Supplemental Online Content

Mueller S, Winzer EB, Duvinage A, et al; OptimEx-Clin Study Group. Effect of high-intensity interval training, moderate continuous training, or guideline-based physical activity advice on peak oxygen consumption in patients with heart failure with preserved ejection fraction. *JAMA*. Published February 9, 2021. doi:10.1001/jama.2020.26812

This supplemental material has been provided by the authors to give readers additional information about their work.

eAppendix. Group Members

Lilian Massen, MSc, Axel Pressler, MD, and Christiane Suchy, MD (Munich, Germany), Øivind Rognmo, PhD, Natale Rolim, PhD, and Atefe R. Tari, MSc (Trondheim, Norway) contributed to the concept and design of the trial. Luciene Azevedo, PhD, Flavia Baldassarri, MSc, Birgit Böhm, PhD, Julia Elmenhorst, MD, Hannes Fricke, MD, Siri Goldschmidt, MSc, Sarah Lang, MSc, Lilian Massen, MSc, Renate Oberhoffer, MD, Kristina Schütt, MSc, Silja Schwarz, MD, Christiane Suchy, MD, Veronika Zeller and Sophia Wachner, MD (Munich, Germany), Justien Cornelis, PhD, Johan Denollet (†), PhD, Inge Goovaerts, Katrien Masset, MSc, Nadine Possemiers, Tibor Stoop, MSc, Christiaan Vrints, MD, PhD, and Kurt Wuyts, PhD (Antwerp, Belgium), Ines Frederix, PhD, and Paul Dendale, MD, PhD (Hasselt, Belgium), Evgeny Belyavskiy, MD, PhD, Martin Kropf, MSc, Daniel A. Morris, MD, and Aravind Kumar Radhakrishnan, MD (Berlin, Germany) contributed to acquisition, analysis, or interpretation of data. Doris Bach, MSc (Berlin, Germany), and Natale Rolim, PhD, (Trondheim, Norway) contributed to administrative, technical or material support. Daniel Kaiser, MA (vitagroup AG, Mannheim, Germany) was responsible for the development and technical support of the smartphone application and telemedical infrastructure. The salaries of Lilian Massen, Natale Rolim, Nadine Possemiers and Daniel Kaiser were (at least in part) funded by the grant of the European Commission. All the other contributors were paid staff members of their respective site but were not paid by the funds of the European Commission.

Viviane Conraads (MD, PhD, Antwerp, Belgium) was an integral part of developing the grant application and participating in the steering committee. Dr. Conraads died on December 12, 2013.

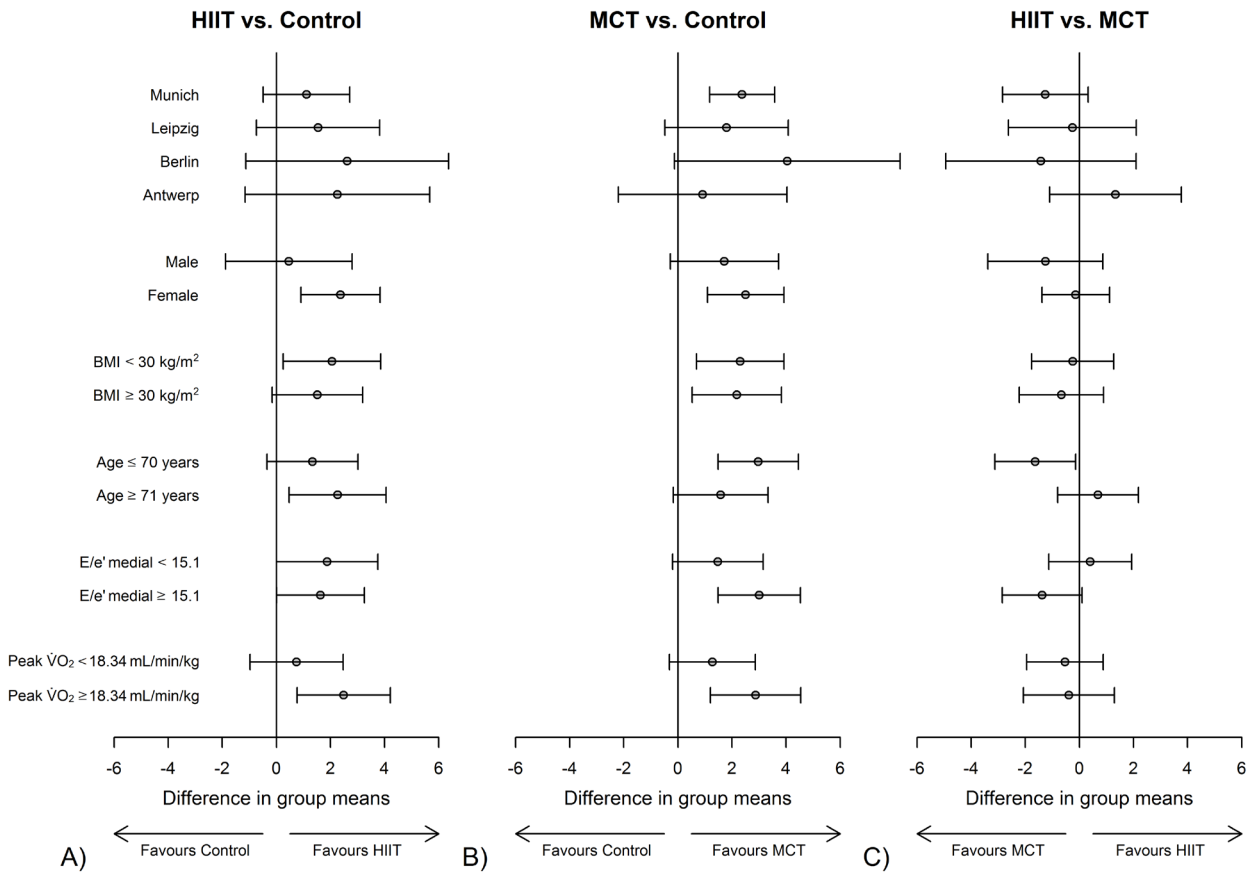
Steering Committee: Martin Halle, MD, Munich, Germany (Chair)**;** Burkert Pieske, MD, Berlin, Germany; Emeline van Craenenbroeck, MD, PhD, Antwerp, Belgium; Volker Adams, PhD, Leipzig/Dresden, Germany; Ulrik Wisløff, PhD, Trondheim, Norway
Endpoint Committee: Marco Guazzi, MD, PhD, Milan, Italy (did not receive compensation)
Safety Committee: Ulf Landmesser, MD, Berlin, Germany; Lars Maier, MD, Regensburg, Germany (did not receive compensation)
Biometry: Bernhard Haller, Dr rer nat, Germany
Study Coordination and Monitoring: Stephan Mueller, MA, Munich, Germany
Responsible personnel in core laboratories:

- Cardiopulmonary Exercise Testing: Martin Halle, MD, Stephan Mueller, MA, Munich, Germany
- Echocardiography: Elisabeth Pieske-Kraigher, MD, Aravind Kumar Radhakrishnan, MD, Daniel Morris, MD, Berlin, Germany
- Clinical chemistry: Hubert Scharnagl, Dr rer nat, Graz, Austria (received compensation for measurements of NT-proBNP)
- Psychometric analysis: Emeline van Craenenbroeck, MD, PhD, Antwerp, Belgium
- Exercise Training: Martin Halle, MD, Stephan Mueller, MA, Munich, Germany

eMethods:

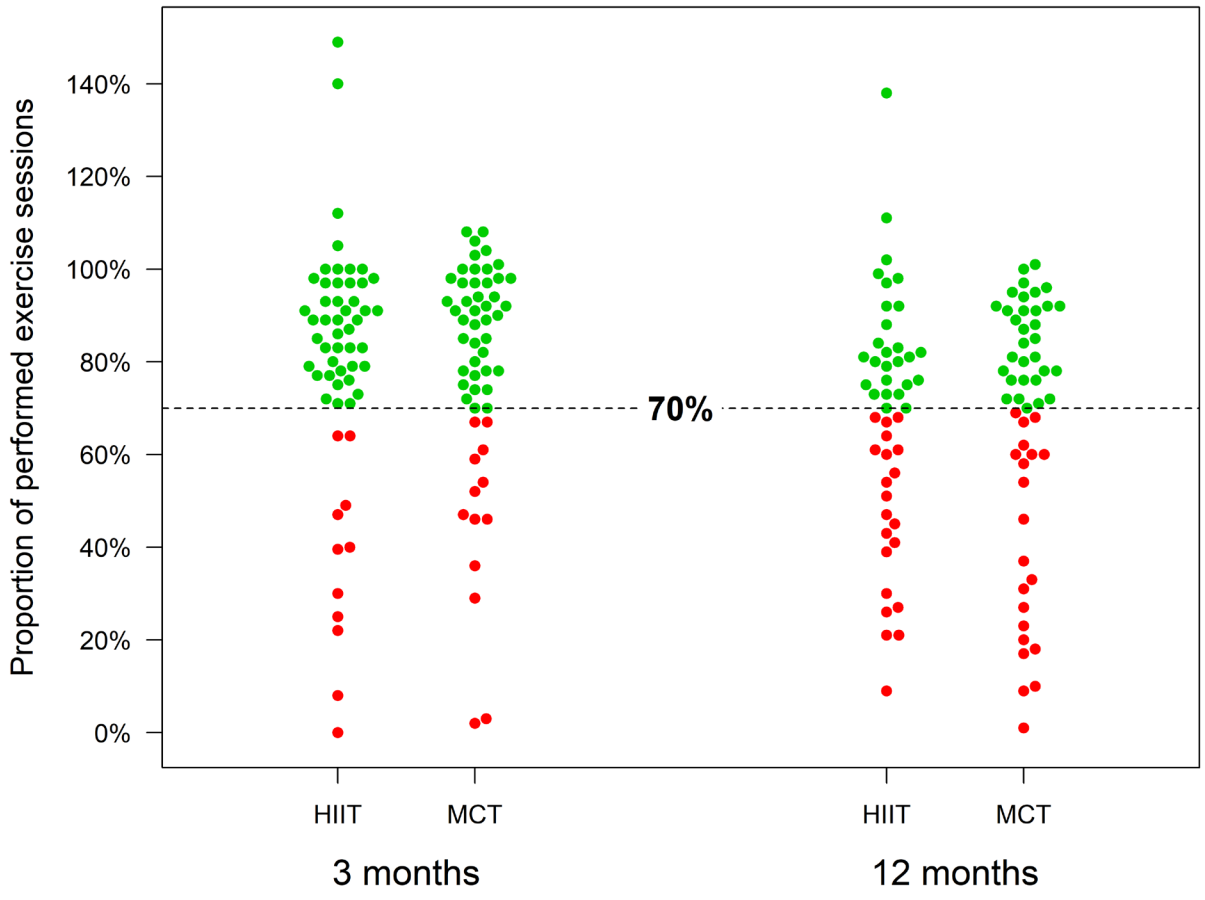
Description of multiple imputation approach:

To account for missing values in the primary efficacy endpoint [change of peak oxygen consumption (peak $\dot{V}O_2$) after three months] a multiple imputation approach was pre-specified in the statistical analysis plan.
Missing peak $\dot{V}O_2$ values were imputed using predictive mean matching implemented in the R[1] library *mice*[2]. Imputation was performed under consideration of the variables age, sex, body mass index, binary indicator for intake of heart failure related medication (angiotensin-converting enzyme inhibitors, angiotensin receptor blocker, beta-blocker and/or diuretics), N-terminal prohormone of brain natriuretic peptide (NT-proBNP), baseline peak $\dot{V}O_2$ and baseline left ventricular filling pressure (E/e' medial). By not adding the treatment group to the predictors of the imputation this approach should produce a rather conservative result, because similar values will be imputed for comparable patients from different groups.
Ten datasets with imputed values were generated and pooled using the function *mi.anova* provided in the R library *miceadds*[3] to test the global null hypothesis of equal group means for all three groups (ANOVA, significance level of $\alpha = 5\%$). All patients were analyzed in the group they were randomized to, irrespective of adherence to group allocation. As the global null hypothesis could be rejected based on the pooled data, pairwise comparisons were performed on a significance level of $\alpha = 5\%$ for each of the ten imputed datasets and results were aggregated using the *pool* function in R (library *mice*). Pooled estimates for the pairwise differences in group means for change of peak $\dot{V}O_2$ over three months are presented with corresponding 95% confidence intervals. Results are also presented considering patients with valid assessment of peak $\dot{V}O_2$ after three months only (complete case analysis).



eFigure 1: Subgroup analysis of the primary endpoint (change in peak $\dot{V}O_2$ after 3 months).

Cutoff points were pre-specified as 30 kg/m^2 (BMI) and the median of age, E/e' medial and peak $\dot{V}O_2$. HIIT: High Intensity Interval Training; MCT: Moderate Continuous Training; Control: Guideline Control; BMI: body mass index; E: peak velocity blood flow from ventricular relaxation in early diastole, e': mitral annular early diastolic velocity, peak $\dot{V}O_2$: peak oxygen consumption



eFigure 2: Relative frequency of performed exercise training sessions within 3-months and 12-months intervention period in High Intensity Interval Training (HIIT) and Moderate Continuous Training (MCT).

The dotted line represents the 70%-cutoff that was defined as the lower limit for an adequate adherence. Green points represent each individual exercising ≥ 70% of prescribed exercise sessions, red points represent individuals exercising < 70% of prescribed exercise sessions.

eTable 1: Ineligible participants not meeting HFpEF criteria who were inadvertently randomized and excluded from the analysis

Group assignment	On-site E/e' medial	On-site BNP (pg/mL)	CoreLab E/e' medial	CoreLab NT-proBNP (pg/mL)
MCT	10.8	33	9.6	102
MCT	10.9	30	9.9	92
HIIT	11.9	44	7.8	134
HIIT	9.8	8	9.4	55

Inclusion criteria: On-site measures of E/e' medial ≥ 15 or E/e' medial ≥ 8 and NT-proBNP ≥ 220 pg/mL or E/e' medial ≥ 8 and BNP ≥ 80 pg/mL MCT: Moderate Continuous Training; HIIT: High Intensity Interval Training; E: peak velocity blood flow from ventricular relaxation in early diastole, e': mitral annular early diastolic velocity, BNP: brain natriuretic peptide, NT-proBNP: N-terminal prohormone of brain natriuretic peptide

eTable 2: Subgroup analysis of the primary endpoint (change in peak $\dot{V}O_2$ after 3 months)

	Difference [95% CI]			Interaction p value
	HIIT vs. Control	MCT vs. Control	HIIT vs. MCT	
Munich (n=72)	1.1 [-0.5 to 2.7]	2.4 [1.2 to 3.6]	-1.3 [-2.8 to 0.3]	.62
Leipzig (n=44)	1.5 [-0.7 to 3.8]	1.8 [-0.5 to 4.1]	-0.3 [-2.6 to 2.1]	
Berlin (n=24)	2.6 [-1.1 to 6.4]	4.0 [-0.1 to 8.2]	-1.4 [-4.9 to 2.1]	
Antwerp (n=36)	2.3 [-1.2 to 5.7]	0.9 [-2.2 to 4.0]	1.3 [-1.1 to 3.8]	
Male	0.5 [-1.9 to 2.8]	1.7 [-0.3 to 3.7]	-1.3 [-3.4 to 0.9]	.31
Female	2.4 [0.9 to 3.8]	2.5 [1.1 to 3.9]	-0.1 [-1.4 to 1.1]	
BMI < 30 kg/m^2	2.1 [0.3 to 3.9]	2.3 [0.7 to 3.9]	-0.2 [-1.8 to 1.3]	.89
BMI ≥30 kg/m^2	1.5 [-0.2 to 3.2]	2.2 [0.5 to 3.8]	-0.7 [-2.2 to 0.9]	
Age ≤ 70 years	1.3 [-0.3 to 3.0]	3.0 [1.5 to 4.5]	-1.6 [-3.1 to -0.1]	.13
Age ≥ 71 years	2.3 [0.5 to 4.1]	1.6 [-0.2 to 3.3]	0.7 [-0.8 to 2.2]	
E/e' medial < 15.1	1.9 [0.0 to 3.7]	1.5 [-0.2 to 3.1]	0.4 [-1.1 to 1.9]	.24
E/e' medial ≥ 15.1	1.6 [0.0 to 3.3]	3.0 [1.5 to 4.5]	-1.4 [-2.8 to 0.1]	
Peak $\dot{V}O_2$ < 18.34 mL/min/kg	0.7 [-1.0 to 2.5]	1.3 [-0.3 to 2.9]	-0.5 [-1.9 to 0.9]	.25
Peak $\dot{V}O_2$ ≥ 18.34 mL/min/kg	2.5 [0.8 to 4.2]	2.9 [1.2 to 4.5]	-0.4 [-2.1 to 1.3]	

Cutoff points were pre-specified as 30 kg/m^2 (BMI) and the median of age, E/e' medial and peak $\dot{V}O_2$. HIIT: High Intensity Interval Training; MCT: Moderate Continuous Training; Control: Guideline Control; BMI: body mass index; E: peak velocity blood flow from ventricular relaxation in early diastole, e': mitral annular early diastolic velocity, peak $\dot{V}O_2$: peak oxygen consumption

eTable 3: Results from cardiopulmonary exercise testing for High Intensity Interval Training (HIIT), Moderate Continuous Training (MCT) and Guideline Control

		Mean (SD) [N]			Difference (95% CI) [N]		
		HIIT	MCT	Control	HIIT vs. Control	MCT vs. Control	HIIT vs. MCT
Values at rest							
$\dot{V}O_2$, mL/min/kg	**Baseline**	3.3 (0.9) [58]	3.3 (0.8) [58]	3.4 (0.7) [60]			
	3 mo	3.2 (0.8) [53]	3.2 (0.8) [54]	3.5 (0.9) [52]	-0.1 (-0.5 to 0.3) [105]	-0.2 (-0.5 to 0.1) [106]	0.1 (-0.2 to 0.5) [107]
	12 mo	3.3 (0.8) [42]	3.3 (0.7) [48]	3.7 (1.3) [49]	-0.3 (-0.8 to 0.3) [91]	-0.3 (-0.8 to 0.2) [97]	0.0 (-0.4 to 0.4) [90]
RER	**Baseline**	0.84 (0.07) [58]	0.85 (0.08) [58]	0.85 (0.08) [60]			
	3 mo	0.86 (0.06) [53]	0.85 (0.07) [54]	0.85 (0.08) [52]	0.01 (-0.03 to 0.04) [105]	-0.01 (-0.04 to 0.03) [106]	0.02 (-0.01 to 0.04) [107]
	12 mo	0.84 (0.10) [42]	0.85 (0.08) [48]	0.85 (0.06) [49]	-0.01 (-0.05 to 0.04) [91]	-0.01 (-0.05 to 0.03) [97]	0.00 (-0.05 to 0.04) [90]
systolic BP, mmHg	**Baseline**	127 (14) [58]	131 (13) [58]	127 (14) [60]			
	3 mo	127 (17) [53]	133 (18) [54]	131 (14) [52]	-2 (-8 to 5) [105]	0 (-7 to 6) [106]	-1 (-8 to 5) [107]
	12 mo	133 (20) [42]	134 (15) [48]	128 (15) [49]	6 (-1 to 14) [91]	2 (-4 to 8) [97]	4 (-3 to 12) [90]
Heart rate, bpm	**Baseline**	65 (12) [58]	65 (10) [58]	65 (11) [60]			
	3 mo	65 (10) [53]	65 (8) [54]	65 (12) [52]	0 (-4 to 4) [105]	-1 (-4 to 3) [106]	1 (-2 to 4) [107]
	12 mo	65 (11) [42]	68 (12) [48]	66 (11) [49]	-2 (-7 to 3) [91]	1 (-4 to 5) [97]	-3 (-7 to 2) [90]
Values at the first ventilatory threshold (VT1)							
$\dot{V}O_2$, mL/min/kg	**Baseline**	11.1 (2.8) [58]	11.2 (3.3) [57]	11.4 (2.8) [58]			
	3 mo	11.9 (2.7) [53]	12.1 (3.5) [53]	11.4 (2.6) [50]	0.8 (-0.1 to 1.7) [103]	1.0 (0.2 to 1.9) [102]	-0.3 (-1.0 to 0.5) [105]
	12 mo	11.3 (2.9) [41]	10.6 (3.1) [47]	10.9 (2.4) [49]	0.6 (-0.5 to 1.6) [90]	-0.1 (-1.0 to 0.9) [95]	0.6 (-0.4 to 1.7) [87]
Workload, watts	**Baseline**	45 (18) [58]	46 (21) [57]	45 (15) [58]			
	3 mo	49 (18) [53]	53 (25) [53]	47 (16) [50]	3 (-2 to 7) [103]	6 (2 to 11) [102]	-4 (-9 to 1) [105]
	12 mo	46 (17) [41]	45 (21) [47]	43 (14) [49]	4 (-1 to 9) [90]	3 (-2 to 7) [95]	2 (-4 to 7) [87]
Heart rate, bpm	**Baseline**	92 (16) [58]	94 (17) [57]	91 (18) [58]			
	3 mo	92 (14) [53]	96 (16) [53]	91 (17) [50]	-1 (-6 to 4) [103]	1 (-4 to 5) [102]	-2 (-6 to 2) [105]
	12 mo	93 (15) [41]	94 (17) [47]	93 (25) [49]	-4 (-13 to 5) [90]	-3 (-12 to 7) [95]	-1 (-7 to 5) [87]
RER	**Baseline**	0.86 (0.05) [58]	0.85 (0.06) [57]	0.84 (0.08) [58]			
	3 mo	0.86 (0.05) [53]	0.85 (0.06) [53]	0.87 (0.06) [50]	-0.04 (-0.07 to -0.01) [103]	-0.03 (-0.06 to 0.00) [102]	0.00 (-0.02 to 0.02) [105]
	12 mo	0.84 (0.06) [41]	0.83 (0.05) [47]	0.85 (0.06) [49]	-0.04 (-0.08 to -0.01) [90]	-0.02 (-0.06 to 0.01) [95]	-0.02 (-0.05 to 0.01) [87]

eTable 3 continued…

		Mean (SD) [N]			Difference (95% CI) [N]		
		HIIT	**MCT**	**Control**	**HIIT vs. Control**	**MCT vs. Control**	**HIIT vs. MCT**
Values at peak exercise							
$\dot{V}O_2$, mL/min/kg	**Baseline**	18.9 (5.4) [58]	18.2 (5.1) [58]	19.4 (5.6) [60]			
	3 mo	20.2 (6.0) [53]	19.8 (5.8) [54]	18.9 (5.7) [52]	1.8 (0.5 to 3.0) [105]	2.2 (1.1 to 3.4) [106]	-0.5 (-1.6 to 0.6) [107]
	12 mo	19.9 (6.1) [42]	18.1 (5.9) [48]	19.5 (5.1) [49]	1.4 (0.1 to 2.8) [91]	0.6 (-0.7 to 1.9) [97]	0.8 (-0.5 to 2.1) [90]
$\dot{V}O_2$, L/min	**Baseline**	1.54 (0.47) [58]	1.55 (0.43) [58]	1.50 (0.47) [60]			
	3 mo	1.59 (0.49) [53]	1.66 (0.46) [54]	1.48 (0.49) [52]	0.11 (0.01 to 0.20) [105]	0.16 (0.07 to 0.25) [106]	-0.05 (-0.14 to 0.03) [107]
	12 mo	1.55 (0.49) [42]	1.53 (0.46) [48]	1.54 (0.42) [49]	0.08 (-0.03 to 0.19) [91]	0.03 (-0.08 to 0.14) [97]	0.05 (-0.06 to 0.16) [90]
Workload, watts	**Baseline**	103 (38) [58]	103 (37) [58]	101 (36) [60]			
	3 mo	110 (38) [53]	112 (42) [54]	101 (39) [52]	9 (4 to 15) [105]	9 (4 to 14) [106]	0 (-6 to 6) [107]
	12 mo	109 (39) [42]	104 (42) [48]	104 (35) [49]	10 (4 to 16) [91]	4 (-1 to 10) [97]	5 (-1 to 12) [90]
RER	**Baseline**	1.12 (0.10) [58]	1.10 (0.09) [58]	1.10 (0.12) [60]			
	3 mo	1.11 (0.10) [53]	1.09 (0.08) [54]	1.11 (0.12) [52]	-0.01 (-0.05 to 0.03) [105]	-0.02 (-0.06 to 0.01) [106]	0.01 (-0.01 to 0.04) [107]
	12 mo	1.10 (0.11) [42]	1.08 (0.07) [48]	1.11 (0.10) [49]	-0.04 (-0.08 to 0.01) [91]	-0.02 (-0.05 to 0.02) [97]	-0.02 (-0.06 to 0.02) [90]
Systolic BP, mmHg	**Baseline**	178 (28) [58]	184 (30) [58]	175 (28) [59]			
	3 mo	180 (28) [53]	181 (30) [53]	177 (26) [52]	-2 (-12 to 7) [104]	-4 (-13 to 5) [104]	2 (-7 to 11) [106]
	12 mo	180 (30) [42]	176 (31) [45]	168 (27) [49]	10 (-2 to 21) [90]	4 (-6 to 14) [93]	6 (-6 to 18) [87]
Heart rate, BPM	**Baseline**	123 (24) [57]	123 (27) [58]	122 (28) [60]			
	3 mo	126 (25) [53]	127 (26) [54]	122 (29) [52]	2 (-4 to 7) [104]	2 (-3 to 8) [106]	-1 (-6 to 4) [106]
	12 mo	127 (27) [42]	127 (29) [48]	126 (26) [49]	-2 (-10 to 6) [90]	1 (-8 to 9) [97]	-3 (-12 to 7) [89]
Other values							
$\dot{V}E/\dot{V}CO_2$ slope	**Baseline**	34.5 (7.9) [58]	34.2 (7.2) [58]	33.2 (5.9) [59]			
	3 mo	35.0 (9.8) [53]	33.7 (6.8) [54]	32.6 (5.3) [51]	1.7 (-0.2 to 3.6) [104]	0.2 (-1.7 to 2.2) [105]	1.5 (-0.3 to 3.2) [107]
	12 mo	36.6 (8.4) [42]	33.9 (7.1) [48]	34.3 (7.4) [49]	0.9 (-1.2 to 3.0) [91]	-1.9 (-3.8 to 0.0) [97]	2.8 (0.7 to 4.8) [90]

$\dot{V}O_2$: oxygen uptake, RER: respiratory exchange ratio, BP: blood pressure, $\dot{V}E/\dot{V}CO_2$ slope: ventilation to carbon dioxide production slope

eTable 4: Results from echocardiography for High Intensity Interval Training (HIIT), Moderate Continuous Training (MCT) and Guideline Control

		Mean (SD) [N]			Difference (95% CI) [N]		
		HIIT	MCT	Control	HIIT vs. Control	MCT vs. Control	HIIT vs. MCT
Diastolic Function							
E, cm/s	**Baseline**	94.3 (21.2) [58]	93.8 (21.2) [58]	93.4 (25.2) [59]			
	3 mo	91.1 (24.2) [54]	89.5 (26.9) [55]	91.3 (29.8) [53]	-1.2 (-8.0 to 5.5) [106]	-2.0 (-9.2 to 5.2) [107]	0.8 (-6.6 to 8.2) [109]
	12 mo	86.3 (23.7) [48]	89.5 (23.8) [52]	91.3 (26.7) [52]	-4.6 (-11.6 to 2.4) [99]	-0.8 (-8.6 to 7.0) [103]	-3.8 (-11.8 to 4.3) [100]
A, cm/s	**Baseline**	82.1 (26.9) [47]	88.5 (27.2) [48]	89.1 (23.2) [54]			
	3 mo	82.7 (24.9) [46]	85.1 (27.3) [47]	81.2 (27.9) [49]	4.1 (-1.6 to 9.7) [89]	-1.8 (-7.3 to 3.6) [90]	5.9 (0.4 to 11.4) [89]
	12 mo	78.7 (26.1) [39]	89.3 (27.4) [45]	87.6 (26.9) [44]	-0.8 (-7.3 to 5.7) [82]	2.4 (-5.1 to 10.0) [86]	-3.2 (-10.6 to 4.2) [80]
E/A	**Baseline**	1.30 (0.79) [47]	1.13 (0.45) [48]	1.15 (0.59) [54]			
	3 mo	1.21 (0.64) [46]	1.11 (0.61) [47]	1.35 (0.97) [49]	-0.14 (-0.32 to 0.04) [89]	-0.04 (-0.23 to 0.15) [90]	-0.10 (-0.27 to 0.07) [89]
	12 mo	1.25 (0.83) [39]	1.07 (0.57) [45]	1.18 (0.73) [44]	-0.09 (-0.27 to 0.09) [82]	-0.07 (-0.25 to 0.11) [86]	-0.02 (-0.2 to 0.15) [80]
e' medial, cm/s	**Baseline**	6.16 (1.79) [57]	6.11 (1.57) [58]	6.25 (1.76) [57]			
	3 mo	6.23 (1.72) [54]	5.95 (1.65) [54]	5.95 (1.84) [53]	0.33 (-0.30 to 0.95) [103]	0.23 (-0.32 to 0.78) [104]	0.09 (-0.48 to 0.66) [107]
	12 mo	6.23 (1.73) [47]	5.93 (1.51) [52]	6.10 (1.66) [52]	0.34 (-0.26 to 0.94) [96]	0.01 (-0.51 to 0.52) [102]	0.33 (-0.20 to 0.86) [98]
e' lateral, cm/s	**Baseline**	8.11 (2.02) [58]	8.78 (2.68) [56]	8.34 (1.98) [58]			
	3 mo	8.18 (2.27) [54]	8.67 (2.48) [55]	8.01 (2.10) [52]	0.13 (-0.53 to 0.79) [104]	-0.03 (-0.76 to 0.70) [103]	0.16 (-0.63 to 0.95) [107]
	12 mo	8.33 (2.23) [47]	8.55 (2.34) [52]	8.36 (2.26) [51]	0.14 (-0.68 to 0.96) [96]	-0.26 (-1.03 to 0.51) [100]	0.40 (-0.40 to 1.20) [98]
e' average, cm/s	**Baseline**	7.15 (1.72) [57]	7.45 (1.92) [56]	7.31 (1.61) [57]			
	3 mo	7.20 (1.71) [54]	7.28 (1.86) [54]	6.96 (1.73) [52]	0.23 (-0.32 to 0.79) [102]	0.11 (-0.43 to 0.65) [101]	0.12 (-0.46 to 0.71) [105]
	12 mo	7.29 (1.82) [46]	7.24 (1.68) [52]	7.25 (1.77) [51]	0.22 (-0.40 to 0.84) [94]	-0.12 (-0.65 to 0.42) [100]	0.33 (-0.25 to 0.91) [96]
E/e' medial	**Baseline**	15.8 (3.7) [57]	15.9 (4.1) [58]	15.7 (5.6) [57]			
	3 mo	15.2 (4.8) [54]	15.6 (5.0) [54]	16.5 (7.2) [53]	-1.5 (-3.2 to 0.3) [103]	-1.1 (-2.7 to 0.5) [104]	-0.4 (-1.9 to 1.2) [107]
	12 mo	14.2 (3.9) [47]	15.6 (4.4) [52]	15.7 (5.5) [52]	-1.4 (-2.9 to 0.1) [96]	0.1 (-1.5 to 1.7) [102]	-1.5 (-3.0 to 0.0) [98]
E/e' lateral	**Baseline**	12.1 (3.3) [58]	11.4 (4.0) [56]	11.7 (4.1) [58]			
	3 mo	11.9 (4.4) [54]	10.9 (3.8) [55]	11.8 (4.2) [52]	0.1 (-1.0 to 1.1) [104]	-0.2 (-1.3 to 0.8) [103]	0.3 (-0.9 to 1.4) [107]
	12 mo	10.9 (3.4) [47]	11.0 (3.6) [52]	11.9 (5.9) [51]	-1.1 (-2.6 to 0.4) [96]	-0.4 (-2.1 to 1.2) [100]	-0.6 (-1.8 to 0.5) [98]
E/e' average	**Baseline**	13.5 (3.2) [57]	13.1 (3.5) [56]	13.2 (4.4) [57]			
	3 mo	13.1 (4.3) [54]	12.7 (3.8) [54]	13.5 (4.9) [52]	-0.6 (-1.7 to 0.6) [102]	-0.4 (-1.5 to 0.7) [101]	-0.2 (-1.3 to 1.0) [105]
	12 mo	12.2 (3.3) [46]	12.7 (3.6) [52]	13.2 (5.1) [51]	-1.0 (-2.3 to 0.3) [94]	-0.1 (-1.5 to 1.3) [100]	-0.9 (-2.0 to 0.2) [96]

eTable 4 continued…

		Mean (SD) [N]			Difference (95% CI) [N]		
		HIIT	**MCT**	**Control**	**HIIT vs. Control**	**MCT vs. Control**	**HIIT vs. MCT**
Dimensions							
LVEDD, mm	**Baseline**	46.9 (5.5) [27]	48.3 (5.2) [26]	45.7 (5.0) [34]			
	3 mo	45.8 (5.6) [24]	47.3 (3.7) [24]	44.6 (3.8) [23]	0.4 (-1.0 to 1.8) [35]	-0.6 (-2.5 to 1.3) [36]	1.0 (-0.5 to 2.6) [33]
	12 mo	46.4 (6.1) [23]	46.5 (3.6) [25]	44.9 (4.1) [23]	-0.6 (-2.9 to 1.6) [33]	0.3 (-1.7 to 2.3) [35]	-0.9 (-3.3 to 1.5) [36]
IVSD, mm	**Baseline**	11.0 (1.9) [27]	10.9 (1.6) [27]	11.1 (2.4) [34]			
	3 mo	10.8 (1.5) [24]	10.7 (1.8) [24]	11.2 (2.8) [23]	0.5 (-0.1 to 1.0) [35]	0.5 (0.0 to 1.1) [36]	-0.1 (-0.7 to 0.5) [33]
	12 mo	10.8 (1.5) [23]	10.9 (1.6) [25]	11.4 (2.8) [23]	0.2 (-0.4 to 0.7) [33]	0.2 (-0.2 to 0.6) [35]	0.0 (-0.6 to 0.5) [36]
LVPWD, mm	**Baseline**	10.1 (1.0) [27]	10.2 (1.6) [26]	10.1 (1.5) [34]			
	3 mo	10.3 (0.8) [24]	10.3 (1.5) [24]	10.4 (1.5) [23]	0.2 (-0.4 to 0.7) [35]	0.1 (-0.7 to 0.8) [35]	0.1 (-0.6 to 0.8) [32]
	12 mo	10.0 (0.9) [23]	10.0 (1.5) [25]	10.4 (1.6) [22]	0.0 (-0.8 to 0.7) [33]	0.4 (-0.4 to 1.1) [34]	-0.4 (-1.2 to 0.4) [35]
Other values							
LVEF - BP, %	**Baseline**	62.1 (6.4) [37]	61.6 (5.7) [38]	62.1 (4.7) [48]			
	3 mo	64.9 (7.3) [35]	61.8 (6.2) [29]	61.6 (4.9) [37]	1.6 (-1.1 to 4.3) [63]	0.4 (-2.2 to 3.0) [60]	1.2 (-1.9 to 4.3) [53]
	12 mo	63.9 (6.4) [33]	63.8 (5.9) [36]	63.2 (5.6) [40]	0.4 (-2.0 to 2.9) [65]	2.0 (-0.4 to 4.4) [68]	-1.6 (-4.3 to 1.1) [57]
TR Vmax, m/s	**Baseline**	2.54 (0.37) [44]	2.51 (0.39) [44]	2.47 (0.41) [48]			
	3 mo	2.52 (0.39) [42]	2.59 (0.33) [39]	2.63 (0.63) [40]	-0.16 (-0.34 to 0.03) [69]	-0.12 (-0.30 to 0.05) [70]	-0.03 (-0.19 to 0.13) [69]
	12 mo	2.55 (0.41) [36]	2.55 (0.36) [34]	2.53 (0.44) [41]	-0.08 (-0.25 to 0.09) [63]	-0.10 (-0.26 to 0.07) [63]	0.02 (-0.15 to 0.18) [58]
TAPSE, mm	**Baseline**	21.8 (3.6) [50]	21.0 (3.8) [53]	21.6 (3.6) [53]			
	3 mo	22.0 (4.1) [47]	20.8 (3.6) [45]	21.8 (4.5) [49]	0.0 (-1.5 to 1.6) [87]	0.0 (-1.4 to 1.3) [88]	0.0 (-1.5 to 1.6) [85]
	12 mo	21.0 (4.1) [41]	20.9 (3.3) [46]	21.8 (3.7) [49]	-1.1 (-2.9 to 0.7) [80]	0.1 (-1.5 to 1.8) [89]	-1.2 (-3.2 to 0.8) [79]
FAC, %	**Baseline**	43.1 (6.1) [21]	50.7 (10.5) [16]	46.0 (6.8) [20]			
	3 mo	45.4 (9.7) [14]	48.4 (8.3) [13]	40.0 (10.8) [13]	7.0 (0.2 to 13.8) [13]	-0.3 (-9.5 to 8.9) [13]	7.3 (-0.9 to 15.5) [14]
	12 mo	50.4 (8.5) [7]	43.2 (11.5) [5]	47.8 (9.8) [9]	- - -	- - -	- - -
LAVI, mL/m^2	**Baseline**	35.4 (9.0) [39]	37.9 (13.0) [42]	39.8 (13.5) [48]			
	3 mo	35.2 (10.2) [34]	36.8 (10.5) [28]	38.4 (14.7) [40]	0.3 (-1.7 to 2.4) [61]	1.2 (-0.9 to 3.4) [60]	-0.9 (-3.2 to 1.4) [51]
	12 mo	37.4 (10.9) [26]	36.6 (9.2) [23]	39.2 (13.8) [38]	0.4 (-2.7 to 3.5) [54]	0.9 (-1.6 to 3.3) [53]	-0.5 (-3.5 to 2.6) [41]
LV mass, g	**Baseline**	178 (45) [27]	189 (52) [26]	174 (51) [34]			
	3 mo	165 (44) [24]	180 (44) [24]	172 (55) [23]	10 (-3 to 23) [35]	3 (-15 to 20) [35]	7 (-8 to 23) [32]
	12 mo	172 (41) [23]	175 (48) [25]	177 (59) [22]	-2 (-21 to 17) [33]	9 (-5 to 23) [34]	-11 (-30 to 8) [35]

E: peak velocity blood flow from ventricular relaxation in early diastole, A: peak velocity flow in late diastole caused by atrial contraction, e': mitral annular early diastolic velocity, LVEDD: left ventricular end diastolic diameter, IVSD: interventricular septum thickness in diastole, LVPWD: left ventricular posterior wall in diastole, LVEF: left ventricular ejection fraction, BP: biplane, TR Vmax: maximum tricuspid regurgitation velocity, TAPSE: tricuspid annular plan systolic excursion, FAC: fractional area change, LAVI: left atrial volume index, LV mass: left ventricular mass

eTable 5: Results from Kansas City Cardiomyopathy Questionnaire for High Intensity Interval Training (HIIT), Moderate Continuous Training (MCT) and Guideline Control

		Mean (SD) [N]			Difference (95% CI) [N]		
		HIIT	MCT	Control	HIIT vs. Control	MCT vs. Control	HIIT vs. MCT
Physical limitation	**Baseline**	68 (24) [57]	62 (25) [55]	64 (26) [57]			
	3 mo	70 (23) [52]	67 (24) [54]	69 (23) [55]	-6 (-12 to 0) [105]	-4 (-11 to 2) [105]	-2 (-8 to 4) [104]
	12 mo	75 (25) [47]	71 (23) [46]	71 (27) [51]	-2 (-9 to 5) [96]	2 (-5 to 9) [93]	-4 (-12 to 4) [91]
Symptom stability	**Baseline**	50 (13) [58]	49 (17) [56]	52 (16) [58]			
	3 mo	59 (19) [54]	60 (22) [55]	51 (18) [55]	9 (2 to 17) [106]	12 (3 to 20) [106]	-2 (-8 to 4) [108]
	12 mo	55 (14) [47]	55 (20) [46]	48 (16) [51]	10 (2 to 18) [96]	10 (0 to 20) [94]	0 (-9 to 10) [92]
Symptom frequency	**Baseline**	76 (24) [58]	69 (22) [56]	67 (23) [58]			
	3 mo	77 (21) [54]	75 (22) [54]	74 (21) [55]	-4 (-11 to 2) [108]	-3 (-9 to 4) [107]	-2 (-7 to 4) [107]
	12 mo	80 (19) [47]	75 (22) [46]	73 (23) [51]	0 (-7 to 7) [97]	1 (-6 to 9) [95]	-1 (-9 to 6) [92]
Symptom burden	**Baseline**	75 (24) [58]	68 (22) [56]	67 (22) [58]			
	3 mo	74 (21) [54]	75 (20) [55]	70 (20) [55]	-3 (-10 to 4) [108]	3 (-3 to 10) [108]	-7 (-12 to -1) [108]
	12 mo	79 (19) [47]	77 (19) [46]	71 (25) [51]	1 (-7 to 8) [97]	7 (0 to 14) [95]	-6 (-13 to 1) [92]
Total symptoms	**Baseline**	75 (23) [58]	68 (21) [56]	67 (22) [58]			
	3 mo	75 (20) [54]	74 (20) [55]	72 (20) [55]	-4 (-10 to 3) [108]	0 (-6 to 6) [108]	-4 (-9 to 1) [108]
	12 mo	80 (19) [47]	76 (20) [46]	72 (23) [51]	0 (-6 to 7) [97]	4 (-2 to 11) [95]	-4 (-10 to 3) [92]
Self-efficacy	**Baseline**	67 (27) [57]	63 (23) [56]	66 (29) [58]			
	3 mo	71 (25) [54]	70 (22) [55]	70 (23) [55]	-2 (-12 to 7) [107]	0 (-8 to 9) [108]	-2 (-10 to 6) [107]
	12 mo	82 (19) [47]	76 (20) [46]	68 (23) [51]	8 (-2 to 19) [96]	8 (-2 to 17) [95]	1 (-8 to 9) [91]
Quality of life	**Baseline**	68 (24) [58]	62 (26) [56]	66 (20) [58]			
	3 mo	73 (26) [54]	74 (20) [55]	72 (21) [55]	1 (-7 to 9) [108]	5 (-3 to 12) [108]	-4 (-11 to 4) [108]
	12 mo	80 (21) [47]	77 (19) [45]	72 (24) [51]	4 (-3 to 12) [97]	11 (2 to 19) [94]	-6 (-15 to 2) [91]
Social limitation	**Baseline**	72 (25) [56]	66 (29) [53]	67 (25) [57]			
	3 mo	76 (26) [51]	75 (28) [54]	73 (23) [54]	-2 (-10 to 6) [101]	0 (-8 to 7) [102]	-2 (-9 to 6) [99]
	12 mo	85 (22) [47]	80 (25) [45]	78 (27) [51]	0 (-9 to 9) [94]	2 (-8 to 11) [92]	-2 (-11 to 8) [88]
Overall summary	**Baseline**	70 (22) [55]	64 (23) [53]	66 (20) [56]			
	3 mo	74 (21) [50]	72 (20) [53]	72 (18) [54]	-3 (-9 to 3) [99]	0 (-6 to 5) [100]	-3 (-8 to 2) [97]
	12 mo	80 (19) [47]	76 (19) [45]	73 (21) [51]	0 (-5 to 6) [93]	4 (-2 to 11) [91]	-4 (-10 to 3) [88]
Clinical summary	**Baseline**	72 (22) [57]	65 (22) [55]	66 (22) [57]			
	3 mo	73 (20) [52]	70 (20) [54]	71 (19) [55]	-5 (-11 to 0) [105]	-2 (-7 to 3) [105]	-3 (-8 to 2) [104]
	12 mo	77 (21) [47]	74 (20) [46]	71 (23) [51]	-1 (-7 to 5) [96]	3 (-3 to 9) [93]	-4 (-10 to 2) [91]

Higher scores indicate better health (score range 1-100, minimal clinically important differences: 5 points).

eTable 6: Exercise training data and adherence to the prescribed exercise intervention for High Intensity Interval Training (HIIT) and Moderate Continuous Training (MCT)

Study phase	group	No. (%)		Median [1st – 3rd quartile]		
		Patients completing each phase	Patients performing ≥ 70% of scheduled exercise sessions	Adherence (%) to scheduled exercise sessions	Performed exercise sessions (no.) per week	Amount (min) of exercise per week
Supervised (month 0-3)	**HIIT**	56 (96.6)	45 (80.4)	84 [73-94]	2.5 [2.1-2.8]	96 [82-105]
	MCT	55 (94.8)	42 (76.4)	85 [70-97]	4.4 [3.4-4.7]	176 [137-188]
Home-based (month 4-12)	**HIIT**	48 (82.8)	23 (47.9)	69 [41-82]	2.0 [1.2-2.4]	77 [46-92]
	MCT	53 (91.4)	31 (58.5)	72 [54-86]	3.6 [2.7-4.3]	144 [108-171]
entire phase (month 0-12)	**HIIT**	48 (82.8)	27 (56.3)	73 [53-82]	2.1 [1.6-2.4]	82 [59-92]
	MCT	53 (91.4)	32 (60.4)	76 [58-89]	3.8 [2.9-4.4]	150 [115-176]

eTable 7: Group differences in primary and secondary endpoints after 3 and 12 months including only the per-protocol population of patients who performed at least 70% of the scheduled training sessions

	Difference [95% CI]			p-value
	HIIT vs. Control	MCT vs. Control	HIIT vs. MCT	
Change baseline to 3 months				
Peak $\dot{V}O_2$, mL/min/kg	2.1 [0.9 to 3.3]	2.6 [1.4 to 3.8]	-0.5 [-1.6 to 0.7]	<.001
$\dot{V}E/\dot{V}CO_2$ slope	1.6 [-0.4 to 3.7]	0.3 [-1.8 to 2.3]	1.4 [-0.6 to 3.3]	.22
Workload at VT1, watts	3 [-1 to 7]	8 [3 to 13]	-5 [-10 to 1]	.008
E/e' medial	-1.6 [-3.5 to 0.3]	-1.3 [-3.1 to 0.5]	-0.3 [-2.2 to 1.6]	.18
e' medial, cm/s	0.4 [-0.3 to 1.1]	0.3 [-0.2 to 0.7]	0.1 [-0.6 to 0.7]	.43
LAVI, mL/m²	0.2 [-2.1 to 2.5]	1.2 [-1.2 to 3.6]	-1.0 [-3.7 to 1.7]	.56
NT-proBNP, pg/mL	-193 [-510 to 124]	-182 [-535 to 171]	-11 [-282 to 261]	.41
KCCQ QoL domain	0.1 [-8.5 to 8.8]	5.6 [-2.2 to 13.4]	-5.5 [-13.8 to 2.8]	.34
Change baseline to 12 months				
Peak $\dot{V}O_2$, mL/min/kg	1.7 [0.3 to 3.0]	1.1 [-0.4 to 2.6]	0.6 [-0.9 to 2.1]	.07
$\dot{V}E/\dot{V}CO_2$ slope	0.6 [-1.6 to 2.8]	-2.1 [-4.2 to -0.1]	2.7 [0.4 to 5.0]	.05
Workload at VT1, watts	8 [3 to 14]	4 [-1 to 10]	4 [-2 to 10]	.01
E/e' medial	-1.8 [-3.5 to -0.2]	-0.4 [-2.2 to 1.5]	-1.5 [-3.4 to 0.5]	.15
e' medial, cm/s	0.6 [0.0 to 1.2]	0.2 [-0.4 to 0.7]	0.4 [-0.2 to 1.1]	.16
LAVI, mL/m²	0.9 [-3.2 to 5.1]	1.1 [-1.7 to 3.9]	-0.2 [-4.4 to 4.1]	.73
NT-proBNP, pg/mL	-256 [-611 to 99]	-197 [-567 to 173]	-59 [-286 to 168]	.40
KCCQ – QoL [a]	3.8 [-5.2 to 12.9]	13.8 [3.7 to 23.8]	-9.9 [-21.3 to 1.4]	.01

[a] higher scores indicate better quality of life (score range 1-100, minimial clinically important differences: 5 points); HIIT: High Intensity Interval Training, MCT: Moderate Continuous Training, Control: Guideline Control, CI: Confidence Interval, $\dot{V}O_2$: oxygen consumption, $\dot{V}E/\dot{V}CO_2$ slope: minute ventilation to carbon dioxide output slope, VT1: ventilatory threshold, E: peak velocity blood flow from ventricular relaxation in early diastole, e': mitral annular early diastolic velocity, LAVI: Left atrial volume index, NT-proBNP: N-terminal prohormone of brain natriuretic peptide, KCCQ: Kansas City Cardiomyopathy Questionnaire, QoL: Quality of life

eTable 8: List of cardiovascular and the most common non-cardiovascular Adverse Events for High Intensity Interval Training (HIIT), Moderate Continuous Training (MCT) and Guideline Control

	HIIT		MCT		Guideline Control	
	No. of Events	No. (%) of Participants	No. of Events	No. (%) of Participants	No. of Events	No. (%) of Participants
Adverse Events	**80**	**36 (62%)**	**79**	**39 (67%)**	**50**	**27 (45%)**
Cardiovascular	**32**	**14 (24%)**	**29**	**17 (29%)**	**19**	**12 (20%)**
Heart Failure related	**15**	**7 (12%)**	**13**	**6 (10%)**	**10**	**6 (10%)**
Worsening heart failure	4	3 (5%)	5	3 (5%)	6	3 (5%)
Atrial fibrillation	9	4 (7%)	7	3 (5%)	3	2 (3%)
Pleural effusion	1	1 (2%)	-	-	1	1 (2%)
Ventricular arrhythmias	-	-	1	1 (2%)	-	-
Cardiac arrest / death	1	1 (2%)	-	-	-	-
Other cardiovascular	**17**	**10 (8%)**	**16**	**12 (21%)**	**9**	**9 (15%)**
Acute coronary syndrome	4	4 (7%)	4	3 (5%)	5	5 (8%)
Supraventricular arrhythmias	2	1 (2%)	1	1 (2%)	1	1 (2%)
Hypertension	-	-	6	4 (7%)	-	-
Hypotension	2	1 (2%)	2	2 (3%)	-	-
Peripheral artery disease / Occlusion of peripheral bypass	2	1 (2%)	-	-	-	-
Thromboembolic occlusion of a femoral artery	-	-	-	-	1	1 (2%)
Sinus bradycardia	1	1 (2%)	1	1 (2%)	-	-
Cardiac syncope	1	1 (2%)	1	1 (2%)	-	-
Pulmonary embolism	1	1 (2%)	-	-	-	-
Deep vein thrombosis	1	1 (2%)	-	-	-	-
Ventilation-perfusion mismatch	1	1 (2%)	-	-	-	-
Endocarditis	-	-	1	1 (2%)	-	-
Dilated aorta with suspected dissection	1	1 (2%)	-	-	-	-
Transient ischemic attack	1	1 (2%)	-	-	-	-
3rd degree AV block	-	-	-	-	1	1 (2%)
Pulmonary hypertension	-	-	-	-	1	1 (2%)
Non-cardiovascular	**48**	**29 (50%)**	**50**	**31 (53%)**	**31**	**19 (32%)**
Respiratory tract infections	7	7 (12 %)	11	10 (17 %)	3	3 (5 %)
Knee / Hip pain (unrelated to falls)	8	7 (12 %)	2	2 (3 %)	1	1 (2 %)
Events related to falls	2	2 (3 %)	5	5 (9 %)	2	2 (3 %)
Back pain	3	3 (5 %)	2	2 (3 %)	2	2 (3 %)
Other non-cardiovascular [a]	28	20 (34 %)	30	22 (38 %)	23	16 (27 %)

[a] including events that occurred less than 5 times

eTable 9: List of Serious Adverse Events (SAEs) for High Intensity Interval Training (HIIT), Moderate Continuous Training (MCT) and Guideline Control

	HIIT		MCT		Guideline Control	
	No. of Events	**No. (%) of participants**	**No. of Events**	**No. (%) of participants**	**No. of Events**	**No. (%) of participants**
Serious Adverse Events (SAEs)	**33**	**18 (31%)**	**28**	**18 (31%)**	**27**	**16 (27%)**
Cardiovascular SAEs	**21**	**10 (17%)**	**18**	**12 (21%)**	**14**	**10 (17%)**
Heart Failure related	**7**	**5 (9%)**	**8**	**4 (7%)**	**5**	**3 (5%)**
Worsening heart failure	2	2 (3%)	3	2 (3%)	4	2 (3%)
Atrial fibrillation	3	2 (3%)	4	2 (3%)	-	-
Pleural effusion	1	1 (2%)	-	-	1	1 (2%)
Ventricular arrhythmias	-	-	1	1 (2%)	-	-
Cardiac arrest / death	1	1 (2%)	-	-	-	-
Other cardiovascular	**14**	**8 (14%)**	**10**	**8 (14%)**	**9**	**9 (15%)**
Acute coronary syndrome	3	3 (5%)	4	3 (5%)	5	5 (8%)
Supraventricular arrhythmias	2	1 (2%)	1	1 (2%)	1	1 (2%)
Hypertension	-	-	2	2 (3%)	-	-
Peripheral artery disease occlusion of peripheral bypass	2	1 (2%)	-	-	-	-
Thromboembolic occlusion of a femoral artery	-	-	-	-	1	1 (2%)
Sinus bradycardia	1	1 (2%)	1	1 (2%)	-	-
Cardiac Syncope	1	1 (2%)	1	1 (2%)	-	-
Pulmonary embolism	1	1 (2%)	-	-	-	-
Deep vein thrombosis	1	1 (2%)	-	-	-	-
Ventilation-perfusion mismatch	1	1 (2%)	-	-	-	-
Endocarditis	-	-	1	1 (2%)	-	-
Dilated aorta	1	1 (2%)	-	-	-	-
Transient ischemic attack	1	1 (2%)	-	-	-	-
3rd degree AV block	-	-	-	-	1	1 (2%)
Pulmonary hypertension	-	-	-	-	1	1 (2%)
Non-cardiovascular SAEs	**12**	**10 (17%)**	**10**	**9 (16%)**	**13**	**9 (15%)**
Orthopedic	**1**	**1 (2%)**	**4**	**4 (7%)**	**1**	**1 (2%)**
Femur fracture	-	-	1	1 (2%)	-	-
Biceps tendon rupture	-	-	1	1 (2%)	-	-
Subacromial syndrome	-	-	1	1 (2%)	-	-
Inflammatory arthritis	-	-	1	1 (2%)	-	-
Gonarthrosis	1	1 (2%)	-	-	-	-
Bacterial osteomyelitis	-	-	-	-	1	1 (2%)

eTable 9 continued…

	HIIT		MCT		Guideline Control	
	No. of Events	No. (%) of participants	No. of Events	No. (%) of participants	No. of Events	No. (%) of participants
Pulmonological	3	2 (3%)	1	1 (2%)	1	1(2%)
COPD exacerbation	2	1 (2%)	-	-	-	-
Pleural effusion	-	-	1	1 (2%)	-	-
Pneumonia	-	-	-	-	1	1 (2%)
Mantel cell lymphoma	1	1 (2%)	-	-	-	-
Gastroenterological	3	3 (5%)	3	3 (5%)	4	4 (7%)
Viral gastro-enteritis	2	2 (3%)	1	1 (2%)	-	-
Gastritis	-	-	1	1 (2%)	1	1 (2%)
Gastric ulcer	-	-	1	1 (2%)	-	-
Symptomatic Choledocholithiasis	1	1 (2%)	-	-	-	-
Diabetic gastroparesis	-	-	-	-	1	1 (2%)
Diverticulitis	-	-	-	-	1	1 (2%)
Abdominal wall hernia	-	-	-	-	1	1 (2%)
Gynecological	-	-	-	-	1	1 (2%)
Ovary cysts	-	-	-	-	1	1 (2%)
Urological/ Nephrological	2	1 (2%)	-	-	2	2 (3%)
Stricture of the urethra	2	1 (2%)	-	-	-	-
Acute renal failure	-	-	-	-	1	1 (2%)
Nephrolithiasis	-	-	-	-	1	1 (2%)
Endocrinological/ Metabolic	2	2 (3%)	-	-	3	3 (5%)
Conn´s syndrome	1	1 (2%)	-	-	-	-
Hypokalemia	-	-	-	-	1	1 (2%)
Hypothyroidism	1	1 (2%)	-	-	-	-
Metabolic disturbance in diabetes	-	-	-	-	1	1 (2%)
Hypoglycemia	-	-	-	-	1	1 (2%)
Neurological	1	1 (2%)	2	2 (3%)	1	1 (2%)
Concussion	1	1 (2%)	1	1 (2%)	-	-
Subdural hematoma	-	-	-	-	1	1 (2%)
Epileptical attack	-	-	1	1 (2%)	-	-

eReferences

1. R Development Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria2019.

2. van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate Imputation by Chained Equations in R. 2011;45:67.

3. Some additional multiple imputation functions, especially for mice. R package version 3.6-21. 2019. at https://CRAN.R-project.org/package=miceadds.)