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FULL RESEARCH PAPER
Cardiac Rehabilitation

Combined aerobic/resistance/inspiratory muscle training as the 'optimum' exercise programme for patients with chronic heart failure: ARISTOS-HF randomized clinical trial

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Aims An 'optimum' universally agreed exercise programme for heart failure (HF) patients has not been found. ARISTOS-HF randomized clinical trial evaluates whether combined aerobic training (AT)/resistance training (RT)/inspiratory muscle training (IMT) (ARIS) is superior to AT/RT, AT/IMT or AT in improving aerobic capacity, left ventricular dimensions, and secondary functional outcomes.

Methods and results Eighty-eight patients of New York Heart Association II–III, left ventricular ejection fraction ≤35% were randomized to an ARIS, AT/RT, AT/IMT, or AT group, exercising 3 times/week, 180 min/week for 12 weeks. Pre- and post-training, peakVO_2 was evaluated with cardiopulmonary exercise testing, left ventricular dimensions using echocardiography, walking distance with the 6-min walk test (6MWT), quality of life by the Minnesota Living with HF Questionnaire (MLwHFQ), while a programme preference survey (PPS) was used. Seventy-four patients of [mean 95% (confidence interval, CI)] age 66.1 (64.3–67.9) years and peakVO_2 17.3 (16.4–18.2) mL/kg/min were finally analysed. Between-group analysis showed a trend for increased peakVO_2 (mL/kg/min) [mean contrasts (95% CI)] in the ARIS group [ARIS vs. AT/RT 1.71 (0.163–3.25)(.), vs. AT/IMT 1.50 (0.0152–2.99)(.), vs. AT 1.38 (-0.142 to 2.9)(.)], additional benefits in circulatory power (mL/kg/min·mmHg) [ARIS vs. AT/RT 376 (60.7–690)*, vs. AT/IMT 423 (121–725)*, vs. AT 345 (35.4–656)*], left ventricular end-systolic diameter (mm) [ARIS vs. AT/RT -2.11 (-3.65 to (-0.561))*, vs. AT -2.47 (-4.01 to (-0.929))**], 6MWT (m) [ARIS vs. AT/IMT 45.6 (18.3–72.9)**, vs. AT 55.2 (27.6–82.7)****], MLwHFQ [ARIS vs. AT/RT -7.79 (-11 to (-4.62))****, vs. AT -8.96 (-12.1 to (-5.84))****], and in PPS score [mean (95% CI)] [ARIS, 4.8 (4.7–5) vs. AT, 4.4 (4.2–4.7)*] [(.) $P \leq 0.1$; *$P \leq 0.05$; **$P \leq 0.01$; ***$P \leq 0.001$; ****$P \leq 0.0001$].

Conclusion ARISTOS-HF trial recommends exercise training for 180 min/week and supports the prescription of the ARIS training regime for HF patients (Clinical Trial Registration: http://www.clinicaltrials.gov. ARISTOS-HF Clinical Trial number, NCT03013270).

Keywords Heart failure • Exercise training • Rehabilitation • Aerobic/Resistance/Inspiratory (ARIS) training

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Introduction

Exercise training is highly recommended by current guidelines to improve functional capacity and symptoms in patients with heart failure (HF).[1] Although moderate continuous aerobic training (MCAT) is the best established training modality,[2] the randomized HF-ACTION trial demonstrated significant but modest improvements of MCAT in exercise capacity and self-reported health status compared with usual care.[3,4] A hypothesis of increasing the training intensity to improve outcomes was tested by the multicentre randomized SMARTEX-HF trial which showed that high-intensity interval training (HIIT) was not superior to MCAT in improving exercise capacity and left ventricular dimensions.[5] A number of studies also report that addition of either resistance training (RT) or inspiratory muscle training (IMT) to aerobic training (AT) (MCAT or HIIT) is safe and produces enhanced benefits in skeletal muscle indices, exercise tolerance, and quality of life (QoL) compared to AT alone.[6–9] Thus, different approaches in exercise prescription are currently used and a universally agreed 'optimum' exercise programme for HF patients has not yet been found.

This background in conjunction with preliminary findings from our laboratory of the incremental benefits of a triple exercise programme of AT/RT/IMT (ARIS) over AT[10] provided the incentive to suggest that recruiting more muscle into exercise training may improve training efficacy[11] and to introduce the 'ARIS muscle training hypothesis'.[12] The ARIS hypothesis states that 'exercise and functional intolerance in patients with HF are associated not only with reduced muscle endurance but also with both reduced muscle strength and decreased inspiratory muscle function, contributing to weakness, dyspnoea, fatigue, and low aerobic capacity, and that the ARIS training programme may result in maximal exercise pathophysiological and functional benefits in HF patients'.[12]

The multicentre ARISTOS-HF (Aerobic, Resistance, InSpiratory Training OutcomeS in Heart Failure) randomized trial was initiated to test this hypothesis and to compare ARIS to AT/RT, AT/IMT and AT, maintaining an equal exercise time among supervised programmes and evaluating both functional and cardiac indices in order to provide the evidence for the 'optimum' exercise programme for HF patients.

Methods

Study design

The ARISTOS-HF trial is a randomized clinical trial conducted at two centres in Greece and one centre in Poland (Onassis Cardiac Surgery Center, Athens, Greece; National Institute of Cardiology, Telecardiology Center, Warsaw, Poland and Asklepieion General Hospital, Athens, Greece) between January 2017 and May 2020. The Clinical Trials database registration reports 88 randomized patients. Details of the rationale and design have previously been published.[12] The trial complies with the Declaration of Helsinki and approved by the Hospital Ethics Committee of each participating centre. Written informed consent was obtained from all patients prior to study entry. Statistical analyses were blindly performed by an independent investigator at the coordinating centre (Onassis Cardiac Surgery Center). (Clinical Trial Registration: http://www.clinicaltrials.gov. ARISTOS-HF Clinical Trial number, NCT03013270).

Patients and interventions

Patients were enrolled from outpatient HF clinics and screened for eligibility in each hospital registry. Exclusion criteria included uncontrolled arrhythmia, pulmonary oedema, or pulmonary congestion in the last 30 days, cognitive, neurological, or orthopaedic limitations, respiratory infection during 30 days before the start of the study and pulmonary limitations (e.g. chronic obstructive pulmonary disease). Eligible stable patients aged 18–80 years with symptomatic New York Heart Association (NYHA) class II–III, with chronic HF under optimum medical treatment and a left ventricular ejection fraction (LVEF) ≤35% were randomized 1:1:1:1 through block randomization to a 12-week programme of supervised training of ARIS or AT/IMT or AT/RT or AT stratified by each study centre. Patients were included at a documented chronic stage of the disease[1] and while exercise training was the major intervention, disease management included other rehabilitation cores such as psychosocial support, nutrition counselling or home visits as required. All patients in each group underwent three supervised sessions for 60 min each and a total of 180 min/week. Continuous AT was performed on a treadmill or a bicycle at a moderate intensity of 60–80% of max heart rate (HR) for all groups, and RT and IMT according to current exercise guidelines and recommendations.[13]

ARIS training consisted of 30 min AT combined with 10 min moderate intensity RT at 50% of I repetition maximum (IRM) for quads training and upper limb exercises (elbow flex/shoulder flex/abd) using dumbbells (1–2 kg) (12–15 reps/3 sets) and with 20 min high-intensity IMT at 60% of maximal inspiratory pressure/sustained maximal inspiratory pressure (PI_{max}/SPI_{max}) using a flow-resistive loading system (TRAINAIR®) as previously described.[10] The IRM was recalculated every second week while PI_{max} and SPI_{max} were measured in each training session.[10] In the AT/IMT group, training consisted of 30 min AT combined with 30 min IMT as above. The AT/RT group underwent 30 min AT combined with 30 min RT at an intensity of 50% of IRM for quads training, pectoralis m, serratus anterior m, and latissimus dorsi m and upper limb exercises (elbow flex/shoulder flex/abd) using dumbbells (1–2 kg) (12–15 reps/3 sets). The AT group received 30 min training combined with 30 min callisthenics with the patients progressing to a total of 60 min AT within the first 2 weeks of training. Patients who were unable to achieve 60 min continuous AT were allowed to perform AT in two 30 min periods using treadmill and/or bicycle.

Study endpoints

Measurements were taken at baseline and after 12 weeks of training. Primary endpoints were changes in peak oxygen consumption ($peakVO_2$) and in left ventricular dimensions [left ventricular end-diastolic diameter (LVEDD) and left ventricular end-systolic diameter (LVESD)]. Secondary endpoints included changes in walking distance, QoL and LVEF as well as programme preference evaluation. Other study outcomes included assessment of perceived dyspnoea, limb, and respiratory muscle function.

Clinical assessments

A symptom limited cardiopulmonary exercise testing (CPX) with respiratory gas exchange measurements was performed using the Medgraphics CPX/MAX (Medical Graphics Corp., St. Paul, MN, USA) or using a Schiller treadmill (Carrollton, USA) which was connected to a computerized breath-by-breath spiroergometry system (ZAN 600, ZAN Messgerate GmbH, Germany) to evaluate $peakVO_2$. Patients were tested on a treadmill according to the Dargie protocol which is based on an exponential increment in workload[14] or a ramp protocol, as recommended by the American Association of Cardiovascular and Pulmonary Rehabilitation.[15] The same protocol was always used for each subject at

baseline and at the end of the 12 weeks of training. Pulmonary gas exchange was analysed breath by breath and averaged every 10 s. On the morning of each test day, gas and volume calibrations were executed. Using a 12-lead electrocardiogram, HR was monitored. PeakVO_2 during exercise was defined as the mean value during the last minute/30 s of exercise. The VO_2 at ventilatory threshold was determined at the point at which expired carbon dioxide increased in a non-linear fashion relative to the rate of oxygen consumption according to the V-slope method.

Standard two-dimensional resting echocardiography using Ultrasound Vivid 7 or 6, General Electric Healthcare, Fairfield, CT, USA, was performed in all patients. The biplane Simpson's method in an apical four-chamber view was used to estimate LVEF (%), while LVEDD (mm) and LVESD (mm) were measured using the Teichholz method.

Walking distance was also evaluated with the 6-min walk test (6MWT), dyspnoea was assessed at the end of the 6MWT ($dyspnoea_{6MWT}$) and of the CPX ($dyspnoea_{CPX}$) with the Borg scale (0–10), and QoL using the Minnesota Living with Heart Failure Questionnaire (MLwHFQ).[16,17] A programme preference survey (PPS) was performed at the end of the 12 weeks using a standardised 5-point Likert scale question 'how much did you enjoy the intervention' by asking the patients to independently grade their programme preference as follows: 1 = very little, 2 = little, 3 = moderate, 4 = very much, and 5 = excellent.[18]

Measurements of inspiratory muscle strength (PI_{max}, mmHg) and inspiratory work capacity (SPI_{max}, $cmH_2O/s/10^3$) were made using an electronic pressure manometer and computer software providing a pressure accuracy of ±0.1% (TRAINAIR®, Project Electronics Ltd, London, UK), while quadriceps muscle strength (QMS) was evaluated with the IRM and quadriceps muscle endurance (QME) as the product of the 50% of IRM multiplied with the number of maximal repetitions as previously described.[10]

Statistical analysis

At design phase, target sample size was estimated to be 22 patients for each group for a power of 84% for a 10% peakVO_2 between-group maximum difference and 93% for a 2 mm respective difference in LVEDD and LVESD. All continuous variables are expressed as the mean along with 95% confidence intervals (CIs). Baseline comparisons between groups were performed using analysis of variance (age, body mass index, peakVO_2, PI_{max}, QMS, and LVEF) and the χ^2 test for the categorical variables (gender, NYHA class, disease aetiology, and medication). The paired *t*-test was used to assess training-induced changes (baseline vs. 12 weeks) within a particular group. Normality was tested using P–P plots. The endpoint analysis was performed through a linear model using the 12-week values as outcome and baseline values as covariates. Between-group analysis is reported as estimated marginal mean contrasts along with 95% CI. In case of significant group-covariate interaction, which reflects different exercise programme effect based on baseline values, interaction slopes are provided and contrasts are given for mean baseline values (Supplementary material online, *Figures S1–S5*). Further between-group analysis (AT/IMT vs. AT; AT/RT vs. AT) is also included in the Supplementary material online, *Table S1*. Pairwise Wilcoxon test was used for PPS comparison. The inflation of type I error due to multiple comparisons was controlled using the Hommel procedure. Statistical analyses were performed with R version 3.6.3 and RStudio version 1.2.5033.

Results

After initial exclusions, 88 patients were included in the ARIS, AT/IMT, AT/RT, and AT groups. One patient died due to respiratory infection and 13 patients withdrew or were lost to follow-up. Thus, 74 patients were assessed after 12 weeks and were included in the present analysis (*Figure 1*). Baseline characteristics were similar in all groups (*Table 1*). Mean age of the 74 patients was 66.1 (64.3–67.9) years with 93% males and the rest females, 55% were in NYHA II and 45% in NYHA III, 64% had HF of ischaemic aetiology, and the rest dilated cardiomyopathy, mean peakVO_2 was 17.3 (16.4–18.2) mL/kg/min and LVEF was 28.4 (27–29.7) %. Medications were not changed during the study protocol. There were no missing data in the resulting database.

Primary endpoints

Between-group analysis did not show significant differences in peakVO_2 for any of the interventions although there was a trend ($P \leq 0.1$) for increased peakVO_2 in the ARIS group compared to all groups (*Figure 2A*). Significant benefits in circulatory power [product of peakVO_2 and peak systolic blood pressure (SBP_{peak})] were demonstrated for the ARIS group compared to all groups. The CPX time further improved in the ARIS group compared to AT and AT/RT groups and a trend ($P \leq 0.1$)of increased CPX time and SBP_{peak} was shown for the ARIS when compared with the AT/IMT group (*Table 2*). Within-group analysis showed significant improvements in peakVO_2 for all interventions and in specific CPX parameters (*Table 3*). Between-group analysis showed a significant benefit in LVESD for the ARIS group when compared with the AT and AT/RT groups (*Figure 2B*) (*Table 2*). Within-group analysis showed improvements in LVEDD and in LVEF for all interventions while LVESD improved only in the ARIS and AT/IMT groups (*Table 3*). Supplementary between-group analysis did not show significant differences in CPX and echocardiography parameters for the AT/IMT and AT/RT groups compared to the AT group (Supplementary material online, *Table S1*).

Secondary endpoints and other study outcomes

Between-group analysis demonstrated significant benefits for the ARIS group in 6MWT and MLwHFQ and in all the other outcomes as well as a trend for improved NYHA compared to AT. ARIS group was superior to AT/IMT group in improving 6MWT, PI_{max} and limb muscle indices while $dyspnoea_{6MWT}$ improved more in the AT/IMT group compared to ARIS. ARIS group showed significant benefits in MLwHFQ, $dyspnoea_{CPX}$ and inspiratory muscle indices compared to AT/RT group (*Table 2*). The PPS score was significantly higher in the ARIS group compared to AT (*Table 3*). Changes in secondary endpoints are shown in *Figure 3A–C*. Within-group benefits are shown in *Table 3*. Supplementary between-group analysis showed significant benefits for AT/IMT in MLwHFQ, $dyspnoea_{6MWT}$, $dyspnoea_{CPX}$, NYHA, and inspiratory muscle indices compared to AT while for AT/RT in 6MWT, $dyspnoea_{6MWT}$, and limb muscle indices in comparison with AT (Supplementary material online, *Table S1*).

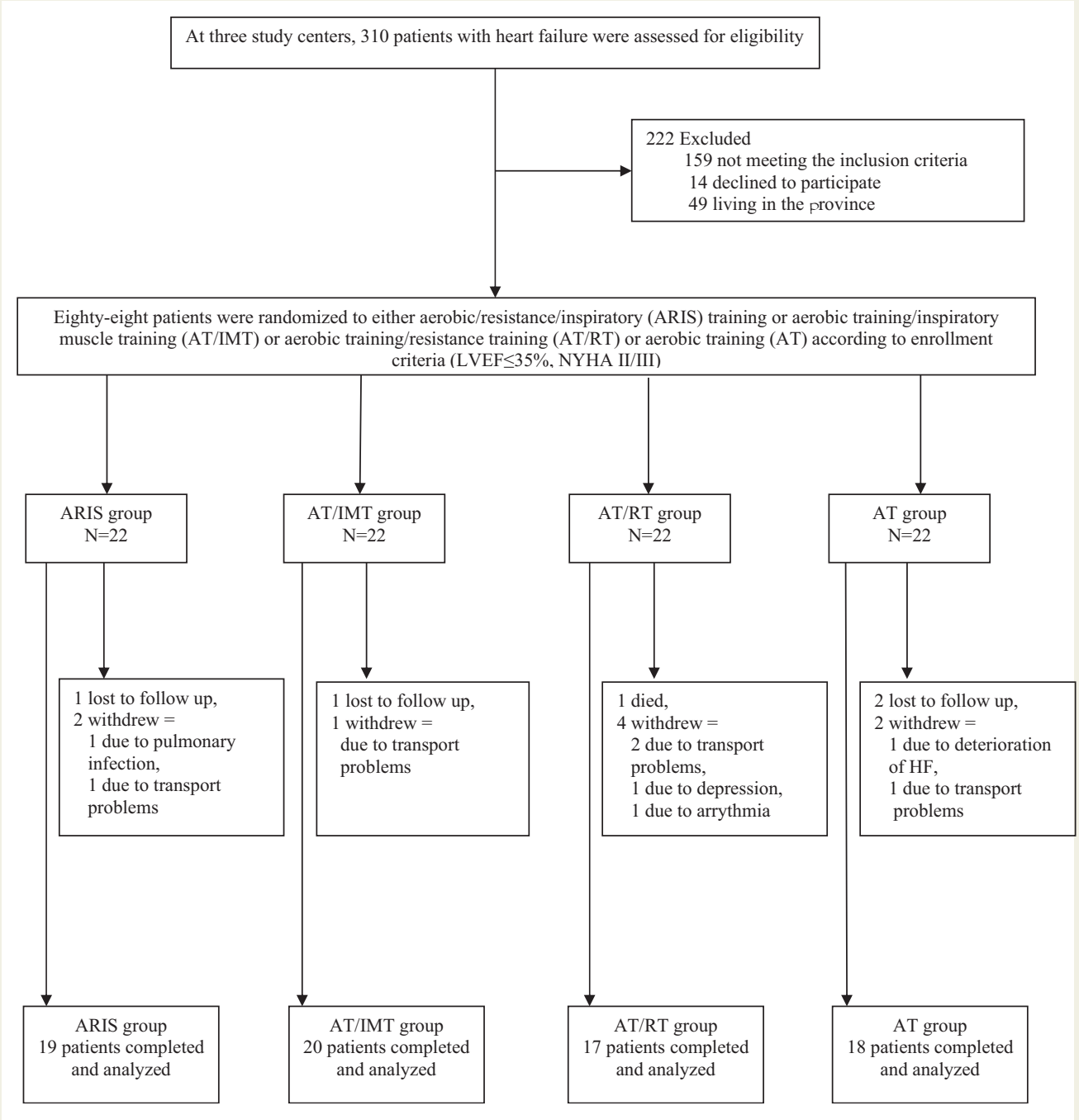

Figure 1 Study enrolment and randomization (ARISTOS-HF CONSORT flow diagram).

Discussion

The present study is the first multicentre randomized trial to evaluate widely used exercise modalities in patients with chronic systolic HF aiming to identify an 'optimus universalis' exercise training programme for HF. The first observation is that all interventions resulted in an improvement of peakVO_2 and LVEF with no significant differences between groups, demonstrating the efficacy of exercise training and the importance of participating in these programmes for HF patients. Improvement was shown after 12 weeks of training while there is evidence that exercise training in patients with chronic HF may be highly effective if performed for a longer period of time (e.g. 6 months).[19] A definite trend was shown for an increased peakVO_2 in the ARIS group compared to all the other groups while percentage increase in peakVO_2 was 19% for the ARIS, 9% for the AT/RT, 11% for the AT/IMT and 10% for the AT group. It is worth mentioning that every 6% increase in peakVO_2 adjusted for significant predictors was shown to be associated with a 5% decrease in all-cause mortality

Table 1 Characteristics of the patients at baseline[a]

Characteristic	ARIS group ($n = 19$)	AT/IMT group ($n = 20$)	AT/RT group ($n = 17$)	AT group ($n = 18$)
Age (years)	63.9 (59.8–68)	68.1 (65.2–71)	67.5 (64–70.9)	64.8 (60.4–69.1)
Males/females	17/2	20/0	16/1	16/2
BMI (kg/m^2)	28.6 (26.7–30.4)	29 (27.4–30.7)	28.6 (26.8–30.3)	26.9 (25.4–28.5)
NYHA class, *n* (%)				
II	9 (47)	11 (55)	10 (59)	11 (61)
III	10 (53)	9 (45)	7 (41)	7 (39)
Disease aetiology, *n* (%)				
DCM	6 (32)	8 (40)	5 (29)	8 (44)
ICM	13 (68)	12 (60)	12 (71)	10 (66)
LVEF (%)	28.3 (25.9–30.7)	28.8 (25.1–32.5)	29.6 (27.2–32.1)	26.8 (24.7–28.8)
peakVO_2 (mL/kg/min)	17.4 (15.2–19.5)	16.6 (15–18.3)	17. 4 (15.6–19.3)	18 (15.9–20)
PI_{max} (cmH_2O)	82.6 (73.9–91.3)	85.6 (75.6–95.5)	79.8 (70.3–89.4)	83.1 (75.3–90.8)
QMS (kg)	23.5 (20.2–26.7)	21.3 (18.5–24.1)	23.2 (19.6–26.8)	22.1 (18.7–25.5)
Medication, *n* (%)				
ACE inhibitors	18 (95)	20 (100)	15 (88)	18 (100)
Beta-blockers	16 (84)	20 (100)	15 (88)	16 (89)
Antiarrhythmic drugs	4 (21)	5 (25)	4 (24)	3 (17)
Diuretics	17 (89)	20 (100)	16 (94)	18 (100)
MRA	12 (63)	15 (75)	12 (71)	13 (72)
ARB	1 (5)	1 (5)	0 (0)	2 (11)

[a]No significant differences (P = ns) were found between baseline characteristics in study groups.
ARB, angiotensin II receptor blockers; BMI, body mass index; DCM, dilated cardiomyopathy; ICM, ischaemic cardiomyopathy; LVEF, left ventricular ejection fraction; MRA, mineral corticoid receptor antagonist; NYHA, New York Heart Association; peak VO_2, peak oxygen consumption; PI_{max}, maximal inspiratory pressure; QMS, quadriceps muscle strength.

and all-cause hospitalization in HF-ACTION trial.[20] The higher increase of peakVO_2 in the ARIS group may be of enhanced importance considering that although the four groups underwent training for equal exercise time, unequal durations of different exercise modalities such as AT, might have given preference to the AT group to further improve peakVO_2. Furthermore, a significant benefit in circulatory power was shown in the ARIS group compared to all the other groups while patients in the ARIS group achieved a higher exercise time during CPX and improved most of the CPX indices among all groups. Circulatory power expressing both peakVO_2 and SBP_{peak} might reflect the performance of the cardiac pump and therefore the cardiac contractile reserve at peak exercise and is considered as a surrogate of cardiac power and a powerful predictor of mortality.[21] The combination of both RT and IMT with AT may have enhanced the aerobic response to training in the ARIS group since selective IMT or RT are known to improve peakVO_2 in HF patients.[7,22,23] Suggested mechanisms include favourable modification of a diaphragmatic metaboreflex with improvements in limb blood flow and perception of dyspnoea for IMT and improved perfusion and skeletal muscle metabolism for RT.[6,7,11,12,24]

Nevertheless, the benefits of the other modes of exercise and especially of the most prevalently prescribed AT should be acknowledged. Improvement in peakVO_2 was higher for the AT group in the present study compared to HF-ACTION and SMARTEX-HF trials in which peakVO_2 improved by 0.6 mL/kg/min (4% increase) and 0.8 mL/kg/min (5% increase) with the patients however, exercising by 75 min/week and 39 min/week respectively less in these studies compared to the ARISTOS-HF trial.[3,5] Although this is a random finding, it is possible that longer exercise training time may also play a significant role towards improvement in peakVO_2 especially when studies indicate a less pronounced pathological skeletal muscle fibre shift in the era of optimal medical therapy.[25]

With respect to the other primary endpoints, an improvement in LVEDD was observed for all groups while a significant decrease in LVESD was shown for the ARIS group compared to the AT/RT and AT but not to AT/IMT. However, a decrease found in LVESD in the AT/IMT group was not significant when compared with the AT group. Thus, the positive outcome in LVESD in the ARIS group may be explained by the contribution of both IMT and RT when added to AT. Both selective IMT and RT have been shown to decrease sympathetic activity resulting in a reduction in peripheral vascular resistance and cardiac afterload,[24,26,27] while combined AT/RT was superior to AT in improving flow-mediated vasodilation and improved neurohormonal and inflammatory activation in HF patients.[28–30] The Vent-HeFT trial also demonstrated enhanced benefits of combined AT/IMT compared to AT in N-terminal pro-B-type natriuretic peptide and C-reactive protein, markers which reflect myocardial stress and inflammatory status.[9] The demonstrated change in LVESD in the ARIS group may prove an important finding since a study in 568 patients with HF and LVEF ≤35% receiving optimal medical therapy reported that LVESD index was the strongest predictor of reverse remodelling.[31] Change in left ventricular dimensions could represent a more significant endpoint compared to peakVO_2 considering that a recent meta-analysis demonstrated that improvement in exercise

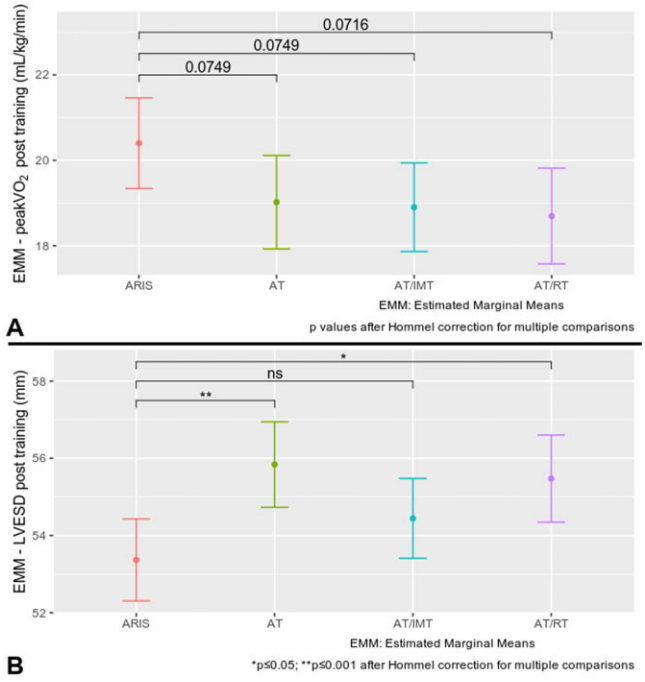

Figure 2 Primary endpoints. (*A*) Trend shown for increased peakVO_2 in the ARIS group compared to all groups. (*B*) Significant benefit shown for LVESD in the ARIS group compared to AT and AT/RT groups.

capacity (peakVO_2 and 6MWT distance) after exercise-based rehabilitation was a poor surrogate endpoint for mortality and hospitalization and had moderate validity as a surrogate for health-related quality of life,[32] although these findings may need further investigation.

Concerning secondary trial endpoints and outcomes, the ARIS programme resulted in significant benefits in both walking distance and QoL compared to AT, in walking distance compared to AT/IMT and in QoL compared to AT/RT. These benefits in the ARIS group may be attributed to additional improvements in inspiratory and limb muscle indices as well as in dyspnoea compared to different groups since exercise intolerance and poor QoL in HF patients have been associated with both muscle fatigue and/or exertional dyspnoea.[12,33] Thus, IMT and RT appear to present with key roles in improving inspiratory muscle performance and dyspnoea and in increasing limb muscle strength respectively, further improving QoL and facilitating daily life activities, indicating that both modalities should ideally complement AT, especially when a reduction in inspiratory and limb muscle function is commonly diagnosed in patients with chronic HF.[6,7,28–30,34]

The programme preference survey demonstrated that the ARIS training programme was preferred to AT, although not to AT/RT or AT/IMT. This finding may be related to the interchange of exercise modalities as previously reported[10] and could be of value in terms of improving long-term adherence to cardiac rehabilitation programmes. Diminished adherence and thus, low volume of training, has been characterized as the 'Achilles heel' of exercise training programmes possibly contributing to the modest findings of HF-ACTION trial as well as to the lack of maintenance of exercise benefits shown by the SMARTEX-HF trial.[3,5]

Considering the benefits of the ARIS programme among the other training programmes, ARIS implementation could be feasible in the real world targeting long-term home-based training, since devices for AT, RT and IMT are available and have been used before,[7,22,23] while tools such as telerehabilitation may facilitate further device evaluation and continuous patient monitoring.[35]

Limitations

The results of ARISTOS-HF trial should be interpreted in the context of the following potential limitations. Although the study design was double-masked, the trial was a behavioural intervention with the investigators having to deal with issues of multiple group training and despite the extensive efforts, blinding of the research personnel was not always possible. However, multicentre studies are more resistant to bias especially when compared with a single-centre setting, while both CPX and echocardiography investigators were masked to the assignments of the interventions. In addition, although conducted as a multicentre study, patient enrolment was slow and the patient number remains small, mainly attributed to practical difficulties arising from a four-arm behavioural intervention and to the lack of financial resources. Thus, considering the trend ($P = 0.07$) for increased peakVO_2 in the ARIS group in comparison with the other three groups, it is very likely that smaller number of patients finally analysed, diminished the study's ability to detect a statistical significant

Table 2 Between-group contrasts of ARIS vs. AT, vs. AT/IMT, vs. AT/RT

	ARIS vs. AT	ARIS vs. AT/IMT	ARIS vs. AT/RT
	Mean contrasts (95% confidence intervals)		
	CPX parameters (primary endpoint: peakVO_2)		
peakVO_2 (mL/kg/min)	**1.38 (−0.142 to 2.9)**	**1.50 (0.0152 to 2.99)**	**1.71 (0.163 to 3.25)**
Exercise time (min)	1.56 (0.739 to 2.38)****	0.776 (-0.0307 to 1.58)	0.980 (0.141 to 1.82)*
VE/CO_2 slope	-0.519 (-3.45 to 2.41)	-1.35 (-4.2 to 1.49)	0.995 (-1.94 to 3.93)
VT (mL/kg/min)	0.654 (-0.854 to 2.16)	0.919 (-0.562 to 2.4)	1.371 (-0.161 to 2.9)
VE (L/min)	3.66 (-4.55 to 11.9)	2.76 (-10.8 to 5.27)	5.18 (-3.12 to 13.5)
HR_{rest} (b.p.m)[a]	-1.41 (-0.585 to 3.4)	3.49 (-1.02 to 8)	1.01 (-3.71 to 5.73)
SBP_{peak} (mmHg)	6.66 (-2.03 to 15.3)	10.30 (1.84 to 18.8)	5.71 (-3.17 to 14.6)
CP (mL/kg/min. mmHg)	345 (35.4 to 656)*	423 (121 to 725)*	376 (60.7 to 690)*
	Echocardiography parameters (primary endpoints: LVEDD, LVESD)		
LVEF (%)	**−0.697 (−2.66 to 1.26)**	**−1.14 (−3.04 to 0.763)**	**−0.197 (−2.18 to 1.79)**
LVEDD (mm)	**−0.3643 (−1.78 to 1.05)**	**0.403 (−0.972 to 1.78)**	**0.0513 (−1.38 to 1.49)**
LVESD (mm)	**−2.47 (−4.01 to (−0.929))****	**−1.08 (−2.56 to 0.405)**	**−2.11 (−3.65 to (−0.561))***
	Secondary endpoints and other study outcomes		
PI_{max} (cmH_2O)	25.4 (19.5 to 31.3)****	6.45 (0.668 to 12.2)*	29.29 (23.3 to 35.3)****
SPI_{max} ($cmH_2O\ s^{-1}\ 10^{-3}$)[a]	105 (90.8 to 119)****	4.68 (-9.36 to 18.7)	108 (93 to 122)****
QMS (kg)	6.61 (4.45 to 8.78)****	6.22 (4.1 to 8.34)****	-0.597 (-2.79 to 1.59)
QME (kg.max reps)	47 (30.4 to 63.5)****	50.6 (34.5 to 66.7)****	-13.3 (-30.1 to 3.48)
6MWT (m)	**55.2 (27.6 to 82.7)*****	**45.6 (18.3 to 72.9)****	**-2.27 (-29.8 to 25.2)**
$Dyspnoea_{6MWT}$[a]	-1.13 (-1.56 to (-0.696))****	0.55 (0.127 to 0.974)*	-0.0966 (-0.565 to 0.372)
$Dyspnoea_{CPX}$[a]	-0.748 (-1.15 to (-0.349))***	-0.210 (-0.595 to 0.176)	-0.925 (-1.32 to (-0.529))****
NYHA[a]	-0.375 (-0.683 to (-0.0658))	-0.0234 (-0.327 to 0.28)	-0.286 (-0.612 to 0.0394)
MLwHFQ	**−8.96 (−12.1 to (−5.84))****	**−0.789 (−3.83 to 2.25)**	**−7.79 (−11 to (−4.62))****

Pre-specified endpoints in bold.
6MWT, 6-min walk test; CP, circulatory power; HR, heart rate; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic diameter; MLwHFQ, Minnesota Living with Heart Failure Questionnaire; NYHA, New York Heart Association; peakVO_2, peak oxygen consumption; PI_{max}, maximal inspiratory pressure; QME, quadriceps muscle endurance; QMS, quadriceps muscle strength; SBP, systolic blood pressure; SPI_{max}, sustained maximal inspiratory pressure; VT, ventilatory threshold.
*$P \le 0.05$; **$P \le 0.01$; ***$P \le 0.001$; ****$P \le 0.0001$ after Hommel correction for multiple comparisons.
[a]Contrasts for mean pre training values due to group-covariate interaction.

between-group difference in peakVO_2. However, the power of the study was maintained above 80% to detect significant differences in left ventricular dimensions as shown for LVESD, while significant differences were also demonstrated for secondary key endpoints. Another study limitation is that patients at different centres underwent CPX using different protocols (Dargie or ramp). Use of a treadmill (Dargie protocol) may be associated with a higher peakVO_2 measurement compared to a cycle ergometer (ramp protocol); however, the training-induced changes were always recorded using the same method. Furthermore, only 7% of the patients included in the study were women and although unintended, it constitutes a limitation of the generalization of the results. Future studies need to include women in a larger proportion. Inclusion of a usual care group may have also provided further information on the effectiveness of the interventions studied.

Conclusions

Based on the study findings, exercise training for 180 min/week is recommended for HF patients. The ARISTOS-HF trial found that the ARIS training programme was superior to other exercise programmes in improving the aerobic response to training, left ventricular dimensions towards reverse remodelling and secondary functional outcomes, supporting the prescription of the triple training regime for patients with chronic systolic HF.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology* online.

Table 3 Baseline and 12-week values

	ARIS group ($n = 19$)		AT/IMT group ($n = 20$)		AT/RT group ($n = 17$)		AT group ($n = 18$)	
	CPX parameters (primary endpoint: peakVO_2)							
	Baseline	**12 weeks**	**Baseline**	**12 weeks**	**Baseline**	**12 weeks**	**Baseline**	**12 weeks**
peakVO_2 (mL/kg/min)	**17.4 (15.2–19.5)**	**20.4 (18.3–22.6)******	**16.6 (15–18.3)**	**18.3 (16.6–20)****	**17.4 (15.6–19.3)**	**18.8 (17.1–20.5)***	**18 (15.9–20)**	**19.5 (17.4–21.7)***
Exercise time (min)	9.0/9 (7.89–10.3)	11.1 (9.94–12.2)****	8.08 (6.76–9.4)	9.58 (8.43–10.7)***	8.19 (6.86–9.52)	9.46 (8.46–10.4)**	8.9 (8.29–9.5)	9.39 (8.66–10.1)
VE/CO_2 slope	37.5 (34–41.1)	35.2 (32.5–37.8)*	34.6 (31.7–37.5)	34.8 (31.6–38)	36.3 (32.1–40.4)	33.4 (30.4–36.4)	34.2 (31.5–36.9)	33.8 (31.1–36.4)
VT (mL/kg/min)	15.4 (13.4–17.5)	17.4 (15–19.8)**	14 (12.5–15.5)	15.2 (13.4–17)	16 (14.2–17.8)	16.6 (14.8–18.4)	15.3 (13–17.7)	16.7 (14.4–19)**
VE (L/min)	53.4 (45.4–61.4)	62.6 (53.8–71.4)*	59.1 (48.5–69.8)	69.5 (59.7–79.3)**	53 (47.7–58.3)	57.1 (49.4–64.8)	57.3 (50.5–64.1)	61.7 (54.7–68.7)*
RER	1.05 (1–1.1)	1.06 (1.03–1.1)	1.05 (0.988–1.12)	1.08 (1.01–1.14)	1.04 (0.958–1.13)	1.06 (0.983–1.13)	1.1 (1.07–1.13)	1.11 (1.03–1.18)
HR_{rest} (b.p.m)	76.7 (70.5–83)	72.6 (68.6–76.6)	70.4 (65.1–75.7)	66.4 (62.9–69.8)	72.8 (68.5–77)	70 (67–73)*	64.8 (57–72.6)	65.8 (57.5–74.2)
HR_{peak} (b.p.m)	130 (117.6–142.4)	135.2 (125.4–144.9)	123.4 (113.5–133.4)	123 (113–133.1)	126.2 (115.5–137)	130.4 (121.7–139)	135.5 (126.4–144.6)	134.8 (125.3–144.4)
SBP_{rest} (mmHg)	111.3 (103.9–118.7)	108.3 (99.94–116.6)	108.4 (100.4–116.3)	108.2 (101.7–114.8)	113.6 (106.3–120.9)	109 (102.7–115.3)	113.1 (105.4–120.8)	108.6 (102.1–115.1)
SBP_{peak} (mmHg)	152.8 (144.8–160.8)	161.9 (152.4–171.4)***	151.5 (138.6–164.4)	150.6 (138.9–162.4)	144.7 (133.3–156.1)	150.2 (140.9–159.6)	150.3 (138.2–162.4)	153.4 (142.7–164.1)
CP (mL/kg/min·mmHg)	2650 (2306–2995)	3282 (2890–3673)****	2568 (2169–2968)	2799 (2409–3188)	2543 (2181–2905)	2828 (2511–3145)*	2719 (2235–3203)	2986 (2618–3355)*
	Echocardiography parameters (primary endpoints: LVEDD, LVESD)							
LVEF (%)	**28.3 (25.9–30.7)**	**29.9 (27.4–32.4)*****	**28.8 (25.1–32.5)**	**31.6 (27.7–35.4)****	**29.6 (27.2–32.1)**	**31.5 (28.9–34.1)****	**26.8 (24.7–28.8)**	**29.1 (25.7–32.4)***
LVEDD (mm)	**65.3 (61.9–68.7)**	**63.9 (60.6–67.2)****	**65.6 (61.4–69.9)**	**63.8 (59.6–68.1)***	**64.4 (60.8–67.9)**	**63 (59.9–66.1)****	**66.7 (64–69.5)**	**65.6 (62.8–68.4)****
LVESD (mm)	**55.1 (50.8–59.3)**	**52.5 (48.6–56.3)*****	**55.9 (51.5–60.3)**	**54.4 (49.8–58.9)***	**54 (49.2–58.8)**	**53.6 (48.7–58.5)**	**59 (55.9–62.1)**	**58.7 (55.8–61.5)**
	Secondary endpoints and other study outcomes							
PI_{max} (cmH_2O)	82.6 (73.9–91.3)	112 (102–122)****	85.6 (75.6–95.5)	108 (99.7–117)****	79.8 (70.3–89.4)	80.4 (71.2–89.5)	83.1 (75.3–90.8)	87 (78.4–95.6)**
SPI_{max} ($cmH_2O\ s^{-1}\cdot10^{-3}$)	308.2 (296.5–319.9)	412.9 (401.3–424.5)****	303.6 (291.8–315.4)	413.6 (396.3–430.9)****	315.3 (296.6–334)	310.9 (295.3–326.5)	313.3 (297.8–328.9)	312.8 (295.2–330.3)
QMS (kg)	23.5 (20.2–26.7)	29.8 (26.2–33.3)****	21.3 (18.5–24.1)	21.6 (18.7–24.5)	23.2 (19.6–26.8)	30.1 (26.2–34.1)****	22.1 (18.7–25.5)	21.9 (18.8–25)
QME (kg·max reps)	151.6 (128.9–174.3)	207 (178.4–235.7)****	149 (124.4–173.7)	153.8 (127.7–180)	147.9 (123.1–172.6)	216.6 (186.3–246.9)****	144.4 (124.8–164)	152.8 (134.2–171.4)*
6 min walk test (m)	**470.4 (438.8–501.9)**	**542.6 (509.1–576.1)******	**424.6 (397.5–451.6)**	**452.2 (416.2–488.2)***	**478.7 (444.4–513.1)**	**553.1 (518.7–587.5)******	**437.7 (403.9–471.4)**	**455.5 (413.1–497.9)***
$Dyspnoea_{6mwt}$ (Borg. 0–10)	3.8 (3.2–4.5)	2.9 (2.5–3.3)****	4.2 (3.5–4.8)	2.4 (2.1–2.8)****	3.2 (2.6–3.8)	2.5 (1.8–3.1)**	4.1 (3.4–4.7)	4.2 (3.6–4.9)
$Dyspnoea_{CPX}$ (Borg. 0–10)	8.4 (8.2–8.7)	7.7 (7.4–8)***	8.5 (8.3–8.7)	8 (7.6–8.3)**	8.4 (8.1–8.6)	8.6 (8.3–8.9)	8.2 (7.9–8.5)	8.3 (7.9–8.6)
NYHA	2.5 (2.3–2.8)	1.9 (1.6–2.2)****	2.4 (2.1–2.6)	2 (1.7–2.2)*	2.3 (2.1–2.5)	2.1 (1.8–2.3)*	2.4 (2.1–2.6)	2.1 (1.7–2.5)*
MLwHFQ	**40.9 (37.3–44.6)**	**31.4 (27.9–34.9)******	**41 (37.1–44.9)**	**32.2 (28.8–35.7)******	**41.3 (37.6–45)**	**39.5 (35.2–43.8)***	**41.6 (38.3–44.9)**	**40.9 (37.6–44.2)**
PPS (1–5)		**4.8 (4.7–5.0)**§		**4.6 (4.3–4.8)**		**4.5 (4.1–4.8)**		**4.4 (4.2–4.7)**

Pre-specified endpoints in bold.

CP, circulatory power; HR, heart rate; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; MLwHFQ, Minnesota Living with Heart Failure Questionnaire; NYHA, New York Heart Association; peakVO_2, peak oxygen consumption; PI_{max}, maximal inspiratory pressure; PPS, programme preference survey; QME, quadriceps muscle endurance; QMS, quadriceps muscle strength; RER, respiratory exchange ration; SBP, systolic blood pressure; SPI_{max}, sustained maximal inspiratory pressure; VT, ventilatory threshold.

*$P \leq 0.05$; **$P \leq 0.01$; ***$P \leq 0.001$; ****$P \leq 0.0001$ *P*-values derived using paired Student's *t*-test after checking for the normality of the distributions for within group differences.

§$P \leq 0.05$ *P*-value derived using Wilcoxon test after Hommel correction for multiple comparisons.

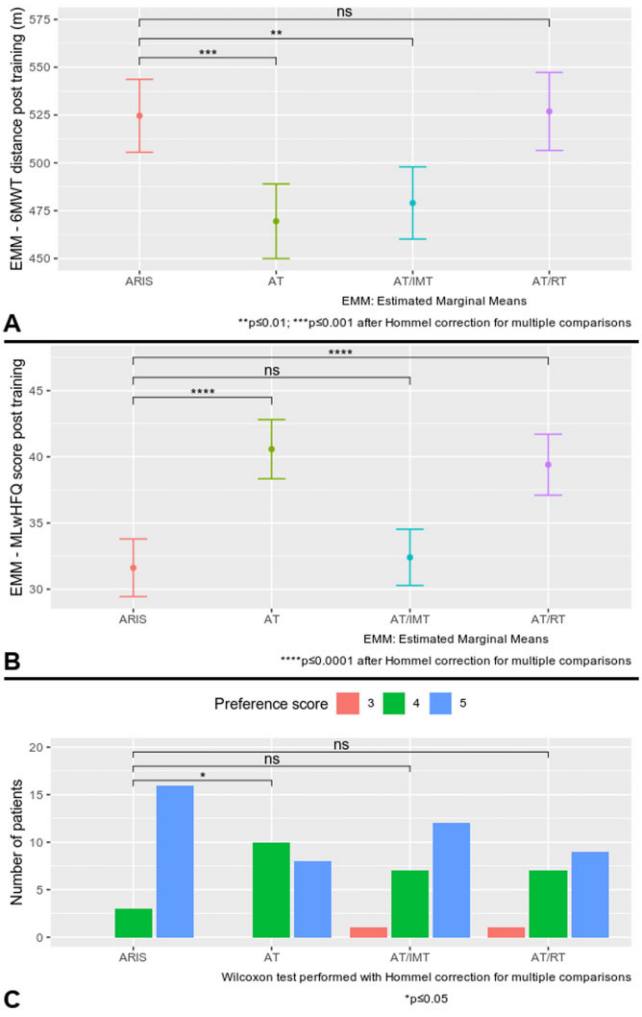

Figure 3 Secondary endpoints. (*A*) Significant benefit shown for 6MWT distance in the ARIS group compared to AT and AT/IMT groups. (*B*) Significant benefit shown for MLwHFQ score in the ARIS group compared to AT and AT/RT groups. (*C*) Significant benefit shown for the programme preference survey score in the ARIS group compared to AT group.

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Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, Falk V, González-Juanatey JR, Harjola V-P, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GMC, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P; Authors/Task Force Members; Document Reviewers. 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 J Heart Fail* 2016;**18**:891–975.
2. Taylor RS, Sagar VA, Davies EJ, Briscoe S, Coats AJ, Dalal H, Lough F, Rees K, Singh S. Exercise-based rehabilitation for heart failure. *Cochrane Database Syst Rev* 2014;**4**:CD003331.
3. O'Connor CM, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ, Leifer ES, Kraus WE, Kitzman DW, Blumenthal JA, Rendall 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.
4. Flynn KE, Piña IL, Whellan DJ, Lin L, Blumenthal JA, Ellis SJ, Fine LJ, Howlett JG, Keteyian SJ, Kitzman DW, Kraus WE, Miller NH, Schulman KA, Spertus JA, O'Connor CM, Weinfurt KP; HF-ACTION Investigators. Effects of exercise training on health status in patients with chronic heart failure: HF-ACTION randomized controlled trial. *JAMA* 2009;**301**:1451–1459.
5. Ellingsen Ø, Halle M, Conraads V, Støylen A, Dalen H, Delagardelle C, Larsen A-I, Hole T, Mezzani A, Van Craenenbroeck EM, Videm V, Beckers P, Christle JW, Winzer E, Mangner N, Woitek F, Höllriegel R, Pressler A, Monk-Hansen T,

Snoer M, Feiereisen P, Valborgland T, Kjekshus J, Hambrecht R, Gielen S, Karlsen T, Prescott E, Linke A; SMARTEX Heart Failure Study (Study of Myocardial Recovery After Exercise Training in Heart Failure) Group. High-intensity interval training in patients with heart failure with reduced ejection fraction. *Circulation* 2017;**135**:839–849.
6. Beckers PJ, Denollet J, Possemiers NM, Wuyts FL, Vrints CJ, Conraads VM. Combined endurance-resistance training vs. endurance training in patients with chronic heart failure: a prospective randomized study. *Eur Heart J* 2008;**29**: 1858–1866.
7. Jewiss D, Ostman C, Smart NA. The effect of resistance training on clinical outcomes in heart failure: a systematic review and meta-analysis. *Int J Cardiol* 2016; **221**:674–681.
8. Winkelmann ER, Chiappa GR, Lima CO, Viecili RPN, Stein R, Ribeiro JP. Addition of inspiratory muscle training to aerobic training improves cardiorespiratory responses to exercise in patients with heart failure and inspiratory muscle weakness. *Am Heart J* 2009;**158**:768.e1.
9. Adamopoulos S, Schmid J-P, Dendale P, Poerschke D, Hansen D, Dritsas A, Kouloubinis A, Alders T, Gkouziouta A, Reyckers I, Vartela V, Plessas N, Doulaptsis C, Saner H, Laoutaris ID. Combined aerobic/inspiratory muscle training vs. aerobic training in patients with chronic heart failure: The Vent-HeFT trial: a European prospective multicentre randomized trial. *Eur J Heart Fail* 2014;**16**: 574–582.
10. Laoutaris ID, Adamopoulos S, Manginas A, Panagiotakos DB, Kallistratos MS, Doulaptsis C, Kouloubinis A, Voudris V, Pavlides G, Cokkinos DV, Dritsas A. Benefits of combined aerobic/resistance/inspiratory training in patients with chronic heart failure. A complete exercise model? A prospective randomised study. *Int J Cardiol* 2013;**167**:1967–1972.
11. Laoutaris ID. Exercise intolerance and skeletal muscle metaboreflex activity in chronic heart failure: do we need to recruit more muscle in exercise training? *Eur J Prev Cardiol* 2020;**25**: 1257–1262.
12. Laoutaris ID. The 'aerobic/resistance/inspiratory muscle training hypothesis in heart failure'. *Eur J Prev Cardiol* 2018;**25**:1257–1262.
13. Ambrosetti M, Abreu A, Corrà U, Constantinos HD, Dominique H, Ines F, Marie CI, Roberto FEP, Jean-Paul S, Carlo V, Heinz V, Matthias W, Massimo FP, Birna B-W, Thomas B, Alain C-S, Veronique C, Paul D, Wolfram D, Dan G, Andreas BG, Hareld K, Nicolle K, Jari L, Miguel M, Josef N, Maria S, Ann-Dorthe OZ. Secondary prevention through comprehensive cardiovascular rehabilitation: from knowledge to implementation. 2020 update. A position paper from the Secondary Prevention and Rehabilitation Section of the European Association of Preventive Cardiolology. *Eur J Prev Cardiol* 2020;doi:10.1177/2047487320913379.
14. Riley M, Northridge DB, Henderson E, Stanford CF, Nicholls DP, Dargie HJ. The use of an exponential protocol for bicycle and treadmill exercise testing in patients with chronic cardiac failure. *Eur Heart J* 1992;**13**:1363–1367.
15. Balady GJ. Medical evaluation and exercise testing. In: MA Williams, ed. *Guidelines for Cardiac Rehabilitation and Secondary Prevention Programs*. 4th ed. American Association of Cardiovascular and Pulmonary Rehabilitation. Champaign, IL:Human Kinetics; 2004. p79.
16. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002;**166**:111–117.
17. Rector TS, Cohn JN. Assessment of patient outcome with the Minnesota Living with Heart Failure questionnaire: reliability and validity during a randomized, double-blind, placebo-controlled trial of pimobendan. Pimobendan Multicenter Research Group. *Am Heart J* 1992;**124**:1017–1025.
18. Likert R. A technique for the measurement of attitudes. *Arch Psychol* 1932;**140**:1–5.
19. Giannuzzi P, Temporelli PL, Corrà U, Tavazzi L. Antiremodeling 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.
20. Swank AM, Horton J, Fleg JL, Fonarow GC, Keteyian S, Goldberg L, Wolfel G, Handberg EM, Bensimhon D, Illiou M-C, Vest M, Ewald G, Blackburn G, Leifer E, Cooper L, Kraus WE; HF-ACTION Investigators. Modest increase in peak VO_2 is related to better clinical outcomes in chronic heart failure patients: results from heart failure and a controlled trial to investigate outcomes of exercise training. *Circ Heart Fail* 2012;**5**:579–585.
21. Cohen-Solal A, Tabet JY, Logeart D, Bourgoin P, Tokmakova M, Dahan M. A noninvasively determined surrogate of cardiac power ('circulatory') at peak exercise is a powerful prognostic factor in chronic heart failure. *Eur Heart J* 2002;**23**: 806–814.
22. Dall'Ago P, Chiappa GRS, Guths H, Stein R, Ribeiro JP. Inspiratory muscle training in patients with heart failure and inspiratory muscle weakness: a randomized trial. *J Am Coll Cardiol* 2006;**47**:757–763.
23. Laoutaris ID, Dritsas A, Brown MD, Manginas A, Kallistratos MS, Degiannis D, Chaidaroglou A, Panagiotakos DB, Alivizatos PA, Cokkinos DV. Immune response to inspiratory muscle training in patients with chronic heart failure. *Eur J Cardiovasc Prev Rehabil* 2007;**14**:679–685.
24. Chiappa GR, Roseguini BT, Vieira PJC, Alves CN, Tavares A, Winkelmann ER, Ferlin EL, Stein R, Ribeiro JP. Inspiratory muscle training improves blood flow to resting and exercising limbs in patients with chronic heart failure. *J Am Coll Cardiol* 2008;**51**:1663–1671.
25. Valborgland T, Isaksen K, Yndestad A, et al. Increased functional capacity after 12 weeks of exercise training does not transform into improved skeletal muscle metabolism or ultrastructure in heart failure patients on modern optimal medical therapy. *Eur J Prev Cardiol* 2020;**27**.doi:10.1177/2047487320919863.
26. Mello PR, Guerra GM, Borile S, Rondon MU, Alves MJ, Negrão CE, Dal Lago P, Mostarda C, Irigoyen MC, Consolim-Colombo FM. Inspiratory muscle training reduces sympathetic nervous activity and improves inspiratory muscle weakness and quality of life in patients with chronic heart failure: a clinical trial. *J Cardiopulm Rehabil Prev* 2012;**32**:255–261.
27. Selig S, Carey M, Menzies D, Patterson J, Geerling R, Williams A, Bamroongsuk V, Toia D, Krum H, Hare D. Moderate-intensity resistance exercise training in patients with chronic heart failure improves strength, endurance, heart rate variability, and forearm blood flow. *J Card Fail* 2004;**10**:21–30.
28. Anagnostakou V, Chatzimichail K, Dimopoulos S, Karatzanos E, Papazachou O, Tasoulis A, Anastasiou-Nana M, Roussos C, Nanas S. Effects of interval cycle training with or without strength training on vascular reactivity in heart failure patients. *J Card Fail* 2011;**17**:585–591.
29. Conraads V, Beckers P, Vaes J, Martin M, Vanhoof V, Demaeyer C, Possemiers N, Wuyts F, Vrints C. Combined endurance/resistance training reduces NT-proBNP levels in patients with chronic heart failure. *Eur Heart J* 2004;**25**: 1797–1805.
30. Conraads VM, Beckers P, Bosmans J, De Clerck LS, Stevens WJ, Vrints CJ, Brutsaert DL. Combined endurance/resistance training reduces plasma TNF-alpha receptor levels in patients with chronic heart failure and coronary artery disease. *Eur Heart J* 2002;**23**:1854–1860.
31. Bhat PK, Ashwath ML, Rosenbaum DS, Costantini O. Usefulness of left ventricular end-systolic dimension by echocardiography to predict reverse remodeling in patients with newly diagnosed severe left ventricular systolic dysfunction. *Am J Cardiol* 2012;**110**:83–87.
32. Ciani O, Piepoli M, Smart N, Uddin J, Walker S, Warren FC, Zwisler AD, Davos CH, Taylor RS. Validation of exercise capacity as a surrogate endpoint in exercise-based rehabilitation for heart failure: A meta-analysis of randomized controlled trials. *JACC Heart Fail* 2018;**6**:596–604.
33. Piepoli MF, Coats AJ. The 'skeletal muscle hypothesis in heart failure' revised. *Eur Heart J* 2013;**34**:486–488.
34. Laoutaris ID, Adamopoulos S, Manginas A, Panagiotakos DB, Cokkinos DV, Dritsas A. Inspiratory work capacity is more severely depressed than inspiratory muscle strength in patients with heart failure: Novel applications for inspiratoty muscle training. *Int J Cardiol* 2016;**221**:622–626.
35. Piotrowicz E, Pencina MJ, Opolski G, Zareba W, Banach M, Kowalik I, Orzechowski P, Szalewska D, Pluta S, Glówczynska R, Irzmanski R, Oreziak A, Kalarus Z, Lewicka E, Cacko A, Mierzynska A, Piotrowicz R. Effects of a 9-week hybrid comprehensive telerehabilitation program on long-term outcomes in patients with heart failure: the Telerehabilitation in Heart Failure Patients (TELEREH-HF) Randomized Clinical Trial. *JAMA Cardiol* 2020;**5**:300.