPM, permanent pacemaker; ICD, implantable cardioverter defibrillator; and CRT, cardiac resynchronization therapy.

Table II. Transthoracic Echocardiography Findings

	All (<i>n</i> = 47)	Improved EF group (<i>n</i> = 20)	Non-improved EF group (<i>n</i> = 27)	<i>P</i>
Initial echocardiography				
LVEF (%)	35.7 ± 8.6	33.4 ± 6.4	37.4 ± 9.6	0.11
LVEDV (mL)	170.1 ± 55.5	173.9 ± 50.9	167.2 ± 59.5	0.48
LVESV (mL)	111.4 ± 46.0	116.6 ± 39.0	107.6 ± 50.9	0.24
LVDd (mm)	60.6 ± 7.1	61.5 ± 6.9	59.9 ± 7.4	0.46
LVDs (mm)	49.7 ± 8.4	51.3 ± 8.6	48.5 ± 8.2	0.26
Left atrial diameter (mm)	50.3 ± 9.7	50.5 ± 6.9	50.2 ± 11.5	0.34
Follow-up echocardiography				
LVEF (%)	44.3 ± 12.6	54.4 ± 7.9	36.8 ± 10.1	< 0.01
LVEDV (mL)	145.7 ± 60.5	130.1 ± 47.1	157.3 ± 67.3	0.16
LVESV (mL)	84.8 ± 49.9	60.1 ± 25.4	103.1 ± 55.9	< 0.01
LVDd (mm)	56.2 ± 9.2	53.7 ± 8.0	58.0 ± 9.7	0.11
LVDs (mm)	43.6 ± 10.0	39.0 ± 8.3	47.0 ± 9.9	< 0.01
Left atrial diameter (mm)	46.7 ± 11.2	45.8 ± 9.2	47.4 ± 12.5	0.67
Echo follow-up interval (months)	8.0 ± 10.7	7.6 ± 2.9	8.3 ± 14.0	0.07
Intervals from revascularization to follow-up echocardiography (months)	7.6 ± 10.7	7.1 ± 3.2	8.0 ± 14.0	0.11

Data are expressed as mean ± SD. LVEF indicates left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVDd, left ventricular diastolic diameter; and LVDs, left ventricular systolic diameter.

Table III. Non-Pharmacological Intervention During Hospitalization

	All (<i>n</i> = 47)	Improved EF group (<i>n</i> = 20)	Non-improved EF group (<i>n</i> = 27)	<i>P</i>
Revascularization by PCIs including CTO, <i>n</i> (%)	12 (25.5)	9 (45.0)	3 (11.1)	0.02
Revascularization by PCIs excluding CTO, <i>n</i> (%)	23 (48.9)	9 (45.0)	14 (51.9)	0.77
Revascularization by CABG including CTO, <i>n</i> (%)	7 (14.9)	2 (10.0)	5 (18.5)	0.68
Revascularization by CABG excluding CTO, <i>n</i> (%)	5 (10.6)	0 (0)	5 (18.5)	0.06
Aortic valve replacement, <i>n</i> (%)	1 (2.1)	0 (0)	1 (3.7)	1.00
Mitral valve replacement, <i>n</i> (%)	0 (0)	0 (0)	0 (0)	-
Mitral valve plasty, <i>n</i> (%)	1 (2.1)	0 (0)	1 (3.7)	1.00
Permanent pacemaker, <i>n</i> (%)	0 (0)	0 (0)	0 (0)	-
Implantable cardioverter defibrillator, <i>n</i> (%)	0 (0)	0 (0)	0 (0)	-

Data are expressed as numbers (%). PCI indicates percutaneous coronary intervention; CTO, chronic total occlusion; and CABG, coronary artery bypass grafting.

Table IV. Medication at Discharge

	All (<i>n</i> = 47)	Improved EF group (<i>n</i> = 20)	Non-improved EF group (<i>n</i> = 27)	<i>P</i>
ACE inhibitor and/or ARB, <i>n</i> (%)	39 (83.0)	20 (100.0)	19 (70.4)	0.01
Beta-blocker, <i>n</i> (%)	38 (80.9)	19 (95.0)	19 (70.4)	0.06
Alpha-blocker, <i>n</i> (%)	1 (2.1)	0 (0)	1 (3.7)	1.00
Calcium channel blocker, <i>n</i> (%)	8 (17.0)	3 (15.0)	5 (18.5)	1.00
Aldosterone receptor antagonist, <i>n</i> (%)	21 (44.7)	11 (55.0)	10 (37.0)	0.25
Diuretic agent, <i>n</i> (%)	40 (85.1)	18 (90.0)	22 (81.5)	0.68
Digitalis, <i>n</i> (%)	2 (4.3)	1 (5.0)	1 (3.7)	1.00
Orally active cardiac stimulant, <i>n</i> (%)	1 (2.1)	0 (0)	1 (3.7)	1.00
Amiodarone, <i>n</i> (%)	5 (10.6)	0 (0)	5 (18.5)	0.06
Anticoagulant agent, <i>n</i> (%)	24 (51.1)	9 (45.0)	15 (55.6)	0.56
Statin, <i>n</i> (%)	39 (83.0)	19 (95.0)	20 (74.1)	0.11
Oral hypoglycemic agent, <i>n</i> (%)	15 (31.9)	8 (40.0)	7 (25.9)	0.36
Insulin, <i>n</i> (%)	11 (23.4)	3 (15.0)	8 (29.6)	0.31

Data are expressed as numbers (%). ACE inhibitor indicates angiotensin converting enzyme inhibitor; and ARB, angiotensin II receptor blocker.

Non-pharmacological interventions during the hospitalization such as PCI, CABG, valve replacement, and permanent pacemaker implantation are presented in Table III. PCI was performed in 35 patients, while CABG was performed in 12 patients. Complete revascularization was performed in 74.3%

(*n* = 26) of the PCI group, whereas in 100.0% (*n* = 12) of the CABG group. We classified the revascularization methods into 4 groups: PCIs including CTO, PCIs excluding CTO, CABG including CTO, and CABG excluding CTO. The prevalence of PCIs including CTO was significantly greater in the improved

Table V. Comparison of CABG Group and non-CABG Group

	All (n = 47)	CABG (n = 12)	Non-CABG (n = 35)	P
Patient characteristics				
Age (years)	64.5 ± 10.8	68.6 ± 8.5	63.1 ± 11.3	0.14
Male sex, n (%)	35 (74.5)	6 (50.0)	29 (82.9)	0.05
BMI (kg/m ²)	24.5 ± 3.9	24.3 ± 2.9	24.6 ± 4.3	0.66
Hypertension, n (%)	37 (78.7)	8 (66.7)	29 (82.9)	0.25
Diabetes mellitus, n (%)	22 (46.8)	8 (66.7)	14 (40.0)	0.18
Dyslipidemia, n (%)	36 (76.6)	11 (91.7)	25 (71.4)	0.24
Chronic kidney disease, n (%)	7 (14.9)	2 (16.7)	5 (14.3)	1.00
Hemodialysis, n (%)	0 (0)	0 (0)	0 (0)	-
Hyperuricemia, n (%)	38 (80.9)	11 (91.7)	27 (77.1)	0.41
Stroke, n (%)	9 (19.1)	5 (41.7)	4 (11.4)	0.04
Anemia, n (%)	17 (36.2)	6 (50.0)	11 (31.4)	0.31
Chronic obstructive pulmonary disease, n (%)	1 (2.1)	0 (0)	1 (2.9)	1.00
Smoking, n (%)	35 (74.5)	5 (41.7)	30 (85.7)	< 0.01
Old myocardial infarction, n (%)	17 (36.2)	3 (25.0)	14 (40.0)	0.49
Atrial fibrillation, n (%)	12 (25.5)	3 (25.0)	9 (25.7)	1.00
Previous hospitalization for heart failure, n (%)	6 (12.8)	4 (33.3)	2 (5.7)	0.03
Post PPM, n (%)	0 (0)	0 (0)	0 (0)	-
Post ICD, n (%)	0 (0)	0 (0)	0 (0)	-
Post CRT, n (%)	0 (0)	0 (0)	0 (0)	-
Initial echocardiography				
LVEF (%)	35.7 ± 8.6	36.1 ± 11.5	35.5 ± 7.5	0.85
LVEDV (mL)	170.1 ± 55.5	173.5 ± 57.2	168.9 ± 55.7	0.81
LVESV (mL)	111.4 ± 46.0	113.0 ± 49.9	110.9 ± 45.3	0.98
LVDd (mm)	60.6 ± 7.1	59.7 ± 8.4	60.9 ± 6.8	0.61
LVDs (mm)	49.7 ± 8.4	47.6 ± 9.9	50.4 ± 7.9	0.32
Left atrial diameter (mm)	50.3 ± 9.7	51.4 ± 15.1	49.9 ± 7.3	0.63
Echo follow-up interval (months)	8.0 ± 10.7	4.2 ± 3.2	9.3 ± 12.0	0.01
Intervals from revascularization to follow-up echocardiography (months)	7.6 ± 10.7	3.8 ± 3.1	8.9 ± 12.1	0.01
Medication				
ACE inhibitor and/or ARB, n (%)	39 (83.0)	6 (50.0)	33 (94.3)	< 0.01
Beta-blocker, n (%)	38 (80.9)	5 (41.7)	33 (94.3)	< 0.001
Alpha-blocker, n (%)	1 (2.1)	0 (0)	1 (2.9)	1.00
Calcium channel blocker, n (%)	8 (17.0)	2 (16.7)	6 (17.1)	1.00
Aldosterone receptor antagonist, n (%)	21 (44.7)	4 (33.3)	17 (48.6)	0.51
Diuretic agent, n (%)	40 (85.1)	10 (83.3)	30 (85.7)	1.00
Digitalis, n (%)	2 (4.3)	0 (0)	2 (5.7)	1.00
Orally active cardiac stimulant, n (%)	1 (2.1)	0 (0)	1 (2.9)	1.00
Amiodarone, n (%)	5 (10.6)	3 (25.0)	2 (5.7)	0.10
Anticoagulant agent, n (%)	24 (51.1)	8 (66.7)	16 (45.7)	0.32
Statin, n (%)	39 (83.0)	9 (75.0)	30 (85.7)	0.40
Oral hypoglycemic agent, n (%)	15 (31.9)	2 (16.7)	13 (37.1)	0.29
Insulin, n (%)	11 (23.4)	5 (41.7)	6 (17.1)	0.12

Data are expressed as numbers (%) or mean ± SD. BMI indicates body mass index; PPM, permanent pacemaker; ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronization therapy; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVDd, left ventricular diastolic diameter; LVDs, left ventricular systolic diameter; ACE inhibitor, angiotensin converting enzyme inhibitor; and ARB, angiotensin II receptor blocker.

EF group (45.0%) compared to the non-improved EF group (11.1%) ($P = 0.02$). The prevalence of PCIs excluding CTO in the improved EF group (45.0%) was comparable to that in the non-improved EF group (51.9%) ($P = 0.77$). The prevalence of CABG including CTO in the improved EF group (10.0%) was also comparable to that in the non-improved EF group (18.5%) ($P = 0.68$). Surprisingly, the prevalence of CABG excluding CTO was greater in the non-improved EF group (18.5%) than in the improved EF group (0%), although the difference was not statistically significant ($P = 0.06$).

Medications at discharge are shown in Table IV. The prevalence of angiotensin converting enzyme inhibitor (ACE inhibitor) and/or angiotensin II receptor blocker (ARB) in the

improved EF group (100.0%) was significantly greater than in the non-improved EF group (70.4%) ($P < 0.01$), whereas the prevalence of beta-blocker in the improved EF group (95.0%) was marginally different from that in the non-improved EF group (70.4%) ($P = 0.06$).

We also analyzed the characteristics of patients who received CABG as revascularization, and compared with non-CABG (= PCI) patients (Table V). In patients with CABG, the prescription rate of an ACE inhibitor and/or ARB was significantly lower (50.0%) than in patients without CABG (94.3%) ($P < 0.01$). The use of a beta-blocker was also significantly lower in patients with CABG (41.7%) than in patients without CABG (94.3%) ($P < 0.001$).

Table VI. Determinants of LVEF Improvement: Univariate and Multivariate Logistic Regression Analysis

Independent variables	Determinant variable: LVEF improvement (delta LVEF $\geq 10\%$)					
	Univariate Logistic Regression Analysis			Multivariate Logistic Regression Analysis		
	OR	95% CI	P	OR	95% CI	P
Age (1 year increase)	0.98	0.93-1.04	0.52	0.99	0.93-1.05	0.72
Male	0.95	0.25-3.60	0.94	2.29	0.38-13.71	0.36
Echo follow-up interval (1 month increase)	0.99	0.94-1.05	0.81			
Revascularization by PCIs including CTO	6.55	1.48-29.01	0.01	5.43	1.06-27.74	0.04
Revascularization by PCIs excluding CTO	0.76	0.24-2.42	0.64			
Revascularization by CABG including CTO	0.49	0.09-2.83	0.42			
Revascularization by CABG excluding CTO*	N/A	N/A	N/A			
ACE inhibitor and/or ARB**	N/A	N/A	N/A			
Beta-blocker	8.00	0.91-70.34	0.06	5.87	0.52-66.66	0.15
Amiodarone*	N/A	N/A	N/A			

Univariate logistic regression analysis was performed to identify variables that had marginal association with LVEF improvement ($P < 0.10$). Age, sex and all variables that had marginal association in univariate analysis were adopted as independent variables in multivariate logistic regression analysis. *Revascularization by CABG excluding CTO and amiodarone were not applicable for univariate logistic regression analysis because there were no patients in the improved EF group. **ACE inhibitor and/or ARB were not applicable for univariate logistic regression analysis because all patients in the improved EF group were prescribed ACE inhibitors and/or ARB. OR indicates odds ratio; CI, confidence interval; LVEF, left ventricle ejection fraction; PCI, percutaneous coronary intervention; CTO, chronic total occlusion; CABG, coronary artery bypass grafting; ACE inhibitor, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; and N/A, not applicable.

The results of univariate and multivariate logistic regression analyses for the improved EF group are shown in Table VI. In the univariate logistic regression analysis, independent variables were age, sex, methods of revascularization, and potential confounding factors that showed a marginal difference ($P < 0.10$) between the improved EF and non-improved EF groups in Table I-IV. Revascularization by CABG excluding CTO and amiodarone were not applicable for univariate logistic regression analysis because there were no patients in the improved EF group. ACE inhibitors and/or ARB were not applicable for univariate logistic regression analysis because all patients of the improved EF group received an ACE inhibitor and/or ARB. In the multivariate logistic regression analysis, age, sex, and variables that showed a marginal association ($P < 0.10$) with LVEF improvement in the univariate logistic regression analyses were adopted as independent variables. Revascularization by PCIs including CTO (OR 5.43, 95% CI 1.06-27.74, $P = 0.04$) was the significant determinant of LVEF improvement in this multivariate analysis.

DISCUSSION

From among 2,229 heart failure patients admitted to our department, we extracted 47 HFrEF patients who underwent revascularization (PCI or CABG) during the hospitalization, and analyzed to identify the determinants of LVEF improvement following revascularization. ACE inhibitors and/or ARB were prescribed to all patients in the improved EF group, and beta-blockers were also prescribed to 95% of patients in the improved EF group. Multivariate logistic regression analysis revealed that revascularization by PCIs including CTO was the only significant determinant of LVEF improvement after adjusting for the confounding factors.

In the present study, CABG was not a determinant of LVEF improvement, which contradicts earlier studies such as CREDO-Kyoto PCI/CABG Registry data that showed CABG is associated with better survival outcomes than PCI in patients

with reduced LVEF.²⁴⁾ To explain this contradiction, there are several confounding factors regarding the association between CABG and LVEF improvement in the present study. First, the most significant confounding factor is the difference in the prescription rate of optimal medical therapy. The prescription rate of optimal medical therapy including ACE inhibitors and/or ARB and beta-blockers was significantly lower in patients with CABG than in patients without CABG ($P < 0.01$ and $P < 0.001$, respectively). Second, the echo follow-up intervals were significantly shorter in the patients with CABG (4.2 ± 3.2 months) than in the patients without CABG (9.3 ± 12.0 months). Therefore, we might have missed the LVEF improvement in the later phase in the patients with CABG. Furthermore, a previous history of stroke and heart failure hospitalization were more common in the patients with CABG, suggesting that the severity of arteriosclerosis or heart failure was greater in the patients in the CABG group. Given these confounding factors, our results may underscore the importance of optimal medical therapy even if the patient receives CABG.

It is well known that coronary CTO is associated with poor clinical outcomes such as acute myocardial infarction or sudden cardiac death.²⁵⁻²⁷⁾ Successful revascularization of coronary CTO is associated with the improvement of left ventricular function in patients with angina pectoris or old myocardial infarction.²⁸⁻³⁰⁾ Recently, George and colleagues reported that successful CTO intervention was associated with a decrease in mortality as compared to unsuccessful CTO intervention using large registry data ($n = 13,443$).³¹⁾ Furthermore, Jang and colleagues reported the long-term survival benefit of CTO revascularization as compared to medical therapy using a propensity score-matched population.³²⁾ However, the association between improvement of LV systolic function and revascularization of coronary CTO has not been investigated in patients with heart failure. Our study focused on a systolic heart failure population, and showed the possible benefit of CTO revascularization for LV systolic function improvement. Since LV systolic function is a significant predictor of long-term outcome in patients

with heart failure,³³⁻³⁶⁾ improvement of LV systolic function following CTO revascularization may improve long-term clinical outcomes in HFREF patients if performed together with optimal medical therapy.

There have been technical issues in PCI to coronary CTO. While the success rate of PCI to coronary CTO was not sufficient (51-74%) until 2009,^{37,38)} the introduction of new devices such as guidewires or microcatheters and bidirectional approaches (antegrade and retrograde) has significantly increased the initial success rate of CTO.³⁹⁻⁴¹⁾ Furthermore, the long-term patency of revascularized CTO was low in patients treated using bare-metal stents,⁴²⁾ however, the long-term patency of revascularized CTO is comparable to non-CTO lesions in patients treated by drug-elution stents.⁴³⁾ Therefore, PCI to CTO is not a special procedure, and patency following drug-eluting stent deployment is to be expected.

Study limitations: Since the present study was designed as a single-center, retrospective, and observational study, there is a possibility of patient selection bias. LVEF was measured using the single plane area-length method, which is less accurate than the bi-plane modified Simpson method. Therefore, the overestimation or underestimation of LVEF was possible. Echocardiographic parameters that were performed before revascularization should be used as initial parameters. However, some cases received only bedside echocardiography that did not include full parameters before revascularization. Therefore, we adopted the echocardiography performed in the echocardiographic laboratory most recently from the day of discharge as the initial echocardiography. Furthermore, the interval between the initial echocardiography and the follow-up echocardiography was not consistent, which may have affected the improvement of LVEF. It would be better to evaluate myocardial viability using stress scintigraphy before revascularization, nevertheless, it was sometimes difficult to perform the stress test for heart failure patients. In most cases, we evaluated myocardial viability by myocardial wall thickness assessed by echocardiography. Finally, although we discussed the indication of revascularization for each patient with coronary artery disease and followed clinical guidelines²¹⁾ in our daily clinical practice, there was a still selection bias regarding the indication of revascularization.

Conclusions: Revascularization by PCIs including CTO was the significant determinant of LVEF improvement in HFREF patients under optimal medical therapy. A low prescription rate for optimal medical therapy may counteract the merit of revascularization by CABG. Our results suggest the possible benefit of CTO PCI in HFREF patients. Our results also underscore the importance of optimal medical therapy even if patients receive complete revascularization such as CABG.

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DISCLOSURE

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