High-Intensity Interval Training in Patients With Heart Failure With Reduced Ejection Fraction

BACKGROUND: Small studies have suggested that high-intensity interval training (HIIT) is superior to moderate continuous training (MCT) in reversing cardiac remodeling and increasing aerobic capacity in patients with heart failure with reduced ejection fraction. The present multicenter trial compared 12 weeks of supervised interventions of HIIT, MCT, or a recommendation of regular exercise (RRE).

METHODS: Two hundred sixty-one patients with left ventricular ejection fraction ≤35% and New York Heart Association class II to III were randomly assigned to HIIT at 90% to 95% of maximal heart rate, MCT at 60% to 70% of maximal heart rate, or RRE. Thereafter, patients were encouraged to continue exercising on their own. Clinical assessments were performed at baseline, after the intervention, and at follow-up after 52 weeks. Primary end point was a between-group comparison of change in left ventricular end-diastolic diameter from baseline to 12 weeks.

RESULTS: Groups did not differ in age (median, 60 years), sex (19% women), ischemic pathogenesis (59%), or medication. Change in left ventricular end-diastolic diameter from baseline to 12 weeks was not different between HIIT and MCT (P=0.45); left ventricular end-diastolic diameter changes compared with RRE were −2.8 mm (−5.2 to −0.4 mm; P=0.02) in HIIT and −1.2 mm (−3.6 to 1.2 mm; P=0.34) in MCT. There was also no difference between HIIT and MCT in peak oxygen uptake (P=0.70), but both were superior to RRE. However, none of these changes was maintained at follow-up after 52 weeks. Serious adverse events were not statistically different during supervised intervention or at follow-up at 52 weeks (HIIT, 39%; MCT, 25%; RRE, 34%; P=0.16). Training records showed that 51% of patients exercised below prescribed target during supervised HIIT and 80% above target in MCT.

CONCLUSIONS: HIIT was not superior to MCT in changing left ventricular remodeling or aerobic capacity, and its feasibility remains unresolved in patients with heart failure.

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Clinical Perspective

What Is New?

- The present multicenter trial did not confirm results from a small previous study that indicated that high-intensity interval training is superior to moderate continuous training (MCT) in reversing left ventricular remodeling and increasing aerobic capacity.
- In both groups, results were only moderately better than a recommendation of regular exercise; improvements were not maintained at the 52-week follow-up.
- Numeric differences in serious adverse events at 52 weeks suggested a favor of MCT, but the study was not powered to compare safety.
- Fifty-one percent of high-intensity interval training patients exercised below prescribed heart rate, and 80% of MCT exercised above their target.

What Are the Clinical Implications?

- Given that high-intensity interval training was not superior to MCT in reversing remodeling or improving secondary end points, and considering that adherence to the prescribed exercise intensity based on heart rate may be difficult to achieve, even when supervised and performed in centers experienced in cardiac rehabilitation, MCT remains the standard exercise modality for patients with chronic heart failure.

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Current guidelines recommend exercise training as an adjunctive therapy in patients with chronic heart failure.[1] A universal agreement on exercise prescription does not exist; thus, an individualized approach, including behavioral characteristics, personal goals, and preferences, is recommended.[2,3] At present, moderate continuous endurance exercise is the best described and established form of training because of its well-demonstrated efficacy and safety.[2] This advice is based mainly on a large multicenter exercise intervention trial (HF-ACTION [Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training]) with 2331 patients with heart failure, which observed a moderate reduction of symptoms, improvement of exercise capacity, and a reduction of hospital readmissions for heart failure.[4]

Exercise of high submaximal intensity performed in intervals of 1 to 4 minutes, also called high-intensity interval training (HIIT), has been tested in a small study of patients with heart failure with reduced ejection fraction, showing that HIIT was superior to moderate continuous training (MCT) in improving exercise capacity, quality of life, endothelial function, and left ventricular diameter and ejection fraction.[5] The results were better than those observed in previous studies and meta-analyses of patients with chronic heart failure.[6,7] They also prompted discussions of whether HIIT should be included in standard care of patients with chronic heart failure.

This background formed the basis for a larger randomized controlled multicenter trial, the SMARTEX Heart Failure Study (Study of Myocardial Recovery After Exercise Training in Heart Failure), to test the hypothesis that HIIT is superior to MCT with regard to improvement of left ventricular dimensions and exercise capacity.

METHODS

Study Design

The SMARTEX Heart Failure Study is an investigator-initiated randomized controlled clinical trial conducted at 9 European centers (Antwerp, Copenhagen, Leipzig, Luxembourg, Munich, Stavanger, Trondheim/Levanger, Veruno, and Ålesund) between June 2009 and July 2014. The final patient was randomized July 1, 2013, and had the 52-week follow-up on July 22, 2014. The Clinical Trials database registration reports 268 patients enrolled in the Web case report form database. However, 7 randomizations were error entries during initial testing and demonstration of the database. Thus, the correct number of patients randomized was 261. The trial was approved by the Regional Committee for Medical and Health Ethics of Central Norway and by national and local committees where required. Informed written consent was obtained from all participants. Details of rationale, design, methods, sample size, randomization, and organization have previously been published.[8] Data management and statistical analyses were performed by the coordinating center with oversight by the steering committee (Ø.E., M.H., A.L., E.P.), whose members had full access to all data and vouch for the accuracy and completeness of data and analyses.

Patients and Interventions

Patients were enrolled from outpatient heart failure clinics, referrals to cardiac rehabilitation, public announcements, and screening of eligible patients in hospital registries. Eligible patients with symptomatic (New York Heart Association class II–III), stable, pharmacologically optimally treated chronic heart failure were randomized 1:1:1 to a 12-week program of HIIT, MCT, or recommendation of regular exercise (RRE), stratified by study center and pathogenesis (ischemic versus nonischemic). Stratification by center was performed to avoid bias from unobserved treatment differences, and stratification by pathogenesis was performed to allow possible post hoc analysis of the influence on left ventricular end-diastolic diameter (LVEDD) changes. Exercise training protocols have been described elsewhere.[5,8] Briefly, HIIT and MCT had 3 supervised sessions per week on a treadmill or bicycle. HIIT included four 4-minute intervals aiming at 90% to 95% of maximal heart rate separated by 3-minute active recovery periods of moderate intensity. HIIT sessions lasted 38 minutes including warm-up and cool-down at moderate intensity. MCT sessions aimed at 60% to 70% of maximal heart rate and lasted 47 minutes. HIIT and MCT sessions were estimated to obtain similar energy expenditures.[9] Patients randomized to RRE were advised to exercise at home according to current recommendations and attended a session of moderate-intensity training at 50% to

70% of maximal heart rate every 3 weeks.[8] In all 3 groups, there were no supervised training sessions after the 12-week interventions, but the investigators had telephone contact with the participants every 4 weeks to register clinical events and to encourage physical activity.

Clinical Assessments

Screening procedures and clinical assessments before and after exercise interventions were performed at local study centers as previously described.[8] Briefly, medical history, anthropometrics, physical examination including fasting blood sampling, quality-of-life questionnaires, cardiopulmonary exercise testing, and echocardiography were performed, in addition to prespecified substudies.

Echocardiography data were acquired according to standard operation procedures of the study, stored digitally, and transferred as DICOM (digital imaging and communications in medicine) files or raw data to the core laboratory in Trondheim, Norway. Analyses were performed by 1 of 2 expert echocardiographers (A.S. and H.D.) blinded to group assignment but not always to time point of assessment on EchoPAC SW (version BT 11–13; GE Ultrasound, Horten, Norway). LVEDD was measured at the tip of the mitral leaflet in the 2-dimensional parasternal long-axis view.[10] Repeatability was tested by Bland-Altman analyses of the first 25 baseline assessments between the 2 investigators. There was no bias (0.3 mm), and the coefficient of variation was 4.1%.

Cardiopulmonary exercise testing was performed with standard equipment for indirect calorimetry in an incremental protocol until exhaustion on either a treadmill or a bicycle ergometer, depending on exercise training equipment. The protocol comprised a 10- or 20-W increase in workload ≈1 minute, starting at 20 or 40 W, respectively. For comparisons per patient, the baseline, 12-week, and 52-week tests were performed with the same protocol. The mean of the 3 highest 10-second consecutive measurements was identified as peak oxygen uptake (Vo_{2peak}). Respiratory quotient and other related values are reported from this time point. Cardiopulmonary exercise testing personnel were not blinded to assignment to intervention group, but analysis was performed separately by an independent investigator (P.B.).

End Points

The primary end point was comparison of groups with respect to change in LVEDD from baseline to the 12-week assessment by echocardiography. Key secondary end points were change in left ventricular ejection fraction and Vo_{2peak}; the latter was also considered a measure of training effect. Safety was assessed by the rate of serious adverse events (SAEs) defined as all-cause and cardiovascular death, worsening heart failure requiring hospitalization or intensified diuretic treatment, atrial and ventricular arrhythmias, unstable angina, inappropriate implantable cardioverter-defibrillator shocks, and other events leading to hospital admission or clinical evaluation. Events were considered training related when occurring during or within 3 hours of supervised exercise training sessions. An independent blinded end-point committee (J.K., R.H., and S.G.) classified all events. Quality of life was assessed with the Kansas City Cardiomyopathy Questionnaire, the Hospital Anxiety and Depression Scale, the Global Mood Scale, and the Type D

Scale 14. Physical activity was assessed with the International Physical Activity Questionnaire (7-day short form), but its reliability and validity have not been established in patients with heart failure, so the data have not been included. The measurements were taken at baseline, at 12 weeks immediately after the intervention, and at follow-up 52 weeks from the start of the training program.

Statistical Analysis

Power calculations for the main end point (comparison of the groups with respect to change in LVEDD from baseline to 12 weeks) have been detailed in a previous article on rationale and design.[8] We estimated that a total number of 200 patients, randomized 1:1:1 between RRE, MCT, and HIIT, would be sufficient to detect a reduction of LVEDD of 3.0 mm between HIIT and MCT and 5.0 mm between HIIT and RRE. Calculations were based on LVEDD of 70 mm, coefficient of variance of 0.04, statistical power of 0.90, and value of $P=0.05$, adjusted for 3 comparisons by the Bonferroni correction. Unless otherwise specified, data are presented as median with 95% confidence interval of the median because many variables were nonnormally distributed or as observed numbers with percentages.

The main end-point analysis was prespecified as mixed-models linear regression with robust standard errors, with 12-week values used as outcome and baseline values used as adjustment variables, and included adjustments for center, ischemic or nonischemic pathogenesis, and height. Model fit was checked by residual plots, and estimated contrasts are presented with 95% confidence intervals and P values corrected for 3 pairwise comparisons with the Scheffé method. For comparisons including the 52-week data, similar analyses were performed. A 2-sided value of $P\leq0.05$ was considered statistically significant.

To monitor adherence to training intensity, heart rate and workload were recorded during training sessions, and average training intensity was calculated as percentage of maximal heart rate at baseline. For HIIT and MCT patients, regression models including average percentage of maximal heart rate during training (continuous variable or lowest versus highest quartile), atrial fibrillation (yes versus no), or smoking (present versus former/never) were developed.

The study was not powered to assess differences in safety or clinical events; therefore, SAEs were not a prespecified end point.[8] However, safety is an important concern in this population, especially when performing exercise. With acknowledgment of the limitations of post hoc analysis,[11] χ^2 tests for cardiovascular, noncardiovascular, and total SAEs during the training intervention period and during follow-up were performed with no corrections for multiple testing. Statistical analyses were performed with Stata (version 13.1, StataCorp, College Station, TX).

RESULTS

Patient Population and Adherence to Intervention

After initial exclusions and withdrawals, 231 patients were included in HIIT, MCT, or RRE. Nine dropped
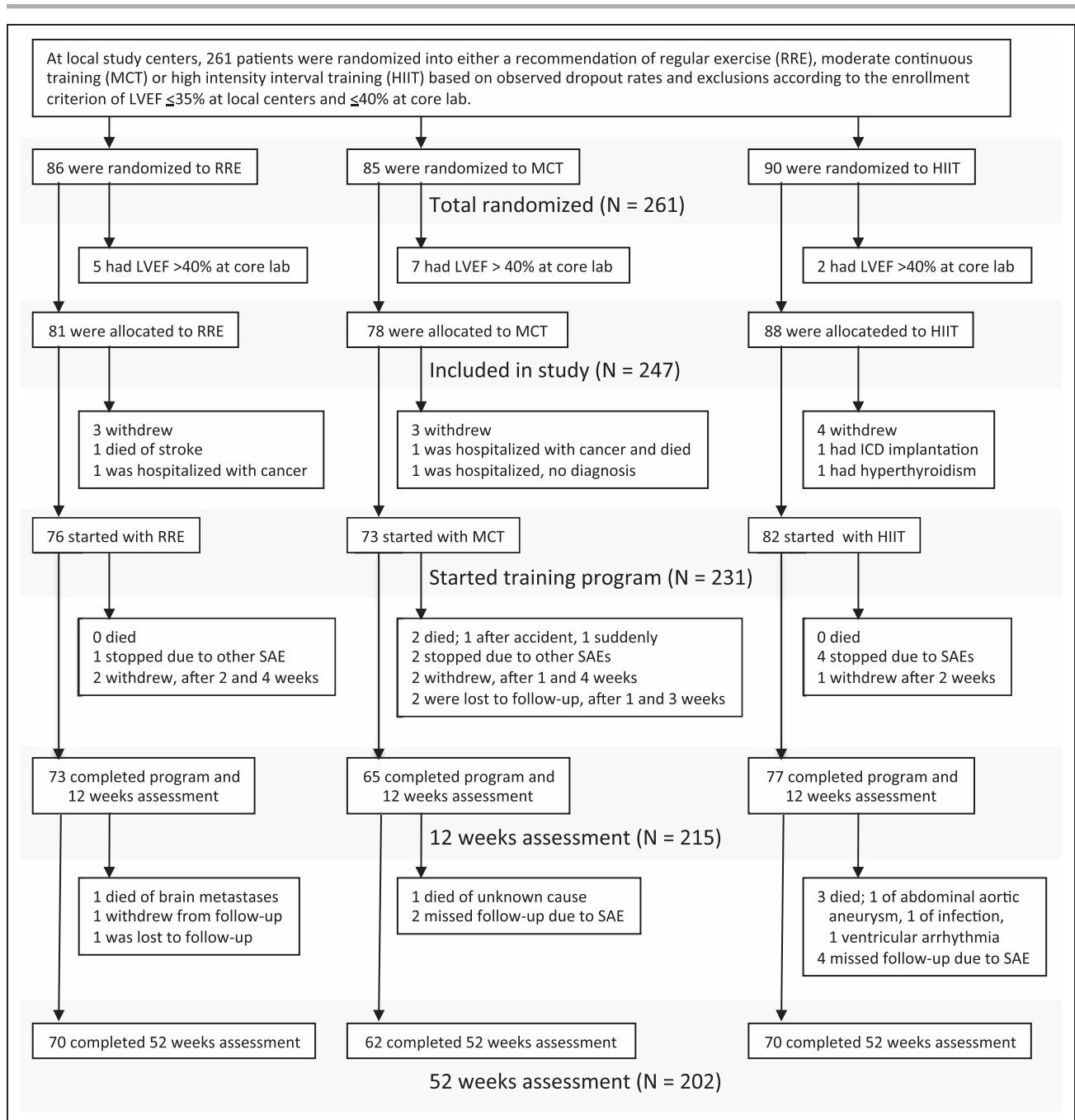
At local study centers, 261 patients were randomized into either a recommendation of regular exercise (RRE), moderate continuous training (MCT) or high intensity interval training (HIIT) based on observed dropout rates and exclusions according to the enrollment criterion of LVEF ≤35% at local centers and ≤40% at core lab.

| 86 were randomized to RRE | 85 were randomized to MCT | 90 were randomized to HIIT |

Total randomized (N = 261)

| 5 had LVEF >40% at core lab | 7 had LVEF > 40% at core lab | 2 had LVEF >40% at core lab |

| 81 were allocated to RRE | 78 were allocated to MCT | 88 were allocateded to HIIT |

Included in study (N = 247)

| 3 withdrew
1 died of stroke
1 was hospitalized with cancer | 3 withdrew
1 was hospitalized with cancer and died
1 was hospitalized, no diagnosis | 4 withdrew
1 had ICD implantation
1 had hyperthyroidism |

| 76 started with RRE | 73 started with MCT | 82 started with HIIT |

Started training program (N = 231)

| 0 died
1 stopped due to other SAE
2 withdrew, after 2 and 4 weeks | 2 died; 1 after accident, 1 suddenly
2 stopped due to other SAEs
2 withdrew, after 1 and 4 weeks
2 were lost to follow-up, after 1 and 3 weeks | 0 died
4 stopped due to SAEs
1 withdrew after 2 weeks |

| 73 completed program and 12 weeks assessment | 65 completed program and 12 weeks assessment | 77 completed program and 12 weeks assessment |

12 weeks assessment (N = 215)

| 1 died of brain metastases
1 withdrew from follow-up
1 was lost to follow-up | 1 died of unknown cause
2 missed follow-up due to SAE | 3 died; 1 of abdominal aortic aneurysm, 1 of infection, 1 ventricular arrhythmia
4 missed follow-up due to SAE |

| 70 completed 52 weeks assessment | 62 completed 52 weeks assessment | 70 completed 52 weeks assessment |

52 weeks assessment (N = 202)

Figure 1. Study enrollment, randomization, and follow-up.
Enrollment was stopped when it was estimated that at least 200 patients would complete the 12-week assessments according to protocol. Two hundred fifteen patients came to follow-up assessments and were included in the intention-to-treat analysis; 207 of these were included in per-protocol analysis. Two hundred two patients came to the 52-week assessments and fulfilled the criterion of having completed either echocardiography or cardiopulmonary exercise testing. LVEF indicates left ventricular ejection fraction; and SAE, serious adverse event.

out because of SAEs, and 7 withdrew or were lost to follow-up (Figure 1). Two hundred fifteen patients were assessed after 12 weeks and were included in the intention-to-treat analysis reported here. Median adherence to supervised training was 35 (34–36) sessions of 36 possible in HIIT and MCT and 4 (3–4) of 4 in RRE. Eight patients completed <24 of 36 exercise

sessions, leaving 207 patients included in the per-protocol analysis that yielded equivalent results (data not shown).

Baseline characteristics were similar in all groups, although more RRE patients had a history of hypertension (Table 1). Median age was 60 years (interquartile range [IQR] 53–70 years); 71% were in New York Heart Asso-

Table 1. Patient Characteristics at Baseline

Characteristics	RRE (n=73)	MCT (n=65)	HIIT (n=77)
Age, y	60 (55–65)	60 (58–65)	65 (58–68)
Women, n (%)	14 (19)	12 (19)	14 (18)
Heart failure <12 mo, n (%)	14 (19)	7 (11)	14 (18)
NYHA class, n (%)			
II	54 (74)	41 (63)	55 (71)
III	19 (26)	24 (37)	22 (29)
Left ventricular ejection fraction, %	30 (28–32)	29 (26–32)	29 (26–31)
Ischemic origin, n (%)	41 (56)	39 (60)	46 (60)
Previous myocardial infarction	32 (44)	36 (55)	44 (57)
Previous CABG	17 (23)	14 (22)	20 (26)
Previous PCI	33 (45)	23 (35)	32 (42)
Device therapy, n (%)			
Pacemaker	2 (3)	0 (0)	2 (3)
Implantable cardioverter-defibrillator	31 (43)	38 (59)	27 (35)
Cardiac resynchronization therapy	3 (4)	1 (2)	1 (1)
Atrial fibrillation, n (%)			
Chronic	6 (8)	8 (12)	14 (18)
Paroxysmal	13 (18)	5 (8)	11 (14)
History of hypertension, n (%)	36 (49)	24 (37)	22 (29)
History of diabetes mellitus, n (%)	14 (19)	21 (32)	16 (21)
History of COPD, n (%)	4 (6)	8 (12)	4 (5)
Current smoking, n (%)	35 (48)	32 (49)	38 (49)
Alcohol drinks per week, n	1 (1–2)	2 (1–3)	1 (1–2)
Medications, n (%)			
ACE inhibitor/ARB	70 (96)	60 (92)	71 (92)
β-Blocker	71 (97)	61 (94)	73 (95)
Aldosterone receptor antagonist	39 (53)	34 (52)	49 (64)
Diuretic	51 (70)	49 (75)	58 (75)
Digoxin or digitoxin	6 (8)	8 (12)	17 (22)
Statin	45 (62)	47 (72)	50 (65)
Body mass index, kg/m²	27.7 (25.7–28.3)	27.5 (26.6–29.7)	27.6 (26.3–28.7)
Systolic blood pressure, mm Hg	120 (116–124)	119 (112–122)	115 (110–120)
Diastolic blood pressure, mm Hg	75 (70–80)	73 (70–80)	71 (70–87)
NT-proBNP, ng/L	895 (635–1110)	976 (725–1348)	1052 (837–1472)

Values are median with 95% confidence interval of the median, because most of the characteristics were nonnormally distributed, or number (percent) as indicated. There were no significant differences between the groups except for history of hypertension (χ^2 test, P=0.04). ACE indicates angiotensin converting enzyme; ARB, angiotensin receptor blockers; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; HIIT, high-intensity interval training; MCT, moderate continuous training; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PCI, percutaneous coronary intervention; and RRE, recommended regular exercise.

ciation class II, and the rest were in class III. All patients were considered to be on optimal medical treatment. Only 19% of the patients were women (Table 1). Median left ventricular ejection fraction at baseline was 29% (IQR, 24%–34%), and median Vo_{2peak} was 17.1 mL·kg⁻¹·min⁻¹ (IQR, 14.2–20.3 mL·kg⁻¹·min⁻¹) with no difference between groups at baseline (Table 2 and Tables I and II in the online-only Data Supplement).

Table 2. Main Echocardiography and Cardiopulmonary Testing Measures at Baseline, 12 weeks, and 52 Weeks With Unadjusted Changes

	RRE (n=73)			MCT (n=65)			HIIT (n=77)		
	Baseline	12 wk	52 wk	Baseline	12 wk	52 wk	Baseline	12 wk	52 wk
LVEDD, mm	68 (67 to 69)	69 (65 to 71)	66 (63 to 67)	69 (66 to 72)	67 (65 to 70)	64 (61 to 70)	68 (65 to 70)	63 (62 to 68)	63 (62 to 66)
LVEF, %	30 (28 to 32)	28 (27 to 30)	28 (27 to 32)	29 (26 to 32)	27 (25 to 31)	33 (26 to 37)	29 (26 to 31)	31 (29 to 31)	28 (26 to 32)
VO_{2peak}, mL·kg^{-1}·min^{-1}	18.4 (16.8 to 19.6)	17.4 (15.7 to 19.8)	18.2 (15.8 to 20.0)	16.2 (15.3 to 18.7)	17.0 (15.7 to 19.6)	16.4 (15.0 to 18.6)	16.8 (15.8 to 17.8)	18.2 (16.3 to 20.0)	17.1 (15.5 to 18.6)
NT-proBNP, ng/L	895 (635 to 1110)	821 (594 to 1079)	626 (419 to 1116)	976 (725 to 1348)	821 (580 to 1169)	698 (544 to 1021)	1052 (837 to 1472)	909 (722 to 1484)	813 (585 to 1615)
Change		Baseline to 12 wk	Baseline to 52 wk		Baseline to 12 wk	Baseline to 52 wk		Baseline to 12 wk	Baseline to 52 wk
LVEDD, mm		0.0 (0.0 to 2.0)	−2.0 (−4.0 to 0.0)		−1.0 (−2.0 to 1.0)	−3.0 (−7.0 to −1.4)		−2.0 (−3.6 to −1.0)	−3.0 (−5.0 to −1.0)
LVEF, %		−0.6 (−2.4 to 1.4)	1.1 (−0.8 to 3.0)		0.7 (−1.8 to 2.6)	0.7 (−1.5 to 4.4)		1.7 (0.0 to 4.5)	−0.2 (−3.1 to 2.8)
VO_{2peak}, mL·kg^{-1}·min^{-1}		−0.1 (−0.9 to 0.4)	−0.4 (−1.3 to 0.4)		1.1 (0.5 to 1.7)	1.2 (−0.2 to 1.4)		0.9 (0.0 to 1.4)	0.1 (−0.4 to 1.0)
NT-proBNP, ng/L		9 (−43 to 112)	−25 (−108 to 76)		2 (−91 to 97)	−101 (−130 to 30)		19 (−76 to 129)	112 (−24 to 236)

Values are median with 95% confidence interval of the median. There were no differences between the groups at baseline (Kruskal-Wallis test, P=0.68, 0.83, 0.21 and 0.30). Additional echocardiography and cardiopulmonary testing outcomes are presented online (Tables I and II in the online-only Data Supplement). HIIT indicates high-intensity interval training; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MCT, moderate continuous training; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; RRE, recommended regular exercise; and VO_{2peak}, peak oxygen uptake.

Training Intensity Compared With Protocol Targets

Heart rate and workload were monitored at all centers during the supervised training sessions (Figure 2). Average heart rate during sessions remained unchanged in the 12 weeks of supervised training, indicating constant relative exercise intensity during interventions (Figure 2A). Workload during intervals in the HIIT group was consistently 33 W (IQR, 24–42 W; P<0.001), higher than during continuous exercise in MCT (Figure 2B). Median relative training intensity based on maximal heart rate was 90% (IQR, 88%–92%) in HIIT and 77% (74%–82%) in MCT. Thus, the difference in training intensity was only 10% (8%–13%) with adjustment for center and pathogenesis (Figure 2C) compared with the protocol target difference of 27.5%. The training records showed that 51% of the patients in the HIIT group exercised at a lower intensity than prescribed, whereas 80% of those in the MCT group trained at a higher intensity than the protocol target (Figure 2D).

Echocardiography and Cardiopulmonary Exercise Testing

Table 2 presents the crude within-group changes in main results from baseline to 12 and 52 weeks. Results of the prespecified primary analyses, the adjusted between-group differences in changes in LVEDD from baseline to 12 weeks (primary end point), are given in Table 3. Change of LVEDD in HIIT was not significantly different from that in MCT (−1.2 mm; −3.6 to 1.2 mm; P=0.45) but larger than in RRE (−2.8 mm; −5.2 to −0.4 mm; P=0.02), whereas the change in MCT was not significantly different from the change in RRE (−1.6 mm; −4.2 to 1.1 mm; P=0.34; Table 3). There were no other significant differences in echocardiographic measurements or in prohormone of brain natriuretic peptide (Table 3 and Table I in the online-only Data Supplement).

Change in VO_{2peak} in HIIT was not significantly different from MCT (−0.4 mL·kg^{-1}·min^{-1}; −1.7 to 0.8 mL·kg^{-1}·min^{-1}; P=0.70) but was 1.4 mL·kg^{-1}·min^{-1} (0.2–2.6 mL·kg^{-1}·min^{-1}; P=0.02) larger than in RRE. Change in VO_{2peak} was 1.8 mL·kg^{-1}·min^{-1} (0.5–3.0 mL·kg^{-1}·min^{-1}; P=0.003) larger in MCT compared with RRE (Table 3 and Table II in the online-only Data Supplement). There were no differences in respiratory quotient between groups at VO_{2peak} at baseline, 12 weeks, or 1 year, indicating similar levels of effort during testing (Table II in the online-only Data Supplement). At the 1-year follow-up, there were no differences in primary or secondary end points between the groups (Table 3 and Tables I–III in the online-only Data Supplement).
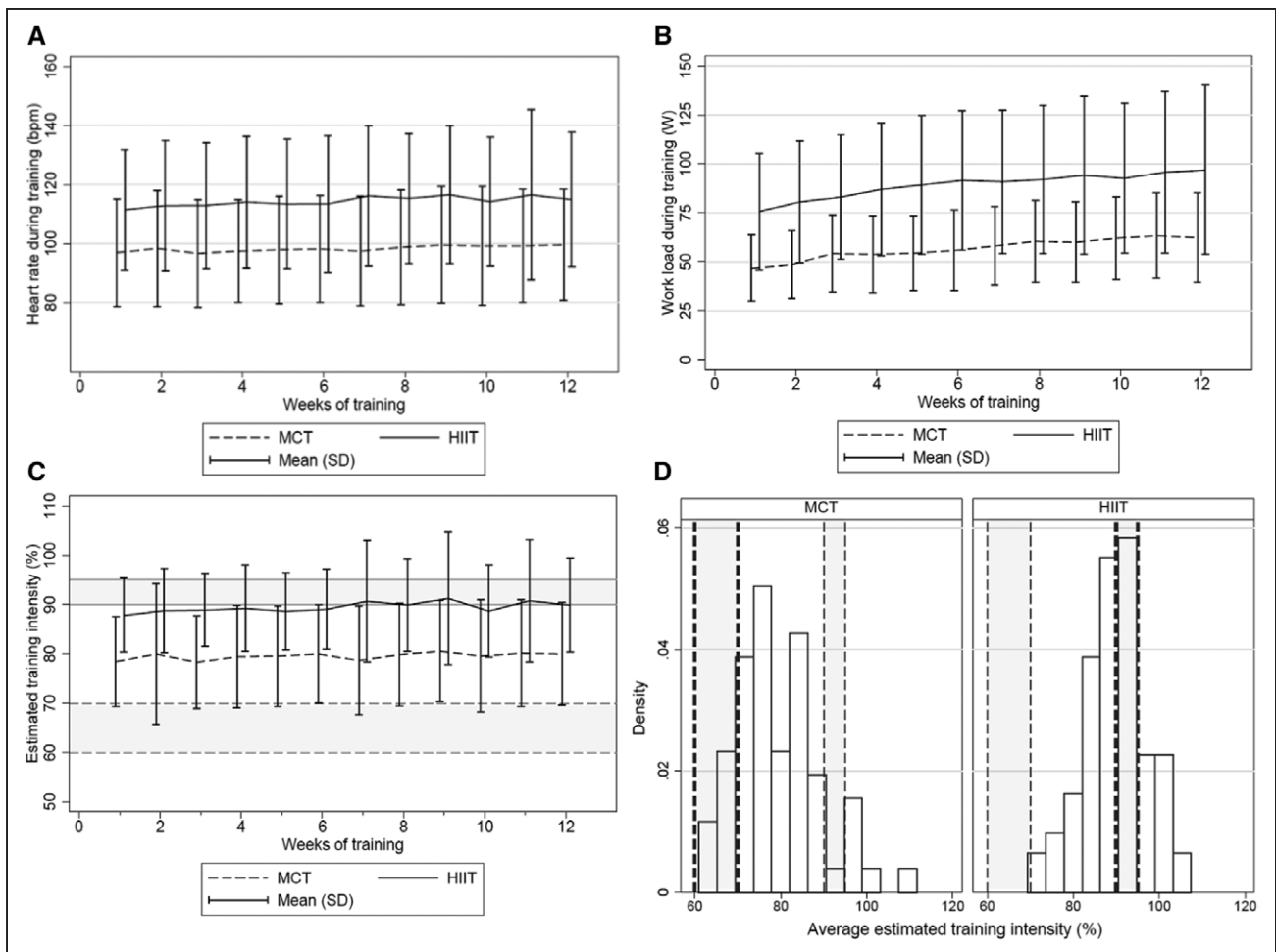
Figure 2. Training intensity during the 12-week intervention.
A, Heart rate during training. Average heart rate during the 12-week intervention, estimated as weekly mean (SD) during moderate continuous training (MCT) and during the last 2 minutes of high-intensity interval training (HIIT). Constant difference between groups: 16 bpm (10–22 bpm; *P*<0.001). **B**, Workload. Average workload estimated as for heart rate. Difference between groups: 33 W (24–42 W; *P*<0.001). **C**, Training intensity. Average relative training intensity (percentage of maximal heart rate) estimated as for heart rate: HIIT, 90% (88%–92%); MCT, 77% (74%–82%); difference, 10% (8%–13%; *P*<0.001). Some of the variability in estimated training intensity probably results from variation in maximal heart rate. Comparing baseline and follow-up assessments in individual patients revealed differences that seemed randomly distributed and independent of intervention group, center, and whether the patients had sinus rhythm or atrial fibrillation (data not shown). Shaded areas mark boundaries of prescribed training intensity: HIIT, 90% to 95%; MCT, 60% to 70%. **D**, Training intensity on target. Distribution of average training intensity during the 12-week intervention; MCT, **left** histogram; HIIT, **right** histogram. Shaded areas mark boundaries for prescribed training intensity. Fifty-one percent of HIIT patients exercised below their prescribed training intensity, and 80% of MCT patients exercised above theirs. Density scales the height of the bars so that the sum of their areas equals 1.00.

Sensitivity analyses exploring factors that might have influenced the changes of LVEDD in response to exercise did not identify predictors of response. Change of LVEDD in HIIT and MCT was not associated with average percentage of maximal heart rate during supervised training sessions when added to the regression model (*P*=0.52) or when used to substitute for intervention group (*P*=0.24). Likewise, findings were similar when comparing patients in the highest and lowest quartiles of achieved percentage of maximal heart rate during training and when using these quartiles as a categorical variable. Change in LVEDD

was also not associated with atrial fibrillation (*P*=0.22). An alternative model for LVEDD changes from baseline to 12 weeks excluding patients with atrial fibrillation gave results comparable to the results from the model with all patients, albeit with slightly larger effect sizes for HIIT versus RRE (−3.7 mm; −6.7 to −0.8 mm; *P*=0.009) and for HIIT versus MCT (−2.0; −4.9 to 0.9 mm; *P*=0.23). Smoking was not significantly associated with change in LVEDD (*P*=0.26). There was no difference in exercise intensity assessed as percentage of maximal heart rate during sessions between centers (*P*=0.61) or between training on treadmill (89%;

Table 3. Main Outcomes

	HIIT vs MCT	HIIT vs RRE	MCT vs RRE
Adjusted contrasts, baseline to 12 wk			
LVEDD, mm	−1.2 (−3.6 to 1.2)	−2.8 (−5.2 to −0.4)*	−1.6 (−4.2 to 1.1)
LVEF, %	1.5 (−2.1 to 5.1)	2.5 (−0.5 to 5.5)	0.9 (−2.7 to 4.6)
Vo$_{2peak}$, mL·kg^{-1}·min^{-1}	−0.4 (−1.7 to 0.8)	1.4 (0.2 to 2.6)*	1.8 (0.5 to 3.0)†
NT-proBNP, ng/L	−95 (−729 to 538)	−52 (−489 to 384)	43 (−500 to 587)
Adjusted contrasts, baseline to 52 wk			
LVEDD, mm	−0.1 (−2.9 to 2.7)	−0.7 (−3.7 to 2.4)	−0.5 (−3.6 to 2.5)
LVEF, %	−1.3 (−3.7 to 1.1)	−0.3 (−2.8 to 2.1)	0.9 (−1.7 to 3.6)
Vo$_{2peak}$, mL·kg^{-1}·min^{-1}	0.1 (−1.8 to 2.0)	−0.3 (−2.3 to 1.6)	−0.4 (−2.3 to 1.5)
NT-proBNP, ng/L	−6 (−528 to 517)	33 (−462 to 529)	39 (−491 to 569)

Between-group comparisons calculated as adjusted contrasts from models adjusted for center, pathogenesis, and height and adjusted for multiple comparisons with the Scheffé procedure. Values are median with 95% confidence interval of the median. HIIT indicates high-intensity interval training; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MCT, moderate continuous training; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; RRE, recommended regular exercise; and Vo$_{2peak}$, peak oxygen uptake.

*P=0.02.

†P=0.003.

82%–92%) versus bicycle (85%; 83%–88%; P=0.20), whether HIIT and MCT were analyzed jointly or separately (data not shown).

Quality of Life

There were no within-group or between-group differences in the quality-of-life measures Kansas City Cardiomyopathy Questionnaire, Hospital Anxiety and Depression Scale, Global Mood Scale, or Type D Scale 14 at baseline, 12 weeks, or 52 weeks (Table III in the online-only Data Supplement).

Serious Adverse Events

There were no statistically significant differences between groups in total number of patients with SAEs or cardiovascular SAEs during the 12-week intervention, although SAEs were numerically higher in HIIT, followed by MCT and RRE (Table 4). During the follow-up period from week 13 to 52, there was a possible trend (uncorrected P=0.10) for more patients admitted to hospital with cardiovascular events in HIIT (n=19) and RRE (n=17) compared with MCT (n=8), mainly because of fewer admissions for heart failure worsening in MCT (Table 4). This was also reflected in the 52-week total number of patients with SAEs: HIIT, 32 (39%); RRE, 26 (34%); and MCT, 18 (25%; P=0.16). The corresponding number of fatal events at 52 weeks was as follows: HIIT, 3; RRE, 1; and MCT 3.

Details of diagnoses and time of events, including multiple diagnoses or multiple admissions in single patients, are reported in Table IV in the online-only Data Supplement. Three events occurred during or within 3 hours of supervised exercise in the HIIT group. One patient had ventricular arrhythmia with cardiac arrest during supervised exercise in week 1, was successfully resuscitated, and stopped the exercise program. This patient had refused cardioverter-defibrillator implantation before inclusion. Another patient had inappropriate implantable cardioverter-defibrillator discharge unrelated to arrhythmia during supervised exercise in week 12 and stopped the exercise program. A third patient experienced dizziness within 3 hours after supervised exercise, with no detectable cardiovascular cause, and continued the exercise program without any reoccurrences.

DISCUSSION

The present study is the first randomized multicenter trial evaluating HIIT in chronic heart failure with reduced ejection fraction. It compares HIIT with the 2 prevalent exercise prescriptions: a supervised program of MCT or RRE. The main finding was that 12 weeks of HIIT was not superior to MCT with respect to left ventricular reverse remodeling assessed as change in LVEDD. Although there was a statistically significant difference in remodeling between HIIT and RRE at 12 weeks, immediately after the supervised exercise intervention, its clinical importance is uncertain.

The effects of HIIT were less than expected from our working hypothesis[8] and from a previous study by Wisløff et al[5] on which it was based. In the present study, change in LVEDD by HIIT was −2.8 mm relative to RRE compared with −4.5 mm from our working hypothesis

Table 4. Serious Adverse Events

Events*	RRE (n=76), n (%)	MCT (n=73), n (%)	HIIT (n=82), n (%)
Cardiovascular, weeks 1–12	5 (7)	6 (8)	9 (11)
Fatal	0	1	0
Ventricular arrhythmia, life threatening	0	1	1
Ventricular arrhythmia, other	0	0	1
Worsening heart failure	2	3	4
Other nonfatal	3	1	3
Cardiovascular, weeks 13–52	17 (22)	8 (11)	19 (23)
Fatal	0	0	2
Ventricular arrhythmia, life threatening	2	1	1
Ventricular arrhythmia, other	2	1	3
Worsening heart failure	13	3	11
Other nonfatal	4	3	4
Noncardiovascular, weeks 1–12	2 (3)	3 (4)	6 (7)
Fatal	0	1	0
Nonfatal	2	2	6
Noncardiovascular, weeks 13–52	7 (9)	2 (3)	3 (4)
Fatal	1	1	1
Nonfatal	6	1	2
Total, weeks 1–12	7 (9)	9 (12)	14 (17)
Fatal	0	2	0
Nonfatal	7	7	14
Total, weeks 13–52	22 (29)	10 (14)	22 (27)
Fatal	1	1	3
Nonfatal	21	9	19
Total, weeks 1–52	26 (34)	18 (25)	32 (39)
Cardiovascular	21 (28)	13 (18)	24 (29)
Noncardiovascular	8 (11)	5 (7)	9 (11)

HIIT indicates high-intensity interval training; MCT, moderate continuous training; and RRE, recommended regular exercise. There was no significant difference between the groups during the 12-week training intervention in terms of cardiovascular, noncardiovascular, or total number patients with serious adverse effects (χ^2 test, P=0.61, 0.37, and 0.33, respectively). During the 13- to 52-week follow-up, there was a trend for higher numbers of patients with cardiovascular events in HIIT compared with MCT (χ^2 test, P=0.10) as a result of fewer hospitalizations for worsening of heart failure in the MCT group but not compared with the RRE group. This same trend is also reflected in the number of cardiovascular events during weeks 1 to 52 and the total number of events during weeks 13 to 52 and 1 to 52 (χ^2 test, P=0.21, 0.06, and 0.16, respectively; P values not corrected for multiple tests).

*Number of patients (percent) with serious adverse effects, defined as fatal events and events leading to hospitalization or clinical evaluation. Patients with multiple diagnoses or multiple events are counted only once; thus, accumulated data are sometimes less than the respective sums. A detailed list of diagnoses and time of events is presented in Table IV in the online-only Data Supplement.

and −7.7 mm reported by Wisløff et al.[5] In contrast, the change in LVEDD was −1.6 mm with MCT, which is similar to our prestudy estimate of −1.5 mm[8] and −0.9 mm observed in the previous study.[5] Post hoc analyses indicated that the magnitude of change in LVEDD may be larger with sinus rhythm compared with atrial fibrillation, but the present study was not powered to undertake a formal comparison. Change in LVEDD was chosen as the primary end point to represent change in cardiac remodeling because the echocardiographic measurement of diameter is more robust and has less relative variation than left ventricular volume estimates.[10] The present study indicated nonsignificant changes in LVEDV of −19 mL with HIIT and −13 mL with MCT. This is in contrast to the large change of −45.2 mL previously observed with HIIT but similar to −15.2 mL observed with MCT[5] and to a −11.5-mL change with MCT in a meta-analysis.[7] The change in Vo_{2peak} in the present study was 1.4 mL·kg^{-1}·min^{-1} with HIIT and 1.8 mL·kg^{-1}·min^{-1} with MCT relative to RRE. This is markedly less than the previously observed 6.0 mL·kg^{-1}·min^{-1} with HIIT but similar to 1.9 mL·kg^{-1}·min^{-1} with MCT[5] and 2.1 mL·kg^{-1}·min^{-1} in a meta-analysis.[12] Nonetheless, it is slightly larger than 0.6 mL·kg^{-1}·min^{-1} in the large HF-ACTION trial.[4] It is notable that the differences observed at 12 weeks, immediately after the supervised interventions, were not maintained at the 52-week assessment, suggesting that the exercise prescriptions had not been followed as closely in the unsupervised period as in the supervised period.

Several factors may account for the small effect size of HIIT in the present study. Multicenter studies are more resistant to bias known to affect the study effects, especially compared with a single-center setting. Differences in the study population between our trial and the previous one by Wisløff and coworkers[5] might also contribute to the different effects: All patients in the previous study had ischemic heart failure, although fewer than a third had a previous revascularization compared with 60% in the present study. Furthermore, patients in the study by Wisløff et al[5] were on average 15 years older and had a much lower Vo_{2peak} at baseline compared with the present trial.

Another factor that may have reduced the response to HIIT is lower training intensity during intervals. In our trial, 51% of the HIIT patients unexpectedly trained at lower intensity than prescribed, whereas 80% in the MCT group trained at higher intensity. Despite the experience of cardiac rehabilitation of the participating centers, HIIT at 90% to 95% of maximal heart rate appeared difficult to achieve in a multicenter cohort of patients, whereas intensities at 60% to 70% of maximal heart rate in MCT seemed too low. It may be speculated that the response to HIIT might have been larger if target intensity had been achieved; however, we could not detect any difference of change in LVEDD when comparing the upper

and lower quartiles of percentage of maximal heart rate during exercise in the present study.

To date, only 1 study has had sufficient statistical power to assess safety with exercise training in patients with heart failure. The HF-ACTION study demonstrated a moderate reduction in the composite end point of mortality and hospital admissions after 1 year.[4] By design, the present study was too small to assess differences in safety among HIIT, MCT, and RRE[8]; however, numeric differences in clinical events could generate hypotheses and identify issues for special attention in future studies and follow-up. During the 12-week supervised training program, the number of patients with SAEs was small in all groups, and few patients withdrew from exercise training. These observations concur with comparisons of safety of HIIT versus MCT in patients with coronary artery disease that detected no differences in SAEs.[13,14] In contrast, there was a numeric difference in patients with SAEs during the follow-up period from week 13 to 52 as a result of more hospitalizations for worsening of heart failure in HIIT and RRE compared with MCT. This trend was not statistically significant and resulted from post hoc subgroup analyses because SAEs were not a pre-specified end point. Hence, conclusions or recommendations could not be based on this finding, but the numeric difference should receive attention in future trials.

Limitations

One of the important objectives of moving from a small proof-of-principle study to a type II multicenter study was to test whether the effect size would be conserved in a setting that is closer to a real-world clinical setting. Although several measures were taken to ensure quality and consistency, including supervised training sessions based on heart rate monitoring, the differences in training intensity between HIIT and MCT were less than intended and partly overlapped. This was an unexpected finding, suggesting that the HIIT prescription of 90% to 95% of maximal heart rate may be too high and the MCT prescription of 60% to 70% too low for some patients. For future studies, we suggest that exercise intensities should be regularly adapted to improvements in exercise capacity and to worsening of symptoms or changes of medication. Repeated assessment of maximal heart rate and more emphasis on adjusting workload according to perceived level of effort might also be helpful. We experienced that questionnaires were of limited value for assessing physical activity outside supervised sessions and recommend accelerometer recordings, particularly in the unsupervised follow-up period. Furthermore, in future studies, women should be a focus because only 19% of the patients in this study were women. Although not unusual in similar studies, this sex bias was unintended and constitutes a limitation of the generalization of the results.

Conclusions

The present multicenter trial did not confirm the hypothesis that a 12-week program of supervised HIIT was superior to MCT in reducing left ventricular remodeling in patients with stable heart failure. None of the interventions led to deterioration of cardiac function compared with RRE, and both exercise programs increased aerobic capacity, an important prognostic parameter of heart failure, to a similar extent. However, these positive changes were smaller than expected and were not maintained at follow-up after 52 weeks. Numeric differences in readmissions for worsening of heart failure suggested a favor of MCT relative to HIIT and RRE, but the study was not powered to assess safety. Training records showed that exercise intensities >90% of maximal heart rate were not achieved in a significant proportion of the patients. Thus, further studies are needed to define the role of HIIT as an alternative exercise modality in patients with heart failure with reduced ejection fraction.

DISCLOSURES

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High-Intensity Interval Training in Patients With Heart Failure With Reduced Ejection Fraction

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SUPPLEMENTAL MATERIAL

Tables S1-S4

Table S1. Echocardiographic Outcomes.

	Recommended Regular Exercise RRE N=73/70*			Moderate Continous Training MCT N=65/62*			High Intensity Interval Training HIIT N=77/70*		
	Baseline	**12 weeks**	**52 weeks**	**Baseline**	**12 weeks**	**52 weeks**	**Baseline**	**12 weeks**	**52 weeks**
LVEDD - mm	68 (67, 69)	69 (65, 71)	66 (63, 67)	69 (66, 72)	67 (65, 70)	64 (61, 66)	68 (65, 70)	63 (62, 68)	63 (62, 66)
LVEF - %	30 (28, 32)	28 (27, 30)	28 (27, 32)	29 (26, 32)	27 (25, 31)	33 (26, 37)	29 (26, 31)	31 (29, 33)	28 (26, 32)
LVEDV - ml	231 (223, 252)	234 (202, 248)	197 (183, 230)	248 (224, 260)	235 (209, 253)	197 (177, 224)	239 (220, 257)	220 (200, 237)	194 (183, 214)
LVESV - ml	167 (155, 181)	156 (142, 179)	138 (126, 165)	178 (156, 207)	158 (145, 180)	133 (110, 157)	165 (152, 187)	149 (130, 163)	134 (124, 159)
LVSV - ml	47 (45, 49)	53 (47, 58)	61 (60, 66)	48 (43, 53)	52 (48, 59)	64 (54, 70)	49 (45, 51)	51 (45, 56)	57 (54, 60)
Heart rate - bpm	70 (66, 73)	68 (65, 73)	69 (66, 71)	67 (63, 70)	65 (63, 68)	67 (64, 71)	68 (63, 71)	67 (62, 72)	67 (64, 69)
E - cm s^{-1}	69 (60, 77)	73 (63, 80)	65 (61, 73)	70 (66, 79)	66 (63, 75)	62 (58, 71)	73 (66, 83)	75 (67, 81)	71 (63, 80)
Dec-t - ms	189 (164, 208)	166 (152, 180)	166 (156, 185)	166 (152, 194)	180 (155, 213)	180 (161, 205)	157 (147, 172)	177 (153, 198)	185 (159, 195)
IVRT - ms	109 (95, 121)	107 (99, 115)	104 (98, 110)	98 (88, 110)	100 (85, 116)	104 (91, 115)	97 (93, 108)	111 (99, 117)	105 94, 111)
MAPSE - mm	8 (7, 8)	7 (7, 8)	7 (7, 8)	8 (7, 8)	7 (7, 8)	8 (7, 9)	7 (7, 8)	7 (7, 8)	8 (7, 8)
S' - cm s^{-1}	5 (5, 5)	5 (4, 5)	5 (4, 5)	5 (5, 5)	5 (5, 5)	5 (5, 6)	5 (4, 5)	5 (5, 6)	5 (5, 5)
e' - cm s^{-1}	5 (5, 6)	6 (5, 7)	6 (6, 7)	6 (5, 7)	6 (6, 7)	6 (6, 7)	6 (6, 7)	6 (6, 7)	6 (6, 7)
E/e'	12 (10, 15)	12 (10, 14)	11 (10-14)	13 (11, 14)	11 (9, 12)	11 (9, 12)	12 (11, 14)	12 (11, 13)	11 (10, 12)

*N, number of patients at 12 weeks/52 weeks. Abbreviations: LVEDD, left ventricular (LV) end-diastolic diameter; LVEF, LV ejection fraction; LVEDV, LV end-diastolic volume; LVESV end-systolic volume; LVSV, LV stroke volume calculated from pulsed wave Doppler flow velocity over area of LV outflow tract; Heart rate at rest from echocardiography; E, peak early diastolic mitral inflow assessed by pulsed wave Doppler from the tip of the mitral leaflet; Dec-t, deceleration time of mitral flow; IVRT, intraventricular relaxation time; MAPSE, mitral annular plane systolic excursion; S', peak mitral annulus velocity during systole; e', peak early diastolic mitral annulus velocity; E/e', ratio of E and e´, used as marker of LV filling pressure. Values are unadjusted median with 95% confidence interval of the median. There were no significant differences between the groups for any of the listed variables at baseline. LVEDD was measured at the tip of the mitral leaflet in two-dimensional parasternal long-axis view. LVEDV and LVESV were calculated from two-dimensional images by tracing the endocardial border in end-diastole and end-systole in 4-chamber and 2-chamber or 3-chamber view. LV volume estimates were uncertain in about 30% of the cases and no differences between groups were detected. LVSV was calculated from pulsed wave Doppler flow velocity over the area of LV outflow tract. Pulsed wave tissue Doppler velocities were measured at the base of the anterolateral and septal LV wall and averaged into mitral annular systolic (S') and early diastolic (e') velocities. MAPSE was measured in reconstructed motion-mode as the average of the systolic excursion of the base of anterolateral and septal wall.

Table S2. Cardiopulmonary Testing Outcomes.

	Recommended Regular Exercise RRE N=73/70*			Moderate Continous Training MCT N=65/62*			High Intensity Interval Training HIIT N=77/70*		
	Baseline	12 weeks	52 weeks	Baseline	12 weeks	52 weeks	Baseline	12 weeks	52 weeks
Peak oxygen uptake[†] **L min^{-1}**	1.47 (1.40, 1.65)	1.47 (1.34, 1.59)	1.51 (1.29, 1.57)	1.39 (1.30, 1.50)	1.47 (1.34, 1.60)	1.51 (1.29, 1.57)	1.45 (1.30, 1.55)	1.52 (1.33, 1.66)	1.50 (1.39, 1.63)
VO_{2peak} - mL kg^{-1} min^{-1}	18.4 (16.8, 19.6)	17.4 (15.7, 19.8)	18.2 15.8, 20.0)	16.2 (15.3, 18.7)	17.0 (15.7, 19.6)	16.4 (15.0, 18.6)	16.8 (15.8, 17.8)	18.2 (16.3, 20.0)	17.1 (15.5, 18.6)
Respiratory quotient at peak oxygen uptake	1.12 (1.10, 1.14)	1.12 (1.10, 1.14)	1.11 (1.09, 1.13)	1.14 (1.11, 1.17)	1.12 (1.11, 1.16)	1.12 (1.10, 1.17)	1.13 (1.10, 1.15)	1.12 (1.10, 1.14)	1.13 (1.09, 1.14)
Weight - kg	84 (78, 91)	85 (80, 90)	84 (80-88)	84 (79, 91)	84 (79, 90)	87 (82, 93)	82 (79, 87)	82 (78, 86)	82 (77, 88)
Ventilation at peak oxygen uptake - l min^{-1}	62 (57, 67)	59 (56, 68)	61 (56, 67)	56 (54, 62)	59 (54, 66)	58 (53, 64)	58 (53, 63)	62 (57, 67)	62 (56, 68)
Heart rate at rest - bpm	71 (68, 74)	71 (68, 75)	70 (65, 74)	68 (66, 73)	67 (66, 70)	68 (65, 72)	72 (68, 76)	70 (68, 73)	70 (66, 75)
Heart rate at peak oxygen uptake - bpm	132 (127, 138)	129 (114, 136)	127 (119, 134)	126 (113, 132)	120 (112, 134)	119 (111, 135)	125 (120, 133)	124 (119, 132)	125 (119, 137)
Workload at peak oxygen uptake - W	110 (100, 120)	110 (100, 127)	110 (90, 120)	90 (90, 100)	105 100, 120)	100 (99, 120)	100 (90, 110)	120 (110, 138)	115 (100, 130)

*N, number of patients at 12 weeks/52 weeks. [†]Values are median with 95% confidence interval of the median. There were no significant differences between the groups for any of the listed variables at baseline or 52 weeks.

Table S3. Quality of Life outcomes.

	Recommended Regular Exercise RRE						Moderate Continuous Training MCT						High Intensity Interval Training HIIT					
	Baseline		12 weeks		52 weeks		Baseline		12 weeks		52 weeks		Baseline		12 weeks		52 weeks	
	median	95% CI	median	95% CI	median	95% CI	median	95% CI	median	95% CI	median	95% CI	median	95% CI	median	95% CI	median	95% CI
KCCQ																		
1. Physical limitation	75	69-83	79	74-86	83	75-88	79	71-83	80	75-83	79	71-83	83	79-88	88	79-90	83	75-92
2. Symptom stability	50	50-50	50	50-50	50	50-50	50	50-50	50	50-50	50	50-50	50	50-50	50	50-75	50	50-50
3. Symptom frequency	83	79-88	88	79-92	88	83-92	83	77-88	88	80-92	83	81-92	88	81-92	88	83-92	90	83-92
4. Symptom burden	83	83-83	83	83-92	83	83-92	83	83-92	83	83-92	92	83-92	92	75-92	58	83-92	92	83-100
5. Total symptom score	83	79-88	85	79-92	88	82-92	83	79-88	85	81-92	88	81-92	87	81-92	87	82-92	90	83-92
6. Self efficacy	75	63-88	75	75-88	75	75-88	75	75-88	75	75-75	75	75-75	75	75-88	75	75-88	75	75-88
7. Quality of life	67	58-75	75	77-83	83	75-83	67	58-75	75	75-83	75	67-83	75	67-83	92	75-83	83	75-92
8. Social limitation	69	63-75	69	63-81	75	67-81	75	63-81	75	69-81	75	63-81	69	58-81	75	69-81	81	69-88
9. Overall summary score	74	67-79	76	69-83	82	74-87	79	68-83	81	77-85	80	71-86	78	71-81	79	75-85	82	73-89
10. Clinical summary score	79	73-83	82	76-88	86	80-88	81	74-86	84	79-86	83	76-86	84	80-89	85	78-89	87	80-90
HADS																		
Anxiety	5.0	3.6-6.4	4.0	3.6-5.0	4.0	2.0-5.0	4.0	4.0-5.9	4.0	3.0-4.9	4.0	3.0-5.9	4.0	3.0-5.0	4.0	3.0-5.0	4.0	2.9-5.0
Depression	3.0	3.0-5.0	3.0	2-4	4.0	2.0-3.0	4.0	3.0-6.0	3.0	2.0-4.9	4.0	2.0-4.0	4.0	2.0-4.0	3.0	2.0-5.0	3.0	2.0-3.7
GMS																		
Positive affect	21	19-22	22	20-23	22	21-23	20	18-21	23	20-25	21	19-23	21	19-24	21	20-24	22	19-24
Negative affect	12	10-14	9	8-14	12	8-14	12	11-14	10	8-13	10	8-14	12	10-14	9	7-12	12	9-13
DS14																		
Social inhibition	8.0	6.0-9.0	8.0	6.0-9.0	8.0	5.6-9.0	7.0	6.0-10.0	7.5	6.0-11.0	8.0	5.0-11.0	7.0	6.0-9.2	7.0	6.0-10.0	8.0	6.8-10.0
Negative affectivity	8.0	6.0-10.0	7.0	6.0-9.0	8.0	6.0-10.0	7.0	6.0-8.0	6.0	4.0-8.0	7.0	4.0-7.0	7.0	6.0-9.0	7.5	6.0-9.0	8.0	6.0-9.0

Values are median and 95% confidence interval of the median. KCCQ: Kansas City Cardiomyopathy Questionnaire, HADS: Hospital Anxiety and Depression Scale, GMS: Global Mood Scale, DS14: Type D personality.

Table S4. Serious Adverse Events in detail.

Events*	Recommended Regular Exercise RRE, N=76	Moderate Continuous Training MCT, N=73	High Intensity Interval Training HIIT, N=82
Cardiovascular week 1-12[†]	**5 (7%)**	**6 (8%)**	**9 (11%)**
Quit week 1-12	**1**	**3**	**2**
Died suddenly / heart failure	0	1[AA]	0
Worsening heart failure	1[AB]	2[AC]	1[AD]
Atrial arrhythmia	1[AB]	0	0
Ventricular arrhythmia	0	0	1[AE]
Unstable angina	0	0	0
ICD-related	0	0	0
Completed 12 weeks	**4**	**3**	**7**
Worsening heart failure	1[AF]	1[AG]	3[AH]
Atrial arrhythmia	1[AI]	1[AJ]	1[AK]
Ventricular arrhythmia	0	1[AL]	1[AM]
Chest pain / unstable angina	1[AN]	0	1[AO]
ICD-related	1[AP]	0	0
Syncope	0	0	1[AQ]
Cardiovascular week 13-52[†]	**17 (22%)**	**8 (11%)**	**19 (23%)**
Quit week 13-52	**0**	**2**	**6**
Died of abdominal aortic aneurysm	0	0	1[BA]
Died of ventricular arrhythmia	0	0	1[BB]
Worsening heart failure[†]	0	2[BC]	4[AH,AK,BD]
Atrial arrhythmia	0	0	1[AK]
Ventricular arrhythmia	0	0	1[BD]
Completed 52 weeks	**17**	**6**	**13**
Worsening heart failure[†]	13[AI,BE]	1[BF]	7[BG]
Atrial arrhythmia	3[BE,BH]	2[AL,BI]	1[BJ]
Ventricular arrhythmia	4[BE, BH, BK]	2[BL]	3[AH,BM]
Chest pain / unstable angina	0	1[BN]	0
ICD/CRT-related	1[BE]	0	3[BO]
Non-cardiovascular week 1-12[†]	**2 (3%)**	**3 (4%)**	**6 (7%)**
Quit week 1-12	**0**	**1**	**2**
Died of pneumonia after accident	0	1[CA]	0
Cholecystitis	0	0	1[CB]
ICD-related	0	0	1[CC]
Completed 12 weeks	**2**	**2**	**4**
Cholecystectomy	0	1[CD]	0
Depression /suicidal attempt	1[CE]	0	0
Dizziness	0	0	1[CF]
Gout	0	0	1[AM]
Infection	1[BE]	1[CG]	2[CH]

	7 (9%)	2 (3%)	3 (4%)
Non-cardiovascular week 13-52	**1**	**1**	**1**
Quit week 13-52	1[DA]	0	0
Died of brain metastases	0	0	1[DB]
Died of infection	0	1[DC]	0
Died of unknown cause	**6**	**1**	**2**
Completed 52 weeks	1[CE]	0	0
Alcohol intoxication	0	1[DD]	0
Appendicitis	1[DE]	0	0
Breast cancer surgery	1[DF]	0	0
Hematoma after muscle biopsy	0	0	1[DG]
Diabetes / hyperglycemia	1[BE]	0	1[DH]
Infection	1[DI]	0	0
Renal failure	1[BH]	0	0
Orthopedic			

*Number of patients (%) with serious adverse effects (SAE), defined as fatal events, events leading to hospitalization or clinical evaluation. Superscripts denote more than one event in a patient, or give further details. Patients with multiple diagnoses or multiple events are only counted once in accumulated data. Week of exercise program or follow-up is given where relevant. Events during or within 3 hours of supervised exercise are specified.

†There was no significant difference between the groups during the 12-week training intervention regarding cardiovascular, non-cardiovascular or total number patients with SAEs (X²-test; P=0.61, 0.37, 0.33, respectively). During the 13-52-week follow-up there was a trend for higher numbers of patients with cardiovascular events in HIIT compared to MCT (X²-test; P=0.10), but not compared to RRE, due to fewer hospitalizations with worsening of heart failure.

AASudden dyspnea and death at home week 7. ABAtrial tachycardia week 3, worsening of heart failure (WHF) week 10. ACTwo patients had single admissions for WHF week 1,7. ADWHF week 12. AEPatient had ventricular arrhythmia and cardiac arrest during supervised exercise, requiring DC-shock week 1, ventricular arrhythmia and ICD discharge after stopping beta-blocker week 18, and admissions for WHF week 22, 48. AFWHF week 8. AGWHF week 7. AHOne patient had 6 admissions for WHF week 2, 3, 4, 5, 15, 50; another had one admission for WHF week 6 and one for ventricular arrhythmia without DC shock week 22; a third had 2 admissions for WHF week 5, 28 and one for ventricular arrhythmia without DC shock week 42. AIOne admission for atrial arrhythmia week 1 and one for WHF week 36. AJAtrial arrhythmia week 12. AKThree patients with admissions for atrial arrhythmia week 4, 5, 16 and one for WHF week 40. ALOne admission for ventricular arrhythmia with ICD discharge week 4 and one for atrial arrhythmia week 40. AMPatient had one admission for ventricular arrhythmia without DC shock week 10 and two admissions for gout week 2, 5. ANChest pain week 8. AOChest pain week 2. APICD repair week 12. AQSyncope week 12.

BAChest pain week 42 without any sign of cardiopulmonary disease, died of abdominal aortic aneurysm week 52. BBDied of ventricular arrhythmia, no further details given week 52. BCOne patient had three admissions for WHF week 16, 46, 50; the second and third related to possible transplant rejection and immune suppression. Another had 2 admissions for WHF week 19, 52. BDOne patient had one admission for WHF week 52 and one for ventricular arrhythmia with ICD shock week 40. Another had two admissions for WHF week 20, 48. BESix patients had single admissions for WHF after week 12. One had one admission for WHF week 24 and one for atrial arrhythmia week 48. Another had one admission for WHF week 20 and one for ventricular arrhythmia with ICD discharge week 24. A third had one admission for WHF week 26 and one for a broken ICD probe week 20. Two patients had single admissions for WHF week 14, 50 and for infection week 4, 13. One had two admissions for WHF week 48, 50. BFOne patient had two admissions for WHF after week 19. BGTwo patients had single admissions for WHF week 24,31. Two had three admissions for WHF week 18-52. Two had two admissions for WHF week 26-44. BHOne patient had one admission for atrial arrhythmia week 28. Another had two admissions for atrial arrhythmia week 32, 52, one for ventricular arrhythmia without DC shock week 50, and one for an orthopedic problem week 29. BIAtrial arrhythmia week 22. BJAtrial arrhythmia week 46. BKTwo patients had single admissions for ventricular arrhythmias week 13, 28 week. One had ICD discharge, the other not. BLTwo patients had single admissions for ventricular arrhythmias week 13- 52. One had ICD discharge, the other not. BMSingle admission for ventricular arrhythmia without DC shock week 52. BNChest pain / angina pectoris week 22.

BOOne patient had one admission for ICD battery change week 44. Another had one admission after ICD discharge, no arrhythmia noted week 46. A third one was admitted for planned CRT implantation week 27.

CAFell at home, was treated on respirator, and died of pneumonia week 4. **CB**One patient had two admissions related to cholecystitis week 6, 8. **CC**ICD discharge during supervised exercise, no arrhythmia week 12. **CD**Cholecystectomy week 1. **CE**One patient had one admission for suicidal attempt and depression week 2, and one for alcohol intoxication week 46. **CF**Dizziness within 3 hours of supervised exercise, without any cardiovascular cause week 1. **CG**Bronchitis week 3. **CH**One patient had tracheal infection week 6, another had bronchitis week 8.

DADied of brain metastases week 48. **DB**Died of non-cardiovascular infection week 36. **DC**Died of unknown cause week 48. **DD**Appendicitis week 48. **DE**Breast cancer surgery week 17. **DF**Hematoma after muscle biopsy week 14. **DG**Diabetes / hyperglycemia week 50. **DH**Infection after foot injury week 36. **DI**Non-cardiovacular renal failure week 19.