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Effects of a 9-Week Hybrid Comprehensive Telerehabilitation Program on Long-term Outcomes in Patients With Heart Failure
The Telerehabilitation in Heart Failure Patients (TELEREH-HF) Randomized Clinical Trial

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IMPORTANCE Guidelines recommend exercise training as a component of heart failure management. There are large disparities in access to rehabilitation, and introducing hybrid comprehensive telerehabilitation (HCTR) consisting of remote monitoring of training at patients' homes might be an appealing alternative.

OBJECTIVE To assess whether potential improvements in quality-of-life outcomes after a 9-week HCTR intervention in patients with heart failure translate into improvement in clinical outcomes during extended 12 to 24 months of follow-up, compared with usual care.

DESIGN, SETTING, AND PARTICIPANTS The Telerehabilitation in Heart Failure Patients (TELEREH-HF) trial is a multicenter, prospective, open-label, parallel-group randomized clinical trial that enrolled 850 patients with heart failure up to 6 months after a cardiovascular hospitalization with New York Heart Association levels I, II, or III and left ventricular ejection fraction of 40% or less. Patients from 5 centers in Poland were randomized 1:1 to HCTR plus usual care or usual care only and followed up for 14 to 26 months after randomization.

INTERVENTIONS During the first 9 weeks, patients underwent either an HCTR program (1 week in hospital and 8 weeks at home) or usual care with observation. The HCTR intervention encompassed telecare, telerehabilitation, and remote monitoring of implantable devices. No intervention occurred in the remaining study period.

MAIN OUTCOMES AND MEASURES The percentage of days alive and out of the hospital from randomization through the end of follow-up at 14 to 26 months.

RESULTS A total of 850 patients were enrolled, with 425 randomized to the HCTR group (377 male patients [88.7%]; mean [SD] age, 62.6 [10.8] years) and 425 randomized to usual care (376 male patients [88.5%]; mean [SD] age, 62.2 [10.2] years). The HCTR intervention did not extend the percentage of days alive and out of the hospital. The mean (SD) days were 91.9 (19.3) days in the HCTR group vs 92.8 (18.3) days in the usual-care group, with the probability that HCTR extends days alive and out of the hospital equal to 0.49 (95% CI, 0.46-0.53; $P = .74$) vs usual care. During follow-up, 54 patients died in the HCTR arm and 52 in the usual-care arm, with mortality rates at 26 months of 12.5% vs 12.4%, respectively (hazard ratio, 1.03 [95% CI, 0.70-1.51]). There were also no differences in hospitalization rates (hazard ratio, 0.94 [95% CI, 0.79-1.13]). The HCTR intervention was effective at 9 weeks, significantly improving peak oxygen consumption (0.95 [95% CI, 0.65-1.26] mL/kg/min vs 0.00 [95% CI, −0.31 to 0.30] mL/kg/min; $P < .001$) and quality of life (Medical Outcome Survey Short Form–36 questionnaire score, 1.58 [95% CI, 0.74-2.42] vs 0.00 [95% CI, −0.84 to 0.84]; $P = .008$), and it was well tolerated, with no serious adverse events during exercise.

CONCLUSIONS AND RELEVANCE In this trial, the positive effects of a 9-week program of HCTR in patients with heart failure did not lead to the increase in percentage of days alive and out of the hospital and did not reduce mortality and hospitalization over a follow-up period of 14 to 26 months.

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Supplemental content

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Heart failure (HF) is a prevalent condition, affecting about 26 million patients worldwide.[1,2] Guidelines of the European Society of Cardiology, American Heart Association, and American College of Cardiology suggest creation of holistic management for patients with HF, which contains appropriate pharmacological and device therapy, cardiac rehabilitation (CR), remote monitoring of cardiovascular implantable electronic devices (CIEDs), and regular follow-up.[1-5] The ideal would be to organize ambulatory outpatient care, enabling patients with HF to maintain the improvement obtained during hospitalization. For this reason, the novel HF care model should focus on the optimal outpatient care to reduce rehospitalizations and improve the prognosis of patients with HF, leading to beneficial effects on patients' conditions and health care system cost reduction.[1-4] Guidelines recommend CR that uses patient education, health behavior modification, and exercise training (an 1A recommendation) to improve secondary prevention outcomes in patients with HF.[1-4,6] Unfortunately, CR programs are considerably underused, with only about 20% of eligible patients participating in one.[7,8] Factors hindering CR include a lack of resources (eg, a lack of caregivers, long waiting lists) as well as logistical and psychological problems (eg, transportation issues, the need to be assisted by relatives or partners, a lack of motivation, nonacceptance of the proposed CR models).[9,10] The development of new technologies provides the opportunity to include telemedicine in the organization of outpatient HF care.[10,11] However, the results of studies focused on remote management of patients with HF have been inconsistent.[12-18] A new promising solution that overcomes the barriers to CR and at the same time provides guideline-consistent monitoring of physical training in patients at moderate and high risk is telerehabilitation.[6,10,11,19] Yet, to date, only a handful of single-center studies have demonstrated that telerehabilitation is safe, effective, and noninferior to a hospital-based or outpatient-based rehabilitation of patients with HF.[19-24] Therefore, the consensus document of the European Society of Cardiology Heart Failure Association Working Group[4] and scientific statement from the American Association of Cardiovascular and Pulmonary Rehabilitation, the American Heart Association, and the American College of Cardiology[6] indicate that home-based CR using telemedicine is a promising direction, but the results should be confirmed by multicenter studies.

Telemedicine offers a novel model of organization and implementation of comprehensive management of patients with HF. Thus, we proposed combining all components of remote monitoring (telecare; structured telephone support and telemonitoring of electrocardiography [ECG], blood pressure, and weight by CIEDs) with telesupervised exercise training to form a hybrid comprehensive telerehabilitation (HCTR) program.[20,21] In contrast with previously proposed approaches, which evaluated only 1 of the telemedical applications in the care of outpatients with HF (telecare, telerehabilitation, or remote monitoring of CIEDs), this model combines all these forms of telemonitoring into 1 program.

An important issue is the adherence to recommendations and maintenance of the effects of telecare and telerehabilitation (when it is implemented) in long-term observation on the completion of the intervention. Only 1 study has been published[25] and 1 congress report[26] presented to date, both of which assessed the possibility of achieving long-term teleintervention effects after the intervention was stopped. We have assumed that the following elements of the HCTR program would have a long-term effect on clinical outcomes: improvement of prognostic indicators (peak oxygen consumption [peak VO_2] and distance on a 6-minute walk test) and strengthening of the capacity for patient's self-management.

The hybrid comprehensive Telerehabilitation in Heart Failure Patients (TELEREH-HF) trial was designed to determine whether potential improvements in functional and quality-of-life outcomes after a 9-week training period translate into improvement in clinical outcomes during the extended follow-up of 12 to 24 months (after the intervention was stopped), compared with usual care (UC). The study design and description of the intervention have been published elsewhere.[27]

Key Points

Question Does a 9-week hybrid comprehensive cardiac telerehabilitation program, compared with usual care, improve the percentage of days that patients with heart failure spend alive and out of the hospital during long-term follow-up?

Findings This multisite randomized clinical trial of 850 patients assigned to hybrid comprehensive telerehabilitation or usual care did not meet its primary outcome of extending the percentage of days alive and out of the hospital during 14 to 26 months of follow-up.

Meaning In this trial, a 9-week hybrid comprehensive telerehabilitation program in patients with heart failure did not increase the percentage of days alive and out of the hospital during 14 to 26 months of follow-up.

Methods

The TELEREH-HF study is a multicenter, prospective, open-label, unmasked (with randomization concealment), parallel-group, randomized clinical trial introducing an HCTR in patients with HF (NCT02523560). The study conduct was guided by good clinical practice, in accordance with the Declaration of Helsinki and the regulations applicable in Poland. The main investigator and steering committee designed the trial and wrote the study protocol. The trial was approved by the local ethics committee (Terenowa Komisja Bioetyczna przy Instytucie Kardiologii im. Prymasa Tysiąclecia Kardynała Stefana Wyszyńskiego). An independent data safety monitoring board reviewed patient data, and a clinical end point committee, blinded to treatment allocation, was appointed to adjudicate deaths and hospitalizations. Each patient provided written informed consent. The study was conducted in 5 centers in Poland: the Institute of Cardiology in Warsaw (coordinating center [site 1]), the Silesian Center for Heart Diseases in Zabrze (site 2), Medical University of Gdansk (site 3), Medical University of Łódź (site 4), and Medical University of Warsaw (site 5).[27] The protocol is presented in Supplement 2.

The study followed the Consolidated Standards of Reporting Trials guidelines.

Participants, Recruitment and Randomization

Between June 8, 2015, and June 28, 2017, we randomized patients who were clinically stable (New York Heart Association [NYHA] class I, II, or III and left ventricular ejection fraction of 40% or less) after a cardiovascular (CV) hospitalization within the 6 months prior to randomization. The inclusion and exclusion criteria are shown in eTable 1 in Supplement 1. Eligible patients were randomized in a 1:1 ratio (block size of 2, stratified by site) to either HCTR plus usual care (the HCTR group) or usual care only (the UC group) via a secure web-based randomization system (Research Electronic Data Capture [REDCap] housed in the coordinating center).[28] All sites used the same allocation process to ensure uniform randomization. Data were collected in REDCap.

Intervention

A detailed description of the intervention has been published elsewhere.[27] The patients in the HCTR group underwent a 9-week HCTR program consisting of 2 stages: an initial stage (1 week) conducted in hospital and a basic stage (8 weeks) of home-based HCTR 5 times weekly. No intervention was designed to occur after the initial 9-week period. The goals of the initial stage were a baseline clinical examination, optimization of treatment, education, planning of exercise training, and performing 5 monitored educational training sessions. The home-based HCTR program consisted of 2 parts: the medical team assessing the patient's ability to proceed safely and consenting to each training session and the training session itself (eTable 2 in Supplement 1).

Telerehabilitation was carried out by a medical team (physicians, physiotherapists, nurses, and a psychologist), and advanced monitoring systems were used. The monitoring system included (1) a special remote device for supervised exercise training monitored with tele-ECG (also called *a telerehabilitation set*; Pro Plus Company), which consists of an EHO mini device, blood pressure device, and body-weight scale; (2) a data transmission set via a mobile telephone; and (3) a monitoring center capable of receiving and storing patients' medical data. The EHO mini device is able to record ECG data from 3 precordial leads and transmit them via a mobile telephone network to the monitoring center. The device has training sessions preprogrammed individually for each patient (with defined exercise duration, breaks, and timing of ECG recording). The details regarding the device, HCTR, and education are presented in eTable 2 in Supplement 1.[27]

Additionally, if technical requirements were complied with, patients in the HCTR group who had CIEDs received the transmitter (CardioMessenger [Biotronik], transmitter [Home Monitor] of the CareLink network [Medtronic], or Merlin@home wireless transmitter [St Jude]), which allowed the automatic transmission of data from the implant to a web-based monitoring platform. Remote monitoring relied on data acquired automatically by the device, with unscheduled transmission of any predefined alerts to the medical staff in each center.[27]

Exercise training was planned individually for each patient according to the guidelines.[6] The telerehabilitation program encompassed 3 training modalities: endurance aerobic Nordic walking training, respiratory muscle training, and light resistance and strength exercises. Details are presented in eTable 3 in Supplement 1.[27]

Assessment of Adherence to HCTR

Adherence during the 9-week HCTR program was assessed by daily telephone contact with the monitoring center, which was required to obtain the necessary permission for the training (the consent procedure) and based on evaluation of the transmitted ECG data after each training session (compliance with exercise training). Patients considered adherent were those who completed both the number of training sessions prescribed and at least 80% of the duration of the prescribed cycles; patients who were nonadherent were those who completed less than 20% to the prescribed number of training sessions and less than 20% of their duration. The remaining patients were classified as partially adherent.[9,27] No measurement of adherence took place after the 9-week training period, because no intervention was intended to occur in this period.

Usual Care

Patients randomized to the UC group underwent baseline clinical examinations during a 3-day hospitalization and then were under observation until the end of the ninth week and received usual care appropriate for their clinical status and standardized within a particular center. Some of them could participate in rehabilitation, and some of them had remote monitoring of CIEDs. After the ninth week, patients underwent final assessments during a 3-day hospitalization. Patients received recommendations for suitable lifestyle changes and self-management according to guidelines.[1-3]

All patients underwent the following assessments at entry (during 5 days of hospitalization [HCTR group] and 3 days of hospitalization [UC group]) and after completing the 9-week program (during 3 days of hospitalization [both groups]): clinical examination with symptom evaluation (by NYHA class), ECG, 2-dimensional echocardiography, a 6-minute walk test, a cardiopulmonary exercise test, 24-hour ECG monitoring, an evaluation of proper CIED functioning, and a psychological assessment of quality of life based on Medical Outcome Survey Short Form-36 Survey. Additionally, during the 9 weeks, the safety of HCTR was ascertained through the collection of adverse events during exercise training, directly following exercise (up to 1 hour) and regardless of the training (eTable 4 in Supplement 1).

All patients were followed up for a minimum of 12 months and a maximum of 24 months after the 9-week period (not later than March 31, 2019) with up to 2 check-up visits. Mortality (all-cause and CV) and hospitalization (all-cause, CV, and HF-associated) data were collected during follow-up.

Statistical Analyses

Primary Outcome, Sample Size Determination, and Subgroup Analyses

The primary study hypothesis was that HCTR benefits would be maintained on extended follow-up from randomization for

a minimum of 14 months and a maximum of 26 months, resulting in an increased probability of a longer percentage of days alive and out of the hospital. Because possible follow-up varied between patients (from 14 to 26 months from randomization), the primary analysis relied on the percentage of days alive and out of the hospital, calculated as a ratio (the number of days alive and out of the hospital divided by the total possible days of follow-up for each patient). The Wilcoxon-Mann-Whitney rank sum test, which calculates the probability that a person assigned to HCTR will have a better outcome (ie, a longer percentage of days alive and out of the hospital) than a person assigned to UC, was used to account for the skewed nature of the data.[29]

The sample size was calculated assuming a 1:1 treatment-allocation ratio, and an overall 2-sided level of significance of .05 was applied. The mean difference in the number of days alive and out of the hospital between arms was assumed to be 21 days, with an SD of 100 days in each arm. A sample size of 400 evaluable participants per study arm (a total of 800) would yield 80% power to declare the observed difference as statistically significant. Accounting for a 5% to 6% loss to the follow-up, the total number was increased to 850 participants. The primary comparison was conducted according to the intent-to-treat comparison, which included the full sample of randomized patients. Sensitivity analysis excluded patients who did not complete the 9-week training period (a modified intent-to-treat analysis) and started after 9 weeks. Subgroup analyses were conducted to assess treatment heterogeneity by study site, age, sex, baseline NYHA class, and peak VO_2.

Secondary Outcomes Assessed During Full Follow-up

The following time-to-event outcomes were prespecified and compared between treatment arms using Cox proportional hazards regression with site and treatment arm as covariates: all-cause mortality and CV mortality; all-cause hospitalizations, CV hospitalizations, and HF-associated hospitalization; and composites of all-cause mortality and all-cause hospitalization, all-cause mortality and CV hospitalization, all-cause mortality and HF hospitalization, and CV mortality and HF hospitalization. A proportional-hazards assumption was verified using plots of log time vs the log of the negative log of survival.

Tertiary Outcomes Assessed at 9 Weeks

The following continuous outcomes were prespecified and compared between treatment arms using analysis of variance adjusted for baseline level of the outcome measure and site: change in cardiopulmonary exercise test duration, peak VO_2, percentage of anticipated peak VO_2, change in 6-minute walk test distance, and quality-of-life measures with the Medical Outcome Survey Short Form-36 instrument. Change in NYHA class was analyzed using an ordinal logistic regression that included terms of baseline NYHA class, site, and treatment arm.

Missing Data

For the primary outcome of the percentage of days alive and out of the hospital, we imputed missing data using a proportional fraction (primary: the proportion of days alive and out of the hospital, calculated for the period that the patient was in the study multiplied by 365), a worst-case scenario (in which the days that a patient was not in the study were counted as not alive or out of the hospital), and a best-case scenario (in which the days that a patient was not in the study were counted as alive and out of the hospital). Patients who were lost to follow-up were censored at the time of the last contact. For patients who did not complete the 9-week training (but did not withdraw informed consent), we assumed no improvement in the parameter of interest. We also reanalyzed the data excluding these patients.

Data were analyzed using SAS version 9.4 (SAS Institute). Statistical significance was set at $P < .05$ for main effects and $P < .15$ for interactions with subgroups. The statistical analysis plan is presented in Supplement 3.

Results

Of the 2333 screened patients, 836 did not meet inclusion or exclusion criteria, and 647 refused to participate. Of the 850 patients randomized (220 in site 1, 178 at site 2, 183 at site 3, 149 at site 4, and 120 at site 5), 425 were assigned to HCTR (377 male patients [88.7%]; mean [SD] age, 62.6 [10.8] years) and 425 to UC (376 male patients [88.5%]; mean [SD] age, 62.2 [10.2] years). The percentage of HF hospitalizations within 6 months prior to randomization were 83% in the HCTR group (353 patients) and 85% in the UC group (361 patients).

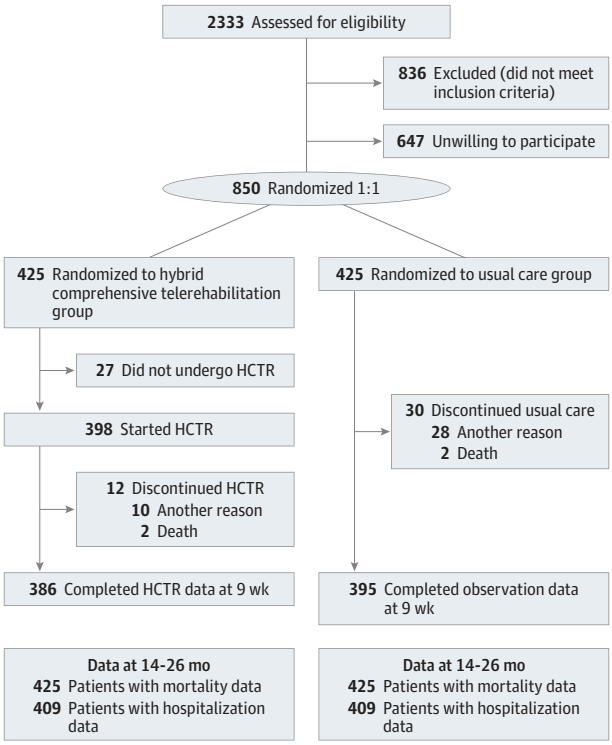
In the HCTR arm, 386 patients completed the 9-week training program; 395 patients in the UC arm completed the 9-week observation (**Figure 1**). Twenty-seven patients did not undergo telerehabilitation because of technical difficulties with operating the telerehabilitation set (21 patients), new onset of comorbidities (4 patients), or a return to work (2 patients). The adherence to HTCR was very high during the 9-week training period. There were 350 patients who were adherent (88.4%), 39 who were partially adherent (9.8%), and 7 patients who were nonadherent (1.8%). In the UC arm, 51 patients (12.0%) participated in CR programs.

Because no patients withdrew informed consent, we were able to obtain complete data for all-cause mortality. Thirty-two participants (3.8%) were lost to follow-up and were censored at the date of last contact. We were able to ascertain mortality status in all patients at study end and hospitalization status in 818 patients (96.2%; 409 in the HCTR arm and 409 in the UC arm). The baseline clinical characteristics of these patients are described in **Table 1** and eTable 5 in Supplement 1. Study arms were not significantly different in terms of demographic data, baseline clinical parameters, and treatment.

Safety of HCTR at 9 Weeks

Neither death nor other serious adverse events occurred during telemonitored exercise training session nor directly afterward (up to 1 hour). Adverse events are listed in eTable 4 in Supplement 1. Two deaths occurred during the 9-week training period in the HCTR arm, 1 of noncardiovascular causes and

Figure 1. Study Flow Diagram



HCTR indicates hybrid comprehensive telerehabilitation.

1 because of a hemorrhagic stroke. Two patients died in the UC arm during the 9-week observation period, 1 via sudden cardiac death and the other at home of an unknown cause.

Primary and Secondary Outcomes After 14 to 26 Months

The study did not meet its primary outcome of extending the percentage of days alive and out of the hospital during the 14 to 26 months of follow-up. The probability that HCTR extends the percentage of days alive and out of the hospital vs UC was 0.49 (95% CI, 0.46-0.53; $P = .74$ by Mann-Whitney test) in the whole group of patients and 0.49 (95% CI, 0.45-0.53; $P = .71$) in the subgroup of patients with CIEDs. **Figure 2** displays the percentage of days alive and out of the hospital by study arm. The mean (SD) number of days in hospital was 14.9 (29.6) days in the HCTR arm (median [interquartile range], 2 [0-16] days) vs 14.8 (28.2) days in UC (median [interquartile range], 2 [0-16] days). The details are presented in eTable 6 and 7 in Supplement 1. During the course of follow-up, 54 patients died in the HCTR arm and 52 died in the UC arm, with mortality rates at 24 months of 12.5% in the HCTR group vs 12.4% in the UC group (hazard ratio [HR], 1.03 [95% CI, 0.70-1.51]). There were also no differences in CV mortality, CV hospitalizations, HF hospitalizations, or composite end points combining mortality and hospitalization (**Table 2**; eFigures 1, 2, 3, 4, 5, and 6 in Supplement 1). Results were consistent on the modified intent-to-treat population, which excluded patients who did not complete the 9-week intervention period.

Table 1. Baseline Characteristics

Characteristic	Patients, No. (%)	
	Group Receiving Hybrid Comprehensive Telerehabilitation (n = 425)	Group Receiving Usual Care (n = 425)
Male	377 (88.7)	376 (88.5)
Age, mean (SD), y	62.6 (10.8)	62.2 (10.2)
Left ventricular ejection fraction, mean (SD), %	31 (7)	30 (7)
Atrial fibrillation or atrial flutter	79 (18.6)	80 (18.8)
BMI, mean (SD)	28.7 (5.0)	29.1 (4.7)
Cause of heart failure		
Ischemic	281 (66.1)	274 (64.5)
Nonischemic	144 (33.9)	151 (35.5)
Medical history		
Myocardial infarction	250 (58.8)	243 (57.2)
Angioplasty	200 (47.1)	196 (46.1)
Coronary artery bypass grafting	70 (16.5)	70 (16.5)
Valve surgery	33 (7.8)	31 (7.3)
Hypertension	257 (60.5)	277 (65.2)
Stroke	28 (6.6)	33 (7.8)
Diabetes	139 (32.7)	152 (35.8)
Chronic kidney disease	78 (18.4)	71 (16.7)
Hyperlipidemia	210 (49.4)	186 (43.8)
Depression [a]	82 (23.1)	103 (28.6)
Functional status by New York Heart Association level		
I	54 (12.7)	50 (11.8)
II	293 (68.9)	284 (66.8)
III	78 (18.4)	91 (21.4)
Treatment		
β-Blocker	409 (96.2)	416 (97.9)
Angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers	395 (92.9)	398 (93.6)
Digoxin	52 (12.2)	52 (12.2)
Loop diuretics	316 (74.4)	334 (78.6)
Spironolactone/eplerenone	351 (82.6)	348 (81.9)
Aspirin/clopidogrel	243 (57.2)	242 (56.9)
Anticoagulants	125 (29.4)	128 (30.1)
Non-vitamin K antagonist oral anticoagulants	71 (16.7)	62 (14.6)
Statins	346 (81.4)	350 (82.3)
Cardiovascular implantable electronic devices	335 (78.8)	347 (81.6)
Implantable cardioverter-defibrillator	206 (61.7)	225 (64.8)
Cardiac resynchronization therapy	4 (1.2)	4 (1.2)
Cardiac resynchronization therapy and cardioverter-defibrillator	122 (36.4)	114 (32.8)
Remote monitoring cardiovascular implantable electronic devices	213 (63.6)	62 (17.9)

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

[a] Defined by a Beck Depression Inventory–II score of more than 13 points.

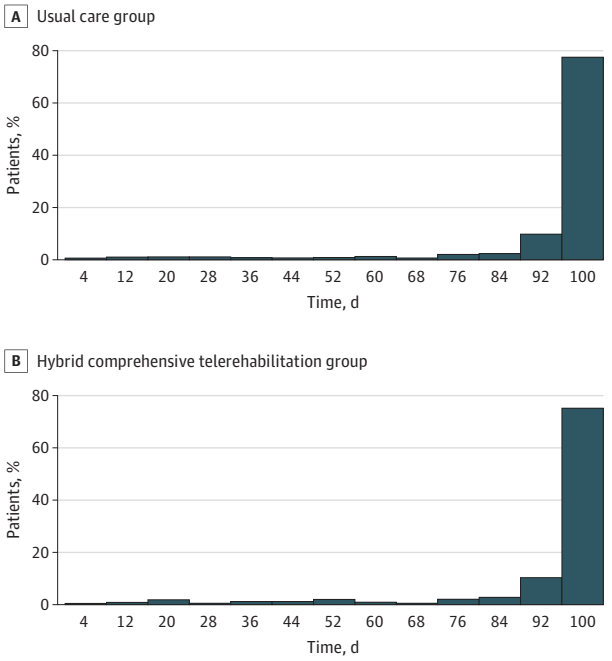
There were no statistically significant differences on the percentage of days alive and out of the hospital, all-cause mortality, or all-cause hospitalizations in prespecified subgroups

(age, sex, peak VO_2, patients in NYHA classes I-II vs those in NYHA class III, and patients with vs without CIEDs; eTables 8, 9, and 10 in Supplement 1), with the exception of the effect of site. Interaction *P* values for the effect of a site were nonsignificant for all-cause mortality and significant for all-cause hospitalization (site 1: HR, 0.91 [95% CI, 0.65-1.28]; site 2: HR, 1.17 [95% CI, 0.81-1.69]; site 3: HR, 0.48 [95% CI, 0.33-0.70]; site 4: HR, 1.08 [95% CI, 0.66-1.78]; site 5: HR, 1.88 [95% CI, 1.07-3.40]; interaction *P* < .001). eFigure 7 in Supplement 1 depicts the effects by site on key secondary outcomes. Site 1 was the only center with a statistically significant reduction in all-cause mortality (hazard ratio, 0.39 [95% CI, 0.16-0.94]), whereas site 3 was the only one with a statistically significant reduction in all-cause hospitalizations (hazard ratio, 0.48 [95% CI, 0.33-0.70]).

Tertiary Outcomes After 9 Weeks

At 9 weeks, all key variables improved significantly more in the HCTR arm than the UC arm after adjustment for site and baseline level. The change in 6-minute walk test distance was 30.0 (95% CI, 24.7-35.3) m vs 20.7 (95% CI, 15.4-26.0) m (*P* = .01). The change in peak VO_2 was 0.95 (95% CI, 0.65-1.26) mL/kg/min vs 0.00 (95% CI, −0.31 to 0.30) mL/kg/min (*P* < .001). The change in quality of life was 1.6 (95% CI, 0.74-2.42) points vs 0.00 (95% CI, −0.84 to 0.84) points (*P* = .008; **Table 3**). The benefits of using HCTR have been demonstrated in patients with CIEDs in eTables 11 and 12 in Supplement 1. We also observed significant improvement in NYHA class in the HCTR vs UC arms (*P* < .001; eTable 13 in Supplement 1).

Figure 2. Days Alive and Out of the Hospital



The group receiving hybrid comprehensive telerehabilitation had a mean (SD) of 91.9 (19.3) days alive and out of the hospital and a median (interquartile range) of 99.6% (96.1%-100%) of days alive and out of the hospital; the group receiving usual care had a mean (SD) of 92.8 (18.3) days alive and out of the hospital and a median (interquartile range) of 99.6% (96.1%-100%) of days alive and out of the hospital.

Discussion

The TELEREH-HF study demonstrated that despite improvements in functional and quality-of-life outcomes after 9 weeks of HCTR, the program does not improve clinical outcomes over a follow-up period extending for 12 to 24 months after the end of telerehabilitation. These findings confirm the results of single-center studies, which indicated that telerehabilitation is well accepted, safe, and effective and has high adherence among patients with HF, including those with CIEDs.[20-22] At the same time, this study demonstrates that the improvements achieved during the 9-week HCTR do not increase the percentage of days alive and out of the hospital or reduce mortality or hospitalization rates on longer-term follow-up (after the intervention was stopped).

The study also signaled possible heterogeneity of treatment effect according to site, which suggests that a positive long-term effect after a 9-week HCTR may depend on several factors, including improvement of patients' capacity of self-management, improvement of prognostic indicators, and the experience of the center that provides care. Still, the observed heterogeneity should not be overinterpreted; the lack of consistency between effects on hospitalization and mortality might indicate a chance outcome.

Several other studies investigated the effect of telemedicine in patients with HF.[12-18] Yet, the results are inconsistent and incomparable because of the different modalities of monitoring, different frequency of data transfer, different evaluation frequency in monitoring center, and different opening hours of specific centers. In the Telemedical Interventional Monitoring in Heart Failure (TIM-HF) trial, Koehler et al[13] assessed the effectiveness of a telemonitoring program without the use of physical training or monitoring of implantable devices (telecare rather than a comprehensive telerehabilitation). Moreover, in contrast with this study, they maintained their intervention throughout the entire observation period, which lasted for a minimum of 12 months. The intervention failed to reduce all-cause mortality, CV death, or hospitalization for HF compared with standard care. Similarly, a telein-tervention implemented in the Better Effectiveness After Transition—Heart Failure (BEAT-HF) study[15] showed that a combination of remote patient monitoring with care-transition management lasting for 180 days did not reduce 180-day all-cause readmission after hospitalization for HF compared with standard care. However, the recent Telemedical Interventional Management in Heart Failure II (TIM-HF2) trial[14] demonstrated that a new model of structured, remote patient-management intervention lasting for 12 months (but similarly to TIM-HF, without incorporation of rehabilitation or remote monitoring of CIEDs), when used in a well-defined HF population without major depression, reduced the percentage of days lost to unplanned CV hospitalizations and all-cause mortality. Therefore, the recent expert consensus

Table 2. Time-to-Event Outcomes From Randomization Through End of Follow-up

Outcome	Group Receiving Hybrid Comprehensive Telerehabilitation (n = 425)		Group Receiving Usual Care (n = 425)		Hazard Ratio (95% Wald CI)[a]	*P* Value
	No. (%)	Event Rate at 26 mo, %	No. (%)	Event Rate at 26 mo, %		
Mortality						
All-cause	54 (12.7)	12.5	52 (12.2)	12.4	1.035 (0.706-1.517)	.86
Cardiovascular	36 (8.5)	8.3	36 (8.5)	8.8	0.985 (0.619-1.569)	.95
Hospitalization						
All-cause	232 (54.6)	58.1	245 (57.6)	60.5	0.913 (0.762-1.093)	.32
Cardiovascular	141 (33.2)	36.8	161 (37.9)	40.7	0.837 (0.667-1.050)	.12
Heart failure	104 (24.5)	26.8	103 (24.2)	26.1	1.001 (0.762-1.326)	.99
All-cause mortality or all-cause hospitalization	246 (57.9)	60.1	253 (59.5)	61.7	0.939 (0.787-1.119)	.48
All-cause mortality or cardiovascular hospitalization	179 (42.1)	44.4	191 (44.9)	46.6	0.896 (0.730-1.099)	.29
All-cause mortality or heart failure–associated hospitalization	133 (31.3)	33.0	123 (28.9)	30.1	1.073 (0.840-1.372)	.57
Cardiovascular mortality or heart failure–associated hospitalization	121 (28.5)	30.4	113 (26.6)	28.0	1.063 (0.822-1.373)	.64

[a] Adjusted for site.

Table 3. Change From Baseline to 9 Weeks in Continuous Outcomes

Parameter	Group Receiving Hybrid Comprehensive Telerehabilitation				Group Receiving Usual Care				*P* Value[a]
	Patients, No.	Mean (SD)		Difference (95% CI)[a]	Patients, No.	Mean (SD)		Difference (95% CI)[a]	
		Baseline	At Ninth Week			Baseline	At Ninth Week		
Distance in 6-min walk test, m	422	419 (100.3)	450 (109.5)	30.0 (24.7-35.3)	423	409 (100.0)	432 (106.7)	20.7 (15.4-26.0)	.01
Cardiopulmonary exercise test time, s	422	383 (183)	428 (190)	45.5 (37.5-53.6)	422	374 (184)	390 (183)	16.7 (8.7-24.8)	<.001
Peak oxygen consumption, mL/kg/min	422	16.9 (6.0)	17.9 (6.2)	0.95 (0.65-1.26)	422	16.6 (6.0)	16.7 (5.9)	−0.00 (−0.31 to 0.30)	<.001
Percentage of expected peak VO_2	422	55.9 (20.4)	58.9 (21.0)	3.00 (1.84-4.10)	422	54.40 (21.1)	53.90 (21.3)	−0.74 (−1.88 to 0.39)	<.001
Respiratory exchange ratio	422	0.96 (0.14)	0.99 (0.12)	0.02 (0.01-0.03)	422	0.97 (0.13)	0.97 (0.13)	0.00 (−0.01 to 0.01)	.02
Quality of life, Medical Outcome Survey Short Form-36 score	417	89.7 (12.6)	91.2 (12.8)	1.58 (0.74-2.42)	416	88.8 (14.1)	88.9 (14.4)	−0.00 (−0.84 to 0.84)	.008

[a] *P* values represent between-group differences in improvement of outcomes; values are adjusted for baseline level of the outcome measure and site.

report of the Heart Failure Association of the European Society of Cardiology indicated that home monitoring similar to the one used in TIM-HF2 may be considered for patients with HF. The latest report from TIM-HF2 indicated that the morbidity and mortality benefits achieved in the remote patient-management group during the 12-month follow-up were not sustained over the 12 months after the intervention was stopped.[26] This suggests that the telemonitoring may only be effective as long as the intervention is in progress.[26]

Our results differ from those of the Participants in Heart Failure: a Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) trial, which showed that after adjustment for highly prognostic factors associated with the primary end point, exercise training was associated with modestly significant reductions for both all-cause mortality or hospitalization and CV mortality or HF hospitalization. However, the HF-ACTION and TELEREH-HF studies differ in terms of rehabilitation methodology (ie, the new model of HCTR used in this study), supervision of home training (remote and unsupervised training in HF-ACTION vs remotely supervised training in TELEREH-HF), and especially the follow-up protocol (in HF-ACTION, patients returned for facility-based training sessions every 3 months, while in TELEREH-HF, there were no such booster visits).[30-32]

Strengths

The main strength of our study is its prospective multicenter design and high quality of collected data, with no patients

revoking their written informed consent. This enabled us to collect all-cause mortality data on all study participants and hospitalization data on more than 96% of participants.

Limitations

Still, there are notable limitations. The interaction between treatment arm and site suggests that center's experience might play an important role in the longer-term outcomes of HCTR. Moreover, only 11.5% of the participants were women in this study, and therefore care needs to be exercised when extrapolating the results to the female population. This reflects a well-documented disparity problem with the participation in CR between men and women in Europe and the United States.[33] The fact that 12.0% of patients in the UC arm participated in the rehabilitation programs might have diluted our results, making it impossible to achieve the aggressive long-term treatment-effect goal. Finally, we have not collected functional status and quality of life data after the 9-week follow-up. Thus, we cannot ascertain if the observed modest improvements at 9 weeks were sustained. It is possible that continued intervention would have led to a positive effect on the percentage of days alive and out of the hospital and other clinical end points.

Conclusions

Positive effects of 9-week hybrid comprehensive telerehabilitation in patients with HF do not lead to the increase in days alive and out of the hospital and do not reduce mortality and hospitalization over 14 to 26 months of follow-up. This indicates a neutral HCTR effect compared with UC in patients with HF in terms of outcomes during long-term follow-up. One possible approach to organize the outpatient management for patients with HF would be to combine several weeks of HCTR (based on our study results) with long-term remote patient monitoring (based on the TIM-HF2 trial).

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