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Cognitive behavioral therapy for insomnia in stable heart failure: Protocol for a Randomized Controlled Trial

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Abstract

Background—Chronic insomnia is associated with disabling symptoms and decrements in functional performance. It may contribute to the development of heart failure (HF) and incident mortality. In our previous work, cognitive-behavioral therapy for insomnia (CBT-I), compared to HF self-management education, provided as an attention control condition, was feasible, acceptable, and had large effects on insomnia and fatigue among HF patients.

Objectives—The purpose of this randomized controlled trial (RCT) is to evaluate the sustained effects of group CBT-I compared with HF self-management education (attention control) on insomnia severity, sleep characteristics, daytime symptoms, symptom clusters, functional performance, and health care utilization among patients with stable HF. We will estimate the cost-effectiveness of CBT-I and explore the effects of CBT-I on event-free survival (EFS).

Methods—Two hundred participants will be randomized in clusters to a single center parallel group (CBT-I vs. attention control) RCT. Wrist actigraphy and self-report will elicit insomnia, sleep characteristics, symptoms, and functional performance. We will use the psychomotor vigilance test to evaluate sleep loss effects and the Six Minute Walk Test to evaluate effects on daytime function. Medical record review and interviews will elicit health care utilization and EFS. Statistical methods will include general linear mixed models and latent transition analysis. Stochastic cost-effectiveness analysis with a competing risk approach will be employed to conduct the cost-effectiveness analysis.

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Competing interests

The authors have no competing interests to declare.

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Discussion—The results will be generalizable to HF patients with chronic comorbid insomnia and pave the way for future research focused on the dissemination and translation of CBT-I into HF settings.

Keywords

self-management; heart failure; insomnia; cognitive behavioral therapy; sleep; symptoms

Introduction

Almost 75% of heart failure (HF) patients, a population of over five million Americans [1] who have poor function and high levels of morbidity and mortality, report poor sleep [2]. As many as 50% [3, 4] report comorbid chronic insomnia (i.e. difficulty initiating or maintaining sleep, or waking early in the morning with associated non-restorative sleep that persists for at least a month [5]). Chronic insomnia is associated with disabling symptoms such as fatigue, dyspnea, anxiety, depression, excessive daytime sleepiness, and pain, and may contribute to the development of HF and incident mortality [6].

Despite the importance of insomnia to critical HF outcomes, HF patients report that health care professionals fail to address it [7]. Patients prefer behavioral approaches to hypnotic medications [7] that are associated with adverse events, such as daytime sleepiness, falls, and altered cognition, but little is known about the impact of behavioral treatment for chronic insomnia among HF patients.

Cognitive behavioral therapy for insomnia (CBT-I), a self-management intervention, focuses on dysfunctional behaviors and cognitions that perpetuate physical and psychological arousal and chronic insomnia [8]. The effects of CBT-I are more durable than hypnotic medications [8, 9] without negative daytime effects [10].

In a pilot RCT, CBT-I improved chronic insomnia, sleep quality, sleep efficiency, and fatigue immediately after treatment in patients with Class II–III HF with chronic insomnia, compared with an attention control group who received HF self-management education alone [11]. Participants reported that it was highly acceptable and feasible. Both groups had stable HF at baseline (BL) and received evidence-based HF disease management. Evidence that chronic insomnia predicts incident HF and mortality [6] suggests the potential benefits of CBT-I to event-free survival (EFS), an outcome of critical importance to HF patients that has not been examined in relation to CBT-I. Although the benefits of CBT-I on sleep and insomnia have been widely documented, little is known about its effects on these important outcomes.

The organizing framework

The organizing framework is based on chronobiologic and homeostatic models of sleep regulation, the “3-p” model of insomnia [12], the Framework for Self- and Family Management of Chronic Conditions [13, 14], and research on symptoms and symptom clusters [15]. Chronic insomnia occurs at least 3 nights/week for at least one month [16] and is associated with one or more of the following: non-restorative sleep, difficulty initiating

sleep, maintaining sleep, and/or waking too early despite adequate sleep opportunity [5]. It is comorbid when it occurs with, but is not explained by, psychiatric, or medical disorders (e.g., HF). Insomnia often persists with optimal treatment of the comorbid condition [17]. The "3-p model" posits that biological, psychological, and social traits (predisposing factors); acute triggers, such as acute illness/treatment (precipitating factors); and maladaptive strategies (dysfunctional beliefs, attitudes, and behaviors) used to compensate for sleep loss (perpetuating factors) contribute to chronic insomnia through chronic somatic and/or psychological arousal – the "final common pathway" to chronic insomnia [17] (Figure 1).

Predisposing and precipitating factors for insomnia are poorly understood, but they are likely multi-factorial. Aging and gender often predispose to insomnia, but among HF patients, age, gender [2, 3], left ventricular ejection fraction (LVEF) [2], cardiac medications [18], and sleep apnea (SA) were not associated with chronic insomnia [3, 19]. Because these factors and comorbidity may contribute to insomnia and other study outcomes, they will be explored as possible covariates (Figure 1).

HF patients attributed awakening to modifiable factors such as increased time in bed awake [2], insufficient sleep, frequent napping [2], and use of TV as white noise at night [7]. Negative associations between sleep hygiene and sleep quality [19] and positive associations between insomnia severity and dysfunctional beliefs and attitudes about sleep, mental anxiety, and sleep effort underscore the contributions of perpetuating factors to chronic insomnia among HF patients.

The Framework for Self- and Family Management that explains the knowledge and skills to manage chronic conditions and related emotions and symptoms [13, 14], is the conceptual basis for CBT-I and the attention control condition (HF self-management education) used in this study. CBT-I includes cognitive and behavioral strategies that address perpetuating factors for insomnia (Figure 1, Table 1).

HF self-management includes behaviors needed to manage HF itself. Although self-care and self-management [20] and symptom clusters [15] have been associated with improved EFS in observational studies, estimates of the effects of self-management on EFS and health care resource utilization, are inconsistent [21, 22]. The effects of CBT-I versus HF self-management education on EFS will be explored in this study.

CBT-I protocols vary in format (group vs. individual), the types of included elements, and session frequency, but consistently address perpetuating factors through behavioral, cognitive, and educational elements [8]. The components of our CBT-I intervention are described in Table 1.

CBT-I has consistent effects on chronic insomnia [17, 23] and sleep efficiency [11, 24, 25], and improves some symptoms (e.g., fatigue, depression) in non-HF groups [26–28]. In our previous work, the observation of large effects of CBT-I on insomnia severity, remission rates, and fatigue [11], its effects on symptom clusters (patterns of severity of two or more symptoms), and its association with improved functional performance among HF patients supports the preliminary efficacy of CBT-I in HF patients, a group highly vulnerable to

disabling symptoms. A symptom cluster, characterized by emotional distress, predicted cardiac events among patients with HF, [15] and insomnia predicted incident HF, death from HF [6], health care resource utilization, and indirect costs [29, 30], but to our knowledge, previous studies have not systematically addressed the impact of CBT-I on these outcomes. Our study will address these gaps in science (Figure 1).

Methods

Design

This 5-year single-center parallel group RCT (October 1, 2015–June 30, 2020) is ongoing. Participants will complete BL assessments and be randomized to four bi-weekly group sessions of cognitive behavioral therapy for insomnia [CBT-I (“Healthy Sleep” - HS)] over eight weeks or an attention-control comparison group [HF self-management education (“Healthy Hearts” - HH)] (Table 2). Follow-up assessments will be conducted at two weeks, and at six, nine, and 12 months from baseline. These time frames were selected to determine short term (immediately after treatment) and sustained effects up to one year, with the intervals in between measurements selected to allow detection of meaningful change over time.

EFS will be evaluated through the end of the five-year funding period or until patient death. Yale University and the Veterans Affairs Connecticut Health Care System Institutional Review Board approval was obtained and all participants will provide written informed consent.

Specific aims and hypotheses

The specific aims of this RCT are to (1) test the sustained effects of CBT-I compared with HF self-management education (attention control comparison) on: (1a) insomnia severity and self-reported and wrist actigraph-recorded sleep characteristics (sleep quality, sleep efficiency, sleep latency, and duration); (1b) symptoms (fatigue, anxiety, depression, pain, dyspnea, sleepiness, sleep-related impairment), and psychomotor vigilance; and (1c) membership in, and transition between, clusters of symptoms that diverge in severity; (2) test the sustained effects of CBT-I on self-reported and objective functional performance; and (3) examine the cost-effectiveness of CBT-I. An exploratory aim is to examine the effects of CBT-I on EFS.

We hypothesize that CBT-I, compared with HF self-management education (attention-control), leads to the following sustained effects at two weeks, six, nine and 12 months after treatment:

- (1a)** decreased insomnia severity and sleep latency and increased sleep quality, duration and efficiency
- 1b)** decreases in severity of symptoms and improvements in psychomotor vigilance
- 1c)** transition between symptom clusters that have higher symptom severity to those that have lower symptom severity
- (2)** increased self-reported and objective functional performance

- (3) CBT-I will be cost-effective relative to HF self-management education.

Setting

Recruitment will occur at the Yale-New Haven Hospital Heart Failure and Transplantation Center and the Veterans Affairs Connecticut Health Care System. Because Yale cardiologists practice in both sites following guidelines from the American Heart Association and American College of Cardiology Foundation [31], HF management is comparable between sites.

Participants

The sample will include 200 individuals who are ≥ 18 years of age with New York Heart Class II–III HF who are cognitively intact by clinical impression, speak and read English, are concerned about sleep for ≥ 1 month, and score ≥ 8 on the Insomnia Severity Index (ISI) [32], an indicator of chronic insomnia, as defined by the International Classification of Sleep Disorders [16]. Participants may have either preserved left ventricular ejection fraction (LVEF) > 45% or reduced systolic function (LVEF ≤ 45%) HF. LVEF was not associated with chronic insomnia [3] in our previous work [3].

Depressive symptoms are common in HF [4] and often comorbid with insomnia. CBT-I improves depression [33] and suicidal ideation [34]. Effects were similar regardless of the presence of depression and its treatment with antidepressant medications [25]. We will include patients with no or moderate depression as defined by a Patient Health Questionnaire (PHQ-9) [35] score < 15 (none-mild depression). Those scoring higher will be further evaluated by a mental health provider. We will track the use of hypnotic and antidepressant medications and depressive symptoms and consider them in all analyses.

Exclusion criteria are untreated restless legs syndrome, night/rotating shift work, travel across ≥ 2 time zones within one month of enrollment, contraindications to sleep restriction [seizure disorder; score of > 18 on the Epworth Sleepiness Scale (indicates severe sleepiness); bipolar disorder], neurological/musculoskeletal conditions affecting arm movement (because of the use of the wrist actigraph), active illicit drug use, dementia, and end-stage renal failure requiring dialysis. Participants who are hospitalized or have emergency department visits, unstable conditions, or changes in vasoactive medications within four weeks of recruitment will not be enrolled until four weeks elapse without new events. Patients who experience these events after enrollment will be retained; events will be tracked and included in analyses. Participants with severe depression, and/or suicidal ideation, or bipolar disorder will not be included, but we will refer them immediately for follow-up.

Chronic insomnia and SA are often comorbid with HF, but SA is not associated with insomnia in HF patients [3, 19] and did not affect CBT-I outcomes in older adults [25]. Given limited evidence of positive airway pressure treatment benefits in very mild SA, we will include patients with an apnea-hypopnea index (sum of apneas and hypopneas/hour with 4% oxygen desaturation) < 10, and refer those with an apnea-hypopnea index ≥ 10 for further evaluation. Participants will be eligible if they continue to have insomnia once adherent to positive airway pressure ≥ 6 hours/night for at least 3 months. Those who have

not been evaluated for SA will be screened in their homes with the Apnea Risk Evaluation System (ARES) [36], a portable sleep recorder for two consecutive nights. If participants have previous SA apnea screening within the past year that meets the study criteria, we will include them in the study.

Participant recruitment

Health care personnel will identify potential participants and elicit permission for contact. We will also use fliers and posters in the clinical sites and advertise the study through the Yale Center for Clinical Investigation's website. A member of the study team will approach the patient, explain the study, and obtain informed consent for initial screening.

Initial screening will include medical record review and patient interview. We will use the PHQ-9 [35] to screen for depression. Medical records will be reviewed to elicit health and medical history as well as prescribed and over the counter medications. Potential participants who meet the initial screening criteria, will be consented for further screening and study participation. Those who have not been evaluated for SA will be screened in their homes with the Apnea Risk Evaluation System (ARES) [36], a portable sleep recorder. Participants who meet the inclusion criteria will proceed to the BL data collection.

Randomization

We will use block randomization with a computer-generated sequence to assign 200 participants in clusters of six to eight participants each to the CBT-I or attention control comparison (Figure 2). Study personnel involved in recruitment, screening, data collection or data entry will be blinded to group assignment. It is impossible to blind participants, but they will not know the group assignment until the first meeting.

Intervention group: CBT-I ("Healthy Sleep", HS)

A manualized protocol will include CBT-I elements (Table 2) in four bi-weekly one-hour face-to-face sessions; a telephone booster call on alternate weeks; the HS Guide, a workbook with CBT-I components; and optional hypnotic tapering. Four sessions of CBT-I were superior to other frequencies in previous studies [37]. Web applications are available for CBT-I, but we will not use them because the group format was feasible and may enhance social support and learning. There is no consistent evidence that one format is superior to the other.

The CBT-I group members will receive instruction and practice techniques to improve their sleep using the content in Tables 1 and 2. Participants will engage in a discussion covering HF medications, symptoms, management of fluids and when to call their health care provider about HF symptoms. The therapist will provide examples and feedback on individual progress with each of the activities at each session. There will be ample opportunity for questions and discussion.

Participants will be expected to practice the HS behaviors and record them, as well as their daily weights, sleep and symptoms, in a HS Log over the course of the intervention.

They will receive electronic bathroom scales (for monitoring daily weights), videos of the CBT-I sessions, the recorded relaxation exercise, the HS Log, instructions for all study elements, and study schedules on a mini-tablet computer provided to each participant. Participants will be encouraged to use the tablets, but paper options are available for those who are not comfortable with electronic technology. The information will be uploaded to the university server when WIFI is available but the forms can also be completed offline and uploaded when WIFI is available. The CBT-I group will also receive the “Healthy Hearts” Guide, a workbook that includes strategies for self-management of HF.

Attention Control Group: HF self-management (“Healthy Hearts”, HH)

Most previous CBT-I studies used usual care, wait-list, or information-only controls, but we will use attention-control because it is more rigorous, and time and attention may improve symptoms and function. The attention control group format is identical to the HS group with didactic sessions on HF self-management education [39, 40] including information about the disease process, symptoms, medications, exercise, managing weight, fluid, and diet, and basic information on stress management and sleep hygiene (Table 2), supported with the HH Guide developed from the “Fight against Heart Failure Workbook [39]. Sleep hygiene will be included, but will not be the active ingredient [8] and was the control condition in past trials [41]. There will be information on stress and relaxation, but no relaxation homework. We will explain that HF self-management may improve sleep by improving HF symptoms. Homework will include practice of HF self-management and tracking these skills, symptoms, and daily weights in a HH Log. Sessions, homework, and the HH Guide are equivalent to CBT-I in frequency, duration, and interventionist time. We will provide all materials, including HH session videos, HH Guide, HH Logs, and mini-tablet (except the CBT-I video, HS Logs, HS Guide, and the relaxation script) formatted identically to those for the HS group.

Procedures

At each session, we will review HH/HS logs with participants to guide practice. We will use scripted telephone boosters of approximately 10 to 15 minutes each on weeks alternate to group sessions to elicit skills use and provide review, problem solving, and reminders to complete logs and attend future sessions. These methods were feasible and acceptable in our preliminary study [11].

Retention and adherence—We will offer makeup sessions, but telephone or Skype make-ups will be used for those unable to attend in person. However, participants will be encouraged to continue with the same group. Make-ups will be held within one week of missed sessions, as in our pilot. We will compare groups (and their attendance rates) on the phone/Skype vs. face-face sessions, and include the number and types of sessions in analyses, if groups are unbalanced on these characteristics.

In order to maintain contact and promote retention, we will send birthday/holiday cards. We will provide \$50 for ARES screening and \$250 disbursed over the study milestones. To promote retention and adherence after the intervention, we will use brief scripted monthly phone calls until the 12 month follow-up, with content identical to the earlier calls, except

meeting reminders. We will resume data collection at later milestones, if participants miss data points and track reasons for missing data and/or attrition.

Treatment fidelity—The study is designed to assure treatment fidelity, and we will use similar materials/homework in both manualized conditions. Separate interventionists, blinded to outcomes data and study hypotheses, will provide the treatment conditions to avoid contamination. To assure protocol adherence, we will record sessions and script and record phone calls. We will randomly select and evaluate the fidelity of 20% of recordings and give feedback to the therapist. We will promote treatment receipt by reinforcing instruction (return demonstration, workbooks, and phone calls) and providing study information to take home for referral.

Study outcomes and measures

The primary outcomes will be insomnia severity, sleep characteristics (sleep duration, sleep efficiency, latency, global sleep quality), symptoms (fatigue, dyspnea, sleepiness, depression, anxiety, pain), psychomotor vigilance, functional performance, and health care utilization. Event-free survival will be the outcome of the exploratory aim.

Participants will complete a battery of questionnaires and objective measures to evaluate insomnia/sleep variables, symptoms, and functional performance (Table 3). All questionnaires and objective measures have established reliability and validity, and will be collected at BL and all follow-up periods (two weeks; six, nine and 12 months). Data on health care utilization will be obtained by self-report and validated through the electronic medical record (EMR), hospital cost accounting database, and the Medicare fee schedule (Table 3).

Direct costs for health care resources used will comprise office and emergency department visits, homecare, hospitalizations including reasons, cardiac devices, over the counter and prescribed medications. We will use the electronic pharmacy system to obtain prescription drug utilization and self-report for over the counter medications and include payments to the interventionists and costs of intervention materials. Deaths and causes of death will be ascertained with the EMR and the National Death Index. Indirect costs will be self-reported time missed from work. Data on direct and indirect costs will be collected monthly after the intervention phase until the 12-month follow-up and bi-monthly thereafter until the end of the study.

EFS will refer to time without events as specified in Table 3, and will be tracked through the second quarter of study year five, enabling monitoring of up to 18–45 months/subject, depending on enrollment times. We will assess events through participant/family report and confirm with the EMR and the National Death Index.

We will use interview and EMR to track demographic/clinical data at BL and all follow-up periods. Self-report data will be validated through EMR and vice-versa. The Charlson Comorbidity Index [53] and Seattle HF Risk Model, a predictor of death [54], will be computed. Due to the possible influence of self-care and self-management, including adherence to HF disease management on the primary study outcomes, we will use the 8-item

Morisky Scale [55], and self-care maintenance and management scales of the Self Care in Heart Failure Index v. 6 [56]. The relationships between these variables and the primary study outcomes will be evaluated and considered as covariates as needed.

Sample size

We performed power analyses to detect the effects of CBT-I on the primary outcomes with pilot data in which we randomized HF patients to CBT-I (HS) or attention control (HH) [11]. We calculated powers to detect differences in changes in the outcomes from BL between the two groups to post-intervention with an alpha level of 0.05 [57]. We also calculated the powers with scenarios of high within-subjects correlations ($Rho=0.6, 0.7, 0.8$) for repeated measures during follow-up (two weeks; six, nine, 12 months) by assuming consistent effect sizes over time. Inclusion of 200 subjects (100/group) will permit sufficient power to detect the association between improved insomnia severity and symptoms including fatigue ($>99.9\%$, $r = 0.526$), depression (99.16% , $r = 0.299$), anxiety ($> 99.9\%$, $r = 0.510$), and pain (92.7% , $r = -0.238$). There will be 92.6% power to detect risk of hospitalization in participants with insomnia remission (9%), compared to no remission (27.8%).

We computed the power for the cost-effectiveness analysis with Willan [58] and Glick's [59] methods, based on an assumed alpha level of 0.05, expected cost difference of \$500, standard deviation for costs of \$2,000, expected correlation between costs and quality-adjusted life years (QALYs) of -0.1 , and willingness-to-pay of \$50,000 per QALY. One QALY expresses the incremental cost per additional unit of effectiveness. Based on the pilot study, the expected difference in QALYs is estimated to be -0.33 . Together, these values suggest that the sample of 100 subjects/group yields 89.7% power for detecting cost-effectiveness of CBT-I.

Statistical methods

To evaluate differences in insomnia severity, sleep characteristics, symptoms, psychomotor vigilance, and functional performance over the five time points, we will use General Linear Mixed Models with a repeated measures statement to examine group, time, and group by time effects. In multivariable models, adjusted intervention effects will be estimated by including covariates that might differ by group assignment. We will use General Estimating Equations with a robust working correlation structure to address within-subjects correlations for non-normally distributed data with repeated measures.

For cluster analysis, we will use Latent Class Analysis to produce a subgroup (class membership) experiencing an identical symptom profile at BL, and use Latent Transition Analysis [60] to assess transitions between the class memberships at follow-ups. The Latent Transition Analysis will evaluate the effect of CBT-I on transitions between the class memberships over time and include the precipitating and predisposing factors as covariates to examine their contributions on transitions over time.

We will use General Linear Mixed Models or General Estimating Equations to determine the extent to which the effects of CBT-I on insomnia, sleep characteristics, symptoms and functional performance at six, nine, and 12 months are non-inferior to outcomes at two

weeks and identify potential barriers to sustained intervention effects by testing interactions between time and covariates associated with outcomes.

To assess cost-effectiveness, we will perform stochastic cost-effectiveness analysis from a societal perspective. We will estimate resource utilization in units for direct and indirect costs and apply prices to each unit. Costs will be the sum of the product of units and prices for both groups. The goal of stochastic cost-effectiveness analysis is to estimate the incremental cost-effectiveness ratio, which measures the additional cost per additional unit of effectiveness, measured as QALYs, the standard in cost-effectiveness research and economic evaluations of sleep disorders [30]. We will estimate QALYs by applying the utility measure derived from the EuroQoL Five Dimensions Questionnaire (EQ-5D) to the time spent during the study. We will consider the limited life expectancy of HF patients by including only time spent alive in the study, adjusted by utility. We will estimate the incremental cost effectiveness ratio and assess uncertainty using bootstrapping. We will also estimate the cost-effectiveness acceptability curve for a range of possible willingness-to-pay thresholds.

We will perform survival analysis to compare time to EFS between the CBT-I and the attention control group. Participants who do not experience events during follow-up will be right-censored. As a secondary analysis, we will examine time to specific events (e.g. hospitalization) with Cox Proportional Hazards model, and adjust for BL measures for the Seattle Heart Failure score [54], depression, LVEF, adherence to the HF treatment regimen [61], and self-care/self-care management [20], as they predicted EFS.

Discussion

Our RCT is designed to evaluate the sustained effects of self-management of insomnia with CBT-I (compared with HF self-management education) on insomnia severity, objective and subjective sleep characteristics, daytime symptoms, functional performance, and cost-effectiveness over twelve months among patients who have stable chronic HF and comorbid chronic insomnia. We will also explore the effects of CBT-I on EFS. Although there have been many other studies that have examined the effects of CBT-I among people with comorbid chronic medical and/or psychiatric conditions, our study is the first, to our knowledge, to examine the sustained effects of this promising treatment in this large and vulnerable population that is at very high risk for excessive symptom burden, poor daytime function, hospitalization, and high levels of health care resource utilization.

Our focus on symptom clusters acknowledges growing evidence that symptoms (e.g., fatigue, sleep disturbance, anxiety, depression, sleepiness) seldom occur in isolation among people with chronic conditions and advances the science of behavioral treatment of insomnia that, for the most part, has considered isolated sleep-related symptom outcomes. Inclusion of objective measures of sleep (actigraphy) and daytime performance (psychomotor vigilance test and Six Minute Walk Test) will also extend previous studies that have predominantly relied on self-report. Evidence from our earlier cross-sectional study [3] that documented significant insomnia-related differences in six-minute walk distance underscores the importance of this outcome. Although polysomnography was used in some previous CBT-I

trials, this method is not diagnostic for insomnia and adds significant subject burden and cost, and will, therefore, not be used in this study.

Our plan to address EFS builds on an earlier epidemiological study [6] that documented that insomnia predicted incident HF and death at a mean of 11 years from baseline. If CBT-I improves EFS, it may become an important intervention for these patients. Based on our findings, additional studies that extend limited understanding of the biology of insomnia and CBT-I will be needed [62]. Given the high costs of health care utilization among HF patients, our plan to examine cost-effectiveness, accompanied by beneficial clinical and behavioral effects of CBT-I may support future dissemination, translation, and effectiveness studies of CBT-I in this population.

In our previous research, HF patients disliked hypnotic medications due to their negative daytime effects [7]. Our behavioral intervention has high potential to improve sleep and sleep-related outcome, while reducing the negative consequences including injury of hypnotic medication.

We expect that this RCT will document the sustained effects of CBT-I among patients with stable HF. Our long term goal is to build on the results of this trial to disseminate and translate CBT-I into clinical HF and other cardiology programs.

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Abbreviations

ARES	Apnea Risk Evaluation System
BL	Baseline
CBT-I	Cognitive behavioral therapy for insomnia
EFS	Event-free survival
EMR	Electronic medical record
HF	Heart Failure
LVEF	Left ventricular ejection fraction
PHQ-9	Patient Health Questionnaire-9
QALY	Quality-adjusted life year
RCT	Randomized controlled trial
SA	Sleep apnea

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Figure 1. Organizing Framework

Solid-lined boxes/arrow = outcomes; double lined box/arrow = intervention; broken boxes/arrows = factors likely to contribute to insomnia, healthcare resource utilization, symptoms, functional performance, and event -free survival (possible covariates);

LVEF = Left ventricular ejection fraction; C-PAP = Continuous positive airway pressure

Figure 2. Participant flow diagram

ISI = Insomnia Severity Index [32]; AHI = Apnea-Hypopnea Index; C-PAP = Continuous positive airway pressure; RLS = Restless legs syndrome; ESS = Epworth Sleepiness Scale [38]; HF = Heart failure

Table 1

Components of cognitive-behavioral therapy for insomnia to be used in RCT [8]

Components	Content
Behavioral	
Stimulus control	Re-associating the bed with sleep; Maintaining a consistent sleep/wake schedule; Arising at the same time each morning; Going to bed only when sleepy; Getting out of bed when unable to sleep; Using bed only for sleep and sex; Avoiding naps
Sleep restriction therapy	With therapist supervision, patient decreases time in bed to maximize sleep efficiency, and then gradually re-increases it until the optimum efficiency and duration is attained.
Relaxation training	Reduction of somatic and cognitive arousal (e.g., progressive muscle relaxation; diaphragmatic breathing)
Cognitive	
Cognitive Therapy	Clarifies misperceptions/misattributions about insomnia/sleep; Reframes unrealistic expectations; Reduces performance anxiety; Increases control over sleep In our RCT: Six basic strategies [9]: (1) Keeping realistic expectations; (2) Not blaming insomnia for all impairments; (3) Never trying to fall asleep; (4) Not giving too much importance to sleep; (5) Not catastrophizing after poor night's sleep; (6) Developing tolerance for the effects of insomnia
Educational	
Sleep hygiene	Focuses on managing lifestyle and environment: Avoiding caffeine, tobacco and alcohol during evening hours; Encouraging physical activity; Avoiding naps; Removing alarm clock from the bedroom; Avoiding use of electronic devices/TV in the bedroom; Use of blue screen filters; Modification of sleep environment (comfortable bed, lighting, temperature, noise); Information on normal sleep, age-associated changes, and potential interactions between heart failure, its treatment and sleep/insomnia
Hypnotic tapering (Optional)	Gradual reduction of over the counter/prescribed hypnotics with supervision of therapist

Table 2

Content and Schedule for CBT-I and Attention Control Conditions

	CBTI: “Healthy Sleep – HS”	Attention Control: “Healthy Hearts- HH”
Week 1: Session 1	Overview of symptoms of HF and HF self-management; Weight & symptom monitoring; Sleep education: overview of CBT-I, sleep stages, circadian rhythm, role of HF & treatment relative to sleep, sleep scheduling/restriction, stimulus control	Overview of symptom of HF and HF self-management; Definitions of HF; Signs & symptoms and their meaning; Weight & symptom monitoring; Diagnostic testing; Medical contacts and how to document
Week 2:	Telephone booster (both groups) *	
Week 3: Session 2	Review sleep diaries; Adjust sleep schedule; Education: physiological arousal/fight or flight vs. relaxation response; Cognitive restructuring; Relaxation training; Optional hypnotic taper	Review progress & homework; HF symptom management monitoring: fatigue, dyspnea, sleep, edema, mood; Fluid and sodium management; Effective communication with healthcare providers
Week 4:	Telephone booster (both groups) *	
Week 5: Session 3	Adjust sleep schedule; Review previous strategies; Lifestyle factors/sleep hygiene: exercise, sleep environment, food, alcohol caffeine; “Mini” relaxation	HF Medications & strategies to promote adherence; Over the counter medications & herbal remedies; Cardiac devices
Week 6:	Telephone booster (both groups) *	
Week 7: Session 4	Reinforce adherence; Call attention to progress; Review; Relapse prevention advice	Healthy lifestyle: diet; risk factors for CVD; stress management/relaxation; exercise; environment and sleep; Review
Week 8:	Telephone booster (both groups) *	

* Elicit skill use; Review and problem solving; Reminders to complete logs and attend future sessions (in both groups)

HF = Heart Failure; CBT-I = Cognitive-behavioral therapy for insomnia; CVD = cardiovascular disease

Table 3

Study variables and measures

Variable Measure	Sleep/Insomnia
Global sleep quality	<ul style="list-style-type: none"> Pittsburgh Sleep Quality Index (PSQI) [42] PROMIS Sleep Disturbance Brief Item Bank [43]
Sleep latency; Wake after sleep onset; Sleep efficiency; Time in bed; Total sleep time	<ul style="list-style-type: none"> Subjective: PSQI [42] Objective: Respironics Actiwatch2 wrist actigraph
Insomnia severity	Insomnia Severity Index (ISI) [32]
Symptoms	
Excessive daytime sleepiness	<ul style="list-style-type: none"> Epworth Sleepiness Scale (ESS) [38] PROMIS Sleep Impairment Brief Item Bank [43]
Fatigue (total, severity, distress, interference, timing)	<ul style="list-style-type: none"> Multi-Dimensional Assessment of Fatigue Scale (MAFS) [44] PROMIS Fatigue Item Bank [43]
Depressive symptoms	<ul style="list-style-type: none"> The Center for Epidemiological Studies of Depression Scale (CESD) [45] PROMIS Depression Item Bank [43]
Stress symptoms	<ul style="list-style-type: none"> Perceived Stress Scale (PSS-10) [46]
Anxious symptoms	<ul style="list-style-type: none"> Spielberger Trait Anxiety Scale (STAI) [47] PROMIS Anxiety Item Bank [43]
Pain (severity, location, and interference)	<ul style="list-style-type: none"> Brief Pain Inventory (BPI) [48] PROMIS Pain Item Bank [43] Pain Catastrophizing Scale (PCS) [49]
Dyspnea (total, severity, distress, interference, timing)	<ul style="list-style-type: none"> Multi-Dimensional Assessment of Dyspnea Scale (MADS) [4]
Neurobiological effects of sleep loss/sleepiness	<ul style="list-style-type: none"> Psychomotor Vigilance Test (PVT-192) [50] PROMIS applied cognition - ability [43] PROMIS applied cognition - general concerns [43]
Functional Performance	
	<ul style="list-style-type: none"> Self-report: SF-36 v2 Physical Function Component [51] Objective: Six Minute Walk Test (6 MWT) [52]
Health Care Resource Utilization	
	Direct and indirect costs (see narrative) elicited through <ul style="list-style-type: none"> Self-report: Interview Objective: Review of EMR and other administrative records (see narrative)
Event Free Survival (Time to first event)	
	Absence of: Death (all cause); HF related hospitalizations; HF related ED visits; Heart transplantation; LVAD Elicited through <ul style="list-style-type: none"> Self-report: Interview of patient/family

Variable Measure	Sleep/Insomnia
	• Objective: EMR review

PROMIS = Patient-Reported Outcomes Measurement Information System; SF-36 = Short Form Health Survey; EMR = Electronic medical record; HF = Heart failure; ED = Emergency department; LVAD = Left ventricular assist device

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