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Gordon R. Reeves
Thomas Jefferson University, gordon.reeves@jefferson.edu

David J. Whellan
Thomas Jefferson University, David.Whellan@jefferson.edu

Pamela Duncan
Wake Forest School of Medicine

Christopher M. O'Connor
Inova Heart and Vascular Institute

Amy M. Pastva
Duke University School of Medicine

See next page for additional authors

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Authors

Gordon R. Reeves, David J. Whellan, Pamela Duncan, Christopher M. O'Connor, Amy M. Pastva, Joel D. Eggebeen, Leigh Ann Hewston, Timothy M. Morgan, Shelby D. Reed, W. Jack Rejeski, Robert J. Mentz, Paul B. Rosenberg, and Dalane W. Kitzman

Rehabilitation Therapy in Older Acute Heart Failure Patients (REHAB-HF) Trial: Design and Rationale

Gordon R. Reeves, MD, MPT[*], **David J. Whellan, MD, MHS**[*], **Pamela Duncan, PT, PhD**[†], **Christopher M. O'Connor, MD**[‡], **Amy M. Pastva, PT, PhD**[ǁ], **Joel D Eggebeen, MS**[#], **Leigh Ann Hewston, PT, Med**[§], **Timothy M. Morgan, PhD**[†], **Shelby D. Reed, PhD**[††], **W. Jack Rejeski, PhD**[**], **Robert J. Mentz, MD**[††], **Paul B. Rosenberg, MD**[††], and **Dalane W. Kitzman, MD**[†] **on behalf of the REHAB-HF Trial Investigators**

[*]Sidney Kimmel Medical College, Philadelphia, PA

[†]Wake Forest School of Medicine, Winston-Salem, NC

[‡]Inova Heart and Vascular Institute, Falls Church, VA

[ǁ]Department of Orthopaedic Surgery, Doctor of Physical Therapy Division

[††]Duke University School of Medicine, Durham, NC

[#]Emory Univeristy Atlanta, GA

[§]Thomas Jefferson University School of Health Professions, Philadelphia, PA

[**]Department of Health and Exercise Science, Wake Forest University, Winston-Salem, NC

[††]Duke University School of Medicine, Durham, NC

Abstract

Background—Acute decompensated heart failure (ADHF) is a leading cause of hospitalization in older persons in the United States. Reduced physical function and frailty are major determinants of adverse outcomes in older patients with hospitalized ADHF. However, these are not addressed by current heart failure (HF) management strategies and there has been little study of exercise training in older, frail HF patients with recent ADHF.

Hypothesis—Targeting physical frailty with a multi-domain structured physical rehabilitation intervention will improve physical function and reduce adverse outcomes among older patients experiencing a HF hospitalization.

Address for Correspondence: Gordon R. Reeves, MD, MPT, Department of Medicine, Sidney Kimmel School of Medicine at Thomas Jefferson University, 925 Chestnut Street, Mezzanine Level, Philadelphia, PA 19107, Telephone: 215-955-2050, Fax: 215-503--0052, gordon.reeves@jefferson.edu.
[*]The first and second authors contributed equally

Study Design—Rehabilitation Therapy in Older Acute Heart Failure Patients (REHAB-HF) is a multi-center clinical trial in which 360 patients ≥ 60 years hospitalized with ADHF will be randomized either to a novel 12-week multi-domain physical rehabilitation intervention or to attention control. The goal of the intervention is to improve balance, mobility, strength and endurance utilizing reproducible, targeted exercises administered by a multi-disciplinary team with specific milestones for progression. The primary study aim is to assess the efficacy of the REHAB-HF intervention on physical function measured by total Short Physical Performance Battery score. The secondary outcome is 6-month all-cause rehospitalization. Additional outcome measures include quality of life and costs.

Conclusions—REHAB-HF is the first randomized trial of a physical function intervention in older patients with hospitalized ADHF designed to determine if addressing deficits in balance, mobility, strength and endurance improves physical function and reduces rehospitalizations. It will address key evidence gaps concerning the role of physical rehabilitation in the care of older patients, those with ADHF, frailty, and multiple comorbidities.

Keywords

Heart Failure; Physical rehabilitation; Frailty; Hospitalization

Introduction

Acute decompensated heart failure (ADHF) is a leading cause of hospitalization in older persons in the United States.[1] Hospitalized ADHF is associated with severely reduced health-related quality of life (QOL),[2] persistently high rehospitalization rates,[2] markedly increased mortality,[3] and costs over $16 billion per year in the United States.[4] Despite advances in the treatment of chronic heart failure with reduced ejection fraction (HFrEF), there has been relatively little progress with respect to ADHF therapies. Current heart failure (HF) management guidelines, even when perfectly adhered to, have had only modest impact on ADHF outcomes, particularly rehospitalizations in the older population.[2, 5] Furthermore, several recent trials of new interventions to improve ADHF outcomes, such as remote monitoring,[6, 7] alternative diuretic regimens,[8] novel pharmacologic agents[9, 10] and biomarker guidance[11] have not proven beneficial. The typical older ADHF patient has >5 comorbidities that contribute to adverse outcomes.[5, 12–14] Frequent non-cardiac comorbidities may explain the unexpected finding from multiple studies that >50% of rehospitalizations in older ADHF patients are due to non-cardiac events rather than recurrent ADHF.[3, 5, 12, 15]

Multiple lines of evidence suggest that severely reduced physical function and frailty are major determinants of adverse outcomes in older patients with hospitalized ADHF.[16] We and others have shown that even when stable with compensated cardiovascular function, older patients with chronic HF have severe impairments in physical function due to the combined effects of aging, cardiovascular dysfunction, and impaired skeletal muscle function.[17–19] As patients with chronic HF transition to ADHF, physical function worsens both because of HF decompensation and accelerated physical deconditioning.[20, 21] This is further exacerbated by the hospital processes, including bed rest which can markedly

exacerbate physical dysfunction and acute muscle loss,[20, 22, 23] contributing to what has now been termed the 'post-hospital syndrome'.[24]

After resolution of the acute HF symptoms and congestion, older ADHF patients continue to have marked impairments in physical function, including deficits in strength, balance, mobility and endurance, and most patients meet formal definitions of frailty.[20, 25] Furthermore, these deficits persist and some patients never recover baseline function.[24, 26, 27] This occurs during the most vulnerable, high risk period for rehospitalization and adverse outcomes, up to 6 months post discharge,[3] and likely contribute to the high costs of rehospitalizations. These costs are now targeted by the Centers for Medicare & Medicaid Services (CMS) penalties reducing payments to hospitals with excess readmissions.[28]

Prior clinical trials of exercise training in HF (n>40), including those used to support the decision by CMS to expand cardiac rehabilitation coverage to HFrEF, were restricted to HF patients with chronic, stable disease.[29–31] The largest of these, the NIH-funded HF-ACTION trial, excluded patients with ADHF and those within 6 weeks of hospital discharge.[29] This prompted CMS to explicitly exclude recently hospitalized HF patients from cardiac rehabilitation coverage[28] and an expert consensus recommendation for a period of stability of at least a month before enrolling HF patients in cardiac rehabilitation.[32] HF-ACTION also enrolled relatively few older patients, particularly those with multiple comorbidities,[33] who may be at increased risk for complications during cardiac rehabilitation.[34] As noted above, physical impairments in older, frail patients with ADHF are broader, including deficits in balance and mobility, and far more severe than those observed in patients with chronic stable HF.[20] Such deficits are not typically targeted by conventional, endurance-based cardiac rehabilitation.[29] Addressing deficits in balance, mobility and functional strength may be important for preventing early injuries in frail, older ADHF patients and for enhancing gains in function.[35, 36]

We hypothesize that targeting physical frailty among older patients experiencing a HF hospitalization with a multi-domain structured physical rehabilitation intervention will improve physical function and reduce adverse outcomes. The current group of investigators completed a pilot study which showed that in older patients with ADHF, a structured intervention targeting physical function can improve the Short Physical Performance Battery (SPPB) score, a strong predictor of hospitalization, disability, and death.[37] Based on these findings, the National Institute of Aging funded the Rehabilitation Therapy in Older Acute Heart Failure Patients (REHAB-HF) Trial to evaluate the efficacy of a novel, tailored, progressive, multi-domain, 12-week physical function intervention initiated during an ADHF hospitalization to improve physical function, as measured by SPPB (primary outcome), and reduce all-cause rehospitalization during the 6 months after initiation of the intervention.[38]

Methods

Study Population

The REHAB-HF Trial has a target enrollment of 360 HF patients admitted for worsening heart failure (HF), based on at least one symptom of HF and at least two signs of HF and a change in medical treatment specifically targeting ADHF (Table 1). There is no left ventricular ejection fraction (EF) criterion. Patients must be at least 60 years of age or greater, performing basic activities of daily living prior to admission, able to walk at least 4 meters at the time of enrollment (assistive device allowed) and expected to be discharged to home.

Patients are excluded if their HF is end-stage, defined as requiring or anticipating heart transplant or left ventricular assist device within the next 6 months or expected discharge on continuous intravenous ionotropic therapy. Patients with HF in the presence of severe primary valvular disease, such as severe aortic stenosis or mitral regurgitation, are excluded. Patients with advanced renal dysfunction who are currently requiring dialysis or at high risk for progressing to dialysis during the course of the study (defined as estimated glomerular filtration rate of < 20 mL/min/1.73 m2) are excluded due to concerns regarding ability to adhere to the study intervention. Similarly, patients are not enrolled if they have clinically evident dementia or significant impairment from a stroke, injury or other medical disorder that precludes participation in the intervention or following study protocol. Potential participants found to have mild cognitive impairment, common in older patients hospitalized with HF,[20, 39] are eligible for enrollment provided there is adequate social support for adherence. Participants undergo screening for potential barriers to adherence using a standardized tool to assess personal commitment to adhering to the study requirements; degree of support from family members, caregivers and outpatient physicians; and potential transportation barriers. Those unable or unwilling to fully commit to all aspects of study participation or who lack support are considered high risk for non-adherence and are excluded from the study.

Eligible patients who provide informed consent and complete baseline testing successfully (Table 2) are randomized to attention control or to the multi-domain rehabilitation intervention. Block randomization is employed and stratified on clinical center and EF category (<45, ≥45). All sites use the same allocation process housed in the Coordinating Center (Wake Forest) database (REDCap) to ensure uniform randomization.

The REHAB-HF trial is being conducted in accordance with the Declaration of Helsinki and has been approved by Institutional Review Boards of all participating institutions. All study participants provide informed written consent. The REHAB-HF trial is registered with Clinicaltrials.gov (NCT02196038).

Attention Control

The usual care arm of REHAB-HF is defined as attention control due to increased surveillance of these participants in an effort to reduce the potential bias created from increased interactions of intervention participants with study personnel. Participants in the attention control group will receive at least bi-weekly contact from study personnel (nurses

or exercise physiologists) by phone or by specified study visits (weeks 4 and 12) during the first 3 months following the index hospitalization. Information regarding symptoms, HF transitional management program use, medical compliance, activity level, rehabilitation received, medical resource utilization, QOL and clinical events will be collected at each of these encounters. Participants in the attention control arm will not receive any specific rehabilitation recommendations or exercise prescription from study personnel. Adherence to medication regimens and follow-up appointments is encouraged.

Participants in both arms receive standard therapies as directed by their clinical providers, which may include any of the following services: inpatient physical therapy, outpatient physical therapy, or cardiac rehabilitation 6 weeks after discharge. All aspects of disease management, including medical therapy and HF management, are left to the discretion of the participant's treating physician and are specifically not addressed by the study protocol for either study arm. Clinical concerns raised by the participant and/or identified by study personnel are referred to the participant's health care provider(s) for further management.

REHAB-HF Intervention

The multi-domain rehabilitation intervention for this study is a novel integration of rehabilitation therapies developed specifically for older HF patients who have been hospitalized for ADHF. The goal of the intervention is to improve balance, mobility, strength and endurance utilizing reproducible, targeted exercises administered by a multi-disciplinary team with specific milestones for progression. The intervention is limited to physical rehabilitation and specifically does not address other aspects of disease management or frailty.

Frequency and Duration—The majority of the study interventions are facility-based in the outpatient setting. These 3 times per week sessions are initiated as soon as possible following hospital discharge, last approximately 60 minutes, and continue for 12 weeks or 36 sessions. For participants with especially low functional performance, a limited number of these sessions may be conducted at home early following discharge (weeks 1–2). When feasible, daily sessions of approximately 30 minutes are conducted in the hospital prior to discharge.

Intensity—Exercise intensity is based upon patient-reported rate of perceived exertion (RPE) using a 6–20 point scale. During the first two weeks, target intensity is low (RPE 12). In the outpatient setting, target RPE is gradually increased to 13 ("somewhat hard") (range of 11–15) for endurance training and 15–16 for strength rehabilitation, as this level of intensity may be necessary to obtain significant functional improvement in strength.[40] After 4 weeks of the endurance intervention, intensity within the target RPE range can be adjusted to ensure a heart rate response of 20 beats per minute above the resting heart rate. This is typically needed to achieve >60% of exercise reserve capacity[41] and is intended to ensure an adequate training effect to minimize non-responders while maintaining safety.[29, 42, 43]

Mode—Each session includes a warm-up, one-on-one targeted rehabilitation training in each domain (balance, mobility, strength and endurance), and a cool-down. At the beginning

of the intervention, participants undergo standardized stratification of functional performance in each of four domains: balance, strength, endurance and mobility (Table 3). We anticipate a range of initial performance levels based on the REHAB-HF pilot study, where 40% of participants were initially at the lowest level of functioning (level 1) for most domains, 33% were at level 2, and 27% were at level 3.[20] Exercises specifically targeted to the participant's functional level in each domain are then selected from the intervention protocols (see Table 4 for examples).

The relative time spent on each domain during the rehabilitation session is also tailored to the participant's physical impairments (Figure). For example, a participant with poor balance and functional mobility spends a greater proportion of time performing exercises focused in these areas. Alternatively, a participant with only modest impairments in balance and functional mobility spends most of the exercise session performing endurance and strengthening exercises.

Progression—Progression is a key aspect of the study intervention. Participants are continually challenged to improve physical function by advancing through a structured, gradual progression using specific small increments in each exercise. Progression is based on performance during one-on-one training sessions and standardized re-assessment of functional performance in each domain conducted every 2 weeks (Table 3 and 4).

Safety—Pre-specified safety protocols based on vital signs and reported symptoms will be followed. Should a participant report a significant change in health status before or during exercise that presents a safety risk for continued exercise participation, a study physician onsite or the participant's primary doctor will be consulted prior to exercise participation. Vital signs, including heart rate, blood pressure and pulse oximetry will be recorded at the beginning and conclusion of each session. Routine assessment of heart rate and RPE during the exercise session will also be used to enhance exercise safety. Exercising blood pressure and pulse oximetry will be monitored on a symptom-driven basis. Telemetry monitoring is not performed.

Intervention fidelity—Several strategies are used to promote consistent implementation of the intervention. These include: 1) a standardized protocol with a) specific rehabilitation exercises for each of the 4 domains; b) selection of initial exercises and progression based on standardized assessments (Table 3); c) detailed progression in small increments for each exercise; 2) training comprised of a) full day of in-person training of the study interventionists (experienced exercise physiologists and physical therapists) prior to study launch, including protocol review, demonstration videos using patient volunteers and hands-on practice sessions; b) interactive study-wide webinars conducted at least annually; 3) continued monitoring to identify and address challenges related to fidelity. This includes tracking of exercises performed during each intervention session through a study-wide database. These reports are reviewed and discussed during bi-weekly teleconferences of study leadership for each participant actively engaged in the study physical rehabilitation intervention. The intervention supervisor at each site also reviews the implementation of the study intervention for each participant with the treating interventionist, addressing any challenges that arise.

Home exercise—All participants randomized to the study intervention receive one home evaluation by study personnel following hospital discharge lasting approximately 30–45 minutes. The purpose of the home visit is to identify areas for safe performance of the home exercise prescription. Participants are instructed in low-intensity walking at their usual pace, gradually increasing toward a goal of 30 minutes daily. Functional strengthening exercises (e.g. sit-to-stand from chair, step-ups, if feasible, and calf raises) are incorporated and customized based on patient goals and identified deficits. This brief home exercise program is to be performed on non-program days at least twice per week. Whenever possible, study personnel attempt to engage the participant's caregivers/family to support home exercise.

Maintenance—Following the completion of the outpatient intervention, an individualized maintenance exercise prescription is developed by the interventionist based on the participant's performance at the end of the 12-week supervised training intervention. Participants in the intervention arm will receive phone calls at months 4, 5, and 6, to discuss adherence to the exercise prescription and to gather information regarding study endpoints (Table 2). Physical activity is also monitored by accelerometers worn by participants in both study arms. These accelerometers are for monitoring only and do not have a display visible to the participant.

Retention and Adherence

Retaining participants with a high disease burden in a study that involves a significant commitment is expected to be challenging. The study addresses retention prior to enrollment by carefully explaining the commitment, identifying and addressing potential barriers, particularly if a participant is randomized to the intervention arm, and having the participant sign a behavioral agreement that details the requirements of the study. Adherence screening confirming participant commitment and support by family or caregivers and personal physicians is conducted prior to randomization. Participants unable to fully commit during this screening will not be randomized. Once randomized, the study will provide a clear schedule of all visits, reminders, same-day phone calls for any missed visits, involvement of family and caregivers, and sharing of test results and intervention progress, if applicable. Transportation support will also be available.

Interruptions to the study intervention, including illness and hospitalization, are anticipated. To help ensure each participant has a reasonable opportunity to complete the study intervention and that the physical performance outcome measures reflect the intended intervention of this study, limited extensions (2–4 weeks) are included in the study protocol for participants in both study arms.

Our primary measure of adherence is the percent of prescribed sessions attended. We will be able to assess this and other aspects of exercise adherence through tracking of sessions attended, sessions missed, reasons for missed sessions, as well as exercise performed in each session attended.

Outcomes

The primary aim of the study is to assess the efficacy of the REHAB-HF intervention on physical function measured by the change in total SPPB score from baseline to 3 months. This and other study measures are obtained by independent, trained assessors who are blinded to participant's intervention allocation. The SPPB measures physical function using 3 components: usual gait speed over 4 meters, time to complete 5 chair rises, and standing balance with progressively narrow base of support. Each component is scored on a 0–4 scale and summed for an overall score range of 0–12.[44] The SPPB was chosen as the primary outcome because it is a well-accepted, standardized, reliable, validated measure of physical function in the older population that can be collected safely and easily in clinic, home, and hospital settings, including in older patients hospitalized with ADHF.[20, 25] The overall SPPB score and components are highly predictive of important clinical outcomes, including disability, hospitalization, nursing home admission, and death.[44–46] The SPPB is sensitive to change in health status[47] and responsive to exercise training.[48–50] Interventions that improve SPPB also improve clinical events.[48] A clinically meaningful but small change in SPPB score is 0.5 units and a substantial change is 1.0 units.[50]

Six-month all-cause rehospitalization was chosen as the key secondary outcome because: it is the most frequent adverse outcome in ADHF; it is associated with impaired physical function, reduced quality of life, increased mortality, and increased cost; and our pilot data and others' suggest that it is responsive to physical function interventions.[37] A rehospitalization is defined as a hospital stay >24 hours, including prolonged emergency department visits or observational unit stays, for any cause. For exploratory analyses and safety monitoring, rehospitalizations will be categorized by the site investigators as primarily due to non-cardiovascular, HF, or other cardiovascular (myocardial infarction, acute coronary syndrome without myocardial infarction, arrhythmia, peripheral vascular) cause, and whether they were related to the study intervention or assessments.

Additional exploratory analyses will examine the effect of the intervention on: the components of the SPPB; 6-minute walk distance; QOL (both HF-specific and global); frailty phenotype as originally described by Fried;[51, 52] depression; cognitive function; all-cause combined rehospitalization and death; global rank endpoint of SPPB score, all-cause rehospitalization and death; HF-specific rehospitalizations; cardiovascular events; rehospitalization days; facility-free days; deaths; falls; and biomarkers. Sub-group analyses based on EF category (<45, 45) are also planned.

Statistical Analysis and Sample Size

The effect of the intervention on SPPB score measured 3 months post-randomization will be estimated and tested for significance using analysis of covariance, where the randomized arm is the between-subject grouping variable and the pre-randomized measure of SPPB score, clinical site, age, gender, and EF category (<45, 45) will be covariates. Least square means will be used to estimate the intervention effect. Tests will be conducted at the 5% two-sided level of significance.

The secondary aim of the study is to assess the intervention's effect on the total number of all-cause rehospitalizations during the 6 months following discharge from the index hospitalization. Since the count of all-cause rehospitalizations per participant may not be normally distributed, the effect of the intervention on total all-cause rehospitalizations will be estimated using a Poisson model for modeling count data, where the randomized arm is the between-subject grouping variable and clinical site, age, gender, and EF category will be covariates. A supplemental analysis will be performed adding the duration of the index hospitalization and the number of inpatient intervention sessions as additional covariates. To account for the expected dropouts or non-compliance with the intervention, we will incorporate compliance ("on treatment") as collected by adherence measurements. Simple observational treatment comparisons that include only patients who complied with specified levels of the intervention protocol will be examined as supportive information, recognizing the limitations of such comparisons.

The REHAB-HF pilot study showed an estimated intervention effect of an increase of 1.13 units in 3-month SPPB score (the primary outcome) or a 17.9% relative increase above the least square mean for the attention control group, with a mean square error from the analysis of covariance model of 3.269.[37] This study is designed to have 80% power to detect a 10% treatment difference (0.63 absolute difference) in the 3-month least square mean of SPPB score. Based on the findings of the REHAB-HF pilot study, this requires 258 evaluable participants. Assuming an 85% retention rate, the study requires randomizing 304 participants (25.3 per site per year).

In the completed pilot study, the number of all-cause rehospitalizations within 6 months was reduced 29.3% by the intervention (1.673±0.392 per patient in the attention control group vs. 1.157±0.349 in the intervention group). We performed additional work with an analysis of a contemporaneous sample of 239 consecutive patients aged 65 years admitted with the primary diagnosis of ADHF. This confirmatory sample yielded a 6-month rehospitalization event rate estimate within 0.5% of our attention control group, giving confidence in our pilot study estimate. This study is designed to have 80% power to detect a 25% reduction (0.41 absolute difference) in the total number of all-cause rehospitalizations during the 6 months following the index hospitalization. This requires 334 participants; assuming loss to follow-up of 5%, the study requires randomizing 352 total participants. Rounding up, this study will randomize a total of 360 patients, providing > 80% power for the primary and secondary aims.

Economic analysis

Patient-level information on medical resource use, patient time spent on rehabilitation-related activities and QOL, as measured with the EuroQol 5-Dimension 5-Level (EQ-5D-5L), is collected throughout the 6-month follow-up period (Table 2). Interventionists and support staff will provide supplemental information to estimate costs to provide the rehabilitation intervention. These data will be used to estimate direct medical costs, non-direct medical costs, indirect (patient time) costs and quality-adjusted survival. Mean costs and quality-adjusted survival over the six-month follow-up period in the

REHAB-HF will be compared between patients randomized to the rehabilitation intervention versus attention control.

If the intervention does not produce a net cost-savings in the short-term, a long-term cost-effectiveness analysis will be performed to assess the incremental costs of the intervention versus the incremental impact of the intervention on quality-adjusted survival. The previously-developed and validated TEAM-HF Cost-Effectiveness Model[53] will be used to generate longer-term estimates of costs, survival and quality-adjusted survival. The economic evaluation of the REHAB-HF intervention will be used to propose payment models for third-party payers (e.g. CMS) and accountable care organizations and health maintenance organizations who provide care to HF patients on a capitated basis.

Support

Discussion

REHAB-HF is a multicenter, prospective randomized controlled trial designed to determine if a tailored, structured, progressive multi-domain physical rehabilitation intervention addressing deficits in balance, mobility, strength, and endurance, improves physical function and reduces rehospitalizations compared to attention control in older patients hospitalized with ADHF. This is the first HF clinical trial to employ a multi-domain physical rehabilitation intervention beginning during ADHF hospitalization and transitioning to the outpatient setting. REHAB-HF is designed to address multiple high-priority gaps in the evidence regarding exercise training in HF patients, including those with markedly reduced physical function who are unable to undertake traditional exercise training, > 60 years, with multiple co-morbidities, who are women, and who have HF with preserved EF (HFpEF).[37, 54, 55] The trial has consistently met enrollment targets with 160 of 360 participants enrolled to date and study completion anticipated in 2019.

We have incorporated several novel features into our study design to meet the specific needs of older, frail recently hospitalized HF patients that distinguishes REHAB-HF from prior[29, 30] and ongoing[56–58] investigations of exercise training in HF. During our pilot study, we observed unexpectedly severe impairments in all functional domains, including balance and mobility.[20] Prior studies have shown that not identifying and correcting balance impairments early during rehabilitation can lead to increased injuries.[36] In response to this and in an effort to maximize training response while minimizing the risk of injuries and

falls, we provide one-on-one training to deliver an individually tailored, multi-domain intervention with an early emphasis on addressing deficits in balance, mobility and functional strength.[34, 59] Progressively more endurance training is incorporated as balance, mobility and strength improve (Figure). The timing of the REHAB-HF intervention is also unique in that it is initiated as early as the time of hospitalization following initial stabilization of ADHF. The study intervention is also highly adaptable to a wide range of functional impairments while promoting gradual, structured progression and maintaining fidelity.

We hypothesize that the widespread, severe functional impairments targeted by our intervention are largely due to skeletal muscle dysfunction as a result of the systemic effects of the HF clinical syndrome, medical comorbidities, aging, acute illness and hospital-related immobility.[16, 55] Given the systemic nature of these mechanisms, we expect the intervention will have similar efficacy in older frail patients recovering from ADHF regardless of EF. This is supported by several observations. Older patients with chronic HFpEF and HFrEF have similar functional impairments with similar underlying skeletal muscle abnormalities, including shift in fiber types, reduced capillary density, and impaired mitochondrial function.[17, 60–63] During ADHF, patients with both types of HF are subject to acute muscle loss and dysfunction associated with hospitalization and immobility.[64–67] In our pilot, the nature and severity of functional impairments in older patients with ADHF were independent of EF.[20] The similarities in functional impairments and their proposed mechanisms may also help explain the remarkably similar vulnerability to adverse clinical outcomes, frequently due to non-cardiac causes, observed in older patients following a HF hospitalization across the spectrum of EF.[3] In fact, many of the proposed contributing factors to functional impairments and clinical outcomes, such as aging, comorbidities and acute immobility, are common to a broader population of older, frail hospitalized patients at risk for the "post-hospital syndrome",[24] supporting the potential further generalizability of study findings.

While the focus of the study is on addressing physical function impairments, descriptors of impairments common in acutely ill, older patients (e.g. frailty, falls, cognition, urinary incontinence) will also be captured. Such syndromes are by nature non-disease specific and are not typically targeted by HF management strategies. However, they may be associated with HF, worsened as components of the post-hospital syndrome,[24] can complicate HF management and contribute to adverse clinical outcomes in older patients with HF. The frequency and severity of these geriatric syndromes will be tracked over the course of the study, and the contribution to QOL, economic and clinical outcomes during the high risk period following ADHF hospitalization will be assessed. Such insights could help inform the design of complimentary novel interventions.

In conclusion, REHAB-HF is a multi-center randomized control trial that will address key evidence gaps by determining if a novel physical rehabilitation intervention will improve physical function and reduce all-cause rehospitalizations following an ADHF hospitalization in older, frail patients with multiple comorbidities and severe impairments in physical function. The trial results could have a major impact on the management of older patients

with ADHF by improving the morbidity, reduced quality-of-life, and high health care costs associated with the nearly 1 million rehospitalizations annually in older HF patients.[68]

Acknowledgments

Abbreviations

ADHF	Acute Decompensated Heart Failure
HF	Heart Failure
CMS	Centers for Medicare & Medicaid Services
EQ-5D-5L	EuroQol 5-Dimension 5-Level
SPPB	Short Physical Performance Battery
REHAB-HF	Rehabilitation Therapy in Older Acute Heart Failure Patients
QOL	Quality of Life
RPE	Rate of perceived exertion
EF	Ejection Fraction
HFrEF	Heart failure with reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction

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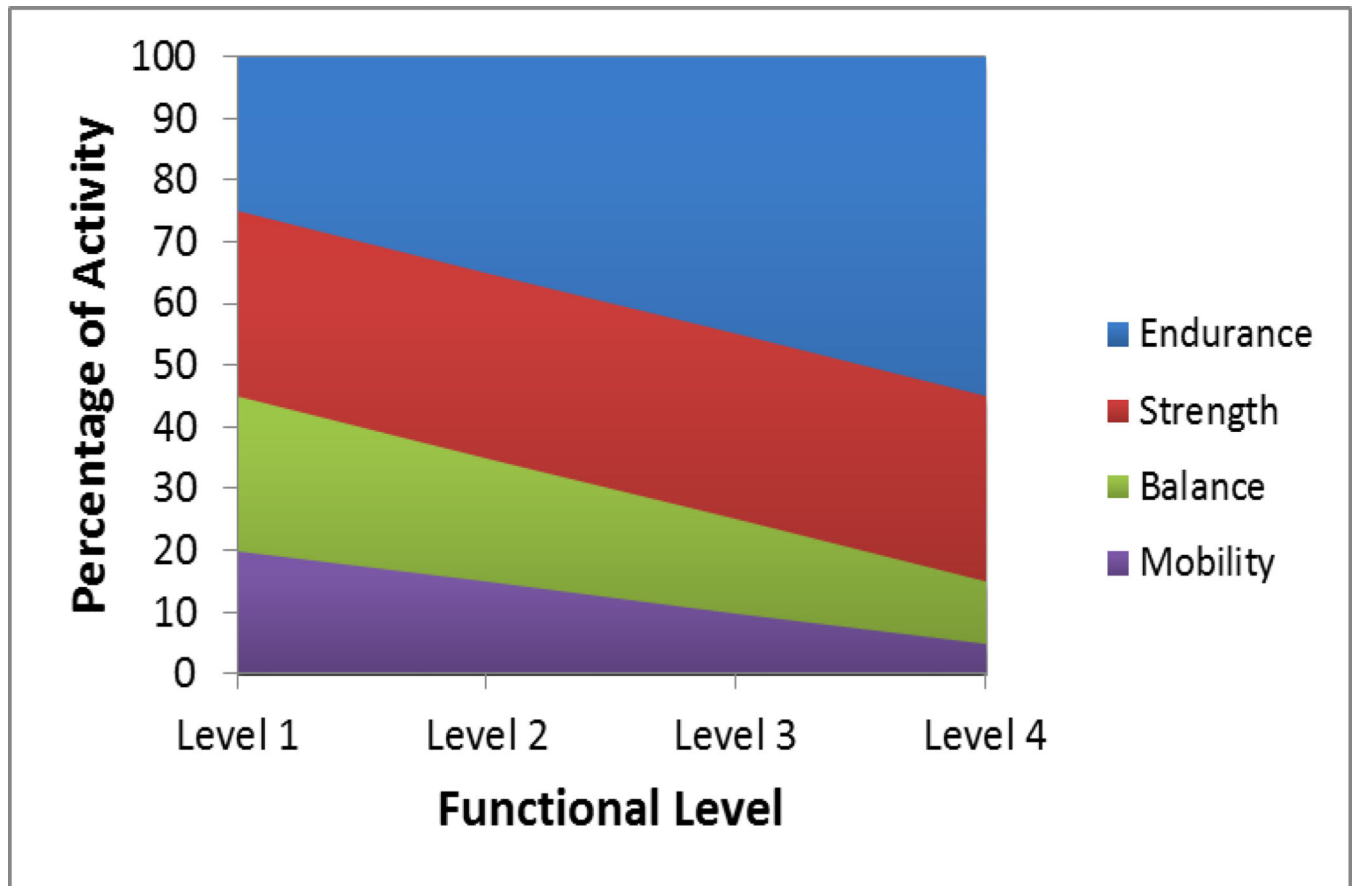
Figure 1.
Approximate percent of exercise time in each physical function domain based on functional level.

Table 1

REHAB-HF Inclusion and Exclusion Criteria

Inclusion Criteria
Patients eligible for the trial must meet the following criteria at randomization:
•   Age 60 years old
•   In the hospital setting >24 hours for the management of ADHF, defined as:
–   At least <u>one</u> symptom of HF which has worsened from baseline:
♦   Dyspnea at rest or with exertion
♦   Exertional fatigue
♦   Orthopnea
♦   Paroxysmal nocturnal dyspnea (PND)
–   At least <u>two</u> of the signs of HF
♦   Pulmonary congestion or edema on exam (rales) or by chest x-ray
♦   Elevated jugular venous pressure or central venous pressure 10 mm Hg
♦   Peripheral edema
♦   Wedge or left ventricular end diastolic pressure 15 mmHg
♦   Rapid weight gain (5 lbs.)
♦   Increased b-type natriuretic peptide (BNP) (100 pg/ml) or N-terminal prohormone BNP (220pg/ml)
–   Change in medical treatment specifically targeting HF defined as change in dose or initiation of or augmentation of at least one of the following therapies
♦   Diuretics
♦   Vasodilators
♦   Inotropes (including digoxin if for HF)
♦   Other neurohormonal modulating agents, including angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, beta-blockers, aldosterone or direct renin inhibitors
•   Clinical stability to allow participation in study assessments and the intervention
•   Prior to admission, patient was independent with basic activities of daily living (ADLs) including the ability to ambulate independently (with or without the use of an assistive device)
•   Able to walk 4 meters (with or without the use of an assistive device) at the time of enrollment
Exclusion Criteria
At the time of randomization, none of the following conditions may exist:
•   Acute myocardial infarction based on clinical diagnosis
•   Requiring care in an intensive care unit
•   Planned discharge other than to where the participant will live independently
•   Dementia that precludes ability to participate in rehabilitation and follow study protocols
•   Impairment from stroke, injury or other medical disorder that precludes participation in the intervention
•   Advanced chronic kidney disease (eGFR < 20 mL/min/1.73 m^2) or dialysis
•   Prior cardiac transplantation or planned within the next 6 months
•   Expected use of continuous intravenous inotropic therapy after discharge
•   Ventricular assist device or anticipated within the next 6 months
•   Severe aortic valve stenosis
•   Already actively participating in facility-based cardiac rehabilitation

Inclusion Criteria

- Anticipated hospital discharge before baseline study measures could be completed

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Table 2

Schedule of Visits and Assessments

	Index Hospitalization (Baseline)	1 Month (Visit)	2 Months (phone call)	3 Months (Visit)	3.5, 4, 5, & 6 Months (phone call)
6MWT	X	X		X	
SPPB	X	X		X	
Frailty Phenotype	X	X		X	
Biomarkers	X			X	
KCCQ	X	X		X	
SF-12	X	X		X	
EQ-5D-5L	X	X		X	X (6 months)
GDS-15	X			X	
MoCA	X			X	
Clinical Events	X	X	X	X	X
Medications Review	X	X	X	X	X
Medical Resource Use		X	X	X	X
Geriatric conditions; Falls Urinary incontinence	X	X	X	X	X

6MWT = Six Minute Walk Test; GDS = Geriatric Depression Scale; KCCQ = Kansas City Cardiomyopathy Questionnaire; MoCA = Montreal Cognitive Assessment; SF = Short Form; SPPB = Short Physical Performance Battery; EQ-5D-5L = EuroQol 5-Dimension 5-Level

Table 3

Performance Levels for Strength, Balance, Mobility and Endurance

	Level 1	Level 2	Level 3	Level 4
Strength: Rise from chair without hand support	unable	at least once	5 times in > 15 but <60 seconds	5 times in 15 seconds
Balance: Standing	unable with feet together for 10 seconds	with feet together for 10 seconds	unsupported and reach forward 10 inches	on 1 leg for 10 seconds
Endurance: Continuous walking	< 2 minutes	2 but < 10 minutes	10 but < 20 minutes	20 minutes
Mobility: Gait speed	0.4 m/s	> 0.4 but 0.6 m/s	> 0.6 but 0.8 m/s	> 0.8 m/s

Table 4

Examples of Exercise Prescription by Performance Levels for each exercise domain: Strength, Balance, Mobility and Endurance

Exercise Examples by Domain	Level 1	Level 2	Level 3	Level 4
Strength a) Sit to stand b) Step-ups (front and side)	On edge of chair leaning forward and pushing with hands 4 inch step [*]	On edge of chair leaning forward with arms reaching out 6 inch step [*]	In back of chair with arms across chest 8 inch step [*]	As in Level 3 at faster pace or from lower surface 10 inch step and/or with resistance [*]
Balance Stand and reach	Stand with feet shoulder width apart; reach forward 6 inches and hold.	Stand with feet shoulder width apart; reach forward 10 inches and hold.	Stand with feet together; reach forward 6 inches (progressing to 10 inches) and hold	Semi-tandem stance; reach forward 6 inches (progressing to 10 inches) and hold
Endurance: Continuous walking	Repeated brief bouts for a total duration of 10 minutes	Repeated brief bouts for a total duration of 20 minutes	Repeated bouts for a total duration of 30 minutes	Continuous for 20-30 minutes
Mobility Gait training	Stop and start abruptly	Brief accelerations during walking	Quick change of direction	Quick change of direction while engaged in activity requiring cognitive attention (e.g. conversation, questioning)

Frequency and duration: Outpatient 3x/week for approximately 60 minute sessions integrating all domains (goal 36 sessions). Inpatient: 30 minute sessions daily until discharge with focus on domains to preserve functional mobility (when feasible; typically 0–2 sessions).

Intensity: RPE <12 initially; increasing to 13 (11–15) for endurance; 15–16 for strength. Balance and mobility not to exceed endurance RPE.

Mode: Exercises appropriate to a participant's performance level in each domain (Table 3) are selected as illustrated in the examples above.

Progression: As performance improves, participants advance to slightly more challenging exercises through structured, small increments. Performance is assessed during one-on-one training sessions, including standardized re-assessment of functional performance in each domain (Table 3) conducted every 2 weeks.

[*] Performed with support of two hands, support of one hand, or no hand support.