Hybrid comprehensive telerehabilitation in heart failure patients (TELEREH-HF): A randomized, multicenter, prospective, open-label, parallel group controlled trial—Study design and description of the intervention

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Background Guidelines recommend exercise training as a component of heart failure (HF) management. There are large disparities in access to rehabilitation and introducing hybrid comprehensive telerehabilitation (TR) consisting of remote monitoring of training in patients' homes might be an optimal solution in Poland.

Purpose The primary objective of the TELEREH-HF trial is to determine whether introducing TR will significantly increase days alive and out of hospital compared with usual care. The secondary objectives including assessment the effects of TR compared to usual care on all-cause and cardiovascular mortality and all-cause, cardiovascular and HF hospitalization. The tertiary analyses include: evaluation of the safety, effectiveness, quality of life, depression, anxiety, patients' acceptance of and adherence to TR.

Methods The TELEREH-HF study is a randomized, multicenter, prospective, open-label, parallel group controlled trial in 850 HF patients after a hospitalization incident in NYHA I-III and LVEF≤40%. Patients were randomized to TR + usual care (TR group) or to usual care only (control group) and are followed for a maximum of 24 months. The TR group patients underwent a 9-week TR program consisting of an initial stage (1 week) conducted at hospital and a basic stage (8-week) home-based TR five times weekly.

Results All patients were randomized and completed initial intervention in the TR group. The follow up of both groups is in progress.

Conclusion The TELEREH-HF trial will provide novel data on the effects of telerhabilitation on hospitalization and mortality in HF patients, and on safety, quality of life, depression, anxiety and acceptance of and adherence to this intervention. (Am Heart J 2019;217:148-58.)

The epidemic of heart failure (HF) is one of the fastest developing unwanted phenomena stimulated by the civilization development, which generates worrying social and economic effects. The estimated number of patients suffering from HF is about 800 thousand in Poland and about 16 million in Europe and around 26 million worldwide.[1-3] The number of HF patients is rising and combined with an increased frequency of HF related hospitalization and rehospitalization leads to financial stress not only for specific health care systems, but also for entire national budgets.[4] The future challenge is to organize effective and holistic management for HF patients, as suggested in the guidelines of the European Society of Cardiology (ESC), American Heart Association (AHA) and American College of Cardiology (ACC).[1-6]

The tailored, holistic management for HF patients could encompass suitable treatment, exercise training, remote monitoring of cardiovascular implantable electronic

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devices (CIEDs) and regular follow-up also using telemedicine approaches. Current guidelines strongly recommend exercise training as an important component of HF patients therapy and also indicate that remote monitoring of CIEDs may be considered for use in the selected patients with HF.[1,2,7-13] Yet remote patient management, due to variable clinical trial results, requires further research.[14-23]

Unfortunately the participation in cardiac rehabilitation programs is insufficient and there are large regional disparities in access to rehabilitation both in Poland and in Europe.[24-27] A ExtraHF survey showed that less than 20% of patients with HF are involved in cardiac rehabilitation.[24] On the other hand, according to data from the Polish Registry of Acute Coronary Syndromes and Acute Myocardial Infarction, cardiac rehabilitation was performed in 19–23% cases in secondary prevention myocardial infarction patients discharged with left ventricular systolic dysfunction.[25] An excessive number of patients in Poland does not have access to this highly recommended therapy, mainly due to lack of resources or logistics, that is, regional disparities with access to ambulatory rehabilitation (eg, long distance transportation issues, lack of local caretakers and referrals, etc) as well as long waiting lists, all in despite the fact that rehabilitation programs are publicly covered.[25]

These problems can be solved by introducing hybrid comprehensive TR in HF patients. According to its definition it includes telecare [telemonitoring of: symptoms, parameters (such as ECG, blood pressure, weight) from external devices and parameters of CIEDs] and the remote supervised exercise training. The hybrid TR program is initiated during an in-hospital stay, and later on patients have to continue the remotely supervised exercise training at home over eight additional weeks combined with a multi-parameter telemonitoring. [28,29] It is worth to point out that in line with current recommendations, proposed model of TR encompasses all core components of comprehensive cardiac rehabilitation.[28] In contrast to the current telemedicine research, in which the usefulness of passive telemonitoring in patients with HF was evaluated, our study will assess multidisciplinary telemonitoring combined with the interactive remote supervised rehabilitation program.

We designed the TELEREH-HF trial—a randomized, multicenter, prospective, open-label, parallel group controlled study to determine if a hybrid model of comprehensive TR in HF patients influences days alive and out of hospital (DAOH) and prognosis when compared with usual care.

Methods

Objectives

The primary objective of the TELEREH-HF trial is to determine whether introducing a novel hybrid model of comprehensive TR in HF patients will significantly increase DAOH when compared with usual care.

The secondary objectives are to assess the effects of a hybrid comprehensive TR compared to usual care on all-cause and cardiovascular (CV) mortality and all-cause, CV and HF hospitalization.

The tertiary analyses will include: evaluation of the safety, effectiveness, quality of life (QoL), depression, anxiety, patients acceptance of and adherence to a hybrid comprehensive TR.

Study design

The TELEREH-HF study is a randomized, multicenter, prospective, open-label, parallel group controlled trial introducing a novel hybrid comprehensive TR in HF patients (Clinical Trials.gov. NCT 02523560).

The study conduct is guided by good clinical practice, in accordance with the Declaration of Helsinki and the laws and regulations applicable in Poland. The main investigator and Steering Committee (see Appendix 1) designed the trial and wrote the study protocol. The study was approved by the local Ethics Committee. An independent Data Safety Monitoring Board reviewed patient data and a Clinical Endpoint Committee, blinded to treatment allocation, is appointed to adjudicate deaths and hospitalizations (Appendix 1). Each patient was obliged to provide written informed consent. The study is ongoing in 5 centers in Poland: Institute of Cardiology, Warsaw (Coordinating Center), Medical University of Warsaw, Medical University of Lodz, Medical University of Gdansk, Silesian Center for Heart Diseases in Zabrze.

Study population, recruitment and randomization

The TELEREH-HF study had a target enrollment of 850 clinically stable HF patients (New York Heart Association [NYHA] class I, II or III and left ventricular ejection fraction [LVEF] ≤40%) after a hospitalization incident within 6 months prior to randomization. The inclusion and exclusion criteria are shown in Table I. Eligible patients were randomized in ratio 1:1 to either hybrid TR + usual care (TR group) or to usual care only control group (CG) via a secure web-based randomization system —Research Electronic Data Capture (REDCap) housed in the Coordinating Center. All sites used the same allocation process to ensure uniform randomization. Randomization proceeded briskly and at the time it was ended, we randomized 850 individuals (versus 842 required based on sample size assumptions). The follow up is now in progress. The results will be available in 2019/2020. The study schedule is shown in Figure 1.

Intervention in telerehabilitation group

The TR group patients underwent a 9-week hybrid comprehensive TR program consisting of two stages: an initial stage (1-week) conducted at hospital and a basic stage (8-week) home-based TR five times weekly. The

Table I. TELEREH-HF Inclusion and Exclusion Criteria.

Inclusion criteria
Patients eligible for the trial had to meet the following criteria of randomization, that is, patients needed to:
- be of either sex with any etiology of left ventricular systolic heart failure as defined in the ESC guidelines
- have a LVEF ≤40% on echocardiography
- belong to NYHA class I, II, or III
- have had a hospitalization incident within 6 months prior to randomization
- be stable clinically (a patient does not need intravenous medication or has not had therapy modified for at least 7 days)
- have no contraindications to undergo cardiopulmonary exercise test
- be able to exercise using the new model of hybrid telerehabilitation
Exclusion Criteria
None of the following condition may exist at randomization:
- NYHA class IV
- unstable angina
- unstable clinical status
- a history of acute coronary syndrome within the last 40 days in patients with LVEF ≤35%
- percutaneous angioplasty within the last 2 weeks
- coronary artery bypass grafting within the last 3 months
- initiation of CRT-P or CRT-D or ICD or PM within the last 6 weeks
- lack of ICD, CRT-P or CRT-D or PM therapy despite the indications for implantation according to ESC guidelines
- intracardiac thrombus
- rest heart rate >90/min
- tachypnea >20 breaths per minute
- symptomatic and/or exercise-induced cardiac arrhythmia or conduction disturbances
- acute myocarditis and/or pericarditis
- valvular or congenital heart disease requiring surgical treatment
- hypertrophic cardiomyopathy
- severe pulmonary disease
- uncontrolled hypertension
- anemia (hemoglobin <11.0 g/ld.)
- physical disability related to severe musculoskeletal or neurological problems
- recent embolism
- thrombophlebitis
- acute or chronic inflammatory disease
- acute or chronic decompensated non-cardiac diseases (thyreotoxicosis, uncontrolled diabetes)
- active malignant neoplastic diseases with survival prognosis below 2 to 5 years
- orthotropic heart transplant in anamnesis
- presence of an implanted left ventricular assist device or biventricular assist device
- aortic aneurysm
- severe psychiatric disorder
- patient's refusal to participate

ESC, European Society of Cardiology; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; CRT-P, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy and implantable cardioverter-defibrillator; ICD, implantable cardioverter-defibrillator; PM, pacemaker.

goals of the initial stage were: a baseline clinical examination, optimization of treatment, education, individual planning of exercise training and performing five monitored educational training sessions. The basic stage, which was conducted at home consisted of two parts, was performed prior to each training session: the first part—the training consent procedure was required for a patient to access each training session, and the second part—the training session.

Telemonitoring

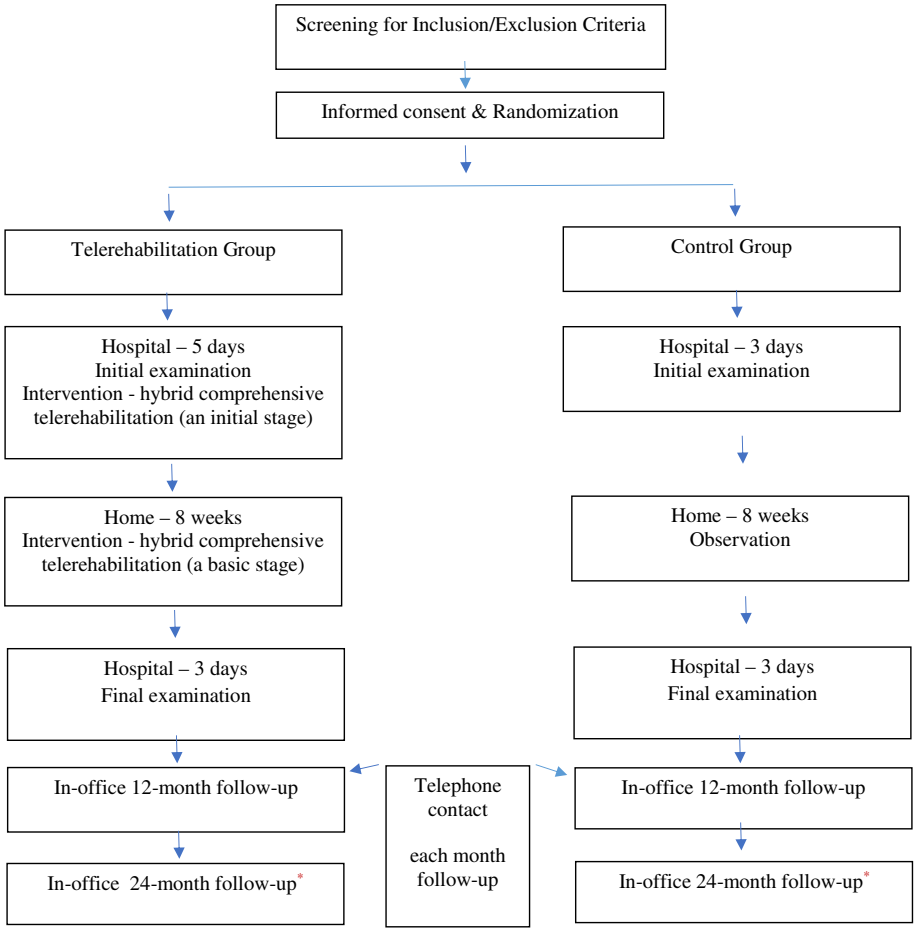
Remote monitoring during rehabilitation and training consent procedure. Telerehabilitation was carried out by a medical team and advanced monitoring systems were used. A TR medical team was composed of: physicians, physiotherapists, nurses and a psychologist. The monitoring system included: (1) a special remote device for tele-ECG-monitored and supervised exercise training—TR set (manufactured by Pro Plus Company, Poland), which consists of: EHO mini device, blood pressure measuring and weighing machine (Figure 2), (2) data transmission set via a mobile phone, (3) a monitoring center capable of receiving and storing patients' medical data (specialized hardware and software were necessary).[30-33]

The TR group patients received a TR set and mobile phone for voice communications. The EHO mini device is able to record ECG data from three pre-cordial leads and transmit them via a mobile phone network to the monitoring center. An EHO mini device has training sessions preprogrammed individually for each patient (defined exercise duration, breaks, timing of ECG recording). The moments of automatic ECG registration are preset and coordinated with the exercise training. The planned training sessions were executed with the device indicating what needed to be done with sound and light signals. There were sound signals in the form of bleeps and light signals from color emitting diodes. Bleeps and green diode blinking meant that the patient had to perform exercise. Another set of bleeps and red diode blinking meant “stop exercise”. The timing of automatic ECG recordings corresponded to peak exercise.

An EHO mini device had a tele-event-Holter ECG feature as well. It enables a patient, whenever a worrying symptom occurs, to register and immediately send the ECG recording via mobile phone network to the telemonitoring center.[30-33]

Before beginning a training session, patients used the mobile phone to answer a series of questions regarding their present condition, including fatigue, dyspnea, blood pressure, body mass, and medication taken. Patients then transmitted resting ECG data to the monitoring center. Before giving permission to start the training session, the medical staff also analyzed data sent from the remote monitoring of CIEDs. If no contraindications to training were identified, patients were given permission to start the training session.[30-33] The system was used to monitor and control the training in any place where the patient elected to exercise. If the training session was completed uneventfully, the patient would transmit the ECG recording via the mobile phone network to the monitoring center immediately after the end of every training session. The ECG recordings were analyzed at the monitoring center, and the safety, efficacy, and accuracy of a tailored patient's rehabilitation program were assessed. Using the data on heart rate (HR) during exercise and the patient's subjective evaluation of the perceived exertion according to Borg scale, consultants were able to adjust the training workload appropriately

Figure 1



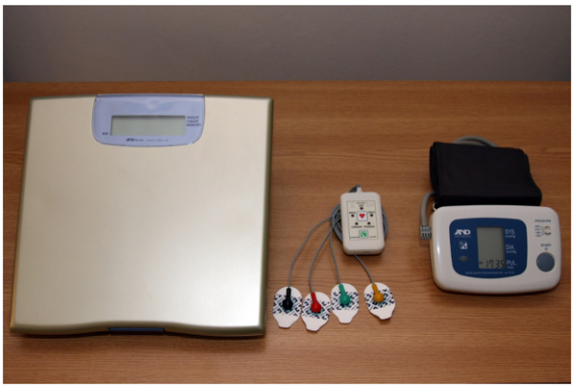
The study schedule and follow-up. *All patients whose 24-month follow up was not later than 31/03/2019 (in accordance with the regulations of the National Center for Research and Development).

or, if necessary, to discontinue the session. Telephone contact was also used for psychological support.[28,30-33]

Remote monitoring of cardiac implantable electronic devices (CIEDs). Additionally, TRG patients with CIEDs (if technical requirements were complied with) received the transmitter (Biotronik—CardioMessenger; Medronic transmitter [Home Monitor] of the CareLink network; St-Jude—Merlin@home wireless transmitter) which allowed the automatic transmission of data from the implant to a web-based monitoring platform (Biotronik—Home Monitoring Service Center, Medtronic—CareLink-Network, St-Jude—Merlin.net Patient Care Network). Remote monitoring relied on data acquired automatically on a daily basis by the device, with unscheduled transmission of any predefined alerts to the medical staff in each center. These alerts involved device integrity [eg, battery status- the battery depletion indicators: end of service (EOS), the elective replacement indicator (ERI) lead impedance], programming issues [eg, disabling of ventricular fibrillation (VF) therapy, antitachycardia pacing (ATP) therapy, insufficient safety margins for sensing or capture], and medical data [eg, arrhythmias—supraventricular tachycardia (SVT)/atrial fibrillation (AF)/atrial flutter (AFl), ventricular tachycardia (VT)/VF, indication of lung fluid accumulation].

In addition, each patient with CIEDs and a remote monitoring device had scheduled standard follow-up visits in order to evaluate the device functioning [after 4 weeks from the beginning of hybrid TR in TRG and usual care in CG and immediately after the intervention (after 9 weeks) in the TG and the observation period in CG]. The following parameters were evaluated: mean heart rates,

Figure 2



Telerehabilitation set — a weighing machine, the EHO mini device, a manometer.

patient activity, supraventricular (SVT, AF/AFl) and ventricular [non-sustained VT (nsVT), VT/VF] arrhythmia, impedance, percentage of resynchronization stimulation, intracardiac electrogram (IEGM).

Exercise training. Cardiac rehabilitation was planned according to the published guidelines for HF patients.[1,2,10] In order to ensure patients safety, the following recommendations were taken into account: (1) special attention was paid to appropriate patient risk stratification before cardiac rehabilitation; (2) contraindications to exercise training were never overlooked (Table II); (3) in patients with an implantable cardioverter-defibrillator (ICD), maximal training HR was set at 20 beat/min. lower than the ICD discharge threshold; and (4) in patients with a pacemaker, cardiac resynchronization therapy (CRT-P), cardiac resynchronization therapy and implantable cardioverter-defibrillator (CRT-D), the rate-response function was switched on, enabling HR adjustment to the physical effort which facilitated reaching the desired training HR.

Exercise trainings were planned individually for each patient during hospitalization.[10] The telerehabilitation program encompasses three training modalities: endurance aerobic Nordic walking training, respiratory muscle training and light resistance and strength exercises. The details are presented in Table III and Appendix 2.[10,31,32,34]

The chosen workload during Nordic walking was supposed to reflect individual effort tolerance with regard to: (1) perceived exertion according to the Borg scale and (2) the training HR range established individually for each patient based on cardiopulmonary exercise test (CPET) performed before the start of the TR program. In line with the recommendations, the assumption was that patients were not to exceed perceived moderate exertion during exercise training (ie, a score of 11-12 on the Borg scale). The training HR was calculated using the method known as HR reserve. This method uses a percentage of the difference between the maximum HR and the resting HR rate, and adds this value to the resting HR. The target training HR was 40% to 70% of the HR reserve. Patients trained five times a week.[10,31,32,34]

Table II. Contraindications to exercise training

Acute worsening of exercise tolerance, dyspnea or chest pain
Increase of 1.8 kg or more in body mass over the previous 1 to 3 days
Supine resting heart rate >90 beat/min
New-onset cardiac arrhythmias: atrial fibrillation/atrial flutter/supraventricular tachycardia, complex ventricular arrhythmia at rest or appearing with exertion
New-onset advanced atrioventricular block
New-onset of significant ischemia during low-intensity exercise
Decrease in systolic blood pressure with exercise
Uncontrolled hypertension, resting blood pressure >140/90 mmHg
Recent embolism
Recent thrombophlebitis
Acute systemic illness
New-onset uncontrolled endocrine and metabolic disorders

Education. Education program was designed and run by the TR team. Patients were taught how to self-evaluate, how to measure HR, blood pressure, body mass, how to performed all modalities of exercise training, how to evaluate the level of perceived exertion according to the Borg scale and how to operate a TR set. Education also encompassed nutritional counseling, lipid management, smoking cessation, vocational and psychosocial support.[8,10,30-33]

Control group

Patients randomized to the CG underwent baseline clinical examinations during 3 days hospitalization and then were under observation until the end of the 9th week and received usual care appropriate for their clinical status and standardized within a particular center (some of them could participate in a rehabilitation program). After the 9th week patients underwent final assessments during a 3-day hospitalization.

All patients, regardless of the treatment group, received recommendations for suitable lifestyle changes and self-management according to guidelines.[1-10]

Clinical examinations

All 850 patients underwent the following assessments at entry (during 5 days of hospitalization-TRG, and 3 days of hospitalization-CG) and after completing the 9-week program (during 3 days hospitalizations—both groups): clinical examination with symptom evaluation (NYHA class), blood testing [blood count, serum creatinine, electrolites (natrium, potassium), glycaemia, N-terminal pro B-type natriuretic peptide (NT-proBNP), aspartate aminotransferase, alanine aminotransferase, thyroid stimulating hormone (TSH), international normalized ratio (INR), urinalysis], ECG, two-dimensional echocardiography, six-minute walking test (6-MWT), CPET, 24 hours Holter ECG monitoring, evaluation of CIEDs proper

Table III. Exercise training model

Type of exercise training	Exercise prescription
Aerobic endurance training	**Devices:** Nordic walking poles **Training session** consists of: 1. Warm-up: breathing and light resistance exercises using poles for Nordic walking; duration 5-10 min 2. Nordic walking training **Intensity:** 40%-70% of heart rate reserve, perceived exertion level—score of 11-12 on the Borg scale **Duration:** start at 10 min per session per day[a], 15 min per session per day[b], 20 min per session per day[c], gradually increased to 30-45 min per session per day. 3. Cool down: relaxation, breathing exercise; duration 5 min **Frequency:** 1 session/day
Respiratory muscle training	**Devices:** Train Air software—during the initial stage at the hospital Threshold Inspiratory Muscle Trainer—during the basic stage at home **Intensity:** start at 30% of the maximal inspiratory mouth pressure (PI_{max}) and readjusted to a maximum of 60% (if possible) **Duration:** minimum 5-10 minutes/day maximum 20-30 minutes/day; **Frequency:** 3-5 times/ throughout the day
Resistance and strength training	**Devices:** Thera Band—yellow color **Intensity:** 5-10 repetitions of each of the seven exercises (see Appendix 2) **Duration:** gradually increased 5-10-15 minutes/day **Frequency:** 1 session/ day

Duration of aerobic endurance training depended on the functional capacity in baseline cardiopulmonary exercise test:
a baseline peak VO2 below 10 mL/kg per minute.
b baseline peak VO2 10-18 mL/kg per minute.
c baseline peak VO2 over 18 mL/kg per minute.

functioning, and psychological assessment: the QoL based on SF-36 Survey; the depression based on Beck inventory; the anxiety based on STAY.[1,2,5,6,35] Additionally, after 9 weeks, the TRG was analyzed for: safety and patients' acceptance of and adherence to hybrid comprehensive TR.

Evaluation of novel model of hybrid comprehensive telerehabilitation in terms of tertiary analyses

Assessment of hybrid comprehensive TR effectiveness. The effectiveness of TR and the comparison of the two arms will be based on the analysis of changes (between entry and 9 weeks—intervention period in TRG and observation period in CG) of the following parameters: HF functional class according to NYHA, CPET duration, peak oxygen consumption (pVO_2), % of predicted peak VO2 (pVO_2%N), 6-MWT distance, QoL (SF-36) score, depression and anxiety assessment.

Assessment of hybrid comprehensive TR safety. The safety assessment will include the incidence of: adverse events (ischemic symptoms, dyspnea—tachypnea >20/min, syncope or fainting, passing to a higher NYHA class, putting on ≥1.8 kg body mass during 1 to 3 days, symptomatic drop in systolic blood pressure, SVT, AF, nsVT, VT, VF, II and III degree atrio-ventricular block, resting HR ≥100/min, left- and/or right-ventricular insufficiency, need for urgent hospitalization, death) during exercise training, directly following it (up to 1 hour) and adverse events regardless of the training (including data from remote monitoring of CIEDs).

Assessment of the patients' acceptance of hybrid comprehensive TR. The patients' acceptance of TR will be analyzed based on a 12-item questionnaire filled out by patients at the end of TR, which will include the assessment of: difficulties in operating the TR set, the influence of the TR set of their perceived safety, patients' compliance to the recommendations on pharmacotherapy, nutrition and their lifestyle.[32,33,36]

Assessment of the adherence to hybrid comprehensive TR. Adherence during TR was assessed based on the daily telephone contact with the monitoring center, which was required to obtain the necessary permission for the training and compliance to the exercise training. Adherence was defined as the percentage of patients who carried out the prescribed exercise training. According to the recommendations, in terms of their adherence, the patients were divided into three groups: the first group were adherent patients, that is, patients who adhered both to the number of training sessions prescribed and to the duration of the prescribed cycle by at least 80%; the

second category consisted of non-adherent patients, who adhered <20% to the prescribed number of training sessions and their duration. The third group corresponded to the partially adherent patients who carried out the prescribed exercise, yet tended to omit some of them or did not carry them out for the prescribed duration (ie, who adhered ≥20% and <80%).[37]

Follow-up

All patients are being followed up for a maximum of 24 months with a maximum of two check-up visits within the 12 and 24 months following the end of the preliminary 9-week training program in TRG and the observational period in CG. Each month follow-up is also conducted via telephone (conversations with the patient and/or family member) in order to collect data about primary and secondary endpoints. All patients will be followed-up for a maximum of 24 months after the 9-week period.

Primary hypothesis sample size considerations

The primary study hypothesis is that TRG strategy is superior to CG strategy resulting in a larger percent of DAOH. Because possible follow-up varies between patients (12 to 24 months after the 9-week training period), the primary analysis will rely on the percent of DAOH calculated as the ratio of the DAOH divided by total days of follow-up for each patient.

The sample size for this study was calculated assuming 1:1 treatment allocation ratio, and an overall two-sided level of significance alpha = 0.05. Mean difference in the number of DAOH for the TRG arm and the CG arm was 21 days with a common standard deviation in each arm of 100. The Wilcoxon–Mann-Whitney test with the above assumptions and with a sample size of 400 evaluable subjects per study arm (a total of 800) yields 80% power to declare the observed difference as statistically significant. Accounting for a 5% loss to the follow-up, the total number increases to 842.

Statistical analyses

Primary outcome. The primary analysis will be based on the percent of DAOH during the 12- to 24-month follow-up and analyzed using the Wilcoxon–Mann-Whitney test. DAOH is defined as the number days out of the first 365 days of follow-up that the patient was alive minus the total number of days the patient spent in the hospital (sum of days spent in the hospital for each hospitalization). Fractions of days spent in the hospital will be rounded up to full days. We plan to conduct two analyses, intent-to-treat (ITT) and modified intent-to-treat (MITT). The follow-up for ITT will start at randomization and extend for a minimum of about 14 months (9 week training period and 12 month follow-up) and a maximum of 26 months (9 week training period plus 24 months of follow-up). For the MITT analysis, the follow-up will start at the end of the 9-week period.

Missing data. If a patient remained in the study for less than 365 days for reasons other than death, the following imputation methods will be applied:

1. Proportional Fraction. The proportion of DAOH will be calculated for the period the patient was on study and multiplied by 365;
2. Worst case scenario. Days not on study will be counted as NOT alive/out of hospital;
3. Best case scenario. Days not on study will be counted as alive and out of hospital.

Subgroup and sensitivity analyses. Subgroup analyses will be conducted to assess treatment heterogeneity by study site, age, sex, baseline NYHA class, peak VO2 consumption and duration of follow-up. An additional sensitivity analysis will be conducted excluding patients from the control arm if they participated in a rehabilitation program.

Secondary outcomes assessed at 12 months. The following time-to-event outcomes will be illustrated using Kaplan-Meier plots and compared between treatment arms using Cox proportional hazards regression with site and treatment arm as covariates: all-cause mortality, CV mortality, all-cause hospitalizations, CV hospitalizations, HF hospitalization, composite of all-cause mortality or all-cause hospitalization, composite of all-cause mortality or CV hospitalization, composite of all-cause mortality or HF hospitalization and composite of cardiovascular mortality or HF hospitalization. All available follow-up will be used with event rates estimated at 12 months.

Tertiary outcomes assessed at 9 weeks. The following continuous outcomes will be compared between treatment arms using analysis of variance adjusting for baseline level of the outcome measure and site: change in CPET duration, change in pVO_2 in CPET, change inpVO_2%N in CPET, change in 6-MWT distance, change in QoL measures with the SF-36 instrument as well as change in depression and anxiety scales. NYHA class will be analyzed as ordinal variable using ordinal logistic regression including terms of baseline NYHA class, site and treatment arm. The summary is included in the Table IV.

Discussion

The TELEREH-HF study is a randomized, multicenter, prospective, open-label, parallel group controlled trial designed to determine whether a novel hybrid comprehensive TR in HF patients influences outcome measured by hospitalizations and death when compared with usual care. The trial will also evaluate TR safety and acceptance. It seemed that the beneficial effect of cardiac rehabilitation in HF patients were unquestionable and well

Table IV. TELEREH-HF endpoints

Primary end-point:

The percent of number of days alive and out of hospital (DAOH) during the12 to 24 months follow-up

Secondary end-points:

Secondary outcomes assessed at 12 to 24 months:
- all-cause and CV mortality
- all-cause, CV and HF hospitalization

Secondary outcomes assessed at 9 weeks—the effectiveness of hybrid TR based on:
- New York Heart Association class
- cardiopulmonary exercise treadmill test duration
- peak oxygen consumption (pVO_2)
- percentage of predicted peak oxygen consumption (pVO_2%N)
- six-minute walking test distance
- quality of life assessment
- depression assessment
- anxiety assessment
- acceptance of TR
- adherence to TR

Composite end-points encompasses:

- CV mortality and HF hospitalization
- CV mortality and CV hospitalization
- CV mortality and non CV hospitalization
- all-cause mortality and CV hospitalization
- all-cause mortality and non CV hospitalization

TRG, telerehabilitation group; CG, control group; CV, cardiovascular; HF, heart failure; TR, telerehabilitation.

documented. Published data demonstrated that exercise training improves functional capacity, QoL and prognosis and reduce hospitalization and mortality rate.[1-10,38] This was reflected in the existing recommendations.[1-11] Yet, the recent meta-analysis of randomized trials which assessed the impact of exercise-based cardiac rehabilitation in HF patients (ExTraMATCH II) indicate that exercise training did not have a significant effect on the risk of mortality and hospitalization in HF with reduced ejection fraction.[39] Therefore, the role of TR in HF patients needs to be evaluated in prospective large randomized trials with long-term follow-up.[40-42]

To date, the role of telemedicine in supervising HF patients has been limited to telecare in the form of monitoring symptoms and parameters and supervising pharmacotherapy.[20-23] Hybrid comprehensive TR can be considered a promising method of approach to HF patients. Nevertheless, only two randomized studies from one center have been published so far and they confirm the effectiveness and safety of TR in HF patients.[31,32,43-45] The first published paper to report that home-based telemonitored walking training enabled HF patients to achieve clinical effects which were comparable with those resulting from cycloergometer rehabilitation in ambulatory settings. Therefore an ESC Heart Failure Association (HFA) Working Group proclaimed in 2011 that "applying telemedicine in rehabilitating HF patients is a promising direction. Yet the results from one report in this matter need to be confirmed by multicenter studies".[10] In addition, ESC guidelines on cardiovascular disease prevention in clinical practice and International Society of Holter and Noninvasive Electrocardiology—Heart Rhythm Society (ISHNE-HRS) expert consensus statement provide information that TR could further broaden participation and provide monitoring and greater individualized behavioral support, but large-scale randomized trials are needed.[7,46] Moreover the AHA scientific statement, regarding exercise training, also indicates that the effectiveness of home-based cardiac rehabilitation is comparable with supervised traditional cardiac rehabilitation.[2]

Promoting this form of cardiac rehabilitation as an alternative to standard forms requires testing in multicenter studies. An important consideration is that the effectiveness of telemedical procedures varies according to regional models of HF patient's treatment determined by logistic.

The vast majority of HF patients who undergo cardiac rehabilitation have CIEDs and their functioning may influence the safety and effectiveness of exercise training as well as have an impact on clinical status and prognosis. One of the means of optimizing the control over their functioning is the remote monitoring of these devices. Numerous studies devoted to this issue provided inconsistent results.[15-19] The most promising were the IN TIME study results and for this very reason they were included in recent ESC Heart Failure Association (HFA) guidelines which point out that multiparameter monitoring based on ICD may be considered in symptomatic patients with HF and reduce LVEF (LVEF ≤35%) in order to improve clinical outcomes yet only in IIb class of recommendations and level of evidence B.[1,18] However ESC guidelines on cardiac pacing and cardiac resynchronization therapy indicate that device-based remote monitoring should be considered in order to provide earlier detection of clinical problems (eg, ventricular tachyarrhythmias, AT) and technical issues (eg, lead fracture, insulation defect) in IIa class of recommendations and level of evidence A.[12]

In contrast, according to HRS Expert consensus statement all patients with CIEDs should be offered remote monitoring as part of the standard follow-up management strategy (1 class of recommendation, level of evidence A).[13] As a consequence, class differences exist between guidelines in reference to the remote monitoring of CIEDs. This is why we decided to take this matter into consideration in our TELEREH-HF study. Accordingly, patients from the TRG (if technical requirements were complied with) had their CIEDs remotely monitored whereas those from the CG had their CIEDs monitored depending on the regional standard HF patient care model.

Being a new scientific field, telemedicine is developing alongside the development of the information and

communication technology. This implies that a multicenter study may affect the development of the information and communication technology in terms of telerehabilitation. The tests and trials planned could optimize the rehabilitation process and eliminate imperfections of the devices.

Implementing a standardized doctrine of comprehensive home-based telemonitored cardiac rehabilitation in HF patients, which is based on the latest technology, creates an opportunity to increase the availability of this form of therapy and enables the elimination of the still existing regional disproportions in this field. It will possibly lower the rehospitalization rate and improve the QoL of HF patients. It may even improve their survival rates. Nevertheless, participating in a multicenter study based on the latest technical and technological achievements is a challenge for patients and for participating centers due to complexity of the study protocol. Therefore assessing patients' acceptance and adherence to the TR process is an important component of this trial. Health care providers will find themselves obliged to broaden their knowledge on the systemic care of patients, especially as far as the importance of cardiac rehabilitation is concerned. Moreover, they will need to acquire skills necessary for the implementation of the "from hospital to home" stipulation with the use of the latest data transmission technology. Eventually, teams with unique experience in this field will be created.

The TELEREH-HF trial will provide data on the effects of the novel model of HF patients management including hybrid comprehensive TR in terms of days alive and out of hospital, hospitalization and mortality rate. In addition, it will become a unique source of data on safety, effectiveness, QoL, depression, anxiety and patients' acceptance of and adherence to this intervention.

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The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Declaration of competing interest

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Appendix 1. Study Committee

Principal Investigator: Ewa Piotrowicz.

Steering Committee Members: Grzegorz Opolski (Warsaw, Poland; Chair), Maciej Banach (Łódź, Poland), Michael Pencina (Durham, NC, USA), Ryszard Piotrowicz (Warsaw, Poland), Wojciech Zaręba (Rochester, NY, USA).

Data Safety Monitoring Board Members: Tomasz Krauze (Poznań, Poland; Chair), Rafał Dąbrowski (Warsaw, Poland), Marcin Grabowski (Warsaw, Poland).

Clinical Endpoint Committee Members: Mariusz Pytkowski (Warsaw, Poland; Chair), Paweł Krzesiński (Warsaw, Poland), Mariusz Kruk (Warsaw, Poland).

Appendix 2. Resistance and strength exercise using Thera band

Upper limbs

Exercise 1. Position: sitting, the center of the band under the right / left foot. We keep the ends of the tape in the right / left hand. Flexing the right / left elbow.

Exercise 2. Position: sitting, the center of the band under the right / left foot. We keep the ends of the band in the right / left hand. Raise the right / left upper limb to the level of the shoulder.

Exercise 3. Position: sitting, band placed on the back. We grab the ends of the band. Upper limbs flex at the elbows at the chest level, hands keep the tape slightly taut. We stretch the tape as far forward as possible, trying to keep the movement horizontally at chest level.

Exercise 4. Position: standing in the middle of the band. The band crossed in front of the body. Abduction of the arms and returning to the starting position.

Lower limbs: Exercise 5. Position: sitting, the center of the band under the foot, the ankle joint extended (dorsiflexion). The ends of the band are held in the hands at the level of the knee joint. The band tight. Plantar flexion of the ankle.

Exercise 6. Position: sitting, the hip and knee joint bent. Wrap the band wrapped around the foot with both hands. Hands are placed on the chest. Extension in the hip and knee joint.

Exercise 7. Position: Standing in a light stride, place the widely spread band under the foot of the supporting leg and attach it at the height of the ankle joint of the other limb. Abduction of the lower limb.

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