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STUDY DESIGN

# Exercise training in Diastolic Heart Failure (Ex-DHF): rationale and design of a multicentre, prospective, randomized, controlled, parallel group trial

**Frank Edelmann[1,2,3,4]*†, Anna Bobenko[1,2†], Götz Gelbrich[5,6], Gerd Hasenfuss[3,4], Christoph Herrmann-Lingen[4,7], André Duvinage[8], Silja Schwarz[8], Meinhard Mende[9], Christiane Prettin[9], Tobias Trippel[1,2], Ruhdja Lindhorst[1,2], Daniel Morris[1], Elisabeth Pieske-Kraigher[1], Kathleen Nolte[3,4], Hans-Dirk Düngen[1,2], Rolf Wachter[3,4], Martin Halle[8,10‡], and Burkert Pieske[1,2,11‡]**

[1]Charité Universitätsmedizin Berlin, Department of Cardiology, Berlin, Germany; [2]DZHK (German Centre for Cardiovascular Research), Partner Site Berlin, Berlin, Germany; [3]University of Göttingen Medical Centre, Department of Cardiology and Pneumology, Göttingen, Germany; [4]DZHK (German Centre for Cardiovascular Research), Partner Site Göttingen, Göttingen, Germany; [5]University of Würzburg, Institute for Clinical Epidemiology and Biometry, Würzburg, Germany; [6]University Hospital Würzburg, Clinical Trial Centre, Würzburg, Germany; [7]University of Göttingen Medical Centre, Department of Psychosomatic Medicine and Psychotherapy, Göttingen, Germany; [8]Technische Universität München, Department of Prevention, Rehabilitation and Sports Medicine, Munich, Germany; [9]University of Leipzig, Clinical Trial Centre (KKS), Leipzig, Germany; [10]DZHK (German Centre for Cardiovascular Research), partner site Munich Heart Alliance, Munich, Germany; and [11]Deutsches Herzzentrum Berlin (DHZB), Department of Cardiology, Berlin, Germany

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Heart failure with preserved ejection fraction (HFpEF) is a common disease with high incidence and increasing prevalence. Patients suffer from functional limitation, poor health-related quality of life, and reduced prognosis. A pilot study in a smaller group of HFpEF patients showed that structured, supervised exercise training (ET) improves maximal exercise capacity, diastolic function, and physical quality of life. However, the long-term effects of ET on patient-related outcomes remain unclear in HFpEF. The primary objective of the Exercise training in Diastolic Heart Failure (Ex-DHF) trial is to investigate whether a 12 month supervised ET can improve a clinically meaningful composite outcome score in HFpEF patients. Components of the outcome score are all-cause mortality, hospitalizations, NYHA functional class, global self-rated health, maximal exercise capacity, and diastolic function. After undergoing baseline assessments to determine whether ET can be performed safely, 320 patients at 11 trial sites with stable HFpEF are randomized 1:1 to supervised ET in addition to usual care or to usual care alone. Patients randomized to ET perform supervised endurance/resistance ET (3 times/week at a certified training centre) for 12 months. At baseline and during follow-up, anthropometry, echocardiography, cardiopulmonary exercise testing, and health-related quality of life evaluation are performed. Blood samples are collected to examine various biomarkers. Overall physical activity, training sessions, and adherence are monitored and documented throughout the study using patient diaries, heart rate monitors, and accelerometers. The Ex-DHF trial is the first multicentre trial to assess the long-term effects of a supervised ET programme on different outcome measures in patients with HFpEF.

**Keywords** Heart failure • Heart failure with preserved ejection fraction • Exercise intervention • Supervised exercise training • Diastolic dysfunction

*Corresponding author. Department of Cardiology and Pneumology, University of Göttingen, Robert-Koch-Straße 40, 37075 Göttingen, Germany. Tel: +49-551-39-12100, Fax: +49-551-3913354, Email: fedelmann@med.uni-goettingen.de; Medizinische Klinik m. S. Kardiologie, Charité Universitätsmedizin Berlin, Augustenburger Platz 1, 13353 Berlin, Germany. Tel: +49-30-450-653-731, Fax: +49-30-450-755-3731, Email: frank.edelmann@charite.de
†These authors contributed equally to first authorship.
‡These authors contributed equally to last authorship.

# Introduction

Heart failure with preserved ejection fraction (HFpEF) is a common disease, especially in the elderly with classical risk factors such as hypertension, diabetes, and sedentary lifestyle. Patients suffer from substantial functional limitation and poor health-related quality of life (HRQoL).[1,2] Furthermore, impaired exercise capacity is related to outcome in these patients.[3] Epidemiological data show that the prevalence of HFpEF has increased in the last decades.[4] Morbidity and mortality rates are quite comparable to heart failure with reduced ejection fraction (HFrEF).[4,5] However, in contrast to HFrEF, no specific therapeutic options have been proved efficacious in HFpEF, although various pharmacological agents have been evaluated in large clinical trials.[6–9] Therefore, currently, usual care mainly consists of risk factor control and diuretic medication for minimizing symptoms.[10]

Exercise training (ET) has emerged as an effective treatment modality in HFrEF. HF-ACTION gave evidence that ET decreases morbidity and hospitalization rate in patients with HFrEF.[11] Exercise training also improves signs, symptoms, and HRQoL in HFrEF significantly.[11–13] In addition, ET has previously been shown to be well tolerated and very safe in patients with HFrEF.[11,14]

In HFpEF, data on the effects of ET are still scarce. Several studies previously showed that ET improves peak and submaximal exercise capacity [measured by peak oxygen uptake (peak$VO_2$), ventilatory anaerobic threshold and 6 min walking distance].[15–19] Exercise training reduces symptoms and improves physical dimensions of HRQoL in HFpEF.[15–17] In addition, it has been shown to improve diastolic function.[17] As previously seen in HFrEF, ET has been proven to be safe and well tolerated in HFpEF patients.[17,18] In particular, none of these trials observed intervention or testing-related adverse events of clinical relevance upon further investigation.

However, long-term efficacy and safety data on ET in HFpEF are lacking. Although ET seems to be a promising therapeutic option for HFpEF patients, findings from all previous ET trials[15–18] cannot necessarily lead to a general endorsement of ET for this patient cohort. None of these predominantly single-centre trials enrolled a sufficient number of patients and enabled a long-term exercise intervention to properly evaluate the impact of ET on clinical outcome measures in HFpEF.

Therefore, the Exercise training in diastolic heart failure (Ex-DHF) trial was designed as the first multicentre trial to evaluate the effects of supervised ET on patient-related outcome measures in a HFpEF population.

# Study design

The primary objective of the Ex-DHF trial is to determine whether ET on top of usual care is superior to usual care alone in improving a clinical composite outcome score in HFpEF patients. The score includes all-cause mortality, hospitalizations, symptoms, global self-assessment, exercise capacity, and diastolic function.

The Ex-DHF trial also evaluates whether ET improves maximal and submaximal exercise tolerance, HRQoL, echocardiographic parameters of diastolic and systolic function, left ventricular geometry and dimensions, and markers of neurohumoral activation in HFpEF patients.

## Trial population

The Ex-DHF trial aims to enrol 320 patients with HFpEF (NYHA classes II and III) according to international guidelines.[20,21] A predefined set of inclusion and exclusion criteria (*Table 1*) was selected in order to ensure that only patients with definite HFpEF are enrolled, to ensure feasibility and safety of both cardiopulmonary exercise testing (CPET) and ET during the trial, and to minimize the number of patients lost to follow-up. Briefly, inclusion criteria are left ventricular ejection fraction of ≥50% and predefined criteria on diastolic function (evaluated by tissue Doppler-derived E/e′ ratio) obtained during baseline echocardiography. Stable optimal pharmacological therapy according to the published guidelines for 4 weeks before enrolment is strongly advocated. Since the Ex-DHF trial wants to determine the effect of supervised training on top of usual care compared with usual care alone, patients are allowed to perform any kind of leisure time physical activity as long as they have a peak$VO_2$ < 25 mL/kg/min at baseline measurement.

## Key measurements

### Echocardiography

To ensure the high quality and validity of echocardiographic data obtained in the Ex-DHF trial, a core lab acts as blinded reference centre for all aspects related to echocardiography. All images from parasternal and apical views are obtained according to a standard operation procedure (SOP), which is based on standard views as described in the guidelines of the American Society of Echocardiography[20] and of the European Society of Cardiology (ESC).[21] Prior to the start of recruitment, all participating echocardiographers are trained and certified by the core lab. At baseline an echocardiograph is performed to assess systolic and diastolic function and to rule out other cardiac disease that may influence exercise capacity. Echocardiography is repeated regularly throughout the trial. Data are stored digitally and analysed by the core lab.

### Cardiopulmonary exercise testing

Before randomization, CPET is performed to determine whether patients can exercise safely, including checking for abnormal blood pressure responses, early ischaemic changes, and significant arrhythmias as recommended by international guidelines.[22] Symptom-limited CPET is performed according to SOP using a bicycle ergometer protocol, starting at a workload of 20 W, followed by a stepwise 20 W increment every 2 minutes. CPET is repeated 3, 6, 9, and 12 months after randomization for all patients. All data are forwarded to a blinded CPET core lab to ensure good data quality. The core lab trains and certifies all investigators performing CPET prior to start of recruitment.

## Randomization and blinding

After informed consent and screening, patients are randomized in a 1:1 ratio to either ET or usual care. The trial uses an online

**Table 1 Inclusion and exclusion criteria of Ex-DHF**

**Inclusion criteria**

- Stable symptomatic heart failure with preserved ejection fraction (diagnosis according to the recommendations of the European Society of Cardiology):[21]
  - NYHA class II–III, peak$VO_2$ <25 mL/kg/min
  - LVEF ≥50%
  - E/e′ >15 **or** 15 ≥E/e′ >8 and any of the following: NT-proBNP >220 ng/L **or** atrial fibrillation
- Age ≥18 years
- Symptom severity and heart failure medication were stable during the last 4 weeks
- General ability of the patient to declare willingness to participate in this trial
- Written informed consent

**Exclusion criteria**

- Non-cardiac causes for heart failure-like symptoms
  - Chronic obstructive pulmonary disease GOLD stages ≥II
  - Anaemia (haemoglobin <11 mg/dL)
  - Significant renal dysfunction (eGFR <30 mL/min/1.73 $m^2$ indexed to BSA)
  - Significant peripheral artery disease (Fontaine ≥IIb)
  - Musculoskeletal disease that contributes to reduced exercise performance
  - Specific cardiomyopathy (e.g. amyloidosis)
  - Haemodynamically significant valvular disorders
- Significant coronary artery disease (current angina pectoris CCS ≥II or positive stress test, myocardial infarction or coronary artery bypass graft within the last 3 months)
- Any inability or contraindication to participate in CPET or in an exercise programme (e.g. physiological, mental) or to supply essential information (e.g. questionnaire, diary)
- Ineffective control of resting blood pressure (≥140/90 mmHg or ≥160/100 mmHg with ≥3 antihypertensive drugs) or of resting heart rate (≥100 b.p.m.)
- Expected low compliance (e.g. by travel distance to trial site; planned absences longer than 4 weeks during follow-up) or ongoing drug abuse
- Pregnant or nursing women
- Concomitant participation in other interventional clinical trials

BSA, body surface area; CCS, Canadian Cardiovascular Society; CPET, cardiopulmonary exercise testing; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; peak$VO_2$, peak oxygen uptake.

randomization protocol of the Coordination Centre for Clinical Trials Leipzig stratified by centre, by NYHA class (II vs. III), and by peak$VO_2$ (≥20 vs. <20 mL/min/kg). Pocock's algorithm[23] is applied. A study flow chart is shown in *Figure 1*.

## Usual care

Since no specific pharmacological therapy has been found for HFpEF so far, guidelines suggest control of both cardiovascular and non-cardiovascular co-morbidities.[10] Also diuretics are recommended to ease heart failure symptoms. The Ex-DHF trial strives to ensure that patients are already receiving appropriate and stable guideline-based care prior to entering the trial.

Patients of both treatment groups receive the same number of visits throughout the trial. All patients are examined at baseline, and at 1, 3, 6, 9, and 12 months after randomization. Examination includes medical history, physical examination, anthropometry, biochemical analysis, ECG, echocardiography, exercise performance testing (6 min walk testing and CPET), and multiple validated self-reporting questionnaires assessing physical activity, exercise motivation, self-efficacy, HRQoL, and distress.

Also all patients are advised to follow their daily leisure time physical activity as usual and are regularly encouraged to be physically active throughout the trial. Since daily physical activity is an important co-variable it is therefore continuously recorded using patient diaries, as well as HRQoL and activity questionnaires. The feasibility and reliability of this approach has been successfully documented in the Ex-DHF pilot trial.[17]

## Exercise training intervention

In addition to usual care, patients randomized to ET perform supervised ET a minimum of three times per week for 12 months (*Figure 1*). Also patients are regularly encouraged to be physically active on the other days. The training is a combination of both endurance and resistance training, based on the Ex-DHF pilot study.[17] The basic training plan for Ex-DHF is summarized in *Table 2*.

### Endurance training

The first 4 weeks of training are exclusively endurance training on a bicycle ergometer. At baseline, exercise intensity of endurance training is determined by CPET using relative to peak$VO_2$ (%peak$VO_2$). Patients start endurance training at 50%peak$VO_2$ in the first 2 weeks and increase intensity up to 70%peak$VO_2$ after 1 month. Also peak$VO_2$ is adapted at 3, 6, and 9 months based on repeated CPET. Including 10 min for warm-up and cool-down, exercise volume of endurance training increases from 30 min in the first 2 weeks to 60 min after 3 months (*Table 2*). During ET, heart rate is monitored by the trainer using a heart rate monitor (Polar FT4, Polar Electro, Finland).

### Resistance training

After the initial 4 weeks, resistance training is included into a minimum of two of the three training sessions per week.

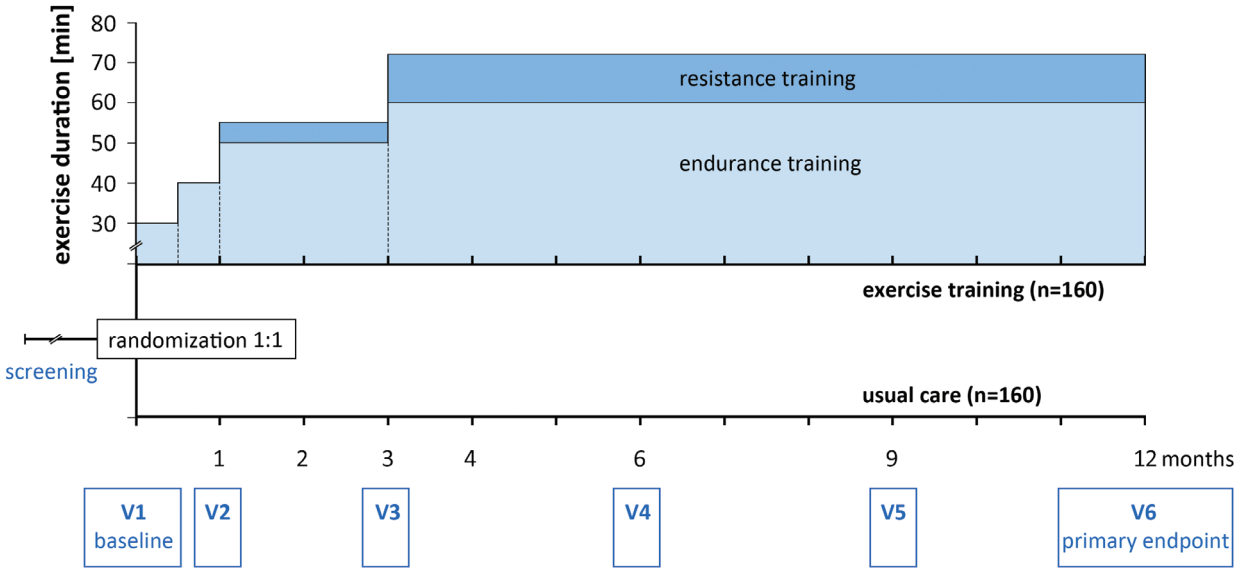


**Figure 1** Flow chart of the trial. After screening, patients are randomized 1:1 at baseline visit to either usual care or exercise training (including endurance and resistance training). Visits are scheduled at 1, 3, 6, 9, and 12 months after randomization. Duration and intensity of supervised exercise training are increased stepwise.

**Table 2 Intervention schedule**

| Week | Endurance training (three per week) | | Resistance training (two per week) | |
|---|---|---|---|---|
| | %peak$VO_2$ | Duration (min) | %1-RM | Duration (min) |
| 1–2 | 50 | 30 | | |
| 3–4 | 60 | 40 | | |
| 5–12 | 70 | 50 | 60 | 5 |
| 13–52 | 70 | 60 | 60 | 12 |

%1-RM, exercise intensity relative to one-repetition-maximum; %peak$VO_2$, exercise intensity relative to peak oxygen uptake.

Resistance training is performed as a set of seven exercises on weight-training machines to work out the major muscle groups. Each exercise consists of 12–15 repetitions and is performed at 60% of one-repetition-maximum (1-RM) with one repetition lasting 3 s; 1-RM testing is performed regularly according to the corresponding SOP. After 3 months of intervention, patients increase resistance training to two sets, allowing 90 s of rest between sets.

## Adherence

Adherence refers to the degree to which trial participants comply with the intervention protocol. In the Ex-DHF trial, this is expected to be challenging due to the frequency and long duration of the ET intervention. Patients need to complete at least 66.6% of the possible supervised training sessions to be considered on-treatment.

The Ex-DHF trial uses several approaches to promote adherence. First, patients randomized to ET are regularly encouraged to attend supervised training sessions by the investigator and by the trainer. All patients are encouraged to engage in leisure time physical activity by the investigator. Training attendance and physical activity diaries are used to monitor adherence of all participants throughout the trial. Furthermore, for a subset of randomly assigned patients ($n = 80$) from both groups, activity data in patient diaries will be correlated with objective physical activity measurement using accelerometers during interim study visits at 3 month intervals.

## Endpoints

The primary endpoint for the Ex-DHF trial is a combined outcome score taking the values 'worsened', 'unchanged', or 'improved'. This score has previously been shown to be useful as expected outcome in specific trials[25] and was modified for a HFpEF population. For each patient who completed the trial, the primary endpoint will be determined using the flow chart shown in *Figure 2*. For every drop-out patient the primary endpoint will be determined using the flow chart shown in *Figure 3*. The outcome score consists of mortality, hospitalizations, symptoms (NYHA class), and global self-rated health (patients' self-assessment of own current health status on a seven-point scale, from 'very bad' to 'very good'),[24] maximal exercise capacity (peak$VO_2$), and diastolic function (E/e').

Secondary endpoints include components of the primary endpoint, submaximal exercise capacity, echocardiographic parameters of left ventricular geometry and dimensions, diastolic and systolic function, HRQoL/distress, and markers of neuroendocrine activation (*Table 3*).

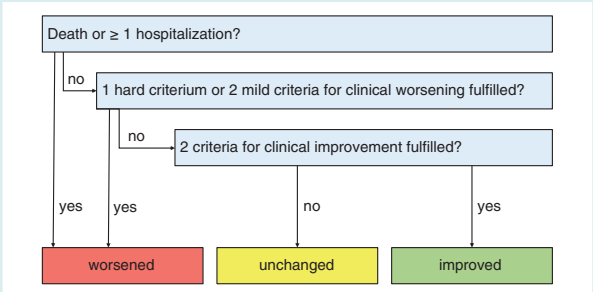


**Figure 2** Primary endpoint flow chart. If hospitalization criterion is fulfilled, it should be evaluated as 'yes' except for reasons definitely unrelated to heart failure or the trial's exercise intervention (to be assessed by blinded endpoint committee). 'Hard criteria for clinical worsening': increase of E/e′ by ≥30% of baseline; decrease of peak oxygen uptake (peak$VO_2$) by ≥30% of baseline; decrease of global self-assessment by ≥3 levels or by 2 levels to the worst level. 'Mild criteria for clinical worsening': increase of E/e′ by ≥15% of baseline; decrease of peak$VO_2$ by ≥15% of baseline; increase in NYHA class; decrease of global self-assessment by 2 levels or to the worst level. 'Criteria for clinical improvement': decrease of E/e′ by ≥15% of baseline; increase of peak$VO_2$ by ≥15% of baseline; decrease in NYHA class; increase of global self-assessment by 2 levels or to the best level.

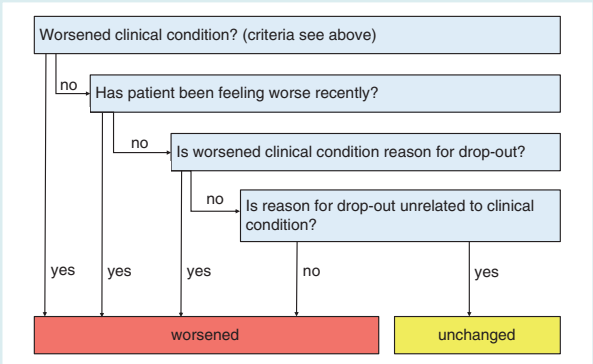


**Figure 3** Primary endpoint flow chart—drop-out. In case of patient drop-out, the primary endpoint will be determined using this flow chart.

## Statistical analysis

Sample size calculation is based on data from our pilot study,[17] where 35% worsening was observed in the usual care group and 30% improvement of peak$VO_2$ was seen in the intervention group within 3 months (when applying primary endpoint criteria of Ex-DHF trial). Corresponding to the I-PRESERVE trial[6] the first assumption is that 25% of usual care patients worsen within 1 year including 10% cases of death or hospitalization, which is much smaller than indicated in observational cohorts in HFpEF.[3,4,7] The second assumption is that 5% of usual care patients improve spontaneously. The third assumption is that there is a small reduction of mortality and hospitalization in the exercise group (10% relative, 1% absolute reduction). The fourth assumption is that clinical worsening without death and hospitalization is substantially reduced but, unlike in the Ex-DHF pilot trial data, not completely avoided (60% relative, 9% absolute reduction). This yields a total rate of 15% of worsening in the exercise group. The fifth assumption is that the anticipated rate of improvement in the exercise group is only 20%, which is two-thirds of the rate observed in the Ex-DHF pilot trial. With these rather conservative assumptions, 160 patients per arm should be available for analysis.

The power of 0.98 is chosen in order to achieve satisfactory power also for secondary endpoints. In particular, a reduction of geometric mean NT-proBNP to two-thirds of the baseline level by the intervention is considered worthwhile to be detected. Assuming no change in the controls, this corresponds to a difference between groups of 0.585 on the $\log_2$ scale. The standard deviation of $\log_2$ (NT-proBNP) in comparable patients of the German Competence Network Heart Failure was 1.665 ($n = 1752$). Assuming that 80% of 320 recruited patients (i.e. $n = 128$ per group) provide baseline and follow-up NT-proBNP, we have a power of 0.8 to detect this difference at type I error level of 0.05. Thus, the sample size chosen for the trial provides excellent power for detecting the hypothesized treatment effect of a prolonged supervised exercise intervention on clinical meaningful endpoints in HFpEF while accounting for realistic levels of adherence.

The primary endpoint in both treatment groups will be compared by the exact test for Kendall's tau-b following the intent-to-treat principle. Ordinal regression will be applied to adjust for covariates. Sensitivity analysis will examine possible

**Table 3 Secondary endpoints of Ex-DHF**

- Components of the primary endpoint (all-cause mortality, cardiovascular hospitalizations, change in NYHA class, change in global self-assessment, change in peak$VO_2$, change in E/e′) after 6 and 12 months
- Change in echocardiographic parameters of diastolic function (LAVI, grade of diastolic function, atrial function, e′, E/A, DT, IVRT), systolic function (e.g. LVEF, GLS), left ventricular dimensions (LVEDD, LVESD), and structure (LVMI) after 6 and 12 months
- Change in quality of life (e.g. SF-36, MLHFQ, HADS, PHQ-9) after 6 and 12 months
- Change in ventilatory efficacy ($VE/VCO_2$) and submaximal exercise capacity (anaerobic threshold, 6 min walk distance) after 6 and 12 months
- Change in neurohumoral activation (NT-proBNP) after 6 and 12 months
- Safety and tolerability of training intervention
- Gender aspects of all primary and secondary endpoints

DT, deceleration time; GLS, global longitudinal strain; HADS, Hospital Anxiety and Depression Scale; IVRT, isovolumic relaxation time; LAVI, left atrial volume index; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVMI, left ventricular mass index; MLHFQ, Minnesota Living with Heart Failure Questionnaire; peak$VO_2$, peak oxygen uptake; PHQ-9, Patient Health Questionnaire; SF-36, short form (36) health survey.

alterations of the primary result when the definition of the combined endpoint is modified. Furthermore, it will be analysed by separate analysis of the components of the primary endpoint whether essentially contradictory statements are suggested.

For secondary endpoints, Kaplan–Meier survival analysis and Cox regression will be carried out for death and hospitalization, their combination, and cause-specific events. Quantitative measures of exercise capacity, diastolic function, myocardial remodelling, physical fitness, neurohumoral activation, and HRQoL will be analysed by repeated measurement analysis of covariance with the baseline quantity of the measure as covariate and treatment as factor. Multiple regression analyses will be carried out for the most important quantitative endpoints. Special attention will be given to the influence of sex, age, training compliance, and daily physical activity.

For safety analysis, a frequency analysis will be carried out for adverse events possibly caused by ET. The extent of ET adjustment following adverse events will be described. Identification of covariates of adverse events will be done by logistic or Cox regression. A possible relationship of drop-out to preceding adverse events will be examined.

## Trial organization

The Principal Investigator, the study coordinator and the Coordination Centre for Clinical Trials Leipzig are responsible for all aspects of the study protocol and amendments. The Steering Committee guarantees scientific oversight and consulting in all study-related aspects. Additional scientific input is provided by an external advisory board which acts in close collaboration with the Steering Committee. The Data Safety and Monitoring Board (DSMB) operates independently of the other study committees and of the sponsor. The DSMB reviews the progress of the trial and, under blinded conditions, controls the safety of the patients enrolled in Ex-DHF. Before enrolling patients, the protocol was approved by the relevant institutional review boards, research ethics boards, and ethics committees of all the participating centres and the Coordination Centre (see *Appendix*).

The clinical trial is conducted in accordance with local laws and ICH guidelines for good clinical practice issued in June 1996 and CPMP/ICH/135/95 from September 1997 taking into account the *Declaration of Helsinki* and all its revisions. The study has been approved by the Regional Committees for Medical Research Ethics of all participating centres. A DSMB and an Endpoint Committee have been established.

The study was registered after preliminary approval by the ethics committee at http://www.isrctn.com. The registration number is ISRCTN86879094.

# Discussion

The Ex-DHF trial is the largest randomized controlled trial on ET in HFpEF performed to date. To our knowledge, of all exercise trials in HFpEF, the Ex-DHF trial has the largest patient number, the longest patient follow-up, and a novel multicentre approach. It represents a critical step to enable a large-scale outcome trial in HFpEF and to establish ET as a therapy for patients with diastolic dysfunction.

Although the prevalence of HFpEF is increasing and its morbidity and mortality are high,[4,5] an evidence-based pharmacological treatment is still missing.[6–9] Exercise training has been found to improve exercise capacity and quality of life in patients with HFrEF and has shown a beneficial effect on mortality and hospitalization rate.[11,12]

Previously a few smaller trials have investigated ET in HFpEF. However, the single-centre trials of Smart *et al.*[15] and Gary *et al.*[16] provided only a short follow-up, did not select patients according to guidelines, and either did not provide a control group or did not evaluate diastolic function. Kitzman *et al.*[18] conducted the first single-centre, single-blind randomized controlled trial on ET in older HFpEF patients. However, diastolic dysfunction was not required as an inclusion criterion. In the multicentre Ex-DHF pilot trial[17] all patients fulfilled the diagnostic criteria for HFpEF defined by the ESC[21] and diastolic function was evaluated as an endpoint. Nevertheless, the follow-up was not sufficient to evaluate the effect of ET on clinical outcome.

The current multicentre Ex-DHF trial adapted the inclusion and exclusion criteria of its pilot trial.[17] The patient population of the Ex-DHF trial will be fundamentally representative of HFpEF patients, including both genders, individuals of low socioeconomic status, and individuals of ethnic minorities. The Ex-DHF trial provides the longest follow-up performed to date. However, the Ex-DHF investigators recognize that the patient number and the duration of follow-up are not sufficient to evaluate pure outcome (e.g. mortality) in a HFpEF population. Therefore, a clinical composite score[25] was chosen to first-time evaluate outcome-related measures. The score has earlier been incorporated into various drug and device trials on treatment of chronic heart failure and has been more sensitive than conventional approaches in evaluating the treatment effect. By choosing the composite score as primary endpoint, the Ex-DHF trial is the first exercise intervention trial that considers clinical outcome in HFpEF patients.

The training programme for the Ex-DHF trial was adapted from its pilot study[17] where it has been shown to be feasible and safe, and achieved high adherence. However, given the current and previous guidelines on exercise in heart failure[10] it would be unethical not to recommend any physical activity. Therefore, all patients of the Ex-DHF trial are encouraged to be physically active in their leisure time. The Ex-DHF investigators recognize that patients in the usual care arm do not have the potential benefit of interacting with exercise trainers, which patients of the ET arm have during supervised training sessions.

Feasibility of supervised training and attendance will be critically evaluated during the Ex-DHF trial. To implement ET as a standard therapy for HFpEF a translation of ET into clinical practice has to be made possible. The Ex-DHF investigators are convinced of its feasibility: endurance training is easy to perform and the chosen resistance training exercises on weight-lifting machines are classical and can be performed on regular fitness centre equipment. Also heart rate monitoring is easy to learn and CPET is done regularly in medical centres. Therefore, translation into clinical practice should be feasible making ET a promising therapy option for HFpEF patients.

Since adherence is a substantial factor for ET to successfully improve exercise capacity in HFpEF patients, we have included several psychological constructs to evaluate adherence barriers. In

addition, we will investigate whether there are patient subgroups that might benefit from ET more than others.

Borlaug[26] suggests that exercise intolerance in HFpEF is associated with reduced peak cardiac output due to impaired myocardial contractility, blunted heart rate response, and peripheral vascular vasodilator reserve. If the supervised ET intervention is identified as beneficial on clinical outcome measures in HFpEF, various possible mechanisms might account for the positive effect. These mechanisms include improvement in central cardiac function,[17,27] in local blood flow and function in metabolically more active skeletal muscle,[28,29] in baroreceptor or muscle chemoreflex function resulting in down-regulation of autonomic function and in inflammatory state,[27] as well as combinations of these mechanisms. Kitzman *et al.*[18,28] suggested peripheral mechanisms such as skeletal muscle perfusion and oxygen utilization to be of major impact for training-related increase of peak$VO_2$. In a sub-analysis, Haykowsky *et al.*[29] demonstrated a significant training-related increase in peak arterial–venous oxygen compared with the control group. In the Ex-DHF pilot trial, Edelmann *et al.*[17] showed that ET is associated with reduced collagen levels compared with usual care, which have previously been shown to be increased in HFpEF and in patients with increased ventricular stiffness.[30] Also ET significantly improves E/e′ and left atrial volume index, and therefore in consequence improves left ventricular filling pressures.[17] However, the definite impact of ET on diastolic function remains unclear[19] and whether E/e′ is a key measure of diastolic function has to be discussed in the future. Substudies of the Ex-DHF trial will therefore assess the effects of ET on inflammatory markers, metabolic parameters,[31] collagen turnover, as well as on vascular function and ventriculo–arterial coupling, and novel non-standard echocardiographic parameters of systolic and diastolic function.

# Conclusion

Ex-DHF will be the first and currently largest randomized multicentre trial to determine the benefit of supervised ET on a clinical composite outcome score in HFpEF patients.

## Funding

The trial is funded by the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG; GE 2048/2-1, HA 5812/4-1, ED 196/2-1).

**Conflict of interest:** none declared.

# Appendix

# Ex-DHF trial organization

**Principal investigator:** Frank Edelmann

**Steering Committee:** Frank Edelmann, Burkert Pieske, Martin Halle, Silja Schwarz, Götz Gelbrich, Stephan Gielen, Hans-Dirk Düngen

**Endpoint Committee:** Albert W. Schömig, Stefan Störk, Rainer Hambrecht

**Data Safety Monitoring Committee:** Stefan Anker, Hugo Saner, Mitja Lainscak, Andrea Berghold

**Biometry:** Götz Gelbrich, Meinhard Mende

**Project and Data Management:** Christiane Prettin, Birgit Saumer

**Monitoring:** Daniela Hesse, Elke Albrecht

**Sponsor:** Georg-August-Universität Göttingen

**Study coordination:** Frank Edelmann

**Coordination of scientific ad-on projects:** Axel Pressler

**Reference centres:** Martin Halle, Silja Schwarz (CPET and exercise training); Dorit Knappe, Frank Edelmann, Elisabeth Pieske-Kraigher, Daniel A. Morris (echocardiography); Christoph Herrmann-Lingen (psychometric analysis); Michael Oellerich, Lutz Binder (laboratory analyses)

**Trial sites:** Frank Edelmann, Rolf Wachter, Göttingen; Hans-Dirk Düngen, Berlin; Andreas Nieß, Tübingen; Jürgen M. Steinacker, Ulm; Alexander Schmeißer, Rüdiger Braun-Dullaeus, Magdeburg; Till Neumann, Essen; Rainer Hambrecht, Bremen; Martin Halle, Silja Schwarz, München; Burkert Pieske, Graz/Austria; Markus Dörr, Greifswald; Markus Knapp, Schwäbisch Hall.

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