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.

**CLINICAL TRIAL REGISTRATION:** URL: http://www.clinicaltrials.gov. Unique identifier: NCT00917046.
Current guidelines recommend exercise training as an adjunctive therapy in patients with chronic heart failure. A universal agreement on exercise prescription does not exist; thus, an individualized approach, including behavioral characteristics, personal goals, and preferences, is recommended. At present, moderate continuous endurance exercise is the best described and established form of training because of its well-demonstrated efficacy and safety. 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.

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. The results were better than those observed in previous studies and meta-analyses of patients with chronic heart failure. 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. 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. 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 80% of MCT exercised above their target.
70% of maximal heart rate every 3 weeks. 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. 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. 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 at1 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 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 analysis 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. 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 $F$0.05 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. However, safety is an important concern in this population, especially when performing exercise. With acknowledgment of the limitations of post hoc analysis, $\chi^2$ 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
- 5 had LVEF >40% at core lab
- 3 withdrew
  - 1 died of stroke
  - 1 was hospitalized with cancer

81 were allocated to RRE
- 0 died
- 1 died of other SAE
- 2 withdrew, after 2 and 4 weeks

76 started with RRE
- 1 died of brain metastases
- 1 withdrew from follow-up
- 1 was lost to follow-up

73 completed program and 12 weeks assessment
- 1 died of unknown cause
- 2 missed follow-up due to SAE

62 completed 52 weeks assessment

85 were randomized to MCT
- 7 had LVEF > 40% at core lab
- 3 withdrew
  - 1 was hospitalized with cancer and died
  - 1 was hospitalized, no diagnosis

78 were allocated to MCT
- 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

65 completed program and 12 weeks assessment

52 weeks assessment (N = 202)

90 were randomized to HIIT
- 2 had LVEF >40% at core lab
- 4 withdrew
  - 1 had ICD implantation
  - 1 had hyperthyroidism

88 were allocated to HIIT

82 started with HIIT
- 0 died
- 4 stopped due to SAEs
- 1 withdrew after 2 weeks

77 completed program and 12 weeks assessment

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

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, mmHg            | 120 (116–124) | 119 (112–122) | 115 (110–120) |
| Diastolic blood pressure, mmHg           | 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 (χ² 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.

Association 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) |
|---------------|------------|------------|-------------|
| **LVEDD, mm** |            |            |             |
| Baseline      | 68 (67 to 69) | 69 (67 to 71) | 69 (66 to 72) |
| 12 wk         | 69 (66 to 72) | 69 (66 to 72) | 69 (66 to 72) |
| 52 wk         | 68 (65 to 70) | 67 (65 to 70) | 67 (65 to 70) |
| **LVEF, %**   | 30 (28 to 32) | 28 (27 to 30) | 28 (27 to 30) |
| **VO₂peak, 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) |
| **NT-proBNP, ng/L** | 895 (635 to 1110) | 821 (694 to 1079) | 626 (419 to 1116) |
| Change        | Baseline to 12 wk | Baseline to 52 wk | Baseline to 12 wk |
| LVEDD, mm     | 0.0 (0.0 to 2.0) | -2.0 (-4.0 to 0.0) | -2.0 (-4.0 to 0.0) |
| LVEF, %       | -0.6 (-2.4 to 1.4) | 1.1 (-0.8 to 3.0) | 0.7 (-1.8 to 2.6) |
| VO₂peak, 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) |
| NT-proBNP, ng/L | 9 (-43 to 112) | -25 (-108 to 76) | 2 (-91 to 97) |

Values are median with 95% confidence interval of the median. There were no differences between the groups at baseline (Kruskal-Wallis test, \( P=0.68, 0.93, 0.21 \) 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 \( VO₂peak \), 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 \( VO₂peak \) 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 \( VO₂peak \) 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 \( VO₂peak \) 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).
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 (data not shown) 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%; 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.
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 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 most 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 and from a previous study by Wisløff et al on which it was based. In the present study, change in LVEDD by HIIT was \(-2.8 \text{ mm} \) relative to RRE compared with \(-4.5 \text{ mm} \) 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                 |
| Total, weeks 1–12     | 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                 | 1                | 1                | 1                 |
| Nonfatal              | 1                | 1                | 1                 |
| Noncardiovascular, weeks 13–52 | 7 (9)            | 2 (3)           | 4 (4)            |
| Fatal                 | 0                | 3                | 6                 |
| 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 ($\chi^2$ 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 ($\chi^2$ 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 ($\chi^2$ 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 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; 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 prespecified 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.

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FOOTNOTES

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REFERENCES

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Celano JD, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Ponikowski P, Ruschitzka F, Smith GL, Stålhane D, van der Meer P. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37:2129–2200. doi: 10.1093/eurheartj/ehw128.

2. Vanhees L, Rauch B, Piepoli M, van Baaren F, Takkun T, Börjeson M, Bjarnason-Weitens B, Doherty P, Dugmore D, Halle M; Writing Group, EACPR. Importance of characteristics and modalities of physical activity and exercise in the management of cardiovascular health in individuals with cardiovascular disease (part III). Eur J Prev Cardiol. 2012;19:1333–1356. doi: 10.1177/2047487312437063.

3. Taylor RS, Sagar VA, Davies EJ, Birsowe S, Coats AJ, Dalal H, Lough F, Rees K, Singh S. Exercise-based rehabilitation for heart failure. Cochrane Database Syst Rev. 2014;4:CD003331.

4. O’Connor CM, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ, Leifer ES, Kraus WE, Kitzman DW, Blumenthal JA, Randall DS, Miller NH, Fleg JL, Schulman KA, McKelvie RS, Zannad F, Piña IL; HF-ACTION Investigators. Efficacy and safety of exercise training in patients with chronic heart failure: HF-ACTION randomized controlled trial. JAMA. 2009;301:1439–1450. doi: 10.1001/jama.2009.454.

5. Wisløff U, Støylen A, Loennechen JP, Bruvold M, Rognmo Ø, Haram PM, Tjønna AE, Helgerud J, Stårdahl SA, Lee SJ, Videm V, Bye A, Smith GL, Najari SM, Ellingsen Ø, Skjaerpe T. Superior cardiovascular effect of aerobic interval training versus moderate continuous training in heart failure patients: a randomized study. Circulation. 2007;115:3086–3094. doi: 10.1161/CIRCULATIONAHA.106.675041.

6. Giannuzzi P, Temporelli PL, Corrà U, Tavazzi L; ELVD-CHF Study Group. Antremodelling effect of long-term exercise training in patients with stable chronic heart failure: results of the Exercise in Left Ventricular Dysfunction and Chronic Heart Failure (ELVD-CHF) Trial. Circulation. 2003;108:554–559. doi: 10.1161/01.CIR.0000081780.38477.FA.

7. Haykowsky MJ, Liang Y, Pechter D, Jones LW, McAlister FA, Clark AM. A meta-analysis of the effect of exercise training on left ventricular remodeling in heart failure patients: the benefit depends on the type of training performed. J Am Coll Cardiol. 2007;49:2329–2336. doi: 10.1016/j.jacc.2007.02.055.

8. Støylen A, Conraads V, Halle M, Linke A, Prescott E, Ellingsen Ø. Controlled study of myocardial recovery after interval training in heart failure: SMARTHEF: rationale and design. Eur J Prev Cardiol. 2012;19:813–821. doi: 10.1177/1742464412403252.

9. Rognmo Ø, Hektoen E, Helgerud J, Hoff J, Stårdahl SA. High intensity aerobic interval exercise is superior to moderate intensity exercise for increasing aerobic capacity in patients with coronary artery disease. Eur J Cardiovasc Prev Rehabil. 2004;11:216–222.

10. Thorstensen A, Dalen H, Amundsen BH, Aase SA, Støylen A. Reproducibility in echocardiographic assessment of the left ventricular regional and global function, the HUNT study. Eur J Echocardiogr. 2010;11:1449–1563. doi: 10.1093/echocard/fqp188.

11. Brookes ST, Whitey E, Egger M, Smith GD, Mulheran PA, Peters TJ. Subgroup analyses in randomized trials: risks of subgroup-specific analyses; power and sample size for the interaction test. J Clin Epidemiol. 2004;57:229–236. doi: 10.1016/j.jclinepi.2003.08.009.

12. Haykowsky MJ, Timmons MP, Kruger C, McNeely M, Taylor DA, Clark AM. Meta-analysis of aerobic interval training on exercise capacity and systolic function in patients with heart failure and reduced ejection fraction. Am J Cardiol. 2013;111:1446–1469. doi: 10.1016/j.amjcard.2013.01.303.

13. Conraads VM, Pattyn N, De Maeyer C, Beckers PJ, Coeckelberghs E, Cornelissen VA, Denollet J, Frederix G, Goetschalckx K, Hoymans VY, Possemiers N, Schepers D, Shivalkar B, Voigt JU, Van Craenenbroeck EM, Vanhees L. Aerobic interval training and continuous training equally improve aerobic exercise capacity in patients with coronary artery disease: the SAINTEX-CAD study. Int J Cardiol. 2015;179:203–210. doi: 10.1016/j.ijcard.2014.10.155.

14. Rognmo Ø, Moholdt T, Bakken H, Hole T, Melstad P, Myhr NE, Grimsjo J, Wisløff U. Cardiovascular risk of high versus moderate-intensity aerobic exercise in coronary heart disease patients. Circulation. 2012;126:1436–1440. doi: 10.1161/CIRCULATIONAHA.112.123117.
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 | Moderate Continuous Training | High Intensity Interval Training |
|-------------------|-------------------------------|-------------------------------|---------------------------------|
|                   | RRE N=73/70* | MCT N=65/62* | HIIT N=77/70* |
|                   | Baseline | 12 weeks | 52 weeks | Baseline | 12 weeks | 52 weeks | Baseline | 12 weeks | 52 weeks |
| LVEDD - mm        |        |        |        |        |        |        |        |        |        |
| Baseline          | 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) |
| 12 weeks          | 28 (27,30) | 29 (26,32) | 27 (25,31) | 33 (26,37) | 29 (26,31) | 31 (29,33) | 28 (26,32) |
| LVEF - %          |        |        |        |        |        |        |        |        |        |
| Baseline          | 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) |
| 12 weeks          | 28 (27,30) | 28 (27,32) | 27 (25,31) | 33 (26,37) | 29 (26,31) | 31 (29,33) | 28 (26,32) |
| LVEDV - ml        |        |        |        |        |        |        |        |        |        |
| Baseline          | 231 (223,252) | 234 (202,248) | 248 (183,230) | 235 (224,260) | 245 (209,253) | 197 (177,224) | 239 (220,257) | 220 (200,237) | 194 (183,214) |
| 12 weeks          | 156 (155,181) | 138 (126,165) | 178 (156,207) | 158 (145,180) | 133 (110,157) | 165 (152,187) | 149 (130,163) | 134 (124,159) |
| LVESV - ml        |        |        |        |        |        |        |        |        |        |
| Baseline          | 67 (66,71) | 69 (66,71) | 67 (63,70) | 65 (63,68) | 67 (64,71) | 68 (63,71) | 67 (62,72) | 64 (62,69) |
| 12 weeks          | 70 (66,73) | 68 (65,73) | 69 (66,71) | 67 (63,70) | 65 (63,68) | 67 (64,71) | 68 (63,71) | 67 (62,72) | 64 (62,69) |
| LVSV - ml         |        |        |        |        |        |        |        |        |        |
| Baseline          | 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) |
| 12 weeks          | 166 (164,208) | 166 (156,185) | 166 (152,194) | 180 (155,213) | 180 (161,205) | 157 (147,172) | 177 (153,198) | 185 (159,195) |
| Heart rate - bpm  |        |        |        |        |        |        |        |        |        |
| Baseline          | 189 (184,208) | 186 (165,185) | 166 (152,194) | 185 (155,213) | 180 (161,205) | 157 (147,172) | 177 (153,198) | 185 (159,195) |
| 12 weeks          | 107 (104,208) | 104 (98,110) | 98 (88,110) | 100 (85,116) | 104 (91,115) | 97 (93,108) | 111 (99,117) | 105 (94,111) |
| IVRT - ms         |        |        |        |        |        |        |        |        |        |
| Baseline          | 8 (7,8) | 7 (7,8) | 7 (7,8) | 8 (7,8) | 7 (7,8) | 8 (7,9) | 7 (7,8) | 7 (7,8) |
| 12 weeks          | 5 (5,5) | 5 (5,5) | 5 (5,5) | 5 (5,5) | 5 (5,5) | 5 (5,6) | 5 (5,6) | 5 (5,6) |
| MAPSE - mm        |        |        |        |        |        |        |        |        |        |
| Baseline          | 5 (5,6) | 6 (5,7) | 6 (5,7) | 6 (5,7) | 6 (5,7) | 6 (5,7) | 6 (5,7) | 6 (5,7) |
| 12 weeks          | 5 (5,6) | 6 (5,7) | 6 (5,7) | 6 (5,7) | 6 (5,7) | 6 (5,7) | 6 (5,7) | 6 (5,7) |
| E'/e'             |        |        |        |        |        |        |        |        |        |
| Baseline          | 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, LV 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.
|                               | Recommended Regular Exercise | Moderate Continuous Training | High Intensity Interval Training |
|-------------------------------|------------------------------|-----------------------------|---------------------------------|
|                               | Baseline | RRE N=73/70* 12 weeks | 52 weeks | Baseline | MCT N=65/62* 12 weeks | 52 weeks | Baseline | HIIT N=77/70* 12 weeks | 52 weeks |
| Peak oxygen uptake[^1^]       | 1.47     | (1.40, 1.65)         | 1.51     | (1.29, 1.57) | 1.39     | (1.30, 1.50)         | 1.51     | (1.29, 1.57) | 1.45     | (1.30, 1.55) | (1.33, 1.66) |
| VO2peak - mL kg[^1^] min[^4^]  | 18.4     | (16.8, 19.6)         | 18.2     | (15.7, 19.8) | 16.2     | (15.3, 18.7)         | 17.0     | (15.7, 19.6) | 16.4     | (15.0, 18.6) | (15.8, 17.8) |
| Respiratory quotient at peak oxygen uptake | 1.12     | (1.10, 1.14)         | 1.11     | (1.09, 1.13) | 1.14     | (1.11, 1.17)         | 1.12     | (1.10, 1.17) | 1.13     | (1.10, 1.15) | (1.10, 1.14) |
| Weight - kg                   | 84       | (78, 91)             | 84       | (80, 90)     | 84       | (79, 91)             | 84       | (79, 90)     | 87       | (79, 87)     | (78, 86)   |
| Ventilation at peak oxygen uptake - l min[^1^] | 62       | (57, 67)             | 61       | (56, 67)     | 56       | (54, 62)             | 59       | (54, 66)     | 58       | (53, 64)     | (53, 63)   |
| Heart rate at rest - bpm      | 71       | (68, 74)             | 71       | (68, 75)     | 68       | (66, 73)             | 67       | (66, 70)     | 68       | (65, 72)     | (68, 76)   |
| Heart rate at peak oxygen uptake - bpm | 132      | (127, 138)           | 127      | (119, 134)   | 126      | (113, 132)           | 120      | (112, 134)   | 119      | (111, 135)   | (120, 133) |
| Workload at peak oxygen uptake - W | 110      | (100, 120)           | 110      | (90, 120)    | 90       | (90, 100)            | 105      | (99, 120)    | 100      | (90, 110)    | (100, 138) |

[^1^] 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.

[^2^] N, number of patients at 12 weeks/52 weeks.
Table S3. Quality of Life outcomes.

|                  | Recommended Regular Exercise |                         | Moderate Continuous Training |                         | High Intensity Interval Training |                         |
|------------------|------------------------------|-------------------------|------------------------------|-------------------------|---------------------------------|-------------------------|
|                  | RRE                          |                         | MCT                          |                         | HIIT                            |                         |
|                  | Baseline median              | 12 weeks                | 52 weeks                     | Baseline median         | 12 weeks                        | 52 weeks                |
|                  | 95% CI                       | median                  | 95% CI                       | median                  | 95% CI                          | median                  |
| KCCQ             |                              |                         |                              |                         |                                 |                         |
| 1. Physical limitation | 75 69-83                    | 79 74-86                | 83 75-88                     | 79 71-83                | 80 75-83                        | 79 71-83                |
| 2. Symptom stability | 50 50-50                    | 50 50-50                | 50 50-50                     | 50 50-50                | 50 50-50                        | 50 50-50                |
| 3. Symptom frequency | 83 79-88                    | 88 79-92                | 88 83-92                     | 83 77-88                | 88 80-92                        | 83 81-92                |
| 4. Symptom burden | 83 83-83                    | 83 83-92                | 83 83-92                     | 83 83-92                | 92 83-92                        | 92 75-92                |
| 5. Total symptom score | 83 79-88                    | 85 79-92                | 88 82-92                     | 83 79-88                | 85 81-92                        | 88 81-92                |
| 6. Self efficacy | 75 63-88                    | 75 75-88                | 75 75-88                     | 75 75-88                | 75 75-75                        | 75 75-75                |
| 7. Quality of life | 67 58-75                    | 75 77-83                | 83 75-83                     | 67 58-75                | 75 75-83                        | 75 67-83                |
| 8. Social limitation | 69 63-75                    | 69 63-81                | 75 67-81                     | 75 63-81                | 75 69-81                        | 75 63-81                |
| 9. Overall summary score | 74 67-79                    | 76 69-83                | 82 74-87                     | 79 68-83                | 81 77-85                        | 80 71-86                |
| 10. Clinical summary score | 79 73-83                    | 82 76-88                | 86 80-88                     | 81 74-86                | 84 79-86                        | 83 76-86                |
| 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             |
| 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             |
| GMS              |                              |                         |                              |                         |                                 |                         |
| Positive affect  | 21 19-22                    | 22 20-23                | 22 21-23                     | 20 18-21                | 23 20-25                        | 21 19-23                |
| Negative affect  | 12 10-14                    | 9 8-14                  | 12 8-14                      | 12 11-14                | 10 8-13                         | 10 8-14                 |
| 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            |
| 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             |

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** | | | |
| Died suddenly / heart failure | 0 | 1AA | 0 |
| Worsening heart failure | 1AB | 2AC | 1AD |
| Atrial arrhythmia | 1AB | 0 | 0 |
| Ventricular arrhythmia | 0 | 0 | 1AE |
| Unstable angina | 0 | 0 | 0 |
| ICD-related | 0 | 0 | 0 |
| **Completed 12 weeks** | 4 | 3 | 7 |
| Worsening heart failure | 1AF | 1AG | 3AH |
| Atrial arrhythmia | 1AI | 1AI | 1AK |
| Ventricular arrhythmia | 0 | 1AL | 1AM |
| Chest pain / unstable angina | 1AN | 0 | 1AO |
| ICD-related | 1AP | 0 | 0 |
| Syncope | 0 | 0 | 1AQ |
| Cardiovascular week 13-52† | 17 (22%) | 8 (11%) | 19 (23%) |
| **Quit week 13-52** | | | |
| Died of abdominal aortic aneurysm | 0 | 0 | 1BA |
| Died of ventricular arrhythmia | 0 | 0 | 1BB |
| Worsening heart failure† | 0 | 2BC | 4AH,AK,BD |
| Atrial arrhythmia | 0 | 0 | 1AK |
| Ventricular arrhythmia | 0 | 0 | 1BD |
| **Completed 52 weeks** | 17 | 6 | 13 |
| Worsening heart failure† | 13AB,E | 1BF | 7BG |
| Atrial arrhythmia | 3BE,BH | 2AL,BI | 1BJ |
| Ventricular arrhythmia | 4BE,BH,BK | 2BL | 3AH,BM |
| Chest pain / unstable angina | 0 | 1BN | 0 |
| ICD/CRT-related | 1BE | 0 | 3BO |
| Non-cardiovascular week 1-12† | 2 (3%) | 3 (4%) | 6 (7%) |
| **Quit week 1-12** | | | |
| Died of pneumonia after accident | 0 | 1CA | 0 |
| Cholecystitis | 0 | 0 | 1CB |
| ICD-related | 0 | 0 | 1CC |
| **Completed 12 weeks** | 2 | 2 | 4 |
| Cholecystectomy | 1CE | 0 | 0 |
| Depression /suicidal attempt | 0 | 0 | 1CF |
| Dizziness | 0 | 0 | 1AM |
| Gout | 1BE | 1CG | 2CH |

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Six patients had single admissions for WHF week 20. 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. One patient had two admissions for WHF after week 19. Two 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. One 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. Two patients had single admissions for ventricular arrhythmias week 13-52. One had ICD discharge, the other not. Two patients had single admissions for ventricular arrhythmias week 13-52. One had ICD discharge, the other not. Single admission for ventricular arrhythmia without DC shock week 52. Chest pain / angina pectoris week 22.
One 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.

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

Died of brain metastases week 48. Died of non-cardiovascular infection week 36. Died of unknown cause week 48. Appendicitis week 48. Breast cancer surgery week 17. Hematoma after muscle biopsy week 14. Diabetes / hyperglycemia week 50. Infection after foot injury week 36. Non-cardiovascular renal failure week 19.