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Early Exercise Program for Patients with Heart Failure after Hospital Discharge

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Abstract

Background: The exercise program (EP) demonstrated beneficial effects on survival and morbidity of patients with chronic and stable heart failure (HF), but there were no evidence of safety and benefit when the EP was implemented early.

Objectives: This study aimed to investigate the effects of early EP for patients with HF.

Methods: We randomly recruited 48 patients with systolic HF early after acute HF hospitalisation, with ejection fraction <40%, age <65 years, resting heart rate <100 bpm, and able to walk more than 100 meters as the intervention group (IG). They participated in in-hospital, low-to-moderate intensity, symptom-limited EP for 1 month. Meanwhile, 65 patients with similar characteristic or refused to be recruited to the IG were allocated as control group (CG) underwent usual care. Pre and post study measurement of 6-minutes walking test (6MWT) distance, NT-proBNP level, quality of life parameters (Minnesota Living with Heart Failure Questionnaire and SF-36), and first major adverse cardiac event (mortality, rehospitalisation or clinical worsening) within 1 month study period.

Results: Both groups had similar baseline characteristics. The patients in IG initiated the early EP on day 5.1+3.5 from hospital discharge. Major adverse cardiovascular events were experienced by 9 (18.8%) of the IG and by 26 (40%) of the CG (p=0.016). At the end of study, the 6MWT distance of IG was higher than that of CG: 398.9 (95% CI: 383.8-414.0) versus 352.7 (95% CI: 318.4-387.0) meters, p=0.016. Mean NT-proBNP level did not change in IG (from 3774 to 3563 pg/mL, p=0.568) nor in CG (from 3784 to 4931 pg/mL, p=0.150). Quality of life parameters improved in IG, but not in CG.

Conclusion: Early EP for patients with HF was safe and effective in improving physical fitness level and quality of life and it did not harm the myocardium.

Keywords: Exercise; Heart failure; Safety

Introduction

Exercise program (EP) has been accepted as an important part of management of heart failure (HF) patients, because it demonstrated various beneficial effects [1,2]. However, recommendations or studies were usually directed towards chronic patients with HF who were already in optimal medical treatment and clinically stable [3-5]. Meanwhile, within the first month after discharge, there would be more than 25% mortality or rehospitalisation [6]. These patients have had no opportunity to commence EP.

Learning from the experience of Man et al. [7] who studied an early rehabilitation program for patients with chronic obstructive lung disease, EP for patients with HF has usually been prescribed at low to moderate intensity, based on individual fitness level, supervised and symptom-limited, so that early EP could be considered safe for patients with HF [8].

This study aimed to investigate the effects of EP when it was implemented early after hospitalisation with acute heart failure, whether the EP was safe and could improve functional capacity and quality of life as was observed from EP studies for patients with chronic and stable HF.

Methods

We randomly recruited patients with systolic HF early after hospitalisation with acute heart failure, acute decompensated heart failure or de-novo heart failure in the National Cardiovascular Center (NCVC) Harapan Kita Jakarta between June 2010 and May 2012 to participate in early exercise-based cardiac rehabilitation program as the Intervention Group (IG), Their ejection fraction (EF) should be <40%, age <65 years old, resting heart rate (HR) <100 beat per minute, should be able to walk more than 100 metres in the 6 minute walk test (6MWT) as safety limit consideration, creatinine level <2.5 mg/dL and consented to participate in the study after appropriate information was given.

The patients were excluded if the primary cause of HF was severe valvular stenoses or regurgitation, acute coronary syndrome, and the presence of problems that caused an inability to participate in EP such as musculoskeletal impairment. This study was approved by the

Research Ethical Committee of NCVC Harapan Kita Jakarta and Research Ethical Committee of Faculty of Medicine, Universitas Indonesia.

The eligible patients who were randomly recruited into the IG participated in EP beside their standard care. Meanwhile other patients with similar characteristic or patients who refused to participate into the IG after randomization continued the standard care without early EP as control group (CG). The EP sessions were conducted in the gymnasium of NCVC Harapan Kita for 1 month, supervised by experienced and trained personnel's, three sessions per week for 20 to 40 minutes per session; the exercise consisted of warming up, low to moderate intensity of endurance training (leg ergocycle and walking or treadmill), with electrocardiogram telemetry when necessary, the EP was expected to increase the heart rate up to 20 bpm above resting, and EP was completed after cooling down.

All patients underwent basic medical examination, NT-proBNP laboratory examination, 6MWT, and quality of life (QoL) assessment using the Minnesota Living with Heart Failure Questionnaire (MLWHFQ) and SF-36 prior to and after intervention or observation period. The examinations were performed by attending cardiologists at the cardiac rehabilitation who planned and supervised the program in daily basis with nurses, physiotherapist and physical trainers.

Regular follow up and medication were performed by other cardiologists at the out-patient clinic. There was no specific and organised medical or nursing service as care manager involved in patient care outside the hospital regarding the EP and treatment program.

The incidence of major adverse cardiovascular events (MACE) such as mortality, rehospitalisation or HF clinical worsening of all patients were regularly examined and recorded by research assistants based on medical records or direct communication by phone or mail within 1 month of study period.

Statistical Analysis

We estimated that this study would have 80% power, 2-sided alpha of 0.05, to detect a 20% absolute difference in major adverse cardiovascular events (mortality, rehospitalisation and clinical worsening of HF). Sample size was calculated based on prediction of significant MACE rate different, level of NT-proBNP different, predicted NT-proBNP level different and change of 6 MWT distance different between both groups. The minimum size was 102 patients.

Continuous data of subjects' characteristic are presented as mean and 95% Confidence Interval (CI) in tables, or as mean and standard deviation (SD); categorical data are presented as a percentage. The comparison of characteristic data between the IG and CG were analysed using the Student t-test or Mann Whitney for continuous data, whereas Pearson's chi square or Fisher's exact test was used for categorical data. Change of 6MWT distance, NT-proBNP level from baseline and follow up intra group were analysed using the dependent Student t-test or Wilcoxon. Univariate analysis with Pearson Chi-square or Fisher's exact test was developed for variables that were considered to be related to MACE. Multivariate regression analysis was performed using Cox Regression to evaluate the role of EP and other confounding variables related to MACE. The confounding variables were taken from univariate analysis with p <0.25, and other variables which was considered having relation with MACE. We analysed the event free or hazard of EP using the Kaplan-Meier survival curve. Statistical significance was stated if p value <0.05.

Result

Subject characteristics

The baseline characteristics of all recruited patients are presented in Table 1. Forty-eight patients participated in IG and 65 patients participated in CG. All patients were in New York Heart Association (NYHA) functional class III.

Variable	Value (N=113)
Age (year)	51.7 (50.2–53.3)
Gender Male	(84.1)
Ischaemic Cause	72 (63.7)
Co-morbidities:	
MCI	65 (57.5)
Hypertension	66 (58.4)
CAD	64 (56.6)
Diabetes	58 (51.3)
Sinus rhythm	95 (84.1)
Atrial Fibrillation	18 (15.9)
Wide QRS (≥ 120 ms)	30 (26.5)
Ejection Fraction: (%)	22.2 (21.3–23.2)
EDD: (mm)	66.6 (65.1–68.1)
ESD: (mm)	59.2 (57.6–60.7)
Lab: Haemoglobin (g/dL)	14.2 (13.8–14.6)
Leukocytes (103/mm3)	9037 (8596–9478)
Urea (mg/dL)	48.2 (43.9–52.6)
Creatinine (mg/dL)	1.25 (1.18–1.32)
Sodium (mEq/L)	137.6 (136.8–138.5)
Potassium (mEq/L)	4.1 (4.0–4.2)
NT-proBNP (pg/mL)	4177 (3632–4723)
Treatment: ACE-I	84 (74.3)
A R B	32 (28.2)
Beta-blocker	87 (77)
Oral Anti-diabetics	48 (42.5)
Insulin	11 (9.7)
Anti-platelet	81 (71.7)
Anti-coagulant	49 (43.3)
6 MWT distance (m)	289.0 (276.8–301.2)
MLWHFQ score	60.4 (56–64.7)

SF-36 (Physical) score	34.4 (33.2–35.6)
SF-36 (Mental) score	42.1 (40.3–43.9)

Numerical data presented in mean (95%CI), categorical data presented in frequency (%), **MCI**: Myocardial Infarction, **CAD**: coronary artery disease, **EDD**: end diastolic diameter, **ESD**: end systolic diameter, **ACE-I**: angiotensin converting enzyme inhibitor, **ARB**: Angiotensin receptor blocker, **6MWT**: 6 min walk distance, **MLWHFQ**: Minnesota Living with Heart Failure Questionnaire.

Table 1: Baseline Characteristic of all Subjects.

Both groups had equal characteristics regarding age, gender proportion, cause of HF, presence of hypertension, CAD, diabetes, history of myocardial infarction, rhythm and QRS complex category, important results from echocardiogram and HF prognosis-related laboratory examinations, medical treatment, fitness level and quality of life (Table 2).

Variable	Intervention Group (N=48)	Control Group (N=65)	P
Age (year)	51.8 (49.3–54.4)	51.7(49.6–53.7)	0.80
Gender, Male	41 (85.4)	54 (83.1)	0.74
Ischaemic Cause	33 (68.8)	39 (60.0)	0.34
Co-morbidity:			
Hypertension	25 (52.1)	41 (63.1)	0.24
CAD	31 (64.6)	33 (50.8)	0.78
Diabetes	25 (52.1)	33 (50.8)	0.89
Myocardial Infarct	27 (56.3)	38 (58.5)	0.81
Atrial Fibrillation	7 (14.6)	11 (16.9)	0.74
Wide QRS complex	11 (22.9)	19 (29.2)	0.45
Ejection Fraction (%)	22.3 (20.8–24.0)	22.2 (21.0–23.4)	0.88
EDD (mm)	66.4 (63.9–68.8)	66.8 (64.9–68.7)	0.78
ESD (mm)	58.7 (55.9–61.5)	59.5 (57.7–61.3)	0.60
Haemoglobin (g/dL)	14.0 (13.3–14.6)	14.4 (13.9–14.5)	0.29
Leukocyte (103/mm3)	0.915 (0.845–0.976)	0.895 (0.832–0.938)	0.66
Urea (mg/dL)	47.3 (41.2–53.4)	48.9 (42.6–55.1)	0.81
Creatinine (mg/dL)	1.29 (1.18–1.40)	1.22 (1.13–1.32)	0.214
Sodium (mEq/L)	136.8 (135.6–138)	138.2 (137–139.4)	0.116
Potassium (mEq/L)	4.1 (3.9–4.3)	4.1 (4.0–4.3)	0.774
NT-proBNP (pg/mL)	3833 (3166–4499)	4437 (3611–5252)	0.280
ACE-I/ARB	47 (97.9)	65 (100)	0.425
Beta blocker	41 (85.4)	46 (70.8)	0.067
Anti-diabetics (OAD)	21 (43.8)	27 (56.3)	0.814
Insulin	4 (8.3)	7 (10.8)	0.666
OAD/Insulin	24 (50)	32 (49.2)	0.936
Anti-platelet	32 (66.7)	49 (75.4)	0.309
Anti-coagulant	19 (39.6)	30 (46.2)	0.486
6MWT distance(m)	295.6 (277.5-313.7)	284.1 (267.3-301)	0.201
MLWHFQ score	63.3 (56.5-63.7)	58.2 (52.4-64.1)	0.226
SF-36 (Physical) score	33.6 (32.1-35.2)	35.0 (33.3-36.8)	0.254
SF-36 (Mental) score	42.4 (39.3-45.6)	41.8 (39.7-44.0)	0.630

CAD: Coronary artery disease, **EDD:** End diastolic diameter, **ESD:** end systolic diameter, **ACE:** Angiotensin converting enzyme, **ARB:** Angiotensin receptor blocker, **6MWT:** 6 minute walk test, **MLWHFQ:** Minnesota Living with Heart Failure Questionnaire. p: from Student t-test or Mann-Whitney for numeric data, and from Pearson Chi Square or Fisher's exact test for categorical data. Numeric data presented in mean (95%CI) and categorical data presented in frequency (%).

Table 2: Baseline Characteristic Comparison between Groups.

Prior to recruitment, all patients of IG and CG experienced hospitalisation for acute heart failure 7.1+4.8 days (mean+SD), range: 2-22 days, and 7.7+4 days, range: 3-26 days consecutively, p=0.477.

Exercise training program

Patients of IG commenced EP at day 5.1+3.5 after hospital discharge (range: 3 days before discharge to 13 days after discharge). They participated in 10.3+2.8 EP sessions within 1 month. The EP increased their heart rate by 12.1+5.1 beat per minute (range: 3 to 29 bpm).

Effects of exercise

There were 9 (18.8%) of the 48 IG patients who experienced MACE, of which 1 patient died, 5 patients experienced rehospitalisation, and 3 patients experienced worsening of their clinical condition. Those MACEs were averagely recorded at day 17.8+9.3 after discharge. None of them experienced acute clinical worsening or complications attributed to exercise training. There were 26(40%) of the 65 CG patients who experienced MACE, of which 4 patients died, 15 patients experienced rehospitalisation, and 7 patients experienced clinical worsening of HF. Those events were recorded at day 17.3+7.5.

Variable	Intervention Group	P	Control Group	P
NT proBNP pre (pg/mL)	3774 (2945-4603)	0.568	3784 (2456-5112)	0.150
NT proBNP post (pg/mL)	3563 (2787-4339)		4931 (2493-7370)	
NT proBNP change (pg/mL)	-211 (-95-532)		1147 (-454-2.749)	0.121*)

6 MWT pre (m)	302.7 (283.8-321.7)	<0.001	283.0 (252-313.3)	<0.001
6 MWT post (m)	398.9 (383.8-414.0)		352.7 (318.4-387.0)	0.016**)
6 MWT change (m)	96.2 (77.5-114.8)		69.8 (42.7-96.6)	0.068*)
Data are presented in mean (95%CI), p for difference within group (pre and post), except *) for the difference between Intervention Group and Control Group. **) for the difference of 6MWT post between groups. 6MWT: 6 minute walk test.				

Table 3: Comparison of NT-proBNP and 6MWT Distance Changes Between Groups.

The changes of NT-proBNP level and 6MWT distance are presented in Table 3. In IG, mean NT-proBNP level decreased after EP, but it was not statistically significant. The 6MWT distance increased significantly in both groups, but the mean improvement in IG was higher than in CG, but not statistically significant (p=0.068), but the post intervention 6MWT distance of IG was higher than that of CG: 398.9 (95% CI: 383.8-414.0) versus 352.7 (95% CI:318.4-387.0) meters, p=0.016. Changes of QoL in both groups were compared in Table 4. There was a significant improvement in quality of life in IG but not in CG.

Variable	Intervention Group	P	Control Group	P
MLWHFQ pre	58.7 (49.3-68.2)	<0.001	54.4 (45.5-63.4)	0.162
MLWHFQ post	32.2 (25.3-39.1)		48.8 (40.4-57.2)	
SF-36 physical pre	33.5 (31.6-35.4)	<0.001	35.5 (31.1-39.8)	0.643
SF-36 physical post	41.2 (38.5-44.0)		36.5 (32.8-40.3)	
SF-36 mental pre	43.7 (39.6-47.8)	0.002	42.7 (37.4-48.1)	0.268
SF-36 mental post	51.1 (47.6-54.6)		45.9 (41.4-50.4)	
MLWHFQ: Minnesota Living with Heart Failure Questionnaire, **p**: for difference within group (pre and post)				

Table 4: Comparison of Quality of Life Scores between Groups.

Prognosis of patients with HF was influenced by several factors such as gender, age, heart rhythm, QRS complex on electrocardiogram, results of several laboratory examinations, and existence of co-morbidities [9]. To evaluate the role of confounding factors besides exercise training on the final results, we identified several variables which were considered to be related to or became risk factors for MACE and then we performed multivariate regression analysis using Cox Regression. The variables were separated by their median or cut-off-point which were assumed to be clinically significant or at the level of abnormal threshold. Exercise training and some variables with p value <0.25 in bivariate analysis (EDD >65 mm, EF<21%, hypertension, atrial fibrillation, without anti-platelet therapy, 6MWT distance <240 metres, wide complex QRS, and age >54 years) were analysed using Cox Regression multivariate analysis as seen in Table 5. This multivariate regression analysis revealed that exercise training consistently had protective effect with adjusted RR of 0.44 (95% CI: 0.2-0.97; p=0.034) for MACE.

Variable	MACE n (%)	No MACE n (%)	RR Adjusted *	95%CI	P
Exercise Training	9 (18.8)	39 (81.3)	0.44	0.20–0.97	0.034
EDD ≥ 65 mm	25 (37.9)	41 (61.2)	1.51	0.68–3.38	0.312
E F ≤ 21%	22 (37.9)	36 (62.1)	1.45	0.71–2.96	0.303
Hypertension	17 (25.8)	49 (74.2)	0,66	0.32–1.39	0.278
Atrial Fibrillation	8 (44.4)	10 (55.6)	1.58	0.68–3.66	0.290
Without anti-platelet	7 (21.9)	25 (78.1)	0.51	0.21–1.21	0.128
6MWT ≤ 240 m	10 (41.7)	14 (58.3)	1.27	0.59–2.77	0.541
Wide QRS	12 (40)	18 (60)	1.11	0.52–2.38	0.788
Age ≥ 54 years	15 (25.9)	43 (74.1)	0.84	0.39–1.78	0.641
MACE: Major adverse cardiovascular events, **RR:** Relative Risk, **EDD:** end diastolic diameter, **6MWT:** 6minutes walk test, **CI:** confidence interval. *) adjusted for other variables.					

Table 5: Multivariate Analysis with Cox Regression.

The comparison of cumulative hazard of IG and CG were also presented as a Kaplan-Meier curve that showed better event-free rate of IG (Figure 1).

Discussion

This study demonstrated that EP which was commenced early (5.1+3.5 days after hospital discharge for acute heart failure) was safe. Rate of MACE (mortality or rehospitalisation or clinical worsening) of IG was 18.8% and was significantly lower than in CG (40%), p=0.016. This study also demonstrated that early EP had an adjusted RR for MACE of 0.44 (95%CI: 0.20–0.97; p=0.034), or a relative risk of MACE reduction 56% after adjustment for other determinants (EDD >65 mm, EF <21%, hypertension, atrial fibrillation, without anti-platelet, 6MWT distance <240 meter, wide QRS, and age >54 year). Kaplan-Meier curve analysis also proved that early EP for patients with HF had a protective effect on MACE, especially after 2 weeks of exercise training.

Previously, exercise training was prohibited and not recommended for patients with HF, since it could worsen their clinical condition. Patients were recommended to prolonged bed rest and restrict activity [10]. The new concept of HF management considered that prolonged bed rest in patients with HF, or even in normal individuals, would worsen clinical conditions because of negative changes within skeletal muscle such as atrophy, muscular fibre-type changes, and decreased dilatation function of peripheral vessels [11-13].

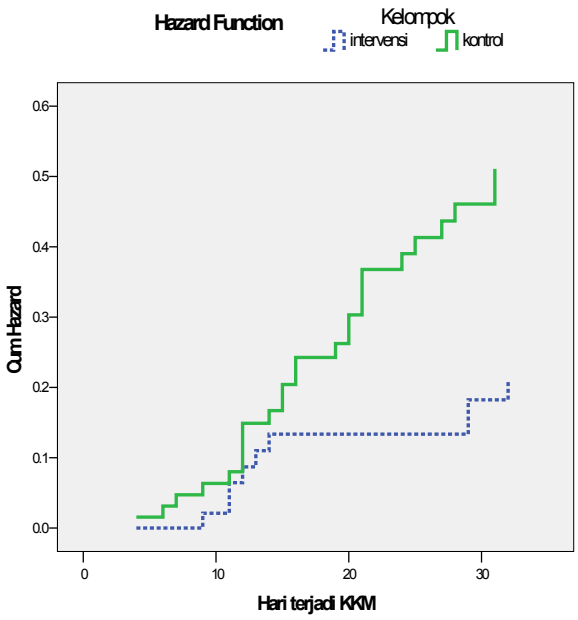

Figure 1: Comparison of Hazard between Groups.

There were similar pathophysiological aspects of patients with HF and deconditioning due to prolonged bed rest, such as alterations of peripheral haemodynamic, autonomic control, functional capacity, muscle structure and psychological aspects [14,15]. However, those alterations were reversible with exercise training through increased cardiac output and peripheral changes [16].

Compared to the subject characteristics of Acute Decompensated Heart Failure Registry (ADHERE) in Indonesia, which was a registry of hospitalised acute decompensated HF cases, the age of our patients was younger because of the differences in recruitment criteria. The majority of patients had already got the recommended treatments of HF [1,2] although all of them were still getting diuretic when they participated in EP.

A pilot study without control of early exercise training for patients with HF was also reported by Houcen et al. [17] who commenced exercise training within the first 30 days after hospital discharge, began on day 11 on average, and early EP resulted in an increased fitness level. A short exercise training study (4 week) of patients with HF after acute myocardial infarction was also reported by Jette et al. [18] Of those 10 patients with EF, <30% who participated in moderate intensity exercise training resulted in an improvement in exercise tolerance.

Exercise training studies that recruited clinically stable, chronic patients with HF were generally considered to be safe, [4] and to decrease the NT-proBNP level, [19] but there was also a study that demonstrated an improvement in fitness level but did change the NT-proBNP level, although the exercise training was conducted for 18 weeks [20]. In this study, there was a trend of decreasing the NT-proBNP level by EP, but this was not statistically significant, probably due to the short duration of exercise training.

Exercise programs improved functional capacity, which could be measured by several methods such as 6MWT, cardiopulmonary exercise testing, and exercise time. In this study, the increased 6MWT distance could be observed in both groups, but the 6MWT distance in IG after intervention was significantly higher than in CG after observation. A meta-analysis which was performed by Rees et al. [21] revealed that the 6MWT distance increased by 40.9 metres, and a study by Arad et al. [20] revealed a 39% improvement of 6MWT distance after exercise training for 18 weeks.

This study also demonstrated a significant improvement of the HF-specific QoL score which was measured using MLWHFQ and generic physical and mental components of the QoL score that was measured using SF-36 in IG but was not observed in CG. Several studies on exercise training in patients with HF measured the improvement of quality of life as a variable which was also measured with MLWHFQ score, as in the study of Bellardinelli et al. [22] Passino et al. and Davidson et al. [23,24]. Their studies demonstrated an improvement in quality of life as a positive effect of EP in patients with HF. This study has also proven that early exercise training in patients with HF could improve quality of life that was measured generally and specifically.

The results of this study have encouraged us to promote EP for patients with HF early after hospital discharge on top of optimal medical treatment. Besides optimal medical treatment and exercise-based cardiac rehabilitation, it is important to consider the availability of patients' care manager. The role of care managers can bridge the patients with the doctors and to facilitate good communication with hospital, clinic, clinic, cardiac rehabilitation unit and its staffs for the benefits of optimal recovery, optimal medical therapy and returning to work.

In this study, however, there was no identifiable role of care managers in outpatient clinic and in primary health care service, because of the healthcare system did not make it possible outside our institution. All patients in this study were treated by their attending cardiologists at outpatient clinic in the National Cardiovascular Center Harapan Kita Jakarta for the first month after discharge until stable condition attained. Consultations regarding exercise training and cardiac rehabilitation program were done at the cardiac rehabilitation unit with cardiologist, nurses, physiotherapist, occupational therapist or psychologist.

This study was a bridging of post-discharge patients with HF with several conditions and risks of rehospitalisation and mortality to established, conservative EP which had more evidence of benefits [4]. After being hospitalised with HF, patients can directly participate in EP. The initiation of EP was not limited by EF level. This early exercise training is also part of an important effort to minimise the deconditioning effect of recurrent hospitalisation and activity restriction after hospitalisation that usually worsens prognosis [12]. This study also demonstrated that early EP could increase physical fitness and could improve QoL within the first month. However, to decrease NT-proBNP level significantly, we probably need a longer period of exercise training, of at least 1.5 months [19].

Limitation

Some limitations should be considered before generalizing this study: The study was not a randomized control trial although baseline characteristic of both groups were comparable.

The EP in this study was conducted in a hospital, and was supervised by trained personnels. The result could not be applied for non-supervised EP. Small sample size.

Conclusions

Early exercise training for patients with HF after hospitalisation was safe. It reduced the relative risk of mortality, rehospitalisation and clinical worsening of heart failure, and was also effective at improving fitness levels and quality of life. Early exercise training for patients with HF did not harm myocardium condition. The evidence of this study could be considered as evidence to promote early EP for patients with HF after hospitalisation to prevent deconditioning effects which usually worsened prognosis.

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