

CIRCULATION AHA/2016/022924

Ellingsen – High Intensity Interval Training in Heart Failure

SUPPLEMENTAL MATERIAL

Tables S1-S4

Table S1. Echocardiographic Outcomes.

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

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	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.

^{AA}Sudden dyspnea and death at home week 7. ^{AB}Atrial tachycardia week 3, worsening of heart failure (WHF) week 10. ^{AC}Two patients had single admissions for WHF week 1,7. ^{AD}WHF week 12. ^{AE}Patient 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. ^{AF}WHF week 8. ^{AG}WHF week 7. ^{AH}One 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. ^{AI}One admission for atrial arrhythmia week 1 and one for WHF week 36. ^{AJ}Atrial arrhythmia week 12. ^{AK}Three patients with admissions for atrial arrhythmia week 4, 5, 16 and one for WHF week 40. ^{AL}One admission for ventricular arrhythmia with ICD discharge week 4 and one for atrial arrhythmia week 40. ^{AM}Patient had one admission for ventricular arrhythmia without DC shock week 10 and two admissions for gout week 2, 5. ^{AN}Chest pain week 8. ^{AO}Chest pain week 2. ^{API}ICD repair week 12. ^{AQ}Syncope week 12.

^{BA}Chest pain week 42 without any sign of cardiopulmonary disease, died of abdominal aortic aneurysm week 52. ^{BB}Died of ventricular arrhythmia, no further details given week 52. ^{BC}One 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. ^{BD}One 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. ^{BE}Six 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. ^{BF}One patient had two admissions for WHF after week 19. ^{BG}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. ^{BH}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. ^{BI}Atrial arrhythmia week 22. ^{BJ}Atrial arrhythmia week 46. ^{BK}Two patients had single admissions for ventricular arrhythmias week 13, 28 week. One had ICD discharge, the other not. ^{BL}Two patients had single admissions for ventricular arrhythmias week 13- 52. One had ICD discharge, the other not. ^{BM}Single admission for ventricular arrhythmia without DC shock week 52. ^{BN}Chest pain / angina pectoris week 22.

^{B0}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.

^{CA}Fell 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.

^{DA}Died 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-cardiovascular renal failure week 19.