ESC European Society of Cardiology

European Journal of Heart Failure (2023) **25**, 2252–2262
doi:10.1002/ejhf.3032

RESEARCH ARTICLE

Supervised exercise training in patients with advanced heart failure and left ventricular assist device: A multicentre randomized controlled trial (Ex-VAD trial)

Anna Feuerstein[1,2,3], Felix Schoenrath[2,3,4], Evgeny Belyavskiy[1,2,5], Jan Knierim[2,4,6], Tim Friede[7,8], Marius Placzek[7,8], Doris Bach[2,3], Elisabeth Pieske-Kraigher[2], Christoph Herrmann-Lingen[8,9], Ralf Westenfeld[10], Michael Roden[11,12,13], Meike Rybczynski[14], Nicolas Verheyen[15], Marcus Dörr[16,17], Stephan von Haehling[8,18], Stefan Störk[19], Martin Halle[20,21], Volkmar Falk[2,3,4], Burkert Pieske[2,3], and Frank Edelmann[1,2,3]*

[1]Department of Cardiology, Angiology and Intensive Care Medicine, Deutsches Herzzentrum der Charité (DHZC) – Medical Heart Center of Charité and German Heart Institute Berlin, Berlin, Germany; [2]Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt Universität zu Berlin, Berlin, Germany; [3]DZHK (German Centre for Cardiovascular Research), Partner Site Berlin, Berlin, Germany; [4]Department of Cardiothoracic and Vascular Surgery, Deutsches Herzzentrum der Charité (DHZC) – Medical Heart Center of Charité and German Heart Institute Berlin, Berlin, Germany; [5]Deutsches Herzzentrum der Charité, Medizinisches Versorgungszentrum, Berlin, Germany; [6]Department of Internal Medicine and Cardiology, Paulinenkrankenhaus gGmbH, Berlin, Germany; [7]Department of Medical Statistics, University of Göttingen Medical Center, Göttingen, Germany; [8]DZHK (German Centre for Cardiovascular Research), Partner Site Göttingen, Göttingen, Germany; [9]Department of Psychosomatic Medicine and Psychotherapy, University of Göttingen Medical Center, Göttingen, Germany; [10]Department of Cardiology, Pulmonology and Vascular Medicine, Heinrich Heine University, University Hospital Düsseldorf, Düsseldorf, Germany; [11]Department of Endocrinology and Diabetology, Heinrich Heine University, University Hospital Düsseldorf, Düsseldorf, Germany; [12]Institute for Clinical Diabetology, German Diabetes Center, Leibniz Center for Diabetes Research, Heinrich Heine University, Düsseldorf, Germany; [13]German Center for Diabetes Research (DZD e.V.), Partner Düsseldorf, München-Neuherberg, Germany; [14]Department of Cardiology, University Heart and Vascular Center Hamburg-Eppendorf, Hamburg, Germany; [15]Department of Cardiology, Medical University of Graz, Graz, Austria; [16]Department of Internal Medicine B, University Medicine Greifswald, Greifswald, Germany; [17]DZHK (German Centre for Cardiovascular Research), Partner Site Greifswald, Greifswald, Germany; [18]Department of Cardiology and Pneumology, University of Göttingen Medical Center, Göttingen, Germany; [19]Department of Clinical Research and Epidemiology, Comprehensive Heart Failure Center Würzburg, University Hospital Würzburg, Würzburg, Germany; [20]Department of Preventive Sports Medicine and Sports Cardiology, Technical University of Munich, Klinikum rechts der Isar, Munich, Germany; and [21]DZHK (German Centre for Cardiovascular Research), partner site Munich Heart Alliance, Munich, Germany

Received 3 May 2023; revised 22 August 2023; accepted 9 September 2023; online publish-ahead-of-print 26 September 2023

Aims Small studies and observations suggested that exercise training may improve peak oxygen consumption ($peakVO_2$) in patients with advanced heart failure and left ventricular assist device (LVAD). We investigated whether in this patient group a supervised exercise training can improve exercise capacity.

Methods and results In this multicentre, prospective, randomized, controlled trial, patients with stable heart failure and LVAD were randomly assigned (2:1) to 12 weeks of supervised exercise training or usual care, with 12 weeks of follow-up. The primary endpoint was the change in $peakVO_2$ after 12 weeks (51 patients provided a power of 90% with an expected group difference in $peakVO_2$ of 3 ml/kg/min). Secondary endpoints included changes in submaximal exercise capacity and quality of life. Among 64 patients enrolled (97% male, mean age 56 years), 54 were included in the analysis. Mean difference in the change of $peakVO_2$ after 12 weeks was 0.826 ml/min/kg (95% confidence interval [CI] −0.37, 2.03; $p = 0.183$). There was a positive effect of exercise training on 6-min walk distance with a mean increase in the

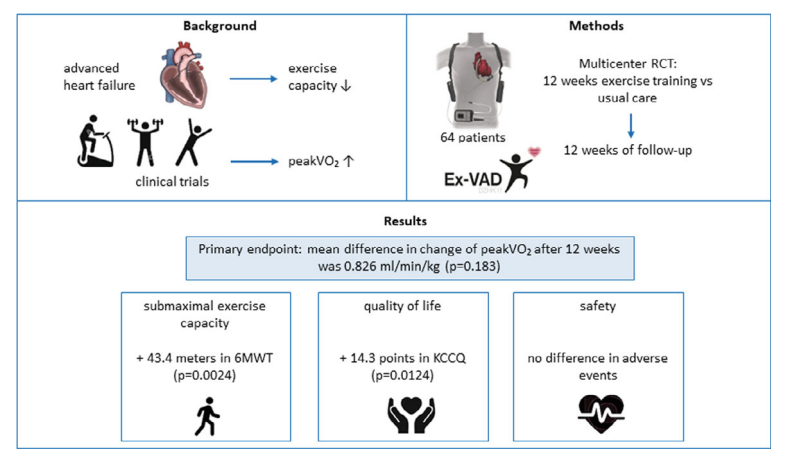
*Corresponding author. Deutsches Herzzentrum der Charité, Klinik für Kardiologie, Angiologie und Intensivmedizin, Campus Virchow-Klinikum, Augustenburger Platz 1, 13353 Berlin, Germany. Tel: +49 30 450653731, Fax: +49 30 4507553731, Email: frank.edelmann@dhzc-charite.de

Anna Feuerstein and Felix Schoenrath contributed equally as first co-authors.
Burkert Pieske and Frank Edelmann contributed equally as last co-authors.

intervention group by 43.4 m (95% CI 16.9, 69.9; $p = 0.0024$), and on the Kansas City Cardiomyopathy Questionnaire physical domain score (mean 14.3, 95% CI 3.7, 24.9; $p = 0.0124$), both after 12 weeks. The overall adherence was high (71%), and there were no differences in adverse events between groups.

Conclusion In patients with advanced heart failure and LVAD, 12 weeks of exercise training did not improve peakVO_2 but demonstrated positive effects on submaximal exercise capacity and physical quality of life.

Graphical Abstract



Exercise training in patients with advanced heart failure and left ventricular assist device (Ex-VAD) trial. 6MWT, 6-min walk test; KCCQ, Kansas City Cardiomyopathy Questionnaire physical domain score; peakVO_2, peak oxygen consumption; RCT, randomized controlled trial.

Keywords Advanced heart failure • Left ventricular assist device • Supervised exercise training • Exercise capacity

Introduction

Evidence-based therapies markedly improved survival in chronic heart failure (HF)[1] and more patients progress to an advanced stage of HF. Left ventricular assist device (LVAD) therapy has become an indispensable option for patients with advanced HF.[2] However, after LVAD implantation functional capacity remains limited[3] as this growing patient cohort suffers from limited quality of life (QoL), device-related side-effects, and lack of therapeutic options.

Exercise training is recommended in patients with HF by current guidelines[1,4] as a safe and effective treatment modality. Exercise significantly improves exercise capacity, QoL and HF signs and symptoms, and also has benefits on morbidity, mortality and hospitalization as demonstrated in previous multicentre randomized controlled trials.[5–9] However, in patients with advanced HF and LVAD, respective evidence is scarce due to lack of prospective multicentre trials.

Several small single-centre trials have previously implied feasibility, safety and a beneficial effect of exercise in patients with advanced HF and LVAD.[10–14] Exercise tends to improve maximal and submaximal exercise capacity (peak oxygen consumption [peakVO_2], 6-min walk distance), muscle strength and QoL in this patient cohort. Nevertheless, because of small sample sizes, low number of training sessions and short intervention periods, available trials showed conflicting results.

The Exercise training in patients with left Ventricular Assist Device (Ex-VAD, DZHK11, NCT03369938) trial was designed to evaluate the effects of supervised exercise training on functional capacity in patients with LVAD.[15] We tested the hypothesis that 12 weeks of supervised exercise training improve peakVO_2 in a multicentre setting.

Methods

A detailed description of the study design has been previously published.[15] Here, we provide a brief description.

Trial overview

The Ex-VAD trial was a multicentre randomized controlled trial conducted at five German sites (Berlin, Hamburg, München, Düsseldorf, Leipzig) assessing the effect of supervised exercise training in patients with LVAD over 6 months. The study was approved by the local ethics committees at all participating sites. All participants provided written informed consent.

Patients

Clinically stable patients with advanced chronic HF, optimal therapeutic treatment according to the European Society of Cardiology HF guidelines, and LVAD support for at least 3 months were eligible to participate in the trial. Patients had to be able to perform cardiopulmonary exercise testing (CPET) for at least 1 min at 20 W, were encouraged to be physically active and were allowed to perform any kind of leisure time physical activity.

Randomization

A web-based system was used to assign patients in a 2:1 ratio to supervised exercise training or usual care alone. Block randomization was stratified by trial centre and indication for LVAD (bridging vs. destination therapy); the block length was 6.

Intervention

Patients randomized to exercise training were encouraged to perform 36 supervised training sessions consisting of combined pre-defined endurance/resistance training three times per week with additional free exercises to improve flexibility, balance, and coordination. Training sessions were implemented on top of usual care and covered a period of 12 weeks. A detailed training schedule has previously been published.[15] Briefly, endurance training was performed on an ergometer, intensity was based on baseline CPET measures (80–100% of watts at anaerobic threshold) and duration was increased stepwise over 12 weeks of intervention. Resistance training consisted of large muscle group exercises (upper and lower extremities), intensity and number of repetitions were increased stepwise over the time of intervention.[15]

Adherence was regularly assessed by staff. Patients needed to complete at least 66% of possible sessions to be considered on-treatment.

Clinical assessments

All patients were assessed at baseline, at 12 and at 24 weeks. Examinations were performed according to standard operating procedures and included medical history, physical examination, anthropometry, electrocardiogram, blood analysis, CPET, 6-min walk test (6MWT), resting and dobutamine stress echocardiography, and QoL assessment through questionnaires, including the Kansas City Cardiomyopathy Questionnaire (KCCQ) and 36-Item Short-Form Health Survey (SF-36). Additionally, safety visits were performed after 2, 4, 8 and 16 weeks. The clinical staff members conducting the evaluations were not blinded to treatment groups.

Cardiopulmonary exercise testing was performed according to current recommendations and analysed centrally by the CPET Core Laboratory at Charité Berlin, blinded to trial visit and to treatment group assignment. PeakVO_2 was defined as the highest oxygen uptake values of the last 30 s prior to termination of the exercise using 10 s-averaged values.[15] The anaerobic threshold (VO_2AT) was set by the V-slope method.[16] The minute ventilation to carbon dioxide production (VE/VCO_2) slope was calculated using the entire exercise data.

Echocardiography was performed by experienced and instructed sonographers. Analyses were performed centrally, blinded to treatment group assignment by the Echocardiography Core Laboratory at Charité Berlin.

Quality of life analyses were performed by the QoL Core Laboratory in Göttingen, blinded to treatment group assignment.

Outcomes

The primary endpoint was the change in peakVO_2 after 12 weeks. Secondary endpoints included changes in 6MWT distance, VE/VCO_2 slope and the physical QoL domain of the KCCQ and the SF-36 (both score range 0–100; higher scores reflect better QoL), changes in echocardiographic parameters of cardiac morphology and function and change in markers of neuroendocrine activation. Adverse events (AEs) and serious adverse events (SAEs) were evaluated by an independent safety committee.

Statistics

Based on previous small single-centre trials and case reports,[10–13] the trial protocol[15] expected a group difference of 3 ml/min/kg in peakVO_2, a standard deviation of 5 ml/min/kg and a correlation of 0.8 between baseline and week 12. Under these assumptions a total sample size of 51 patients with 2:1 randomization (34 intervention, 17 control group) provided a power of 90% for a comparison of group means at the one-sided significance level of 2.5% in an analysis of covariance (ANCOVA) with baseline adjustment. Considering the extended duration of the intervention and the multicentre design, a conservative dropout rate of 20% was expected. Thus, a total number of 66 patients was intended to be included in the trial. In June 2020, a blinded sample size review observed a lower drop-out rate (15%) and a smaller residual variance for the primary endpoint than initially assumed. Given that statistical assumptions underlying the sample size calculation were prematurely fulfilled, the blinded review board decided to stop trial recruitment after 64 patients.

The primary endpoint peakVO_2 at week 12 was analysed by ANCOVA with treatment group, trial centre, indication for LVAD implantation as factors, and baseline peakVO_2 as covariate using the full analysis set. The null hypothesis was tested one-sided at a significance level of 2.5%. All patients were analysed according to their randomization group. To account for missing values in the primary endpoint variable, a pre-specified multiple imputation approach was performed (see also statistical analysis plan in online supplementary *Appendix S1*).

Secondary endpoints were analysed by means of a Gaussian linear model for repeated measures (mixed model repeated measures). It was used to investigate the sustainability of the intervention effect over 12 and 24 weeks adjusted for baseline values and stratification factors. The model contains main effects for the treatment group, trial visit and interaction between both. The 95% confidence intervals (CI) for mean changes between groups were presented.

Furthermore, we performed a per-protocol analysis including only patients adhering to at least 66% to the scheduled exercise sessions. Subgroup analyses for the different indications for LVAD implantation and duration of LVAD therapy were performed. All statistical analyses were performed using R (Version 4.0.4).

Results

Inclusion of patients started in December 2017, the last patient completed the trial in September 2020. After initial exclusions and withdrawals, 64 patients were enrolled in the trial. Eight patients discontinued trial participation, 10 were excluded from analysis due to missing data at 12 weeks (*Figure 1*). Accordingly, 54 patients were included in the analysis.

Patients were predominantly male (97%) with a typical risk and comorbidity profile. Baseline patient demographic and clinical characteristics are shown in *Table 1*. Between groups, there were no major differences in baseline characteristics regarding exercise capacity (peakVO_2, VO_2AT and 6MWT distance), SF-36 or KCCQ physical domain score, or echocardiographic parameters.

Adherence

Overall adherence to the training intervention was 71% ($n = 41$, 95% CI 57, 85). Eleven patients did not reach the required adherence of 66% of sessions to be considered on-treatment and were excluded from per-protocol analysis. Adherence of the patients considered on-treatment was 83% ($n = 29$, 95% CI 69, 97).

Primary endpoint and secondary endpoints

After 12 weeks of intervention, we observed a non-significant group difference of 0.826 ml/min/kg in peakVO_2 (95% CI −0.37, 2.03; $p = 0.183$) after adjusting for baseline differences (*Figure 2*). Analysis of secondary endpoints showed a positive treatment effect of 43.4 m in 6MWT between groups after 12 weeks (95% CI 16.9, 69.9; $p = 0.0024$). Likewise, the intervention group scored 14.3 points higher in the KCCQ physical domain compared to the control group (95% CI 3.65, 24.94; $p = 0.0124$). There were no significant differences in SF-36 physical domain score, in ventilatory efficiency (VE/VCO_2 slope) or in other secondary endpoints within or between groups (online supplementary *Table S1*).

Safety

The overall number of AEs and SAEs was high (*Table 2*). Thirty-four patients (82.9%) in the intervention and 21 (91.3%) in the control group had at least one AE during the trial participation. In the intervention group, 14 patients (34.1%) and 11 (47.8%) in the control group had at least one SAE during the trial. All SAEs involved hospitalization and were due to typical complications of HF and LVAD therapy (decompensated HF, stroke, anaemia

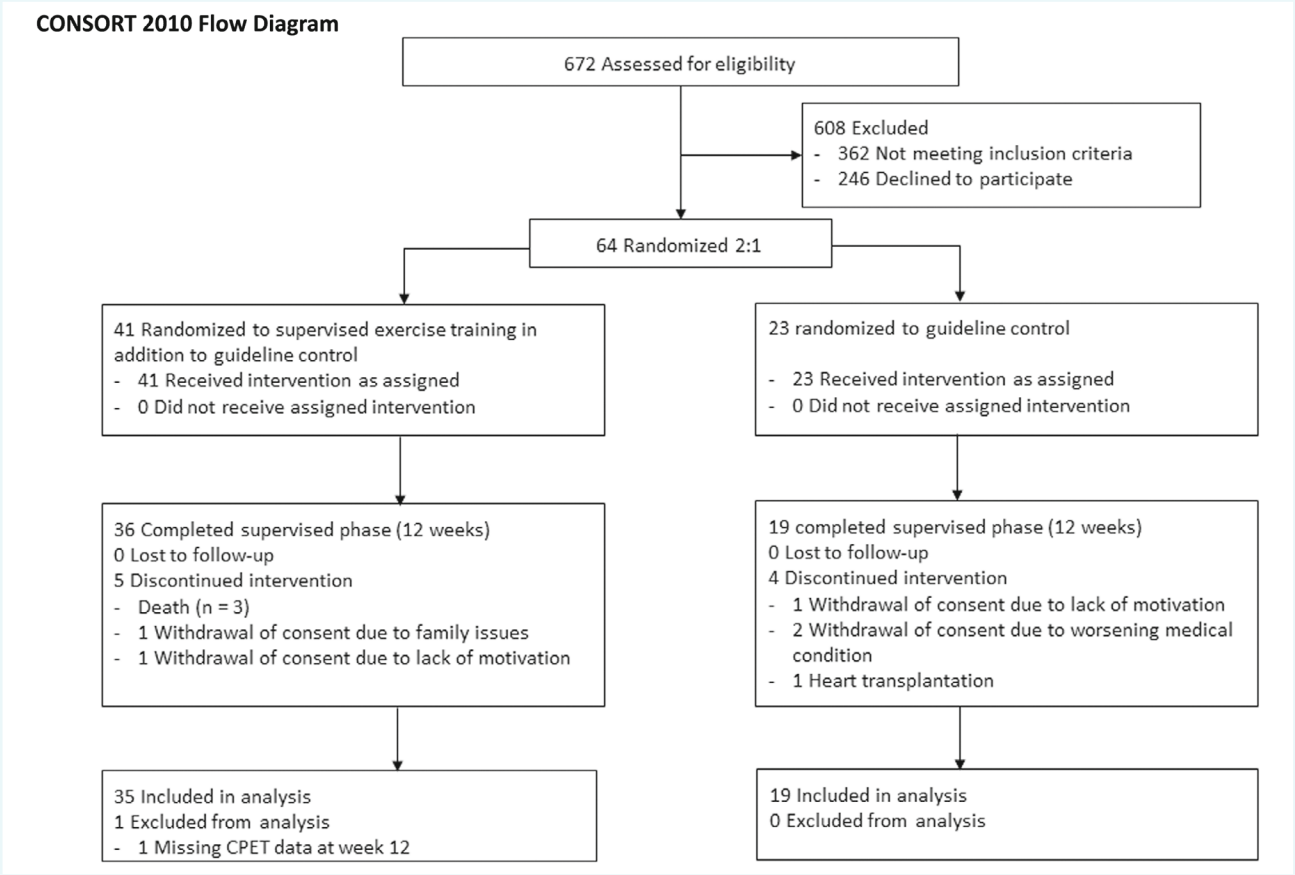


Figure 1 Patient recruitment, randomization, and follow-up in the Ex-VAD trial. CPET, cardiopulmonary exercise test.

Table 1 Baseline characteristics of the Ex-VAD cohort

Characteristic	Training ($n = 41$)	Control ($n = 23$)
Age, years	55 ± 12	58 ± 11
Sex (male/female), *n*	40/1	22/1
Caucasian, *n* (%)	36 (87.8)	23 (100)
Height, cm	179.6 ± 7.6	180.4 ± 6.9
Weight, kg	95.9 ± 17.6	97.4 ± 16.4
BMI, kg/m^2	29.7 ± 5.0	30.1 ± 5.8
Waist-to-hip-ratio	1.01 ± 0.1	0.99 ± 0.1
Heart rate, bpm	72 ± 13	71 ± 7
Mean arterial pressure, mmHg	85 ± 14	80 ± 12
Cardiovascular risk factors, *n* (%)		
Hypertension	22 (53.7)	14 (60.9)
Dyslipidemia	18 (43.9)	15 (65.2)
Diabetes mellitus	15 (36.6)	9 (39.1)
Familial history of myocardial infarction or stroke	15 (36.6)	8 (34.8)
Smoking		
Current	6 (14.6)	4 (17.4)
Ex (>6 months clean)	22 (53.7)	17 (73.9)
Never	12 (29.3)	2 (8.7)
Cardiovascular disease, *n* (%)		
Coronary artery disease	19 (46.3)	12 (52.2)
History of myocardial infarction	17 (41.5)	10 (43.5)
Cardiomyopathy	27 (65.9)	13 (56.5)
Dilated cardiomyopathy	19 (46.3)	11 (47.8)
Heart failure	39 (95.1)	22 (95.7)
Previous decompensation	28 (68.3)	13 (56.5)
Current NYHA functional class		
I	12 (29.3)	1 (4.4)
II	20 (48.8)	18 (78.3)
III	7 (17.1)	3 (13.0)
Atrial fibrillation/flutter	15 (36.6)	7 (30.4)
Valvular disease	20 (48.8)	11 (47.8)
Endocarditis	1 (2.4)	0 (0)
Congenital heart disease	2 (4.9)	2 (8.7)
Peripheral artery disease	2 (4.9)	1 (4.4)
Sleep apnoea syndrome	5 (12.2)	2 (8.7)
Comorbidities, *n* (%)		
Hyperuricemia	7 (17.1)	7 (30.4)
Chronic kidney disease	31 (75.6)	17 (73.9)
History of stroke	8 (19.5)	6 (26.1)
Syncope	10 (24.4)	2 (8.7)
Chronic obstructive pulmonary disease	2 (4.9)	5 (21.7)
Asthma	1 (2.4)	0 (0)
Primary pulmonary hypertension	3 (7.3)	1 (4.4)
Depression	5 (12.2)	3 (13.0)
History of cancer	6 (14.6)	3 (13.0)
LVAD history		
Years since LVAD implantation, *n* (%)		
<1 year	20 (48.8)	8 (34.8)
1–2 years	7 (17.1)	7 (30.4)
2–3 years	12 (29.3)	2 (8.7)
>3 years	2 (4.8)	6 (26.1)
Type of LVAD device, *n* (%)		
HeartMate II	0 (0)	1 (4.4)
HeartMate 3	20 (48.8)	11 (47.8)
HeartWare HVAD	21 (51.2)	11 (47.8)
Underlying disease for LVAD implantation, *n* (%)		
Chronic heart failure	21 (51.2)	13 (56.5)
Acute myocardial infarction	14 (34.2)	6 (26.1)
Primary cardiomyopathy	21 (51.2)	12 (52.2)
Myocarditis	4 (9.8)	2 (8.7)
LVAD indication, *n* (%)		
Bridging (to transplant/recovery)	24 (58.5)	12 (52.2)
Destination therapy	17 (41.5)	11 (47.8)
Pump flow, L/min	4.6 ± 0.9	4.6 ± 0.7
Medication, *n* (%)		
ACE-inhibitor/AT$_1$-receptor blocker	28 (68.3)	13 (56.5)
Sacubitril/valsartan	11 (28.8)	4 (17.4)
Aldosterone antagonist	30 (73.2)	21 (91.3)
Loop diuretic	32 (78.1)	19 (82.6)
Beta-blocker	36 (87.8)	22 (95.7)
Calcium channel blocker	4 (9.8)	5 (21.7)
Amiodarone	22 (53.7)	5 (21.7)
Statin	22 (53.7)	14 (60.9)
Other lipid-lowering agent	1 (2.4)	2 (8.7)
Acetylsalicylic acid	26 (63.4)	19 (82.6)
Thienopyridine (clopidogrel)	3 (7.3)	1 (4.35)
Vitamin K antagonist	40 (97.6)	23 (100)
Heparin	1 (2.4)	1 (4.4)
Insulin	5 (12.2)	5 (21.7)
Oral antidiabetic	3 (7.3)	3 (13.0)
Antiobstructive inhalative drug	4 (9.8)	3 (13.0)
Antidepressant	5 (12.2)	1 (4.4)
Sleep medication/anxiolytic	0 (0)	2 (8.7)
Proton pump inhibitor	37 (90.2)	19 (82.6)
Antibiotic	4 (9.8)	2 (8.7)
Analgesic	3 (7.3)	0 (0)
Laboratory results		
NT-proBNP, µg/L, median (IQR)	882.0 (461.0, 1561.0)	770.0 (420.5, 2672.0)
Creatinine, mg/dl	1.4 ± 0.5	1.4 ± 0.6
Potassium, mmol/L	4.3 ± 0.6	4.4 ± 0.5
Sodium, mmol/L	139 ± 2.8	138 ± 6.5
hs-CRP, mg/dl	0.6 ± 0.8	0.7 ± 1.0
Haemoglobin, g/dl	13.5 ± 1.8	13.1 ± 1.7
CPET		
PeakVO_2, ml/min/kg	13.2 ± 3.9	12.5 ± 4.3
Maximum load level, W	90.3 ± 31.1	85.4 ± 35.9
VO_2 AT, ml/min	912 ± 295.7	786.3 ± 213.0
VO_2 AT, ml/min/kg	9.5 ± 2.6	8.1 ± 2.0
VE/VCO_2 slope	39.3 ± 10.3	41.7 ± 7.8
RER max workload	1.06 ± 0.07	1.05 ± 0.12
RER max (afterload)	1.21 ± 0.14	1.14 ± 0.12
6-min walking distance, m	421 ± 115	393 ± 118
SF-36 physical domain	58.4 ± 21.8	48.6 ± 22.4
KCCQ physical domain	69.7 ± 15.2	64.4 ± 19.6
Echocardiography		
LVEDD, mm	58.9 ± 12.0	61.9 ± 16.2
IVSD, mm	9.7 ± 1.7	9.7 ± 1.7
LVPWD, mm	9.3 ± 1.5	9.5 ± 1.6
LVEDV, ml	182.7 ± 92.2	211.1 ± 136.0
TAPSE, mm	11.5 ± 2.9	10.8 ± 3.7

Values are presented as mean ± standard deviation, unless otherwise indicated.
ACE, angiotensin-converting enzyme; BMI, body mass index; hs-CRP, high-sensitivity C-reactive protein; IQR, interquartile range; IVSD, interventricular septal diameter; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVAD, left ventricular assist device; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVPWD, left ventricular posterior wall diameter; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; peakVO_2, peak oxygen consumption; RER, respiratory exchange ratio; SF-36, 36-Item Short-Form Health Survey; TAPSE, tricuspid annular plane systolic excursion; VE/VCO_2, minute ventilation to carbon dioxide production VO_2 AT, oxygen consumption at anaerobic threshold.

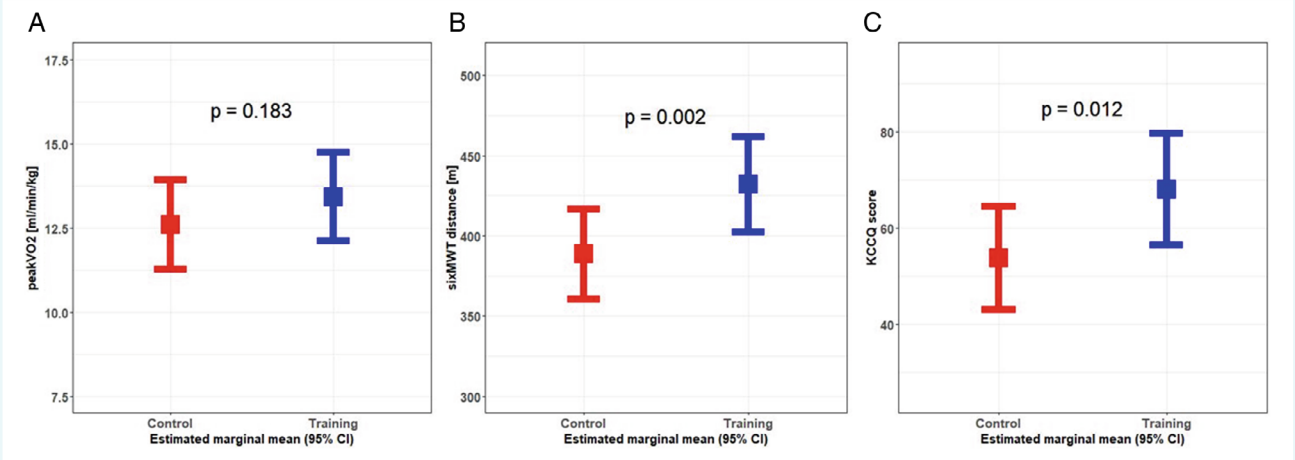


Figure 2 Primary endpoint and secondary endpoints. Marginal means and 95% confidence interval (CI) for (*A*) peak oxygen consumption ($peakVO_2$), (*B*) 6-min walk test (MWT) distance and (*C*) Kansas City Cardiomyopathy Questionnaire (KCCQ) physical domain after 12 weeks for control versus intervention group. Mean difference in the change of $peakVO_2$ after 12 weeks was 0.826 ml/min/kg (95% CI −0.37, 2.03; $p = 0.183$). There was no significant change in the 36-Item Short-Form Health Survey physical score and in the minute ventilation to carbon dioxide production slope between intervention and control group.

Table 2 Safety

	Training ($n = 41$)	Control ($n = 23$)
Total AE, *n*	100	54
During training	3	n.a.
Within 2 h after training	6	n.a.
Patients with at least one AE during trial participation, *n* (%)	34 (82.9)	21 (91.3)
Total SAE, *n*	26	18
Planned/unplanned hospitalization, *n*	3/23	1/17
Cardiovascular hospitalization, *n* (%)	10 (38.5)	9 (50.0)
Cardiovascular hospitalization with worsening heart failure, *n* (%)	3 (11.5)	4 (22.2)
Other hospitalization, *n* (%)	13 (50.0)	5 (27.8)
Death, *n* (%)	3 (11.5)	0 (0)
Patients with at least one SAE during trial participation, *n* (%)	14 (34.1)	11 (47.8)

AE, adverse event; SAE, serious adverse event.
Death causes: One patient died because of pump thrombosis, one because of subdural and subarachnoid haematoma (after a fall with head injury), one died of multi-organ failure due to sepsis based on a driveline infection in addition to right heart failure.

with need of transfusion, infection). There were no statistically significant differences between groups in total number of SAEs.

Three AEs occurred during training: one patient had epistaxis, one had diarrhoea and one an accidental pull of the driveline which led to a small injury of the driveline exit point and was treated with medical honey and sterile change of bandage. Six AEs appeared within 2 h after training: three patients reported problems with circulation or had an intermittent decrease in kidney function, which were successfully treated with oral fluids. One reported ankle pain and one a local allergic reaction to the accelerometer of the Ex-VAD trial. One patient had a polymorphic ventricular tachycardia, which was successfully terminated by two shocks of his implanted defibrillator system. There were no SAEs during training.

In the intervention group, three patients died during the trial period and no patient died in the control group. One patient died because of pump thrombosis, one after a fall with head injury and consecutive subdural and subarachnoid haematoma, and one died of multi-organ failure due to sepsis following driveline infection in addition to right HF.

We observed a non-significant difference in driveline infections with numerically more events in the intervention group ($n = 6$ [6.0%] vs. $n = 2$ [3.7%] in the control group).

Subgroup analysis

Subgroup analysis focusing on indication for LVAD implantation (bridging vs. destination therapy) demonstrated that patients of the bridging group were younger (mean age 52 vs. 64 years), had

Table 3 Subgroup baseline data for groups of indication (bridge to transplant/recovery vs. destination therapy)

	Bridging			Destination therapy		
	Total	Training	Control	Total	Training	Control
n	36	24	12	28	17	11
Male sex, *n* (%)	34 (94.4)	23 (95.8)	11 (91.7)	28 (100)	17 (100)	11 (100)
Age at baseline, years	52 ± 11	51 ± 11	53 ± 11	62 ± 10	61 ± 12	63 ± 8
Height, cm	182 ± 7	182 ± 8	182 ± 7	177 ± 7	176 ± 7	179 ± 7
Weight, kg	99 ± 16	99 ± 17	98 ± 15	94 ± 18	92 ± 18	97 ± 18
BMI, kg/m^2	30 ± 5	30 ± 5	30 ± 5	30 ± 6	30 ± 5	30 ± 6
Time on LVAD, *n* (%)						
<1 year	16 (44.4)	12 (50.0)	4 (33.3)	12 (42.9)	8 (47.1)	4 (36.4)
>1 year	20 (55.6)	12 (50.0)	8 (66.7)	16 (57.1)	9 (52.9)	7 (63.6)
PeakVO_2, ml/min/kg	14 ± 4	14 ± 4	12 ± 3	12 ± 4	12 ± 3	13 ± 6
Maximum load level, W	101 ± 35	104 ± 29	94 ± 46	73 ± 21	71 ± 23	76 ± 18
VO_2 AT, ml/min	927 ± 296	1009 ± 309	757 ± 182	790 ± 225	773 ± 216	819 ± 248
VE/VCO_2 slope	38 ± 9	37 ± 10	40 ± 7	43 ± 10	42 ± 11	44 ± 8

Values are presented as mean ± standard deviation unless otherwise indicated.
BMI, body mass index; LVAD, left ventricular assist device; peakVO_2, peak oxygen consumption; VE/VCO_2, minute ventilation to carbon dioxide production; VO_2 AT, oxygen consumption at anaerobic threshold.

a higher mean peakVO_2 (14 vs. 11 ml/min/kg), higher VO_2AT and a lower mean VE/VCO_2 slope at baseline (*Table 3*). The subgroup analyses regarding primary and secondary endpoints are presented in *Figure 3A*. There was no difference in peakVO_2, VE/VCO_2 slope and SF-36 physical domain between groups regarding indication for LVAD implantation. However, in the intervention group, patients with LVAD as bridging therapy had a significantly greater increase in 6MWT distance ($p = 0.001$) and in KCCQ physical domain ($p = 0.021$) than patients with LVAD as destination therapy.

Subgroup analysis focusing on duration of LVAD therapy (<1 year vs. >1 year) showed no difference in age between groups (*Table 4*). However, patients on LVAD therapy for less than 1 year exhibited a slightly lower weight and thus lower body mass index. At baseline, there was no difference in peakVO_2 between groups, but VO_2AT and VE/VCO_2 slope were lower in patients on LVAD therapy for less than 1 year. The subgroup analyses regarding primary and secondary endpoints are presented in *Figure 3B*. Again, there was no difference in peakVO_2, VE/VCO_2 slope and SF-36 physical domain between groups regarding duration of LVAD therapy. In the intervention group, patients on LVAD therapy for less than 1 year had a significantly higher increase in 6MWT distance ($p = 0.018$) than patients on LVAD therapy for more than 1 year. Yet, patients on LVAD therapy for more than 1 year showed a significant increase in KCCQ physical domain ($p = 0.007$) in the intervention group, whereas there was no intervention effect in patients on LVAD therapy for less than 1 year.

Discussion

In this multicentre randomized controlled trial, supervised exercise training did not increase peakVO_2 in patients with advanced HF and LVAD therapy. Among secondary endpoints, 6MWT distance as a measure of submaximal exercise capacity and KCCQ physical domain as a measure of physical QoL in HF increased significantly with supervised training (*Graphical Abstract*).

We chose peakVO_2 as primary endpoint since it is a robust and reproducible parameter and has an important prognostic role in HF and in LVAD recipients.[17] In patients with HF and LVAD, improvement in peakVO_2 after exercise training was reported in many single-centre trials, but the degree of improvement in peakVO_2 varied. A meta-analysis by Ganga *et al.*[14] calculated an overall improvement of 1.46 ml/min/kg in peakVO_2 after 6–18 weeks of supervised exercise training. However, patients in the pooled trials[10–12,18] were younger with lower body mass index, and within 6 months after LVAD implantation as bridging therapy. In two of the included trials,[12,18] baseline peakVO_2 was noticeably higher than in Ex-VAD. Also, many trials did not report a control group. When compared to the control group, Kugler *et al.*[18] demonstrated a significant positive effect of exercise training on peakVO_2. However, in this single-centre trial patients were included 6 weeks after LVAD implantation. This early intervention is comparable with a classic rehabilitation programme, which is recommended to all patients after cardiac surgery. Our study focuses on patients on the ambulatory setting at least 3 months after LVAD implantation to evaluate the potential beneficial effect of an additional exercise training programme. Thus, these data underline our findings that patients shortly after LVAD implantation may benefit more from exercise training than patients with long-term LVAD therapy. Also, patients with LVAD as destination therapy were underrepresented in previous trials and should further be investigated.

Training modality has been shown to affect peakVO_2 in exercise interventions in large HF cohorts. The HF-ACTION trial showed a change in peakVO_2 of 0.6 ml/min/kg in the exercise group within 3 months (vs. 0.2 ml/min/kg in the control group) by supervised aerobic training alone.[5] Bouchla *et al.*[19] describe an additional

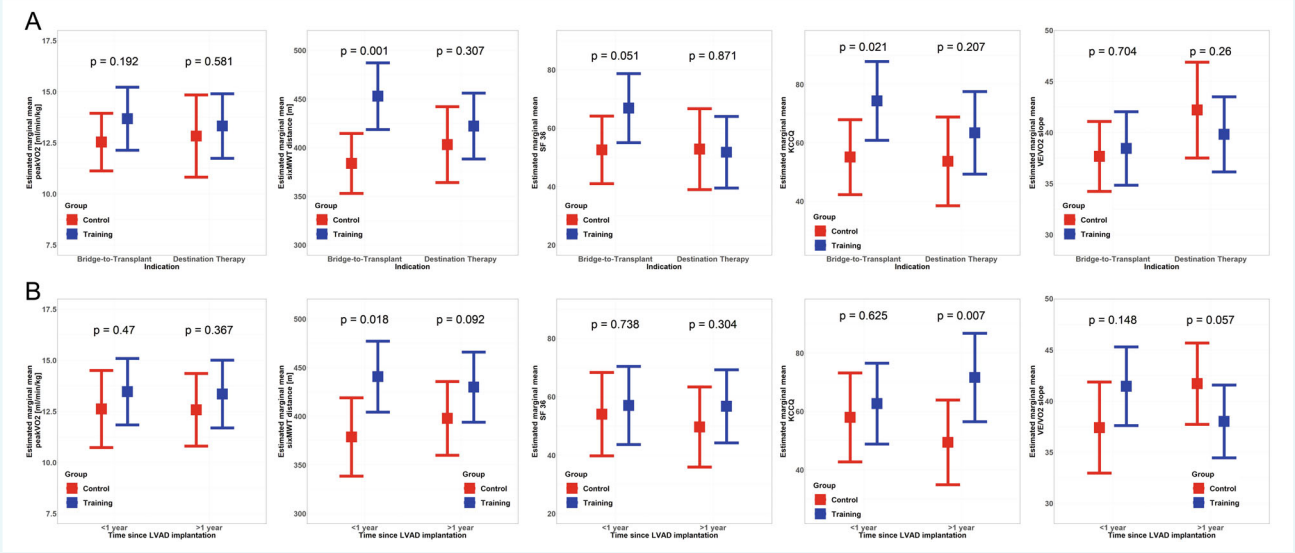


Figure 3 Subgroup analysis: change in parameter after 12 weeks separated by (*A*) indication for left ventricular assist device (LVAD) implantation (bridging vs. destination therapy), (*B*) duration of LVAD therapy (<1 vs. >1 year) prior to randomization. 6MWT, 6-min walk test; KCCQ, Kansas City Cardiomyopathy Questionnaire; peakVO_2, peak oxygen consumption; SF-36, 36-Item Short-Form Health Survey; VE/VCO_2, minute ventilation to carbon dioxide production.

Table 4 Subgroup baseline data for time on left ventricular assist device therapy (less vs. more than 1 year)

	Time on LVAD <1 year			Time on LVAD >1 year		
	Total	**Training**	**Control**	**Total**	**Training**	**Control**
n	28	20	8	36	21	15
Male sex, *n* (%)	27 (96.4)	19 (95)	8 (100)	35 (97.2)	21 (100.0)	14 (93.3)
Age at baseline, years	55 ± 13	54 ± 14	57 ± 11	57 ± 11	56 ± 11	58 ± 11
Height, cm	179 ± 8	178 ± 8	182 ± 6	181 ± 7	181 ± 7	179 ± 7
Weight, kg	90 ± 14	90 ± 15	92 ± 13	101 ± 18	102 ± 18	100 ± 18
BMI, kg/m^2	28 ± 4	28 ± 4	28 ± 5	31 ± 6	31 ± 5	31 ± 6
Indication for LVAD, *n* (%)						
Bridging	16 (57.1)	12 (60)	4 (50)	20 (55.6)	12 (57.1)	8 (53.3)
Destination therapy	12 (42.9)	8 (40.0)	4 (50.0)	16 (44.4)	9 (42.9)	7 (46.7)
PeakVO_2, ml/min/kg	14 ± 4	13 ± 3	14 ± 6	13 ± 4	13 ± 5	12 ± 3
Maximum load level, W	91 ± 35	89 ± 26	97 ± 55	86 ± 31	91 ± 36	79 ± 21
VO_2 AT, ml/min	802 ± 255	829 ± 266	727 ± 218	922 ± 282	1000 ± 307	816 ± 212
VE/VCO_2 slope	38 ± 7	38 ± 8	38 ± 6	42 ± 11	41 ± 12	44 ± 8

Values are presented as mean ± standard deviation unless otherwise indicated.
BMI, body mass index; LVAD, left ventricular assist device; peakVO_2, peak oxygen consumption; VE/VCO_2, minute ventilation to carbon dioxide production; VO_2 AT, oxygen consumption at anaerobic threshold.

increase in peakVO_2 of 1.0 ml/min/kg within 3 months of training by combining aerobic and muscle training. Although some small trials in HF suggest that resistance training does affect peakVO_2,[20,21] a meta-analysis by Jewiss *et al.*[22] demonstrated a mean difference of 1.43 ml/min/kg peakVO_2 in combined aerobic/resistance training versus control and a mean difference of 3.99 ml/min/kg peakVO_2 in resistance training versus control. Tucker *et al.*[23] found that peakVO_2 was significantly greater after long versus short-duration moderate intensity continuous training, which is likely due to central adaptations. In patients with LVAD, Hayes *et al.*[11] reported an increase in peakVO_2 of 3.0 ml/min/kg after only 8 weeks of moderate intensity endurance and resistance training. In a case study, we observed a significant improvement by submaximal intensity interval training.[13] Moreover, recently, Moreno-Suarez *et al.*[24] demonstrated that in patients with LVAD 12 weeks of high-intensity interval training (HIIT) increased peakVO_2 to higher degree than moderate continuous training (MCT). However, this study was single-centre, small ($n = 21$), did not report a control

group and the patients presented with a higher baseline peakVO_2 than the Ex-VAD cohort. Since the large multicentre SMARTEX trial[8] ($n = 261$) demonstrated no significant difference between HIIT and MCT in a HF cohort with similar baseline peakVO_2 to the findings of Moreno-Suarez *et al.*, we would suggest to further investigate the effect of HIIT in LVAD in a multicentre setting.

In retrospect, our assumed group difference of 3 ml/min/kg peakVO_2 was too ambitious and a more conservative approach might have been more appropriate (e.g. 10% difference in peakVO_2, based on what is considered clinically meaningful for HF patients). In addition, the impact of training modality is not fully understood to date. Some trials in HF showed a trend to increase peakVO_2 by adding inspiratory muscle training to a combined aerobic/resistance training.[25] In our trial resistance training was started after 4 weeks to ensure patient adherence and motivation. It is unclear whether an additional inspiratory muscle training or an earlier beginning of resistance training might have influenced parameters of exercise capacity. Thus, factors of exercise response should be investigated further in patients with HF and LVAD.

The 6MWT is a widely used measure of submaximal exercise capacity.[26] In a recent study, 14 m was reported as the minimal clinically important difference (MCID) in patients with HF and reduced ejection fraction.[27] However, MCID depends on the underlying condition, comorbidities, and the patients' self-perception. Previous trials on exercise training in HF demonstrated significant improvement in 6MWT distance.[5,28] In patients with LVAD, a meta-analysis by Ganga *et al.*[14] did not observe a beneficial effect of exercise training on 6MWT when compared to controls. This might have been due to the still modest sample size of the pooled trials and the fact that some trials did not assess submaximal exercise capacity. Ex-VAD demonstrated a mean increase of 43.4 m in the 6MWT. This order of magnitude can be considered clinically relevant[27] for the group of patients studied in Ex-VAD, and may be very important for the patients' well-being and mobility in everyday life. Furthermore, it is considerably higher than in most pharmacological HF trials.[29,30]

Previous trials have suggested a beneficial effect of exercise training on QoL.[10–12,18] In concordance with these studies, in our trial the intervention group scored significantly higher in the KCCQ physical domain (14.3 points, with 5 points considered clinically meaningful) compared to the control group (*Figure 2*). This was due to a small improvement in KCCQ in the intervention group and a significant decrease in KCCQ in the control group (online supplementary *Table S1*.). Our results indicate that exercise training has potential to improve QoL in LVAD patients.

In accordance with previous trials, Ex-VAD demonstrated that exercise is safe in patients with LVAD. Still, the overall number of AEs was high. Previous exercise trials in patients with LVAD did not report overall AEs, but only AEs during exercise: Kerrigan *et al.*[10] reported a syncope in a patient immediately after completing an exercise session. Marko *et al.*[31] reported an episode of non-sustained ventricular tachycardia during exercise training. Ganga *et al.*[14] did not find any relation between aerobic exercise training and AEs. This is compatible with our results: Although the overall number of AEs was high in both groups – which is indicative for disease severity and multimorbidity of the cohort – there were only a few events during and shortly after an exercise session (*Table 2*). We believe that patient education is the most effective way to prevent and to reduce AEs. As such, patients need to learn how to manage fluid and electrolyte intake while training and how to use training equipment without hurting themselves. Electrolytes and kidney function should be monitored carefully, especially when starting a training programme. Further clinical application of exercise training will require well-trained and guided training facilities to recognize and act on AEs from an early stage on.

Adherence to the exercise protocol is a major concern in exercise intervention trials. In the present trial the overall adherence was high given the disease severity of the patient cohort. We noticed a high interest for participation in an exercise intervention. However, traveling to the training facility was a major limitation for many patients on a physical and financial level. We suggest that future trials address this issue.

Ex-VAD is the first trial to compare exercise training in LVAD used as bridging versus destination therapy. As the number of patients receiving an LVAD as destination therapy is steadily growing and life expectancy in this cohort is increasing, we believe that it is of great importance to further investigate this subgroup of LVAD recipients.

Limitations

The Ex-VAD trial has several limitations. The assumptions underlying the power calculation of the primary endpoint were too optimistic as a difference in peakVO_2 of 3 ml/min/kg could not be achieved. The staff conducting the evaluations was not blinded to the treatment group, which could have affected the maximal exhaustion achieved during CPET. However, the respiratory exchange ratio at peak exercise did not differ between groups at baseline and at 12 weeks indicating similar levels of effort during exercise testing. Selection bias might have affected our findings, since only rather mobile and motivated patients participated in the trial. Only very few female participants were included, which is partly due to the small number of female patients with LVAD in the outpatient clinics of the recruiting trial sites (approximately 10%). However, further reasons should be investigated. Although the Ex-VAD trial is the largest trial so far conducted in LVAD patients and the only one with a multicentre setting known to date, the patient number is yet small, and a risk of type I error cannot be excluded.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Acknowledgements

Haley Hartmann, Svenja Broschag, Yasmina Menzel, Lena Gehring; Data Safety Monitoring Board: Stefan Felix, Karl Wegscheider,

Karl-Ludwig Laugwitz. Open Access funding enabled and organized by Projekt DEAL.

Funding

The trial is financially supported by the DZHK (German Centre for Cardiovascular Research; DZHK; GE 2048/2-1, HA 5812/4-1, ED 196/2-1) and by the BMBF (German Ministry of Education and Research).

Conflict of interest: F.S. received institutional grants from Novartis, Abbott, non-financial support from Medtronic and institutional fees (speaker honoraria) from Orion Pharma and Abiomed, outside of the submitted work. C.H.L. declares that he is receiving royalties from Hogrefe Publishers for the German version of the Hospital Anxiety and Depression Scale; during the last 3 years, he has received a lecture honorarium from Pfizer; his research is funded by the German Ministry of Education and Research, the German Research Foundation, and the EU Commission. S.v.H. has been a paid consultant for and/or received honoraria payments from Amomed, AstraZeneca, Bayer, Boehringer Ingelheim, BRAHMS, Edwards Lifesciences, MSD, Novartis, Pfizer, Pharmacosmos, Respicardia, Roche, Servier, Sorin, and Vifor; he reports research support from Amgen, AstraZeneca, Boehringer Ingelheim, Pharmacosmos, IMI, and the German Center for Cardiovascular Research (DZHK). F.E. reports lecture honoraria/research funding from the German Ministry of Education and Research, the DZHK, the German Research Foundation, and the EU Commission; further from Servier, AstraZeneca, Bayer, Merck, Boehringer Ingelheim, BRAHMS, MSD, Novartis, Pfizer, PharmaCosmos, and Vifor. All other authors have nothing to disclose.

References

1. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, *et al.*; ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2022;**24**:4–131. https://doi.org/10.1002/ejhf.2333
2. Crespo-Leiro MG, Metra M, Lund LH, Milicic D, Costanzo MR, Filippatos G, *et al.* Advanced heart failure: A position statement of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2018;**20**:1505–1535. https://doi.org/10.1002/ejhf.1236
3. Jakovljevic DG, McDiarmid A, Hallsworth K, Seferovic PM, Ninkovic VM, Parry G, *et al.* Effect of left ventricular assist device implantation and heart transplantation on habitual physical activity and quality of life. *Am J Cardiol* 2014;**114**:88–93. https://doi.org/10.1016/j.amjcard.2014.04.008
4. Adamopoulos S, Corrà U, Laoutaris ID, Pistono M, Agostoni PG, Coats AJS, *et al.* Exercise training in patients with ventricular assist devices: A review of the evidence and practical advice. A position paper from the Committee on Exercise Physiology and Training and the Committee of Advanced Heart Failure of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2018;**21**:3–13. https://doi.org/10.1002/ejhf.1352
5. O'Connor CM, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ, *et al.*; 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. https://doi.org/10.1001/jama.2009.454
6. Pandey A, Parashar A, Kumbhani D, Agarwal S, Garg J, Kitzman D, *et al.* Exercise training in patients with heart failure and preserved ejection fraction: Meta-analysis of randomized control trials. *Circ Heart Fail* 2015;**8**:33–40. https://doi.org/10.1161/CIRCHEARTFAILURE.114.001615
7. Gomes Neto M, Durães AR, Conceição LSR, Saquetto MB, Ellingsen Ø, Carvalho VO. High intensity interval training versus moderate intensity continuous training on exercise capacity and quality of life in patients with heart failure with reduced ejection fraction: A systematic review and meta-analysis. *Int J Cardiol* 2018;**261**:134–141. https://doi.org/10.1016/j.ijcard.2018.02.076
8. Ellingsen Ø, Halle M, Conraads V, Støylen A, Dalen H, Delagardelle C, *et al.* High-intensity interval training in patients with heart failure with reduced ejection fraction. *Circulation* 2017;**135**:839–849. https://doi.org/10.1161/CIRCULATIONAHA.116.022924
9. Taylor RS, Long L, Mordi IR, Madsen MT, Davies EJ, Dalal H, *et al.* Exercise-based rehabilitation for heart failure: Cochrane systematic review, meta-analysis, and trial sequential analysis. *JACC Heart Fail* 2019;**7**:691–705. https://doi.org/10.1016/j.jchf.2019.04.023
10. Kerrigan DJ, Williams CT, Ehrman JK, Saval MA, Bronsteen K, Schairer JR, *et al.* Cardiac rehabilitation improves functional capacity and patient-reported health status in patients with continuous-flow left ventricular assist devices: The Rehab-VAD randomized controlled trial. *JACC Heart Fail* 2014;**2**:653–659. https://doi.org/10.1016/j.jchf.2014.06.011
11. Hayes K, Leet AS, Bradley SJ, Holland AE. Effects of exercise training on exercise capacity and quality of life in patients with a left ventricular assist device: A preliminary randomized controlled trial. *J Heart Lung Transplant* 2012;**31**:729–734. https://doi.org/10.1016/j.healun.2012.02.021
12. Laoutaris ID, Dritsas A, Adamopoulos S, Manginas A, Gouziouta A, Kallistratos MS, *et al.* Benefits of physical training on exercise capacity, inspiratory muscle function, and quality of life in patients with ventricular assist devices long-term postimplantation. *Eur J Cardiovasc Prev Rehabil* 2011;**18**:33–40. https://doi.org/10.1097/HJR.0b013e32833c0320
13. Christle JW, Boscheri A, Pressler A, Grinninger C, Schramm R, Hagl CM, *et al.* Interval exercise training increases maximal and submaximal exercise performance in heart failure with biventricular assist device therapy. *Int J Cardiol* 2015;**187**:104–105. https://doi.org/10.1016/j.ijcard.2015.03.296
14. Ganga HV, Leung A, Jantz J, Choudhary G, Stabile L, Levine DJ, *et al.* Supervised exercise training versus usual care in ambulatory patients with left ventricular assist devices: A systematic review. *PLoS One* 2017;**12**:e0174323. https://doi.org/10.1371/journal.pone.0174323
15. Bobenko A, Schoenrath F, Knierim JH, Friede T, Verheyen N, Mehra MR, *et al.* Exercise training in patients with a left ventricular assist device (Ex-VAD): Rationale and design of a multicentre, prospective, assessor-blinded, randomized, controlled trial. *Eur J Heart Fail* 2019;**21**:1152–1159. https://doi.org/10.1002/ejhf.1431
16. Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. *J Appl Physiol (1985)* 1986;**60**:2020–2027. https://doi.org/10.1152/jappl.1986.60.6.2020
17. Mirza KK, Szymanski MK, Schmidt T, de Jonge N, Brahmbhatt DH, Billia F, *et al.*; PRO-VAD Investigators. Prognostic value of peak oxygen uptake in patients supported with left ventricular assist devices (PRO-VAD). *JACC Heart Fail* 2021;**9**:758–767. https://doi.org/10.1016/j.jchf.2021.05.021
18. Kugler C, Malehsa D, Tegtbur U, Guetzlaff E, Meyer AL, Bara C, *et al.* Health-related quality of life and exercise tolerance in recipients of heart transplants and left ventricular assist devices: A prospective, comparative study. *J Heart Lung Transplant* 2011;**30**:204–210. https://doi.org/10.1016/j.healun.2010.08.030
19. Bouchla A, Karatzanos E, Dimopoulos S, Tasoulis A, Agapitou V, Diakos N, *et al.* The addition of strength training to aerobic interval training: Effects on muscle strength and body composition in CHF patients. *J Cardiopulm Rehabil Prev* 2011;**31**:47–51. https://doi.org/10.1097/HCR.0b013e3181e174d7
20. 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. https://doi.org/10.1093/eurheartj/ehn222
21. Jankowska EA, Wegrzynowska K, Superlak M, Nowakowska K, Lazorczyk M, Biel B, *et al.* The 12-week progressive quadriceps resistance training improves muscle strength, exercise capacity and quality of life in patients with stable chronic heart failure. *Int J Cardiol* 2008;**130**:36–43. https://doi.org/10.1016/j.ijcard.2007.07.158
22. 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. https://doi.org/10.1016/j.ijcard.2016.07.046
23. Tucker WJ, Beaudry RI, Liang Y, Clark AM, Tomczak CR, Nelson MD, *et al.* Meta-analysis of exercise training on left ventricular ejection fraction in heart failure with reduced ejection fraction: A 10-year update. *Prog Cardiovasc Dis* 2019;**62**:163–171. https://doi.org/10.1016/j.pcad.2018.08.006
24. Moreno-Suarez I, Scheer A, Lam K, Dembo L, Spence AL, Hayward C, *et al.* High-intensity interval training in patients with left ventricular assist devices: A pilot randomized controlled trial. *J Heart Lung Transplant* 2020;**39**:1380–1388. https://doi.org/10.1016/j.healun.2020.08.005
25. Laoutaris ID, Piotrowicz E, Kallistratos MS, Dritsas A, Dimaki N, Miliopoulos D, *et al.*; ARISTOS-HF trial (Aerobic, Resistance, InSpiratory Training OutcomeS in Heart Failure) Investigators. Combined aerobic/resistance/inspiratory muscle training as the 'optimum' exercise programme for patients with chronic heart failure: ARISTOS-HF randomized clinical trial. *Eur J Prev Cardiol* 2021;**28**:1626–1635. https://doi.org/10.1093/eurjpc/zwaa091
26. Rostagno C, Galanti G, Comeglio M, Boddi V, Olivo G, Neri Serneri GG. Comparison of different methods of functional evaluation in patients with chronic

heart failure. *Eur J Heart Fail* 2000;**2**:273–280. https://doi.org/10.1016/s1388-9842(00)00091-x

27. Khan MS, Anker SD, Friede T, Jankowska EA, Metra M, Piña IL, *et al.* Minimal clinically important difference for six-minute walk test in patients with HFrEF and iron deficiency. *J Card Fail* 2023;**29**:760–770. https://doi.org/10.1016/j.cardfail.2022.10.423
28. Giannuzzi P, Temporelli PL, Corrà U, Tavazzi L. Antiremodeling effect of long-term exercise training in patients with stable chronic heart failure. *Circulation* 2003;**108**:554–559. https://doi.org/10.1161/01.CIR.0000081780.38477.FA
29. Anker SD, Comin Colet J, Filippatos G, Willenheimer R, Dickstein K, Drexler H, *et al.*; FAIR-HF Trial Investigators. Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med* 2009;**361**:2436–2448. https://doi.org/10.1056/NEJMoa0908355
30. Abraham WT, Lindenfeld J, Ponikowski P, Agostoni P, Butler J, Desai AS, *et al.* Effect of empagliflozin on exercise ability and symptoms in heart failure patients with reduced and preserved ejection fraction, with and without type 2 diabetes. *Eur Heart J* 2021;**42**:700–710. https://doi.org/10.1093/eurheartj/ehaa943
31. Marko C, Danzinger G, Käferbäck M, Lackner T, Müller R, Zimpfer D, *et al.* Safety and efficacy of cardiac rehabilitation for patients with continuous flow left ventricular assist devices. *Eur J Prev Cardiol* 2015;**22**:1378–1384. https://doi.org/10.1177/2047487314558772